Assessment of Transepidermal Water Loss From the Ocular Area in Dry Eye Disease

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Purpose. To investigate transepidermal water loss (TEWL) from the ocular area in dry eye disease (DED) and evaluate the correlation between ocular TEWL and other DED parameters.

Methods. Transepidermal water loss from the ocular area in 56 eyes with DED and 38 healthy eyes was measured using a Tewameter TM300 that was equipped with custom made goggles (measuring temperature 24°C–26°C and relative humidity 35%–45%). The DED group was classified into two subgroups, aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE). Correlations between ocular TEWL and other DED parameters, such as tear osmolarity, tear break-up time (TBUT), corneal staining, conjunctival staining, Schirmer I test, Ocular Surface Disease Index (OSDI), and Visual Analogue Scale score were evaluated.

Results. Ocular TEWL was significantly higher in the DED group (63.0 ± 12.2 g/h/m^2) than in the control group (54.7 ± 14.2 g/h/m^2; $P = 0.003$). Although there was no significant difference, TEWL was higher in the ADDE subgroup (64.0 ± 10.7 g/h/m^2) compared with the EDE subgroup (61.1 ± 14.9 g/h/m^2). Tear break-up time, corneal staining score, and OSDI were significantly correlated with ocular TEWL ($P < 0.05$) in all participants. Ocular TEWL loss was negatively correlated with Schirmer I test value in the DED group.

Conclusions. Ocular TEWL was significantly higher in DED patients compared with controls, reflecting higher tear evaporation in DED patients. Patients who have shorter Schirmer I test values tend to have higher TEWL values. Not only EDE but also ADDE patients may have increased tear evaporation.

Keywords: dry eye disease, tear evaporation, tewameter, transepidermal water loss

Increased tear evaporation (TE) and decreased tear production are the main causes of dry eye disease (DED).[1] Excessive TE results in tear hyperosmolarity, which is considered as the central mechanism causing ocular surface inflammation in DED development.[1] Current tests for the assessment of DED yield highly variable results and many of them have low sensitivity and specificity when used alone.[2] Therefore, the practitioner has to use several tools to evaluate tear production, tear film stability, ocular surface damage, and other subjective symptoms. Tear evaporation measurements using devices with a closed chamber system,[3–5] ventilating chamber system,[6] or infrared thermography[7] have been reported previously. However, direct measurement of TE is not currently feasible in clinical practice.

Tewameter TM300 (Courage & Khazaka Electronics GmbH, Cologne, Germany) is a noninvasive diagnostic tool widely used in dermatology clinics for evaluating the barrier function of the skin through the measurement of transepidermal water loss (TEWL) of the skin.[8–10] Higher values of TEWL are regarded as having compromised barrier function.[8] In DED patients, TE from the ocular surface may increase if the lipid barrier is defective, or may decrease if tear production is severely decreased and there is scarcity of tear film on the ocular surface.

We hypothesized that the Tewameter, which was originally developed for dermatologic evaluation, may be used for evaluation of DED patients and help identify pathomechanisms for DED. We assessed TEWL from the ocular area in patients with moderate to severe DED, classified as aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE), using the Tewameter TM300 and compared the values with those of healthy controls. We also evaluated the correlation between TEWL from the ocular area and other DED parameters.

Methods

Participants

This prospective, case-control study included 56 eyes of 28 patients with moderate to severe DED (Dry Eye Workshop dry eye severity level ≥ 2)[1] and 38 eyes of 19 age-matched healthy subjects as controls. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Seoul National University Bundang Hospital, South Korea. The inclusion criteria were as follows: (1) age 20 years or older, (2) dry eye severity level of 2 or more assessed by the Dry Eye Workshop[1] (for inclusion in the DED group), (3) absence of DED symptoms without presence of corneal damage

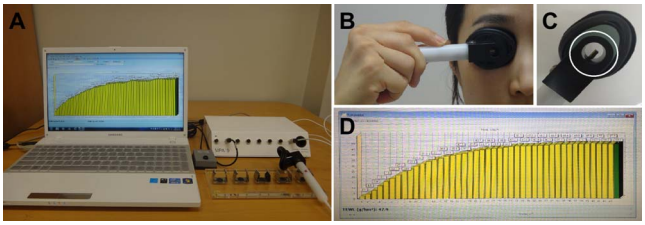

FIGURE 1. Measurement of TEWL from the ocular area using a Tewameter TM300. (**A**) The Tewameter was connected to a computer. (**B**) Measurement of TEWL from the ocular area using custom made goggles, which are tightly fitted to the periocular area. (**C**) Custom made probe of the Tewameter TM300 (*white circle line*, an open ventilated chamber system). (**D**) Bar graphs showing measurements taken at 1-second intervals until the values reach a plateau.

(for inclusion in the control group), and (4) patients in the DED group were divided into two subgroups: Schirmer I test results of 5 mm/5 min or less were regarded as ADDE subgroup and Schirmer I test results above 5 mm/5 min were regarded as EDE subgroup. The exclusion criteria included a history of meibomian gland dysfunction (MGD) above grade 2 (plugging with cloudy particulate or toothpaste-like fluid following compression of the lid margin with moderate or hard pressure),[11,12] Sjogren's syndrome, contact lens use, history of ocular surgeries within the past 6 months, active ocular surface conditions that may affect tear film stability, systemic disease or medication use that may cause DED, and skin disease that may affect evaporation. Subjects who used eye drops other than artificial tears, who had punctal plugs, and who were pregnant at the time of the study were also excluded. As MGD patients are expected to have increased TE, we excluded MGD patients with grade 2 or above to eliminate the main effect of MGD on TE. Potential participants were screened for eligibility and written informed consent was sought from each participant by an investigator.

TEWL From the Ocular Surface and Periorbital Skin

In this study, the Tewameter TM300 was used to measure TEWL from the ocular area. The original probe of the Tewameter TM300 indirectly measures the density gradient of water evaporation from the skin by using two pairs of sensors (temperature and relative humidity) located inside the open hollow cylinder. Using a customized adapter cap, which is similar in appearance to a swimming goggle, TEWL from the ocular surface and surrounding periocular skin can be measured with an open ventilated chamber system (Figs. 1A–C). The participant was seated and was instructed to look forward with their eyes open. An experienced investigator (HEJ), trained in the use of the device, performed the TEWL measurements at 1-second intervals until the values reached a plateau (Fig. 1D). The average of five values was used for further analyses. The measurements were performed in an observation room at an ophthalmology clinic, which had a relatively constant room temperature (24°C–26°C) and relative humidity (35°C–45 °C), after a 10-minute equilibration period.

Dry Eye Parameters (Tear Osmolarity, Tear Break-Up Time, Corneal and Conjunctival Staining Score, and Schirmer I Test) and Symptom Score (Ocular Surface Disease Index [OSDI] and Visual Analogue Scale [VAS])

Other DED parameters were also evaluated in the same room, as described above. Tear osmolarity was measured using a handheld device (TearLab Osmolarity System; TearLab Corp., San Diego, CA, USA). Tear samples (50 nL) were collected from the inferior lateral meniscus immediately following TEWL measurements and were simultaneously analyzed. A 5 minute Schirmer-I test, without anesthesia, was performed using sterile strips (Color Bar; EagleVision, Memphis, TN, USA). The Schirmer strip was placed at the notch of the inferior fornix and removed 5 minutes later. The values are reported as millimeters of wetting. The ocular surface was stained with fluorescein by introducing a wetted Fluomet (1 mg Fluorescein Sodium Ophthalmic Strip; Bausch & Lomb, Rochester, NY, USA) into the inferior fornix and the participant was instructed to blink forward. The tear break-up time (TBUT) was measured by recording the time taken for any dry spot to form over the tear film from the moment of eye opening. The corneal and conjunctival staining scores were graded according to the Oxford score system, following an examination with a slit lamp equipped with a yellow barrier filter and cobalt blue illumination. The OSDI questionnaire (Allergan, Inc., Irvine, CA, USA) consists of 12 questions related to symptoms within the past week and yields scores ranging from 0 (least severe) to 100 (most severe). The VAS system consisted of three questionnaires, each with an answer scale ranging from 0 (none) to 10 (very severe), respectively, for dryness, foreign-body sensation, and pain. Therefore, the total VAS score ranged from 0 to 30.

Statistical Analysis

The data were analyzed using SPSS software version 22.0 (SPSS, Inc., Chicago, IL, USA). A Mann-Whitney *U* test was used to compare TEWL and other DED parameters between DED and control groups and between the two subgroups. Fisher's exact test was used to compare the sex ratio between the two groups. Intraclass correlation coefficient (ICC) from the last five TEWL values after reaching a plateau was calculated. The correlation between TEWL and other DED parameters was determined using Pearson's correlation test and Spearman correlation test. A P value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of Participants

Of the 50 subjects, 47 (4 men and 43 women; mean age, 46.1 years; age range, 21–74 years) were included in the analysis. Three subjects were excluded due to measurement errors. The DED group included 56 eyes from 28 DED patients and the control group included 38 eyes from 19 subjects without DED. The ADDE subgroup included 38 eyes and the EDE subgroup included 18 eyes.

Comparison of TEWL and Other DED Parameters Between DED and Control Groups

Transepidermal water loss values for the DED group (63.0 ± 12.2 g/h/m^2) were significantly higher than those of the control group (54.7 ± 14.2 g/h/m^2; $P = 0.003$; Table 1). The TEWL showed acceptable agreement among the final five values (ICC = 0.99).

Tear osmolarity of the DED group (300.8 ± 16.2 mOsm/L) was significantly higher than that of the control group (292.7 ± 11.1 mOsm/L; $P < 0.001$). Tear break-up time of the DED group (2.3 ± 1.5 s) was significantly shorter than that of the control group (7.3 ± 2.4 s; $P < 0.001$). Corneal staining score of the DED group (0.8 ± 0.8) was significantly higher than that

Table 1. Characteristics of Patients With Dry Eye Disease and Control Subjects

Parameters	DED Group	Control Group	*P* Value*
Subjects (number of eyes)	28 (56)	19 (38)	
Age (y), mean (SD)	51 (15)	45 (13)	0.19
Sex (F:M)	26 : 2	17 : 2	0.99†
Temperature (°C), mean (SD)	25.1 (0.8)	25.1 (0.6)	0.93
Relative humidity (%), mean (SD)	40.2 (3.7)	41.0 (4.5)	0.54
TEWL (g/h/m^2), mean (SD)	63.0 (12.2)	54.7 (14.2)	**0.003**
Tear osmolarity (mOsm/L), mean (SD)	300.8 (16.2)	292.7 (11.1)	**<0.001**
TBUT (s), mean (SD)	2.3 (1.5)	7.3 (2.4)	**<0.001**
Corneal staining, mean (SD)	0.8 (0.8)	0.0 (0.0)	**<0.001**
Conjunctival staining, mean (SD)	1.1 (1.4)	0.03 (0.16)	**<0.001**
Schirmer I test (mm/5 min), mean (SD)	5.7 (3.7)	10.9 (7.9)	**<0.001**
OSDI score, mean (SD)	33.1 (16.7)	4.1 (5.4)	**<0.001**
VAS score, mean (SD)	5.4 (2.1)	0.6 (0.9)	**<0.001**

Bold numbers indicate statistically significant results.
* Mann-Whitney *U* test.
† Fisher's exact test.

Table 2. Comparison of Signs and Symptoms in the Subgroups Between ADDE and EDE Patients

Parameters	ADDE Group	EDE Group	*P* Value*
Number of eyes	38	18	
Age (y), mean (SD)	53 (13)	46 (16)	0.103
Sex (F:M)	35:3	17:1	0.99†
Temperature (°C), mean (SD)	25.1 (0.9)	25.0 (0.6)	0.529
Relative humidity (%), mean (SD)	40.2 (3.3)	40.2 (4.4)	0.992
TEWL (g/h/m^2), mean (SD)	64.0 (10.7)	61.1 (14.9)	0.409
Tear osmolarity (mOsm/L), mean (SD)	301.8 (18.3)	298.6 (10.6)	0.487
TBUT (s), mean (SD)	2.2 (1.5)	2.5 (1.5)	0.505
Corneal staining, mean (SD)	0.9 (0.9)	0.7 (0.8)	0.436
Conjunctival staining, mean (SD)	1.4 (1.6)	0.6 (0.9)	**0.047**
Schirmer I test (mm/5 min), mean (SD)	3.7 (1.0)	9.8 (4.0)	**<0.001**
OSDI score, mean (SD)	33.98 (16.97)	31.30 (16.57)	0.580
VAS score, mean (SD)	5.2 (2.0)	5.8 (2.3)	0.349

Bold numbers indicate statistically significant results.
* Mann-Whitney test.
† Fisher's exact test.

of the control group (0.00 ± 0.00; $P < 0.001$). Conjunctival staining score of the DED group (1.1 ± 1.4) was significantly higher than that of the control group (0.03 ± 0.16; $P < 0.001$) and Schirmer I test values of the DED group (5.7 ± 3.7 mm) were significantly lower than those of the control group (10.9 ± 7.9 mm; $P < 0.001$). The OSDI of the DED group (33.1 ± 16.7%) was significantly higher than that of the control group (4.1 ± 5.4%; $P < 0.001$). Finally, the VAS of the DED group (5.4 ± 2.1) was significantly higher than that of the control group (0.6 ± 0.9; $P < 0.001$).

Subgroup Analysis (ADDE Subgroup Versus EDE Subgroup)

A cutoff value of 5 mm/5 min was used to categorize the eyes with DED into the ADDE subgroup ($n = 38$) and EDE subgroup ($n = 18$). As shown in Table 2, there were no significant differences between the two subgroups in terms of age, sex, temperature, and relative humidity. Conjunctival staining score (1.4 ± 1.6, 0.6 ± 0.9; $P = 0.047$) was significantly higher and Schirmer I test value (3.7 ± 1.0, 9.8 ± 4.0 mm; $P < 0.001$) was significantly lower in the ADDE subgroup compared with the EDE subgroup. There were no significant differences in the other DED signs and symptoms between the two subgroups. Although there was no significant difference, mean TEWL was higher in the ADDE subgroup (64.0 ± 10.7 g/h/m^2) compared with the EDE subgroup (61.1 ± 14.9 g/h/m^2; $P = 0.409$).

Correlation Between TEWL and DED Parameters

Transepidermal water loss measured with both eyes open was found to be significantly correlated with TBUT ($r = -0.280$, $P = 0.006$; Fig. 2A), corneal staining score ($r = 0.262$, $P = 0.011$; Fig. 2B), and OSDI ($r = 0.249$, $P = 0.016$; Fig. 2C; Pearson's correlation test) in all participants. However, there was no correlation of TEWL with conjunctival staining score ($r = 0.146$, $P = 0.160$), Schirmer I test value ($r = -0.229$, $P = 0.099$), tear osmolarity ($r = 0.026$, $P = 0.865$), or VAS score ($r = 0.144$, $P = 0.166$) for all participants.

In the DED group, Schirmer I test value was significantly correlated with TEWL ($r = -0.273$, $P = 0.044$; Fig. 3A), while the other DED parameters were not significantly correlated with TEWL. In the EDE subgroup, TBUT ($r = -0.539$, $P = 0.021$; Fig. 3B) was significantly correlated with TEWL, while the other DED parameters were not significantly correlated with TEWL. In the ADDE subgroup, there were no significant correlations between DED parameters and TEWL.

Receiver Operating Characteristic (ROC) Curve Analysis

The diagnostic results from the receiver operating characteristic (ROC) curve analysis are summarized in Figure 4. The area under the curve (AUC) of TEWL (0.671; 95% confidence interval [CI], 0.557–0.785) was similar to that of tear osmolarity (0.664; 95% CI, 0.553–0.775). Tear osmolarity showed a sensitivity of 55.4% and a specificity of 63.2% at a cutoff value of 295.5 mOsm/L. Transepidermal water loss from the ocular area showed a sensitivity of 60.7% and a specificity of 63.2% at a cutoff value of 61.65 g/m^{2}h. The VAS score demonstrated the greatest AUC (0.975; 95% CI, 0.951–0.999), followed by OSDI (0.972; 95% CI, 0.945–0.998). The VAS score showed a sensitivity of 82.1% and a specificity of 94.7% at a cutoff value of 2.5. The OSDI showed a sensitivity of 89.3% and a specificity of 89.5% at a cutoff value of 11.71.

Discussion

This study shows that TEWL from the ocular area, measured using a Tewameter with modified goggles, is significantly higher in DED patients compared with healthy subjects. The results also demonstrate a significant correlation between TEWL from the ocular area and conventional DED parameters, including TBUT, ocular staining score, Schirmer I test value, and OSDI score. Previous studies evaluating TE in DED patients have generally used a ventilating chamber with air flowing in and out,[5,13] and suggested the use of an evaporimeter as an alternative device to evaluate DED. However, these are complex devices for use in a clinical setting because they are research prototypes and measurement values are spread over a wide range due to differences in the measuring technique.[4,5,13,14] We used a Tewameter TM300, which is a dermatology instrument with an open ventilated chamber system and equipped with custom made goggles to tightly fit the probe to the periocular area. With a hand-held probe, the modified Tewameter can

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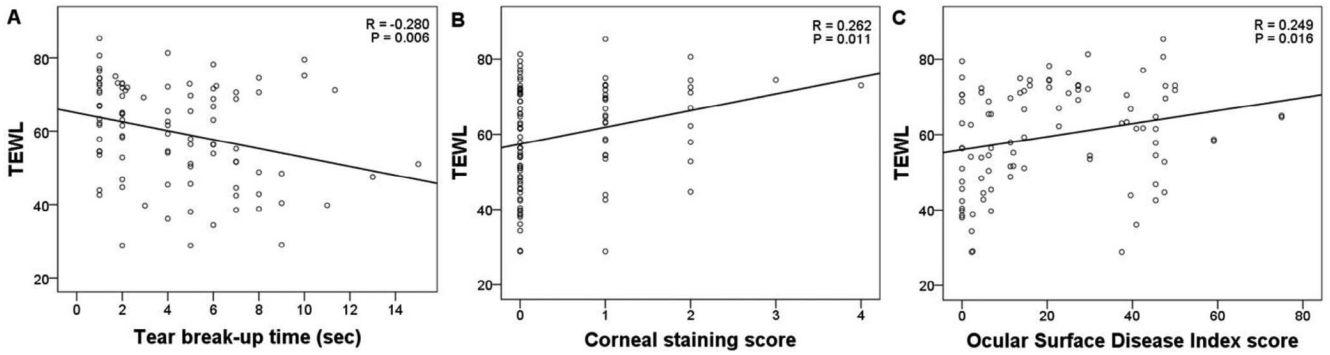

Figure 2. Correlation between TEWL and TBUT (**A**), corneal staining score (**B**), and OSDI score (**C**) in all participants ($n = 94$). Transepidermal water loss was significantly negatively associated with TBUT ($r = -0.280$, $P = 0.006$) and significantly positively correlated with corneal staining ($r = 0.262$, $P = 0.011$) and OSDI scores ($r = 0.249$, $P = 0.016$). Data were analyzed using a Pearson's correlation test.

continuously measure TEWL at 1-second intervals. Thus, the examiner may acquire data after the TEWL values reach a plateau, rather than acquiring a single point value.

Most previous studies have generally demonstrated that TE is elevated in DED patients,[4,15–17] while some have reported a decreased TE in DED patients.[3,18] In accordance with former studies, our results showed significantly higher TEWL values for the DED group and TEWL was negatively correlated with the Schirmer I test value in the DED group. In other words, ADDE patients tend to have higher TEWL values. As we used the Schirmer I test to divide DED group into two subgroups, the Schirmer I test value was significantly lower in the ADDE subgroup. Moreover, the conjunctival staining score was significantly higher in the ADDE subgroup than in the EDE subgroup. Failure of water secretion by the conjunctiva in ADDE patients may affect conjunctival damage. We considered that patients in the ADDE subgroup in our study may have higher severity of DED than the EDE subgroup. Although there was no significant difference in mean TEWL values between the two subgroups, it was higher in the ADDE subgroup than in the EDE subgroup. This is partially due to DED severity rather than type of DED. Clinically, it is quite difficult to classify DED patients into ADDE and EDE types, even though practitioners can classify DED through dominant causes. Our results suggest that most DED patients may have increased TE resulting from surface inflammation and loss of tear film stability, irrespective of DED type.

Several researchers have reported TE measurements using various devices.[4,5,14,19,20] However, there are few reports on the evaluation of correlation between TE and other DED parameters. In our study, ocular TEWL showed significant correlation with TBUT, corneal staining score, and OSDI in all participants. It is notable that subjects with short TBUT showed higher ocular TEWL. Tear break-up time has been used to evaluate tear film stability.[2] Increased TEWL may reflect a dysfunctional lipid layer, as well as tear film instability. Moreover, patients who have a higher corneal staining score are expected to have an unstable tear film. This can also be exlained by the relationship between ocular TEWL values and corneal staining score, which was observed in our study. Interestingly, not only signs of DED but also the symptoms described by OSDI showed correlation with ocular TEWL values.

In our study, AUC of TEWL from the ocular area was 0.671 and showed a 60.7% sensitivity and 63.2% specificity at a cutoff value of 61.65 g/h/m^2. The parameters that showed the greatest AUC values were VAS (0.975) and OSDI (0.972). These values may have been affected by selection bias, because we classified patients without DED symptoms as controls. Among other DED parameters, tear osmolarity demonstrated similar

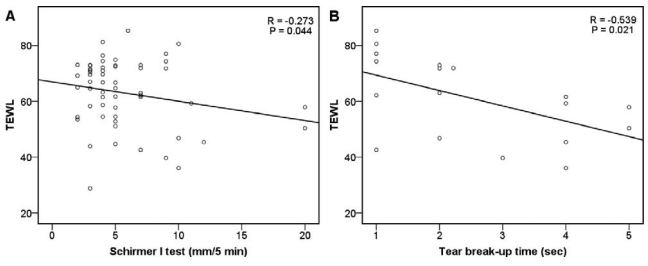

Figure 3. Correlation between TEWL and Schirmer I test (**A**), and TBUT (**B**) in DED group. (**A**) Transepidermal water loss was significantly negatively correlated with the Schirmer I test in the DED group ($n = 56$; $r = -0.273$, $P = 0.044$). (**B**) Transepidermal water loss was significantly negatively correlated with TBUT in the EDE subgroup ($n = 18$; $r = -0.539$, $P = 0.021$). Data were analyzed using a Spearman correlation test.

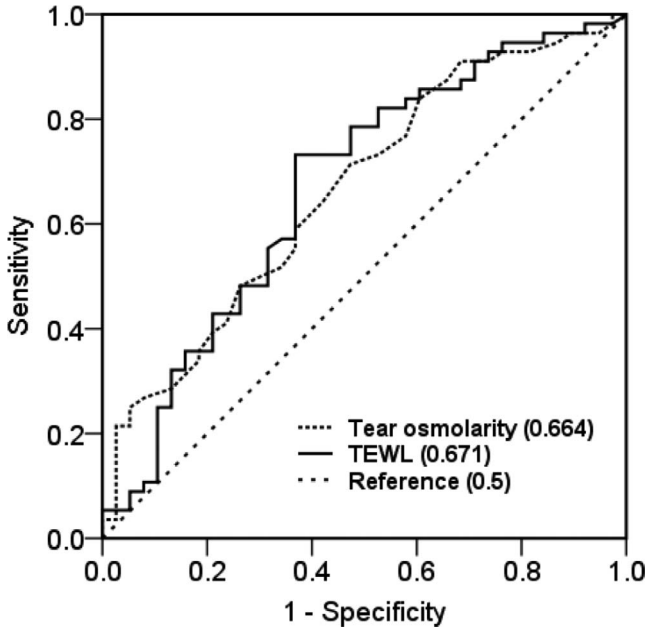

Figure 4. Reciever operating characteristic curves for tear osmolarity and TEWL from the ocular area. The area under the curve of TEWL (0.671; 95% CI, 0.557–0.785) was similar to that of tear osmolarity (0.664; 95% CI, 0.553–0.775).

AUC, sensitivity, and specificity as TEWL (AUC = 0.664; sensitivity = 55.4% and specificity = 63.2% at a cutoff value of 295.5 mOsm/L). Currently, tear osmolarity is believed to be the best single metric to diagnose and assess DED, due to its linearity, objectivity, quantitative nature, and operator-independence.[2,21,22] Tear osmolarity threshold values ranging from 305 mOsm/L[23] to 316 mOsm/L have been reported.[24] Currently, a value of 308 mOsm/L is the widely accepted threshold for discriminating between healthy eyes and those presenting with early stages of DED.[24,25] Using a tear osmolarity threshold of 316 to 317 mOsm/L, the reported sensitivity varied from 59%[26] to 81%[16] and the specificity varied from 78%[27] to 94%.[26] In our study, at a cutoff of 308 mOsm/L, tear hyperosmolarity exhibited 23.2% sensitivity, 97.4% specificity, and 92.3% positive predictive value. Compared with previous studies, these relatively lower cutoff values and sensitivity of tear osmolarity may have been influenced by the inclusion of patients with less severe DED in the study and may be related to the fact that tear osmolarity increases in proportion to the severity of DED.[21,23] Similar to tear osmolarity, selection bias should be considered while interpreting the TEWL values in this study.

Our study has some limitations. First, TEWL from the ocular area includes evaporation from not only the ocular surface but also from the periocular skin. Measurement error due to evaporation from the skin of the lid margin can be minimized by subtracting values acquired from closed eyes[4,13,14,20,28,29] and/or using petroleum jelly on the periocular skin,[6,14] as reported previously. However, in our results, TEWL from the ocular area showed significant differences between DED patients and normal controls. Although the data does not exclusively represent TE from the ocular surface, this suggests that there is excessive water evaporation from the ocular area in DED patients and further implies that not only the evaluation of TE from the ocular surface but also the TEWL from the ocular area may be meaningful. As DED is a multifactorial disease and the eyelids include a meibomian gland structure, it is noteworthy that evaluating evaporation from the periocular skin may be important. We plan to measure ocular TEWL that reflects true TE. Second, even though we did classify the DED group into two subgroups and excluded patients with Sjogren's syndrome and moderate to severe MGD, TEWL of each subgroup could not represent themselves. However, included patients are those who can meet easily in clinical situation. Significant differences in TEWL measurements in such patients are notable. Studies including patients with variable degrees of disease severity are necessary to identify a more exact DED pathomechanism. Third, temperature and humidity were not strictly controlled during TEWL measurements. However, because it is well known that TE is affected by relative humidity,[30,31] we monitored temperature and relative humidity simultaneously and verified that they were maintained within a certain range and were not significantly different between the two groups. Lastly, we did not include DED severity as one of the factors in the study. However, this is the first trial to evaluate TEWL from the ocular area in DED patients. We report encouraging results and suggest a broader application of this modified dermatology instrument in DED patients.

In conclusion, TEWL from the ocular area was significantly higher in DED patients than in controls, and correlated with TBUT, corneal staining score, and OSDI scores in all participants. Ocular TEWL was negatively correlated with the Schirmer I test value in the DED group. Aqueous deficient dry eye and EDE patients may have increased tear evaporation, possibly resulting from surface inflammation and loss of tear film stability. We propose the possibility of considering ocular TEWL as a potential parameter for diagnosis and monitoring of DED. For this to be validated and used in ophthalmology, further studies evaluating the repeatability and accuracy of the method are needed.

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