When first adding tear osmolarity testing into their practice, many colleagues have called me with questions about integrating this new diagnostic test with respect to patient flow, interpreting results, understanding inter-eye and temporal variations, and whether they can rely on this one metric alone to diagnose dry eye. I have been involved in a number of investigations of TearLab tear osmolarity testing dating back to the initial validation study to comparisons with other dry eye tests and studies of the response of tear osmolarity to treatment regimens. This experience has provided me with a framework and overview of how this single metric fits into the diagnosis and severity grading of dry eye and its response to treatment.

**Diagnosing in the Dark**

To put office-based tear osmolarity testing in context, the best analogy I can think of is to imagine what the internist faced over 100 years ago in diagnosing and treating diabetes without the benefit of blood glucose or Hemoglobin A1C testing. Since elevated blood glucose is so central to both type I and type II diabetes (similar to what tear hyperosmolarity is to all forms of dry eye), not having reliable glucose metrics of fasting blood sugar, response to glucose challenge or variations in blood glucose during the day would severely limit the ability of the internist or endocrinologist in the diagnosis, control and management of diabetes, forcing him or her to rely predominantly upon assessment of symptoms (e.g., polydypsia, polyphagia and polyuria) or signs of end organ damage (e.g., renal failure, neuropathy or retinopathy).

Having these essential glucose metrics does not tell the internist what type of diabetes the patient has, what organ damage has occurred or the type or etiology of the diabetes (e.g., acute onset of type I diabetes at age 10 following mumps or slow onset of type II at age 45 coincident with the development of obesity). The internist still needs to be a cognitive physician,
examine the patient and integrate the patient’s history, physical findings and laboratory results, but he or she is far better equipped by having essential objective laboratory data that are directly related to the central factor underlying disease pathogenesis.

**Elevated Tear Osmolarity is Seminal to Dye Eye Disease**

Dry eye is a progressive disease of inherent tear film instability, leading to variable signs and symptoms\(^1\,^2\). There is generally poor correlation between signs and symptoms. Up to 30% of dry eye patients are asymptomatic, particularly during early stages of disease. Many common complaints, such as burny, itchy, gritty, irritated eyes, along with other vague symptoms, are common to many conditions besides dry eye. Some patients may have enough compensatory homeostatic mechanisms functioning to be completely asymptomatic unless placed under stress situations, such as flying in an airplane, wearing contact lenses all day, or staring at a computer, and they may not spontaneously voice any complaints without soliciting this history. Others may not voice complaints because the ocular surface is desensitized and hypoesthetic.

Tear hyperosmolarity is central to all forms of dry eye (i.e., aqueous deficient, evaporative or mixed) and categorical cutoffs of this continuous variable (discussed below) correlate well with disease severity. Just as there are many mechanisms that tightly regulate blood sugar, many homeostatic mechanisms exist that maintain tear osmolarity in the range between 290 mOsm/L to 300 mOsm/L, with less than 8 mOsm/L difference between eyes. These mechanisms include increased aqueous tear production, increased meibomian gland secretion, increased mucin production and a more rapid blink rate. Elevated tear osmolarity greater than 300 mOsm/L along with an inter-eye tear osmolarity difference above 8 mOsm/L is a signature of dry eye disease (Figure 1). Over time, the mean tear osmolarity often continues to progressively increase in steps as homeostatic mechanisms progressively fail, creating a new and more elevated set point. Elevated osmolarity can lead to dysregulation of the tear film and more inflammation and damage to both the ocular surface and the tubuloacinar architecture of the lacrimal gland.
Determining Referent Tear Osmolarity Values for Various Stages of Dry Eye Disease

It has been shown that tear osmolarity greater than 300 mOsm/L is seen in mild dry eye disease, above 320 mOsm/L in moderate and above 340 mOsm/L in severe, untreated dry eye, along with inter-eye differences of greater than 8 mOsm/L \( \text{(Figure 2)} \). Just as tear osmolarity becomes more variable with increasing severity of dry eye, the other tests of dry eye (e.g., vital dye staining, Schirmer’s, meibomian gland disease) show even more variation. In fact, tear osmolarity is the least variable across repeated office
visits. Just as intraocular pressure can fluctuate, tear osmolarity in each eye may vary and cycle and this variation may not be synchronous between the two eyes. This is in response to various environmental stresses such as computer or contact lens use, wind or low humidity, increased tear evaporation, and varying recruitment of compensatory mechanisms, such as reflex tearing and increased production of different layers of the tear film. Therefore, the higher osmolarity reading between the two eyes should be used in assessing severity. Since the different signs and tests of dry eye give different and overlapping information, poorly correlate and may vary depending on the type of dry eye, these can be mathematically weighted to minimize the overlap creating a composite dry eye index. When the various signs and symptoms are mathematically combined into a composite index, it has been shown that tear osmolarity is an excellent indicator of dry eye severity regardless of its etiology (i.e., aqueous-deficiency, evaporative or combined).¹

![Figure 2. A dry eye osmolarity severity scale was developed, allowing the clinician to plot severity and monitor therapeutic progress. To account for overlapping information between a variety of dry eye metrics, independent component analysis was used to derive an overall dry eye composite index that could be compared to tear osmolarity. Of interest, inter-eye differences in tear osmolarity increased with increasing disease severity.](image)

**Use of Tear Osmolarity in Clinical Practice**

The TearLab Osmolarity instrument (Figure 3) consists of a reader and two pens. It is compact and designed for the office setting. Without using any drops or topical anesthetic that could cause dilution or alter tear stability, the
lab-on-a-chip inside each TearLab disposable quickly and atraumatically collects 50 nanoliters of fluid from the anterior marginal tear meniscus near the lateral canthus (Figure 4). This minimizes both tear evaporation and reflex tearing and analyzes the result in only a few seconds. The test can be easily performed by a technician with minimal training.

Figure 3. TearLab’s osmolarity instrument

Figure 4. Tears are collected from the inferior tear lake near the lateral canthus. Collection takes a fraction of a second.

Tear osmolarity should be taken two hours after the instillation of any eye drops, which could result in a falsely low osmolarity reading, and could be disturbing the ocular surface and creating reflex tearing when performing the test. Elevated tear osmolarity readings are strongly indicative of dry eye disease and in my experience, false positive results are rare. Repeatedly normal osmolarity with inter-eye variation of less than 8 mOsm/L should prompt a search for other root causes of symptoms, such as allergy or
conjunctivochalasia. Tear osmolarity is an important component in the diagnosis of dry eye, but is not a substitute for a careful history, review of medications, examination of the eyelids and ocular surface, and performance of other dry eye tests. Hyperosmolar tears, while consistent and necessary for the diagnosis of dry eye disease and highly correlated to disease severity, do not differentiate between aqueous deficient versus evaporative or mixed disease, and additional signs should be evaluated to aid in this distinction.

**Who Should Have Tear Osmolarity Tested?**

Since nearly one in five people in North America have dry eye, this may be one of the most common, yet frequently undiagnosed and untreated problems seen every day by ophthalmologists. While patients who have symptoms suggestive of dry eye should have a tear osmolarity evaluation, even some asymptomatic patients may have dry eye — which is likely to progress and lead to further inflammation if not treated early. Fluctuation in vision is a common complaint which the patient may not relate to dry eye disease. There is no financial pushback from most patients for tear osmolarity testing, as the test for each eye has been issued a CPT code from the Centers for Medicare and Medicaid Services (83861 “Microfluidic analysis utilizing an integrated collection and analysis device; tear osmolarity,”) and is reimbursed by Medicare and insurance carriers with no temporal window for repeat testing.

Of concern to ophthalmic surgeons, dry eye has a profound impact on both high and low contrast vision and contrast sensitivity, since tears represent the most anterior refractive surface of the eye. Tear osmolarity assessment is therefore essential for patients undergoing cataract and refractive surgery. The surgical trauma of cataract and refractive surgery in itself, with concomitant severing of nerves and associated inflammation, presents a challenge to the ocular surface and patients with dry eye lose the ability to respond to these challenges. We want to know ahead of time who is at high risk by having pre-existing dry eye and who needs to be pre-treated to optimize the tear film and ocular surface.
A recent study presented by Dr. David Eldridge and colleagues at ARVO 2012 showed that patients who had hyperosmolar tears pre-LASIK had statistically worse outcomes at the three-month time point and may have benefitted from chronic dry eye therapy.\(^9\) Whether a patient is considering cataract surgery with a conventional or premium IOL or LASIK surgery, pre-existing dry eye is a risk factor for a suboptimal visual outcome, fluctuating vision and reduced contrast sensitivity. Avoiding this end result requires accurate dry eye diagnosis, distinct staging of disease severity and appropriate preemptive and postoperative treatment.

**The Test Could Assess the Efficacy of Specific Dry Eye Therapies**

Studies using topical cyclosporine A (Restasis, Allergan) showed that treatment was associated with a drop in tear osmolarity that preceded the reductions of symptoms.\(^{10}\) Similar results have been found following treatment with artificial tears containing hyaluronic acid. While larger, masked, controlled trials are needed, these preliminary results suggest that monitoring tear osmolarity can be a useful indicator of the efficacy of specific dry eye treatments.

In my experience, the addition of tear osmolarity testing to your practice gives you the ability to diagnose dry eye more easily, quantify the severity of the disease and monitor the efficacy of specific dry eye treatment protocols. It is a vital test in the preoperative assessment of cataract and refractive surgery patients, who expect crisp, non-fluctuating uncorrected high and low contrast vision. Finally, it also is an excellent tool to augment the referral of dry eye patients to your practice.

**References**