Morphological and Functional Assessment of Meibomian Glands in Keratoconus

Ömür Ö Uçakhan (✉ omuru@yahoo.com)

Ankara University Faculty of Medicine: Ankara Universitesi Tıp Fakultesi

Gökçen Özcan

Ankara University Faculty of Medicine: Ankara Universitesi Tıp Fakultesi

Research Article

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Abstract

Purpose: To evaluate the morphology and function of the meibomian glands (MG) in keratoconus patients.

Methods: One hundred eyes of 100 keratoconus patients and 100 eyes of 100 age-matched healthy subjects were included into this study. Ocular Surface Disease Index (OSDI) scores, non-invasive break up time (NIBUT), meibography findings, fluorescein staining of the ocular surface, tear film break-up time (TBUT), and Schirmer I test were recorded in all patient eyes and were compared with controls.

Results: The mean TBUT and NIBUT were significantly lower, corneal staining and OSDI scores were statistically higher in the keratoconus group ($p < 0.05$). The mean meiboscore, partial gland, gland dropout and gland thickening scores of the upper and lower eyelids were significantly higher in keratoconus patients compared to controls ($p < 0.05$). The NIBUT measurements significantly correlated with MG loss in both upper and lower eyelids ($p < 0.05$). The severity of keratoconus seemed to correlate with meiboscore, partial gland, gland thickening scores in both upper and lower eyelids.

Conclusion: Our data suggest that corneal ectasia in keratoconus is associated with alterations in ocular surface, tear film function and MG morphology. Early screening and treatment of MG dysfunction may improve ocular surface quality and allow better disease management in keratoconus patients.

Introduction

Keratoconus is a progressive, bilateral, ectatic disease of the central and paracentral cornea characterized by stromal thinning, irregular corneal astigmatism, and myopia. The etiology of the disease remains unknown, however, possible linkage with systemic diseases, a combination of genetic predisposition and environmental factors such as excessive eye rubbing and use of contact lenses, have been proposed as possible mechanisms.

Although keratoconus has long been described as a non-inflammatory disorder, many studies have pointed to the possibility of underlying inflammatory mechanism which may link keratoconus to tear film and ocular surface dysfunction [1, 2]. Tissue degradation in keratoconus, involves the expression of inflammatory mediators, such as proinflammatory cytokines, cell adhesion molecules, and matrix metalloproteinases (MMP). Overexpression of interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- α), MMP-9 was found in the tear film of keratoconic eyes when compared to normal [3]. Eye rubbing, which is very common in keratoconus patients also results in an additional increase in levels of MMP-13, IL-6, and TNF- α levels in the tear film [4].

Recently, there has been an increased interest in ocular surface and tear film alterations of keratoconus. Ocular surface damage with corneal and conjunctival staining, tear film instability, and squamous metaplasia with goblet cell loss and decreased mucin levels have been demonstrated in keratoconic eyes in few studies [5–7]. Fukuchi et al demonstrated that the levels of lysosomal hydrolases are elevated in

both conjunctival and corneal epithelium of patients with keratoconus, suggesting that the whole ocular surface epithelium may be potentially altered in keratoconus [8].

Meibomian gland dysfunction (MGD) is the leading cause of evaporative dry eye. It is characterized by terminal MG duct obstruction and/or altered changes in the meibum secretions, leading to tear film instability, thus having the potential of initiating and perpetuating the vicious circle of dry eye disease, which may ultimately lead to inflammation and ocular surface damage [9–12].

Our purpose in this study was to investigate the MG function and morphology in keratoconic eyes and evaluate any possible influence of MGD in the ocular surface damage and tear film instability that may be encountered in these eyes.

Methods

Patient Selection

This study was approved by the Institutional Review Board Committee of the Ankara University and was performed according to the ethical principles of the Declaration of Helsinki. The medical records of consecutive keratoconus patients who were examined using a standardized protocol between the years 2016 to 2020 at the Cornea, Contact Lens and Refractive Surgery Service of Ankara University School of Medicine were retrospectively reviewed. Exclusion criteria included history of dry eye diagnosis or ocular surgery, soft or rigid contact lens wear, use of systemic medications that may cause dry eye or MG dysfunction, presence of rosacea, allergic, atopic or vernal keratoconjunctivitis or any other coexisting ocular surface disease.

All patients underwent complete ophthalmologic evaluation including slit lamp examination (SLE, at 40× magnification), corneal tomography (The Oculus Pentacam® Oculus Optikgeräte GmbH, Wetzlar, Germany) and noncontact meibography (Sirius Scheimpflug Camera; Bon Optic VertriebsgmbH, Lübeck, Germany). The diagnosis of keratoconus was made based on the presence of slit lamp biomicroscopy findings such as Fleischer ring, stromal thinning or Vogt striae, together with corneal tomographic evidence of ectasia. If both eyes of one patient had keratoconus, only the eye with more advanced keratoconus was included into the study. Keratoconic eyes were staged according to the Amsler-Krumeich classification [13].

Slit lamp biomicroscopy Findings and Functional Analysis

Patients were asked to rate their dry eye symptoms using the Ocular Surface Disease Index [OSDI] questionnaire. Ocular examinations were performed in the following order; evaluation and measurement of spectacle-corrected distance visual acuity (CDVA), non-invasive break up time (NIBUT) and MG morphology measurements using non-contact meibography (Sirius Scheimpflug Camera; Bon Optic VertriebsgmbH, Lübeck, Germany), Scheimpflug corneal tomography (Pentacam® Oculus Optikgeräte

GmbH, Wetzlar, *Germany*), slit-lamp biomicroscopy, fluorescein break up time (TBUT), ocular surface staining, and Schirmer I test. Corneal and conjunctival staining was graded according to the Oxford grading scale [14].

Morphological Analysis

The best recorded images of the upper and lower lids were chosen and the morphological characteristics of the meibography images were evaluated by one examiner (GO) who was blinded to the medical records of the patients. All morphological assessments were obtained from the middle two thirds of the eyelids on meibography.

The “total meiboscore” was the percentage of partial or total loss of MG on a defined area on the everted eyelid. Degree of meibomian gland loss was calculated with the software of the device automatically and given as percentage. The meiboscore was graded as grade 0 (no loss of MG), grade 1 (the affected area, less than 33% of the total area occupied by the MG), grade 2 (the affected area between 33% and 66% of the total area occupied by the MG), and grade 3 (the affected area more than 66% of the total area occupied by the MG) [15].

“Partial gland” was defined as partial loss of meibomian gland from the orifice or fornix, and “gland dropout” was defined as complete loss of meibomian gland from orifice to fornix. Scores were identified by the number of affected MGs according to grading suggested by Arita et al.¹⁵ Partial loss of MGs was graded as grade 0 (no partial glands), grade 1 (less than three partial glands), grade 2 (three or more partial glands and less than three partial glands with loss of half or more of the full length), or grade 3 (three or more partial glands with loss of half or more of the full length) (Figure 1).

Gland dropout was graded as grade 0 (no gland dropout), grade 1 (less than three gland dropouts), or grade 2 (three or more gland dropouts) (Figure 2). Glands that appeared curly compared to other glands of the patient’s eye were defined as “curled glands” and glands that appeared at least twice the thickness of other glands of the same patient eye were defined as “gland thickening” and scores were identified by the number of affected MGs according to grading of Aslantürk and Uçakhan; grade 0 (no affected gland), grade 1 (less than three curled glands or thickened glands), or grade 2 (three or more curled glands or thickened glands) (Figure 3-4) [16].

Statistical Analysis

Descriptive statistics were expressed as mean $\pm$ standard deviation and median (min–max) for continuous variables, and as number and percentage for categorical variables. Statistical tests and correlation coefficients were chosen according to whether the data distribution was normal or not. Categorical variables were compared using Chi-Square or Fisher’s Exact Test as appropriate. The differences between the groups were evaluated by Mann-Whitney U test. P-values less than 0.05 were

considered as statistically significant. Statistical analyses were performed using SPSS (Statistical Package for Social Sciences; version 11.5).

Results

A hundred eyes of 100 patients with the diagnosis of keratoconus (55 males, 45 females) and 100 eyes of 100 healthy control subjects (55 males, 45 females) were included in this retrospective study. The mean age of the patients was 22.6 ± 6.0 years (range; 11 to 43 years) in the keratoconus group and 23.5 ± 6.9 years (range; 11 to 45 years) in the control group. There were no statistically significant differences between the two groups in terms of age and sex ($p > 0.05$).

Slit Lamp Biomicroscopy Findings And Functional Analysis

The functional parameters analyzed in the keratoconus and control groups are summarized in Table 1. Accordingly, the mean OSDI scores, NIBUT, TBUT, and corneal staining were significantly worse in the keratoconus group ($p < 0.05$) compared to healthy eyes.

Table 1
Functional parameters analyzed in the keratoconus and control groups

	Keratoconus (n = 100)	Control (n = 100)	P values
OSDI score (mean)	43.8 ± 22.6	18.2 ± 15.7	p = 0.003*
NIBUT (mean, sec)	8.7 ± 6.6	12.9 ± 6.9	p < 0.001*
TBUT (mean, sec)	7.7 ± 3.3	10.6 ± 2.5	p = 0.011*
Schirmer I (mean, mm/10 seconds)	22.0 ± 9.8	22.3 ± 9.8	p = 0.119*
Corneal Staining Score (mean ± SD, %)	0.63 ± 0.69	0.21 ± 0.58	
grade 0	65.3%	87.1%	p = 0.006+
grade 1	27.7%	12.9%	
grade 2	5.9%	-	
grade 3	1.1%	-	
grade 4	-	-	
grade 5	-	-	
* Mann–Whitney U test., + Fisher Exact test			

Morphological Analysis Of Mg

The non-contact meibography findings were evaluated separately for the upper and lower eyelids. In the upper eyelids, MG loss was $24.0 \pm 15.7\%$ in the keratoconus group and $13.7 \pm 5.9\%$ in the control group ($p < 0.001$). In the lower eyelids, MG loss was $34.0 \pm 16.2\%$ in keratoconus group and was $20.4 \pm 11.2\%$ in the control group ($p < 0.001$) (Fig. 5).

Table 2 shows the mean meiboscore, partial gland, gland dropout, as well as curled and thickened gland scores in the two groups. The mean meiboscore, partial gland, gland dropout, and thickened gland scores of the upper/lower eyelids were significantly higher in keratoconus group compared to the control group ($p < 0.05$). The mean curled gland score of the upper/lower eyelids was also higher in the keratoconus group compared to the control group, however, this difference reached statistical significance only for the lower eyelids.

Table 2
Morphological alterations in the meibomian glands in keratoconus and control groups as measured using non-invasive meibography

	Keratoconus (n = 100)	Control (n = 100)	P values ⁺
Upper Eyelid Mean ± SD, % Mean ± SD, %			
Meiboscore	1.23 ± 0.51	1.02 ± 0.51	p < 0.001
grade 0	1.0%	2.0%	
grade 1	80.0%	93.0%	
grade 2	15.0%	5.0%	
grade 3	4.0%	-	
Partial gland	2.22 ± 0.71	1.25 ± 0.67	p < 0.001
grade 0	-	9.9%	
grade 1	16.7%	58.4%	
grade 2	45.1%	28.7%	
grade 3	38.2%	3.0%	
Gland dropout	0.28 ± 0.58	0.07 ± 0.25	p = 0.002
grade 0	78.4%	93.1%	
grade 1	14.7%	6.9%	
grade 2	6.9%	-	
Curled gland	1.57 ± 0.62	1.43 ± 0.66	p = 0.099
grade 0	6.0%	8.9%	
grade 1	32.0%	40.6%	
grade 2	62.0%	50.5%	
Gland thickening	1.26 ± 0.56	0.93 ± 0.63	p < 0.001
grade 0	5.9%	23.8%	
grade 1	62.4%	59.4%	
grade 2	31.7%	16.8%	
Lower Eyelid Mean ± SD, % Mean ± SD, %			

⁺ Pearson Chi Square and Fisher Exact test

	Keratoconus (n = 100)	Control (n = 100)	P values [†]
Meiboscore	1.53 ± 0.57	1.19 ± 0.35	p < 0,001
grade 0	-	-	
grade 1	51%	89.1%	
grade 2	45%	9.9%	
grade 3	4%	1.0%	
Partial gland	2.44 ± 0.68	1.5 ± 0.78	p < 0,001
grade 0	-	7.9%	
grade 1	10.7%	43.7%	
grade 2	34.5%	38.5%	
grade 3	54.8%	9.9%	
Gland dropout	0.55 ± 0.76	0.12 ± 0.35	p < 0,001
grade 0	61.7%	89.1%	
grade 1	21.6%	9.9%	
grade 2	16.7%	1.0%	
Curled gland	0.92 ± 0.62	0.58 ± 0.62	p < 0,001
grade 0	23.8%	47.5%	
grade 1	60.4%	46.6%	
grade 2	15.8%	5.9%	
Gland thickening	1.16 ± 0.59	1.06 ± 0.59	p = 0.017
grade 0	10.9%	18.8%	
grade 1	62.3%	66.3%	
grade 2	26.8%	14.9%	
[†] Pearson Chi Square and Fisher Exact test			

Correlations Between Functional And Morphological Alterations

Table 3 shows the correlations between the functional and morphological parameters studied in the keratoconus group. Among functional parameters, NIBUT correlated with partial or total MG loss, and meiboscore for both the upper and lower eyelids ($p < 0.05$), whereas, TBUT correlated with meiboscore and partial gland loss only in the upper lid ($p < 0.05$).

Correlations Between Functional And Morphological Alterations And Keratoconus Severity

Of the total 100 eyes, 30% had grade 1, 25% had grade 2, 25% had grade 3, 20% had grade 4 keratoconus. Table 4 shows the correlations between functional and morphological alterations in the upper and lower eyelids and the keratoconus severity. Correspondingly, there were statistically significant correlations between disease severity and OSDI scores, TBUT, NIBUT, meiboscore, partial gland, and gland thickening scores for upper/lower eyelids and gland dropout scores for lower eyelids ($p < 0.05$).

Table 3
Correlations between functional and morphological alterations in the keratoconus group

Variables*	TBUT	NIBUT	Schirmer I test	Corneal staining	OSDI
Upper eyelid					
Meiboscore	p = 0.058	p = 0.031 (R= -0.385)	p = 0.717	p = 0.805	p = 0.270
Partial gland	p = 0.028 (R= -0.218)	p = 0.042 (R= -0.369)	p = 0.926	p = 0.632	p = 0.133
Gland dropout	p = 0.454	p = 0.028 (R= -0.219)	p = 0.491	p = 0.016 (R = + 0.225)	p = 0.153
Curled gland	p = 0.779	p = 0.099	p = 0.709	p = 0.480	p = 0.911
Gland thickening	p = 0.009 (R= -0.258)	p = 0.295	p = 0.730	p = 0.219	p = 0.400
Lower eyelid					
Meiboscore	p = 0.107	p = 0.001 (R= -0.687)	p = 0.789	p = 0.513	p = 0.224
Partial gland	p = 0.484	p < 0.001 (R= -0.997)	p = 0.474	p = 0.800	p = 0.005 (R = + 0.335)
Gland dropout	p = 0.034 (R= -0.210)	p = 0.043 (R= -0.200)	p = 0.694	p = 0.603	p = 0.845
Curled gland	p = 0.067	p = 0.203	p = 0.839	p = 0.182	p = 0.330
Gland thickening	p = 0.060	p = 0.561	p = 0.853	p = 0.538	p = 0.647
<p>* Spearman's correlation test used.</p> <p>R: correlation coefficient</p> <p>Values between 0 and 0.3 (0 and - 0.3) indicate a weak positive (negative) linear relationship</p> <p>Values between 0.3 and 0.7 (-0.3 and - 0.7) indicate a moderate positive (negative) linear relationship</p> <p>Values between 0.7 and 1.0 (-0.7 and - 1.0) indicate a strong positive (negative) linear relationship</p>					

TABLE 4. Correlations between keratoconus stage and functional/morphological MG parameters

Variables*	Keratoconus stage	
	P values	Correlation Coefficient
OSDI	p = 0.006	R = + 0.335
Schirmer	p = 0.790	R= -0.027
TBUT	p = 0.049	R= -0.195
NIBUT	p = 0.030	R= -0.391
Upper eyelid		
Meiboscore	p = 0.011	R = + 0.285
Partial gland	p = 0.009	R = + 0.261
Gland dropout	p = 0.621	R = + 0.050
Curled gland	p = 0.639	R = + 0.048
Gland thickening	p = 0.009	R = + 0.262
Lower eyelid		
Meiboscore	p = 0.047	R = + 0.203
Partial gland	p = 0.002	R = + 0.312
Gland dropout	p < 0.001	R = + 0.342
Curled gland	p = 0.289	R = + 0.119
Gland thickening	p = 0.018	R = + 0.362
<p>* Spearman's correlation test used.</p> <p>R: correlation coefficient</p> <p>Values between 0 and 0.3 (0 and – 0.3) indicate a weak positive (negative) linear relationship</p> <p>Values between 0.3 and 0.7 (-0.3 and – 0.7) indicate a moderate positive (negative) linear relationship</p> <p>Values between 0.7 and 1.0 (-0.7 and – 1.0) indicate a strong positive (negative) linear relationship</p>		

Discussion

In our study, there were significant functional and morphological alterations in the MG of keratoconic eyes compared to normals. The keratoconus group showed significantly higher OSDI scores and lower NIBUT, TBUT, greater corneal and conjunctival staining compared to the control group. Meiboscore, partial gland, gland thickening, and gland dropout scores were also significantly higher in the keratoconus group compared to age-matched controls both for the upper and lower eyelids. Furthermore, OSDI scores, tear film instability and most morphological alterations correlated with disease severity.

Keratoconus is a multifactorial disease with genetic, environmental, inflammatory, hormonal risk factors and eye rubbing playing role in etiopathogenesis [17]. In the literature, few studies reported on increased dry eye symptoms [7, 18], tear film instability [6, 19], ocular surface staining [6, 7] and conjunctival metaplasia with goblet cell loss in keratoconus patients [5–7]. indicating involvement of whole ocular surface epithelium and tear film in the disease process in these eyes. Although the reason for such findings is not clear, inflammatory changes were detected in the tear film of keratoconic eyes, which were suggested to lead to goblet cell loss and alterations in mucin secretion with resultant tear film instability [3, 4]. On the other hand, whereas, MGD is considered the most common reason for tear film instability, and evaporative dry eye, knowledge on the role of MGD in signs and symptoms of ocular surface disease in keratoconus is scarce [20].

Meibomian gland disease is a chronic condition of the MG, characterized by terminal duct obstruction and/or qualitative or quantitative changes in glandular secretion. Although traditionally MGD is diagnosed on the basis of subjective symptoms and slit lamp biomicroscopy findings such as; lid margin abnormalities, the condition of the gland orifices, and meibum grade, rapid objective evaluation of the MG with high reproducibility is only possible with noncontact meibography [21]. This method is now widely adopted in clinical practice for evaluation of meibomian gland–related diseases. Meibomian gland dropout on meibography has been reported to be correlated with NIBUT, TBUT, lipid layer thickness, meibum expressibility and tear film osmolarity [22–24].

Previously, Mostafa et al reported increased OSDI scores, decreased TBUT and Schirmer test results, and increased MG dropout in keratoconus patients compared to controls. In their study, in which only upper eyelid meibography measurements were performed, meiboscore grades were not significantly different between the two groups. The authors could not demonstrate any correlation between TBUT, Schirmer test results, gland dropout or gland distortion versus severity of keratoconus. In our study, we observed significant differences in OSDI, TBUT, and MG morphology between keratoconic eyes and normals. Among the MG morphologic parameters meiboscore and partial gland, gland dropout and, gland thickening scores were significantly higher in KC group compared to controls in both upper and lower eyelids. Furthermore, we evaluated NIBUT as has been suggested by the TFOS DEWS II report [26] to evaluate tear film stability, and the NIBUT measurements in these patients showed moderate to strong correlations with upper lid and lower lid meiboscore and partial gland scores. We could also demonstrate significant correlations between meiboscore, partial gland and gland thickening scores of both the upper and lower eyelids and the severity of keratoconus, with worsening of meibography findings as the disease stage increased.

To our knowledge, our study is the first study showing such correlations between OSDI, NIBUT, meibography findings and keratoconus severity. The reason for the morphological changes in MG is not clear, however, ocular surface inflammation initiated by tear film instability, or directs mechanical irritation of the lids by the conic cornea or vigorous eye rubbing may be possible underlying mechanisms. Although tear film dysfunction or MGD cannot cause keratoconus, such ocular surface problems may further exacerbate the disease through increased eye rubbing.

One of the limitations of the present study is its retrospective nature. We could not reach lid margin abnormality data of all patients from patient charts and therefore did not include slit lamp biomicroscopy gradings of MG orifices or secretion quality into the study, which could have increased the accountability of our current findings. However, our patients were not MGD patients per se, furthermore, at the outpatient clinic we found evaluation of gland orifices via observation of meibography images much easier and reliable as compared to evaluation at the slit lamp with or without digital pressure on the lids. Therefore, we believe, the outcomes of our study confirm the presence of signs and symptoms of tear film instability in keratoconus patients and add new information to our knowledge of MG morphology in these eyes as measured by non-invasive meibography.

In summary, keratoconus seems to be associated with significant morphological alterations in MG of both upper and lower eyelids. Furthermore, the morphological alterations in these eyes seemed to correlate with symptoms, tear film instability (particularly NIBUT) and keratoconus stage. Although further longitudinal studies are required to elucidate the mechanism underlying the association between keratoconus and MGD, the present findings indicate the possibility that MGD may be one of the underlying factors in dry eye symptoms and tear film instability in patients with keratoconus.

Declarations

The authors have no conflicts of interest to disclose.

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Figures

Figure 1

Representative images of partial gland loss grading marked with black stars. (A,E) Partial gland loss grade 0, no partial glands. (B,F) Partial gland loss grade 1, less than three partial glands. (C,G) Partial gland loss grade 2, three or more partial glands and less than three partial glands with loss of half or more of the full length. (D,H) Partial gland loss grade 3, three or more partial glands with loss of half or more of the full length

Figure 2

Representative image of gland dropout grading marked with black stars. (A,D) Grade 0, no gland dropout. (B,E) Grade 1, less than three MG dropout. (C,F) Grade 2, three or more MG dropouts. MG, meibomian gland.

Figure 3

Representative images of “MG curling” marked with black stars. (A,D) Grade 0, no affected gland. (B,E) Grade 1, less than three curled glands. (C,F) Grade 2, three or more curled glands. MG, meibomian gland.

Figure 4

Representative images of “MG thickening” marked with black stars. (A,D) Grade 0, no affected gland. (B,E) Grade 1, less than three thickened glands. (C,F) Grade 2, three or more thickened glands. MG, meibomian gland

Figure 5

Comparisons of the mean MG loss for the upper (blue) and lower (green) eyelids in the control group and different stages of keratoconus.