Title

Correlation of Measures From the OCULUS Keratograph and Clinical Assessments of Dry Eye Disease in the Dry Eye Assessment and Management Study

Journal

Cornea, 41(7)

ISSN

0277-3740

Authors

Sutphin, John E
Ying, Gui-shuang
Bunya, Vatinee Y
et al.

Publication Date

2022-07-01

DOI

10.1097/ico.0000000000002804

Peer reviewed

Correlation of Measures From the OCULUS Keratograph and Clinical Assessments of Dry Eye Disease in the Dry Eye Assessment and Management Study

John E. Sutphin, MD, Gui-shuang Ying, PhD,† Vatinee Y. Bunya, MD, MSCE,† Yinxi Yu, MS,† Meng C. Lin, OD, PhD,‡ Kathleen McWilliams,† Elizabeth Schmucker, BA,§ Eric J. Kuklinski, BA,¶ Penny A. Asbell, MD,‖ and Maureen G. Maguire, PhD,†*
for the Dry Eye Assessment and Management (DREAM) Study Research Group

Purpose: The purpose of this study was to compare objective, noninvasive assessments of tear function using the OCULUS Keratograph with the corresponding clinical assessments [tear break-up time (TBUT), Schirmer test, and bulbar erythema] among patients with moderate-to-severe dry eye disease.

Methods: Participants in the Dry Eye Assessment and Management study at centers having an OCULUS Keratograph were assessed using standardized procedures. Associations between the assessments from the Keratograph [noninvasive keratograph break-up time (NIKBUT), tear meniscus height (TMH), and bulbar redness (BR)] and clinical examination (TBUT, Schirmer test, and bulbar erythema) and between these test results and Ocular Surface Disease Index (OSDI) scores were summarized with Spearman correlation coefficients (r_s); 95% confidence intervals (95% CI) accounted for intereye correlation.

Results: Among 288 patients (576 eyes), the mean (standard deviation) age was 56.6 (13.8) years, 78.1% were female, and the mean baseline OSDI score was 44.3 (14.0). The mean was 2.9 (1.5) seconds for TBUT and 8.2 (5.7) seconds for NIKBUT (their correlation $r_s = 0.18$, 95% CI = 0.09–0.28). The mean was 10.6 (7.6) mm for the Schirmer test and 0.3 (0.2) mm for TMH ($r_s = 0.15$, 95% CI = 0.04–0.25). The median clinical grade redness was mild, and the mean BR score was 1.1 (0.5) ($r_s = 0.25$, 95% CI = 0.15–0.35). Correlation between results of each of the 6 tests and OSDI scores was low (r_s from −0.07 to 0.05).

Conclusions: In the Dry Eye Assessment and Management study, NIKBUT, TMH, and BR were weakly correlated with their clinical counterparts. No measurements were correlated with the OSDI score.

Key Words: dry eye disease, Keratograph, DREAM study, tear film

(*Cornea* 2021;00:1–7)

Although dry eye disease (DED) is a common ocular eye condition, routine diagnosis and clinical evaluation are not precisely specified.[1] The severity of symptoms is not highly correlated with the severity of signs that are used to assess tear production and the quality and damage to the ocular surface.[2] Routine measures of symptoms and signs vary both within and between examination sessions.[1,3] At least part of the variability is due to subjective components of the measurement of signs and variation in the administration of the testing procedures. These subjective components are also vulnerable to evaluation error and bias by the examiner. In addition, current clinical assessment requires topical administration of fluorescein dye solution [corneal staining and tear break-up time (TBUT)] or lissamine green dye solution (conjunctival staining) or attaching paper strips to the eyelid (Schirmer test) that may be uncomfortable for the patient. Noninvasive or minimally invasive objective metrics would help standardize the clinical assessment of DED and

Received for publication March 29, 2021; revision received April 23, 2021; accepted May 11, 2021.

From the *Department of Ophthalmology, University of Kansas, Prairie Village, KS; †Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA; ‡School of Optometry, University of California, Berkeley, CA; §Department of Mathematics, Cornell University, Ithaca, NY; ¶Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY; and ‖Department of Ophthalmology, University of Tennessee, Memphis, TN.

Supported by cooperative agreements from the National Eye Institute, National Institutes of Health, Department of Health and Human Services (U10EY022879, U10EY022881, and R21EY031338). Additional support provided by grants from the Office of Dietary Supplements National Institutes of Health, Department of Health and Human Services. Immco Diagnostics, Inc. (Buffalo NY) provided blood drawing supplies and shippers to the study clinical centers and provided test results on autoantibodies from their Sjo test.

P. A. Asbell has received research funding from MC2 Therapeutics and Novartis; consultant fees from Novartis, ScientiaCME, Shire, and WebMD; and travel/financial compensation from Novartis, Santen, ScientiaCME, and Shire. V. Y. Bunya has received research funding from Bausch & Lomb/Immco Diagnostics and support from the National Eye Institute R01 EY026972. The remaining authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

The members of the Dry Eye Assessment and Management (DREAM) Research Group are listed in the Appendix (Supplemental Digital Content 15, http://links.lww.com/ICO/B249).

Correspondence: John E. Sutphin, MD, Department of Ophthalmology, University of Kansas, 7400 State Line Rd, Suite 100, Prairie Village, KS 66208 (e-mail: jsutphin@kumc.edu).

may provide better outcome measures for monitoring the effects of treatment.[4]

Recently, methods have been introduced to provide noninvasive, objective measures of some of the signs of DED. The OCULUS Keratograph 5M (OCULUS, Wetzlar, Germany) is a point-of-care device that provides assessments of noninvasive tear break-up time (NIKBUT), as assessed by Keratograph, tear meniscus height (TMH), and bulbar redness (BR), and allows infrared imaging of the meibomian glands, meibography. The Keratograph does not require the use of any drops or contact with the eye.

The Dry Eye Assessment and Management (DREAM) study was a multicenter, randomized clinical trial of omega-3 fatty acid supplementation for DED.[5] Enrolled subjects had moderate-to-severe DED symptoms, as defined by the results from the Ocular Surface Disease Index (OSDI), and demonstrated the same signs of DED on slit-lamp examination (TBUT, corneal staining, and conjunctival staining and/or Schirmer test with anesthesia) on 2 visits approximately 2 weeks apart. The DREAM study used minimally restrictive inclusion and exclusion criteria to include a wide range of patients with moderate-to-severe DED. This population represents patients with typical symptomatic DED who request further treatment from eye care providers despite their current dry eye treatments. The data from the DREAM study provide an opportunity to explore the association of these noninvasive measures (referred to hereafter as "keratographic" measures) with their traditional counterparts and with symptoms in a group of well-defined patient population with moderate-to-severe DED. In addition, the data allow the exploration of whether any of these tests may better separate aqueous deficient patients [patients with Sjögren syndrome (SS) as an example] from evaporative loss patients (patients with meibomian gland dysfunction as an example).

METHODS

Study Cohort and Study Design

The DREAM study was a multicenter, double-masked clinical trial designed to evaluate the effectiveness and safety of omega-3 fatty acid supplements for the treatment of DED. Details of the study methods have been published previously.[5,6] In brief, patients were recruited at 27 sites throughout the United States. Patients were required to be 18 years of age or older, demonstrating at least 2 of 4 qualifying signs (conjunctival staining $\geq$1, corneal fluorescein staining $\geq$4, TBUT $\leq$7 seconds, and Schirmer test $\geq$1 to $\leq$7 mm/5 min) in the same eye at a screening and at an eligibility confirmation visit approximately 14 days later. The patient's average score from the 2 visits on the OSDI needed to be 23 or greater. Patients were excluded if they were pregnant or nursing, had a history of contact lens wear during 30 days before the screening visit, had ocular surgery within 6 months of the screening visit, used glaucoma medication, or had eyelid abnormalities that affect lid function. Patients who were regularly using treatments for DED, including artificial tears, cyclosporine, lid soaks, lid scrubs, and baby shampoo, were allowed to continue those treatments if they committed to using them for the next 12 months. The study protocol was approved by the institutional review board associated with each center, performed under an Investigational New Drug application for the Food and Drug Administration, and registered on ClinicalTrials.gov (NCT02128763). All patients provided written informed consent.

Clinical Measurements

A DREAM clinician who had completed a certification program for clinical assessment performed an examination of each eye during the screening and eligibility confirmation visit (eg, baseline). Bulbar erythema was evaluated during slit-lamp examination as none (normal), mild (a flush reddish color), moderate (more prominent red color), or severe (definite redness). Scores for these grades of erythema were 0 to 3, respectively. To measure TBUT, 5 μL of 2% fluorescein was instilled in the inferior cul-de-sac of the eye by using an Eppendorf micropipette. The measurement of TBUT began 30 seconds after instillation of fluorescein dye. The examiner viewed the cornea through a slit lamp using broad beam cobalt blue illumination and a yellow barrier filter. The examiner instructed the patient to blink and used a stopwatch to measure the time between the blink and the appearance of the first discontinuity in the tear film. TBUT was measured 3 times and averaged for each eye. The Schirmer test was performed bilaterally using Schirmer test strips. Approximately 5 minutes after instillation of a topical anesthetic, test strips were hung onto the lower conjunctival sac in the temporal one-third of the lid. The patient was instructed to close both eyes. After 5 minutes, as measured by a stopwatch, the strips were removed and the length of wetting of the strip recorded in millimeters. A novel device (Meibomian Gland Evaluator, Johnson & Johnson) to apply a standard amount of pressure against approximately 5 meibomian glands of the lower eyelid was used, and the glands were observed for the presence or absence of secretion and recorded as the number of glands with secretion. The secretions were classified as clear, opaque, or thick. The SS status was determined by serologic results.[7]

Keratographic Measurements

The OCULUS Keratograph 5M was used by DREAM-certified clinical staff (technician or clinician) to measure NIKBUT, TMH, and BR. Measurements were taken during the eligibility confirmation visit at the 13 DREAM centers with the keratograph available. The examiner followed the instructions of the manufacturer as provided in the DREAM manual of procedures (OCULUS). For the assessment of NIKBUT, the patient was instructed to blink twice and then keep their eyes open without blinking for as long as possible. The keratograph uses infrared illumination and automatically measured the time taken for the first appearance of a break in the tear film. The keratograph displayed the time to the nearest one-hundredth second. The first NIKBUT measurement, rather than the average, was recorded for statistical analysis. For the measurement of TMH, the examiner focused the keratograph's camera on the tear meniscus of the central

lower eyelid and captured an image. The examiner used the built-in ruler to measure the tear meniscus at 3 points: directly below the pupil, below the 5 o'clock position of the cornea, and below the 7 o'clock position of the cornea. The keratograph displayed the height to the nearest one-hundredth millimeter. BR was classified automatically by using the eye-image function; scores were displayed to the nearest 10th, with higher scores indicating greater redness.

Measurement of Symptoms

Each patient completed the OSDI questionnaire to assess the severity of dry eye symptoms. The OSDI is a 12-item patient-report outcome questionnaire with scores that range from 0 to 100, with higher scores indicating more severe symptoms.[8]

Statistical Analysis

The 3 Keratograph measures were compared with clinical examination results that corresponded to the same feature of DED; specifically, NIKBUT was compared with TBUT (tear stability), TMH was compared with the Schirmer test (quantity of tears), and BR was compared with bulbar erythema (BR). Intraclass correlation coefficients and 95% confidence intervals (95% CI) were used to evaluate the agreement between continuous measures from the right and left eyes of the same person. A weighted kappa statistic (mean-squared error weights) was used to evaluate the agreement between eyes for ordered categorical measures. Nonparametric Spearman correlation coefficients (r_s) were used to evaluate the correlation between noninvasive keratographic measurements and their traditional counterparts. The 95% CIs for r_s were calculated using a bootstrap procedure to account for the intereye correlation,[9] and statistical significance was indicated when the 95% CI for r_s did not cross 0. The following descriptors were used for the magnitude of the correlation coefficients: very weak ($0.0 < r_s \leq 0.1$), weak ($0.1 < r_s \leq 0.3$), moderate ($0.3 < r_s \leq 0.5$), and strong ($0.5 < r_s \leq 1.0$). Subgroup analyses were performed by the presence of SS and by the presence of meibomian gland dysfunction (plugging of or paste secretions from the central 5 glands of the lower eyelid). These correlation analyses were performed for each time point (baseline, 6, and 12 mo). The comparison of clinical and keratographic signs across 3 time points (baseline, 6, and 12 mo), between groups of patients with and without SS, and between eyes with and without meibomian gland dysfunction was performed using generalized linear models, and the correlations among repeated measures and between 2 eyes of the same subject were accounted for using generalized estimating equations.[10] Standard deviations for eye-specific measurements were calculated using generalized estimating equations to account for intereye correlation. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC), and $P < 0.05$ was considered to be statistically significant.

RESULTS

Among the 535 patients who were randomized in the DREAM study, 320 were enrolled through clinical centers having a Keratograph and 288 (90%) had imaging performed that yielded data for analysis of both eyes (see Figure 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B219). Most patients were female (78.1%) with a mean (SD) of 56.6 (13.8) years for age and 41.9 (15.4) points for the OSDI total score (Table 1). Among the 576 eyes of these 288 patients with the keratograph, the mean (SD) for TBUT was 2.9 (1.5) seconds, lower than the 8.2 (5.7) seconds for NIKBUT ($P < 0.001$). The mean (SD) for the Schirmer test was 10.6 (7.6) mm and for TMH was 0.4 (0.2) mm. Most eyes (84.6%) had bulbar erythema graded as either none (39%) or mild (46%) with a mean (SD) score of 1.2 (0.5) for BR from the Keratograph. The correlation [r_s (95% CI)] of

TABLE 1. Patient and Ocular Characteristics at Enrollment for Patients Included in This Study

Characteristic	Patients Included in This Study (N = 288)
Age (yr), mean (SD)	56.6 (13.8)
Sex, n (%)	
Female	225 (78.1)
Male	63 (21.9)
Ethnicity, n (%)	
Hispanic or Latino	56 (19.4)
Other	232 (80.6)
Race, n (%)	
White	204 (70.8)
Black or African American	25 (8.7)
Other	59 (20.5)
OSDI score, mean (SD)	41.9 (15.4)
SS*, n (%)†	28 (10.2)
	Eyes Included in This Study (N = 576)
TBUT (s), mean (SD)	2.90 (1.54)
Noninvasive keratograph break-up time (s), mean (SD)‡	8.24 (5.66)
Schirmer test (mm), mean (SD)	10.58 (7.58)
TMH at 6 o'clock (mm)	0.35 (0.18)
Conjunctiva-erythema, n (%)	
None (normal)	222 (38.5)
Mild (flush reddish color)	264 (45.8)
Moderate (more prominent red color)	86 (14.9)
Severe (definite redness)	4 (0.7)
BR score§	1.15 (0.47)
Conjunctival staining score, mean (SD)	2.88 (1.59)
Corneal staining score, mean (SD)	3.61 (3.00)
Meibomian gland dysfunction‖, n (%)	286 (49.7)

*Defined as an antibody profile that met ACR criteria and with a score of ≥3 on DREAM ocular surface staining tests.[7]
†Thirteen are missing.
‡Six are missing.
§Fifty are missing.
‖Meibomian gland dysfunction is defined as the central 5 meibomian glands plugged or secretions graded as paste or obstructed on clinical examination at baseline.
ACR, American College of Rheumatology.

measurements of clinical signs between the screening and eligibility confirmation visits was 0.64 (0.57–0.70) for TBUT, 0.70 (0.64–0.76) for Schirmer test, and 0.67 (0.61–0.74) for bulbar erythema. The mean of TBUT at 6 months and 12 months was significantly higher than baseline (3.5 vs. 3.5 vs. 2.9 seconds, $P < 0.001$, Table 2). There are no significant changes in all other clinical measures and keratography measures over time (all $P \geq 0.35$, Table 2).

When data from baseline, 6 months, and 12 months were analyzed together, SS was significantly associated with lower TBUT ($P = 0.01$) and NIKBUT ($P = 0.04$), and Schirmer test ($P = 0.005$) and TMH ($P < 0.001$). Meibomian gland dysfunction was only significantly associated with lower TBUT ($P = 0.002$) and was not significantly associated with any other clinical measures or keratography measures (all $P \geq 0.53$, Table 3). Similar results were found when data from baseline, 6 months, and 12 months were analyzed separately (see Supplemental Tables 1A, 1B, 1C, Supplemental Digital Content 2–4, http://links.lww.com/ICO/B220, http://links.lww.com/ICO/B221, http://links.lww.com/ICO/B222).

The intraclass correlation coefficient between right and left eyes at baseline was 0.63 (95% CI, 0.56–0.70) for TBUT and 0.47 (0.37–0.55) for NIKBUT. The corresponding values were 0.80 (95% CI, 0.76–0.84) for Schirmer test, 0.74 (0.68–0.79) for TMH, 0.94 (0.91, 0.98) for bulbar erythema, and 0.67 (0.61–0.74) for BR.

At baseline, weak correlations were found between TBUT and NIKBUT (Table 4, $r_s = 0.18$, 95% CI, 0.09–0.28), Schirmer test and TMH (rs = 0.15, 95% CI, 0.05–0.25), and bulbar erythema and BR ($r_s = 0.25$, 95% CI, 0.15–0.35). Similar correlations were found at 6 months and 12 months (Table 4). The correlation between their change from baselines was all weak with the largest correlation coefficient ($r_s = 0.14$, 95% CI, 0.04–0.24) for change of bulbar erythema and change of BR at 6 months (Table 4). When the correlations were evaluated within subgroups based on the presence of SS, correlations were stronger within the group of patients with SS, with a correlation coefficient of 0.35 to 0.55 at baseline (see Supplemental Table 2A, Supplemental Digital Content 5, http://links.lww.com/ICO/B223), 0.27 to 0.43 at 6 months (see Supplemental Table 2B, Supplemental Digital Content 6, http://links.lww.com/ICO/B224), and 0.26 to 0.49 at 12 months (see Supplemental Table 2C, Supplemental Digital Content 7, http://links.lww.com/ICO/B225). Correlations were similar within the groups based on the presence of Meibomian gland dysfunction (see Supplemental Tables 2A, 2B, 2C, 2D, 2E, Supplemental Digital Content 5–9, http://links.lww.com/ICO/B223, http://links.lww.com/ICO/B224, http://links.lww.com/ICO/B225, http://links.lww.com/ICO/B226, http://links.lww.com/ICO/B227).

TABLE 2. Summary of Keratography Measures and Clinical Measures Over Time

	Baseline (N = 576)	6 mo (N = 500)	12 mo (N = 518)	*P*
TBUT (s), mean (SD)	2.90 (1.54)	3.51 (3.01)	3.45 (2.51)	**<0.001**
NIKBUT (s), mean (SD)	8.24 (5.66)	7.84 (5.20)	7.92 (5.60)	0.46
Schirmer test (mm), mean (SD)	10.58 (7.58)	10.71 (7.42)	10.44 (7.22)	0.79
TMH at 6 o'clock (mm), mean (SD)	0.35 (0.18)	0.34 (0.17)	0.35 (0.23)	0.35
Bulbar erythema, n (%)				0.94
None (normal)	222 (38.5)	219 (43.8)	207 (40.0)	
Mild (flush reddish color)	264 (45.8)	243 (48.6)	245 (47.3)	
Moderate (more prominent red color)	86 (14.9)	37 (7.4)	64 (12.4)	
Severe (definite redness)	4 (0.7)	1 (0.2)	2 (0.4)	
BR score, mean (SD)	1.15 (0.47)	1.16 (0.50)	1.17 (0.48)	0.71

Bold indicates statistical significance at $P < 0.05$.

The correlation of the 6 clinical and keratographic signs with OSDI scores was assessed at baseline, 6 months, and 12 months (Table 5). All the correlations of the 6 clinical and keratographic signs with OSDI scores were very weak ($r_s \leq 0.12$) (Table 5). When the correlations were evaluated within subgroups based on the presence of SS at baseline, 6 months, and 12 months, only the correlation between TBUT and the OSDI score ($r_s = 0.33$, 95% CI, 0.01–0.65) in the subgroup of patients with SS at baseline was statistically significant because its 95% CI did not cross 0. When the correlations were evaluated within subgroups based on the presence of Meibomian gland dysfunction at baseline, 6 months, and 12 months (see Supplemental Tables 3A, 3B, and 3C, Supplemental Digital Content 10–12, http://links.lww.com/ICO/B228, http://links.lww.com/ICO/B229, http://links.lww.com/ICO/B230), only the correlation between TMH and the OSDI score ($r_s = 0.20$, 95% CI, 0.05–0.34) in the subgroup of patients without meibomian gland dysfunction was statistically significant (see Supplemental Tables 3A, 3B and 3C, Supplemental Digital Content 10–12, http://links.lww.com/ICO/B228, http://links.lww.com/ICO/B229, http://links.lww.com/ICO/B230). When the correlation between change of the 6 clinical and keratographic signs from baseline and change of OSDI scores from baseline was assessed within subgroups at 6 months and 12 months, correlation between change of bulbar erythema and change of OSDI score at 6 months ($r_s = 0.39$, 95% CI, 0.02–0.77, see Supplemental Table 3D, Supplemental Digital Content 13, http://links.lww.com/ICO/B231) in the subgroup of patients with SS was statistically significant, and their correlation ($r_s = -0.00$, 95% CI, −0.38 to 0.47, see Supplemental Table 3E, Supplemental Digital Content 14, http://links.lww.com/ICO/B232) was not significant at 12 months. The correlation between change of TMH and change of OSDI score at 6 months ($r_s = 0.19$, 95% CI, 0.05–0.32, see Supplemental Table 3D, Supplemental Digital Content 13, http://links.lww.com/ICO/B231) in the subgroup of patients with meibomian gland dysfunction was statistically significant, and this correlation ($r_s = 0.04$, 95% CI, −0.10 to 0.18, Supplemental Digital Content 14, http://links.lww.com/ICO/B232) was not significant at 12 months.

DISCUSSION

Among patients enrolled in the DREAM study at centers having keratography, the noninvasive assessments

TABLE 3. Summary of Keratography Measures and Clinical Measures for All Eyes and by the Presence of SS and Meibomian Gland Dysfunction*—Analysis of Combined Data From Baseline, 6, and 12 Months

		SS			Meibomian Gland Dysfunction*		
	All Eyes (N = 1594 Eye Visits)	No (N = 1372 Eye Visits)	Yes (N = 152 Eye Visits)	P†	No (N = 826 Eye Visits)	Yes (N = 768 Eye Visits)	P†
TBUT (s), mean (SD)	3.27 (2.41)	3.36 (2.51)	2.66 (1.82)	**0.01**	3.52 (2.76)	3.00 (1.94)	**0.002**
NIKBUT (s), mean (SD)	8.01 (5.50)	8.22 (5.55)	6.80 (5.20)	**0.04**	7.89 (5.49)	8.15 (5.51)	0.53
Schirmer test (mm), mean (SD)	10.58 (7.41)	10.94 (7.37)	7.58 (7.26)	**0.005**	10.47 (7.35)	10.69 (7.48)	0.70
TMH at 6 o'clock (mm), mean (SD)	0.35 (0.19)	0.35 (0.20)	0.26 (0.12)	<**0.001**	0.35 (0.18)	0.34 (0.21)	0.59
Bulbar erythema (%)				0.38			0.93
None (normal)	648 (40.7)	538 (39.2)	66 (43.4)		337 (40.8)	311 (40.5)	
Mild (flush reddish color)	752 (47.2)	669 (48.8)	59 (38.8)		391 (47.3)	361 (47.0)	
Moderate (more prominent red color)	187 (11.7)	158 (11.5)	27 (17.8)		96 (11.6)	91 (11.9)	
Severe (definite redness)	7 (0.4)	7 (0.5)	0 (0.0)		2 (0.2)	5 (0.7)	
BR score, mean (SD)	1.16 (0.48)	1.17 (0.48)	1.11 (0.51)	0.54	1.16 (0.48)	1.16 (0.49)	0.91

Bold indicates statistical significance at $P < 0.05$.
*Meibomian gland dysfunction is defined as the central 5 meibomian glands plugged or secretions graded as paste or obstructed on clinical examination at baseline.
†From the generalized linear model that included the visit (as categorical) and the indicator variable for Sjögren syndrome or meibomian gland dysfunction.
SS, Sjogren Syndrome.

of the quality of the tear film, the quantity of tears, and BR correlated only weakly with their clinical counterparts. In addition, the noninvasive assessments did not correlate with the severity of symptoms, as measured by the OSDI. The noninvasive tests did correlate strongly between right and left eyes of the same patient, as did the clinical assessments.

Previous studies of the relationship between these noninvasive assessments and their associated clinical assessment have provided inconsistent results. Data from several previous studies[11–15] have shown longer NIKBUT than TBUT, whereas some studies have had shorter NIKBUT than TBUT.[16–18] In the DREAM study, the mean NIKBUT was 8.2 seconds, considerably greater than the mean TBUT of 2.9 seconds. Given the different approaches to measurement between the keratography and the clinician, a systematic difference between the 2 measurements might be expected; however, the correlation between the 2 measurements (r_s = 0.18) was weak, implying that eyes with higher values of NIKBUT did not necessarily have higher values of TBUT. When the correlation between NIKBUT and TBUT was evaluated within subgroups, the correlation was stronger in patients with SS than in those without SS (r_s = 0.48 at baseline) (see Supplemental Table 2A, Supplemental Digital Content 5, http://links.lww.com/ICO/B223). Hence, the correlation was stronger when dry eye was postulated to be related to decreased flow more than evaporated loss. These results suggest that the noninvasive assessments by the Keratograph provide objective measurements but do not measure the same qualities as clinical tests, for instance NIKBUT is measured by image distortion, versus TBUT looks at the fluorescein pattern. Although it was hoped that the noninvasive tests would provide alternative more objective measurements than clinical tests, our data suggests that this is not the case. These findings contradict the recommendation in Dry Eye Workshop (DEWS) that suggested noninvasive measure of tear stability was preferred in the diagnosis of dry eye.[1]

Recent studies have shown good intraexaminer repeatability and interexaminer reproducibility of NIKBUT in normal patients and patients with DED.[16,19] The reproducibility of the clinical test was assessed between the screening and the baseline for the invasive tests. There was strong correlation between the screening and baseline measures for BR, Schirmer testing, and TBUT. We were unable to assess the reproducibility and repeatability of the keratographic noninvasive methods because they were not used until the baseline testing and they were not repeated during the testing in the same way as TBUT was determined with multiple measures.

TABLE 4. Correlation [r_s (95% CI)] Between Clinical and Keratograph Signs

Signs of Dry Eye Disease						
Clinical	Keratograph	Baseline (N = 576)	6 mo (N = 500)	12 mo (N = 518)	Change From Baseline at 6 mo (N = 500)	Change From Baseline at 12 mo (N = 518)
TBUT	NIKBUT	0.18 (0.09 to 0.28)	0.23 (0.14 to 0.32)	0.26 (0.16 to 0.36)	−0.06 (−0.16 to 0.04)	0.10 (0.01 to 0.20)
Schirmer test	TMH	0.15 (0.05 to 0.25)	0.22 (0.12 to 0.32)	0.24 (0.14 to 0.34)	0.02 (−0.08 to 0.12)	0.05 (−0.05 to 0.14)
Bulbar erythema	BR	0.25 (0.15 to 0.35)	0.22 (0.11 to 0.34)	0.23 (0.12 to 0.34)	0.14 (0.04 to 0.24)	0.06 (−0.04 to 0.17)

TABLE 5. Correlation [r_s (95% CI)] Between Signs and the Score on the OSDI for All Eyes

Sign	Baseline (N = 576)	6 mo (N = 500)	12 mo (N = 518)	Change From Baseline at 6 mo (N = 500)	Change From Baseline at 12 mo (N = 518)
TBUT	−0.05 (−0.15 to 0.06)	−0.04 (−0.15 to 0.08)	−0.06 (−0.18 to 0.05)	−0.02 (−0.12 to 0.08)	−0.11 (−0.21 to −0.01)
NIKBUT	−0.07 (−0.18 to 0.03)	−0.05 (−0.16 to 0.06)	−0.11 (−0.22 to −0.01)	0.03 (−0.06 to 0.12)	0.04 (−0.05 to 0.14)
Schirmer test	−0.07 (−0.17 to 0.04)	−0.09 (−0.20 to 0.03)	−0.12 (−0.24 to −0.00)	0.03 (−0.09 to 0.14)	0.08 (−0.03 to 0.20)
TMH	0.01 (−0.10 to 0.13)	0.07 (−0.04 to 0.18)	−0.00 (−0.12 to 0.11)	0.14 (0.04 to 0.24)	0.08 (−0.03 to 0.18)
Bulbar erythema	0.03 (−0.09 to 0.14)	0.07 (−0.05 to 0.18)	0.09 (−0.03 to 0.21)	0.13 (0.00 to 0.26)	0.07 (−0.05 to 0.19)
BR	0.02 (−0.09 to 0.13)	0.02 (−0.10 to 0.14)	0.04 (−0.08 to 0.16)	0.12 (0.02 to 0.22)	0.06 (−0.04 to 0.17)

Finally, none of the measures, clinical or noninvasive, were correlated significantly with the OSDI, the primary outcome measure in the DREAM study.

Other studies have shown correlation in different populations between the OSDI and the noninvasive tests, but these populations of patients were typically younger or were control populations without evidence of dry eye.[14,20,21] This conflicting information is very typical of the literature involving the study of dry eye, as summarized in the DEWS II report, under clinical testing.[1]

The mean value for OSDI in our study was higher than in most of the previous reports,[22,23] suggesting that we were looking at a population with significant DED. The parameters of dry eye measurements, however, were consistent with previous reports for all measures. The repeatability and reproducibility of the keratograph has been established in smaller populations of patients convincingly with intraclass correlations.[14,16,24] There has been no consensus on the best measures for TBUT, including the concentration and volume of fluorescein and the use of the yellow filter. In our study, we used a common quantity and concentration of the dye and allowed time for the tear film to equilibrate, before taking 3 measurements using a stopwatch. This gave us a significantly shorter TBUT than that measured noninvasively. There have been several suggestions of why the tear fluorescein method leads to, in general, lower measures than the noninvasive including perturbation of the tear film, inconsistent observation of the entire tear film in real time and variation in the site of break-up. However, when both measures were obtained in the same cohort, both clinically and with the Keratograph, there remained a very weak correlation between the findings, including BR. We were unable to confirm that noninvasive testing using the Keratograph is an equal substitute to the more invasive clinical methods. Therefore, there remains an unmet need for objective measures of dry eye that correlate with patient symptoms. We were also unable to establish correlations between patient symptoms and other clinical and noninvasive tests, even in subsets of patients with dry eye, including those with high tear osmolarity or younger age, as had been previously reported.[25,26]

The strength of the study is the larger number of patients and eyes that were included and that they were from a large geographical distribution in the United States. The study was meticulously conducted following the protocols specifically designed to improve the reproducibility of data across the different centers. Significant attempt to standardize the noninvasive testing with the sole use of 1 device across the different centers and the methodology chosen for the clinical parameters was well established and widely accepted.

CONCLUSIONS

We determined that routine noninvasive testing is not yet a substitute for clinical testing, and when we determine dry eye based on patient symptoms, there is not a specific test that can objectively and solely support the diagnosis. This is very similar to the DEWS II findings from the Wolffsohn cohort, "So we continue to look for the holy grail of diagnosis for dry eye patients."[1]

We did not determine a clinical or noninvasive test that reliably separated aqueous deficiency (SS) from evaporative loss (meibomian gland dysfunction) as the cause for dry eye syndrome. As we continue to search for the best metrics to define DED and its severity, we continue to depend on clinical tests that are themselves variable and often not reproducible; the search for objective minimally invasive metrics that best "capture" DED diagnosis and severity and correlate with symptoms continues.

These weak correlations suggest that keratographic measures are not equivalent substitutes to the clinical measures that are in wide use. However, the keratography may have other value in the diagnosis and management of dry eye that we did not explore.

REFERENCES

1. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. *Ocul Surf*. 2017;15:539–574.
2. Bartlett JD, Keith MS, Sudharshan L, et al. Associations between signs and symptoms of dry eye disease: a systematic review. *Clin Ophthalmol*. 2015;9:1719–1730.
3. Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea*. 2004;23:272–285.
4. Roy NS, Wei Y, Kuklinski E, et al. The growing need for validated biomarkers and endpoints for dry eye clinical research. *Invest Ophthalmol Vis Sci*. 2017;58:BIO1–BIO19.
5. The Dry Eye Assessment and Management Study Research Group. n-3 fatty acid supplementation for treatment of dry eye disease. *N Engl J Med*. 2018;378:1681–1690.
6. Asbell PA, Maguire MG, Peskin E, et al. The dry eye assessment and management (DREAM) study: study design and baseline characteristics. *Contemp Clin Trials*. 2018;71:70–79.

7. Bunya VY, Ying GS, Maguire MG, et al. Prevalence of novel candidate Sjogren syndrome autoantibodies in the dry eye assessment and management (DREAM) study. *Cornea*. 2018;37:1425–1430.
8. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol*. 2000;118: 615–621.
9. Efron B, Gong G. A leisurely look at the bootstrap, the jackknife, and cross-validation. *Am Statistician*. 1983;37:36–48.
10. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13–22.
11. Cho P, Douthwaite W. The relation between invasive and noninvasive tear break-up time. *Optom Vis Sci*. 1995;72:17–22.
12. Nichols JJ, Nichols KK, Puent B, et al. Evaluation of tear film interference patterns and measures of tear break-up time. *Optom Vis Sci*. 2002;79:363–369.
13. Best N, Drury L, Wolffsohn JS. Clinical evaluation of the Oculus keratograph. *Cont Lens Anterior Eye*. 2012;35:171–174.
14. Lan W, Lin L, Yang X, et al. Automatic noninvasive tear breakup time (TBUT) and conventional fluorescent TBUT. *Optom Vis Sci*. 2014;91: 1412–1418.
15. Cox SM, Nichols KK, Nichols JJ. Agreement between automated and traditional measures of tear film breakup. *Optom Vis Sci*. 2015;92: e257–e263.
16. Hong J, Sun X, Wei A, et al. Assessment of tear film stability in dry eye with a newly developed keratograph. *Cornea*. 2013;32:716–721.
17. Hong J, Liu Z, Hua J, et al. Evaluation of age-related changes in noninvasive tear breakup time. *Optom Vis Sci*. 2014;91:150–155.
18. Jiang Y, Ye H, Xu J, et al. Noninvasive keratography assessment of tear film break-up time and location in patients with age-related cataracts and dry eye syndrome. *J Int Med Res*. 2014;42:494–502.
19. Tian L, Qu JH, Zhang XY, et al. Repeatability and reproducibility of noninvasive keratograph 5M measurements in patients with dry eye disease. *J Ophthalmol*. 2016;2016:8013621.
20. Abdelfattah NS, Dastiridou A, Sadda SR, et al. Noninvasive imaging of tear film dynamics in eyes with ocular surface disease. *Cornea*. 2015; 34(suppl 10):S48–S52.
21. Raj A, Dhasmana R, Nagpal RC. Anterior segment optical coherence tomography for tear meniscus evaluation and its correlation with other tear variables in healthy individuals. *J Clin Diagn Res*. 2016;10: NC01–NC04.
22. Ozcura F, Aydin S, Helvaci MR. Ocular surface disease index for the diagnosis of dry eye syndrome. *Ocul Immunol Inflamm*. 2007;15: 389–393.
23. Hashemi H, Khabazkhoob M, Kheirkhah A, et al. Prevalence of dry eye syndrome in an adult population. *Clin Exp Ophthalmol*. 2014;42: 242–248.
24. Canan H, Altan-Yaycioglu R, Ulas B, et al. Interexaminer reproducibility of optical coherence tomography for measuring the tear film meniscus. *Curr Eye Res*. 2014;39:1145–1150.
25. Papas EB. Key factors in the subjective and objective assessment of conjunctival erythema. *Invest Ophthalmol Vis Sci*. 2000;41:687–691.
26. Altan-Yaycioglu R, Sizmaz S, Canan H, et al. Optical coherence tomography for measuring the tear film meniscus: correlation with Schirmer test and tear-film breakup time. *Curr Eye Res*. 2013;38:736–742.