Comparative of Meibomian Gland Morphology in Patients With Evaporative Dry Eye Versus Non-Dry Eye

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Research Article

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Abstract

Many recent studies have demonstrated that morphological changes are one of the key signs of Meibomian gland disease (MGD). These changes can be seen even before symptom onset, potentially underestimating the prevalence of MGD; however, Until now, there is no conclusive information about the impact of MG morphology in tear film physiology and disease. This study aimed to investigate the prevalence of anatomical and morphological MG alterations between patients with evapo-rative DED and healthy controls. Retrospective chart review of Seventy-five patients with evaporative dry eye and healthy individuals who had dry eye assessments included Ocular Surface Disease Index questionnaire, Meibum quality, meibum expressibility, lid margin abnormality, ocular staining, non-invasive tear film break-up time, and Meibography. We did not find significant differences in MG alterations in the upper lid between healthy and dry-eye subjects. Patients with evaporative dry eye presented MG alterations in the lower lid more frequently than healthy subjects (54.8 vs 30.3%; $p=0.03$). The presence of shortened glands was the only MG alteration that was more prevalent in the lower lid in dry-eye patients than in healthy subjects ($p < 0.05$). Subjects with evaporative dry eye presented more alterations in the lower lid than healthy subjects.

Introduction

According to the second DEWS report, dry eye disease (DED) is defined as “a multifactorial disease of the ocular surface characterized by loss of the homeostasis of the tear film, and its accompanied by visual symptoms in which tear film instability, hyperosmolarity, damage and inflammation of the ocular surface and neuro-sensorial abnormalities play a role”.¹ DED and its symptoms are one of the most common causes of ophthalmological consultations, with a worldwide prevalence of 50-80.4%.^{2,3} The most common symptoms are irritation, foreign body sensation, eye pain and redness.² DED etiology is divided in aqueous deficient, evaporative, and mixed, the latter two are largely due to meibomian gland dysfunction (MGD).^{2,4}

Meibomian glands (MG) are sebaceous glands located in both eyelids that provide the lipid layer of the tear film, mainly providing tear film stabilization and increasing its break-up time.

The global prevalence of MGD is 3.6-68%, and it is more common in Asian patients than in Caucasians.⁵ This can be an asymptomatic disease which is only detected by glandular expression and meibography, or it can be symptomatic, accompanied by signs and symptoms of dry eye.⁶ The diagnosis in asymptomatic patients is performed based on qualitative or quantitative alterations of the MG expression.⁶ There are various tools for the diagnosis of MGD such as symptom questionnaires, invasive or non-invasive tear film break-up time (NIKBUT), lipid interferometry, staining with fluorescein or lisamine green, slit lamp examination (anatomical changes in the eyelid, gland expressibility and quality of the secretion) and meibography.⁵ Although there are several tools for the diagnosis and follow-up of

MGD, there is no standardization yet.⁷ Infrared meibography is the most used equipment to evaluate and assess the morphological and anatomical characteristics of the MG.

Previous studies show that morphological changes are one of the key signs of MGD.^{6,8} These changes can be seen even before symptom onset, potentially underestimating the prevalence of MGD. For the evaluation of MGD, morphological assessment of meibography images are required since dry eye tests cannot identify all MGD cases.⁹ Although there are several studies that demonstrate a good correlation between MGD clinical parameters,^{4,10} only a few have described the relationship between the MG morphologic characteristics seen in meibography with other clinical parameters, and more studies are required to improve this correlation.^{5,7} Until now, there is no conclusive information about the impact of MG morphology in tear film physiology and disease. This study aims to investigate the prevalence of anatomical and morphological alterations in MG in healthy individuals and patients with evaporative DED and whether there is a correlation between these alterations and clinical parameters used in the study of MGD.

Materials And Methods

A retrospective chart review of patients with evaporative dry eye and healthy individuals was performed. The study was approved by the Research Committee and the Bioethics Committee of the Health Sciences Division of the University of Monterrey. Requirement for a written informed consent was waived by the Comité de Investigación de la Vicerrectoría de Ciencias de la Salud de la Universidad de Monterrey (ref: 05132020-a-OFT-CC-CI) due to the retrospective observational nature of the study and information that allows the identification of the patient was not used, and adhered to the tenets of the Declaration of Helsinki.

Study population

The inclusion criteria for healthy individuals included an Ocular Surface Disease Index (OSDI) of <12 points, non-invasive tear film break-up time (NIBUT) > 10 s, and no ocular surface staining, so patients with any type of dry eye was excluded. Patients with evaporative dry eye were included according to the criteria of the International Workshop on Meibomian Gland Dysfunction.⁶ Briefly, the patients were required to achieve an OSDI score > 12 points, NIBUT < 10 s, expressibility grades 1 to 3, and MG yielding liquid secretion (MGYLS) score > 1.⁶ The exclusion criteria for both groups were any uncontrolled systemic conditions and any history of refractive or eyelid surgery, corneal infection, or active ocular disease with the exception of dry eye, history of facial paralysis, or use of contact lenses in the past 7 days.

Evaluation of signs of dry eye

All assessments of signs were performed by one ophthalmologist specialist in cornea and ocular surface diseases (MGL). The following information was studied: self-administered OSDI questionnaire (Allergan,

Irvine, CA) which had been validated in Spanish,²⁴ for ocular surface staining 5 µL of 2% fluorescein diluted in saline solution was instilled in the cul-de-sac, and 2 minutes later, the corneal damage was assessed under the slit lamp using a cobalt blue and yellow filter. Stratification was performed using the classification of the Ocular Staining Score.²⁵

Evaluation of non-invasive tear film breakup time (NIBUT) was calculated with the Antares topographer (Construzione Strumenti Oftalmici, Florence, Italy) according to the manufacturer's guidelines. Briefly, two readings are provided at the end of every assessment: NIBUT-Initial, the time taken for the first appearance of a break in the tear film, and the NIBUT-Average is the average of the time taken to break-up in all the regions monitored over the 17 seconds. For the statistical analysis, the average of three consecutive measurements was used.

Meibomian gland characteristics

Meibomian gland characteristics of the upper and lower eyelids (UL and LL, respectively) was studied included secretion, number of expressible glands, and dropout rate and morphological characteristics of the central area of eyelids by infrared meibography with the Antares topographer.

According to the report by Arita et al.²⁶ the eyelid margin characteristics were classified in an incremental way as normal, irregular, telangiectasias, orifice obstruction, and displacement of the mucocutaneous junction.

An expression instrument was used to evaluate the characteristics of the meibomian secretion of the LL. A force was applied to the nasal, central, and temporal regions of the LL, and each region contained eight consecutive MG orifices. The classification used to evaluate gland expressibility was 0= all glands expressible, 1 = 3–4 glands expressible, 2 = 1–2 glands expressible, 3 = no glands expressible.²⁷ In addition, the MGYLS score of the whole lid was determined according to Korb et al.^{13,28} The classification proposed by Bron et al.²⁹ was used to evaluate the meibum characteristics as follows: clear (0), opaque (1), opaque with detritus (2), and toothpaste (3). Only the highest grade found among the expressed glands was recorded.

Meibography was performed according to the manufacturer's protocols. The characteristics of the MG on infrared meibography were observed as aggregates in the form of grape-like clusters acini that are directed toward the palpebral margin in a straight or slightly tortuous line and that are hyperreflective.³⁰ The area of gland dropout was defined according to Pult et al. by "(1) the actual ending of glands, (2) the width of the area, defined to be between at least from the tear punctum, and the temporal border defined to be to the most well visible tarsal conjunctiva of the everted lid, and (3) the maximal depth of the area was estimated to be where glands would have ended in normal MG morphology".^{11,13} including the ghost and fluffy areas, as suggested by Daniel et al.⁷ For the quantification of the percentage of loss of the MG, we used the Phoenix software (version 3.2, Construzione Strumenti Oftalmici, Firenze, Italy) in

accordance with previous reports.^{26,31,32} Only images with good or fair quality of lid eversion were used according with Daniel et al. protocol.⁷

For the Meibomian gland morphology classification, the definition of DREAM protocol was used ⁷ (Figure 1A-D). Two readers graded each lid meibography image independently. The readers were blinded to all demographic, clinical, and treatment data. Only morphological characteristics with agreement between both readers was included.

Statistical analysis

Descriptive statistics were employed to describe the clinical signs using the SPSS software (v24 for Mac; IBM, Chicago, IL). Paired t-tests and Wilcoxon matched-pairs tests were employed to compare data with normal and non-normal distributions, respectively.

All analyses were performed separately for the upper and lower lids. Associations between continuous measures of MG features and signs were evaluated with linear regression, where the MG feature was the dependent variable. Associations between binary measures of MG features were evaluated with logistic regression, where the MG feature was the dependent variable. All regression models involving signs measured on a continuous scale and symptoms were calculated using the continuous values as independent variables. Regression models were adjusted for age and sex. All statistical analyses were performed with SPSS software (v24 for Mac; IBM, Chicago, IL).

We evaluated the correlations between all clinical parameters and morphological characteristics with logistic regression using the RStudio software (v4.0.2 for Windows, RStudio, Boston, MA). We controlled for sex (coded 1 = female; 0 = male) and age to account for factors that might bias our results.

Results

75 eyes of 75 subjects were studied with an average age of 40.68 ± 18.43 (range: 28–78 years old), 42 of them (56%) were female, the right eye (OD) was studied in 41 (54.7%) individuals, 42 (56%) of the studied cases had dry eyes and 33 (44%) were healthy individuals. The demographic characteristics are presented in table 1.

Meibomian gland morphological alterations in the upper lid (UL) were present in 68 (90.7%) of the studied subjects, while only 33 (44%) had some type of alteration in the lower lid (LL). We did not find significant differences in the presence of any given anatomical alteration in the UL between healthy and dry-eye subjects (92.9% vs. 87.9%; $p=0.69$). In the LL, morphological alterations in general were more common in patients with evaporative dry eye than in healthy subjects (54.8% vs. 30.3%; $p=0.03$). However, for any given individual alteration in the LL, only the presence of shortened glands was more common in subjects with evaporative dry eye than in healthy subjects. The distribution of all MG morphological alterations is presented in table 2.

The analysis by gender did not show any difference in the presence of alterations in general or by groups. When analyzing the prevalence of alterations by age, the presence of ghost glands in the UL was more common in subjects older than 40 years (11 vs 2, $p = 0.012$, OR 7.13 IC 95% 1.45 to 34.89). Fluffy areas were more common in subjects younger than 40 years old (0 vs 5, $p = 0.025$, OR 1.15 IC 95% 1.01 to 1.31). There were no significant differences in the anatomical alterations in the LL between the two age groups.

The logistic regression of clinical parameters and morphological characteristics show a statistically significant relationship mostly in UL, between OSDI score and thinned gland (estimate: -25.04, p -value: 0.01), initial NITBUT and tortuous and distorted glands (estimate: 2.82, p -value: <0.01, estimate: -2.56, p -value: 0.04, respectively), average NITBUT and shortened and tortuous glands (estimate: -1.73, p -value: 0.05, estimate: 2.10, p -value: 0.01, respectively). In the LL there was a significant relationship between meibomian gland loss and distorted glands (figures 2A to F). All other parameters did not show significant correlations.

Discussion

The results of this study confirm the high prevalence of meibomian gland morphological alterations in patients with dry eye disease and in healthy adults; interestingly, without significant differences in the upper lid. we found a higher frequency of morphological alterations of MG in the lower eyelid of patients with evaporative dry eye compared with healthy individuals. Since morphological changes in MG are one of the key signs of MGD,⁶ some authors have proposed a method to objectively evaluate morphological changes in MGD.^{11,12} Most of the studies about morphological changes in MG focus on the presence and severity of dropout of MG, as a marker for severity in the assessment of MGD.^{6,8,13-16} Recently, Daniel et al.⁷ proposed a classification system that not only evaluates the percentage of MG dropout but also analyzes different morphological alterations that could be correlated with other clinical parameters

We found that the upper lid had higher frequency of morphological alterations than the lower lid, this result was also found by Daniel's study,⁷ but the frequency of subjects with LL alterations was bigger in our study, this could be related to the population studied since we focused in evaporative dry eye and healthy subjects, while in the Daniel's population, patients with all types of dry eye and almost 40% patients with autoimmune diseases were included. Patients with autoimmune disease demonstrated a lower frequency of alterations, mainly distorted glands and ghost glands in the UL and shortened glands in the LL, also, the difference in the frequency of alterations could be related to the largest sample size of the Daniel's study.⁷

The reason of a greater frequency of alterations in the inferior eyelid in subjects with dry eyes (54.8 vs 30.3%, $p = 0.03$, OR 2.78, 1-06,7.26) may be related to that the damage of the meibomian glands of the lower eyelid has a greater impact on the development of MGD according to that reported by Eom et al.¹⁷

The only morphological alteration statistical different between evaporative dry eye and healthy subjects was shortening of MG.^{6,8,17} This is consistent with that reported by Bilkhu et al. who found that

expression is dependent on residual gland length in the LL, with no gland <70 % of the lower lid length giving clear meibum expression and glands of less than 10 % of the lid length did not express and those less than 25 % did not express or the meibum was inspissated.¹⁸ Daniel et al.¹⁹ analyzed 394 ULs and found out that the presence of tortuous glands in the UL were associated with a better TBUT and longer Schirmer test. In our findings, there was also a statistically significant positive correlation of the presence of tortuous glands in the UL with a better initial and average NIKBUT. Since we focus on subjects with evaporative dry eye and that in the new DEWS II¹ report the use of the Schirmer test is not suggested, we did not carry out this study so we cannot corroborate the finding described by Daniel et al.¹⁹

Other studies have reported other morphological alterations, in patients with dry eye and other ocular surface diseases, Mathers et al. suggest that that MG distortion is the first-stage morphological alteration that occurs in MG.²⁰ Lin et al.²¹ reported that the average tortuosity of all MGs was significantly increased in the MGD group compared to the normal controls, and higher in the symptomatic MGD patient group compared to the asymptomatic MGD patient group. MG tortuosity has been associated with contact-lens wear and more commonly observed in Caucasians.^{22,23} Gu et al.¹⁴ found that MG distortion and dropout was higher in DED patients compared to normal patients. However, they found that only dropout could distinguish DED patients from healthy patients in both Contact-lens wearing patients and non-contact lens wearing patients, while MG distortion could only distinguish this in non-contact lens wearers. Finally, other authors have reported, thin or attenuated MG have been associated with worse expressibility of meibum, while thickening has been associated with tear osmolarity and increased abnormal spaces with progressive MG loss.^{8,22} We did not find a higher frequency of other morphological characteristics in patients with evaporative dry eye, this could be related to the fact that in our study we only evaluated the central glands of each eyelid, following the protocol of Daniels et al. and Yin and Gong¹⁵ found that there was a greater loss of MG in the nasal and temporal zones in patients with MGD.

Our study has some limitations, subjects with evaporative dry eye were older than the healthy subjects, also, we studied only the central glands and according to Yin et al. study, the nasal ones are the most important,¹⁵ finally, due to the lack of previous information, it was not possible to calculate a sample size, so, it is not possible to know the power of the study to detect a difference between both groups for each of the morphological alterations.

In conclusion, subjects with evaporative dry eye seem to have more alteration in the lower lid than non-dry eye subjects, and the shortening of meibomian gland could be the most important morphological alteration in patients with dry eye.

Declarations

COMMERCIAL RELATIONSHIP DISCLOSURE

Ricaurte Ramiro Crespo Treviño none, Anna Karen Salinas Sánchez none, Francisco Amparo none, Manuel Garza Leon: Alcon (R), SIFI (R).

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Authors contribution statement

Ricaurte Ramiro Crespo Treviño MD : Acquisition, analysis, interpretation of data and approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work

Anna Karen Salinas Sánchez: Acquisition, analysis, interpretation of data and approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work

Francisco Amparo MD PhD: Analysis, interpretation of data and approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work

Manuel Garza Leon MD: Acquisition, analysis, interpretation of data and approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work

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Tables

Table 1. Demographic and general characteristics

Variable	Total n= 75	Non-dry eye n= 33	Dry eye N= 42	p
Right eye (%)	41 (54.7)	19 (57.6)	22 (52.4)	0.415
Female sex (%)	42 (56)	14 (42.4)	28 (66.7)	0.060
Age (years)	40.68±18.43	33.70±14.72	47.93±20	0.007
OSDI	31.20±20.12	9.18±6.90	49.55±20.13	<0.001
Initial NIKBUT seconds	10.11±4.30	13.86±3.27	7.01±1.91	<0.001
Average NIKBUT seconds	11.86±3.72	14.65±2.67	9.62±2.82	<0.001
Gland expressibility *	1.49±0.79	1.42±0.70	1.55±0.86	0.498
Meibum characteristics ⁺	1.08±0.85	0.97±0.77	1.17±0.90	0.313
UL meibomian drop out (%)	20.08±8.04	19.29±7.36	21.48±8.63	0.493
LL meibomian drop out (%)	21.41±7.99	21.71±7.95	21.99±8.043	0.761
UL Morphological alterations	1.56±0.94	1.48 ±0.87	1.66±1.00	0.412
LL Morphological alterations	0.56±0.70	0.36±0.60	0.71±0.74	0.037

* The classification used to evaluate gland expressibility was 0= all glands expressible, 1 = 3–4 glands expressible, 2 = 1–2 glands expressible, 3 = no glands expressible

⁺ The classification proposed by Bron et al. was used to evaluate the meibum characteristics as follows: clear (0), opaque (1), opaque with detritus (2), and toothpaste (3). Only the highest grade found among the expressed glands was recorded.

UL= Upper eyelid, LL= Lower eyelid.

Table 2. Morphological alterations

Anatomical alteration	Total n= 75	Non-dry eyes n= 33	Dry eye n=42	P *
Upper eyelid				
Distorted n(%)	12 (16)	3 (9.1)	9 (21.4)	0.209
Tortuous n(%)	23 (30.7)	13 (39.4)	10 (23.8)	0.207
Hooked n(%)	17 (22.7)	8 (24.2)	9 (21.4)	0.788
Drop out n(%)	1 (1.3)	0 (0)	1 (2.4)	1.00
Shortened n(%)	23 (30.7)	7 (21.2)	16 (38.1)	0.137
Thickened n(%)	1 (1.3)	1 (3)	0 (0)	0.440
Thinned n(%)	6 (8)	3 (9.1)	3 (7.1)	1.00
Overlapping n(%)	9 (12)	2 (6.1)	7 (16.7)	0.283
Ghost n(%)	13 (17.3)	3 (9.1)	10 (23.8)	0.128
Tadpoling n(%)	1 (1.3)	0 (0)	1 (2.4)	1.000
Abnormal gap n(%)	6 (8.0)	4 (12.1)	2 (4.8)	0.395
Fluffy areas n(%)	5 (6.7)	4 (12.1)	1 (2.4)	0.163
No extension to lid margin n(%)	2 (2.7)	1 (3.0)	1 (2.4)	1.000
Any alteration n(%)	68 (90.7)	29 (87.9)	39 (92.9)	0.692
Lower eyelid				
Distorted n(%)	5 (6.7)	2 (6.1)	3 (7.1)	1.000
Tortuous n(%)	0 (0)	0 (0)	0 (0)	
Hooked n(%)	3 (4)	0	3 (7.1)	0.251
Drop out n(%)	6 (8)	3 (9.1)	3 (7.1)	1.000
Shortened n(%)	15 (20)	3 (9.1)	12 (28.6)	0.04
Thickened n(%)	1 (1.3)	0 (0)	1 (2.4)	1.000
Thinned n(%)	0 (0)	0 (0)	0 (0)	
Overlapping n(%)	0 (0)	0 (0)	0 (0)	
Ghost n(%)	1 (1.3)	1 (3)	0 (0)	0.440
Tadpoling n(%)	0 (0)	0 (0)	0 (0)	
Abnormal gap n(%)	1 (1.3)	0 (0)	1 (2.4)	1.000

Fluffy areas n(%)	6 (8)	1 (3.0)	5 (11.9)	0.220
No extensión to lid margin n(%)	4 (5.3)	2 (6.1)	2 (4.8)	1.000
Any alteration n(%)	33 (44)	10 (30.3)	23 (54.8)	0.03

Figures

Figure 1

A. Morphological characteristics of Meibomian Glands. A) distorted. B) tortuous. C) thinned. D) thickened. B. Morphological characteristics of Meibomian Glands. A) shortened. B) Dro out. C) ghost. D) hooked. C. Morphological characteristics of Meibomian Glands. A) tadpoling. B) abnormal gap. C) fluffy areas D) no extension to lid margin D. Morphological characteristics of Meibomian Glands. A) overlapping

Figure 2

Logistic regression between clinical parameters and morphological characteristic A) initial NITBUT (TBUT_I) on distorted glands in upper eyelids (UL). B) Logistic regression of Meiboscore on distorted glands lower eyelids (LL). C) Logistic regression of OSDI on thinned glands in UL. D) Logistic regression of average TBUT (TBUT_A) on shortened glands in UL. E) Logistic regression of average TBUT (TBUT_A) on tortuous glands in UL. F) Logistic re-gression of initial NITBUT (TBUT_I) on tortuous glands in UL.