Increased Tear Fluid Production as a Compensatory Response to Meibomian Gland Loss

A Multicenter Cross-sectional Study

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Purpose: To compare tear film parameters as well as meibomian gland morphologic features and function among patients with meibomian gland dysfunction (MGD), those with non−Sjögren syndrome aqueous-deficient dry eye (non-SS ADDE), those with non-SS ADDE and MGD, and normal subjects.

Design: Multicenter, cross-sectional, observational case series.

Participants: Forty-one eyes of 41 patients (all women; mean age ± standard deviation, 62.1±9.9 years) with non-SS ADDE, 70 eyes of 70 patients (all women; 66.0±8.7 years) with MGD, 17 eyes of 17 patients (all women; 72.4±7.8 years) with non-SS ADDE and MGD, and 70 eyes of 70 normal control subjects (all women; 65.0±7.1 years).

Methods: Ocular symptoms were scored from 0 to 14 and lid margin abnormalities from 0 to 4 according to their respective number. Meibomian gland changes were scored from 0 to 6 (meiboscore) on the basis of noncontact meibography findings, and meibum was graded from 0 to 3 depending on its volume and quality. Conjunctival and corneal epithelial damage were scored from 0 to 9 (fluorescein score). Tear film break-up time (TBUT) was measured as an index of tear film stability, and tear fluid production was evaluated with Schirmer's test.

Main Outcome Measures: Ocular symptom score, lid margin abnormality score, meiboscore, meibum grade, fluorescein score, TBUT, and Schirmer's test value.

Results: The ocular symptom score did not differ significantly between the MGD and non-SS ADDE groups ($P = 0.762$). The lid margin abnormality score, meiboscore, and meibum grade were significantly higher in the MGD group than in the non-SS ADDE group ($P = 0.0012$, $P < 0.0001$, and $P < 0.0001$, respectively). The fluorescein score, TBUT, and Schirmer's test value were significantly worse in the non-SS ADDE group than in the MGD group ($P < 0.0001$, $P = 0.0061$, and $P < 0.0001$, respectively). The meiboscore correlated significantly with Schirmer's test value only in the MGD group ($\rho = 0.508$, $P = 8.3 \times 10^{-6}$).

Conclusions: An increase in tear fluid production likely compensates for loss of meibomian glands in individuals with MGD. *Ophthalmology 2015;122:925-933 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Homeostasis in living organisms refers to the maintenance of a relatively stable milieu despite changes in internal or external conditions.[1,2] The concept of homeostasis thus has been thought to be applicable to automatically controlled systems. The existence of homeostasis in the tear film has been suggested,[3] but the role of components of the tear film in such homeostasis has not been evaluated.

The tear film is composed of an aqueous layer produced by lacrimal glands as well as an overlying oily layer, the lipid components of which are secreted by meibomian glands. Dry eye is a disorder of the tear film caused by tear deficiency or excessive tear evaporation, and it can result in damage to the interpalpebral ocular surface. This condition is associated with symptoms of ocular discomfort,[4] and various mechanisms and definitions have been proposed.[5] Dry eye thus has been divided into 2 main categories: aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE).[5] Non−Sjögren syndrome (non-SS) ADDE is a common subtype of ADDE, whereas meibomian gland dysfunction (MGD) is a major cause of EDE.[6] Although non-SS ADDE and MGD account for most cases of dry eye, the relationship between clinical parameters in ADDE and those in EDE has remained unclear.

We hypothesized that the aqueous and oily layers of the tear film may compensate for each other to maintain homeostasis at the ocular surface. To investigate the concept

of homeostasis in the tear film, we compared tear film parameters as well as the function and morphologic features of meibomian glands among individuals with non-SS ADDE, those with MGD, those with both conditions, and normal controls.

Methods

Subjects

This study was approved by the Institutional Review Boards of The University of Tokyo, Yamaguchi University, Osaka University Hospital, Keio University School of Medicine, Nihon University Itabashi Hospital, and Itoh Clinic, and it adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects before examination.

Clinical Examinations

Women older than 40 years of age who reported dry eye symptoms, who did not have systemic disease or a past history of ocular surgery, and who were not taking oral medications or applying topical eyedrops with the exception of artificial tears were considered to be potential patients for this study. Those individuals who used artificial tears were instructed not to apply them for at least 2 hours before examinations. Individuals with a punctal plug were excluded. Patients who were scheduled to undergo cataract surgery were examined for enrollment as normal subjects, and the clinical examinations were performed before the surgery.

All physicians (R.A., N.M., S.K., R.S., M.K., T.S., and T.S.) who examined candidate subjects were specialists in the field of ocular surface. Data were obtained from the right eye of each subject unless this eye was excluded from the study, in which case data were collected from the left eye. Examinations were performed sequentially as follows. (1) All patients were questioned regarding the absence or presence of 14 ocular symptoms (Table 1). Symptoms were scored from 0 through 14 according to the number present. (2) Abnormalities of the upper and lower lid margins (Table 1) were scored from 0 through 4 according to the number present. (3) Fluorescein staining of the ocular surface was divided into 3 zones comprising nasal conjunctival, corneal, and temporal conjunctival areas.[7] The staining score ranged from 0 to 3 for each zone, yielding a total score of 0 to 9 for the ocular surface.[7] (4) Tear film break-up time (TBUT) was measured after instillation of 1 µl of a preservative-free solution of 1% fluorescein dye into the conjunctival sac with the use of a micropipette, and the subjects were asked to blink several times. The TBUT was measured 3 times consecutively with a stopwatch, and the mean of the 3 values was calculated. (5) The upper and lower eyelids were evaluated with the use of a noncontact meibography system, and the meibomian glands were observed. Partial or complete loss of meibomian glands was scored according to the meiboscore for each eyelid as previously described (Table 1).[8] The meiboscores for the upper and lower eyelids were summed to obtain a score from 0 to 6 for each eye. (6) A Schirmer strip (Whatman no. 41; Showa, Tokyo, Japan) was inserted over the lower lid margin, midway between the middle and outer thirds, for 5 minutes without topical anesthesia. Subjects were asked to close their eyes during the measurement. Schirmer's test thus was performed within the limits of evaluable situations. (7) Digital pressure was applied to the upper tarsus, and the degree of ease with which meibomian secretion (meibum) was induced was evaluated semiquantitatively (Table 1).[9]

After these clinical examinations, the candidate subjects were classified into 4 groups (Fig 1). The normal group included subjects who fulfilled the following criteria: (1) ocular symptom score of less than 3, (2) no tear film abnormality (Schirmer's test value of $\geq$5 mm and TBUT of $\geq$5 seconds), and (3) no abnormalities of the lid margins or meibum. The non-SS ADDE group comprised subjects who met the following conditions that conform to the definition of dry eye proposed by the Dry Eye Research Group in Japan[10]: (1) the presence of dry eye symptoms, (2) abnormal tear production as determined by Schirmer's test (<5 mm after 5 minutes) or abnormal tear film stability as determined by TBUT (<5 seconds), and (3) the presence of conjunctival and corneal epithelial damage as evidenced by a fluorescein staining score of $\geq$3, according to the van Bijsterveld method.[7] Patients with Sjögren syndrome were excluded. The MGD group included subjects who fulfilled the diagnostic criteria for obstructive MGD[11]: (1) the presence of ocular symptoms (ocular symptom score of $\geq$3), (2) at least 1 lid margin abnormality, and (3) poor meibum secretion (meibum grade of 1 to 3). The non-SS ADDE and MGD group comprised candidates who fulfilled the entry criteria for both non-SS ADDE and MGD groups. Exclusion criteria for all subjects included ocular allergies, contact lens wear, a history of eye surgery, and systemic or ocular diseases that may interfere with tear film production or function. Individuals whose eyes showed excessive meibomian lipid secretion also were excluded. The normal, non-SS ADDE, MGD, and non-SS ADDE

Table 1. Clinical Parameters and Their Evaluation

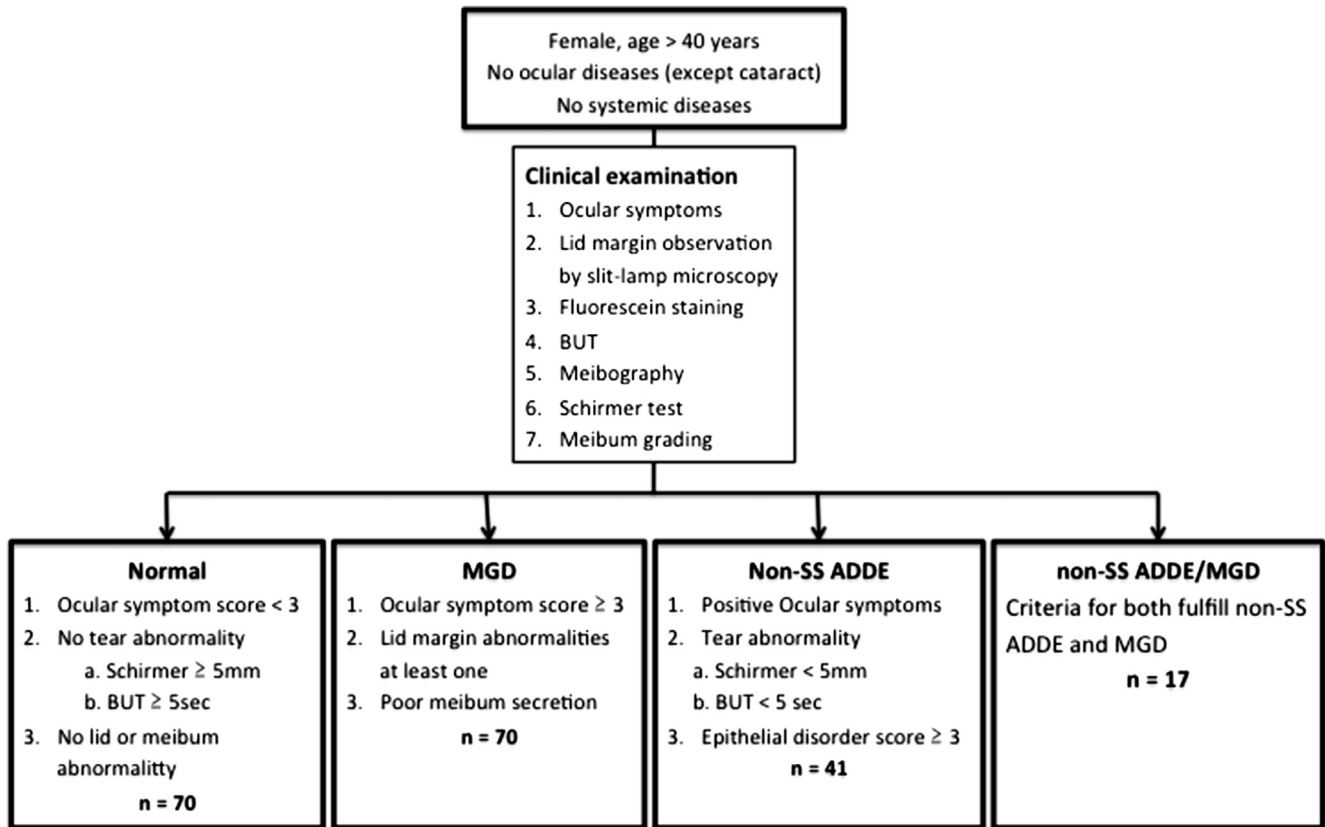| Examination	Evaluation
Ocular symptoms	Ocular fatigue, discharge, foreign body sensation, dryness, uncomfortable sensation, sticky sensation, pain, epiphora, itching, redness, heavy sensation, glare, excessive blinking, history of chalazion or hordeolum
Lid margin abnormality	Irregular lid margin, vascular engorgement, plugged meibomian gland orifices, anterior or posterior replacement of the mucocutaneous junction
Fluorescein staining	Nasal conjunctiva (0–3), cornea (0–3), temporal conjunctiva (0–3)
Tear film break-up time	Less than 5 seconds: decreased
Meiboscore	Grade 0: no dropout Grade 1: dropout of <1/3 of lid area Grade 2: dropout of 1/3–2/3 of lid area Grade 3: dropout of >2/3 of lid area Total meiboscore (0–6): upper eyelid + lower eyelid
Schirmer's test	Less than 5 mm: decreased
Meibum grade	Grade 0: clear meibum readily expressed Grade 1: cloudy meibum expressed with mild pressure Grade 2: cloudy meibum expressed with more than moderate pressure Grade 3: meibum not expressed even with strong pressure

Figure 1. Flowchart showing participant progress through the study. ADDE = aqueous-deficient dry eye; MGD = meibomian gland dysfunction; non-SS = non−Sjögren syndrome; TBUT = tear film break-up time.

and MGD groups finally consisted of 70 (mean age ± standard deviation, 65.0±7.1 years), 41 (62.1±9.9 years), 70 (66.0±8.7 years), and 17 (72.4±7.8 years) subjects, respectively.

Statistical Analysis

Data for all parameters are presented as mean ± standard deviation and were compared among non-SS ADDE, MGD, non-SS ADDE and MGD, and control groups with the use of the Steel-Dwass test. Regression curves comparing meiboscore and Schirmer's test value were calculated on the basis of scatterplots and were evaluated with Spearman's rank-correlation coefficient (ρ). A *P* value of less than 0.05 was considered statistically significant.

Results

Representative lid margin, fluorescein staining, and meibography findings for normal control, non-SS ADDE, and MGD subjects are shown in Figures 2, 3, and 4, respectively. No loss of meibomian glands and only minimal meibomian gland changes were observed in the normal control (Fig 2) and non-SS ADDE (Fig 3) subjects, respectively. In contrast, various meibomian gland changes, including dropout, shortening, distortion, and dilation, were apparent in the MGD subject (Fig 4).

Data for the clinical parameters in each group of study subjects and the *P* values for pairwise comparisons of the values among the 4 groups are presented in Tables 2 and 3, respectively. Age did not

differ significantly within each pair of subject groups, with the exception of pairs including the non-SS ADDE and MGD group. The ocular symptom score did not differ significantly among the non-SS ADDE, the MGD, and the non-SS ADDE and MGD groups. The lid margin abnormality score was significantly higher in the MGD and the non-SS ADDE and MGD groups than in the non-SS ADDE group ($P = 0.0012$ and $P = 0.0105$, respectively). The fluorescein score was significantly higher in the non-SS ADDE and the non-SS ADDE and MGD groups than in the MGD group ($P < 0.0001$ and $P < 0.0001$). The TBUT was significantly shorter in the non-SS ADDE and the non-SS ADDE and MGD groups than in the MGD group ($P = 0.0061$ and $P = 0.0017$, respectively). The meiboscore was significantly higher in the MGD group than in the non-SS ADDE and the non-SS ADDE and MGD groups ($P < 0.0001$ and $P = 0.0012$, respectively). Meibum grade was significantly higher in the MGD and the non-SS ADDE and MGD groups than in the non-SS ADDE group ($P < 0.0001$ and $P < 0.0001$). Schirmer's test value was significantly lower in the non-SS ADDE and the non-SS ADDE and MGD groups than in the MGD group ($P < 0.0001$ and $P < 0.0001$). Of note, Schirmer's test value was actually highest in the MGD group among the 4 groups of subjects.

A scatterplot and regression curve for Schirmer's test value versus meiboscore in each group of subjects are shown in Figure 5. Spearman's ρ was −0.0838 in the normal group, 0.253 in the non-SS ADDE group, 0.508 in the MGD group, and 0.256 in the non-SS ADDE and MGD group. A significant correlation
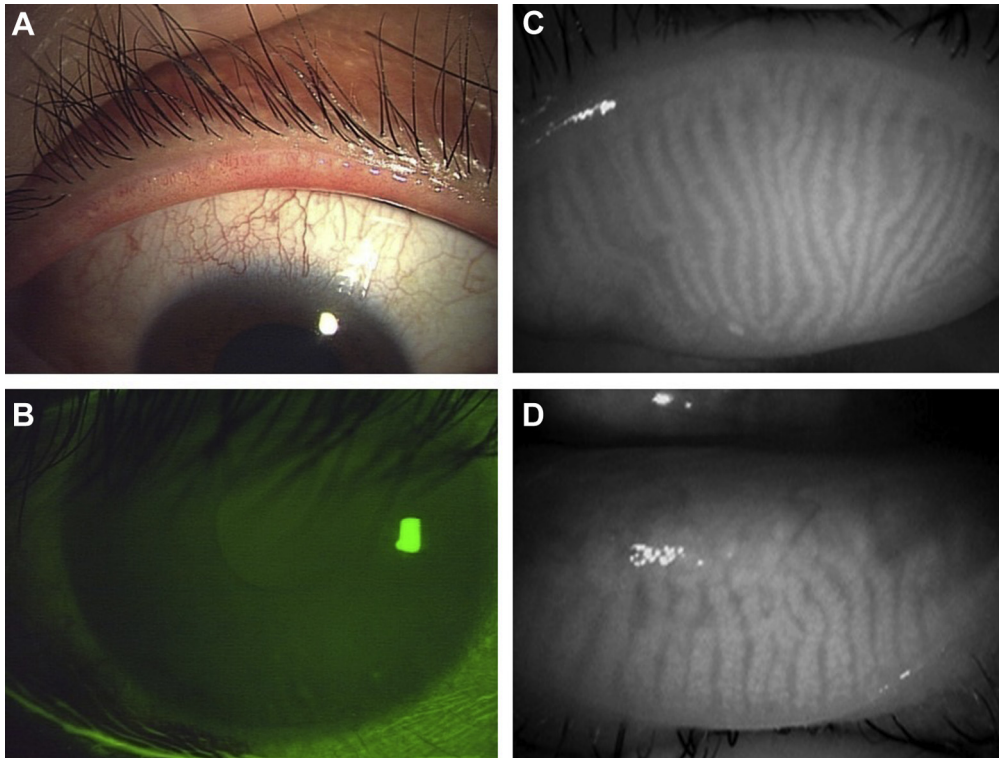
Figure 2. Representative slit-lamp photographs and meibographic images for a normal control subject (62-year-old woman with a Schirmer's test value of 9 mm and tear film break-up time of 8 seconds). **A,** Slit-lamp photograph of the upper lid margin. **B,** Slit-lamp photograph of the cornea and conjunctiva after fluorescein staining and observation with a blue-free filter. **C, D,** Noninvasive meibographic images of the upper and lower eyelids, respectively. Note that no morphologic changes of meibomian glands in either eyelid were apparent (meiboscore of 0).

between the 2 parameters was apparent only in the MGD group ($P = 8.3 \times 10^{-6}$).

Discussion

We compared clinical parameters among normal control subjects, patients with non-SS ADDE, patients with MGD, and patients with both conditions. To clarify the relationship between meibomian gland condition and tear secretion, we focused on comparison of the non-SS ADDE and MGD groups. Our data showed that tear fluid secretion (as reflected by Schirmer's test value) was related closely to the severity of meibomian gland abnormality (as reflected by the meiboscore, which indicates meibomian gland loss). Our findings thus suggested that tear fluid secretion may increase as a compensatory response to the loss of tear film stability caused by deficiency of the oily layer.

Tear secretion in the MGD group increased markedly according to the extent of meibomian gland loss (meiboscore). Consistent with our previous observations,[11] the meiboscore was significantly higher in the MGD group than in the other groups. The meiboscore also indicates the thickness of the oily layer of the tear film,[12] with a higher meiboscore corresponding to a thinner oily layer and consequent tear film instability. Tear film instability is associated with a shorter TBUT and results in ocular

surface stimulation and reflex tear secretion. Our present data suggest that tear secretion is increased in patients with MGD to compensate for the reduced meibomian gland function and to stabilize the tear film. This notion is consistent with the previous finding that the tear meniscus height of patients with MGD is similar to that of normal controls, whereas that of non-SS ADDE patients is significantly lower than that of patients with MGD.[13] We also did not detect a significant difference in Schirmer's test value between normal subjects and patients with MGD. Schirmer's test provides an index of lacrimal gland function,[14,15] whereas meibomian gland area reflects meibomian gland function. The fact that a decrease in meibomian gland area is associated with an increase in tear meniscus height suggests that tear fluid production increases as a compensatory response to meibomian gland loss to maintain ocular surface homeostasis. In contrast, we found that the meiboscore of non-SS ADDE patients was increased compared with that of normal controls, suggesting that meibomian gland function was not increased in individuals with reduced lacrimal gland function. The homeostatic system of the tear film thus may function only 1 way, with the aqueous layer compensating for deficiency of the oily layer, but not vice versa.

Indeed, in clinical practice, the administration of artificial tear eyedrops to some patients with MGD improves ocular discomfort or the condition of the ocular surface. The
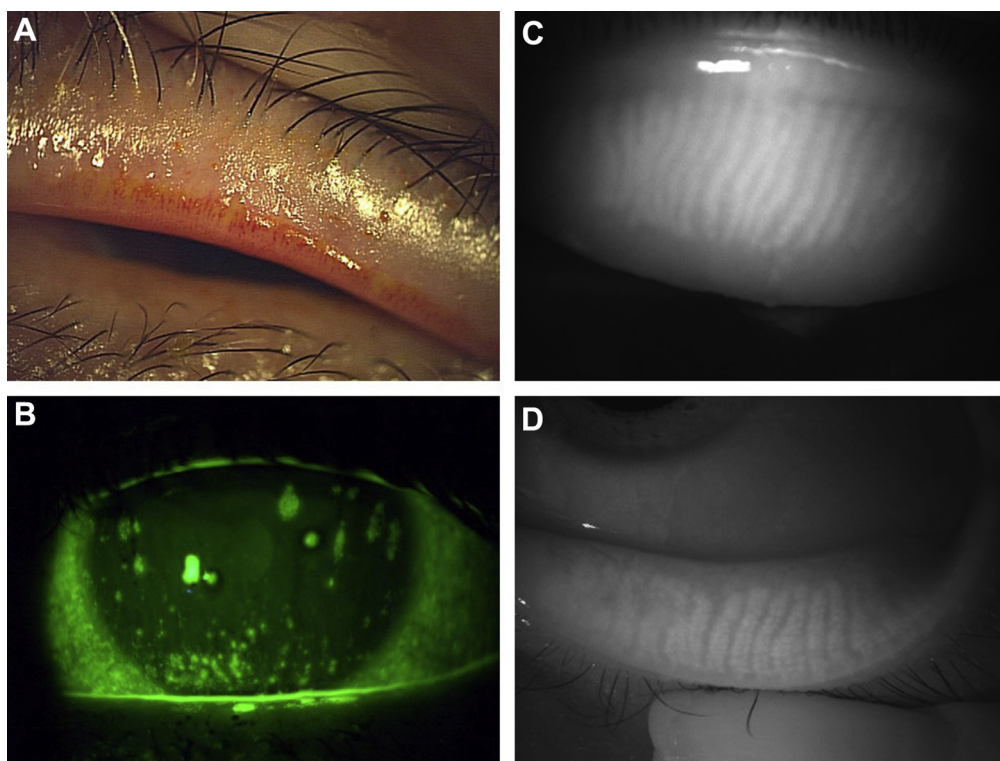
Figure 3. Representative slit-lamp photographs and meibographic images for a non—Sjögren syndrome aqueous-deficient dry eye subject (67-year-old woman with a Schirmer's test value of 1 mm and tear film break-up time of 1 second). **A,** Slit-lamp photograph of the upper lid margin. **B,** Slit-lamp photograph of the cornea and conjunctiva after fluorescein staining and observation with a blue-free filter. Note that corneal epithelial disorders were apparent. **C, D,** Noninvasive meibographic images of the upper and lower eyelids, respectively. Note that minor morphologic changes of meibomian glands in both upper and lower eyelids were apparent (meiboscore of 1).

addition of aqueous tear volume by the administration of artificial tears or insertion of punctal plugs may support the compensatory response to reduced meibomian gland function. The increase in tear secretion in patients with MGD also may reduce friction between the eyelid and the cornea caused by deficiency of the oily layer of the tear film. Increased friction during blinking may stimulate the ocular surface and thereby trigger tear secretion.[16] Tear secretion in patients with MGD thus may increase in response to tear film instability to reduce ocular discomfort.

A previous study demonstrated a compensatory response of the tear film to surgical obstruction of the orifices of meibomian glands on only 1 side of the eye in a rabbit model.[17] Both Schirmer's test value and tear film osmolarity in the affected eye were increased compared with those in the control eye. Tear production also was found previously to be higher in MGD patients than in ADDE patients, suggestive of the operation of a compensatory system in the tear film.[9] Furthermore, another study found that tear flow tended to be increased in patients with MGD compared with control subjects.[18] However, a few reports[19,20] describe the relationship between tear secretion and oily layer, suggesting that a compensatory response to aqueous deficiency remains controversial. Taken together, these various experimental and clinical observations support the existence of a compensatory response to a diminished oily layer by increasing tear fluid.

In this study, we determined Schirmer's test value and the meiboscore as measures of tear fluid secretion and meibomian gland abnormality, respectively. The aqueous layer of the tear film is derived primarily from lacrimal glands[21] and constitutes most tear volume. The outermost oily layer of the tear film is produced by meibomian glands.[22] Schirmer's test has been adopted as a common method for clinical evaluation of tear secretion.[5] We previously evaluated various diagnostic criteria for distinguishing between subtypes of dry eye disease, and we concluded that the meiboscore and Schirmer's test value are the most reliable parameters measured in the clinic for differentiation of patients with MGD from those with non-SS ADDE.[23] Indeed, a recent multicenter study[6] classified dry eye disease into 3 categories—ADDE, MGD, and mixed type—on the basis of these parameters. Although no gold standard test for detection of either ADDE or EDE currently exists, our protocol seems appropriate for this type of multicenter study.

The TBUT was found to be shorter in the non-SS ADDE group than in the MGD group. Measurement of TBUT with fluorescein is one of the most common clinical tests to evaluate tear film stability. A variety of factors can cause breakup of the tear film.[24] Thus, TBUT has been found to depend mainly on the mucin layer of the tear film, the aqueous layer, and the condition of the ocular surface epithelium.[25] Recent studies have shown tear film breakup largely is the
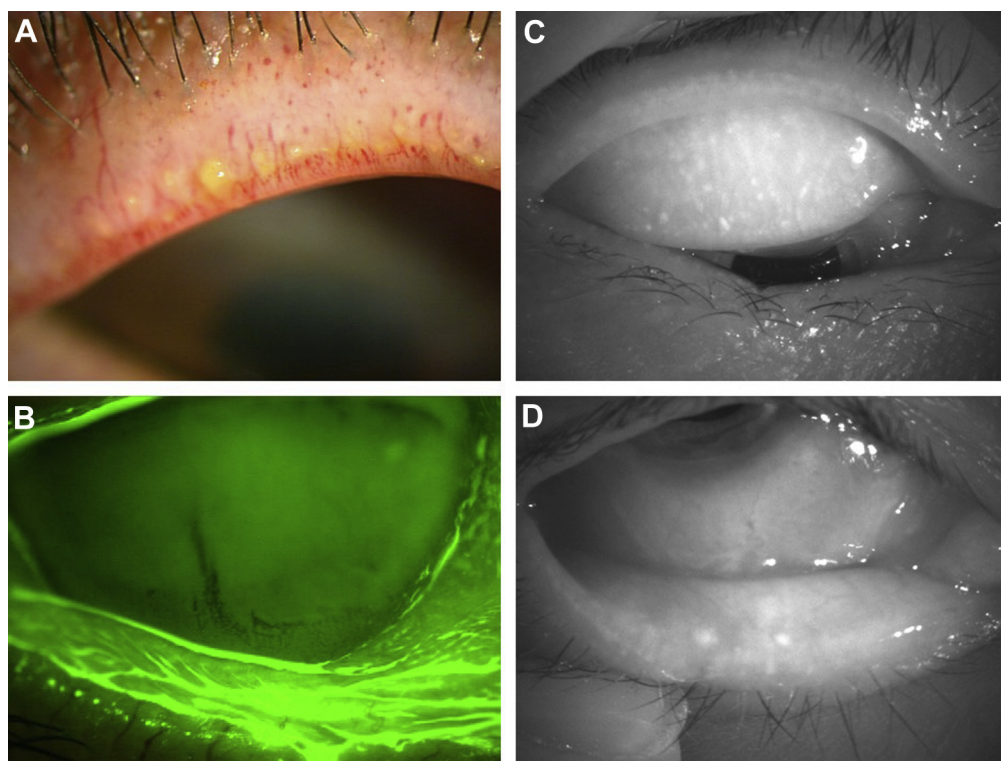
Figure 4. Representative slit-lamp photographs and meibographic images for a meibomian gland dysfunction (MGD) subject (65-year-old woman with a Schirmer's test value of 8 mm and tear film break-up time of 5 seconds). **A**, Slit-lamp photograph of the upper lid margin. Lid margin abnormalities, including vascularity, dislocation of the mucocutaneous junction, and secretion of yellow meibum, were observed. **B**, Slit-lamp photograph of the cornea and conjunctiva after fluorescein staining and observation with a blue-free filter. **C, D**, Noninvasive meibographic images of the upper and lower eyelids, respectively. Dropout, shortening, distortion, and dilation of meibomian glands were observed in both eyelids (meiboscore of 5).

result of evaporation.[26–28] A high concentration of fluorescein also was found to be associated with a more rapid breakup of the tear film.[27] We instilled 1 μl of 1% fluorescein in the subjects of the present study. Given that tear production was significantly lower in the non-SS ADDE group than in the MGD group, the concentration of dye was likely higher in the non-SS ADDE group than in the MGD group. Moreover, the fluorescein staining score was significantly higher in the non-SS ADDE group than in the MGD group. A higher effective concentration of fluorescein and more severe ocular surface epithelial damage indicated by the higher fluorescein score thus may contribute to the instability of the tear film in the non-SS ADDE group. We did not measure the thickness of the oily layer in the present study. Further studies thus are warranted to measure this parameter and to determine its relationship to TBUT in each group of subjects.

There was no significant difference in the ocular symptom score between the MGD group and the non-SS ADDE group, whereas the fluorescein score in the latter group was significantly higher than that in normal controls or the MGD group. Epithelial disorders at the ocular surface thus were associated with symptoms in the non-SS ADDE group. In

Table 2. Clinical Parameters for the 4 Groups of Study Subjects

Parameter	Normal	Non-SS ADDE	MGD	Non-SS ADDE and MGD
No. of subjects	70	41	70	17
Age (yrs)	65.0 ± 7.1	62.1 ± 9.9	66.0 ± 8.7	72.4 ± 7.8
Symptom score (0−14)	1.0 ± 1.3	4.9 ± 2.1	4.5 ± 3.5	6.5 ± 2.9
Lid margin score (0−4)	0.3 ± 0.5	1.7 ± 0.9	2.4 ± 1.0	2.6 ± 1.1
Fluorescein score (0−9)	0.0 ± 0.2	4.0 ± 2.0	0.7 ± 0.8	3.1 ± 2.1
Tear film break-up time (seconds)	6.0 ± 1.7	2.1 ± 1.1	3.5 ± 2.1	1.5 ± 0.8
Meiboscore (0−6)	1.1 ± 0.8	2.2 ± 1.2	4.1 ± 1.3	2.8 ± 1.0
Schirmer's test value (mm)	10.3 ± 3.0	2.3 ± 1.7	12.5 ± 7.6	2.8 ± 1.7
Meibum grade (0−3)	0.4 ± 0.5	0.7 ± 0.6	1.8 ± 0.8	2.3 ± 0.5

Non-SS ADDE = Non-Sjogren Syndrome aqueous deficient dry eye; MGD = meibomian gland dysfunction.
Data are means ± standard deviation.

Table 3. *P* Values for Statistical Comparison of Clinical Parameters among Subject Groups with the Steel-Dwass Test

Parameter	Normal vs. Non-SS ADDE	Normal vs. MGD	MGD vs. Non-SS ADDE	Non-SS ADDE vs. Non-SS ADDE and MGD	MGD vs. Non-SS ADDE and MGD	Normal vs. Non-SS ADDE and MGD
Age	0.4873	0.9265	0.2575	0.0023	0.0402	0.005
Symptom score	<0.0001	<0.0001	0.762	0.2374	0.0919	<0.0001
Lid margin score	<0.0001	<0.0001	0.0012	0.0105	0.8717	<0.0001
Fluorescein score	<0.0001	<0.0001	<0.0001	0.1842	<0.0001	<0.0001
Tear film break-up time	<0.0001	<0.0001	0.0061	0.2600	0.0017	<0.0001
Meiboscore	<0.0001	<0.0001	<0.0001	0.1259	0.0012	<0.0001
Schirmer's test value	<0.0001	0.7891	<0.0001	0.7214	<0.0001	<0.0001
Meibum grade	0.0203	<0.0001	<0.0001	<0.0001	0.0723	<0.0001

Non-SS ADDE = Non-Sjogren Syndrome aqueous deficient dry eye; MGD = meibomian gland dysfunction.

the MGD group, however, the ocular symptom score was high, whereas the fluorescein score was low. Such a discrepancy between subjective symptoms and objective signs is observed frequently in the clinic. The reason why the ocular symptom score was high in the MGD group is unclear, but it may be related to sensory nerve stimulation in the vicinity of meibomian glands. Although information is available regarding the release of neurotransmitters from such nerve fibers and the expression of corresponding receptors,[29–32] little is known about the consequences of such transmission. Nerve endings have been found to form a nerve plexus around the ducts and acini of meibomian glands. The abnormalities of meibomian glands in patients with MGD thus may result in the stimulation of these nerve fibers and thereby give rise to the ocular symptoms reported by such individuals. Characterization of the mechanism of tear film compensation by increased tear secretion will require identification of signaling systems activated in response to dryness at the ocular surface or tear film instability. The sensory system for detection of ocular surface abnormalities is thought to include corneal or conjunctival nociception. Recent studies also indicate that thermal nociception at the ocular surface is regulated by transient receptor potential channel proteins.[33,34] Sensory and transduction systems for the detection of ocular surface abnormalities may play key roles in maintenance of the ocular surface condition as well as in the pathogenesis of ocular surface disorders.

Current treatments for dry eye or MGD are targeted to improvement of the corresponding abnormal components of the tear film. Treatments for patients with non-SS ADDE thus include administration of the aqueous component in the form of artificial tears as well as the insertion of punctal plugs, whereas those for patients with MGD include administration of the oily component in the form of eye ointment. We showed that the reduced function of the oily layer of the tear film in patients with MGD is compensated for by an increased secretion of tear fluid, suggesting that maintenance of the balance between tear film components may be important for stability of the tear film. Indeed, the administration of eye ointment alone for patients with MGD previously was shown to worsen their symptoms and findings if the tear volume was not sufficient.[35] In such cases, the addition of not only eye ointment but also artificial tears improved subjective symptoms and objective findings. We also propose that treatment of tear diseases focus on improvement of the balance between tear film components. Such a treatment strategy requires clinical evaluation of tear parameters to identify the abnormality. The common aim of present and future dry eye treatments thus should be to maintain or recover homeostasis of the tear film.

Further investigations of tear film homeostasis might consider the contributions of mucin, tear osmolarity, and blinking. Mucin plays a key role in tear stability,[36] but it is difficult to evaluate clinically. We therefore performed the present study with the assumption that mucin kinetics are
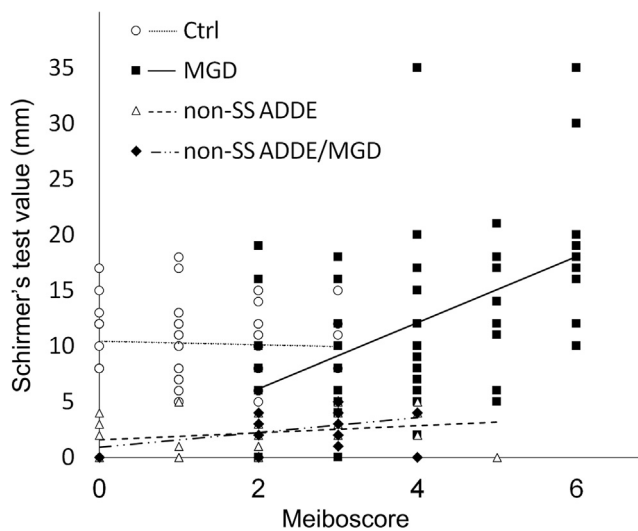

Figure 5. Scatterplot showing the meiboscore and Schirmer's test values for each of the 4 groups of study subjects. Open circles and dotted lines represent normal control (Ctrl) subjects ($y = -0.155x + 10.40$, $R^2 = 0.0019$, $P = 0.492$), open triangles and dashed line represent non−Sjögren syndrome (non-SS) aqueous-deficient dry eye (ADDE) subjects ($y = 0.318x + 1.5775$, $R^2 = 0.0470$, $P = 0.115$), closed squares and solid line represent meibomian gland dysfunction (MGD) subjects ($y = 2.975x + 0.219$, $R^2 = 0.2527$, $P = 8.3 \times 10^{-6}$), and closed diamonds and dotted-dashed lines represent non-SS ADDE and MGD subjects ($y = 0.668x + 0.918$, $R^2 = 0.1483$, $P = 0.115$).

likely to resemble those of the aqueous layer of the tear film. Tear osmolarity, which is thought to play a major role in the vicious circle that underlies the pathologic features of dry eye disease,[36] has been found to be related to goblet cell density or to a mucin reduction. Furthermore, tear osmolarity tends to be increased in patients with MGD.[6,17,37,38] Increased tear fluid secretion in such patients therefore may maintain tear osmolarity. Blinking is a physical movement to distribute tear fluid over the ocular surface. Blinking rate[39] and blinking tension[40] therefore are thought to affect the condition of the tear film. Moreover, complete blinking is necessary to stabilize the tear film.[41] Forceful closure of the eyelids was found to increase meibomian gland secretion and the thickness of the oily layer of the tear film.[40] Blinking itself thus may represent an important compensatory mechanism distinct from that operative at the level of tear film components in the maintenance of tear film homeostasis.

We enrolled only age-matched female subjects in the present study to minimize variability in hormonal effects on lacrimal and meibomian glands.[10,42,43] Our preliminary data indicated that male subjects are similar to females with regard to the findings of the present study. In conclusion, our present results suggested that a homeostatic system operates in the tear film, with tear secretion increasing to compensate for a deficiency of the oily layer by increasing tear film stability. Our findings thus reveal the importance of maintaining a balance between tear film components. Further studies are necessary to establish the operation of this compensatory mechanism and to provide additional insight into various aspects of tear film homeostasis, including blinking, tear osmolarity, the condition of the mucin layer, and the presence of inflammatory factors.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

ADDE = aqueous-deficient dry eye; **EDE** = evaporative dry eye; **MGD** = meibomian gland dysfunction; **non-SS** = non−Sjögren syndrome; **TBUT** = tear film break-up time.

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