Article

Tear Strip Meniscometry and Its Clinical Application: Analysis of More Than 2000 Cases

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Purpose: To evaluate the association of strip meniscometry tear meniscus volume measurement with signs and symptoms related to dry eye.

Methods: This cross-sectional study enrolled 2234 consecutive outpatients and used dry eye symptomatology and related ocular surface examinations, including the Schirmer test, fluorescein tear film break-up time (BUT), corneal fluorescein vital staining and strip meniscometry. The strip meniscometry cut-off was estimated using a receiver operating characteristic analysis. The subjective symptoms consisted of six binarized items: dryness, fatigue, photophobia, pain, irritation, and blurring. The clinical signs were also binarized by the cut-off in each test. The presence of all signs and symptoms were then analyzed using Hayashi's quantification theory type III analysis.

Results: The mean age of the participants was 59.3 ± 17.3 years. The mean values for Schirmer test, BUT, corneal fluorescein staining, and strip meniscometry were 13.6 ± 9.6 mm, 3.1 ± 2.1 seconds, 0.40 ± 0.66, and 2.4 ± 2.7 mm, respectively. The Schirmer test was negatively correlated with age ($r = -0.152$; $P < 0.01$), whereas the BUT and strip meniscometry were not. All pairs of Schirmer test, BUT, and strip meniscometry had significant correlations, but the greatest correlation was found between BUT–strip meniscometry ($r = 0.238$; $P < 0.01$). An strip meniscometry cut-off length of 2.5 mm (area under the curve = 0.618) was calculated. Hayashi's analysis found high similarity among the presence of signs by strip meniscometry, BUT. and corneal fluorescein staining, and three nonvisual symptoms (pain, irritation, and dryness) had a distinct similarity.

Conclusions: Strip meniscometry results using the cut-off of 2.5 mm could be a useful clinical indicator for the initial screening of dry eye.

Translational Relevance: This large-scale case-control study further confirmed tear strip meniscometry with the new cut-off is a useful tear function examination for dry eye; it is a 5-second noninvasive procedure and associated with clinical symptoms and corneal parameters.

Introduction

Dry eye disease (DED) has been recently defined as "a multifactorial disease characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation and neurosensory abnormalities."[1] The key criteria for the diagnosis of DED includes unstable tear film and ocular discomfort. The tear function test is an essential examination for the diagnosis of DED and to determine the therapeutic strategy.[2,3] Tear strip meniscometry is an alternative to the Schirmer test and was first introduced in 2006 to measure aqueous availability at the lower tear meniscus.[4] As described in detail elsewhere, in strip meniscometry the wetted length is indicated by a blue stained line along the tear absorption path in the round-tipped strip (Fig. 1).

Strip meniscometry values have been reported to show a statistically significant linear correlation with Schirmer test values, tear break-up time (BUT), corneal
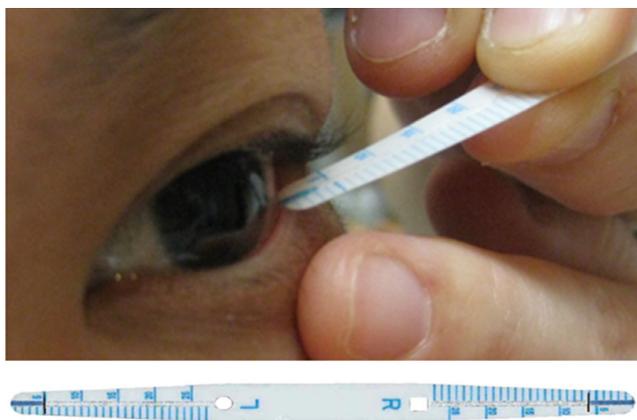
Figure 1. Tear strip meniscometry using an SMTube. A strip of SMTube is designed to perform the tear volume measurements on both eyes. Its dimensions are 85 mm in length, 7 mm in width and, 0.3 mm thick. Once the tip of the SMTube strip is immersed in the tear meniscus on the ocular surface, tear liquid is instantaneously absorbed into and propagated along the column (tear absorption path) owing to capillary action. A blue dye is impregnated at the end the column to work as an indicator for the wetting length. The representative strip measures 5 mm in the left eye and 6 mm in the right eye.

staining score and tear meniscus height measurement by anterior segment optical coherence tomography.[5,6] Strip meniscometry has also been used for numerous clinical and experimental studies, including in veterinary medicine.[7–17] However, the practical association of strip meniscometry and other DED-related parameters has not been determined fully. In particular, the cut-off value for strip meniscometry has not yet been repeatedly evaluated owing to the procedure being new.

This study aimed to evaluate the association between strip meniscometry tear meniscus volume measurement and DED-related signs and symptoms in a case series of more than 2000 samples. This study sought to identify the ideal cut-off value for strip meniscometry and explore the clinical applicability of strip meniscometry by correlating it with clinical tests and subjective DED-related symptoms.

Methods

Ethics Approval and Patient Recruitment

The present cross-sectional study was conducted at Tsukuba Central Hospital from January 2016 to December 2020. The Institutional Review Boards and Ethics Committees of the Tsukuba Central Hospital (approved December 12, 2014, permission number 141201) and the Kanagawa Medical Association (approved November 12, 2018, permission number krec2059006) approved this study and participants were recruited from January 2019 to December 2020 at the Otake Clinic Moon View Eye Center. These studies were conducted in accordance with the Declaration of Helsinki. The need for consent was waived by the institutional review board. The Institutional Review Board and Ethics Committee of Keio University School of Medicine approved this study (28 June 2021; approval number 20210080) to permit authorship for authors (K.N. and M.A.) who have appointments in the Keio University School of Medicine.

Inclusion and Exclusion Criteria

Inclusion criteria was a best-corrected visual acuity of greater than 20/30 and participants were enrolled only at their first visit. Individuals were excluded if they had vitreoretinal disease, any ocular surgery in the previous month, or acute ocular disease in the previous 2 weeks.

Dry Eye Symptomatology and Ocular Surface Examinations

We used dry eye symptomatology and related ocular surface examinations, including the Schirmer test, strip meniscometry, fluorescein BUT, and corneal fluorescein vital staining. During the examination, room temperature and humidity were maintained at 21°C to 24°C and 40% to 60%, respectively. Subjective symptoms used in this study were composed of six items: dryness, eye fatigue, photophobia, pain, irritation, and blurring. These were selected from the Dry Eye-Related Quality-of-Life Score questionnaire,[18] and their presence or absence were determined by questions.

Each patient underwent the ocular surface examinations of strip meniscometry testing, BUT, corneal fluorescein staining, and Schirmer testing, in that order.[19] Strip meniscometry testing was performed using SMTube strips (Echo Electricity Co., Ltd., Fukushima, Japan).[7] SMTube is a single-use medical device developed specifically for strip meniscometry testing. The tip of the SMTube strip was gently immersed into the lower tear meniscus on the lateral side of the eyelid without touching the cornea or the conjunctiva and statically held for 5 seconds. The resting tear immediately begun to be absorbed into the column part of SMTube with the tear propagation path stained by blue-colored dye. The length of the blue-staining was easily recognizable with the aid of the scale marks (millimeter units) printed on the strip, and the value was recorded as the strip meniscometry score.

Right before the BUT and corneal fluorescein staining measurements, two drops of saline solution on a fluorescein test strip (Showa Yakuhin Co., Tokyo, Japan) were gently placed onto the central lower lid margin. After several natural blinks from the patient, the BUT was measured three times, and the mean value was recorded as the BUT score. Corneal epitheliopathy severity was graded at 0 to 2 points, and used for the corneal fluorescein staining score. Schirmer test was performed using a dedicated strip (Showa Yakuhin Kako, Tokyo, Japan) without topical anesthesia. The Schirmer test strips were statically placed at the temporal sides of the lower conjunctival fornix for five minutes. The length of the wetted part of the strip was then read and recorded (millimeter units) as the Schirmer test score.

Statistical Analysis

To avoid a potential statistical bias for ocular surface examination results, only test scores obtained from the right eye were used in the present study. A correlation ratio was calculated for pairs between categorical symptom results and quantitative corneal and lacrimal scores. Pearson's correlation was used to evaluate the correlation coefficients among ocular surface examination results. The strip meniscometry cut-off was estimated using receiver operating characteristic curve analysis. The subjective symptoms consisted of six binarized items: dryness, fatigue, photophobia, pain, irritation, and blurring. To binarize each item, one or zero was assigned to express the presence or absence of the symptom, respectively. Likewise, clinical signs were also binarized based on the cut-off value for each test, where the respective clinical signs were considered present if the Schirmer test was 5 mm or less, the BUT was 5 seconds or less, corneal fluorescein staining was 1 point or higher, and the strip meniscometry score was less than 2.5 mm. The presence of symptoms and signs were then analyzed using Hayashi's quantification method type III analysis to visualize their mutual relationships.[20] All statistical tests were two sided, and the significance level was set to an α of 0.05. All analyses were programmed using Mathematica version 12.1 (Wolfram Research, Champaign, IL).

Results

We enrolled 2234 consecutive outpatients (686 men, 1548 women) with a mean age of 59.3 ± 17.3 years. Of these participants, 664 (29.7%) used dry eye eyedrops (hyaluronic acid and mucin secretagogue) and 199 (8.9%) used glaucoma eyedrops (prostaglandin analogues, beta-blockers, and carbonic anhydrase inhibitors). The mean values from ocular surface examinations were 13.6 ± 9.6 mm for the Schirmer test, 3.1 ± 2.1 seconds for the BUT, 0.40 ± 0.66 for corneal fluorescein staining, and 2.4 ± 2.7 mm for strip meniscometry. The percentage of participants with a short BUT (≤5 seconds) was 72.2%, positive corneal fluorescein staining (≥1) was 29.8%, and a low Schirmer test (≤5 mm) was 22.6%. The prevalence of each symptom and their correlation ratios with corneal and lacrimal test scores are shown in Table. The BUT showed a positive correlation with all symptoms except fatigue; strip meniscometry correlated with dryness, and the Schirmer test did not correlate with any symptom. Figure 2 is a matrix showing the correlation between individual pairs for age, Schirmer test, BUT, and strip meniscometry. The Schirmer test had a negative correlation with age ($r = –0.152$; $P < 0.01$), whereas the BUT and strip meniscometry did not. All pairs between Schirmer test, BUT, and strip meniscometry had significant correlations, with the highest value found in the BUT–strip meniscometry pair ($r = 0.238$; $P < 0.01$).

Figure 3 represents the receiver operating characteristic curve of the strip meniscometry test from the present study, obtained based on the large-scale sample size ($n = 1162$). This analysis identified an strip meniscometry cut-off length of 2.5 mm (area under the curve = 0.618). Based on this cut-off, 61.1% of participants

Table. Prevalence of Symptoms and Their Correlation With Ocular Signs

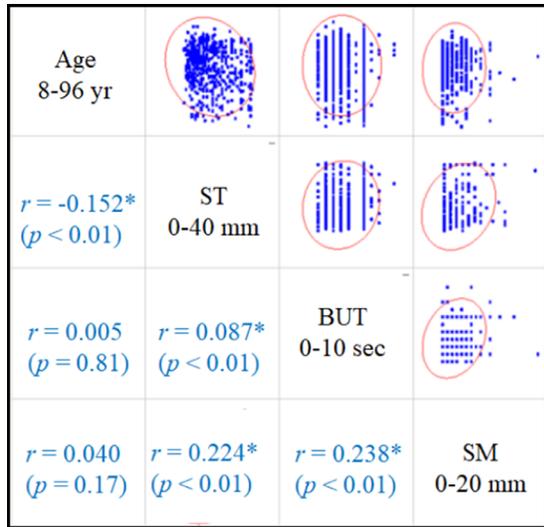| Symptom	Prevalence (%)	η With Schirmer Test	η With BUT	η With Strip Meniscometry
Dryness	32.6	0.014	0.139[*]	0.096[*]
Irritation	29.1	0.002	0.148[*]	0.054
Pain	13.5	0.005	0.079[*]	0.012
Fatigue	35.4	0.006	0.035	0.005
Blurring	33.1	0.041	0.128[*]	0.036

η, correlation ratio.
[*]$P < 0.01$.

Figure 2. Matrix showing the Pearson's correlation for individual pairs among age, ST, BUT, and SM examinations. The observation range for each examination is shown in the *diagonal cells* (*top left to bottom right*). The *upper right cells* show the scatter plots for each pair. The *lower left cells* show the correlation coefficient values (*r*). The presence of a significant correlation is indicated by * (*P* < 0.01). Only ST showed a negative correlation with age. All pairs among corneal and lacrimal tests (ST, BUT, and SM) had positive correlations, but the most significant association was found in the BUT–SM pair. SM, strip meniscometry; ST, Schirmer test.
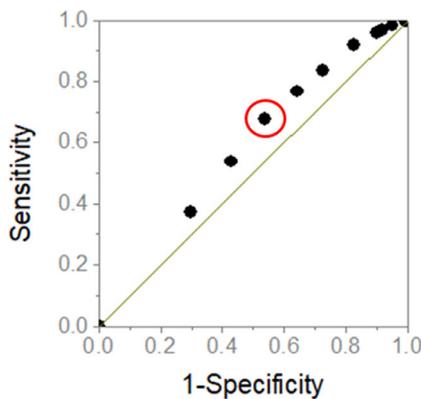

Figure 3. ROC curve of strip meniscometry. The ROC curve is shown to estimate the cut-off length of strip meniscometry based on the present large-case series data. The area under the curve value was 0.618. By optimizing the balance between the sensitivity (0.679) and specificity (0.464) (indicated by a *red circle*), the cut-off value was calculated to be 2.5 mm. ROC, receiver operating characteristic.

had a low strip meniscometry (≤2.5 mm) compared with 87.4% considered low using the previous cut-off value (strip meniscometry ≤4.5 mm).

Figure 4 depicts the two-dimensional map of eigenvector components obtained through Hayashi's quantification type III analysis. This analysis was performed on the dataset in relation to the presence of subjective symptoms and clinical signs. It found a high
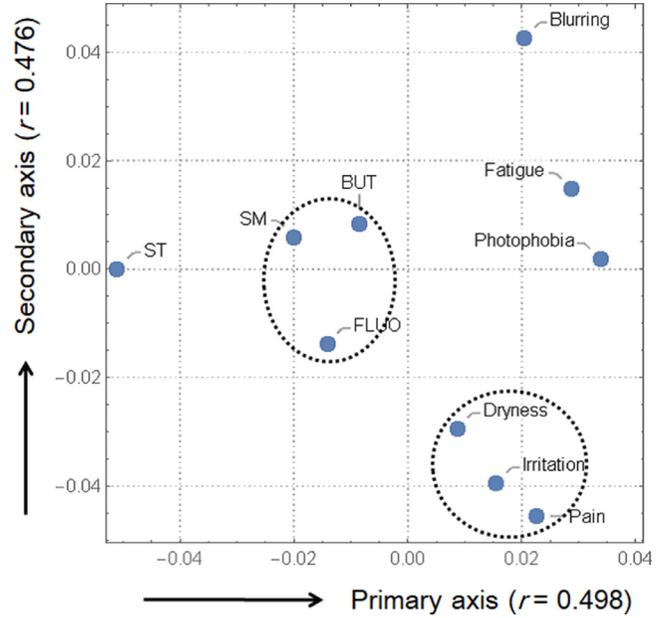

Figure 4. Hayashi's quantification type III analysis. A two-dimensionally mapped schematic result of the Hayashi's quantification type III analysis. This plot is constructed using eigenvectors from the categorical data along the primary and secondary axes. The correlation coefficient (*r*) of each eigenvector is given in the axis labels. The distance between any pair from the clinical signs (ST, BUT, FLUO, and SM) and six subjective symptoms represents the similarity of that pair. *Dotted circles* indicate specific domains, suggesting the presence of a significant similarity. Signs from BUT, FLUO, and SM were similar, whereas ST was an outlier. Dryness, irritation, and pain showed a specific association with one another. FLUO, corneal fluorescein vital staining; SM, strip meniscometry; ST, Schirmer test.

similarity among the presence of signs by strip meniscometry, BUT and corneal fluorescein staining, while Schirmer test appeared to be isolated from the other signs. Three nonvisual symptoms (pain, irritation, and dryness) had a distinct similarity.

Discussion

To the best of our knowledge, this study is the largest on the application of strip meniscometry in a clinical setting, where typical ocular surface examinations, such as the Schirmer test, BUT, and corneal fluorescein staining, were undertaken along with subjective symptomatology data. Previous studies of strip meniscometry were mostly conducted with a comparative study design between two groups, typically DED and normal groups, with moderate sample sizes of up to 100 in each group.[4,5] In contrast, this study enrolled more than 2000 cases and was conducted in a more clinical setting compared with previous reports.

The correlation ratio (η) is a convenient measure to evaluate an association between a categorical outcome with quantitative data. In this study, age correlated with the Schirmer test; however, this association could be ascribed to the tearing capability reflex decreasing with increasing age, which agrees with previous reports.[7]

The cut-off length of strip meniscometry was previously reported as 4.5 mm (4 or 5 mm),[4,5] but the present receiver operating characteristic analysis calculated it at 2.5 mm. The previous value was obtained using a comparative study design of moderate sample size ($n < 100$), whereas our value calculated here used a comprehensive outpatient cohort comprising a large number of cases. As expected, the area under the curve value in this study tended to be lower than the previously reported values. Despite a weak area under the curve (0.618), our data clearly suggest a lower strip meniscometry cut-off length may be more practical for discriminating DED cases in daily clinical practice.

Results from ocular surface examinations are commonly provided as a quantitative measure. However, in clinical practice, the actual presence or absence of clinical signs is generally considered a stronger indicator than the test score itself. In other words, the categorical determination (presence or absence) of symptoms and signs is more useful in the clinical setting. As such, in the present study we sought to identify associations with all categorical data available. Furthermore, machine learning methods would be useful for data analysis in the future.

The Hayashi's quantification type III analysis, equivalent to a correspondence analysis, is best suited for this purpose. This analysis does not require an objective variable, and thus allows us to equally handle all categorical data to find their mutual similarities.[20] Although the use of this analysis has been minimal in medical science to date, it was well-suited to the present study owing to the large sample size of the cross-sectional cohort. It should be noted that this analysis is equivalent to the procedure to obtain eigenvalues and eigenvectors upon a particular matrix, where each element corresponds with the presence or absence of a symptom or sign. The acquisition of eigenvectors allows us to construct a multidimensional space, and its interpretation is intuitive; the similarity is expressed as the interdistance between the tests. For the sake of perception, results are often mapped onto two-dimensional representations, where the primary and secondary axes are usually selected in descending eigenvalue order. Interpretation of the axes, however, can be subjective.

The Hayashi's quantification type III analysis clearly visualized similarity relationships between respective pairs of subjective symptoms and clinical signs (Fig. 4). Objective clinical signs were explicitly discriminated from subjective symptoms. Strip meniscometry with the cut-off of 2.5 mm had a noticeable similarity with BUT and corneal fluorescein staining. The Schirmer test results, however, were somewhat outlying, which is attributable to the Schirmer test results being potentially highly confounded by reflex secretion, whereas the other tests are not. This observation suggests that strip meniscometry could be more useful than the Schirmer test for initial diagnosis of DED with respect to the evaluation of lacrimal function. This result also demonstrated that there are distinct differences between nonvisual symptoms (dryness, irritation, and pain) and visual symptoms (fatigue, blurring, and photophobia) in relation to objective signs, although all symptoms are commonly experienced in patients with DED.

This study has several limitations. First, there was a potential recruitment bias and heterogenicity might not be completely eliminated because the study involved consecutive patients only at first visit under inclusion and exclusion criteria. Additionally, this study lacks a control group without DED and it is a considerable limitation to calculate the cut-off value for strip meniscometry. The comparison between dry eye and control groups under the relevant diagnostic criteria would further enhance the current results. The large sample size and multicenter study design may, however, overcome these limitations. Second, the Schirmer test and strip meniscometry were indicated for suspected DED and a selection bias was not excluded. Because the majority of participants complained of DED-related symptoms, the current study used both DED and non-DED participants to calculate the strip meniscometry cut-off value. Third, the results may not be conclusive owing to it being a single study. The clinical application of strip meniscometry should, therefore, be further confirmed in various clinical settings. Fourth, strip meniscometry measurements show diurnal variationin[15] and may vary depending upon season, climate, environment, medications, and systemic comorbidities. Finally, DED-related examinations based on validated questionnaires are necessary to confirm the present results, including tear osmolarity, corneal sensitivity, visual function, and DED symptoms.

This study has several strengths. First, our detailed and comprehensive collection of data on subjective symptoms and clinical manifestations associated with DED were all evaluated by a single experienced dry eye specialist (M.A.), according to the most frequently used and standardized Japanese dry eye criteria. This factor may have maximized the study's validity. Second,

the samples were collected from multiple institutions in Japan, allowing us to conduct a large-scale case-control study enriched for ophthalmic parameters in a rigorous manner.

Conclusions

For the sake of clinical utility, the relationships between clinical signs and symptoms were discussed based on their presence and absence. Strip meniscometry results using a cut-off of 2.5 mm may be a more useful clinical indicator for the initial screening of dry eye.

Acknowledgments

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