Application of CASIA SS-1000 Optical Coherence Tomography Tear Meniscus Imaging in Testing the Efficacy of New Strip Meniscometry in Dry Eye Diagnosis

Megumi Shinzawa, M.D., Murat Dogru, M.D., Ph.D., Keiichi Miyasaka, Ph.D., Jun Shimazaki, M.D., Ph.D., and Tetsuju Sekiryu, M.D., Ph.D.

Purpose: To investigate the applicability of CASIA SS-1000 anterior-segment optical coherence tomography (AS-OCT) imaging parameters in testing the efficacy of the new strip meniscometry (SM) namely "Strip Meniscometry Tube" (SMTube) in the diagnosis of dry eyes.

Methods: Forty-three eyes of 22 patients (4 men and 18 women) with definite dry eye disease (DED) and 49 eyes of 28 normal controls (6 men and 22 women) were studied. All subjects underwent symptom questionnaires, SMTube, the Schirmer-1 test, tear film break-up time measurement, vital staining examinations, as well as tear meniscus height (TMH) and TM area (TMA) measurements using an AS-OCT system. We evaluated the cutoff values for the diagnosis of DED, looked into the correlations between TMH, TMA, and SMTube scores and checked the sensitivity and specificity of these parameters in the diagnosis of DED.

Results: The mean values of TMH, TMA, and SMTube scores in the patient group were 0.138 ± 0.102 mm, 0.013 ± 0.015 mm^2 and 1.4 ± 2.3 mm, whereas those for the control group were 0.27 ± 0.10 mm, 0.033 ± 0.025 mm^2 and 5.8 ± 2.8 mm, respectively. The differences between both groups were significant ($P<0.001$). The cutoff values of TMH, TMA, and SMTube for DED were 0.197 mm, 0.020 mm^2 and 3.8 mm, respectively. SMTube had significant correlations with TMH ($r=0.82$, $P<0.001$) and TMA ($r=0.86$, $P<0.001$).

Conclusions: The SMTube was useful in DED diagnosis, the validity of which could be effectively evaluated by the CASIA SS-1000 AS-OCT TM parameters.

Key Words: Strip meniscometry—Dry eye—Optical coherence tomography.

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Dry eye disease (DED) has been defined as a chronic disorder of the tears and the keratoconjunctival epithelium accompanied by symptoms of discomfort and visual disturbance.[1] Widely used diagnostic examinations of DED include symptom questionnaires, Schirmer test, and the tear film break-up time (BUT) measurement, as well as vital staining using fluorescein (FS), rose bengal, and lissamine green (LS) dyes for evaluating the status of the keratoconjunctival epithelium. Reflective meniscometry based on noninvasive measurement of the tear meniscus (TM) curvature,[2] interferometry based on measuring the tear film thickness,[3] the videokeratography,[4] and the wavefront higher-order aberrations are the other reported methods used for the evaluation of tear functions.[5] Among various tests, the Japanese dry eye diagnostic criteria as well as the 2007 International dry eye workshop report have emphasized the importance of "conciseness" and "noninvasiveness" of the testing methods.

In recent years, the anterior-segment optical coherence tomography (AS-OCT) has received increasing attention owing to its ability in assessing the TM volume noninvasively, due to the use of an invisible (near infrared) light source minimizing photostimulation against subject's eyes and any reflex tear secretion. Analyses of the TM data obtained from OCT paved the way for the creation of useful parameters such as TM height (TMH), TM depth, TM area (TMA), and the TM curvature.[6] However, the OCT systems are still very expensive, limiting their widespread applications in dry eye diagnosis.

In 2006, Dogru et al[7] reported a novel diagnostic method for the assessment of TM volume in a swift and noninvasive manner, which has been termed strip meniscometry (SM) (Fig. 1A). Similar to the conventional Schirmer test, SM method adopted a strip-shaped tool composed of a fluid-absorbing material, but the testing was designed to touch the strip into the TM only (without anesthesia) instead of inserting the strip into the conjunctival sac. The testing time was remarkably short (5 sec) in contrast to 5 min of testing with the Schirmer strips. Strip meniscometry has been demonstrated to have a strong correlation with the Schirmer test, FS BUT, ocular surface vital staining scores, and tear film lipid layer interferometry grades.[7] Strip meniscometry strips have then been modified to enable better absorption of tears and testing of both eyes with a single strip with a design change, and the latest version has been coined the term SMTube (Strip Meniscometry Tube) (Fig. 1B).

In this article, we investigated for the first time the applicability of CASIA SS-1000 AS-OCT system to evaluate the efficacy of new SM (SMTube) testing in the diagnosis of DED.

MATERIALS AND METHODS

Subjects and Examinations

This pilot, descriptive study followed the tenets of the Declaration of Helsinki and was approved by the research review

From the Department of Ophthalmology (M.S., T.S.), Fukushima Medical University, Fukushima, Japan; Department of Ophthalmology (M.S., M.D., J.S.), Ichikawa General Hospital, Tokyo Dental College, Chiba, Japan; Department of Ophthalmology (M.D.), Keio University School of Medicine, Tokyo, Japan; and Research Unit Echo Electricity Co., Ltd (K.M.), Tokyo, Japan.

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Address correspondence to Megumi Shinzawa, M.D., Department of Ophthalmology, Ichikawa General Hospital, Tokyo Dental College, Sugano 5-11-13, Ichikawa, Chiba 272-8513, Japan; e-mail: mshinz2003@yahoo.co.jp

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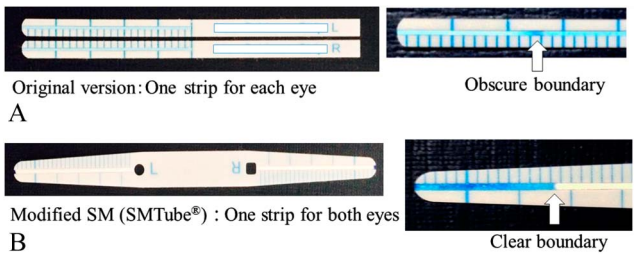

FIG. 1. Difference in the form of original version and modified strip meniscometry (SM) (SMTube). (A) Original strips (left insert) strips disclosed obscure staining (right insert). (B) New SM tube strips show sharp tear film staining due to structure and material change and better absorptive features.

board of Fukushima Medical University. Forty-five eyes of 22 patients (4 men and 18 women) with definite DED according to the Japanese dry eye diagnostic criteria, and 49 eyes of 28 normal controls (6 men and 22 women) were enrolled (Table 1). There were no statistically significant differences in relation to age and gender between both groups. Each subject underwent questionnaires for subjective dry eye symptoms, TMH and TMA measurements using OCT (CASIA SS-1000; TOMEY, Nagoya city, Aichi, Japan), SM test (SMTube; Echo Electricity, Shirakawa city, Fukushima, Japan), tear film BUT measurement, ocular surface vital staining examinations, as well as the Schirmer test (Colorbar Schirmer; EagleVision, Memphis) without anesthesia. The temperature and humidity of the examination room during all tests were maintained at 20 to 24°C and 45% to 55%, respectively. The diagnosis of dry eye was based on the diagnostic criteria of the Dry Eye Research Group in Japan. In brief, patients with (1) dry eye–related symptoms (2) positive staining with FS or Rose bengal and (3) Schirmer-1 test results of less than 5 mm or tear film BUT less than 5 sec were diagnosed as having dry eyes.

The New Strip Meniscometry Tube

The original version of meniscometry strips used one strip for each eye. The adsorbent was fitted in a ditch of the polyurethane matrix. The undersurface of the polyurethane matrix was masked, but the top surface was exposed. The adsorbent comprised of nitrocellulose, and the pore size was 8 μm. A thin coat of blue dye 1 was applied to the whole adsorbent. The new SM (SMTube) used one strip for both eyes. The polyurethane matrix masking was available both under the surface and on the top of the strip surface, providing a vacuum tube structure. The adsorbent is interwoven fibers of rayon and pulp, with a pore size of 20 μm. Blue dye 1 was impregnated at both tips (Fig. 2).

TABLE 1. *Subject Demographics*

Diagnosis	Subjects	Gender[a]		Age Range, yrs	Mean Age,[a] yrs
		Men	Women		
DED	22 (43)	4 (8)	18 (35)	36–86	58.3±14.0
Normal controls	28 (49)	6 (9)	22 (40)	14–82	56.1±15.3

Subjects with dry eye symptoms, presence of a vital staining score of >3 points, and decreased tear break-up time or tear quantity were diagnosed as having definite dry eye disease according to the 2006 Japanese Dry Eye Research Society Diagnostic Criteria.

[a]No statistically significant differences were found in terms of male-to-female ratio (P=1.0 with Fisher exact test) and the age distribution (P=0.86 with Mann–Whitney U test).

Dry Eye Symptom Questionnaires

The Ocular Surface Disease Index (OSDI) and the Dry Eye–related Quality-of-life Score (DEQS) were used. The OSDI includes 12 questions comprising 5 terms for ocular symptoms, 4 terms for vision-related functions, and 3 terms for environmental triggers.[8] The DEQS consists of six questions for ocular symptoms and nine questions for vision-related functions, which enables more generalized assessment of DED, not only the symptoms but also the influence to everyday life as well as the mental state.[9] The mean DEQS scores for the diagnosis of dry eye patients and control subjects have been reported to be 33.7 and 6, respectively.[8] The mean OSDI scores for the diagnosis of severe dry eye patients with mild to moderate DED and control subjects were 36, 21, and 10, respectively.[9]

OCT: Inferior TMH and TMA Measurements

Image acquisition was carried out using a Fourier domain swept source AS-OCT (CASIA SS-1000) with an infrared light source (wavelength=1,310 nm) soon after a blink, which allowed us to obtain the three-dimensional data composed of a series of vertical cross-sectional images with the axial resolution of approximately 8 μm and the transverse resolution of approximately 30 μm. The scan conditions were customized as the raster H scan range 16 mm, A/B scan 512, and B/C scan 32, resulting in the single acquisition time of 0.6 sec. Patients were directed to look straight at a fixation target installed within the OCT while maintaining spontaneous blinking during the examination. A cross-sectional image positioned at the central cornea was then selected and magnified by 300% to perform the subsequent image processing for the inferior TMH and TMA measurements. Figure 3 shows a typical cross-sectional image of lower TM obtained by OCT, in which points A, B, and C represent the eyelid–meniscus junction, the meniscus–eye junction, and the eye–eyelid junction, respectively.[10] After manual estimation for those points together with their additional midpoints (points between AB, BC, and CA), the programmed calipers measured the value of TMH as the distance between A and B, as well as the value of TMA as the area of zone surrounded by a closed contour approximated by a spline curve passing through all the points above. The correction factor (the refractive index of balanced saline=1.343) was applied to the value of TMA.[6]

SMTube Testing

The SMTube testing was conducted in accordance with the protocol described in the original reports of SM method.[7,11] In brief, a subject was first asked to look straight while placing the face on a chin rest, followed by the TM observation through a biomicroscope illumination system (Carl Zeiss Meditec, Inc., Dublin, CA). Immediately after a couple of blinks by the subject, the tip of the meniscometry strip (marked as "R") was gently immersed into the inferior TM of the right eye of a subject and held statically at the same position for 5 sec (Fig. 4). An electronic metronome was used for the strict measurement of the testing duration. The blue-stained length of the tear-absorbing column was then swiftly read and recorded as the SMTube score. Subsequently, the same procedure was repeated on the left eye of a subject using the other side of the tip (marked as "L").

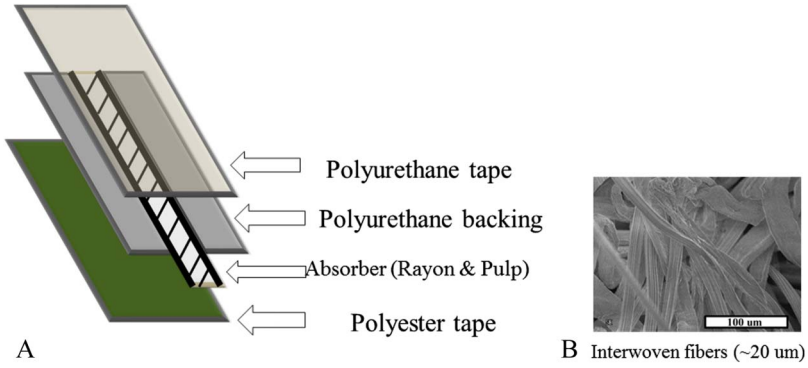

FIG. 2. Structure of the SMTube. (A) SMTube is made up of absorber in a ditch of polyurethane backing that is pressed by machine, and it is an empty tube structure that is sealed with polyurethane tape and polyester tape. (B) A scanning electron microscopy image of an absorber consisting of single fiber of nonwoven fabric that is composed of multiple straight subfibers, and its aggregate forms an intricate connection of subfibers.

Tear Function Examinations and Ocular Surface Vital Staining

Vital staining examinations were performed using FS and LG dyes to evaluate the ocular surface staining scores. First, a FS strip was gently immersed to the conjunctival sac, and the standard tear film BUT measurement was carried out. To ensure appropriate mixing of FS, the subjects were asked to blink several times. 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 value of the observation was taken as the BUT score, followed by the subsequent evaluation of the FS score ranging between 0 and 9 points.[1] In relation to LG staining, 1% LG dye was instilled into the conjunctival sac, and the subjects were requested to blink several times. The LS scores ranged between 0 and 9 points.[1] In accordance with the Japanese dry eye diagnostic criteria,[1] a tear film BUT less than 5 sec was considered to be abnormal. Based on the same criteria, an FS/LS score greater than 3 points was considered to be abnormal.

In addition, the Schirmer test-1 was performed without topical anesthesia. Standardized strips of filter paper (Colorbar Schirmer, EagleVision) were placed in the lateral canthus away from the cornea and left for 5 min with the eyes closed. The readings were reported in millimeters as the length of the wet part of a strip. A reading of less than 5 mm was regarded as abnormal in line with the Japanese diagnostic criteria.[1]

Statistical Analyses

The Fisher exact test was used to check the differences of the male-to-female ratio between the DED and control groups. The Mann–Whitney *U* test was used to check the consistency of the age distribution, and to compare the changes in individual testing results between the DED and control groups. The Spearman rank correlation coefficient was calculated to evaluate the correlation between each pair of examinations. The receiver operating characteristic curve analysis was performed to assess the sensitivity and specificity as a function of the cutoff values for TMH and TMA measurements as well as for the SMTube testing.

RESULTS

Subjects and Examinations

No statistically significant differences were found in both age and male-to-female ratio between the DED and normal control groups. The ages of the subjects ranged from 36 to 86 years in the DED group, and from 14 to 82 years in normal control group, respectively. There were no statistically significant differences between the testing scores of the right and left eyes at any examination point in DED subjects and control subjects ($P>0.6$). All test scores obtained from DED subjects were significantly lower than those from the control subjects (Mann–Whitney *U* test, $P<0.001$).

Dry Eye Symptom Questionnaires

The mean OSDI total score was 36.0±27.2 in the DED group and 11.4±13.0 in the control group. However, the mean DEQS total score was 34.9±22.0 in the DED group and 9.8±13.6 in the control group (Table 2).

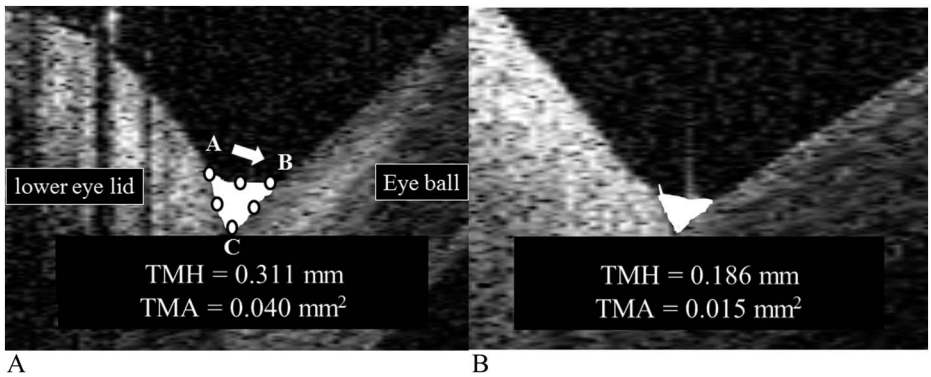

FIG. 3. Schema showing tear meniscus height (TMH) and TM area (TMA) calculations in a normal (A) and dry eye subject (B). A cross-sectional image across a central cornea is shown. Points A, B, and C represent "eye lid–tear meniscus" junction, "tear meniscus–eye" junction, and "eye–eye lid" junction, respectively. TMH measure is defined as the length between points A and B, whereas the TMA measure (overpainted with white color) was defined as the internal area of the zone wrapped by the peripheral curves passing through points A, B, C, and their midpoints in the prescribed order (indicated by an *arrow*).

FIG. 4. The setting of SMTube testing. The examination in this study was conducted with the aid of a chin stage, a slitlamp, and a biomicroscopy unit.

TMH and TMA Measurements

In this study, we merely analyzed the inferior TM parameters because the inferior TM dominates the total volume of the present tears.[12] Both TMH and TMA calculations showed significantly lower values in the DED subjects (0.138±0.102 mm and 0.013±0.015 mm^2, respectively) compared with the normal controls (0.271±0.108 mm and 0.033±0.025 mm^2, respectively) ($P<0.001$) as shown in Table 2.

SMTube Testing

The mean SMTube values were found to be 1.4±2.3 mm for the DED group and 5.8±3.2 mm for the control subjects, respectively (Table 2).

TABLE 2. *Comparison of DED Parameters Between the DED Subjects and Controls*

Ocular Surface Test	DED, n=43 Eyes	Controls, n=49 Eyes
OSDI	36.0±27.2 (0–93.2)	11.4±13.0 (0–68.8)[a]
DEQS	34.9±22.0 (5–83.3)	9.8±13.6 (0–50.0)[a]
SMTube, mm	1.4±2.3 (0–13)	5.5±2.8 (2–14)[a]
OCT-TMH, mm	0.138±0.102 (0–0.426)	0.271±0.108 (0.132–0.685)[a]
OCT-TMA, mm^2	0.013±0.015 (0–0.067)	0.033±0.025 (0.007–0.152)[a]
BUT, sec	2.4±1.2 (1–6)	10.0±2.5 (6–16)[a]
Schirmer, mm	1.7±3.0 (0–11)	17.1±11.4 (6–36)[a]
FS	5.2±2.0 (1–9)	0.0±0.0 (0–0)[a]
LS	6.1±2.1 (3–9)	0.0±0.0 (0–0)[a]

Values are given as mean±SD (range).

[a]Statistically significant differences were found by Mann–Whitney *U* test ($P<0.001$).

DED, dry eye disease; OSDI, Ocular Surface Disease Index; DEQS, Dry Eye–related Quality-of-life Score; SMTube, Strip Meniscometry Tube; OCT, optical coherence tomography; TMH, tear meniscus height; TMA, tear meniscus area; BUT, break-up time; FS, fluorescein; LS, lissamine green.

Tear Function and Vital Staining Examinations

As shown in Table 2, the BUT and vital staining scores were significantly worse in the DED group than in the control subjects ($P<0.001$). The Schirmer test score was also found to be significantly lower in the DED patients compared with the normal controls ($P<0.001$) (Table 2).

Correlation Among SMTube and DED Parameters

The results of Spearman correlation by rank test is shown in Figure 5. A strong linear positive correlation between the SMTube score, BUT, Schirmer test, and OCT parameters were observed. The correlation between the SMTube score and the TMA in confocal microscopy was notably strong ($r=0.86$). A strong linear negative correlation between the SMTube scores, confocal parameters, and vital staining scores were also observed (Fig. 5).

Sensitivities and Specificities of SMTube and TMH and TMA

When the cutoff value of SMTube testing was set at less than 4.0 mm, the sensitivity and specificity of SM Tube were found to be 93% and 72%, respectively. Similarly, when the cutoff value of TMH was set at less than 0.197 mm, the sensitivity was 74% and the specificity was 78%. When the cutoff value of TMA was set at less than 0.020 mm^2, the sensitivity of testing was 81% and the specificity was 67% (Fig. 6). The selection of these cutoff values was based on the highest diagnostic accuracy.

DISCUSSION

SMTube is a simple and a noninvasive tool for measuring the TM volume, which can be swiftly performed in 5 sec without anesthesia, using a slitlamp microscopy. The original SM was reported in 2006 by Dogru et al.[7] who have shown a statistically significant linear correlation with DR-1 grades, the Schirmer test, tear film BUT, and ocular surface vital staining scores. The authors also noted a strong correlation between the original SM and the Schirmer test ($r=0.59$) with the Spearman correlation by rank test.[7] Ibrahim et al.[13] reported the efficacy of TMH measurement in the diagnosis of DED using the Visante AS-OCT (Carl Zeiss Meditec, Inc. Oberkochen, Germany). The correlation between the original SM and the lower TMH measured by Visante AS-OCT was found to be strong at 0.70 (Spearman correlation test, $P\leq0.001$).[13] Fukuda et al.[6] used the CASIA SS-1000 AS-OCT TMH and TMA parameters in the evaluation of the TM of 26 healthy subjects for the first time and concluded the testing to be a practical method for quantitatively evaluating the tear fluid with satisfactory intergrader and interimage repeatability. In addition, the authors reported significant correlations between TM measurements by CASIA SS-1000 AS-OCT and vital staining scores, Schirmer test values, and tear film BUT scores in DED subjects.[14] The authors also concluded that an investigation into the correlation of OCT parameters with SM would add to the literature. We used the same system in dry eye patients comparing the results with healthy individuals and also evaluated the correlation of OCT parameters with SMTube testing and two symptom questionnaires, the DEQS and the OSDI. The correlation between the SMTube and TMH measured by CASIA SS-1000 AS-OCT was

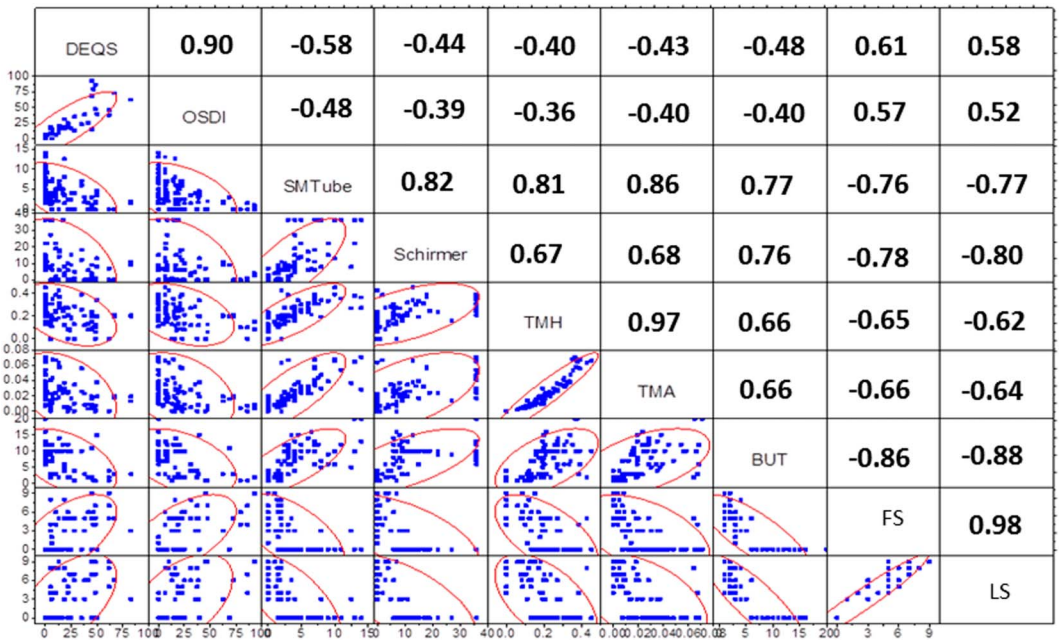

FIG. 5. Spearman correlation by rank test of the tear meniscus and dry eye test parameters.

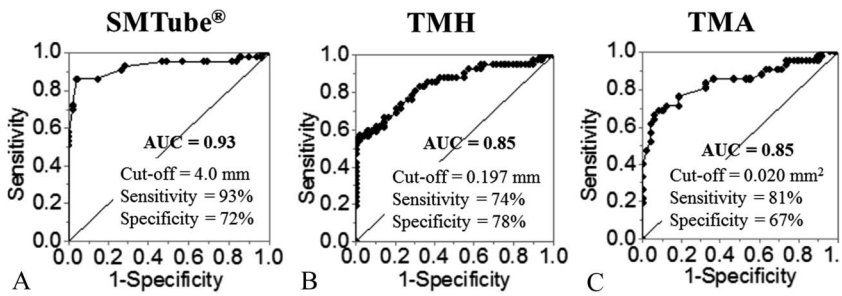

FIG. 6. Receiver operating characteristic analysis for cutoff values, sensitivities and specificities of SMTube and tear meniscus height and TM area.

higher in our study (at 0.81) than that reported by Ibrahim et al using the Visante AS-OCT system. We believe that this difference may be due to the difficulties of alignment of Visante AS-OCT during testing because it is a manual and a time domain system, and the image is two dimensional. The capturing of a satisfactory image from the onset of a blink at the right location on the TM and the related measurement may take time. However, the aligning of CASIA SS-1000 AS-OCT is automatic and the measurement is completed in an instant. Such a system may be more useful for the measurement of an unstable meniscus with a low tear retention volume after blinking in dry eye subjects. Based on the results of the current study, we believe that TMH measured by CASIA SS-1000 AS-OCT is useful in evaluating the TM status in dry eyes showing a good correlation with the SMTube testing. Comparative studies using both systems on the same subjects might provide more precise information in future trials. The SMTube testing should also be applied to the evaluation of the efficacy of different dry eye treatment modalities in the near future. It should be noted that the current investigation was a pilot, descriptive but not a diagnostic accuracy study showing preliminary data on cutoff and diagnostic accuracy of the SMTube and CASIA SS-1000 AS-OCT testing that needs to be validated in future trials. A broader diagnostic accuracy study is underway that is testing the repeatability, reproducibility, and interobserver agreement. It should also be noted that binocular analysis of the data might have introduced bias, and future research should include single-eye analysis. Finally, subjects with definite DED according to the Japanese dry eye diagnostic criteria were registered in this study. Most patients in this trial had severe dry eye disease and the results should be judged accordingly. Further trials including dry eye patients with mild to moderate disease should be conducted.

In conclusion, the SMTube testing seems to be useful in the diagnosis of DED. The CASIA SS-1000 AS-OCT TM measurement was also found to be helpful in the evaluation and verification of the efficacy of SMTube testing for the diagnosis of DED.

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