

Ocular Surface Changes and Discomfort in Patients With Meibomian Gland Dysfunction

Jun Shimazaki, MD; Miki Sakata, MD; Kazuo Tsubota, MD

Objective: To determine the importance of meibomian gland dysfunction (MGD) on the ocular surface.

Design: Prospective study.

Setting: A university-based referral practice.

Patients: Patients with ocular discomfort (147 eyes) and without ocular discomfort (54 eyes) were examined. In the total 201 eyes, MGD was defined as the presence of an obstruction of the meibomian orifices (obstruction group [n=54]) or the absence of a gland structure (gland dropout group [n=36]), or both of these findings (combined group [n=38]). There were not any findings of MGD in 73 eyes (non-MGD group).

Main Outcome Measures: Scores that were obtained from fluorescein and rose bengal staining, the breakup

time of the tear film, the rates of tear evaporation and tear production, and meibography.

Results: Of the 147 eyes with ocular discomfort, 95 (64.6%) had either an obstruction of an orifice or gland dropout, or both. The combined group had higher scores for staining with fluorescein ($P=.002$) and rose bengal ($P=.021$) compared with that in the non-MGD group. The rate of tear production was increased more in the gland dropout group than in the non-MGD group ($P=.002$). The rate of tear evaporation was significantly increased in the gland dropout group ($P=.017$).

Conclusion: Meibomian gland dysfunction is a major cause of ocular surface abnormalities and ocular discomfort.

(*Arch Ophthalmol.* 1995;113:1266-1270)

MEIBOMIAN glands secrete lipids into the precorneal tear film. These lipids function as a barrier to the inward movement of skin surface lipids, make the eyelid margin hydrophobic, reduce the evaporation of tears, and lubricate the ocular surface to provide a clear optical image.^{1,2} Obstructive-type meibomian gland dysfunction (MGD), also called meibomianitis, is characterized by the inspissation of meibomian lipids, resulting in a hyposecretion of lipids in tears.³ From clinical experiences, MGD has been believed to be one of the major causes of ocular discomfort and abnormalities of the ocular surface. However, the incidence of MGD in eyes with and without ocular discomfort is not known. Although tear deficiency has been a well-known cause of ocular discomfort, MGD may be another major cause of the symptom. Also, the nature of the changes in the ocular surface and in the tear function of patients with MGD is not fully understood.

To determine the importance of MGD on the ocular surface, we prospectively studied the association of the changes in the meibomian gland and that in the ocular surface and tear function. The involvement of the oily layer of the tear film caused by MGD was investigated by using measurements of tear evaporation.

RESULTS

INCIDENCE OF MGD AND ITS ASSOCIATION WITH OCULAR DISCOMFORT

Severe obstruction of the meibomian gland orifice without gland dropout (obstruction group) was identified in 54 of 201 eyes (**Table 1**). Meibomian

See Patients and Methods on next page

From the Departments of Ophthalmology, Tokyo Dental College, Chiba, Japan (Drs Shimazaki, Sakata, and Tsubota), and the Keio University School of Medicine (Drs Shimazaki and Tsubota) and the Showa University School of Medicine (Dr Sakata), Tokyo, Japan.

PATIENTS AND METHODS

PATIENTS

One hundred forty-seven eyes in 82 patients with ocular discomfort (14 men and 68 women; mean \pm SD age, 54.4 ± 14.2 years) and 54 eyes without ocular discomfort in 29 patients (11 men and 18 women; mean \pm SD age, 61.2 ± 14.2 years) were analyzed in this study. The relation between meibomian gland function and changes in ocular surface and tear function in the total 201 eyes in the 111 patients was studied. We excluded from the study any patients with eyes with disorders that could have affected the ocular surface (eg, patients with infectious conjunctivitis, diabetes mellitus, allergic diseases, autoimmune diseases, and collagen diseases, and users of preservative-containing eyedrops). Patients whose eyes had excessive meibomian lipid secretion (seborrhic MGD) were also excluded, in that seborrhic MGD is a distinct clinical entity.³

ASSESSMENT OF OCULAR SURFACE CHANGES

To determine the presence of damage to the conjunctival and corneal epithelia, we instilled 2 μ L of mixtures (1:1) of preservative-free-staining solutions that consisted of 1% fluorescein (Fluorescite injection, Alcon Japan Co, Tokyo, Japan) and 1% rose bengal powder (Rose Bengal, Wako Pure Chemical Industries Ltd, Osaka, Japan) dissolved in saline solution.⁴ Results were assessed semiquantitatively by using a grading scale for fluorescein staining in the cornea (range of grades, 0 to 3) and a scale for rose bengal staining in both the cornea and conjunctiva (range of grades, 0 to 9), according to previously described methods.^{4,6} The breakup time of the tear film was subsequently measured three times. The average of these three measurements is presented in the "Results" section. Subjective symptoms of these patients were examined by a questionnaire as described previously.⁶

EXAMINATION OF TEAR FUNCTION

The rate of tear secretion was determined by using Schirmer's test after the application of a topical anesthetic agent (0.4% benoxinate hydrochloride [oxybuprocaine hydrochloride] [Benoxil], Santen Pharmaceutical Co, Osaka, Japan). Tear deficiency was defined as a wet length (<5 mm) on a test strip by using Schirmer's test. The tear clearance test was performed at the same time as Schirmer's test by evaluating the dilution rate of fluorescein, which was instilled 5 minutes before Schirmer's test was performed.⁷ Clearance was defined as $1\times$, $2\times$, $4\times$, $8\times$, $16\times$, $32\times$, $64\times$, $128\times$, and $256\times$. The logarithm of the result was used as a parameter for tear dynamics. We also performed the cotton thread test to measure the amount of tears in the tear meniscus.⁸

The rate of tear evaporation was measured in selected patients by using a previously reported method.⁹ The tear evaporation rate at 40% humidity was used as a representative number of the measurement.⁹

ASSESSMENT OF MEIBOMIAN GLAND FUNCTION

We used two techniques for evaluating meibomian gland function: (1) observation of meibomian gland orifices by using biomicroscopy and (2) transillumination observation techniques by using a light probe (meibom[ology]).¹⁰⁻¹⁶

We did not use the volume and viscosity scales of meibomian gland expression¹³ because we found that lipid secretion varied among meibomian orifices and depended on the day on which measurements were obtained. We therefore used a simplified criterion to determine the decrease in meibomian secretions. The lack of secretion following the application of moderate digital pressure on the tarsus of the upper eyelid was considered as a decrease in the secretion. The procedure was performed by a single investigator (J.S.), who attempted to apply a constant pressure during the study. Temperature and humidity of the examination room were maintained at a range from 15°C to 20°C and 30% to 50%, respectively.

Meibography was performed by using a transillumination device for vitrectomy with a fiberoptic light source (L-3920, Inami Co, Tokyo, Japan) with a 20-gauge disposable fiber light guide.¹⁴ This device presents advantages over a conventional transilluminator in that the fine tip of the light guide can be hidden behind an everted eyelid, making it possible to observe gland structure without interference from a bright light. Loss of visible meibomian gland structure ("gland dropout") has been observed in patients with severe MGD.^{12-14,16} Therefore, the presence of gland dropout at the central two thirds of the lower tarsus indicated the presence of MGD in this study.

Observations and tests were conducted in the following order to avoid the influence of one procedure on another: tear evaporation, rose bengal and fluorescein staining, breakup time of the tear film, cotton thread test, Schirmer's test, tear clearance test, meibography, and, finally, evaluation of meibomian secretion. In some patients, the evaporation of tears was determined on a different day from that of the other examinations.

STATISTICAL ANALYSIS

Data are presented as mean \pm SE. Between-group differences in the mean age, breakup time of the tear film, Schirmer's test, tear clearance test, cotton thread test, and tear evaporation rate were evaluated by using the one-way analysis of variance test. The Mann-Whitney *U* test was used to evaluate differences in the results of the scores for the fluorescein and rose bengal staining. Differences in the incidence was evaluated by using the χ^2 test.

gland dropout without obstruction of the orifice (gland dropout group) was present in 36 eyes. Significant obstruction of the orifice and gland dropout were both present in 38 eyes (combined group). No obstruction of the orifice or gland dropout was present in 73 eyes (non-MGD group). There were no differ-

ences in the mean age and sex distribution among these groups (Table 1).

In 147 of the total 201 eyes, there were symptoms (eg, foreign-body sensation, conjunctival injection, and photophobia) of ocular discomfort. In 54 eyes, there were not any symptoms of ocular discomfort.

Among 147 eyes of patients with ocular discomfort, there was tear deficiency in 53 (36.1%). In 95 (64.6%) of these 147 eyes, there was either an obstruction of the orifice or gland dropout (**Table 2**). In 94 eyes with ocular discomfort that had normal tear secretion, 70 (74.5%) had either an obstruction of the orifice or gland dropout, or both of these changes. The incidence of combined changes of obstruction of the orifice and gland dropout in eyes with ocular discomfort was significantly higher than those without discomfort (33 [22.4%] vs five [9.3%] eyes, $P=.03$).

MEIBOMIAN GLAND FUNCTION AND OCULAR SURFACE CHANGES

The score for fluorescein staining was correlated with the presence of obstruction of the orifice and gland dropout (**Table 3**, $P=.01$). Scores for fluorescein and rose bengal staining were higher in the combined group than in the non-MGD group ($P=.002$ and $P=.021$, respectively). There were no significant differences in the scores for the fluorescein and rose bengal staining between the non-MGD and obstruction groups. Breakup times of the tear film were shorter in the dropout and combined groups than in the non-MGD group; however, the differences were not statistically significant ($P=.19$ and $P=.06$, respectively).

The rates of tear evaporation were measured in 61 eyes in 31 patients (eight men and 23 women; mean \pm SD age, 52.3 \pm 13.8 years) with and without MGD. The mean \pm SE rate of tear production, measured by using Schirmer's test, was 10.1 \pm 1.0 mm/5 min in these 61 eyes. The rates of tear evaporation were significantly different among the groups (Table 3, $P=.02$). The rate in the gland dropout group was

significantly increased compared with that in the non-MGD group ($P=.017$). The rates of tear evaporation in the obstruction group and combined group were not different significantly with those in the non-MGD group.

Meibography showed variations in gland destruction that ranged from the dropout of a single gland structure to a total destruction. In the present study, the score for fluorescein staining was correlated with the degree of gland dropout (**Table 4**, $P=.003$). The score for rose bengal staining and the breakup time of the tear film also changed as the severity of gland dropout increased, although they did not reach statistically significant levels (Table 4).

MEIBOMIAN GLAND AND TEAR FUNCTION

The tear production, as measured by using Schirmer's test, was significantly increased in the gland dropout group compared with that in the non-MGD group ($P=.002$). Results of the cotton thread and tear clearance tests did not differ among the groups (**Table 5**).

COMMENT

By using the criteria of obstruction of the orifice or gland dropout, we identified MGD in 95 (64.6%) of 147 eyes with symptoms of ocular discomfort (Table 2). In eyes with normal tear secretion, abnormalities in the meibomian gland were attributed to more than two thirds (74.5%) of the ocular discomfort. One of us (K.T.)¹⁷ defined "dry eye" as "a disorder which causes abnormalities of the ocular surface by changing the quality and/or quantity of tears"; thus, MGD is the major cause of dry eye as well as tear deficiency.

Disorders of the ocular surface were found to be more severe in the eyes with significant obstruction of the meibomian orifice and gland dropout compared with those in the eyes without MGD (Table 3). Scores for fluorescein and rose bengal staining reflected the damage of the ocular surface, indicating that these were appropriate parameters for evaluating MGD-related ocular surface changes. We found the rate of tear production to be higher in the gland dropout group than in the non-MGD group (Table 5). This finding is in contrast to that found in a previous report that described tear deficiency as being often associated with MGD.³ Although the reason for the difference is unknown, increased rates of tear production were also

Table 1. Age and Sex Distribution in the Non-MGD, Orifice Obstruction, Gland Dropout, and Combined Groups*

Group	No. of Patients	Age, y			Mean \pm SE Age, y	No. (%) of Women
		≤ 40	41-60	≥ 61		
Non-MGD	73	11	37	25	54.2 \pm 1.59	54 (74.0)
Obstruction	54	5	27	22	56.6 \pm 1.91	41 (75.9)
Gland dropout	36	5	11	20	57.9 \pm 2.73	28 (77.8)
Combined	38	5	15	18	57.8 \pm 2.40	32 (84.2)

*Non-MGD indicates group in which there were no findings of meibomian gland dysfunction in the eyes.

Table 2. Incidence of Tear Deficiency, Orifice Obstruction, Gland Dropout, and Combined Orifice Obstruction and Gland Dropout in Patients With and Without Ocular Discomfort*

Ocular Discomforts	Tear Deficiency	No. of Patients	MGD, No. (%)			
			Non-MGD	Obstruction	Gland Dropout	Combined
Present	Present	53	24 (45.3)	13 (24.5)	7 (13.2)	9 (17.0)
Present	Absent	94	28 (29.8)	23 (24.5)	19 (20.2)	24 (25.5)
Absent	Present	12	8 (66.7)	2 (16.7)	1 (8.3)	1 (8.3)
Absent	Absent	42	13 (29.3)	16 (39.0)	9 (22.0)	4 (9.8)

*MGD indicates meibomian gland dysfunction; non-MGD, group in which there were no findings of MGD in the eyes.

Table 3. Scores for Fluorescein and Rose Bengal Staining, Tear Breakup Time, and Tear Evaporation Rate in the Non-MGD, Orifice Obstruction, Gland Dropout, and Combined Groups*

Group	Score		Breakup Time, s	Tear Evaporation Rate, ⁻⁷ g/s per Eye
	Fluorescein	Rose Bengal		
Non-MGD	0.56±0.09	0.66±0.14	7.24±0.76	13.09±1.35 (n=24)
Obstruction	0.65±0.12	1.02±0.19	7.17±0.70	10.41±1.28 (n=9)
Gland dropout	0.89±0.17	0.78±0.20	5.68±0.68	18.39±1.43† (n=13)
Combined	1.16±0.20‡	1.32±0.29§	5.17±0.42	14.43±1.87 (n=15)
P	.01	.09	.13	.02

*Non-MGD indicates group in which there were no findings of meibomian gland dysfunction in eyes. Data are given as mean±SE.

†P=.017 compared with that for the non-MGD group.

‡P=.002 compared with that for the non-MGD group.

§P=.021 compared with that for the non-MGD group.

Table 4. Scores for Fluorescein and Rose Bengal Staining and Tear Breakup Time in Eyes With Various Degrees of Meibomian Gland Dropout*

Measurement	Meibomian Gland Dropout			P
	None (n=127)	Less Than Half (n=52)	More Than Half (n=22)	
Score				
Fluorescein stain	0.60±0.07	0.92±0.15	1.27±0.26	.003
Rose bengal stain	0.81±0.11	0.92±0.18	1.36±0.41	.22
Breakup time, s	7.21±0.52	5.61±0.49	4.95±0.64	.056

*Data are given as mean±SE.

Table 5. Tear Function in the Non-MGD, Orifice Obstruction, Gland Dropout, and Combined Groups*

Group	Schirmer's Test, mm/5 min	Tear Clearance Test†	Cotton Thread Test, mm/15 s
Non-MGD	6.51±0.64	4.40±0.49	20.9±1.56
Obstruction	8.24±0.85	3.54±0.21	20.8±1.39
Dropout	10.75±1.40‡	4.03±0.43	21.2±2.00
Combined	8.26±0.95	5.03±0.71	20.3±1.31
P	.015	.19	.98

*Non-MGD indicates group in which there were no findings of meibomian gland dysfunction in the eyes. Data are given as mean±SE.

†Values indicate the dilution rate of fluorescein.

‡P=.002 compared with that for the non-MGD group.

noted in the obstruction and combined groups, suggesting that this finding is not incidental. This may be a compensation for the abnormality of the ocular surface, or a result of increased reflex tearing. The fact that more severe changes were seen in the ocular surface in the obstruction, gland dropout, and combined groups, despite an increase in tear secretion, indicated that a change in meibomian function, rather than an abnormality in tear function, was responsible for the changes that were observed. Although the effects of MGD on the ocular surface have been recognized clinically, no previous report, to our knowledge, has shown that MGD produces changes in the ocular surface.

We found that the rate of tear evaporation was increased in the gland dropout group (Table 3). This suggests that changes in the oily layer of the tear film occurs in MGD. This finding is in good accordance with that found in the study by Mathers,¹⁵ who reported that the numbers of gland dropout were correlated with the increase in the rate of tear evaporation. The absolute value for tear evaporation in the MGD group was considerably smaller in our study than in that of Mathers,¹⁵ perhaps because of the differences in the methods that were used. Another explanation for the increased rate of tear evaporation in the gland dropout group could have been that these eyes had more of a tear reservoir on their ocular sur-

face, as indicated by the results of Schirmer's test. This appeared to be unlikely, however, since the values of the cotton thread test, which reflects the amount of tears in the inferior cul-de-sac, were not different in the gland dropout and non-MGD groups (Table 5).

Clinically, MGD is characterized by a stagnation of meibomian secretion. Obstruction of a meibomian gland duct is caused by either keratinization of the duct or qualitative changes in the meibomian lipids.¹⁸ A previous histological study of MGD has revealed an obstruction and dilatation of the ducts, enlargement of acini, foreign reactions, and, in an advanced stage, a total destruction of the gland structure.¹⁹ The gland dropout that was detected by using meibography was believed to show a destruction of the meibomian gland structure.¹⁹ Therefore, gland dropout is more likely to represent more severe changes in the meibomian gland than in the obstruction of the orifice. The score for fluorescein staining and the rate of tear evaporation were higher in the gland dropout group than in the obstruction group in the present study; these findings are consistent with this theory. These changes in the ocular surface were more severe in the eyes with gland dropout in more than half of the tarsus of the inferior eyelid than in those with the gland dropout in less than half of that region (Table 4). It is likely that at some critical point the other vital glands are unable

to compensate for the impairment of meibomian gland function. Although both biomicroscopy and meibography are useful for assessing MGD, meibography appears to be more appropriate because it is more stable, is less subject to interobserver variation, and allows for a semiquantitative assessment.

In summary, our results showed that MGD is one of the major causes of ocular discomfort and abnormality in the ocular surface. Tear deficiency may or may not be accompanied with the disorder. An excessive evaporation of tears may have been responsible for the changes that were observed. The results of the meibomian orifice observation and meibography were associated with the severity of the changes in the ocular surface. The procedures that were used in the present study are convenient for clinical use and provide reproducible results without requiring expensive instruments or special techniques.

Accepted for publication May 16, 1995.

Reprint requests to Department of Ophthalmology, Tokyo Dental College, 5-11-13 Sugano, Ichikawa-shi, Chiba, 272 Japan (Dr Shimazaki).

REFERENCES

- Mishima S, Maurice DM. The oily layer of the tear film and evaporation from the corneal surface. *Exp Eye Res.* 1961;1:39-45.
- Tiffany J. The lipid secretion of the meibomian glands. *Adv Lipid Res.* 1987; 22:1-62.
- McCulley JP. Meibomitis. In: Kaufman HE, Barron BA, McDonald MB, Waltman SR, eds. *The Cornea*. New York, NY: Churchill Livingstone Inc; 1988:125-138.
- Toda I, Tsubota K. Practical double vital staining for ocular surface evaluation. *Cornea.* 1993;12:366-367.
- van Bijsterveld O. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol.* 1969;82:10-14.
- Toda I, Fujishima H, Tsubota K. Ocular fatigue is the major symptom of dry eye. *Acta Ophthalmol (Copenh).* 1993;71:347-352.
- Xu K-P, Yagi Y, Toda I, Tsubota K. Tear function index: a new measure of dry eye. *Arch Ophthalmol.* 1995;113:84-88.
- Sakamoto R, Bennett ES, Henry VA, et al. The phenol red thread test: a cross-cultural study. *Invest Ophthalmol Vis Sci.* 1993;34:3510-3514.
- Tsubota K, Yamada M. Tear evaporation from the ocular surface. *Invest Ophthalmol Vis Sci.* 1992;33:2943-2950.
- Tapie R. Etude biomicroscopique des glandes de meibomius. *Ann Oculist.* 1977; 210:637-648.
- Jester JV, Rife J, Nii D, Luttrull JK, Wilson L, Smith RE. In vivo biomicroscopy and photography of meibomian glands in a rabbit model of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci.* 1982;22:660-667.
- Robin JB, Jester JV, Nobe J, Nicolaides N, Smith RE. In vivo transillumination biomicroscopy and photography of meibomian gland dysfunction: a clinical study. *Ophthalmology.* 1985;92:1423-1426.
- Mathers WD, Shields WJ, Sachdev MS, Petroll M, Jester JV. Meibomian gland dysfunction in chronic blepharitis. *Cornea.* 1991;10:277-285.
- Mathers WD, Billborough M. Meibomian gland function and giant papillary conjunctivitis. *Am J Ophthalmol.* 1992;114:188-192.
- Mathers WD. Ocular evaporation in meibomian gland dysfunction and dry eye. *Ophthalmology.* 1993;100:347-351.
- Shimazaki J, Tsubota K. Evaluation of meibomian gland dysfunction via meibography. *Atarashii-Ganka.* 1993;10:1031-1034.
- Tsubota K. SS dry eye and non-SS dry eye: what are the differences? In: Homma M, Sugai S, Tojo T, Miyasaka N, Akizuki M, eds. *Sjögren's Syndrome—State of the Art*. Amsterdam, the Netherlands: Kugler Publications; 1994:27-31.
- Nicolaides N, Santos EC, Smith RE, Jester JV. Meibomian gland dysfunction, III: meibomian gland lipids. *Invest Ophthalmol Vis Sci.* 1989;30:946-951.
- Jester JV, Nicolaides N, Smith R. Meibomian gland studies: histologic and ultrastructural investigations. *Invest Ophthalmol Vis Sci.* 1981;20:537-547.

Correction

Error in Text. In the article "Abnormal Disc Vessels After Diabetic Papillopathy" in the February issue of the ARCHIVES (1995;113:245-246), on page 245, the last complete sentence in the second column should have read "Two months after their appearance, the abnormal disc vessels regressed spontaneously, leaving a thin rim of white fibrous tissue anterior to the optic nerve head (Figure 4)." We regret the error.