

The Efficacy, Sensitivity, and Specificity of Strip Meniscometry in Conjunction with Tear Function Tests in the Assessment of Tear Meniscus

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PURPOSE. To evaluate the specificity and sensitivity of strip meniscometry (SM) testing in conjunction with tear function tests in the diagnosis of dry eye (DE) disease and to investigate the effect of SM on reflex tearing.

METHODS. One hundred seven left eyes of 107 patients with definite DE disease according to the Japanese DE diagnostic criteria and 68 left eyes of 68 age- and sex-matched control subjects were studied. Tear meniscus height (TMH) measurements, fluorescein tear film break-up time (FTBUT), fluorescein (F) and rose bengal (RB) staining, and Schirmer's test-1 (ST) were also performed. The assessment of reflex tearing before and after SM application was assessed with a graticule scale at the slit lamp and by optical coherence tomography. The sensitivity and specificity of SM alone and in combination with tear function tests were also sought.

RESULTS. The SM scores, TMH measurements, FTBUTs, and STs were significantly lower in dry eye patients than in the controls ($P < 0.001$). The RB and F staining scores were significantly higher in the dry eye group than in the control group ($P < 0.001$). The meniscometry strips did not induce significant changes in relation to reflex tearing. SM had an acceptable sensitivity and specificity.

CONCLUSIONS. SM is a swift, noninvasive, promising method of assessing tear meniscus volume. The combined SM and FTBUT examination appears to be a sensitive approach to the assessment of dry eye disease. (*Invest Ophthalmol Vis Sci.* 2011;52:2194–2198) DOI:10.1167/iovs.10-5986

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The 2007 Report of the International Dry Eye Work Shop defined dry eye (DE) disease as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.¹ The 2007 International Dry Eye Work Shop report also noted that the term *dysfunctional tear syndrome* embraces the essential features of DE disease, recognizing the work and efforts of the Delphi Panel, but concluded that retention of the name DE had much to recommend it and that its use was embedded in the literature. DE disease is an important health problem as reported by several epidemiologic studies.^{2–4}

Large-scale epidemiologic studies on DE, such as the Women Health Study, estimated that approximately 3.23 million American women 50 years and older had DE disease, tens of millions more experience symptoms to a degree and probably a more episodic manifestation of the disease that is notable when exposed to adverse environmental conditions.² In Japan, the prevalence of DE disease was estimated to be 33%.³ A recent study showed that 10.1% of male and 21.5% of female subjects had DE disease.⁴ The International DE Work Shop also provided recommendations in relation to diagnostic DE methodologies.

Several methods are used for the assessment of DE diseases,⁵ including the Schirmer test, invasive and noninvasive tear film break-up time assessment, vital stainings, and tear meniscus evaluation. Tear meniscus variables, such as height, width, cross-sectional area, and meniscus curvature, have been reported to be important in DE diagnosis,^{6–10} with limitations of the reported techniques, due to their invasive nature causing stimulation of reflex tearing or changes in tear volume by addition of fluorescein dye to the tear film.¹¹ The assessment of the tear volume has been regarded as essential for the diagnosis of DE disease. Tear meniscus has been reported to contain 75% to 90% of the aqueous tear volume, which was observed to be positively correlated with the lacrimal secretory rate.¹² The tear meniscus volume has been reported to be reduced in tear-deficient DE and its measurement to be of great value in the diagnosis of the disease.⁶ The Schirmer test has been reported to be an indispensable tool for tear volume assessment. There is, however, wide intrasubject and time-wise variability, as well as problems of irritation and induction of reflex tearing.¹²

We have reported a swift, noninvasive method of quickly measuring tear volume, for which we coined the term strip meniscometry (SM).¹³ SM has been shown by us to have a strong correlation with the Schirmer test, FTBUT, ocular surface vital staining scores, and tear film lipid layer interferome-

try grades. In this study, we compared the extent of reflex tearing induced by the meniscometry strips and assessed the sensitivity and specificity of the new methodology, alone and when combined with other tear function and ocular surface tests in the diagnosis of DE disease.

MATERIALS AND METHODS

Subjects and Examinations

One hundred seven left eyes of 107 patients with definite DE disease according to the Japanese diagnostic criteria of DE (23 men, 84 women; mean age, 44.6 ± 13.7 years) and 68 eyes of 68 age- and sex-matched normal control subjects (28 men, 40 women; mean age, 38 ± 12.2 years) were recruited in this prospective controlled study. The study protocol and examination were reviewed and approved by the Ethics Committee of the Japan Preventive Medicine Society. The study was in compliance with the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject. Patients and control subjects who had a history of atopy; allergies; Stevens-Johnson syndrome; chemical, thermal, or radiation injury; or any other ocular or systemic disorder or had undergone any ocular surgery or contact lens use that would create an ocular surface problem or DE were excluded from the study. The DE diagnosis was made according to the Japanese DE diagnostic criteria as follows: (1) presence of qualitative or quantitative disturbance of the tear film (Schirmer test ≤ 5 mm or FTBUT ≤ 5 seconds); (2) presence of conjunctivocorneal epithelial damage (fluorescein [F] staining score ≥ 3 points or RB staining score ≥ 3 points); and (3) presence of DE symptomatology. The presence of all the above criteria was necessary for a diagnosis of definite DE disease.¹ The severity grading of DE patients included in this study was based on the 2007 International Dry Eye Work Shop severity grading scheme.¹

The ophthalmic examination consisted of slit lamp microscopy, administration of a DE symptom questionnaire, tear meniscus height (TMH) measurement with a graticule millimeter scale, SM, determination of FTBUT, fluorescein and RB stainings, and the Schirmer-1 test without anesthesia. Optical coherence tomographic (OCT; Visante; Carl Zeiss Meditec, Tokyo, Japan) TMH measurement for assessment of reflex tearing was also performed. No subject used topical artificial tear drops within 2 hours before the examinations.

Dry Eye Symptom Questionnaire

The questionnaire consisted mainly of three symptom question categories: DE symptoms (12 questions, part A), visual symptomatology (9 questions, part B), and environmental symptoms (8 questions, part C). The questionnaire consists of 29 questions. Possible answers to the questions about the frequency of symptoms within a 1-week recall period were "often, sometimes, rarely, or never". Each frequency was assigned a severity score from 0 to 4 points.

Structure and Composition of Meniscometry Strips

Meniscometry strips were made of a 25-mm polyethylene terephthalate, on which a urethane-based material of the same size containing a central ditch of 0.40 mm in depth was pasted. A nitrocellulose membrane filter paper strip with a pore size of $8 \mu\text{m}$ impregnated in natural blue dye 1 was then placed into the central ditch, which served as a reservoir for the tear absorption (Fig. 1).

TMH Assessment and SM

The tear meniscus was observed with a biomicroscope illumination system (Carl Zeiss Meditec, Inc.) set at a 90° angle and tangential to the central inferior meniscus. The beam width was 0.05 mm and the height 5 mm, with the magnification set at $32\times$. TMH was assessed by a graticule millimeter scale in the ocular eyepiece (Carl Zeiss Meditec, Inc.). The tip of the meniscometry strip was briefly inserted for 5 seconds into the lateral lower tear meniscus without touching the

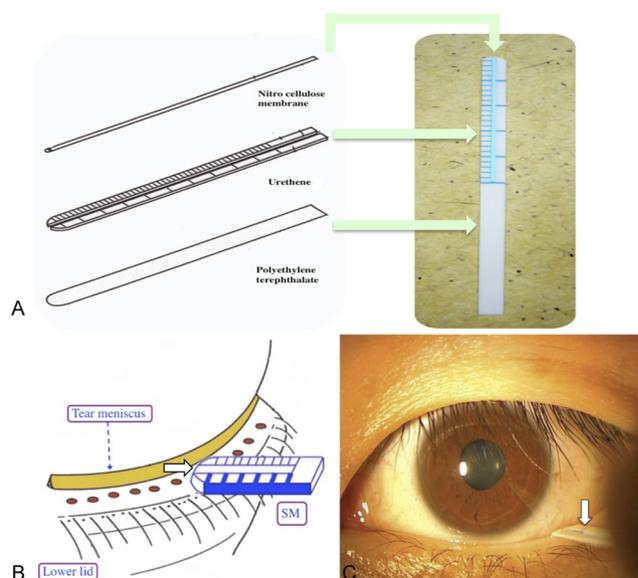


FIGURE 1. The SM design and test. (A) The strip is composed of polyethylene terephthalate, on which a urethane-based material of the same size containing a central ditch of 0.40 mm in depth is pasted. A nitrocellulose membrane filter paper strip with a pore size of $8 \mu\text{m}$ impregnated in natural blue dye 1 is then placed into the central ditch. (B) The strip is applied to the lateral lower lid tear meniscus without touching the ocular surface. (C) Slit lamp image demonstrates the SM test; *arrow*: length of the stained tear column in the central membrane ditch, regarded as the SM value.

ocular surface. The duration of the test was measured strictly by a stopwatch chronometer at each testing. The length of the stained tear column in the central membrane ditch was regarded as the SM value in that eye in millimeters. The temperature and humidity of the examination room during the SM procedure were maintained at 24°C and 30%, respectively. Soon after the test, the patients were asked whether they had experienced irritation, discomfort, or touch sensation during the application of the strip.

OCT TMH Measurements

OCT TMH measurements were performed as reported previously.¹⁴ Briefly, each subject was asked to rest his or her chin on the chin rest, with the forehead pressed against the forehead band, and then to look straight at a fixation target within the device. The subject blinked spontaneously during the examination. The OCT light beam was focused on the ocular surface and a 10-mm long vertical scan was then performed. Immediately after a blink, the image that showed the lower tear meniscus and the central corneal reflectivity was processed to obtain the TMH.

Tear Function Examinations and Ocular Surface Vital Staining

Two microliters of a preservative-free, 1% fluorescein dye was initially instilled into the conjunctival sac with a micropipette. The standard FTBUT measurements were performed after instillation. The subjects were instructed to blink several times for a few seconds, to ensure adequate mixing of the fluorescein. The interval between the last complete blink and the appearance of the first corneal black spot in the stained tear film was measured three times, and the mean of the measurements was calculated. An FTBUT of ≤ 5 seconds was considered abnormal.¹⁵ After assessment of FTBUT and fluorescein staining, 1% RB dye was instilled into the conjunctival sac. Fluorescein and RB stainings of the ocular surface were scored as described elsewhere.^{16,17} In brief, fluorescein staining scores ranged between 0 and 9 points. A score greater than or equal to three points was regarded as abnormal.

The RB staining scores (van Bijsterveld) of the ocular surface ranged between 0 and 9 points. Any score greater than or equal to three points was regarded as abnormal.

For further evaluation of tears, the standard Schirmer-1 test without topical anesthesia was performed. The standardized strips of filter paper (Alcon Inc., Fort Worth, TX) were placed in the lateral canthus away from the cornea and left in place for 5 minutes with the eyes closed. Readings were reported in millimeters of wet strip after 5 minutes. A reading of ≤ 5 mm was regarded as abnormal. According to the study protocol, TMH measurements were performed initially, followed by SM, and the TMH measurements to test the extent of reflex tearing. After the noninvasive tests, FTBUT measurements, fluorescein staining, RB vital staining of the ocular surface, and the Schirmer-1 test were performed. All SM and ocular surface vital staining examinations were performed by one ophthalmologist (MD). Another clinician performed the Schirmer tests (SW), and another (AT) administered the symptom questionnaires. The reflex tearing examination using OCT and graticule scale TMH measurements were performed by another clinician (OI). Since the final diagnosis of DE disease requires information from all tests, none of the examiners was provided with information on the final diagnosis of an individual.

Reflex Tearing Examination

The differences in TMH measurement before and after SM was assessed with a graticule millimeter scale and OCT. The assessments were performed on the same day on the same subjects with a 5-minute interval between the first and the second TMH assessments after SM.

In Vivo Repeatability Examination

The in vivo repeatability of SM was also investigated. Subjects were examined by SM, a graticule millimeter scale, OCT TMH measurements, vital stainings, FTBUT, and Schirmer test. The same subjects underwent the same examinations in the same order 2 weeks later.

Statistical Analysis

The comparisons of mean symptom scores, graticule scale TMH, SM scores, FTBUT, RB, fluorescein, and Schirmer test results were performed by Mann-Whitney U test. The differences in TMH before and after SM were assessed with the Wilcoxon matched-pairs test.

The receiver operating characteristic (ROC) curve technique was used to test the sensitivity and specificity of SM alone and when combined with other DE diagnostic tests. A probability level of less than 1% was considered statistically significant. The correlation between the SM and graticule scale TMH measurements was studied by using the Spearman nonparametric correlation analysis. The data analyses were performed by a statistician who was masked to whether the data came from a normal subject or a DE patient.

RESULTS

Subjects and Examinations

Thirty percent of the patients included in this study had a severity grade of 2, and 70% of the patients had a severity grade of 3, based on the 2007 International Dry Eye Work Shop severity grading scheme.¹

Modified OSDI Questionnaire

Only the irritation symptom score was significantly higher in the DE subjects (1.9 ± 1.3 points) compared with the control subjects (1.4 ± 1.0 points; $P < 0.001$; Table 1).

TMH Assessment and SM

The graticule millimeter scale TMH and SM scores were significantly lower in the DE patients than in the healthy controls ($P < 0.001$; Table 1). None of the subjects experienced irrita-

TABLE 1. Comparison of Tear Functions and Ocular Surface Findings in the Normal Control Subjects and Dry Eye Patients

Tear Film Examination and Irritation Symptom Score	Dry Eye Patients ($n = 107$ eyes)	Normal Controls ($n = 68$ eyes)
Irritation symptom score	1.9 ± 1.3	1.4 ± 1.0
GTMH, mm	0.15 ± 0.1	0.25 ± 0.2
SM, mm	3.0 ± 1.9	5.4 ± 2.2
FTBUT, s	2.8 ± 1.2	8.3 ± 2.9
Fluorescein score	4.2 ± 2.3	0.3 ± 0.6
Rose-Bengal score	2.9 ± 1.7	0.4 ± 0.6
Schirmer test, mm	8.9 ± 8.7	22.1 ± 10.0

All differences are $P < 0.001$.

tion, discomfort, or touch sensation during the conduct of the testing.

Tear Function Examinations and Ocular Surface Vital Staining

The FTBUTs and vital staining scores were significantly worse in patients with DE disease than in control subjects ($P < 0.001$), as summarized in Table 1. The mean Schirmer test values were significantly lower in the DE patients compared to the controls ($P < 0.001$), as shown in Table 1.

Reflex Tearing Examinations

OCT showed absence of significant reflex tearing for TMH measurements investigated in the same normal (Figs. 2A, 2B) and DE subjects (Figs. 2C, 2D) as shown in Figure 2. TMH assessed by graticule millimeter scale showed a significant decrease after the application of the SM in the examined subjects ($P < 0.001$; Figs. 2E, 2F).

In Vivo Repeatability Examination

SM, graticule scale, and OCT TMH examinations performed initially and 2 weeks later showed no statistically significant differences. Tear quantity, stability, and vital staining scores measured twice at the same times as SM and TMH measurements, did not reveal statistically significant differences, as well (data not shown).

Sensitivity and Specificity of SM Combined with Tear Function and Ocular Surface Tests

The AUC (area under the curve) calculated by the ROC technique was 0.794 (0.721–0.856), suggesting an acceptable sensitivity and specificity of SM in all subjects. When the cutoff value of the SM result was set at ≤ 4 mm, the sensitivity and specificity of the SM procedure was found to be 83.52% and 58.16%, respectively. The specificity of SM markedly increased when combined with tear function and ocular surface tests as shown in Table 2.

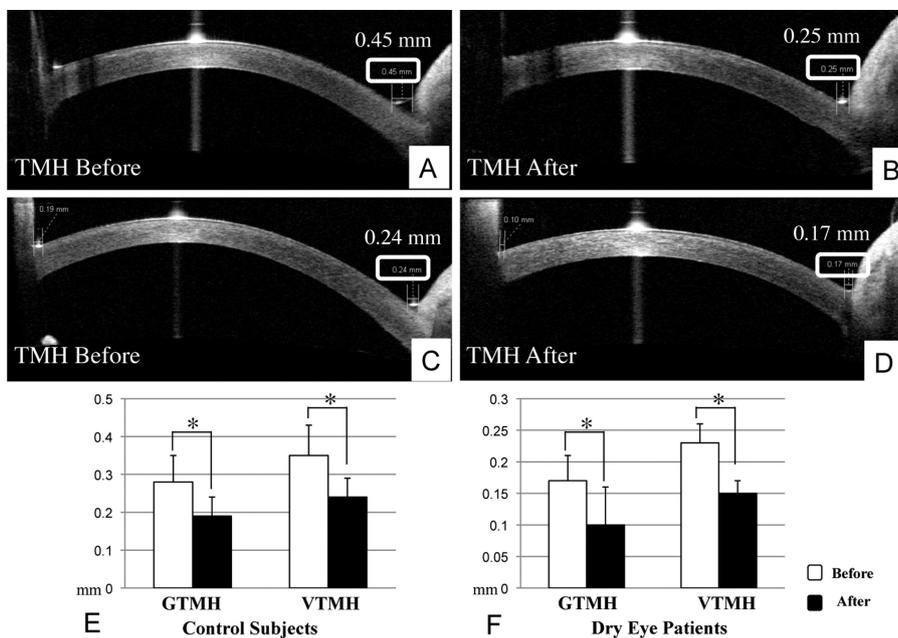
Correlation between SM and Graticule Scale TMH Measurement

Using Spearman's correlation coefficient by rank test, we found a significant linear positive correlation between SM and graticule scale TMH measurement ($r = .51$; $P < 0.001$).

DISCUSSION

Conventional methods for the diagnosis of DE disease in many eye centers include FTBUT, vital stainings, and Schirmer's test. Tear film break-up time assessment by fluorescein instillation

FIGURE 2. Assessment of reflex tearing associated with SM using a slit lamp graticule scale and OCT. (A) Representative OCT scan of the lower TMH before SM in a normal subject; *rectangle*: the TMH (0.45 mm). (B) TMH after SM in the same normal subject. Note the decrease in TMH after SM (0.25 mm). (C, D) OCT scans of the lower TMH before and after SM in a dry eye patient. A decrease in TMH was observed after SM. (E) Tear meniscus height measured by slit lamp graticule scale and OCT showed a significant decrease in TMH after SM in the control subjects ($P < 0.001$; Wilcoxon matched-pairs test). (F) Similar changes were observed in the dry eye patients after SM. GTMH, graticule scale tear meniscus height; VTMH, Visante OCT TMH.



onto the ocular surface affects the tear film stability due to the invasive nature of the test.¹⁸

The Schirmer test, on the other hand, still the gold standard for tear quantity assessment, has been reported to be associated with irritation, pain, and induction of reflex tearing.¹⁹ In addition, several studies have indicated high variability in the results obtained from the Schirmer test.^{20,21}

Several noninvasive methods have been used for assessment of DE disease including tear stability analysis system (TSAS) and anterior segment optical coherence tomography (AS-OCT).^{14,22,23} The TSAS device measures tear stability by providing consecutive corneal topograms measured over 10 seconds but does not provide information on tear volume or tear meniscus parameters. Moreover, sustained eye opening during the TSAS testing may induce reflex tearing.²² Anterior segment optical coherence tomography has also been reported to be a noninvasive DE test for tear meniscus assessment that provides high resolution and detailed information about the ocular surface.^{14,23} However, there are limitations related to the device in terms of high cost and the need to provide space in clinical settings to perform the examination. The short examination time needed for SM, on the other hand, may eliminate the possibility of reflex tearing compared to the relatively longer examination time needed for OCT examinations, making SM suitable for busy clinical settings. Moreover, the light weight and size of the meniscometry strips enable conducting large-scale DE epidemiologic studies outside clinical settings.

We previously reported SM to have good *in vivo* reproducibility and correlate well with tear quantity, stability, ocular surface vital staining scores, and lipid layer interferometry grades.¹³

TABLE 2. Sensitivity and Specificity of Tear Functions and Ocular Surface Tests Combined with SM

	Sensitivity (%)	Specificity (%)
SM	83.52	58.16
SM+Schirmer	38.31	100
SM+FTBUT	80.52	99.25
SM+F	65.58	100
SM+RB	48.05	100
SM+GTMH	57.14	82.09

SM was observed by us to be an effective tool for tear meniscus evaluation in patients with applicability among a wide age range, including elderly subjects (DE patients were aged between 18 and 76 years, and control subjects were aged from 15 to 70 years).¹³

The unique composition of the nitrocellulose membrane, the small pore size, and the use of the capillary tube effect phenomenon allow very quick absorption of tears into the press-cut central ditch, allowing the assessment of tear volume in the tear meniscus *in vivo*. SM has the advantage of being performed noninvasively, without fluorescein dye instillation onto the tear film, without touching the eyelids and the ocular surface, and without causing pain. The test had high sensitivity and specificity in our experience.¹³ Another advantage of SM is the low volume of tears absorbed by the strips. The minimal volume absorbed by a meniscometry strip allows other DE tests to be performed shortly after SM, with no need to leave a time interval before the next test. These advantages may eliminate the limitations of existing invasive methodologies.¹³

Moreover, SM also correlated well with the OCT TMH measurements in a previous study.¹⁴ In the present study we also observed a positive linear correlation between SM testing and graticule scale TMH.

The *in vivo* reproducibility of SM performed on DE and healthy subjects on two different occasions separated by 2 weeks revealed no statistically significant differences in the SM scores, suggesting acceptable intraobserver variability. In our previous report, SM was performed by six ophthalmologists who were not informed whether they were performing the examination on a patient with DE or a control subject. SM proved to have acceptable interobserver variability.¹³

The relation of SM with reflex tearing has not been reported previously. In the present study, SM was used in a large number of subjects to assess whether the meniscometry strip would induce reflex tearing. Both the graticule scale and OCT measurements of the TMH showed no significant changes in the TMH, suggesting the lack of reflex tearing induction after SM, both in the controls and especially in DE subjects, which verifies that it is a desirable noninvasive tear meniscus/tear volume quantification test.

In the present study, we also estimated the cutoff values of SM alone and in conjunction with other tear function and

ocular surface tests. SM was shown to have an acceptable sensitivity for DE diagnosis in this report. The combination of SM with tear function and ocular surface tests showed improvement in the specificity of SM compared with when it is performed as a solitary test.

It should be noted that SM requires the application of the meniscometry strip onto the tear meniscus without touching the ocular surface, the examiner needs to receive some training on how to perform the examination procedure adequately. The test may be invasive if the strips touch the conjunctival surface, especially in cases of severe aqueous tear deficiency.

In our view, SM holds the potential to be a quantitative and swift method of assessment of the tear meniscus in large epidemiologic studies when the Schirmer test may not be applicable due to time constraints and concerns of invasiveness and reflex tearing induction.

In conclusion, the present study confirmed the efficacy SM as a noninvasive diagnostic tool for DE that can be performed in 5 seconds with no induction of reflex tearing. The combination of SM with other tear function tests, especially the FTBUT had an acceptable sensitivity and specificity, which can be of value in the assessment of ocular surface diseases in the future.

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