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Correlation between optical coherence tomography-derived assessments of lower tear meniscus parameters and clinical features of dry eye disease

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Abstract

Purpose—To measure the correlation between subjective symptom score, conventional clinical tests, and Fourier-domain optical coherence tomography (FD-OCT) of lower tear meniscus parameters in patients with dry eye disease.

Methods—Eighteen patients with dry eye disease requiring medical therapy and/or punctal occlusion were recruited for this prospective, nonrandomized, observational case series.

Severity of symptoms of dry eye disease was assessed using the Indiana Dry Eye Questionnaire 2002. Clinical assessments were completed using slit-lamp biomicroscopy, rose bengal dye staining, fluorescein tear break-up time (TBUT), and 5-minute Schirmer's test with topical anesthesia. The lower tear meniscus was imaged using a FD-OCT system with 5-μm axial resolution and measured manually by a masked grader using computer calipers. Correlation was assessed using Spearman's correlation coefficient (ρ).

Results—The mean scaled symptom score was 58 ± 21 (±SD), with a range of 0 to 100. Vital staining test averaged 1.7 ± 3.4, TBUT averaged 4.4 ± 1.8 seconds, and Schirmer's tests averaged 10.2 ± 8.1 mm. As determined by OCT, the meniscus height was 228 ± 153 μm, depth was 127 ± 79 μm, and cross-sectional area was 0.018 ± 0.021 mm^2. OCT meniscus area was negatively correlated with the symptom questionnaire score ($P < 0.01$) and positively correlated with Schirmer's test results ($P < 0.01$). There was no significant correlation between symptom score and rose bengal staining, TBUT, or Schirmer's test results ($P > 0.01$).

Conclusions—Lower tear meniscus measurement with FD-OCT is an objective, noninvasive test that correlates well with symptoms of dry eye disease and the Schirmer's test.

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Keywords

dry eye disease; optical coherence tomography; tear meniscus; symptoms; rose bengal; Schirmer's; tear breakup time

Dry eye disease is a common condition worldwide.[1-7] Severe dry eye disease may cause significant discomfort and ocular surface damage. Despite the availability of numerous clinical and investigational tools, no gold standard diagnostic test exists.[8-10] The complexity of diagnosis and management of dry eye disease pertains to the difficulty of correlating patient symptoms and objective, quantitative clinical findings.[8-17] Therefore, many clinicians diagnose and manage dry eye disease based solely on symptoms. Disease management and development of new therapies[18-25] could be aided by the development of a reliable noninvasive diagnostic approach to evaluate disease severity and treatment efficacy.

The current literature on tomographic characterization of the tear film and tear menisci suggests that parameters produced by optical coherence tomography (OCT) are good quantitative indicators of tear volume.[26-35] Fourier-domain (spectral) OCT allows much faster data acquisition compared to time-domain OCT and may also improve measurement reliability and accuracy.[26-27] Before adopting OCT for management of dry eye disease, correlations between OCT measurements and conventional clinical tests should be evaluated. In this report, we sought to determine the correlation between subjective symptoms, rose bengal vital staining score, tear break-up time (TBUT), Schirmer's test, and OCT lower tear meniscus parameters in patients with a clinical diagnosis of dry eye disease.

MATERIALS AND METHODS

Patients and procedures

Patients with dry eye disease requiring artificial tears, medical therapy (cyclosporine 0.05%), and/or punctal occlusion were recruited from the Doheny Eye Institute Dry Eye Clinic for this prospective, non-randomized, observational study. The only exclusion criterion was a requirement that no eye drops be instilled 2 hours before OCT imaging, to ensure that the effects of medications on tear film was negated. The research was approved by the Institutional Review Board at the University of Southern California and was in accordance to the tenets set forth in the Declaration of Helsinki. Written informed consent was obtained from each patient and all procedures and data management conformed to the Health Insurance Portability and Accountability Act of 1996.

A single certified clinical coordinator technician (SR) conducted all tests, including OCT imaging, rose bengal dye staining, TBUT, and the 5-minute Schirmer's test with topical 0.5% proparacaine (Proparacaine hydrochloride ophthalmic solution, 0.5%, Alcon Laboratories, Fort Worth, TX, USA). Rose bengal dye staining, TBUT, and 5-minute post-anesthetic Schirmer's test were performed and scored as previously described.[36] Both rose bengal and fluorescein TBUT staining were performed on the same day, after OCT imaging. Briefly, for rose bengal, a drop of sterile non-preserved saline was instilled on a dye-impregnated strip (RoseGlo™, Sigma Pharmaceuticals, Monticello, IA). Excess fluid was shaken off before gentle application of the tip of the strip on the inferior palpebral conjunctiva. The patient was requested to blink a few times to promote uniform coating of the ocular surface. After 30 seconds, slit-lamp examination was performed for staining pattern and density, and a numerical score was obtained per the National Eye Institute workshop grading system.[36] Fluorescein TBUT was performed in a similar fashion using a fluorescein-impregnated strip (Ful-Glo™, Akorn Pharmaceuticals, Lake Forest, IL). The TBUT was recorded in seconds, from the time of eyelid opening to the appearance of the

first dry spot formation on the cornea. Schirmer's test was performed by placing a Schirmer's strip (TearFlo™, HUB Pharmaceuticals, Rancho Cucamonga, CA) at the junction of the mid and lateral thirds of the lower eyelid after instillation of one drop of proparacaine and removal of the excess fluid with a dry cotton-tipped applicator. Subsequently, the patient was instructed to look forward for five minutes, blinking normally but refraining from talking. After 5 minutes, the Schirmer's strip was removed, and the amount of wetting was measured. Examination by slit-lamp biomicroscopy was performed by an ophthalmologist.

Scaled Symptom Score

The patients were instructed to complete the 6-page Indiana University Dry Eye Questionnaire 2002 (research.opt.indiana.edu/Labs/CorneaContactLens/DEQ.pdf) for symptom assessment by one investigator (SR) at the beginning of the visit. A scaled symptom score, i.e., a disease severity index, was computed from an average of scores collected from questions 6-18. The graded responses were scaled such that "0" was the least severe and "100" was the most severe. No distinction was made between eyes.

OCT imaging procedure

The lower tear meniscus was imaged at the inferior cornea-lid junction with a 6-mm vertical × 2.8-mm depth scan using a Fourier-domain OCT system (RTVue, Optovue, Inc., Fremont, CA). The OCT system was equipped with a corneal adaptor module with a 5-μm axial resolution and 15-μm transverse resolution (Fig. 1A, inset). Ambient temperature was regulated at 21°C, and there was no airflow except for the ceiling central air conditioning system. Each patient was directed to rest his or her chin on the chinrest with the forehead pressed against the forehead band. The patient was then instructed to fixate on an internal target, blink, and then refrain from blinking until completion of the 3-second scan. Immediately after completion of the scan and storage of the data, the patient was instructed to blink before a second scan. Both scans were performed 2 seconds after the blink. For each patient, only measurements from the right eye were included for analysis.

OCT lower tear meniscus parameter measurement

The measurement techniques have been described previously.[27] Briefly, the OCT images (Fig. 1) were exported for manual computer caliper measurement using the ReVue RTVue software (version 4.0, Optovue). The lower tear meniscus height was defined as the distance from the cornea-meniscus junction to the lower eyelid-meniscus junction (Fig. 1B). The depth was measured from the midpoint of the air-meniscus interface to the cornea-lower eyelid intersection (Fig. 1B). The two-triangle approximation was used for area calculation (Fig. 1C). The angle was estimated from the angle between the inferior cornea and the lower tear meniscus surface. The two-triangle approximation was selected for its simplicity and for its good approximation of the tear meniscus compared to polygonal approximation (unpublished data). The saline group refractive index of 1.342 at the 830-nm wavelength was used to correct measurements for the effect of refraction at the air–meniscus interface.[37-38] All measurements were performed by one masked experienced investigator (PN).

Statistical analysis

To avoid statistical complications from correlation between the right and left eyes, measurements from only the right eye of each patient were analyzed. The statistical significance level was set to $P < 0.01$ to minimize spurious correlation.[39] The between-test correlations were assessed by means of non-parametric Spearman's correlation coefficient

(ρ) because of the small sample size. Descriptive statistics were calculated for all variables and expressed as mean ± standard deviation (SD), unless stated otherwise.

RESULTS

A total of 18 patients and 18 right eyes were included in this study. The patient characteristics are detailed in Table 1. Most of the patients were both Caucasian and female. The mean age was 56.6. Many of these patients had other systemic co-morbidities. All were using artificial tears, and two-thirds were using topical cyclosporine. Other therapies included punctal plugs and punctal cauterization (Table 1).

The dry eye symptom score and measurements are provided in Table 2. The mean scaled symptom score was 58, suggesting persistence of symptoms despite polytherapy. The vital staining score with rose bengal was 1.7, and in 15 of our 18 patients the staining score was within the normal range according to the criterion recommended by the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes.[36] Tear film stability measured by TBUT was 4.4, compared to the commonly accepted normal limit of 10 seconds.[36] The basal tear secretion rate measured by Schirmer's test ranged from 0 - 25 mm, encompassing values characteristic of normal and severe aqueous tear deficiencies.

Lower tear meniscus measurements by Fourier-domain OCT are also detailed in Table 2. The meniscus height averaged 228, depth averaged 127, and area averaged 0.018. The meniscus angle averaged 30 degrees. Spearman's analysis did not reveal any significant association between the angle and any other diagnostic test, including OCT area, height, and depth, and thus was omitted from any further analysis.

Spearman's correlation coefficient analysis did not reveal a significant relationship between symptom score and staining score, TBUT, or Schirmer's tests, (Spearman's $\rho = 0.168$, -0.229, and -0.357, respectively, with $P > 0.01$). Vital staining score and TBUT were not significantly correlated with any of the OCT meniscus variables; but vital staining score showed a trend toward a negative correlation with Schirmer's test score ($\rho = -0.488$, $P = 0.04$, (Table 3). Here, we observed negative correlation between the symptom score and the meniscus height (Spearman's $\rho = -0.556$, $P = 0.018$, Table 3), the meniscus depth (Spearman's $\rho = -0.595$, $P = 0.009$, Table 3), and the area (Spearman's $\rho = -0.602$, $P = 0.008$, Table 3, Fig. 2). Similarly, there was a strong positive correlation between the Schirmer's test results and OCT meniscus parameters. The overall significance was supported by each of the three lower meniscus variables (Table 3): height ($\rho = 0.754$, $P < 0.001$), depth ($\rho = 0.772$, $P < 0.001$), and area ($\rho = 0.729$, $P < 0.001$, Table 3, Fig. 3).

DISCUSSION

Despite the availability of numerous quantitative tools to assist the diagnosis and management of dry eye disease, correlating symptoms and signs remains a challenge. Vital dye staining test, tear break-up time, Schirmer's test, and the cotton-thread test are easily administered, but the correlations between these various tests and between the tests and the patients' subjective symptoms are poor in many published studies.[8-17] These tests could confound results by disrupting the natural tear film, affecting tear production, and modifying the meniscus structure. Although these tests are helpful, the low repeatability and poor correlation with symptoms highlight the need for minimally invasive, objective, and informative tools.

Tear film insufficiency is correlated with tear meniscus measurements.[15,30,40-45] OCT has the advantage of being a noninvasive *in vivo* technique for quantitative measurement of the tear film and tear menisci, not requiring ocular surface contact or dye instillation. Compared

to time-domain OCT, Fourier-domain OCT provides higher scan speed and image resolution and may allow even more precise and expedient tear meniscus evaluation. Review of the literature suggests that OCT technology provides an objective and reliable tool for quantitative lower tear meniscus measurement.[29-35]

We performed a quantitative analysis of the lower tear meniscus using Fourier-domain OCT. The OCT lower tear meniscus results were consistent with previous publications in this area. [28,30,32-33,35,40,42,43,45-48] The meniscus measurements for patients in this cohort were lower than those of normal patients and were in concordance with previously reported measurements for patients with dry eye disease. For healthy subjects, the published mean OCT lower meniscus heights ranged from 190 to 400 μm, with most values falling between 240 and 290 μm. Published mean OCT lower meniscus areas ranged from 0.016 to 0.034 mm^2, with most researchers reporting values between 0.021 and 0.029 mm^2.[28,30,32-33,43,45-48] For dry eye patients, most reported mean OCT lower meniscus heights ranged from 140 to 250 μm, and most lower meniscus areas were in the range of 0.0095 to 0.018 mm^2.[30,33,43,48-49] The values from our cohort were in good agreement with Ibrahim et al.[33,49] and Yuan et al.[43] In fact, Ibrahim and colleagues found a significant correlation between upper, as well as lower, tear meniscus height measurement, with slit lamp measurement, strip meniscometry, TBUT, vital stain, and Schirmer's test, using Spearman's correlation. Caution is advised, however, when performing comparisons among studies. Variability among patient demographics, measurement protocols, or OCT systems may yield different results.

The present work demonstrated significant correlations between the Schirmer's scores and all three OCT-determined lower meniscus parameters ($P < 0.01$). Our data are consistent with recent findings by Kim et al.,[45] though a stronger correlation was detected in our study. One would expect to find a good correlation between the Schirmer's test and lower tear meniscus parameters because the Schirmer's test measures tear production and the tear meniscus area is related to tear volume.[49] And tear production rate should be closely related to tear volume. This correlation suggests that noninvasive OCT has the potential to serve as a good substitute for Schirmer's test, which if not performed with care, could be irritating to the patient, provoke variable reflective tearing, and yield unreliable results.

We found a significant negative correlation between symptom scores and the OCT lower meniscus area ($P < 0.01$). In contrast, the symptom scores were not significantly correlated with the rose bengal staining score, TBUT, or Schirmer's test. Although symptoms of ocular discomfort represent only one aspect of dry eye disease, these symptoms are the primary driver of clinical management.[50] Neither TBUT nor Schirmer's test alone were sufficiently sensitive and specific indicators. The good correlations between OCT lower meniscus parameters and Schirmer's test and subjective symptoms suggest that they may be useful in the diagnosis and management of dry eye disease. The Indiana questionnaire was selected in this study instead of validated instruments such as the NEI Visual Functioning Questionnaire-25 (NEI VFQ-25) and the Ocular Surface Disease Index (OSDI) for the following reasons. The VFQ-25 evaluates visual function and ocular health in general. The OSDI surveys vision related function, ocular symptoms and enviromental triggers. Schiffman et al, 2000 demonstrated that the OSDI is an excellent tool for the evaluation of dry eye disease with good correlation well with other questionnaires.[51] The authors, however, found that the OSDI scores do not correlate well with traditional objective clinical measures of dry eye, such as Schirmer test type I. Begley et al, 2002 concluded that the Indiana DEQ is a sensitive test for dry eye disease.[52] Accordingly, we used the Indiana questionaire to correlate subjective symptoms with objective clinical measures and OCT tear meniscus measurements. Consequently, the correlations found in this study may not be extrapolated to other validated symptom assessment surveys.

In this study, we demonstrated a significant correlation between FD-OCT lower tear meniscus parameters and a scaled subjective score, as well as the conventional Schirmer's test. We did not detect a significant correlation between symptom scores and rose bengal staining score, TBUT, or Schirmer's score. These findings suggest that FD-OCT measurement of the lower tear meniscus may be useful for the quantification of tear volume and evaluation of dry eye disease, especially when reliable and objective outcomes are required, such as in clinical trials and epidemiological studies.[50,53-54] Given our small sample size, larger studies are needed to validate the clinical utility of FD-OCT in the diagnosis and management of dry eye disease.

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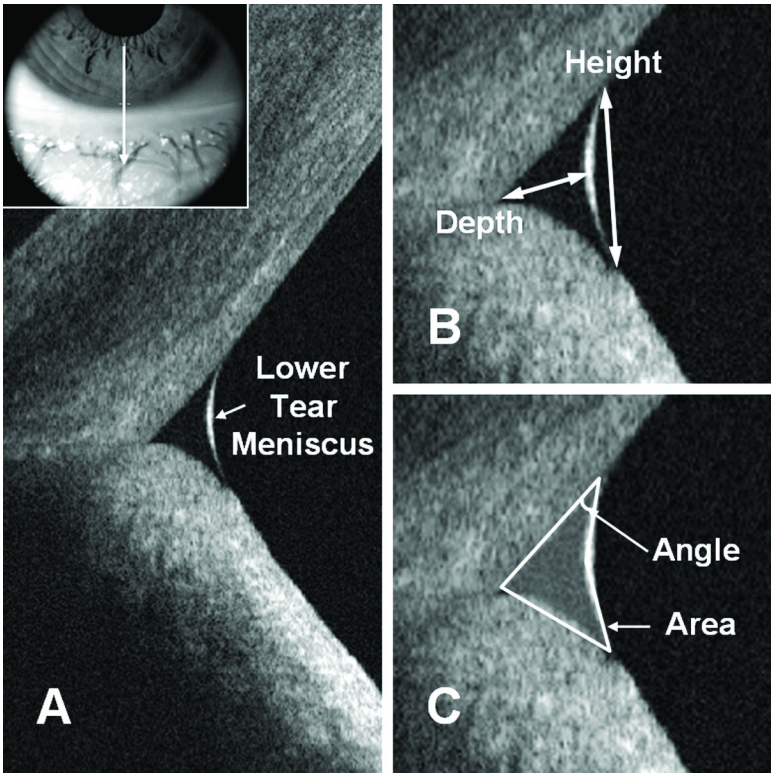

Figure 1.
Lower tear meniscus measurement. **(A)** Anatomy of the lower tear meniscus; the inset illustrates the scan position. **(B)** and **(C)** Caliper measurement protocol.

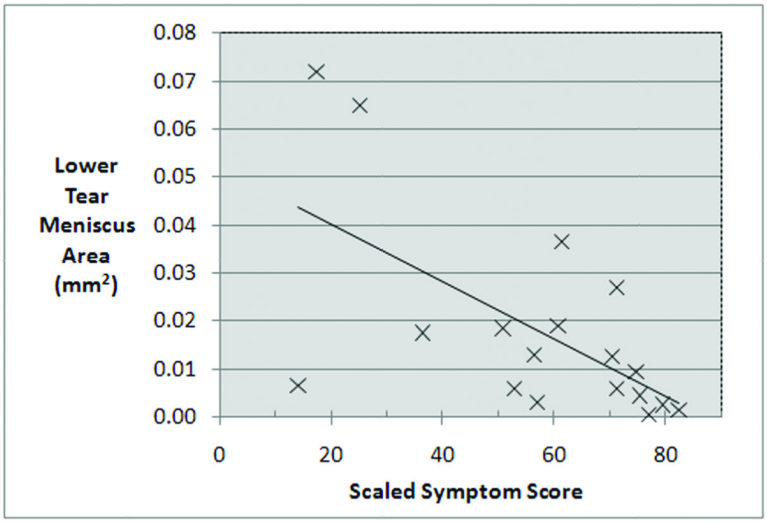

Figure 2.
Scatter plot of OCT lower tear meniscus area versus scaled symptom score. There was a significant negative correlation between the lower tear meniscus area and the scaled symptoms score.

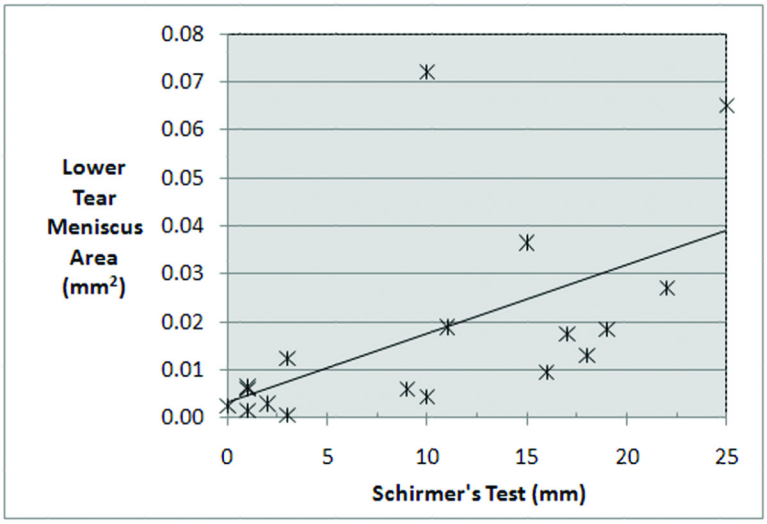

Figure 3.
Scatter plot of OCT lower tear meniscus area versus Schirmer's test. There was a significant positive correlation between the lower tear meniscus area and the Schirmer's test score.

Table 1

Characteristics of Dry Eye Patients in This Study

Demographics	
No. of patients	18
Age (mean ± SD, range)	56.6 ± 15, 19 - 88
Race (% Caucasian)	61
Gender (% female)	72
Contact lens wearer (%)	28
Best corrected visual acuity (mean, range)	20/23.3, 20/15 - 20/40
Right (range)	20/20 - 20/40
Left (range)	20/15 - 20/40
Intraocular pressure (mmHg)	13.0 ± 2.8
Right (mean ± SD)	12.8 ± 2.9
Left (mean ± SD)	13.1 ± 2.8
Dry eye therapy (%)	
Artificial tears	100
Topical cyclosporine 0.5%	67
Punctal plugs	39
Punctal cauterization	11
Ocular co-morbidity (%)	
Meibomian gland disease	67
Sjögrens syndrome	11
History of LASIK	11
Systemic co-morbidity (%)	
Hypertension	44
Drug or seasonal allergy	39
Hypothyroidism	22
Rheumatoid arthritis	22
Psychiatric disorders	22
Cancer	17
Sinus disease	11
Asthma	11
Diabetes mellitus	11
Lupus	6

Table 2

Summary of Test Results for Dry Eye Patients

	Conventional Clinical Dry Eye Tests				OCT Lower Tear Meniscus			
	Symptom Score	**Rose Bengal**	**TBUT (s)**	**Schirmer's (mm)**	**Height (mm)**	**Depth (mm)**	**Area (mm2)**	**Angle (deg)**
Mean	58	1.7	4.4	10.2	228	127	0.018	30
Standard Deviation	21	3.4	1.8	8.2	153	79	0.021	10
Minimum	14	0.0	1.0	0.0	38	18	0.001	17
Maximum	82	12.0	8.0	25.0	591	294	0.072	65

Table 3

Correlations among Measurements by Nonparametric Spearman's (ρ)

	Rose Bengal	Tear Breakup	Schirmer's Test	OCT Lower Tear
Scaled Symptom Score	-	-	-	-0.602 *0.008*
Rose Bengal		-	-	-
Tear Breakup Time			-	-
Schirmer's Test				0.729 *0.0006*

OCT= optical coherence tomography.

Note: For each cell, the top number represents Spearman's coefficient ρ and the bottom italicized number denotes the P value. Nonsignificant correlations (P > 0.01) are not shown.