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Original article

LOSS OF MEIBOMIAN GLANDS ANALYZED BY MEIBOGRAPHY IN PATIENTS WITH EVAPORATIVE DRY EYE DISEASE CAUSED BY MEIBOMIAN GLAND DYSFUNCTION

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Abstract

Introduction: Meibomian gland dysfunction is the most common cause of evaporative dry eye disease. Meibography is a modern imaging tool that provides insight into the anatomical and morphological characteristics of the meibomian glands. The aim of this study was to determine the degree of meibomian gland loss using meibography in patients with meibomian gland dysfunction who suffer from evaporative dry eye disease.

Materials and methods: The study included 20 patients diagnosed with meibomian gland dysfunction who suffer from evaporative dry eye disease. A clinical examination of the eyelids of both eyes was performed; the clinical grade of the disease was determined, and the TBUT, Schirmer II test, and meniscometry were conducted. Subsequently, meibography was performed on all four eyelids.

Results: Statistical analysis of the 40 eyes showed a strong positive correlation between the meiboscore and clinical grading (r=0.**8809**, p<0.0001), while the correlation with the TBUT test showed a strong negative relationship (r=**-0.7726**, p<0.0001). Schirmer II test and meniscometry demonstrated a weak, statistically insignificant correlation with the Meiboscore.

Conclusion: Meibomian gland loss is assessed by meibography, which is an important modern tool in ophthalmology that can facilitate an easier and more efficient diagnosis of meibomian gland dysfunction in patients with evaporative type of dry eye disease.

Keywords: meibomian gland dysfunction, meibography, meiboscore, TBUT, Schirmer II test

Introduction

Evaporative dry eye disease is a condition characterized by increased tear evaporation. It is a tear film disorder that results from quantitative and qualitative changes in the lipid component of the tear film[1].

Meibomian gland dysfunction (MGD) is the most common cause of evaporative dry eye disease[2]. MGD is a chronic, diffuse abnormality of the meibomian glands, characterized by terminal duct obstruction and/or qualitative/quantitative changes in gland secretion. This condition results in eye irritation, ocular surface inflammation, and the development of dry eye disease[3].

The tear film, and especially the lipid layer of the tear film, is extremely important for the preservation of the ocular surface. MGD is a condition in which gland dysfunction leads to a disruption of the quality of the meibum, and thus the lipid layer of the tear film.

Analyzing the impact of MGD on the ocular surface, the literature reports a high incidence of MGD in patients in whom cataract surgery is planned. At the same time, authors speak of the fact that if the condition is not treated before the surgical procedure, the postoperative visual acuity may be lower than expected, and patient satisfaction after surgery may also be reduced[4].

Regarding the importance of ocular surface health, the European Society of Cataract and Refractive Surgery (ESCRS), as well as the American Society of Cataract and Refractive Surgery (ASCRS), give recommendations that MGD should be diagnosed and treated before proceeding with intraocular surgery[5].

Diagnosis, and especially classification of evaporative dry eye disease, is complex and time-consuming in ophthalmological clinical practice due to the numerous tests that need to be performed[6].

Material and methods

The study was designed as a cross-sectional cohort study and included 20 subjects suffering from MGD who presented for examination at the University Clinic for Eye Diseases in Skopje. Informed consent was obtained from the participants included in the study and the Institutional Ethics Committee approved the study. The study included patients who met the following criteria:

1. At least one symptom of dry eye
2. At least one sign of lid margin abnormality
3. Poor meibum expressibility.

Exclusion criteria were: subjects under 18 years of age, subjects who had undergone ocular surgery less than 3 months ago, patients with dry eye with exclusively aqueous component deficiency, patients who had undergone eyelid surgery, patients with eyelid abnormalities, patients with acute ocular surface infection or ocular allergy, patients with Punctal plugs, patients with nasolacrimal duct stenosis, patients using regular topical ocular therapy, patients with autoimmune diseases, patients with Stevens–Johnson syndrome, patients with rosacea and seborrheic dermatitis.

Criteria for removing subjects from the study: subjects whose meibographic images obtained did not meet the quality criteria (insufficient eversion of the eyelids or inability to blink adequately/non-cooperation of the subject).

After signing the informed consent, an examination of the eyelids of both eyes was performed; the clinical stage of the disease was determined (from grade 1 to grade 4), TBUT / (tear break up time), Schirmer II test and meniscometry were performed, and then meibography (LacryDiag, Quantel medical) was performed on all four eyelids.

Following meibography, the percentage of gland loss was analyzed, expressed in a score/MEIBOSCORE (grade 0: meibomian gland loss 0%, grade 1: meibomian gland loss 0-33%, grade 2: meibomian gland loss 34-66%, grade 3: meibomian gland loss 67-100%) depending on the percentage of ML loss. A summary meiboscore was made for each eye of each subject as the sum of the grades of the upper and lower eyelids.

Results

The study included 20 subjects, both eyes of whom were analyzed, with a diagnosis of meibomian gland dysfunction.

Most patients had clinical grade 2 of the disease-14(35%).

The mean value of the tear film break-up time determined by the TBUT test was 4.30±2.1 seconds. According to the median value, this time was shorter than 4 seconds in 50% of eyes. Significantly worsened condition, with a time shorter than 5 seconds, was measured in 23 (57.5%) eyes.

The mean value of the aqueous component of the tear film, determined by the Schirmer II test, was 18.25±8.9 mm. According to the median value, in 50% of eyes the aqueous component was less than 16 mm.

The average tear film height determined by the TMH test was 0.29±0.1 mm. According to the median value, in 50% of eyes the tear film height was less than 0.29 mm, and it was within the reference values in 23(57.5%) eyes.

The average meiboscore, which determines the percentage of meibomian gland loss and ranges from 1 to 6, was 3.8±1.4. According to the median value, 50% of eyes had a score greater than 4. The worst score of 6 was determined in 5(12.5%) eyes.

This descriptive analysis is shown in Table 1.

Table 1. Description of the analyzed eyes in terms of clinical grade and results of TBUT, Schirmer II, TMH and meiboscore

Variable	
clinical grade n(%)	
1	7(17.5)
2	14(35)
3	11(27.5)
4	8(20)
TBUT / c	
(mean ± SD)(min – max) [median (IQR)]	(4.30±2.1)(1-9) [4(2.5-5.5)]
TBUT	***n(%)***
<5 s	23(57.5)
>5 s	17(42.5)
Schirmer II / mm	
(mean ± SD)(min – max) [median (IQR)]	(18.25±8.9)(6-35) [16(10-24)]
TMH /mm	
(mean ± SD)(min – max) [median (IQR)]	(0.29±0.1)(0.1-0.53) [0.29(0.22-0.33)]
TMH	***n(%)***
0.2-0.3	23(57.5)
<0.2	3(7.5)
>0.3	14(35)
meiboscore	
(mean ± SD)(min – max) [median (IQR)]	(3.8±1.4)(2-6) [4(2-5)]
Meiboscore	***n(%)***
2	11(27.5)
3	4(10)
4	12(30)
5	8(20)
6	5(12.5)

Table 2. Distribution of meiboscore depending on clinical grade

Meiboscore	**n**	**Clinical grade** **1** **n(%)**	**2** **n(%)**	**3** **n(%)**	**4** **n(%)**
2	11	7 (100)	4 (28.57)	0	0
3	4	0	3 (21.43)	1 (9.09)	0
4	12	0	7 (50.0)	5 (45.45)	0
5	8	0	0	5 (45.45)	3 (37.5)
6	5	0	0	0	5 (62.5)
total	40	7	14	11	8

Table 2 shows the distribution of the meiboscore value depending on the clinical grade of the disease. The best score of 1 was obtained in all eyes with clinical grade 1, and 4 (28.57%) eyes were with clinical grade 2. The worst score of 6 was determined in 5 (62.5%) eyes with clinical grade 4.

Table 3. Correlation between meiboscore with clinical grade, TBUT, Schirmer II and TMH

Correlations	Spearman R	t(N-2)	p-level
meiboscore & clinical grade	0.8809	11.4764	<0.0001
meiboscore & TBUT	-0.7726	-7.5013	<0.0001
meiboscore & Schirmer II	-0.0787	-0.4865	0.63
meiboscore & TMH	0.1498	0.9342	0.36

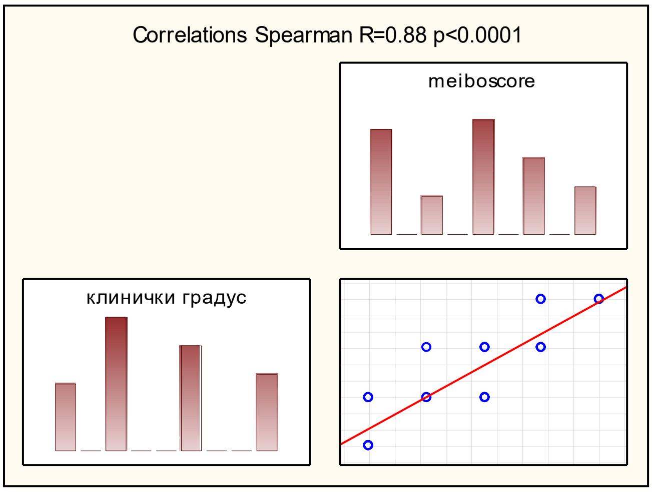

Fig. 1. Correlation between meiboscore and clinical grade

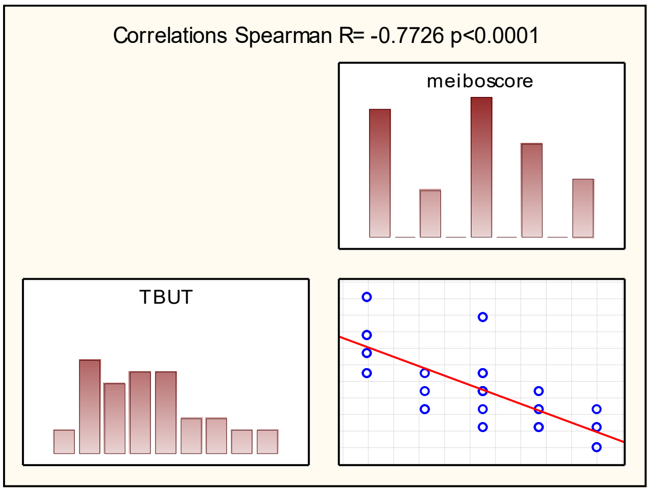

Fig. 2. Correlation between meiboscore and TBUT

The meiboscore value correlated significantly with the clinical grade of the disease and with the findings obtained with the TBUT test (p<0.0001), and insignificantly with the findings of the Schirmer II test (p=0.63) and the TMH test (p=0.36). Spearman's rank correlation coefficient showed that the correlation between the meiboscore and clinical grade was positive (R=0.8809), indicating that with increasing clinical grade of the disease, the meiboscore value increases, and *vice versa*; the correlation between the meiboscore and the TBUT was negative

(R=-0.7726), indicating that with increasing tear film breakup time, the meiboscore value decreases, and *vice versa* (Table 3, Figure 1, Figure 2).

The mean meiboscore value was highest in the group of eyes with clinical grade of disease 4, followed by the groups with clinical grade 3, 2 and 1 (4.36±0.7, 3.21±0.9, and 2.0±0, respectively) (Table 4, Figure 3).

An overall statistically significant difference in the value of meiboscore (p<0.0001) was confirmed depending on the clinical grade of disease. Post-hoc analysis for intergroup comparisons confirmed all intergroup comparisons as significant (Table 4).

Table 4. Average meiboscore value depending on clinical grade

clinical grade	meiboscore n	mean ± SD	min - max	p-level	
1	7	2.0±0	2	F=41.21 p<0.0001	
2	14	3.21±0.9	2-4	1 *vs* 2 **p=0.0027	1 *vs* 3 ***p=0.00016
3	11	4.36±0.7	3-5	1 *vs* 4 ***p=0.00016	2 *vs* 3 **p=0.0011
4	8	5.62±0.5	5-6	2 *vs* 4 ***p=0.00016	3 *vs* 4 **p=0.0019

F (Analysis of Variance), post-hoc Tukey honest test, **sig p<0.01, ***sig p<0.0001

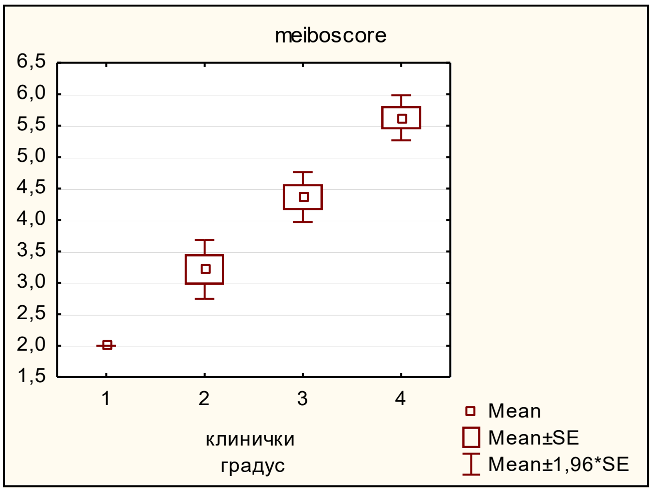

Fig. 3. Graphical representation of the average meiboscore depending on the clinical grade

Table 5. Average meiboscore value depending on TBUT less than and greater than 5

TBUT	Meiboscore n	mean ± SD	min - max	p-level
<5	23	4.65±0.9	3-6	t=6.52 p<0.0001
>5	17	2.65±0.9	2-4	

t (Student t-test)

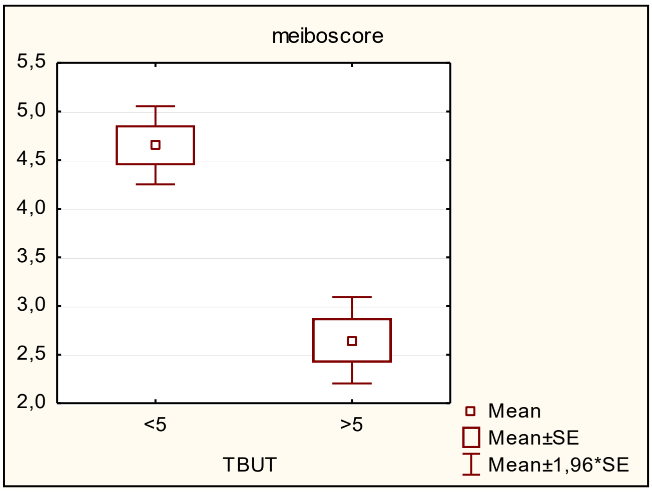

Fig. 4. Graphical representation of the average meiboscore depending on TBUT

In the group of eyes with TBUT<5, a significantly higher meiboscore was recorded compared to the group of eyes with TBUT>5 (4.65 ± 0.9 *vs*. 2.65 ± 0.9, p<0.0001) (Table 5, Figure 4).

Meiboscore value did not differ significantly between the groups of eyes with normal height, reduced and increased tear film height (3.65 ± 1.4 mm *vs*. 4.0 ± 1.0 mm *vs*. 4.0 ± 1.0 mm, respectively) (p=0.74) (Table 6).

Table 6. Average meiboscore value depending on TMH

TMH	Meiboscore			p-level
	n	mean ± SD	min - max	
0.2-0.3	23	3.65±1.4	2-6	F=0.29 p=0.74
<0.2	3	4.0±1.0	3-5	
>0.3	14	4.0±1.5	2-6	
F(Analysis of Variance)				

The statistical analysis of the data obtained in the study was done with the statistical program Statistical Package for the Social Sciences programme (SPSS Inc, Chicago, Illinos), version 25.0. Shapiro Wilk's W test was used to test the distribution of data.

Qualitative variables are shown with absolute and relative numbers. Quantitative variables are shown with average, minimum and maximum values, standard variation, median and interquartile rank.

The correlation between the meiboscore and the clinical grade, TMH, TBUT and Schirmer II was analyzed with Spearman's rank correlation coefficient.

The difference of the average meiboscore value in relation to clinical grade and TMH was tested with Analysis of Variance, and in relation to TBUT with Student's t-test.
Statistical significance was defined at the level of p<0.05.

Discussion

Meibomian gland dysfunction is a chronic condition characterized by diffuse disruption of the meibomian glands, and its diagnosis involves a series of subjective symptoms and findings on the eyelid margin[1].

The eyelid margin examination includes a detailed analysis of any abnormalities on the lid margin such as the appearance of telangiectasias, “plugging” of the gland openings, irregularity and thickening of the eyelid margin[7]. In addition, the examination includes an assessment of the ocular surface epithelium using a slit-lamp bimicroscope, and finally an assessment of the expressibility and quality of the meibomian fluid[6]. Qualitative and quantitative changes in meibomian gland secretion are considered the most significant aspects of MGD[5].

As mentioned above, MGD is the main cause of evaporative dry eye disease, so in these patients it is necessary to perform dry eye tests, such as Schirmer's tests, tear film break-up time (TBUT), lid-parallel conjunctival folds test (LIPCOF), meniscalmetry, etc[8].

Establishing the diagnosis and classifying the disease requires considerable time from the ophthalmologist, given the numerous tests that has to be performed. Studies increasingly emphasize determination of the degree of the disease in order to provide appropriate medical treatment for each patient[1].

The International Workshop on Meibomian Gland Dysfunction divides the disease into 4 clinical degrees[9]. According to the International Workshop on Meibomian Gland Dysfunction, the subjects included in our study were classified into 4 groups (4 grades) after the scores obtained by the examination of the lid margin, expressibility and assessment of the quality of the meibum.

This study evaluated meibography as a new and modern method in ophthalmology, analyzing one of its parameters - loss of glandular tissue / meiboscore - which was correlated with the clinical findings and disease grade in patients suffering from meibomian gland dysfunction.

Meibography is a new imaging tool in ophthalmology that allows the display of the anatomical-morphological characteristics of each of the meibomian glands, while in a non-contact manner, the image is taken on everted eyelids. Today's meibographs have built-in software that allows, in addition to analyzing the anatomy of the gland, to calculate the percentage of glandular tissue loss, which percentage is then expressed in the so-called meiboscore[10]. Meibography as an objective and highly reproducible method can lead to an effective diagnosis of the disease[11], and at the same time can evaluate the status of its severity[12].

This study also analyzed the obtained meiboscore for each eye individually in relation to TBUT, Schirmer II tests and the height of the tear meniscus, thus correlating the loss of meibomian glands with dry eye tests.

In our study, majority of patients had clinical grade 2 disease; the mean value of the TBUT test was 4.30±2.1 seconds, the mean value of the Schirmer II test was 18.25±8.9 mm, the mean value of the TMH was 0.29±0.1 mm, and the mean meiboscore was 3.8±1.4.

Regarding the meiboscore and the TBUT test, very similar values were found in the study by Arita R *et al*., where the mean meiboscore value was 3.8±1.7, and the mean value of the TBUT test was 3.1±1.2 seconds[1].

The analysis of the correlation of the meiboscore and the clinical findings in our study showed a significant correlation, i.e. with increasing clinical grade of the disease, the value of the meiboscore increased, and *vice versa*. This means that patients who had a worse clinical grade, also had a greater meibomian gland loss.

Both Gulmez Sevim *et al.,* in their study analyzing the meiboscore and correlating it with the clinical grade, concluded that meibography is consistent with the clinical grade and correlates significantly with the signs of the ocular surface and symptoms[10]. Sarwarte *et al.* also found a strong correlation (statistically significant) with the meiboscore and the clinical grade of the disease[13]. A similar positive statistically significant correlation was found by Nishant *et al*., comparing the meiboscore with the so-called MGD clinical score[7].

Interest in the loss of meibomian glands and its contribution to the evaporative type of dry eye disease dates back to the 1990s, when several researchers emphasized the importance of meibomian gland loss as a useful data for obstructive MGD. However, the performance of meibography as a non-contact method was not present in clinical ophthalmological practice until recently[14,15].

The Committee on Diagnosis of the Disease at the International Workshop on MGD recommends that tests such as TBUT, Schirmer test, and meniscometry be performed to differentiate evaporative from water-deficient dry eye[2].

These tests were therefore included in our study.

The TBUT test value indicates the time it takes for the tear film to break up. A value of less than 10 seconds indicates an inadequate balance between the aqueous and lipid layers of the tear film[2]. By measuring tear film stability using the TBUT test, we can indirectly assess meibomian gland function, knowing that meibomian gland dysfunction leads to impaired gland function[16,17].

The study by CHV *et al.* clearly demonstrates the association of low TBUT values in patients with MGD[18]. However, there are also studies in the literature suggesting that tear film breakup time as a test alone is not sufficient to differentiate between the evaporative type and water-deficiency dry eye[16].

In our study, the correlation analysis between the meiboscore and the TBUT test showed a negative correlation (R=-0.7726), i.e. with increasing tear film breakup time, the meiboscore value decreased, and *vice versa*, suggesting that patients with a higher meiboscore had faster tear film breakup, and thus the protection provided by the tear film on the ocular surface was significantly reduced.

This correlation was also confirmed in the studies by Mounika *et al*., and Tanriverdi *et al.* [19,20].

Our study further analyzed the correlation of the meiboscore with the Schirmer II test and with the tear film height (separately). The meiboscore correlated insignificantly with the findings of the Schirmer II test (p=0.63) and the TMH test (p=0.36). This finding does not indicate that in MGD, as an evaporative type of dry eye disease, the aqueous component of the tear film is not directly affected, as it would be in the presence of dry eye caused by deficiency of the aqueous component, such as in Sjögren's syndrome.

This issue has also been discussed in the literature. The report of the second workshop of the Tear Film and Dry Eye Society (TFOS DEWS II) explains the so-called “circulus vitiosus” in which the patient with dry eye enters. The authors believe that the quantitative and qualitative characteristics of the tear film complement each other. Thus, in a condition in which the patient initially experiences changes in one component of the tear film, the condition progresses with the appearance of instability, inflammation and hyperosmolarity, changes that further lead to compensatory mechanisms of increase, then decrease in the other components of the tear film. According to them, all this in the advanced stages of the disease leads to a significant difficulty in detecting the basic or primary etiology of dry eye disease, i.e. defining whether it is just a lack of the aqueous layer or an evaporative type of dry eye disease[21]. This explanation is the basis of their recommendation (TFOS DEWS II) that dry eye disease should not be defined by the principle of exclusivity in the classification itself, which defined them in the past as two independent conditions, but that dry eye disease should be seen as a continuum of one condition. When making a diagnosis, our approach should classify the disease according to the predominant component, taking into account the elements of each of the disease categories, regardless of whether it is a lack of the aqueous layer or an evaporative type of dry eye disease[8].

The above finding explains our non-significant correlation of the meiboscore with the Schirmer II test and with the tear film height.

Conclusion

Meibography, as a method that visualizes the meibomian glands *in vivo*, is easy and fast to perform, completely non-contact and reproducible.

Meibomian gland loss, which is assessed by meibography, is an important modern tool in ophthalmology that can facilitate an easier and more efficient diagnosis of meibomian gland dysfunction in patients with evaporative type of dry eye disease.

Conflict of interest statement. None declared.

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