Knowing the osmolarity of your patient's tears is essential

The Gold Standard for the diagnosis and management of Dry Eye Disease.

TearLab™

Hyperosmolarity can be a critical determinant of quality of vision and quality of life for patients.

Osmolarity has the highest positive predictive value for Dry Eye Disease.

CLINICAL TEST	POSITIVE PREDICTIVE VALUE
Osmolarity	87%
Schirmer's	31%
TBUT	25%
Staining	31%
Meniscus Height	33%

Dry Eye Workshop. 2007 Report of the Dry Eye WorkShop. *Ocul Surf.* 2007;5:2.
Tomlinson A, et al. *IOVS.* 47(10)2006.

Osmolarity has superior correlation to composite Dry Eye Disease severity compared to other tests.

Sullivan BD, Whitmer D, Nichols K, Tomlinson A, et al. An Objective Approach to Dry Eye Severity *IOVS* Dec 2010;51(12):6125-6130.

The severity scale places the diagnosis in context.

- The higher the osmolarity, the more severe the disease.
- Patient confidence and comprehension are enhanced when they see where their condition falls in the range of severity.

Tear film instability is a hallmark of Dry Eye Disease.

- Elevated osmolarity indicates the presence of Dry Eye Disease.
- Readings between eyes with a difference greater than 8 mOsms/L confirms the diagnosis and defines an unstable tear film.
- Because of tear film instability in DED, both eyes should always be tested.
- The higher of the two numbers should be used for clinical assessment.

VARIABILITY OF NORMAL AND DRY EYE PATIENTS

		MILD/MODERATE DRY EYE PATIENT OSDI = 22.92		NORMAL PATIENT OSDI = 4.17	
		RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE
DAY 1	1 min	311	326	286	288
	2 min	304	324	285	289
	3 min	308	308	281	281
	4 min	337	334	287	286
DAY 2	1 min	315	321	296	284
	2 min	305	313	296	291
	3 min	315	323	285	291
	4 min	297	343	291	287
DAY 3	1 min	308	307	290	292
	2 min	320	312	287	291
	3 min	307	309	286	286
	4 min	333	332	292	295
MEAN		**313**	**321**	**289**	**288**
STDEV		**11.8**	**11.5**	**4.6**	**3.9**

Eldridge DC, et al. *IOVS*. 2010;51:ARVO E-Abstract 3379.

97.9% (n=659) of doctors surveyed reported that using TearLab in clinical practice improved:

- *Patient compliance*
- *Patient interaction*
- *Patient education*

Data on File, TearLab.

Osmolarity reliably measures therapeutic response.

- Osmolarity is a leading indicator of response to treatment.

  - More Severe Measurement
  - Average Between OD/OS

Sullivan BD, Crews LA, Sönmez B, et al. Clinical Utility of Objective Tests for Dry Eye Disease: Variability Over Time and Implications for Clinical Trials and Disease Management. *Cornea*. 2012 Sep;31(9):1000-8.

- Months 1-3 – No treatment. Beginning in month 3 - Treatment with cyclosporine.

TearLab™

THE GOLD STANDARD · www.tearlab.com

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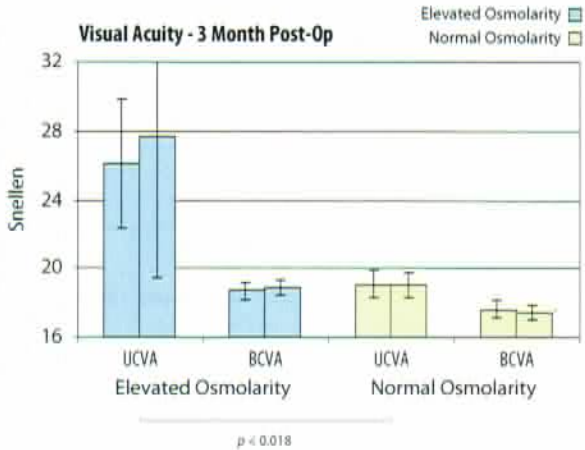
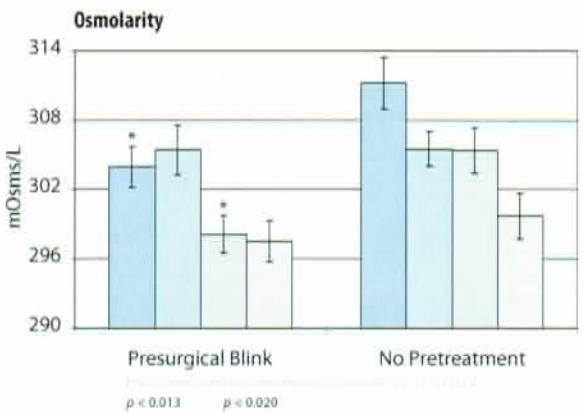
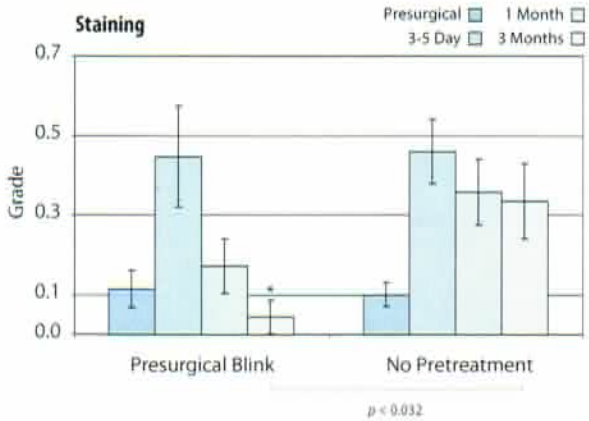
NASDAQ: TEAR · TSX: TLB · www.thedryeyereview.com

CE | FDA 510(k) Cleared (k083184) | One or more of the following patents may apply: U.S. Patents 7,017,394; 7,051,589; 7,111,508; 7,169,717; 7,204,122 | 980034 REV F

PRESURGICAL HYPEROSMOLARITY PREDICTS REFRACTIVE OUTCOMES. David C. Eldridge[1], Eric Donnenfeld[2], Tina Burr[1], Christopher Freeman[1], Dawn Holsted[1], Christine Kantor[1], Don Miller[1], Mark Slosar[1], James Thimons[3], Joel Sturm[1].
[1]Clinical Affairs, TearLab, Corp, San Diego, CA; [2]Ophthalmic Consultants of Long Island, Rockville Centre, NY; [3]TLCVision.







Purpose: To determine if tear osmolarity relates to visual acuity outcome following refractive surgery.

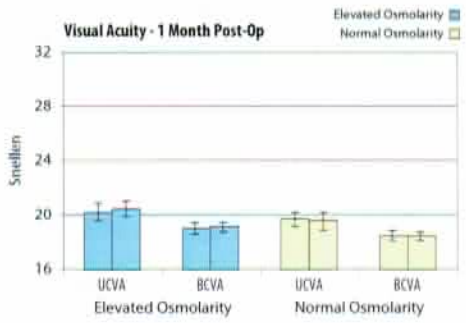
Methods: 128 subjects (48% female, 52% male, 34.7±8.9 years old) from 8 study sites were randomized into two arms: pre-surgically treated or untreated with an ocular lubricant containing hyaluronic acid (AMO Blink Tears). Hyperosmolar subjects were classified as ≥ 308 mOsm/L based on the initial visit. All patients followed standard pre & post-surgical therapeutic regimen including fluoroquinolone, steroid and cyclosporine drops as appropriate. LASIK vision correction was performed with the VISX STAR S4 with IR. Tear osmolarity, staining, TBUT, uncorrected and best corrected visual acuity assessments were performed at preop, 3-5 days, 1 and 3 months post-surgery.

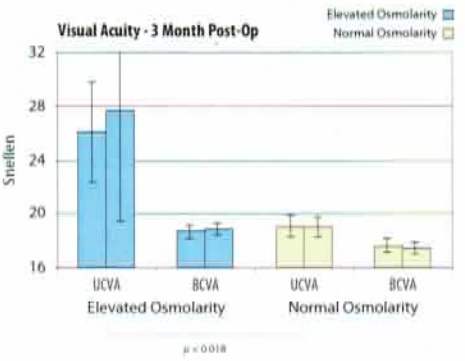
Results: Subjects with preoperative hyperosmolarity (≥ 308 mOsm/L) demonstrated significantly worse refractive outcomes at 3 months than their normal counterparts. Hyperosmolar UCVA was 20/26 and 20/28 (OD/OS), on average, compared to 20/19 and 20/19 for normal subjects. The upper range for hyperosmolar subjects was 20/200 at three months, while the upper range for normal subjects was 20/40. There were no significant differences observed in UCVA at 1-month (20/20 and 20/20 OD/OS for hyperosmolar subjects, 20/20 and 20/19 for normal subjects), suggesting that visual acuity diverged once treatments became uncontrolled. Hyperosmolar patients averaged a score of 0.2 out of 4 for ocular surface staining before surgery, making it virtually impossible to distinguish any differences between the two groups using staining. Patients treated preoperatively with AMO Blink demonstrated faster recovery than those without pretreatment. Both osmolarity at 1 month ($p < 0.020$) and staining at 3 months ($p < 0.032$) were significantly lower than those patients who did not receive preoperative AMO Blink. TBUT & symptoms showed no significant differences after 1 month.

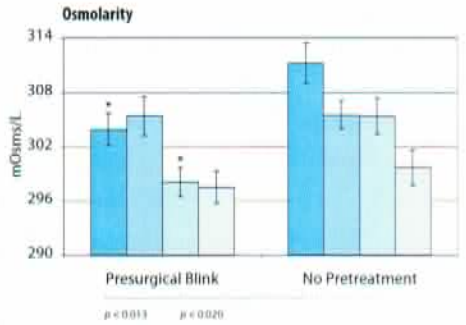
These findings suggest that stabilizing the tear film prior to laser vision correction can help doctors to achieve a significantly better initial surgical outcome for patients with pre-operative hyperosmolarity. These data also indicate that in order to maintain those initial outcomes and reduce the potential need for future enhancement procedures, maintaining therapy for DED patients with hyperosmolarity for an extended period of time following LASIK may be necessary.

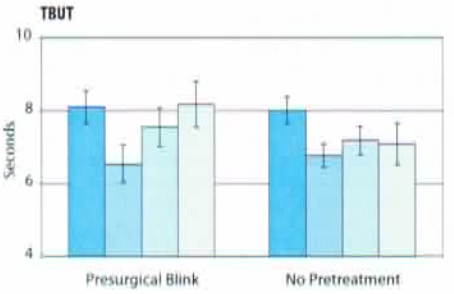
Conclusions: Surgeons should measure tear osmolarity before surgery as staining was too insensitive to identify at-risk patients. Patients with preoperative hyperosmolarity (≥ 308 mOsm/L) demonstrated worse uncorrected visual acuity. For hyperosmolar patients, it may be important to continue postoperative therapy for at least 3 months. Preoperative treatment with AMO Blink demonstrated faster postsurgical recovery.

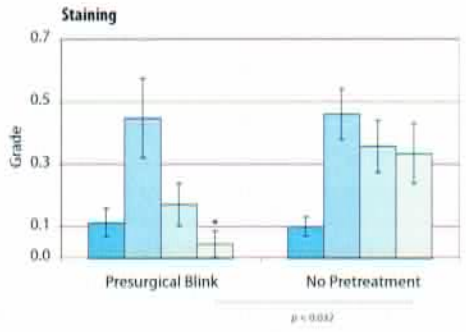
Commerical Relationships: David C. Eldridge, TearLab Corp. (E); Eric Donnenfeld, AMO (R), TearLab (R); Tina Burr, None; Christopher Freeman, None; Dawn Holsted, None; Christine Kantor, None; Don Miller, None; Mark Slosar, None; James Thimons, AMO (C); Joel Sturm, None

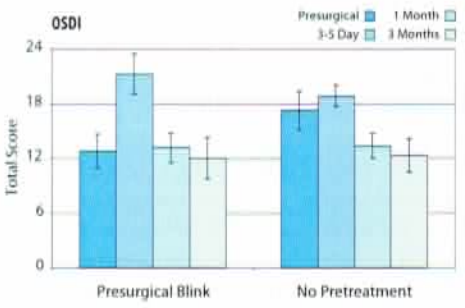

Visual Acuity - 1 Month Post-Op
Elevated Osmolarity
Normal Osmolarity
Snellen
32
28
24
20
16
UCVA
BCVA
UCVA
BCVA
Elevated Osmolarity
Normal Osmolarity


Visual Acuity - 3 Month Post-Op
Elevated Osmolarity
Normal Osmolarity
Snellen
32
28
24
20
16
UCVA
BCVA
UCVA
BCVA
Elevated Osmolarity
Normal Osmolarity
p < 0.018


Osmolarity
mOsms/L
314
308
302
296
290
Presurgical Blink
No Pretreatment
p < 0.013
p < 0.026


TBUT
Seconds
10
8
6
4
Presurgical Blink
No Pretreatment


Staining
Grade
0.7
0.5
0.3
0.1
0.0
Presurgical Blink
No Pretreatment
p < 0.032


OSDI
Presurgical
1 Month
3-5 Day
3 Months
Total Score
24
18
12
6
0
Presurgical Blink
No Pretreatment

TEARLAB™ OSMOLARITY AS A BIOMARKER FOR DISEASE SEVERITY IN MILD TO MODERATE DRY EYE DISEASE

Gary N Foulks MD FACS[1], Michael A Lemp MD[1,2], Michael Berg[2], Rahul Bhola MD[1], Benjamin D Sullivan PhD[3]. [1] University of Louisville, [2] TearLab Corp., [3] Georgetown University

1. Purpose

Recently, lab-on-a-chip technology has been developed to address the barriers to *in vitro* diagnostic tear testing. The TearLab (Fig. 1), the first in a series of assays utilizing this methodology, is "intended to measure the osmolarity of human tears to aid in the diagnosis of dry eye disease in patients suspected of having dry eye disease, in conjunction with other methods of clinical evaluation (FDA k083184)." The TearLab measures osmolarity within ten seconds, integrating seamlessly into clinical workflow. The current investigation evaluates the performance of common dry eye tests, including osmolarity, against overall disease severity.

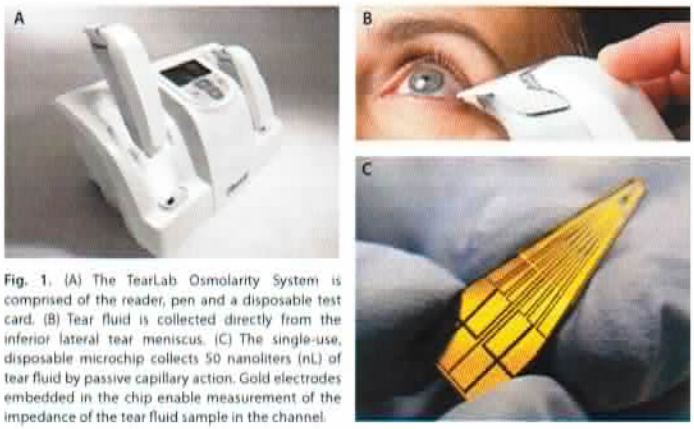


Fig. 1. (A) The TearLab Osmolarity System is comprised of the reader, pen and a disposable test card. (B) Tear fluid is collected directly from the inferior lateral tear meniscus. (C) The single-use, disposable microchip collects 50 nanoliters (nL) of tear fluid by passive capillary action. Gold electrodes embedded in the chip enable measurement of the impedance of the tear fluid sample in the channel.

2. Methods

Data are derived from a 300 subject, 11 site prospective clinical trial (n = 218 F, n = 81 M, average age = 46.3). An expert panel of physicians and optometrists provided a progression of signs across a discrete severity scale, as shown in Table 1. Continuous functions were fit to normalized versions of these progressions, and a composite disease severity index was created using equalized input from each of the measured signs. To ensure that each clinical variable carried equivalent correlation risk against the overall index, Jon Shlens' infomax ICA algorithm was used to subtract out mutual information [1, 2]. The highest severity measurement from each sign for each eye was used to construct the index.

Table 1. Modified Dry Eye Workshop Severity Scale [3].

Severity Grade	0	1	2	3	4
Schirmer I (mm)	35	7	5	2	0
TBUT (seconds)	45	7	5	3	0
Staining (NEI scale)	0	3	8	12	20
OSDI	0	15	30	45	100
Meibomian Grading	0	5	12	20	28
Osmolarity (mOsms/L)	275	308	324	364	400

3. Results

At a diagnostic cutoff of 308 mOsms/L, osmolarity was found to have superior performance, especially in the Mild to Moderate cohort. Osmolarity exhibited an 88% specificity for Normal subjects, a 75% sensitivity for Mild/Moderate patients, and a 95% sensitivity for the Severe patients. Within the Mild/Moderate cohort, the other six tests showed sensitivities of [68%, 28%, 42%, 69%, 50%, and 49%] for TBUT, Schirmer I, corneal & conjunctival staining, meibomian grading, and OSDI, and Normal specificities of [60%, 79%, 85%, 67%, 76%, and 79%] respectively. These data suggest that symptoms alone are insufficient to grade dry eye severity.

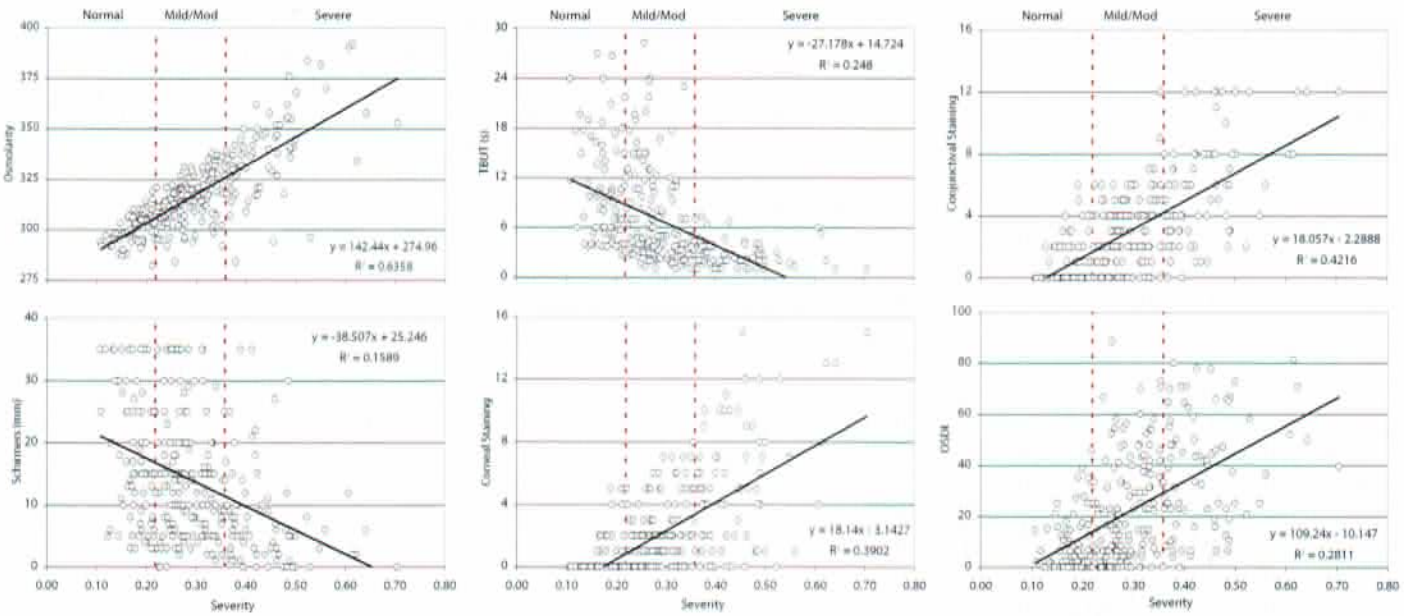


Fig. 2. The three quartile-derived groups; Normal (1st Quartile), Mild/Moderate (2nd, 3rd Q), and Severe (4th Q), are demarcated by the vertical dashed lines. Within the Normal to Moderate cohort, only osmolarity shows significant correlation to disease severity. Symptoms show reasonable discrimination for the Normal group, but are of little value for determining disease severity. The other clinical signs perform well for the Severe patients, but poorly for Normal through Moderate quartiles.

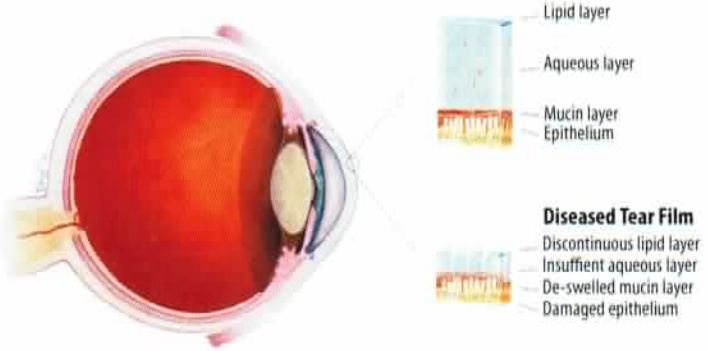
1. Shlens J., Independent Component Analysis, http://www.snl.salk.edu/~shlens/pub/code/ica.infomax.zip, 2003. 2. Bell AJ, Sejnowski TJ. The "independent components" of natural scenes are edge filters. Vision Research 37(23):3327 1997
3. 2007 Report of the Dry Eye WorkShop. Ocul Surf 2007;5[2]:65-204. Contributing authors: Schaumberg DA, Baudoin C, Benitez-del-Castillo JM, Figueiredo F, Geerling G, Geffen D, Mundorf T, Nichols K, Pepose J, Rolando M, Tauber J, Tomlinson A, Tsubota K, Kosheleff V, Porreco A, Whitmer D. Financial support was provided by Alcon Laboratories. Financial Disclosure: Employee, Owner, Patents: Sullivan. E.O: Berg. Consultant, Grant Support: Foulks, Consultant, Owner: Lemp. 920014RevA.

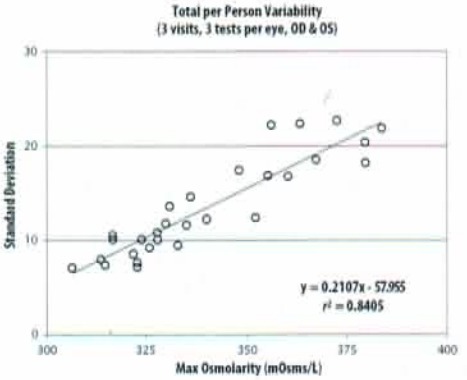
LONGITUDINAL VARIABILITY OF TEAR FILM OSMOLARITY IN NORMAL AND DRY EYE PATIENTS.

David C. Eldridge[1], Benjamin D. Sullivan[1], Michael S. Berg[1], Michael A. Lemp[2], Daniel S. Durrie[3]. [1]TearLab, Corp., San Diego, CA; [2]Departments of Ophthalmology, Georgetown and George Washington University, Washington, DC, [3]Durrie Vision, Overland Park, KS.

TearLab™

Tear Film Characteristics in Dry Eye Disease





The tear film is a complex thin film that provides hydration, lubrication, and immunity for the ocular surface. Hydration comes from the micron-thick aqueous layer[1], and is thought to be mainly supplied by the lacrimal gland. The meibomian glands, located in the lids, secrete a thin layer of interfacial polar lipids and a thicker contingent of nonpolar lipids that act in unison to inhibit evaporation of the aqueous layer. Supporting the aqueous and lipid layer is a gel-like mucin layer than helps to lubricate the ocular surface and protect the epithelial cells against shear stress.

In dry eye disease, the tear film becomes compromised and unstable, reducing both the quantity and quality of tears[2]. As the lipid layer degrades, the already small amount of tear film evaporates in just a few seconds[3].

With each blink, the aqueous layer is reconstituted from a small, variable pool of tear in the lower meniscus[4]. A rough corneal surface destabilizes the tear film, contributing to rapid tear film breakup[5]. Without a stable tear film, the image formed on the retina becomes blurry and distorted within seconds after each blink, regardless of the health of the lens or retina[6].

1. Purpose

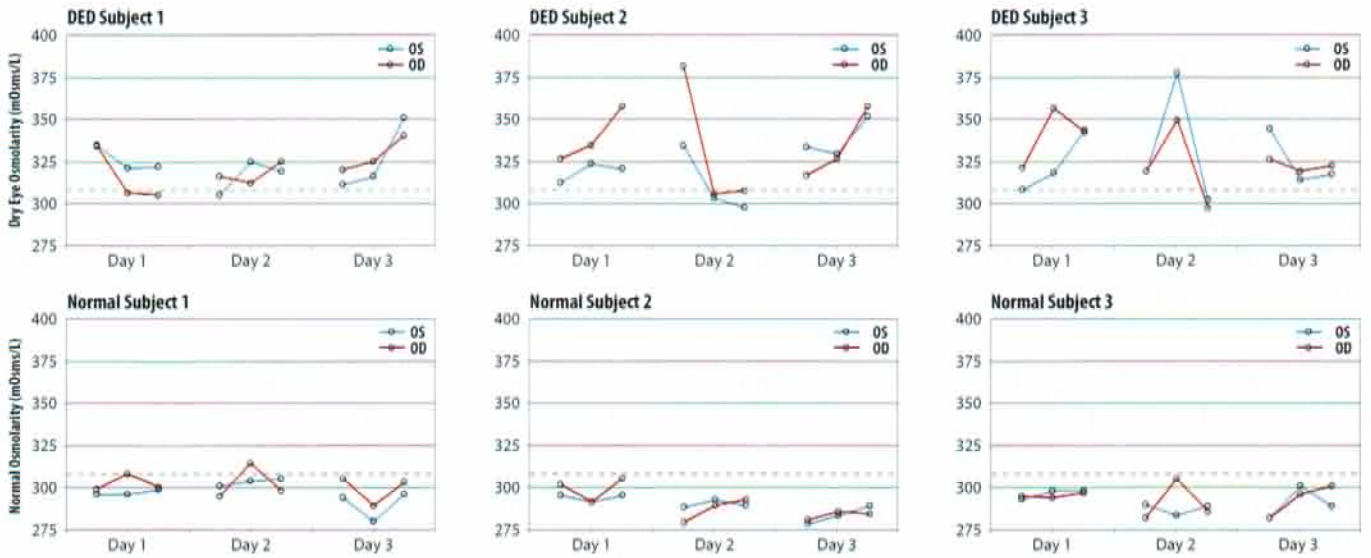
Tear film hyperosmolarity and tear film instability are recognized as the two causative mechanisms of dry eye disease, yet the relationship between the signs are poorly understood. The purpose of this study was to evaluate the variability of OD vs OS tear film osmolarity relative to tear film instability in the diagnosis of dry eye disease.

2. Methods

Bilateral tear osmolarity was measured on three different days, with at least 2 weeks between each patient visit. 30 subjects were recruited for the study (n=16 normal, n=14 dry eye, determined by an average osmolarity > 308 mOsms/L across all tests). At each visit, 50 nanoliters of tear fluid was simultaneously collected and analyzed (OD and OS) by the TearLab™ Osmolarity System, in triplicate.

3. Results

- The average (x) of normal subjects was 301.8±4.8 mOsms/L [range x=290.2–307.7] while the average of the hyperosmolar subjects was 315.6±6.6 mOsms/L [range x=308.1–329.4, indicating early stage mild disease].
- Variability was significantly lower in normals than in dry eye (7.9 vs. 14.7 mOsms/L, $p<<0.001$) and strongly correlated to the maximum of the bilateral measurements (r^2=0.84), which is the recommendation for clinical assessment.
- When the highest of either the OD or OS osmolarity result of an individual patient was considered, 86% of the early stage, mild dry eye subjects were correctly diagnosed with the first set of measurements. This number rose to 100% if eyes were measured in triplicate.
- If only one eye was used in the diagnosis, the mild dry eye subjects were correctly identified 69% (OD) and 62% (OS) of the time with the first set of measurements.
- These data indicate that tear film instability increased in dry eye disease (DED).

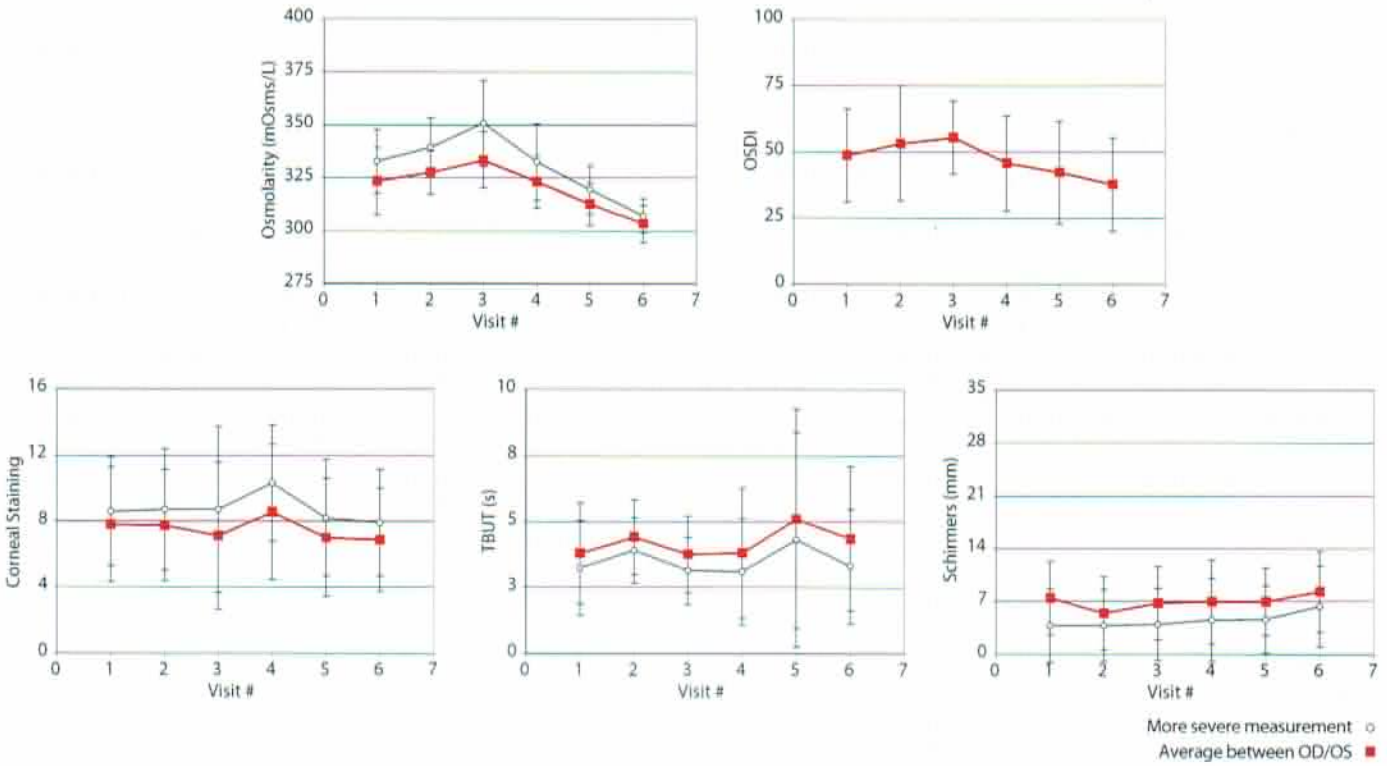


1. King-Smith PE et al. Curr. Eye. Res. 2004, 29(4–5):357–368. 2. Sullivan DA et al. Ann. N.Y. Acad. Sci. 2002, 966:211–222. 3. Tsubota K et al. Invest Ophthalmol Vis Sci. 1992, 33:2942–2950. 4. Gaffney EA et al. Prog Retinal & Eye Res. 2010, 29:59–78. 5. Lemp MA et al. Arch Ophthalmol. 1973, 89(2):103–5. 6. Toda I et al. J Refract Surg. 2009, 25(1):69–73. Funding provided by Alcon Laboratories & TearLab Corp., Financial Disclosure: TearLab Employee, Owner, Patents: Sullivan. TearLab Employee,Owner: Lemp, Berg, Eldridge. TearLab Owner: Durrie.

920019 Rev A

LONGITUDINAL VARIATION IN SIGNS AND SYMPTOMS OF DRY EYE DISEASE AS COMPARED TO A COMPOSITE SEVERITY INDEX.

Benjamin D. Sullivan[1], Baris Sonmez[2], Ebru Comert[2], Michael S. Berg[1], Michael A. Lemp[3]. [1]TearLab Corp, 7360 Carroll Road, San Diego CA, [2]Ondokuz Mayis University, School of Medicine, Samsun Turkey, [3]Georgetown University Department of Ophthalmology, Washington DC.



Purpose: The objective of this study was to evaluate the longitudinal variability and track the impact of anti-inflammatory therapy on signs and symptoms of dry eye disease.

Methods: 21 subjects (n=18 female, n=3 male, 47±13 years old) with a history of dry eye symptoms were recruited at a single site. Prior to initiation of therapy, tear osmolarity, tear film breakup time (TBUT), Schirmer's test, corneal staining (NEI/Industry), meibomian dysfunction assessment (Bron/Foulks scoring), and symptoms (OSDI) were evaluated on three separate days, spaced roughly at time 0, 30 and 90-day timepoints. Longitudinal variability was defined as the ratio of the standard deviation of all measurements to the dynamic range of each clinical test. Following the initial longitudinal study, 10 of the twenty-one subjects were enrolled in a therapeutic arm of the study. These subjects began a 90-day course of Cylosporine A (Restasis®, Allergan Inc.) after visit #3. Subsequent visits (#4-#6) were spaced roughly one month apart, and signs and symptoms were recorded at each visit.

Results: There were no significant differences in the longitudinal variability of each of the clinical signs or symptoms. In particular, osmolarity (11.6% variation over time) was found not to be significantly different than TBUT, Schirmer's, corneal staining, OSDI (13.1%, 11.8%, 11.4%, and 10.2%, with p=0.46, 0.94, 0.89, 0.42 respectively). The maximum change between timepoints was also similar between tests, with osmolarity, TBUT, Schirmer's, corneal staining, and OSDI (62.4%, 100%, 91.4%, 43.8%, 40.8%, respectively) all exhibiting substantial movement over time. Of interest, 71.4% subjects were hyperosmolar (average across all tests > 308 mOsms/L), 48% had breakup times < 5 s, 57% reported Schirmer's values < 10 mm, and 67% showed a corneal staining value > 3/16.

For subjects enrolled in the therapeutic arm, the average osmolarity of the first three visits was significantly reduced from 341 ± 18 to 307 ± 8 mOsms/L (p =0.000002), while OSDI was significantly reduced from 51 ± 18 to 38 ± 18 (p=0.04). A change of 7-10 points on the OSDI was recently found to carry clinical significance for mild to moderate DED patients [Miller KL]. While the improvements in osmolarity were observed for all subjects receiving therapy, none of the other signs demonstrated a significant change. This suggests that osmolarity is a leading indicator of therapeutic effect. Of note, there was a corresponding increase in osmolarity and symptoms on the third visit, prior to the onset of therapy, that was not reflected by the other signs.

Conclusions: These data demonstrate that 1) Restasis has a profound effect on tear osmolarity, 2) osmolarity and symptoms are well related, and 3) osmolarity leads the other signs in revealing a therapeutic effect. The lack of change in Schirmer's values in this study also indicate that an increase in tear volume may not be entirely responsible for the benefits of topical cyclosporine. Rather, the data support a therapeutic mechanism wherein cyclosporine interrupts the pro-inflammatory cycle (*e.g.*, HLA-DR [Brignole], etc.), restoring healthy ocular surface regulation and lowering the tear film osmolarity. In turn, the lowered osmolarity likely alleviates dry eye symptoms.

The normative longitudinal data also reveal the effect of compensatory mechanisms; wherein the "worse eye" can change depending on the day of measurement. This underscores the importance of using the "most severe result" from a bilateral measurement during each timepoint of a clinical trial, rather than following the "worse eye" as suggested in earlier studies [Sall K, 2000].

1) Miller KL et al., Arch Ophthalmol. 2010 Jan;128(1):94-101. 2) Nelson JD, Farris RL. Arch Ophthalmol 1988; 106:484-487 3) Sall K, et al. Ophthalmology, 2000 Apr; 107(4):631-639. 4) Brignole F, et al. IOVS. 2001 Jan;42(1):90-5. Support: TearLab Inc.: BDS (E,I,P), MSB (E,I), MAL (C,I).