

VARIABILITY IS A HALLMARK OF DRY EYE DISEASE

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If tear osmolarity is variable, how can it be a useful marker of disease? The answer is simple; while tear osmolarity in Dry Eye Disease patients can be highly variable, in normal subjects it is not. Thus variability is an independent marker of DED.

“Osmolarity is a good test, Dry Eye is a bad disease.” *Eric Donnenfeld, 2013*

Whether Dry Eye Disease is caused by inadequate tear production or increased tear evaporation, each results in hyperosmolarity. Hyperosmolarity contributes to tear film instability—the hallmark of Dry Eye Disease—and an unstable tear film leads to fluctuations in visual acuity.

Look for Tear Film Instability to Diagnose Dry Eye Disease

To remain healthy, the human body and its organs need to be in homeostasis. Dry Eye Disease patients have lost the ability to maintain tear film homeostasis. This is similar to a diabetic patient’s loss of homeostasis of blood glucose levels or a glaucoma patient’s ability to regulate intraocular pressure.

In a recent publication in *Current Eye Research*, evidence clearly revealed that tear film instability is a hallmark of Dry Eye Disease. The authors of the paper concluded:

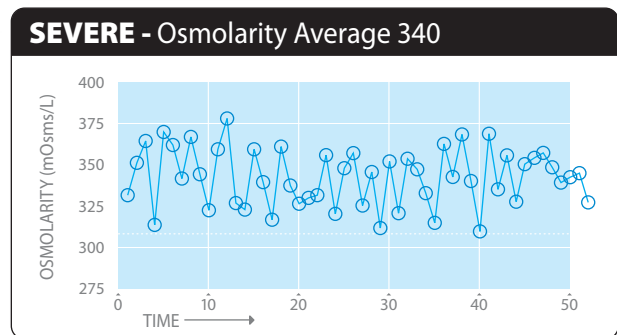
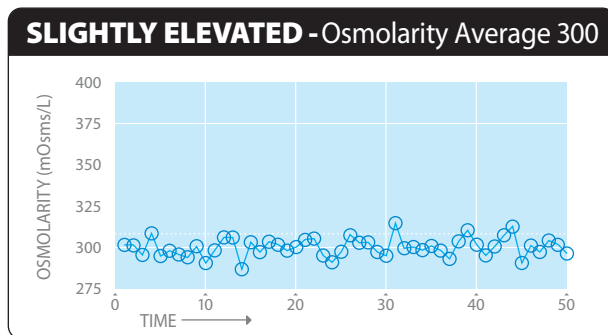
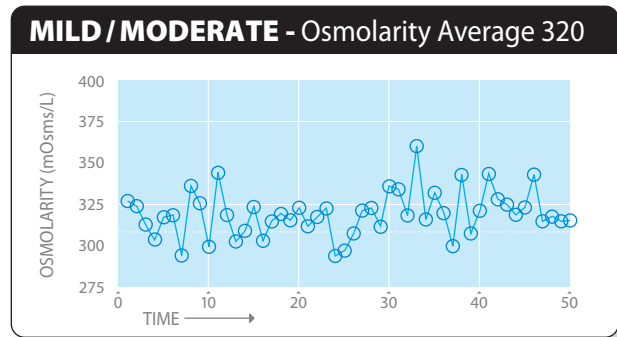
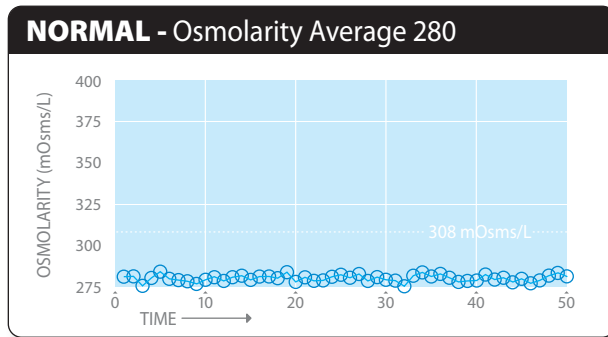
“Clinically, if variability is observed eye-to-eye or over time in a patient, it may help confirm a diagnosis of dry eye, as normal subjects exhibit a very tight band of values within the homeostatic range, while dry eye subjects frequently eclipse the healthy range...this relationship suggests that the tear film becomes increasingly unstable in Dry Eye Disease. Those subjects well below the cut-off for Dry Eye Disease (< 308mOsms/L) exhibit standard deviations near that of the analytical variation of the TearLab device, suggesting that the increase in variability is an inherent biologic characteristic of the disease and is not due to measurement technique.”¹

The following tables demonstrate what Keech et al are referring to in the paper. Most important, normal subjects have essentially zero variation in osmolarity over time. The TearLab Osmolarity System has a very low coefficient of variation at only 1.5%, thus “normals” have less variation than the analytic error (st dev bilaterally < 5) of the test, which is approximately a mere 5-6 mOsms/L.

This data has allowed clinicians to rethink Dry Eye Disease (DED) and better identify who truly is a Dry Eye Disease patient and, perhaps more important, who isn't. DED patients have elevated osmolarity and significant variability, while normals have low osmolarity with little, if any, fluctuation.

BIOLOGICAL VARIABILITY OF 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

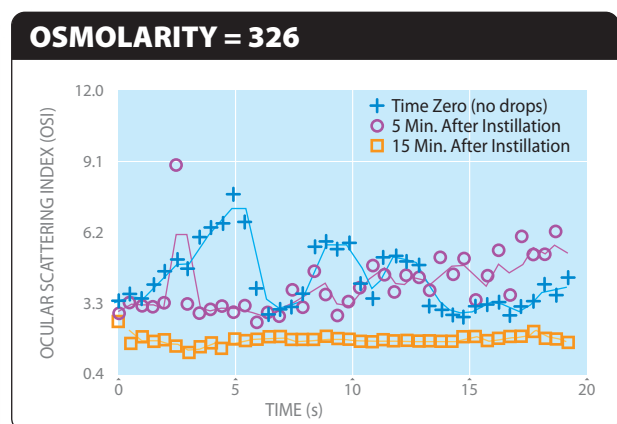
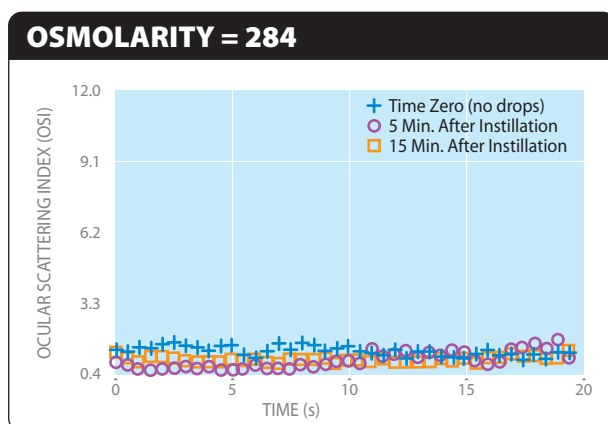
Mathematical Model Representing Instability Over Time



The above simulation is similar to real visual scatter data (Pisella et al). Shown below, normal osmolarity subjects have a stable tear film, good focus and visual acuity, while DED subjects have an unstable tear film that may result in dramatic shifts in visual acuity from blink to blink. Each graph represents one eye of a patient over time. The fellow eye in DED patients is typically "out of phase," thus demonstrating inter-eye differences.

Disease Severity Over Time Utilizing Visual Scatter Data

The ocular scatter in the hyperosmolar patient secondary to an unstable tear film.



When patients are successfully treated for Dry Eye Disease, the tear film regains stability, as evidenced by stable and lower osmolarity readings. In practice, we typically see a physiologic reduction in osmolarity just prior to improvement in signs and symptoms of DED. This “symptom lag,” when explained to patients in treatment with falling osmolarity, is quite reassuring and motivating.

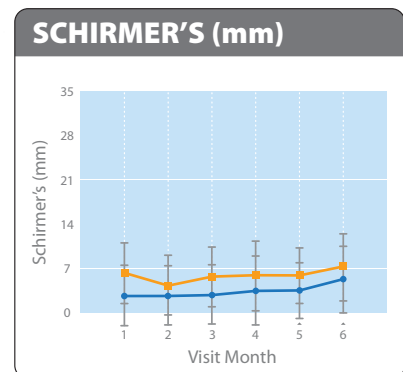
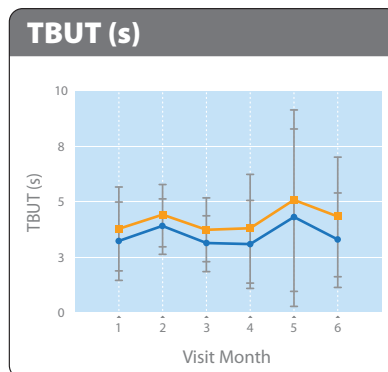
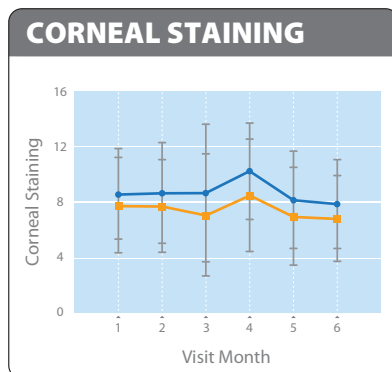
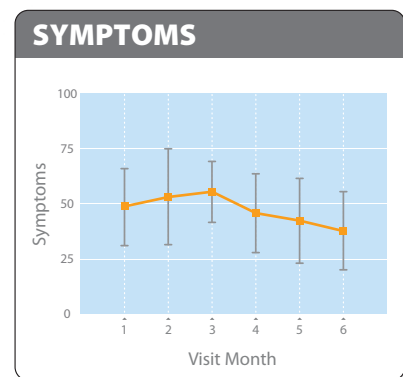
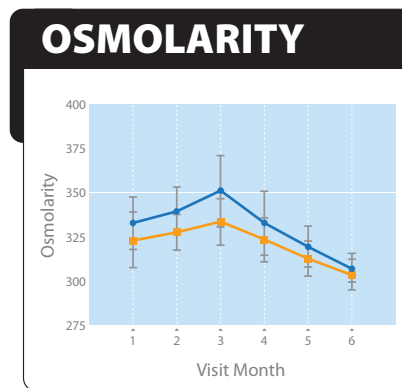
The study graphs below demonstrate this very well. After the initiation of Restasis® or hyaluronic acid, the error bars diminish along with the normalization of the patients’ osmolarity. Note that this is not the case for other tests for Dry Eye Disease utilized in these studies. Tear film breakup time and staining do not show the same improvement or stability.

The data below shows the average osmolarity and the higher measurement of each eye. Research shows that treatment decisions should always defer to the higher of the two eyes.

Clinical Utility of Objective Tests for Dry Eye Disease

Osmolarity is a leading indicator of response to treatment.

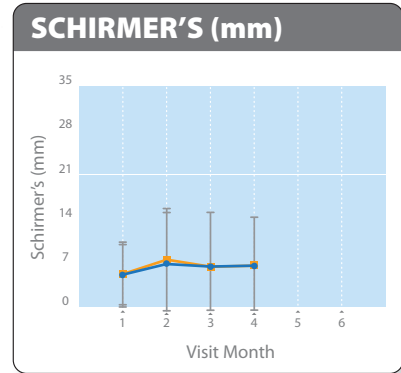
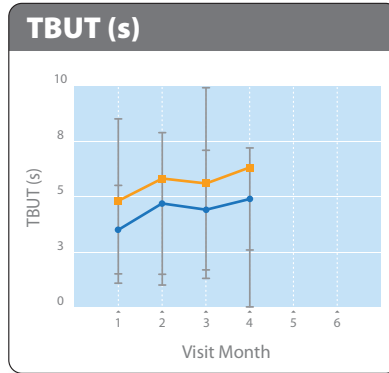
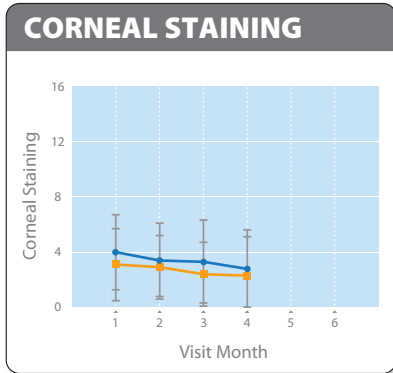
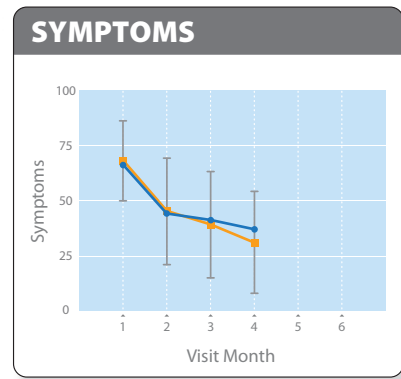
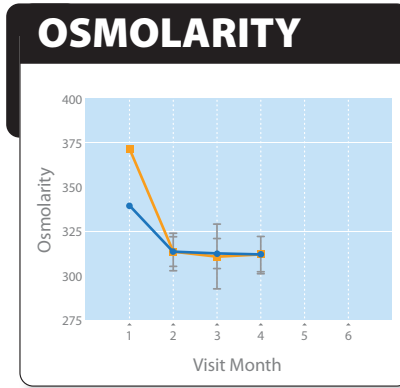
- Treatment: Restasis®
- More Severe Measurement
- Average between OD/OS



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.

TearLab helps to simplify diagnosis & management.

- Treatment: Hyaluronic Acid
- 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.

Dry Eye Disease Is Complicated. TearLab Helps to Simplify.

Clinicians now have the capability to use at the point of care a lab test that is extremely precise. It can provide totally objective data that reveals two valuable diagnostic keys to better understand Dry Eye Disease. Elevation of osmolarity and inter-eye variability are both hallmarks of an unstable tear film and evidence of pathogenetic changes in the ocular surface that should be addressed. Dry Eye Disease is complicated. TearLab helps to simplify the diagnosis and management.

FOOTNOTES

1 Keech A, Senchyna M, Jones L. Impact of Time Between Collection and Collection Method on Human Tear Fluid Osmolarity. *Curr Eye Res*. 2013 Apr;38(4):428-36. Epub 2013 Feb 12.

2 Sullivan BD, Crews LA, Sönmez B, de la Paz MF, Comert E, Charoenrook V, de Araujo AL, Pepose JS, Berg MS, Kosheleff VP, Lemp MA. 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.