



The utility of a normal tear osmolarity test in patients presenting with dry eye disease like symptoms: A prospective analysis



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ABSTRACT

Objective: To explore the diagnostic utility of normal tear osmolarity in patients with symptoms suggestive of dry eye disease (DED).

Methods: Prospective observational cohort study of 100 patients that underwent tear osmolarity testing (TearLab™) if they endorsed one or more symptoms of potential DED. Patients were included for the study if they had a normal tear osmolarity test (value < 308 mOsm/L in each eye, and an inter-eye difference < 8 mOsm/L). The main outcome measure was the presence of any alternate diagnosis to explain the patient's symptoms. Results were recorded and descriptive and univariate statistics were employed.

Results: Mean tear osmolarity was 293.40 mOsm/L (± 6.82), with a mean absolute difference of 2.85 mOsm/L (± 1.98) between the eyes. A possible alternate diagnosis was established in 89% of patients with normal tear osmolarity testing. The most frequent diagnoses included anterior blepharitis (26%) and allergic conjunctivitis (21%).

Conclusions: Common symptoms of DED overlap significantly with a wide variety of other ocular surface diseases, and a normal tear osmolarity test should increase clinical suspicion for alternate causes of those symptoms. Anterior blepharitis and allergic conjunctivitis were the most common diagnoses made in symptomatic patients with normal tear osmolarity who may have otherwise been misdiagnosed and treated for DED.

1. Introduction

Dry eye disease (DED) is one of the most frequently encountered diagnoses in primary eye care, with a prevalence ranging from 5% to over 30% [1]. In fact, up to 30% of patients seeking care by an eye care specialist describe symptoms consistent with DED [2]. These commonly described symptoms include foreign body sensation, grittiness, dryness, redness, fatigue, pruritis and fluctuating vision. Despite the prevalence of DED, research has shown that these subjective symptoms do not correlate well with clinical objective measures of DED severity [3,4]. The disparity between signs and symptoms of DED can prove challenging in both establishing a diagnosis and effectively treating this common condition. Several studies have demonstrated that abnormal tear film osmolarity may be responsible for the ocular surface symptoms associated with DED [5–8]. In fact, the Dry Eye Workshop reports (TFOS DEWS) I and II both included tear film hyperosmolarity in the definition of DED, and recognize it as one of the key pathophysiologic mechanisms of DED [9,10]. As such, tear film osmolarity testing has emerged as a useful tool to aid in the diagnosis of DED.

Point of care diagnostic testing, such as the TearLab™ Osmolarity

System, has been established as a useful tool in the diagnosis and staging of DED across many studies [6,11–13]. In fact, a review of the literature found a 72% positive impression of tear osmolarity testing in establishing a DED diagnosis [11]. This testing is particularly attractive because it offers an objective value for stratifying abnormal results which are linearly related to DED severity [14]. These values can also be used for assessing treatment efficacy as decreasing osmolarity suggests improving DED.

Hyperosmolarity of the tear film is highly pathognomonic for DED, and as such, is included as one of the key diagnostic markers of DED in the TFOS DEWS II clinical protocol for DED diagnosis [15]. The clinical protocol states that in patients with symptoms of DED and abnormal tear osmolarity a diagnosis of DED can be confidently made. Despite the significant literature on the value of abnormal tear osmolarity in establishing a DED diagnosis, little data has been published on the diagnostic value of normal tear osmolarity in symptomatic patients. If abnormal osmolarity confirms DED, then there may be diagnostic value in a normal osmolarity in ruling out DED. Therefore a negative test may alert the clinician to determine a possible alternate ocular surface disease (OSD) cause for the DED-like symptoms. The purpose of this study

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is to explore the diagnostic utility of a normal tear osmolarity test in patients with symptoms suggestive of DED.

2. Materials and methods

A single center prospective observational study of 100 total patients was conducted from January 2016 to September 2016. Patients were recruited from a single surgeon general/cornea practice (CES) at Weill Cornell Medicine. Ethics approval was obtained from the Weill Cornell Medicine Institutional Review Board prior to enrolling study participants. The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from study participants after explanation of the nature and possible consequences of the study. Participants were enrolled for study if they endorsed any one of the following symptoms: any fluctuations in vision (with refractive correction), ocular surface irritation (including foreign body sensation, grittiness, tiredness, or dryness), eye redness, or pruritis. Symptoms were determined by targeted questions from the ophthalmic technician at the start of the visit. In order to limit bias from environmental effects, patients were excluded from the study if they had used any eye drops within 2 h of the clinical encounter. Participants then underwent bilateral tear osmolarity testing (TearLab™) by a trained technician prior to any further ocular workup or instillation of eye drops. All devices were appropriately calibrated and all technicians abided by the testing protocol as established by the TearLab™ technician in-service review [16]. Patients were only included for study if they exhibited a normal tear osmolarity test (value < 308 mOsm/L in each eye, and an inter-eye difference < 8 mOsm/L). A cornea specialist (CES) then performed a thorough external and anterior segment slit-lamp examination in those patients included for final study, examining for any evidence of potential OSD. Further history taking was then used to help determine a possible alternate cause for the patient's symptoms. The main outcome measure was the presence of any alternate OSD to explain the patient's most prominent symptom. The secondary outcome measure evaluated the association between primary patient symptomatology and diagnosis. Results were recorded and descriptive and univariate statistics were employed (SAS Analytics Pro, 2016). P-values less than 0.05 were considered statistically significant.

3. Results

Baseline characteristics of participants are listed in Table 1. Mean tear osmolarity was 293.40 mOsm/L (\pm 6.82). The mean absolute difference in tear osmolarity between left and right eyes was

Table 1
Baseline characteristics of participants.

| Characteristics | n (%) |
|--|----------------------|
| Mean Age Years (SD) ^A | 59.50 (\pm 16.80) |
| Sex | 27 (27%) |
| Male | 73 (73%) |
| Female | |
| Drop Use | 67 (67%) |
| Artificial Tears | 2 (2%) |
| Antibiotic | 11 (11%) |
| Cyclosporine-A | 20 (20%) |
| Presenting Symptoms | 18 (18%) |
| Pruritis | 46 (46%) |
| Eye Redness | 76 (76%) |
| Visual Acuity Fluctuations | 50 (50%) |
| Ocular Surface Discomfort ^B | 40 (40%) |
| Total Presenting Symptoms | 10 (10%) |
| One | |
| Two | |
| Three | |

^A Standard Deviation (SD).

^B Includes foreign body sensation, grittiness, tiredness, and dryness.

2.85 mOsm/L (\pm 1.98) (Fig. 1). Of the four symptom categories included in the study, 50% of patients endorsed more than one symptom, and 10% of patients endorsed more than two symptoms. A primary alternate diagnosis was established in 89% of patients with normal tear osmolarity testing.

The most frequent diagnoses included anterior blepharitis (26%) and allergic conjunctivitis (21%). Other common diagnoses encountered were epithelial basement membrane dystrophy (EBMD) (8%), contact lens intolerance (6%), conjunctivochalasis (5%), neuropathic pain (4%), and computer vision syndrome (4%). Of note, 11% patients were persistently symptomatic despite active treatment with topical cyclosporine-A. They were included for study based on the assumption of 'treated DED' but with persistent symptoms, which may signal an alternate OSD diagnosis. Based on examination findings, all topical cyclosporine-A patients had persistent signs of DED despite treatment and a normal tear osmolarity, and were diagnosed as incomplete resolution of DED. Therefore, 89% of patients included for study had an alternate OSD diagnosis. Table 2 summarizes all alternate diagnoses that were encountered in our study.

Univariate statistics were employed for the secondary outcome measures. There was a statistically significant association between pruritis and diagnosis of allergic conjunctivitis ($P < 0.001$). However, there was no statistically significant association between other presenting symptoms and alternate diagnoses.

4. Discussion

The aim of this study was to evaluate for the presence of any alternate OSD in patients with DED-like symptoms and a normal tear osmolarity. This study highlights the diagnostic value of a normal osmolarity with an extremely high proportion of patients exhibiting an alternate OSD diagnosis to account for their symptoms.

In our study, patients were determined to have DED-like symptoms if they answered 'yes' to any triaging questions for DED (see methods section). Directed questions are extremely useful in the day-to-day clinical setting, however standardized questionnaires may also be used.⁹ A small portion of patients in this study exhibited multiple ocular surface diseases on clinical examination. However, for the purpose of this study, their 'primary' diagnosis was determined based on their most significant symptomatic complaint. Of note, there was a statistically significant association between pruritis and the diagnosis of allergic conjunctivitis. Other studies have also noted this association, therefore the presence of pruritis as a main symptomatic complaint, especially when osmolarity is normal, should alert the clinician to the possibility of allergic conjunctivitis [17]. However, although pruritis is a hallmark symptom of allergy, significant overlap exists between the signs and symptoms of DED and allergic conjunctivitis, and these conditions can often co-exist [18]. In fact, although this and prior studies concluded that pruritis is significantly associated with allergic conjunctivitis, another study showed that patients with DED also have higher rates of self-reported pruritis and erythema [19]. Therefore, the symptomatology alone can make these conditions somewhat difficult to diagnose from one another. Tear osmolarity testing may play an important role in helping to distinguish between the two conditions when the symptomatology may be inconclusive. Point-of-care tear IgE, matrix metalloproteinase 9 (MMP-9), and/or other objective diagnostic tests could also be employed when available to help differentiate between allergic conjunctivitis and DED [18].

One of the most common alternate diagnoses made in this study was of anterior blepharitis, including staphylococcal blepharitis, seborrheic blepharitis and demodicosis. Some forms of anterior blepharitis are associated with bacterial overgrowth on the external lid margins, culminating in inflammation. Infestation by *Demodex folliculorum* typically manifests as cylindrical scurf at the base of the lashes. A common presenting symptom of demodicosis is pruritis, however our study found no significant association between all forms of anterior

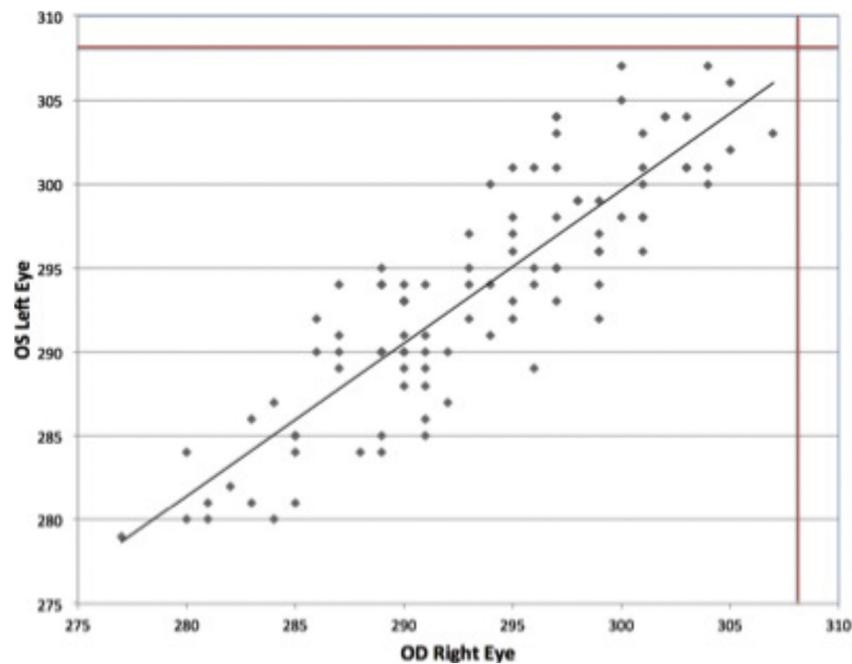


Fig. 1. Correlation between left eye and right eye tear osmolarity levels ($R^2 = 0.76$). Red lines denote the 308 mOsm/L cut-off for abnormal tear testing.

Table 2

Established primary alternate diagnosis explaining dry eye disease like symptoms in patients with normal tear osmolarity testing.

| Diagnosis | n (%) |
|--|---------|
| Anterior blepharitis | 26 (26) |
| Allergic conjunctivitis | 21 (21) |
| Treated DED with cyclosporine-A | 11 (11) |
| Epithelial basement membrane dystrophy | 8 (8) |
| Contact lens intolerance | 6 (6) |
| Conjunctivochalasis | 5 (5) |
| Keratoneuralgia “Pain without stain” | 4 (4) |
| Computer vision syndrome | 4 (4) |
| Pterygium/Pinguecula | 4 (4) |
| Floppy eyelid syndrome | 3 (3) |
| Trichiasis | 2 (2) |
| Lagophthalmos | 2 (2) |
| Salzmann’s nodular dystrophy | 2 (2) |
| Sub-epithelial infiltrates | 1 (1) |
| Drop preservative toxicity | 1 (1) |

blepharitis and pruritis. Anterior blepharitis can exist independently of meibomian gland dysfunction, and can cause ocular surface symptoms without the other classic findings of DED. The tear film can be normal and stable despite significant scurf, dandruff and lid margin telangiectasia, which ultimately can be responsible for a patient’s presenting symptoms [20].

EBMD was another common alternate diagnosis. The importance of a careful slit lamp examination cannot be understated as these corneal changes can be subtle, and may be missed on cursory examination. Findings often reside in the superior cornea, and so lifting the lid to identify these changes is an essential component of the ocular surface and corneal examination. Blurry and/or variable vision is a commonly reported symptom associated with EBMD that may easily be misdiagnosed as DED [21]. Symptoms of recurrent erosions may also occur, however when these symptoms are not the presenting complaint, or when they are frequent and mild and limited to awaking, they can be erroneously attributed to DED.

Contact lens intolerance was determined based on history of contact lens wear, symptoms exacerbated by contact lens wear, and physical signs of lens over-wear including pannus and giant papillary

conjunctivitis (GPC). Contact lens wear is a known risk factor for the development of meibomian gland dysfunction and eventual DED [22,23]. Even non-complicated contact lens wear is intrinsically inflammatory, and can lead to symptoms of discomfort with chronic use [24]. Prior studies have found that a large portion of contact lens wearers exhibit morphologic changes in meibomian gland structure and function, and this may be partially responsible for the ocular surface discomfort encountered with extended periods of wear [23].

Eyelid abnormalities, including floppy eyelids, incomplete/reduced blink, lagophthalmos and lid positional issues, can contribute significantly to DED like symptoms. These conditions are commonly encountered in day-to-day practice, more so even than this small cohort demonstrates. Of note, nocturnal lagophthalmos can be responsible for daytime symptoms that are not specifically DED. The ocular surface may be inflamed or injured due to lid eversion during sleep, however the tear film itself is normal in composition and production [25]. Again, recognizing and treating the predominant underlying cause is essential to effectively managing the patient’s symptoms. In this case, standard daytime DED treatments would likely be largely inadequate in reversing the patient’s complaints.

The interest in neuropathic pain, or keratoneuralgia, has increased considerably, and the TFOS DEWS II added a subcommittee report on pain and sensation in their most recent report [26]. Neuropathic pain describes a lesion of the somatosensory system without any evidence of physical tissue damage [27]. Symptoms specific to neuropathic pain have been described as burning pain and electric shocks. Studies suggest that DED-like symptoms in the absence of objective signs of corneal or conjunctival staining may suggest an element of neuropathic pain [26]. There are currently no diagnostic tests specific for neuropathic pain, however some clinicians anecdotally suggest that persistent symptoms after instilling topical anesthesia may be suggestive. Some studies propose in-vivo confocal microscopy (IVCM) for imaging corneal nerves, however no diagnostic parameters have yet been established [28,29]. Therefore, in the subset of patients that we determined to have ‘neuropathic pain’, the diagnosis was determined based on symptoms (including those specific to neuropathic pain), in the absence of any clinical signs and persistence of eye discomfort after instillation of topical anesthetic drops.

The diagnosis of computer vision syndrome was determined by

symptoms that worsened with the use of electronic devices, in the setting of a normal ocular surface and normal osmolarity. This illustrates how further history taking by the primary eye care specialist can help to direct the diagnosis.

Lastly, 11% of patients in our study were using cyclosporine-A eye drops for previously diagnosed DED. Due to the prospective nature of this study, these patients were included because they elicited symptoms significant for DED despite being presumed 'treated' DED. The use of this medication likely contributed to the normal tear osmolarity value despite persistent DED symptoms, and all patients had persistent corneal staining despite being on cyclosporine-A drops. In fact, it has been shown that reduction in tear osmolarity may occur sooner than the improvement in DED symptoms, Schirmer's testing, tear break up time, or corneal staining after therapeutic intervention (i.e. *symptom lag*) [30]. Drop toxicity was determined based on history of eye drop use containing preservative, illustrating the importance of clinical history in establishing a diagnosis.

There are conflicting results across the literature about the effects of environmental factors on tear osmolarity (ex: drop use prior to tear osmolarity testing) [14,31,32]. However, for the purposes of our study, we ensured the tear osmolarity testing occurred before the instillation of any eye drops or ocular manipulation during the clinic visit as well as any prior eye drop use by the patient in the preceding 2 h before testing. The authors felt that by excluding patients with recent drop use, we would limit this as a possible confounder for normal tear osmolarity in the setting of DED-like symptoms.

A limitation of this study is that the clinician was not blinded to the results of the tear osmolarity before performing the examination for an alternate diagnosis to explain symptoms. Although blinding the examiner was considered in the initial study design, the authors believed that in a 'real world' clinical situation, the tear osmolarity value would often be known before examination and would thereby be used to direct the patient encounter, slit lamp exam, further history taking and diagnostic thought process.

Although the purpose of this study was to specifically determine the value of a normal tear osmolarity in the setting of DED-like symptoms, clinicians may also employ other diagnostics tests to evaluate for the presence of DED. If Schirmer's, fluorescein corneal staining and tear break up time are also normal in conjunction with a normal tear osmolarity test, the negative predictive value and specificity may be heightened. However, multiple studies have shown poor correlation between these metrics for signs of DED and patient symptoms [3,33]. In fact, one study determined that elevated tear osmolarity was found to have a higher positive predictive value for DED than Schirmer's testing [30]. In addition, other advanced diagnostic tests such as meibography, lipid layer interferometry, confocal microscopy, tear IgE and lactoferrin, and non-invasive tear break up time can be used to narrow the differential diagnosis in ocular surface diseases. In reality, many of these modalities may not be widely available or commonly utilized by most eye care practitioners. Based on the recommended clinical protocol for diagnosis of DED by the TFOS DEWS II report, only 1 positive marker is needed in conjunction with DED symptoms to diagnose DED [15]. As such, we felt it appropriate to evaluate a normal tear osmolarity in the setting of DED-like symptoms, without the need to correlate with other DED diagnostic tests. Even though a careful slit-lamp examination and clinical history is warranted for all patients, simple and rapid point-of-care in office tests, like osmolarity, can aid the clinician in establishing a correct diagnosis, especially in the setting of subtle, early, non-obvious and/or multifactorial situations of ocular surface disease, as well as in cases of keratoneuralgia and corneal pain syndromes.

DED-like symptoms are among the most common presenting complaints in primary eye care. However, despite the high incidence of DED, this condition can ultimately be difficult to diagnose accurately. Common symptoms can overlap with a wide variety of other OSDs. If the clinician relies too heavily on symptoms, alternate causes for the

patient's complaints may be missed. Making the proper diagnosis and choosing the appropriate treatment plan for the underlying condition may help limit patient and clinician frustrations. As well, recognizing there may be multiple conditions contributing to the patient's symptoms will help to better direct treatment options in the setting of ocular surface disease. If a normal tear osmolarity test rules out traditional DED as the underlying cause of the patient's symptoms, as it did for the purposes of this study, then the clinician must employ a careful clinical examination and other diagnostic tools when available to find a potential alternate underlying diagnosis or diagnoses. It should also be noted that no single diagnostic test has a specificity or negative predictive value of 100%, therefore a single normal osmolarity measurement does not always rule out DED in real world practice. The reported specificity of the TearLab™ osmolarity device in one study of 300 patients was 88%, and therefore it is reasonable for the practicing clinician to be on the lookout for non-DED diagnoses when confronted with a normal osmolarity in a symptomatic patient [34].

Accurately diagnosing and treating common ocular surface diseases with modern techniques will lead to fewer treatment failures, faster management of symptoms, and better patient outcomes.

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