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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 ($\rho = 0.508$, $P = 8.3\times10^{-6}$).

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

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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 ≥5 mm and TBUT of ≥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 ≥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 ≥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