Automated Measurement of Tear Meniscus Height with the Kowa DR-1α Tear Interferometer in Both Healthy Subjects and Dry Eye Patients

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PURPOSE. To develop and assess a method for quantitation of lower tear meniscus height (TMH) with the Kowa DR-1α tear interferometer.

METHODS. Sixty-nine eyes of 49 men and 20 women (36 healthy volunteers, 33 patients with aqueous-deficient dry eye [ADDE]; mean age ± SD, 50.0 ± 14.0 years) were enrolled. TMH of each subject was measured by two observers both with DR-1α and newly developed software and with anterior-segment swept-source optical coherence tomography (SS-OCT). Intraoperator repeatability and interoperator and intersession reproducibility of measurements were assessed based on the within-subject SD (Sw), coefficient of variation (CV), and intraclass correlation coefficient (ICC). Agreement between the two devices was assessed by regression and Bland-Altman analysis.

RESULTS. The CV for system repeatability of DR-1α was <2.0%. The CV for intraoperator repeatability and interoperator and intersession reproducibility for DR-1α measurements was ≤9.6%, ≤4.5%, and ≤4.4% in healthy subjects, respectively, and ≤16.8%, <9.8%, and <10.3% in ADDE patients. All corresponding ICC values were >0.87 in healthy subjects and >0.48 in ADDE patients. Bland-Altman plots indicated a high level of agreement between the two devices. Schirmer test value was significantly correlated with interferometric TMH in both healthy subjects (β = 0.59, P < 0.001) and ADDE patients (β = 0.47, P = 0.017).

CONCLUSIONS. Tear interferometry allows measurement of TMH as reliably as does SS-OCT. DR-1α may inform not only the diagnosis of dry eye disease but also identification of disease subtype.

Keywords: tear film, dry eyes, tear meniscus, tear interferometry, meibomian gland

Dry eye disease (DED) is a global clinical problem, with a reported prevalence of 5% to 50% among adults and afflicting >30 million people in the United States alone. It is one of the most frequent causes of patient visits to eye care practitioners. According to the definition of DED by the International Dry Eye Workshop II (DEWS II), DED is a multifactorial disorder of the ocular surface that is characterized by a loss of homeostasis of the tear film and is accompanied by ocular symptoms in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiologic roles.

The tear meniscus is a reservoir of tear fluid that contains 75% to 90% of the total tear volume. Measurement of tear meniscus height (TMH) has proved informative for DED diagnosis, showing a relatively high sensitivity and specificity. TMH also correlates well with symptoms and tear function such as the Schirmer test. Several methods have been applied to measure TMH including those based on the use of a graticule, fluorescein staining, reflective meniscometry, the TearScope Plus (Keeler) instrument, optical coherence tomography (OCT), and keratography. TMH measured by OCT has been described as reliable for diagnosis of DED with high sensitivity and specificity.

We previously reported that the amounts of aqueous layer and lipid layer of the tear film compensate with each other for deficiencies in order to maintain homeostasis of the tear film. Thus, both these tear film components would be examined in the evaluation of DED. To date, however, tear interferometry has been applied only to observe the kinetics of the lipid layer of the tear film, with Schirmer test or fluorescein staining still being required for evaluation of the volume of tear fluid. The development of a new system would be required to allow evaluation of both the lipid and aqueous layers of the tear film noninvasively based on interferometry with one instrument. In this study, the tear volume was evaluated by measuring TMH, which is automatically recognized and analyzed in order to ensure the high accuracy of the measurement. The DR-1α tear interferometer (Kowa, Tokyo,
Japan) allows evaluation of the lipid layer of the tear film but has not previously been shown to be used in assessing the aqueous layer.\textsuperscript{19,20} The purpose of the present study was to develop a method for quantitation of TMH with the DR-1\textsubscript{a} instrument. To do this, we compared intraoperator repeatability as well as interoperator and intersession reproducibility of TMH measurement with newly developed software for DR-1\textsubscript{a} and by anterior-segment swept-source (SS) OCT (CASIA 2 instrument; Tomey, Aichi, Japan), which has been widely used and is a well-established method to measure TMH accurately. Also, we assessed the agreement of TMH between the two devices in both healthy subjects and patients with aqueous-deficient dry eye (ADDE).

METHODS

Algorithm Development

DR-1\textsubscript{a} was used to obtain lower tear meniscus images at the border between the cornea and lower eyelid with the “tear meniscus mode.” The optics for tear interferometric meniscometry (Fig. 1) result in visualization of a single obvious bright line when the instrument is focused on the edge of the lower eyelid, likely as a result of the light from DR-1\textsubscript{a} being vertically reflected at the base of the rounded surface of the tear meniscus (Fig. 2). The brightness histogram for the lower tear meniscus image was used to measure TMH in a noninvasive manner (Figs. 3A, 3B). The bright area of the meniscus image consists of three components: a specular line (SL) that is a specular reflection of the illuminating light, and brighter interferometric fringe regions (BIFRs) located above and below the SL (Figs. 3C, 3D) The bright area of the meniscus image consists of three components: a specular line (SL) that is a specular reflection of the illuminating light, and brighter interferometric fringe regions (BIFRs) located above and below the SL (Figs. 3C, 3D). The interferometric fringe images are colored in a manner dependent on the thickness of the lipid layer of the tear film. We therefore used the maximal value from three color channels (red, green, and blue) as the brightness of each pixel to determine the optimal brightness histogram from color images as follows:

\[
V = \text{Max}(I_\text{R}, I_\text{G}, I_\text{B})
\]

where \(V\) is the determined brightness of the pixel and \(I_\text{R}, I_\text{G}, I_\text{B}\) are the values for the color channels of the pixel. We hypothesized that the height of the BIFRs would show a correlation with the curvature of the lower tear meniscus formed by the surface of pooled tear fluid, and that the determination of the curvature would depend on the amount of pooled tear fluid at the lower tear meniscus. According to this hypothesis, BIFRs corresponding to a smaller amount of pooled tear fluid would have a smaller height (Figs. 3C, 3E, 3F) than those corresponding to a larger amount of pooled tear fluid (Figs. 3D, 3G, 3H). In both cases shown in Figure 3, the amount of tear fluid pooled at the eyelid is sufficient to form BIFRs both above and below the SL. However, if the amount of tear fluid is reduced to the point that it is insufficient to form a complete meniscus, then the upper BIFR can be lost as a result of its approach to the SL. Even though ADDE patients may have a small tear volume, the disappearance of the upper BIFR does not occur in all cases. The heights of the upper and lower BIFRs can be extracted by adjustment of the threshold of pixel brightness so that the brightness increases sufficiently above the dark area (Figs. 3C, 3D). If the height is not sufficient for extraction of the upper BIFR, then the height of the upper BIFR is considered to be 0. We then calculated the sum of the heights of the SL and the upper and lower BIFRs as TMH, so that our TMH measurement algorithm would be applicable not only to healthy eyes but also to the eyes of patients with DED. We here designate this total height as the interferometric TMH.

In practical implementation, our software is not completely automated. For measurement of TMH with DR-1\textsubscript{a}, TMH is calculated at four points in an image that are selected by the operator by mouse-clicking on the display monitor, and the mean TMH is then calculated from these four values.
System Repeatability

In order to verify system repeatability for TMH measurement using our algorithm, we extracted four tear meniscus images (as discussed further below) randomly from all collected images, which are from different patients. For each image, we measured TMH 10 times, respectively, and calculated the mean, standard deviation (SD), and coefficient of variation (CV) for 10 measurements of TMH, with the TMH measurements performed as described below.

Sample Size Estimation

There are two main statistical comparisons in the present study: comparison of TMH measured by DR-1a with that measured by CASIA 2 in all our subjects, and comparison of TMH of normal subjects with that of ADDE patients. In a previous study,16 TMH of normal subjects and dry eye patients measured by SS-OCT was found to be 260.5 ± 56.6 and 183.5 ± 50.4 μm (means ± SD), respectively. We calculated the sample size for our study on the basis of these values, which were averaged to give a corresponding value for all subjects of 222.0 ± 53.6 μm.

With regard to the comparison of TMH measured by DR-1a or by CASIA 2 in all our subjects, we assumed that μ1 and σ1 are the mean and SD of TMH measured by DR-1a, and that μ2 and σ2 are the mean and SD of TMH measured by CASIA 2. Whereas we applied 222.0 ± 53.6 μm as the mean ± SD of TMH measured by CASIA 2, the mean and SD for TMH measured by DR-1a were estimated as follows. SD was assumed to be the same as that for CASIA 2 (σ1 = σ2 = σ = 53.6 μm), so that σd2 = 2 × σ2 and σd = 75.8 μm, where σd is SD for all measurements. On the other hand, the difference in the mean values between DR-1a and CASIA 2 was estimated to be 5%. In addition, the resolution of the meniscus image acquired by DR-1a is 15 μm per pixel, so that we allowed an error of 30 μm in pointing to the edge positions of TMH; that is, |μ1 - μ2| = (222.0 × 0.05) + (15 × 2) = 41.1 μm. This gives: Δ = |μ1 - μ2|/σd = 41.1/75.8 = 0.54. On the basis of these values, the calculation of sample size with a statistical power (1 - β) of 0.8 and α level of 0.05 in a paired t-test becomes: n = [(2zα - z1-β)/Δ]2 + zα2/2 = 28.8, where n is the required sample size, za is the normal deviate at a level of significance (za is 1.96 for 5%
Automated Measurement of Tear Meniscus Height

Outcome Measures

For all subjects, measurements were performed sequentially as follows: (1) Ocular symptom scores were determined with the Dry Eye–Related Quality of Life Score (DEQ5S) questionnaire.24
(2) The lower TMH was measured with DR-1zx and by SS-OCT (CASIA 2) in a random order.15 (3) The breakup time (BUT) of the tear film was measured after instillation of 1 μL of a preservative-free solution of 1% fluorescein into the conjunctival sac with the use of a micropipette. The subjects were asked to blink several times, BUT was determined three times with a stopwatch, and the mean of the three values was calculated. (4) Fluorescein staining of the cornea and conjunctiva was graded from 0 to 9 (van Bijsterveld’s grade).25 (5) Schirmer test was conducted without topical anesthesia.26
All examinations with the exception of those made with the DR-1zx and SS-OCT devices were performed by the same examiner (R.A.).

TMH Measurement

Images were obtained from all subjects with the DR-1zx and CASIA 2 instruments by two trained nonphysician medical staff. The DR-1zx tear interferometer was set to “tear meniscus mode” so as to acquire a photograph of the lower tear meniscus with the same light source as used for capture of the interferometric image of the lower tear meniscus was observed noninvasively by focusing on the lower lid margin (Fig. 2). The capture size was 7.2 mm in width and 8.0 mm in height.

Measurement of TMH by SS-OCT was performed at high speed in a single vertical scan with the anterior-segment lens and image capture software in the “tear meniscus mode” (Fig. 4). The CASIA 2 instrument is an upgraded version of the SS-1000 device and performs 16 radial scans at 1-mm intervals in the “tear meniscus mode.”15 It was used to obtain 16 cross-sectional images of the anterior segment in 0.3 second. A scan with an angle of 90° visualized the lower tear meniscus. Final OCT images consisted of 800 A-scans, with an axial resolution of ~10 μm and a transverse resolution of ~30 μm.

The same region, immediately below the corneal vertex and centered on the inferior cornea and lower eyelid, was imaged with both devices. The corneal vertex was determined by the position of specular reflection. The subject was asked to blink naturally during both imaging procedures while looking straight at a fixation target within the device. Images were captured within the first second immediately after a blink. One image was obtained from each patient with each of the two devices and by each of the two staff members, for a total of four images per eye. The same two staff members, who were blinded to each other’s results, took measurements in random order from the two photographs obtained from each subject with each device. For DR-1zx images, the newly developed software described above was applied and the lower interferometric TMH was measured. In this study, to investigate the intraoperator repeatability, one examiner (examiner 1) performed eight times measurements, and to investigate the intersession reproducibility, one more examiner (examiner 2) performed eight times measurements on two occasions. For the SS-OCT measurements, the software calipers provided with the device were used, with the outline of the tear meniscus being plotted from seven points.15 The mean and SD values of TMH were determined from the four measurements for each device. A week later, one member of the trained medical staff repeated the measurements for the previously obtained images, also in random order, in order to determine the intersession reproducibility of measurements.

Subjects

Healthy subjects and patients with ADDE were prospectively enrolled in this observational cross-sectional study at Itoh Clinic in Saitama, Japan. Healthy individuals were excluded if they had a history of refractive surgery; had ever been diagnosed with DED21 or meibomian gland dysfunction;22 manifested symptoms of DED, an ocular surface abnormality (including conjunctivochalasis or substantial anterior blepharitis), or a lid abnormality; had ever worn contact lenses; or currently had any other eye or systemic disease. ADDE was diagnosed on the basis of the criteria proposed by the Dry Eye Research Group in Japan.23 The right eye was subjected to measurements. No eye drops were applied for at least 4 hours before examinations. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Itoh Clinic. Written informed consent was obtained from each participant before examinations. Subjects were tested between 10:00 AM and 12:00 PM. Both room temperature (21.6 ± 1.2°C) and humidity (40.4 ± 3.3%) were relatively constant. The two instruments for comparison were placed side by side in the same room so as to shorten the examination session.

level of significance), z1−β is the normal deviate at 1 − β% power with β% of type II error (0.84 at 80% power).

For comparison of TMH of normal subjects with that of ADDE patients, we used the mean and SD values from the previous study16 directly; that is, \( \sigma_w^2 = \sigma_1^2 + \sigma_2^2 = 56.6^2 + 77.0^2 \), so that \( \sigma_w = 75.8 \) μm. The difference between the mean values of normal subjects and dry eye patients was calculated as 260.5 – 183.5 = 77.0 μm, with the result that \( \Delta = 77.0/75.8 = 1.02 \). The calculation of sample size for a statistical power (1 − β) of 0.8 and z level of 0.05 in an unpaired Student’s t-test thus becomes \( n = \frac{2(\sigma_w – z_{1-\beta})/\Delta^2 + z_{\beta/2}^2}{\sigma_w} = 12.6 \).

On the basis of the above calculations, we considered that a sample size of 30 would be sufficient for each of the normal subject and ADDE patient groups in the present study.

FIGURE 4. Lower tear meniscus imaged by anterior-segment SS-OCT with CASIA 2. Pooled tear fluid is detected as a triangular shape at the region between the cornea and lower eyelid.

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**Statistical Analysis**

Statistical analysis was performed with the use of Microsoft Excel 2016 (Microsoft Japan, Tokyo, Japan) and SPSS software version 24 (IBM Japan, Tokyo). Unpaired Student’s *t*-test was applied to compare parameters between the healthy subjects and ADDE patients. For each eye, mean TMH for each device was calculated from the four measurements (made by the two observers on the two images in the first session). For determination of intraoperator repeatability, we calculated within-subject SD (Sw), test–retest repeatability, CV, and the intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) for three sets of eight times measurements made by the two examiners with each device.

Test-retest repeatability was defined as $2.77 \times Sw$, on the basis of the interval within which 95% of the differences between measurements are expected to lie. The CV was calculated by dividing $Sw$ by the overall mean. For determination of interoperator or intersession reproducibility, the mean and SD values for the two measurements made by both examiners or in both sessions were calculated along with the variables described above (Sw, test–retest repeatability, CV, and ICC). Consistency between the two measurement methods was assessed by determination of Sw, test–retest repeatability, CV, and ICC. Receiver operating characteristic (ROC) curve analysis with calculation of the area under the curve (AUC) was performed to assess the accuracy of TMH determined with DR-1z for differentiation of ADDE patients from healthy subjects. A Bland-Altman plot was also constructed to compare the results from the two devices. The correlation between interferometric TMH and other tear film parameters was assessed by Pearson’s correlation coefficient analysis, after which the relation between TMH and correlated parameters was evaluated by multiple linear regression analysis. Multivariate analysis of covariance (ANCOVA) was applied to evaluate the correlation between TMH and Schirmer test value with adjustment for the covariates described above (Sw, test–retest repeatability, CV, and ICC).

Intraoperator repeatability was similar for both DR-1z and SS-OCT in healthy subjects and ADDE patients. Sw for ADDE patients was greater than for healthy subjects. The mean SD age of all 69 subjects included in the study was 50.0 ± 14.0 years (range, 23–77 years), with the corresponding values for the 36 healthy subjects and 33 ADDE patients being 43.5 ± 9.4 years (range, 23–57 years) and 51.7 ± 15.4 years (range, 24–77 years), respectively (*P* = 0.0094, unpaired Student’s *t*-test). The characteristics of the right eyes of the study subjects are shown in Table 1, and the mean SD values of TMH determined with the DR-1z and CASIA 2 devices are presented in Table 2.

### Table 2. Mean ± SD for Lower TMH Measured by DR-1z and CASIA 2

<table>
<thead>
<tr>
<th>Image</th>
<th>Normal Subjects, n = 36</th>
<th>ADDE Patients, n = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DR-1z, μm</td>
<td>CASIA 2, μm</td>
</tr>
<tr>
<td>Observer 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First image</td>
<td>240.5 ± 63.5</td>
<td>247.5 ± 63.1</td>
</tr>
<tr>
<td>Second image</td>
<td>244.6 ± 63.9</td>
<td>252.4 ± 62.3</td>
</tr>
<tr>
<td>Observer 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First image, second session</td>
<td>249.2 ± 63.4</td>
<td>255.5 ± 60.3</td>
</tr>
<tr>
<td>Second image, second session</td>
<td>248.0 ± 70.0</td>
<td>254.4 ± 60.2</td>
</tr>
</tbody>
</table>

The newly developed software for measurement of the lower TMH with DR-1z showed high repeatability (Table 3), with no misevaluation for three of four images and only one misevaluation for the remaining image. The resolution of the camera system of DR-1z is 15 μm, and the one mistake resulted in an SD of 4.74 μm and CV of 1.87% for the 10 measurements of image 2.

### Results

The mean ± SD age of all 69 subjects included in the study was 50.0 ± 14.0 years (range, 23–77 years), with the corresponding values for the 36 healthy subjects and 33 ADDE patients being 43.5 ± 9.4 years (range, 23–57 years) and 51.7 ± 15.4 years (range, 24–77 years), respectively (*P* = 0.0094, unpaired Student’s *t*-test). The characteristics of the right eyes of the study subjects are shown in Table 1, and the mean ± SD values of TMH determined with the DR-1z and CASIA 2 devices are presented in Table 2.
Interoperator Reproducibility

The mean ± SD, Sw, 2.77Sw, CV, and ICC values for interoperator reproducibility of TMH measurement for the two DR-1 images and two CASIA 2 images are presented in Table 5. The Sw and CV values for DR-1 were similar to those for SS-OCT, indicating that interoperator reproducibility for DR-1 was as good as that for SS-OCT. Interoperator reproducibility with each device was higher for healthy subjects than for ADDE patients.

Intersession Reproducibility

The mean ± SD, Sw, 2.77Sw, CV, and ICC values for intersession reproducibility of TMH measurement are also shown in Table 5. The CV and ICC values for DR-1 over the two sessions were indicative of high intersession reproducibility. Again, intersession reproducibility with each device was higher for healthy subjects than for ADDE patients.

Comparison of TMH Between Healthy Subjects and ADDE Patients

TMH in healthy subjects (DR-1, 245.57 ± 61.33 μm; CASIA 2, 252.45 ± 57.78 μm) was significantly greater than that in ADDE patients (DR-1, 180.82 ± 25.91 μm; CASIA 2, 195.94 ± 21.87 μm; unpaired Student’s t-test, P = 4.0 × 10^−7 for DR-1 and 1.5 × 10^−4 for CASIA 2). ROC curve analysis for TMH determined with DR-1 in healthy subjects and in ADDE patients yielded a cutoff value of 180 μm (AUC of 0.79, with a 95% CI of 0.66–0.88, 73% sensitivity, and 75% specificity) for distinguishing between the two groups of subjects (Fig. 5).

Comparison Plot for DR-1 Versus CASIA 2

TMH measured by DR-1 was directly compared with that measured by CASIA 2 (Fig. 6). The two sets of measurements agreed well with each other for all subjects (DR-1, 214.61 ± 57.56 μm; CASIA 2, 225.42 ± 52.46 μm; P = 0.25, paired Student’s t-test) as well as for healthy individuals (DR-1, 245.57 ± 61.33 μm; CASIA 2, 252.45 ± 57.78 μm) and ADDE patients (DR-1, 180.82 ± 25.91 μm; CASIA 2, 195.94 ± 21.87 μm) separately, with an overall correlation coefficient (r) of 0.96 and regression line of y = 1.05x – 23.18. The statistical power was verified as >0.8 for evaluation of both the correlation and differences between the two methods, so that these results are sufficiently comparable. TMH measurements for all subjects were also analyzed with a Bland-Altman plot (Fig. 7A). The difference in TMH values between DR-1 and CASIA 2 was thus plotted against the mean value of the measurements by both devices. This plot also revealed a high level of agreement between the two devices, with the mean ± SD difference between the two instruments being −10.8 ± 16.1 μm, which lies within the range including zero with a probability of 67%. In addition, as mentioned above with regard to system repeatability, the resolution for measurement probability of 67%. In addition, as mentioned above with regard to system repeatability, the resolution for measurement probability of 67%. In addition, as mentioned above with regard to system repeatability, the resolution for measurement probability of 67%. In addition, as mentioned above with regard to system repeatability, the resolution for measurement probability of 67%. In addition, as mentioned above with regard to system repeatability, the resolution for measurement probability of 67%. In addition, as mentioned above with regard to system repeatability, the resolution for measurement probability of 67%. 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The agreement between data recorded with the two devices is also evaluated in Table 6. For all measurements, the CV was 9.7% in healthy subjects and 13.8% in ADDE patients.
patients, with the respective ICC values being 0.97 and 0.95, indicative of a high correlation between the two instruments.

**Correlation Analysis**

The factors influencing TMH were analyzed by calculation of Pearson’s correlation coefficient. TMH showed significant positive correlations with BUT and Schirmer test values as well as negative correlations with age, DEQS, and fluorescein staining scores for all study subjects (Table 7). TMH showed a positive correlation with Schirmer test value for both healthy subjects and ADDE patients, as well as negative correlations with age and fluorescein staining score for ADDE patients (Table 7). Multiple regression analysis of the influence of these various parameters on TMH revealed that the Schirmer test value showed a significant positive correlation for all study subjects as well as healthy subjects and ADDE patients, as well as negative correlations with age, fluorescein staining score, and BUT. TMH and Schirmer test value showed a significant association in all study subjects as well as healthy subjects and ADDE patients separately (ANOVA $P < 0.001$, $< 0.001$, and $= 0.017$, respectively).

**DISCUSSION**

We have here developed a system for measurement of TMH by tear interferometry with the DR-1z instrument and demonstrated a high interoperator and intersession reproducibility for this system. The values for TMH obtained with DR-1z were highly similar to those obtained by anterior-segment SS-OCT as performed with the CASIA 2 device in both healthy subjects and patients with ADDE. The DR-1z interferometer thus allows evaluation of both the kinetics of the lipid layer of the tear film and the volume of tear fluid. It thereby provides important information not only for the diagnosis of DED but also for identification of the subtype of DED (aqueous deficient or evaporative).

We applied tear interferometry to the evaluation of TMH. The greatest advantage of this method is that it allows noninvasive and automatic analyzing measurements of the tear film. The mean ± SD value of TMH obtained with DR-1z in healthy subjects was 245.57 ± 61.33 μm, which corresponds well with previous measurements obtained by OCT or with the Keratograph 5M instrument. One of the most common methods for TMH measurement currently applied is fluorescein staining of the meniscus, but this is an invasive approach and shows high interobserver variability. A convenient scale for measurement of TMH has also been developed, but again such measurements show not insubstantial variation among examiners, possibly because the scale is not fine enough for precise measurements. Measurement of TMH based on photographs of fluorescein staining was found to be relatively reliable, but the fact that the measurements are not immediately available limits the clinical application of this approach. Tear meniscometry was introduced as a noninvasive and precise method for evaluation of the tear meniscus but again such measurements show not insubstantial variation among examiners.

The recent development of anterior-segment OCT provided a new means to evaluate the tear meniscus but again such measurements show not insubstantial variation among examiners, possibly because the scale is not fine enough for precise measurements. Measurement of TMH based on interferometric reflection pattern and intensity histogram and is automated. The measurement of interferometric TMH is thus highly repeatable based on our results and can be performed by trained nonphysician medical staff.
Automated Measurement of Tear Meniscus Height

The mean ± SD values for TMH obtained with the DR-1 and CASIA 2 instruments in our study were 245.57 ± 61.35 and 252.45 ± 57.78 μm for healthy subjects and 180.82 ± 25.91 and 195.94 ± 21.87 μm for ADDE patients, respectively. The values measured by DR-1 were thus lower than those measured by CASIA 2 for both groups of subjects. Measurement of TMH by DR-1 is based on the recognition of three components of the interferometric image: the SL, upper BIFR, and lower BIFR. The measurement algorithm recognizes these three components by image analysis and measures the distance between the outer edges of the BIFRs as TMH. It is therefore important that the BIFRs be distinguished from the outer background regions (cornea and lower eyelid). For image analysis, the threshold for distinguishing each BIFR from the corresponding outer background region should be set as low as possible so as to detect the entire meniscus. However, if the threshold is set too low, a portion of the outer background region might also be falsely identified as part of the tear meniscus, resulting in a measurement error. We therefore set the threshold so as to recognize ~60% of the BIFR peak. In contrast, measurement of TMH visually from tomographic images provided by CASIA 2 is based on the distance between the two outer edges of the tear meniscus, which is equivalent to measurement by DR-1 based on recognition of 100% of the BIFRs.

The reproducibility of TMH measurement by SS-OCT instruments other than CASIA 2 has been determined,15,16,32 with CV values for inter-session reproducibility of 7.1% to 19.7% and for inter-operator reproducibility of 6.4% to 10.7% for healthy subjects, and corresponding values of 23.9% and 14.5% for dry eye patients. All of these values are higher than the corresponding ones we obtained with CASIA 2 in the present study (Table 5). We found that the CV values for inter-session and inter-operator reproducibility for CASIA 2 in dry eye patients were approximately twice those in healthy subjects, similar to the previous results for SS-OCT.15,16 Both inter-session and inter-operator reproducibility for DR-1 were lower than those for CASIA 2 but higher than those for SS-OCT in normal subjects were approximately the same as those for CASIA 2 in the present study. In ADDE patients, however, both inter-session and inter-operator reproducibility for DR-1 were lower than those for CASIA 2 but higher than those for SS-OCT in previous studies.15,16,32 For measurement of TMH with DR-1, the operator has to manually select four points on a meniscus image, so the measurement positions selected by different operators may not be the same, potentially resulting in a measurement error. In addition, even during repeated measurements of one meniscus image by the same operator, he or she might not always select the same points, possibly because of a distorted form of the meniscus or other practical reasons, which might again result in a measurement error. In order to avoid such the measurement error, all processing would be automated, including determining the measurement positions, which were performed manually in this study.

We analyzed the factors influencing TMH with univariate and multiple regression analysis (Table 7). After adjustment for the influence of confounding variables, we found that the interferometric TMH was significantly correlated with the Schirmer test value in both healthy subjects and ADDE patients.

Table 6. Agreement Between Measurements of Lower TMH by DR-1 and by CASIA 2

<table>
<thead>
<tr>
<th>Observer</th>
<th>Healthy Subjects, n = 36</th>
<th>ADDE Patients, n = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD, μm</td>
<td>2.77Sw, μm</td>
</tr>
<tr>
<td>Observer 1</td>
<td>246.2 ± 63.2</td>
<td>22.2</td>
</tr>
<tr>
<td>Observer 2</td>
<td>251.8 ± 63.5</td>
<td>19.4</td>
</tr>
<tr>
<td>All measurements</td>
<td>249.0 ± 63.4</td>
<td>24.1</td>
</tr>
</tbody>
</table>
Table 7. Pearson’s Correlation Coefficient and Standard Partial Regression Coefficient for TMH Determined with DR-1z and Tear Film Parameters for All Study Subjects, Healthy Subjects, and ADDE Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Subjects</th>
<th>Healthy Subjects</th>
<th>ADDE Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>−0.352</td>
<td>−0.060</td>
<td>−0.584</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>0.003*</td>
<td>0.73</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BUT</td>
<td>−0.476</td>
<td>−0.032</td>
<td>−0.187</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>&lt;0.001*</td>
<td>0.85</td>
<td>0.30</td>
</tr>
<tr>
<td>Fluorescein staining score</td>
<td>−0.463</td>
<td>0.000</td>
<td>−0.349</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>&lt;0.001*</td>
<td>1.0</td>
<td>0.047*</td>
</tr>
<tr>
<td>Schirmer test value</td>
<td>0.736</td>
<td>0.626</td>
<td>0.522</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*P < 0.05.

(Table 7). Previous studies have revealed a positive correlation between the Schirmer test value and the lower TMH and tear meniscus area measured by time-domain OCT. After the correction for confounding variables by ANCOVA, we did not detect a significant correlation between BUT and lower TMH in this study (Table 7), which is consistent with some previous findings but not with others. This discrepancy might be explained by the fact that BUT reflects the stability of the tear film rather than the quantity of tear fluid and that BUT is affected by not only the aqueous layer of the tear film but also the mucin and lipid layers. The use of fluorescein for determination of BUT also might alter the condition of the tear film. In contrast, interferometry allows visualization of the tear meniscus in its natural state and in real time. The repeatability of both BUT measurement and Schirmer test has also been found to be low to moderate, with ICC values of 58% and 43.8%, respectively, whereas that for TMH measurement by DR-1z was high (≥87% for healthy subjects).

After adjustment for the influence of confounding variables with ANCOVA, we found that the interferometric TMH was significantly correlated with age in ADDE patients but not in healthy subjects in this study (Table 7). Previous studies reported that lower tear meniscus values were negatively correlated with age using anterior-segment OCT, whereas that for TMH measurement by DR-1z was high (≥87% for healthy subjects).

Limitations of the present study include the small number of subjects. Establishment of a reliable procedure for interferometry-based measurement of TMH will require the performance of multicenter studies with larger numbers of subjects. We also measured TMH only at just below the center of the cornea. Evaluation of additional regions of the meniscus will be required positioning of the instrument for imaging, that is, the center of the cornea for determination of lipid layer thickness and tear film stability versus the lower eyelid for that of TMH. The relation between TMH and the stability of the tear film is of interest and will likely be addressed as an application of DR-1z in the future.

In conclusion, tear interferometry with the DR-1z system has the potential to allow diagnosis of DED as well as to identify the disease subtype. It therefore provides information required for determination of the treatment strategy necessary to compensate for deficiencies in tear film components. It allows monitoring of the balance between the lipid and aqueous layers of the tear film by not only evaluating the lipid layer but also measuring TMH automatically.

Acknowledgments

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References


