Tear Osmolarity in the Diagnosis and Management of Dry Eye Disease

MICHAEL A. LEMP, ANTHONY J. BRON, CHRISTOPHE BAUDOUIN, JOSÉ M. BENÍTEZ DEL CASTILLO, DAVID GEFFEN, JOE TAUBER, GARY N. FOULKS, JAY S. PEPOSE, AND BENJAMIN D. SULLIVAN

• PURPOSE: To evaluate the use of tear osmolarity in the diagnosis of dry eye disease.

• DESIGN: A prospective, observational case series to determine the clinical usefulness of tear osmolarity and commonly used objective tests to diagnose dry eye disease.

• METHODS: A multicenter, 10-site study consisting of 314 consecutive subjects between 18 and 82 years of age. Bilateral tear osmolarity, tear film break-up time (TBUT), corneal staining, conjunctival staining, Schirmer test, and meibomian gland grading were performed. Diagnostic performance was measured against a composite index of objective measurements that classified subjects as having normal, mild or moderate, or severe dry eye. The main outcome measures were sensitivity, specificity, area under the receiver operating characteristic curve, and intereye variability.

• RESULTS: Of the 6 tests, tear osmolarity was found to have superior diagnostic performance. The most sensitive threshold between normal and mild or moderate subjects was found to be 308 mOsms/L, whereas the most specific was found at 315 mOsms/L. At a cutoff of 312 mOsms/L, tear hyperosmolarity exhibited 73% sensitivity and 92% specificity. By contrast, the other common tests exhibited either poor sensitivity (corneal staining, 54%; conjunctival staining, 60%; meibomian gland grading, 61%) or poor specificity (tear film break-up time, 45%; Schirmer test, 51%). Tear osmolarity also had the highest area under the receiver operating characteristic curve (0.89). Intereye differences in osmolarity were found to correlate with increasing disease severity ($r^2 = 0.32$).

• CONCLUSIONS: Tear osmolarity is the best single metric both to diagnose and classify dry eye disease. Intereye variability is a characteristic of dry eye not seen in normal subjects. (Am J Ophthalmol 2011;151:792–798. © 2011 by Elsevier Inc. All rights reserved.)

DRY EYE DISEASE IS A COMMONLY ENCOUNTERED condition in clinical practice and affects up to 20% of the population in North America.[1] The knowledge base concerning its pathogenesis, classification, and characteristics has grown considerably over the last 15 years, but its diagnosis, particularly in the early or mild stages, has been hampered by the lack of objective tests with sufficient sensitivity and specificity, adequate repeatability, ease of performance, and suitability for the clinical practice setting.[2] In addition, although symptoms of ocular irritation are common, there is a lack of correlation between signs and symptoms, particularly in mild dry eye disease, rendering symptoms alone unreliable for diagnosis and determination of disease severity.[3] Moreover, there is a lack of consensus on the clinical usefulness of individual objective tests in the diagnosis of dry eye disease.[2]

An increase in tear osmolarity is a hallmark of dry eye disease and is thought to be the central mechanism in the pathogenesis of ocular surface damage in the disease, as noted in the Dry Eye Workshop Report.[4] Tear osmolarity has been reported to be the single best marker for dry eye disease,[4] but measurement has been limited to laboratory instruments requiring large microliter volumes; collection and manipulation of the tear specimens induce reflex tearing in most subjects, and collected specimens can be concentrated by evaporative loss during handling and collection.[2] Further, microliter volumes are not available in many dry eye patients. The current study was undertaken to determine the clinical usefulness of tear osmolarity in the diagnosis and management of dry eye disease using a new tear osmometer that minimizes the previous limitations[5] compared with the other most commonly used tests.[6]

METHODS

A PROSPECTIVE, EXPLORATORY, MULTICENTER STUDY WAS undertaken at 10 sites in the European Union and the United States. The subject population consisted of randomly presenting subjects between the ages of 18 and 82 years of both sexes, including those with and without a history of dry eye disease. Investigators were instructed to recruit roughly a 2:1 ratio of presumed dry eye patients to normals. This report documents the results of the analysis of the initial 314 subjects, 15 of whom were removed for

incomplete data reporting (n = 218 female, n = 81 male; average age, 46.3 ± 16.9 years).

Subjects were excluded from the study if they exhibited any active infection of the eye, active ocular allergy, evidence of lid deformity or abnormal lid movement disorder, refractive surgery within one year of the study visit, pregnancy or lactation, abnormal nasolacrimal drainage, punctal plug placement within 30 days of testing, or evidence of a systemic disease (except Sjögren syndrome) known to affect tear production, such as thyroid eye disease or graft-versus-host disease. Moreover, patients were excluded if they initiated or altered the dose of chronic systemic medication known to affect tear production within 30 days of testing (for instance, initiation or dosage change of antihistamines, antidepressants, diuretics, corticosteroids, or immunomodulators were listed as exclusion criteria) or had a known hypersensitivity to any of the agents used in testing (eg, sodium fluorescein or lissamine green). Subjects were required to remove contact lenses at least 8 hours before examination and not to use artificial tears within two hours of screening. Patients were excluded from the study if they did not wish to participate in the study or could not cooperate with the collection of tear samples.

This single visit study included the following common objective tests for dry eye disease,[6] performed on both eyes: tear osmolarity, tear film breakup time (TBUT), corneal staining (National Eye Institute/Industry scale), conjunctival staining, Schirmer test without anesthesia, and meibomian gland grading (Foulks/Bron scoring[7]). Data including demographic information were recorded on case report forms and sent to a central data collecting center, where they were entered in digital form for analysis. The more severe of the bilateral measurements was used in analysis because of the asymmetrical effects of transient compensatory mechanisms attempting to drive down tear osmolarity in response to environmental stress. Intereye variability in osmolarity was calculated as the absolute difference in the two eye measurements (|OD−OS|).

Optimal cutoff values for each sign were determined post hoc, assuming equal risk for false-positive and false-negative results. In particular, Gaussian distributions were generated based on the mean and standard deviation of normal and dry eye disease populations. Diagnostic cutoff thresholds were located at the intersection between these curves. Sensitivity was determined as the percentage of true positives, whereas specificity was calculated as the percentage of true negatives.

In certain clinical situations, the acceptable risks of false-positive or false-negative diagnosis are unequal. Although the exact weighting for these risks has not been quantified in the literature, more sensitive or specific thresholds were established at the intersection between normal and mild or moderate or between normal and severe subsets of the patient population. For more sensitive detection, cutoff values were located at the intersection

TABLE 1. Sensitivity and Specificity of Objective Clinical Signs of Dry Eye Disease[a]

Test	Cutoff	Sensitivity (n = 224)	Specificity (n = 75)
Osmolarity	>311 mOsms/L	72.8%	92.0%
TBUT	<10 secs	84.4%	45.3%
Schirmer	<18 mm	79.5%	50.7%
Corneal stain	>Grade 1	54.0%	89.3%
Conjunctival stain	>Grade 2	60.3%	90.7%
Meibomian grade	>Grade 5	61.2%	78.7%

TBUT = tear film break-up time.
[a]Cutoff values were located at the intersection between normal subjects and the entire subset of dry eye patients.

between normal and mild or moderate subjects, whereas more specific detection thresholds were located at the intersection between normal and severe dry eye patient distributions.

Classification of mild or moderate and severe patients was based on a composite disease severity index, derived from the Dry Eye Workshop severity scale.[4] To convert the various clinical measurements into common units, an expert panel of clinicians, using a consensus approach, agreed to the severity distribution for each diagnostic test, based on the Dry Eye Workshop categorical severity scale. For each test performed, the more severe of the bilateral measurements for each clinical sign was mapped onto a 0 (least evidence of disease) to 1 (greatest evidence of disease) scale, normalized by an independent component analysis to remove overlap in mutual information, and then combined into a single Euclidean distance from the origin to produce a final composite severity score for each subject.[8] In this way, no single test outweighed the others. In terms of classification, the composite severity score does not reveal etiologic information; rather, it provides an unbiased, objective quantification of dry eye disease severity that does not vary according to the cause of the disease.

Normal, mild, moderate, and severe patients were assigned according to the 4 quartiles of composite disease severity, but because of the lack of clinical differentiation between the mild and moderate quartiles, they were combined into a single group, mild or moderate. The independent component analysis methodology is discussed in detail in a recently published report.[5]

RESULTS

TEAR OSMOLARITY WAS FOUND TO HAVE A 72.8% SENSITIVity and 92.0% specificity at a cutoff value of 312 mOsms/L (i.e., values > 311 mOsms/L; Table 1). No other clinical sign exhibited more than 62% performance in both categories. Corneal staining, conjunctival staining, and meibomian grading lacked sensitivity (54.0%, 60.3%, and

TABLE 2. Percentage of Correctly Diagnosed Subjects of Objective Clinical Signs of Dry Eye Disease[a]

		% Correctly Diagnosed		
Test	Cutoff	Normal (n = 75)	Mild/ Moderate (n = 149)	Severe (n = 75)
Osmolarity	>311 mOsms/L	92.0%	64.4%	89.3%
TBUT	<10 secs	45.3%	76.5%	100.0%
Schirmer	<18 mm	50.7%	75.2%	88.0%
Corneal stain	>Grade 1	89.3%	43.6%	74.7%
Conjunctival stain	>Grade 2	90.7%	49.7%	81.3%
Meibomian grade	>Grade 5	78.7%	51.7%	80.0%

TBUT = tear film break-up time.
[a]Cutoff values were located at the intersection between normal subjects and the entire subset of dry eye patients.

TABLE 3. Percentage of Correctly Diagnosed Subjects of Objective Clinical Signs of Dry Eye Disease Using the Intersection of Normal and Mild or Moderate Population Distributions as a More Sensitive Detection Threshold[a]

		% Correctly Diagnosed		
Test	Mild Cutoff	Normal (n = 75)	Mild/ Moderate (n = 149)	Severe (n = 75)
Osmolarity	>308 mOsms/L	81.3%	73.2%	90.7%
TBUT	<11 secs	40.0%	83.2%	100.0%
Schirmer	<20 mm	42.7%	82.6%	90.7%
Corneal stain	>Grade 0	82.7%	60.4%	85.3%
Conjunctival stain	>Grade 1	73.3%	73.2%	90.7%
Meibomian grade	>Grade 4	74.7%	54.4%	81.3%

TBUT = tear film break-up time.
[a]Cutoff values were located at the intersection between normal subjects and the mild/moderate subset of dry eye patients.

TABLE 4. Percentage of Correctly Diagnosed Subjects of Objective Clinical Signs of Dry Eye Disease Using the Intersection of Normal and Severe Population Distributions as a More Specific Detection Threshold[a]

		% Correctly Diagnosed		
Test	Severe Cutoff	Normal (n = 75)	Mild/ Moderate (n = 149)	Severe (n = 75)
Osmolarity	>314 mOsms/L	96.0%	56.4%	86.7%
TBUT	<6 secs	69.3%	63.8%	97.3%
Schirmer	<16 mm	57.3%	71.8%	86.7%
Corneal stain	>Grade 1	89.3%	43.6%	74.7%
Conjunctival stain	>Grade 2	90.7%	49.7%	81.3%
Meibomian grade	>Grade 5	78.7%	51.7%	80.0%

TBUT = tear film break-up time.
[a]Cutoff values were located at the intersection between normal subjects and the severe subset of dry eye patients.

TABLE 5. Demographics of Dry Eye Disease Severity Broken Down by Age and Sex, Reported as Number of People of the 299 Evaluated in the Current Study

Test	Normal	Mild/Moderate	Severe
<30 years of age	33	37	7
30 to 50 years of age	21	50	14
50 to 70 years of age	17	45	44
>70 years of age	4	17	10
Male	26	44	10
Female	49	105	65

61.2% respectively), whereas TBUT and Schirmer results lacked specificity (45.3% and 50.7%, respectively). The performance of osmolarity was consistent with earlier studies. In particular, the meta-analysis performed by Tomlinson and associates reported a 69% sensitivity and 92% specificity at a referent value of 316 mOsm/L.[9] Citing the 15% prevalence used in Tomlinson and associates, tear osmolarity was found to have an 88.6% accuracy in the current study.

The average osmolarity values across normal, mild or moderate, and severe severity grades were 300.8 ± 7.8 mOsms/L, 315.5 ± 10.4 mOsms/L, and 336.7 ± 22.2 mOsms/L, respectively. Within each severity subset, no significant differences were found across age or sex. Specifically, there was no difference in mean for subjects younger than 30 years, 30 to 50 years, 50 to 70 years, and older than 70 years (all $P > .01$, with a Bonferroni correction of n = 6 on 2-tailed t tests). Similarly, there was no difference between males or females across different levels of disease severity (all $P > .20$). Therefore, the primary determinant of osmolarity was disease severity.

Calculated cutoff thresholds for each test generally were in agreement with published values, although the Schirmer results were much higher than the clinically accepted range of 5 to 10 mm/5 minutes.[2] When placed at a cutoff of 5 mm or less, the Schirmer test results improved the classification of normal subjects to 84.0%, but suffered in diagnosis of dry eye subjects, correctly reporting 24.2% of the mild to moderate patients and 57.3% of the severe patients.

The percentages of correctly diagnosed subjects, segregated by disease severity, are shown in Table 2. Osmolarity was revealed to be exceptionally good at differentiating normal subjects (92.0% correctly diagnosed) from severe dry eye subjects (89.3% correctly diagnosed), while still correctly identifying approximately two thirds of the difficult-to-diagnose early stage and mild or moderate subjects (64.4%). By contrast, only TBUT and the Schirmer test were more effective identifying the early stage and mild or
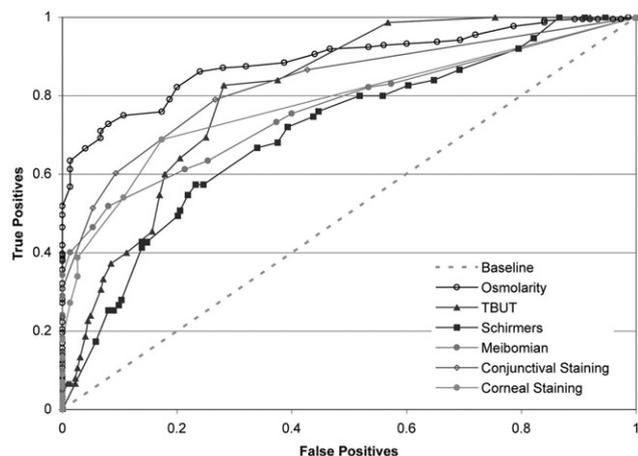
FIGURE 1. Receiver operator characteristic (ROC) curves of objective clinical signs of dry eye disease. Osmolarity exhibits the greatest area under the curve of the common clinical signs for dry eye disease. Tear film break-up time (TBUT) achieves a higher sensitivity toward the upper right side of the graph, although it shows poor performance against most other signs in specificity (when less than 40% false positives are required). Also of note, Schirmer strips consistently are inferior to all other signs across the full range.

FIGURE 2. Absolute difference in intereye tear osmolarity (OD–OS) versus disease severity. Normal, mild or moderate, and severe groups are segregated by the vertically dashed lines. Intereye differences generally increase with increasing disease severity and are most pronounced in the severe subset. OD = right eye; OS = left eye.

moderate subjects (76.5% and 75.2%, respectively), but both of those examinations had a high rate of false positives in the normal cohort (only 45.3% and 50.7% correctly diagnosed, respectively).

Changing the diagnostic cutoff to a more sensitive threshold at the intersection of normal and mild or moderate subjects (Table 3) resulted in the predictable increase in correctly diagnosed dry eye subjects at the expense of an increased false-positive rate. Tear osmolarity, at a cutoff of more than 308 mOsms/L, achieved a 90.7% rate of proper diagnosis of severe dry eye patients, while accurately classifying 81.3% of the normal subjects. Corneal staining seemed to benefit the most from a lower threshold (from grade 2 to grade 1), improving to an 85.3% mark in the severe category, although in practice, distinguishing between a single corneal staining grade is quite challenging.

Conversely, changing the diagnostic cutoff to a more specific threshold at the intersection of normal and severe subjects (Table 4) weakened performance in the overall dry eye population. The corresponding improvement in normal classification (4.0% for osmolarity) did not seem to warrant the loss in dry eye performance (8.0% in the mild or moderate group and 2.0% in the severe group).

The demographics of disease severity broken down by age and sex are shown in Table 5. Both the relative level of severity and the ratio of people with dry eye disease increased with increasing age. Many more females (2.4 times as many) had severe dry eye than males.

Diagnostic results are summarized in Figure 1, shown as a receiver operating characteristic curve. Osmolarity dem-
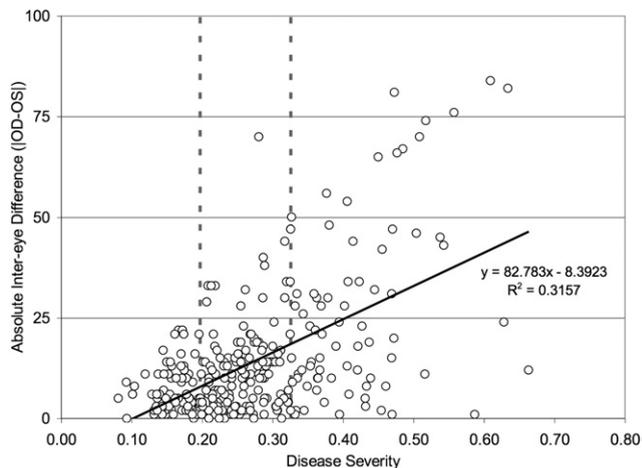
TABLE 6. Intereye Differences of Clinical Signs across Dry Eye Disease Severity

Test	Normal	Mild/Moderate	Severe
Osmolarity (mOsms/L)	6.9 ± 5.9	11.7 ± 10.9[a]	26.5 ± 22.7[a]
TBUT (secs)	3.2 ± 4.7	2.8 ± 3.9	1.3 ± 3.4[a]
Schirmer (mm)	3.5 ± 6.2	4.3 ± 6.1	2.7 ± 3.3
Corneal stain	0.2 ± 0.6	0.7 ± 1.2*	1.3 ± 1.6[a]
Conjunctival stain	0.3 ± 0.6	0.8 ± 1.2*	1.2 ± 1.4[a]
Meibomian grade	0.4 ± 0.9	0.4 ± 1.0	1.2 ± 2.7[a]

TBUT = tear film break-up time.

Data reported in native units as the absolute difference between the 2 eye measurements (OD–OS), where OD is the right eye and OS is the left eye.

[a]$P < .01$, 2-tailed Student t test versus normal subjects.

onstrated the greatest area under the curve (0.89), followed by conjunctival staining (0.83), TBUT (0.81), meibomian grading (0.78), corneal staining (0.77), and Schirmer test (0.71).

Also of clinical interest, the intereye difference in osmolarity was found to be correlated to disease severity ($r^2 = 0.32$; $P = <0.0001$; Figure 2). Normal subjects demonstrated a mean absolute intereye difference of 6.9 ± 5.9 mOsms/L, whereas mild or moderate subjects demonstrated 11.7 ± 10.9 mOsms/L, and severe patients demonstrated 26.5 ± 22.7 mOsms/L (Table 6). The normal intereye variability was near the analytical precision of the TearLab test (TearLab Corp, San Diego, California) when measured with reference tear solutions (approximately ± 5 mOsms/L; Food and Drug Administration 510(k) Cleared

Product Insert k083184). These data suggest that large differences in osmolarity between eyes reflects increasing disease severity, rather than an error in the test measurement. Corneal and conjunctival staining also demonstrated significant increases in measurements between eyes as disease severity increased. Conversely, TBUT showed a significant reduction in intereye difference in severe subjects compared with normal subjects, because most severe subjects had very low breakup times. This relationship was not seen in mild or moderate subjects, who showed similar intereye breakup time differences as normal subjects.

DISCUSSION

THE DEVELOPMENT AND AVAILABILITY OF A NEW TECHnology (TearLab; FDA 510(k) k083184) enables the clinician to collect and measure osmolarity in a 50 nL sample with minimal disturbance of the tear film.[5] This microfluidic lab-on-a-chip device both collects tears and produces a reading within seconds before evaporation can influence solute concentration. This eliminates the need for sample transfer or user handling. This technique is applicable in the near-patient setting and overcomes many of the prior limitations to practical clinical measurement of tear film osmolarity. Despite using only 50 nL, the technology was shown to be substantially equivalent to laboratory osmometers.[10]

In a recent report, compared with a panel of the most commonly used objective tests for dry eye disease,[6] tear osmolarity was found to represent "the best single test for the diagnosis of dry eye" and is suitable for use in the clinical setting.[2,9] In the present clinic-based study, we also demonstrated that tear osmolarity is the most useful single objective test of the most commonly used tests to differentiate those with early stage mild or moderate dry eye from those with severe disease. A cutoff threshold of more than 308 mOsms/L was found to be the most sensitive in differentiating normal from mild to moderate subjects.

Because referent values are dependent on the distribution of disease severity within the study population, it was interesting to note that the cutoff threshold for this study (312 mOsms/L) was lower than the 316 mOsms/L referent value obtained by Tomlinson and associates, which was derived from a meta-analysis of osmolarity studies in the past 25 years.[9,11] The intersection between normal and severe subjects in this study was 315 mOsms/L, essentially equivalent to the global cutoff found in the Tomlinson and associates meta-analysis. It is quite possible that the widely representative nature of the general ophthalmology practices drawn on in this study included more mild or moderate patients than the university-based tertiary referral centers prominent in the historical literature. More severe cases of dry eye disease, such as those patients with Sjögren syndrome, also were common in prior studies. Further, 32% of the subjects in the current study were being treated with some form of therapy, included among them: cyclosporine, hyaluronic acid, autologous serum, and lubricant eye drops. Studies with less stringent inclusion criteria for dry eye disease, such as Mathers and associates' 1996 study that defined patients as those with a Schirmer values less than 10 mm or a tear flow of 0.10 μL/minute or less reported the midpoint of normal and dry eye groups to be 308 mOsms/L.[12] Other recommended cutoff points have ranged from 304 to 312 mOsms/L.[13–15] Nonetheless, it is clear from this study that test results located between 308 and 316 mOsms/L are elevated compared with the normal distribution of osmolarity values. Given that most normal subjects are asymptomatic in clinical practice, we recommend that values of more than 308 mOsms/L be used as the threshold for the most sensitive detection of dry eye subjects.

All signs were shown to be capable of classifying severe patients, the one exception being corneal staining, for which 1 in 4 severe dry eye subjects showed little or no evidence of staining. It should be noted that despite using the intersection of mild or moderate and normal subjects as a threshold, there were no clinical signs that classified better than 85% of the mild or moderate patients, which may be the result of the intermittency of dry eye disease during its early stages. Because of the broad overlap in distributions of corneal staining, conjunctival staining, and meibomian grading, the intersection between the normal and the severe subset of curves did not alter the cutoff point as compared with the values obtained using the intersection between the normal and the entire dry eye population (Table 2).

One possible reason for the difficulty in diagnosing early stage disease is that dry eye is a disease of gradual onset and progression. The initiation of the dry eye disease process is hypothesized to be characterized by a breakdown of compensatory mechanisms intended to restore the normal homeostatic conditions to the ocular surface.[16] These include increased blinking and reflex stimulation of the lacrimal or meibomian glands. Compensatory mechanisms likely result in transient improvements in tear stability marked with periods of hyperosmolarity, especially in the early or mild forms of the disease. Such variability between eyes and over time has been noted earlier, but not previously understood.[13,14,17] Loss of homeostatic control may raise tear osmolarity transiently and asymmetrically between eyes. Therefore, the reported cutoff thresholds are guideposts along a spectrum of severity and should be used in conjunction with a clinical examination to distinguish dry eye subtypes, that is, aqueous tear deficiency from evaporative tear deficiency.

Intereye variability was shown to be another characteristic of dry eye disease not seen in normal subjects. Although intereye variability was significantly increased in the early stage disease and may be considered a hallmark of dry eye, we did not find that it improved the diagnostic performance of hyperosmolarity, because many of the

moderate to severe patients reported consistently high results. Rather, intereye variability should be unsurprising if encountered clinically. Because variability is likely reflective of tear film instability, the higher, more severe result of the 2 eyes should be considered the relevant one because it is more reflective of the disease state. Future studies will examine the longitudinal variability of osmolarity in dry eye disease.

Potential limitations of the study include the fact that we did not control or attempt to measure environmental stress, climate, diurnal variation, or season. The study was conducted on 2 continents over an 8-month period encompassing spring, summer, and fall, and only a single time point was measured for each subject. It is not yet known the extent to which these variables affect the distribution of osmolarity in normal persons or dry eye disease patients. In particular, diurnal and longitudinal variability will be topics of future studies. That said, the strength of this study lies in its broad international scope and representation of patients seeking treatment at ophthalmic practices. The study population was that of ambulatory clinic patients over a wide age range and not a highly specific one, for example, nursing home or military groups. A substantial percentage of the subjects also were being treated, although no initiation or recent change was allowed. Therefore, the results contained herein should be generally representative of dry eye patients as they seek treatment and a diagnosis.

Recent developments in our understanding of dry eye disease have resulted in a more comprehensive approach to its development and the assessment of the severity of the disease process. Dry eye disease is thought to be a condition in which there are a number of entry points or risk factors, including: aging, androgen deficiency, chronic environmental stress, changes in blinking patterns, systemic autoimmune disease, systemic drugs, surgery in which the corneal nerves are severed, contact lens wear, and preservative toxicity from topical medications. Regardless of which of the risk factors or combinations thereof initiate the process, the Dry Eye Workshop reports that the final common pathway leads to the core manifestations of tear film instability and tear hyperosmolarity.[4]

The report continues to note that tear hyperosmolarity damages the surface epithelium through activation of a cascade of inflammatory events with an increase in inflammatory tear cytokines, increasing apoptotic cell death in surface cells and initiating alterations in mucin expression.[4] Laboratory studies have confirmed that, independent of its association with dry eye disease, tear hyperosmolarity leads to a cycle of inflammation and damage to the ocular surface,[18–23] as well as a direct link between hyperosmolarity and tear instability, indicating that transient shifts in osmolarity in the precorneal tear film lead to chronic epithelial stress, inflammation, and symptoms of ocular irritation.[24]

Tear osmolarity is considered to be a global marker of dry eye disease. The two major mechanistic subtypes of dry eye disease, aqueous tear deficiency and evaporative dry eye, both result in an increase in tear osmolarity. Both subtypes frequently coexist. No statistically significant difference in the means of these subtypes was found in this study, but a more complete study of this subject will be forthcoming in another analysis. In addition, this study did not investigate regional variations in the ocular surface, such as conjunctivochalasis, which occurs in some dry eye patients and may contribute to elevated tear osmolarity.[22]

Interestingly, there were 35 contact lens wearers in the population, of which 26 were classified as dry eye and 9 as normal. The dry eye patients who were contact lens wearers demonstrated a significantly higher osmolarity than normal patients who were contact lens wearers (322.3 $\pm$ 20.1 mOsms/L vs 300.1 $\pm$ 6.3 mOsms/L; $P = .003$). These data suggest that contact lens wear alone does not predict the onset of dry eye. The impact of contact lens wear on tear osmolarity should be monitored on an individual basis. Certainly, dry eye patients should explore the possibility of more biocompatible lenses that may have less of an impact on tear film stability. More data are needed to understand the relationship between lens type and tear film osmolarity.

Consistent with the observations above, it should be recognized that dry eye is a chronic disease of gradual onset and progression. Because compensatory mechanisms play an intermittent role, and although 308 mOsms/L has been shown to be quite valuable in identifying dry eye patients, it should not be viewed as an absolute value, but rather as a guidepost along a gradient of severity. Those patients with values less than 308 mOsms/L and who are symptomatic may represent an early manifestation of disease. Tear osmolarity should be used in conjunction with other clinical tests, or when a conflict between signs and symptoms arise. Although tear osmolarity can identify patients with dry eye, can assess severity, and can record response to treatment, subtyping according to aqueous deficient or evaporative disease also is important in formulating a treatment plan. In addition, intereye variability has been found to be a hallmark of dry eye disease, suggesting that the higher osmolarity of the 2 eyes be used in clinical practice, because the lower value seems to reflect the transient effects of compensatory mechanisms.

REFERENCES

1. Tomlinson A. Epidemiology of dry eye disease. In: Asbell P, Lemp MA, eds. Dry Eye Disease: The Clinician's Guide to Diagnosis and Treatment. New York: Thieme, 2006:1–15.

2. International Dry Eye Workshop. Methodologies to diagnose and monitor dry eye disease. In: 2007 Report of the International Dry Eye Workshop (DEWS). Ocul Surf 2007;5(2):108–123.

3. Begley CG, Chalmers RL, Abetz L, et al. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. Invest Ophthalmol Vis Sci 2003;44(11):4753–4761.

4. International Dry Eye Workshop. The definition and classification of dry eye disease. In: 2007 Report of the International Dry Eye Workshop (DEWS) Ocul Surf 2007;5(2):75–92.

5. Sullivan BD, Whitmer D, Nichols KKAn objective approach to severity in dry eye disease. Invest Ophthalmol Vis Sci 2010;51(12):6125–6130.

6. Korb DR. Survey of preferred tests for the diagnosis of the tear film and dry eye. Cornea 2000;19(4):483–486.

7. Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification and grading. Ocul Surf 2003;1(3):107–126.

8. Bell AJ, Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. Neural Comp 1995;7(6):1129–1159.

9. Tomlinson A, Khanal S, Ramaesh K, Diaper C, McFadyen A. Tear film osmolarity: determination of a referent for dry eye diagnosis. Invest Ophthalmol Vis Sci 2006;47(10):4309–4315.

10. Tomlinson A, McCann LC, Pearce EI. Comparison of human tear film osmolarity measured by electrical impedance and freezing point depression techniques. Cornea 2010;29(9):1036–1041.

11. Khanal S, Tomlinson A, McFadyen A, et al. Dry eye diagnosis. Invest Ophthal Vis Sci 2008;49(4):1407–1414.

12. Mathers WD, Lane JA, Sutphin JE, Zimmerman MB. Model for ocular tear film function. Cornea 1996;15(2):110–119.

13. Gilbard JP, Farris RL, Santamaria J 2nd. Osmolarity of tear film microvolumes in keratoconjunctivitis sicca. Arch Ophthalmol 1978;96(4):677–681.

14. Rolando M, Refojo MF, Kenyon KR. Increased tear evaporation in eyes with keratoconjunctivitis sicca. Arch Ophthalmol 1983;101(4):557–558.

15. Versura P, Profazio V, Campos EC. Performance of tear osmolarity compared to previous diagnostic tests for dry eye diseases. Curr Eye Res 2010;35(7):553–564.

16. Bron AJ, Yokoi N, Gafney E, Tiffany JM. Predicted phenotypes of dry eye: proposed consequences of its natural history. Ocul Surf 2009;7(2):78–92.

17. Farris RL, Stuchell RN, Mandel ID. Tear osmolarity variation in the dry eye. Trans Am Ophthalmol Soc 1986;84:250–268.

18. Pflugfelder SC, diPavia CS, Tong L, Luo L, Stern ME, Li DQ. Stress activated protein kinase signaling pathways in dry eye and ocular surface disease. Ocul Surf 2005;3(4):S154–S157.

19. Li DQ, Chen Z, Song XJ, Luo L, Pflugfelder SC. Stimulation of matrix metalloproteinases by hyperosmolarity via a JNK pathway in human corneal epithelial cells. Invest Ophthalmol Vis Sci 2004;45(12):4302–4311.

20. Luo L, Li DQ, Corrales RM, Pflugfelder SC. Hyperosmolar saline is a proinflammatory stress on the mouse ocular surface. Eye Contact Lens 2005;31(5):186–193.

21. Lam H, Bleiden L, de Paiva CS, et al. Tear cytokine profiles in dysfunctional tear syndrome. Am J Ophthalmol 2009;147(2):198–205.

22. De Paiva CS, Corrales RM, Villarreal AL, et al. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. Exp Eye Res 2006;83(3):526–535.

23. Luo L, Li DQ, Pflugfelder SC. Hyperosmolarity-induced apoptosis in human corneal epithelial cells is mediated by cytochrome c and MAPK pathways. Cornea 2007;26(4):452–460.

24. Liu H, Begley C, Chen M, et al. A link between tear instability and hyperosmolarity in dry eye. Invest Ophthalmol Vis Sci 2009;50(8):3671–3679.