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Influence of Meibomian Gland Dysfunction and Friction-Related Disease on the Severity of Dry Eye

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Purpose: To evaluate the effect of meibomian gland dysfunction (MGD) and friction-related disease (FRD) on the severity of dry eye disease (DED).

Design: Cross-sectional observational study.

Participants: This study enrolled 449 patients with DED (63 men and 386 women; mean age, 62.6±15.7 years [range, 21−90 years]) for analysis.

Methods: Subjective symptoms, the ocular surface, tear function, and the presence of MGD and FRD (superior limbic keratoconjunctivitis, conjunctivochalasis, and lid wiper epitheliopathy) were investigated.

Main Outcome Measures: Schirmer value, tear film breakup time (TBUT), and keratoconjunctival score.

Results: We classified the participants into aqueous-deficient dry eye (ADDE; n = 231 [51.4%]) and short TBUT dry eye subtype (TBUT-DE; n = 109 [24.3%]) subgroups. The TBUT was shorter in patients with MGD than in those without MGD, whereas other ocular signs showed no difference (TBUT: MGD present, 1.97±1.02 seconds; MGD absent, 2.94±1.63 seconds [$P < 0.001$]; ADDE/MGD present, 1.94±1.08 seconds; ADDE/MGD absent, 2.77±1.61 seconds [$P < 0.001$]; short TBUT-DE/MGD present, 2.07±0.97 seconds; short TBUT-DE/MGD absent, 2.94±1.23 seconds [$P = 0.01$]). The ADDE patients with FRD showed a worse TBUT than ADDE patients without FRD (TBUT: ADDE/FRD present, 2.08±1.39 seconds; ADDE/FRD absent, 2.92±1.54 seconds; $P < 0.001$).

Conclusions: This study showed associations between MGD, FRD, or both and ocular signs in DED. In the presence of MGD, FRD, or both, TBUT was significantly shortened regardless of the dry eye status or subtype. *Ophthalmology 2018;■:1−8 © 2018 by the American Academy of Ophthalmology*

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Dry eye disease (DED) is a multifactorial disease of the tears and ocular surface that is the result of compromises in the quality or quantity, or both, of the tears and ocular surface. Conventionally, aqueous deficiency and increased evaporative loss from the ocular surface are etiologic causes associated with DED.[1]

As the disease concept has become more apparent, researchers have described a new dry eye subtype: short tear film breakup time dry eye (TBUT-DE). Tear instability and the presence of dry eye symptoms of similar severity to those in aqueous-deficient dry eye (ADDE) with a normal tear volume and limited ocular surface damage characterize short TBUT-DE.[2,3] Recently, epidemiologic studies in Asia have reported the emerging role of short TBUT in DED.[4−6] Uchino et al[6] reported that the major type of DED was short TBUT-DE in the Osaka study. The pivotal role of tear instability also has been emphasized in the new definition of DED from the Asia Dry Eye Society.[5] Although a paradigm shift in the perception of dry eye with regard to tear instability and the introduction of the short TBUT-DE subtype took place in Asia, there is a limited understanding of the relationship between short TBUT-DE and other DED-related conditions in the literature.

Meibomian gland dysfunction (MGD), a common cause of excessive evaporation of the tear film, has been regarded internationally as the major cause of DED.[7,8] Superior limbic keratoconjunctivitis, lid wiper epitheliopathy (LWE), and conjunctivochalasis are disorders arising from frictional force between the eyelid and the ocular surface, which results in mechanical trauma and consequent inflammation during blinking.[4] To describe the set of diseases, we introduced the term *friction-related disease* (FRD) in our previous report.[4] Superior limbic keratoconjunctivitis, LWE, and conjunctivochalasis were reported to be associated with DED[9−12]; however, no study has taken into consideration mechanical forces occurring during blinking in combination with conventional dry eye causes.

Because DED causes are not mutually exclusive, but rather interconnected, it is necessary to determine the relationships between these causes in DED as a whole.

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Changes observed clinically in association with MGD or FRD in patients with DED are well documented in the literature. However, there has been no attempt to determine their interactions in contributing to the severity of DED. Therefore, in this study, we evaluated the effect of MGD and FRD, separately and in combination, on DED and dry eye subgroups (the ADDE and short TBUT-DE subgroups).

Methods

Study Participants

We collected data from the Dry Eye Cross-Sectional Study in Japan, which was a cross-sectional, observational study held at 10 eye clinics in Japan from December 2014 through February 2015.[4] All investigators at the study sites were ocular surface and DED specialists and belonged to the Japanese Dry Eye Society. To maintain high quality during the survey, investigators met twice to discuss the study protocol and examination procedures before beginning patient enrollment. We distributed an instructional video to each investigator to ensure standard procedures.

Participants were outpatients older than 20 years who had already been diagnosed with DED or were newly diagnosed with DED. The diagnostic criteria were as follows: (1) 1 or more abnormal tear examination results (Schirmer test I value, $\leq$5 mm; tear film breakup time [TBUT], $\leq$5 seconds), (2) abnormal results on the ocular surface vital staining test (fluorescein corneal or conjunctival staining score, $\geq$3), and (3) positive symptoms of DED.[4,13] Those who met 2 of the criteria or all 3 criteria were recruited as patients with DED in this study.

This study was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki and Ethical Guidelines for Medical and Health Research involving Human Subjects in Japan. The Institutional Review Board of Clinical Study, Ryogoku Eye Clinic, Tokyo, Japan, approved the study protocol. Participants received a full explanation of the procedures and provided their informed consent for participation before inclusion in the study. We registered the study in a public registration system (University Hospital Medical Information Network; registry no., UMIN 000015890).

Clinical Assessment

Subjective Eye Symptoms Questionnaire. We used the Dry Eye-Related Quality-of-Life Score questionnaire developed and validated in Japan to assess dry eye symptoms.[14] The questionnaire comprises 15 items under an overall summary scale and 2 subscales, namely bothersome ocular symptoms and impact on daily life. Positive symptoms of DED were determined when participants responded affirmatively to 1 or more of the 6 questions on the bothersome ocular symptoms subscale.[14]

Tear Function Tests and Ocular Surface Evaluation. We performed ophthalmic examinations sequentially as follows: TBUT, conjunctival and corneal vital staining with fluorescein, FRD evaluation, morphologic and qualitative eyelid and meibomian gland evaluations, and Schirmer test I. As described in a previous report,[4] we used test strips containing fluorescein sodium (Fluores Ocular Examination Test Paper; Ayumi Pharmaceutical Co., Tokyo, Japan) for TBUT measurement and vital staining. We performed the fluorescein staining procedure after applying 2 drops of saline solution to the test strip. We then shook the strip vigorously and gently touched its edge to the inferior temporal lid margin. After blinking 3 times to facilitate adequate mixing of the fluorescein dye with tears, the patient was instructed verbally to close the eye gently and then quickly open the eye. We measured the interval between the last complete blink and the appearance of the first corneal dark spot with a stopwatch and regarded the mean of 3 measurements as the TBUT in this study. Subsequently, we evaluated corneal and conjunctival epithelial damage by using fluorescein vital staining viewed through a blue-free filter. The results were scored according to the grading system proposed by van Bijsterveld.[15] In brief, we divided the ocular surface into 3 sections (the temporal conjunctiva, cornea, and nasal conjunctiva) and scored the damage severity in each section from 0 to 3. The final score ranged from 0 (minimum) to 9 (maximum) points. We performed the Schirmer test I without topical anesthesia. The Schirmer test I was chosen because it was considered a standardized test that provides an estimation of stimulated reflex tear flow, according to the Dry Eye Workshop (DEWS) reports.[16,17] We placed a Schirmer test strip (Ayumi Pharmaceutical Co.) on the outer one third of the lower temporal conjunctival fornix for 5 minutes. Then, we removed the strip and recorded the length of wetted filter paper (in millimeters).

Meibomian Gland Dysfunction and Friction-Related Disease Evaluations. We evaluated meibomian gland function in the central one third of the upper eyelid by using a slit-lamp biomicroscope. The patient was instructed to look down while the investigator gently and partially everted the upper lid to examine the lid margin. Typical pictures of the following signs or findings were distributed to each investigator to aid in the examination: (1) 1 or more abnormal findings around the meibomian gland orifices such as vascular engorgement, anterior or posterior displacement of the mucocutaneous junction, or irregularity of the lid margin[18]; (2) orifice obstruction such as plugging, pouting, or ridges[18]; and (3) hypersecretion or hyposecretion of the meibum.[19,20] We diagnosed MGD when all of the signs and findings listed in the criteria were present. We considered that participants had friction-related conditions when any of the following conditions were present: LWE (upper and lower lids), conjunctivochalasis (at the central site of the lower eyelid), or superior limbic keratoconjunctivitis.[10,21,22]

Classifications of the Dry Eye Disease Subgroups. We classified the participants into the ADDE and short TBUT-DE subgroups. We chose Schirmer test values of 5 mm or less according to the Japanese diagnostic criteria for DED as the cutoff point for the 2 groups. This cutoff value used for the Schirmer I test demonstrated a good balance between sensitivity and specificity and seemed to be reasonable in the classification of the DED subgroups.[23] The ADDE group comprised participants who fulfilled the following criteria: (1) the presence of dry eye symptoms and (2) decreased tear production (Schirmer value, $\leq$5 mm). The short TBUT-DE subgroup included participants who met the following conditions: (1) the presence of dry eye symptoms, (2) abnormal tear stability (TBUT, $\leq$5 seconds), (3) no abnormality in tear production (Schirmer test value, $>$5 mm), and (4) no abnormality in the ocular surface vital staining test (keratoconjunctival score, $<$3).

Statistical Analyses

We used 1 eye from each participant for analysis. Based on the Japanese Dry Eye Society criteria for dry eye diagnosis, the eye fulfilling the most criteria was selected; when both eyes met the same number of criteria, we analyzed the eye with (1) the higher staining score or (2) the shorter TBUT. If the staining score and TBUT were the same in both eyes, we used the right eye for analysis. Data for all parameters are the mean $\pm$ standard deviation. We performed all statistical analyses using SAS software version 9.4 (SAS, Inc., Cary, NC). For comparisons between groups, we used the Fisher exact test for dichotomous variables and the