AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Update in Current Diagnostics and Therapeutics of Dry Eye Disease

Praneetha Thulasi, MD,[1] *Ali Reza Djalilian, MD*[2]

Dry eye disease (DED) represents a heterogeneous group of conditions with tear film insufficiency and signs and/or symptoms of ocular surface irritation. The clinical manifestations of DED can be highly variable; hence the diagnosis is often based on a combination of symptoms, signs, and clinical tests, given that any one of these alone would miss a significant number of patients. Similarly, the treatment must often be tailored to each patient by targeting the specific mechanisms involved in his or her disease. The purpose of this review is to summarize recent advances that have allowed us to better recognize, categorize, and treat patients with DED. The most notable new diagnostic tests in DED are tear film osmolarity, inflammatory biomarkers, and meibomian gland imaging. Therapeutically, anti-inflammatory therapy, meibomian gland heating and expression, and scleral contact lenses are some of the latest options available for treating DED. *Ophthalmology 2017;124:S27-S33 © 2017 by the American Academy of Ophthalmology*

Dry eye disease (DED) has multifactorial etiologies and pathophysiologies that ultimately lead to tear film insufficiency and signs and/or symptoms of ocular surface disease. The signs and symptoms of DED often have poor correlation. Likewise, diagnostic tests of the ocular surface often have significant variability. Thus, the diagnosis of DED is typically based on a combination of symptoms, signs, and clinical tests, because any one of these alone would miss a number of patients. Similarly, there is no single therapeutic strategy that fits all patients; instead, treatment is best individualized by targeting the specific mechanisms that are driving the disease process in each patient. The purpose of this review is to summarize recent advances that have allowed us to better recognize, categorize, and manage patients with DED. In particular, the emphasis is placed on the technology without specifically endorsing or recommending any particular product.

Diagnostic Testing

Though clinical history and examination remain the mainstay of DED diagnostics, ancillary testing with newer imaging technology has added much to our armamentarium. Many of these are available as point-of-care tests, making them widely available to clinicians. An important point to reiterate is that because DED is a heterogeneous disease, the tests described below may be useful for some subtypes of DED, but not all. Therefore, the results of each test should be interpreted in the context of each patient and not as an absolute measure of whether a patient has DED.

Tear Osmolarity

Tear osmolarity has been widely studied both in research and in clinical settings and is thought to represent one of the best global markers of DED. An insufficient or unstable tear film would by definition become hyperosmolar. The more widely available point-of-care testing device uses microelectrode technology to measure the number of charged particles in a tear sample to provide an estimate of the tear osmolarity. Normal tear osmolarity has a value of 302 mOsm/L, with minimal intereye difference. A value of 308 mOsm/L in either eye is often used as the threshold in differentiating normal and early stages of DED, with 316 mOsm/L used as a cutoff for more advanced DED.[1] An important characteristic of tear osmolarity is its variability, both intereye and in repeat measurements in the same eye. The worse the severity is of dry eyes, the more variable tear osmolarity has been found to be (6.9±5.9 mOsm/L in mild, 11.7±10.9 mOsm/L in moderate, and 26.5±22.7 mOsm/L in severe DES, respectively).[2] Thus, a difference of 8 mOsm/L between 2 eyes is also considered to be significant and compatible with an unstable tear film.

As noted previously, given the variability of the results, there are patients with symptoms of DED whose tear osmolarity may be measured as normal. A normal value does not always rule out DED; hence, an elevated tear osmolarity should not be considered a prerequisite for the diagnosis. However, an elevated osmolarity strongly suggests presence of an inadequate tear film compatible with DED. Furthermore, it is worth noting that osmolarity is best not used as a static measure (e.g., not like height measurement). Rather, in some ways, it is analogous to clinical tests such as blood glucose, where there can be moment-to-moment variability depending on the time of the day, the patient's food intake, physical activity, etc. The same way that the average blood sugar (hemoglobin A1C) provides a more reliable measure of the patient's glucose control, in a patient with an unstable tear film, the average tear film osmolarity over a specific

Statement of Potential Conflict of Interest and Funding/Support: See page S32.

http://dx.doi.org/10.1016/j.ophtha.2017.07.022
ISSN 0161-6420/17

period would likely be elevated, and thus a single measurement may not best reflect the overall status of the tear film. Therefore, by standardizing the clinical measurement to minimize the setting and operator variability, and by focusing on the trends and averages, tear osmolarity can offer valuable insights into the status of the tear film and potentially guide therapy in many subtypes of DED.

Inflammatory Biomarkers

Inflammation is a key driving mechanism in many cases of DED. However, differentiating cases of DED with a major inflammatory component from those in which inflammation plays a less fundamental role can be challenging. Biomarkers that can detect subclinical inflammation and, ideally, even provide information about the severity of inflammation can significantly improve our ability to individualize therapies. One key inflammatory biomarker that is now in clinical use is matrix metalloproteinase (MMP)-9. This endopeptidase is part of the extracellular matrix remodeling that takes place after injury and has been found to be a key component of the inflammatory cycle in DED.

Quantitative assessments of MMP-9 levels seem to correlate well with DED. One study showed a level of 7.2 U/mg in controls, compared with 473 U/mg in patients with meibomian gland disease (MGD) and 651 U/mg in patients with Sjögren syndrome.[3] However, qualitative measurements of MMP-9 levels have shown variable sensitivities and specificities, likely reflecting the myriad of etiologies leading to elevated inflammation.[3–6] Although it is not yet clear whether a negative qualitative test of MMP-9 is a reflection of lack of inflammation, stage of DED, or a cutoff value that is not sensitive enough, a positive MMP-9 test can certainly help guide a treatment plan and support the use of anti-inflammatory therapy.[7] In particular, a positive test would prompt the early use of anti-inflammatory medications, as outlined later in this review.

Meibomian Gland Imaging

MGD is a major, and perhaps the most common, etiologic factor in the pathogenesis of many subtypes of DED. Clinical diagnosis is often limited to examination of the lid margin by slit lamp to assess the degree of inspissation and telangiectasias, as well as subjective assessment of meibomian gland openings and meibum quality. However, information about the integrity of the glands within the tarsus has generally been more cumbersome to obtain using older meibography techniques. Recently, infrared-based noncontact imaging modalities of the meibomian gland have offered detailed imaging to guide the diagnosis and treatment of MGD-related DED.

Infrared meibography utilizes noncontact methods to image both upper and lower lids. Meibomian gland dropout as assessed by this method correlates well with signs and symptoms of DED.[8,9] The commercially available imaging systems in the United States utilize automated meibomian gland grading, which further reduces the subjectivity of meibomian gland evaluation.[10] Spectral-domain optical coherence tomography (OCT) and confocal microscopy have similarly been used to evaluate meibomian gland function, although they are less automated and less convenient.[11–13]

These imaging modalities can provide valuable objective information about the integrity of meibomian glands, which in turn helps identify patients in whom MGD is an underlying cause of their DED and thus guide appropriate therapy.

Tear Film Stability and Volume

Traditionally, tear film stability and volume/production are assessed by fluorescein tear breakup time (TBUT) and Schirmer testing. Though these tests remain essential components of the ocular surface examination, they are subjective and are influenced by many factors, including fluorescein volume.[14] Several noninvasive tests now provide objective measure of these variables.

Noninvasive Tear Breakup Time. Noninvasive measures of TBUT have been in practice for a long time and provide advantages over the fluorescein TBUT. Generally, these are topography-based imaging systems that provide automated measurement of TBUT using mire distortion reflected from the precorneal tear layer.[9] Despite its advantages over fluorescein TBUT, particularly reduced variability and subjectivity, the use of noninvasive TBUT has not yet become a routine part of the DED examination and is limited mostly to clinical studies.

Lipid Layer Thickness. Another useful parameter in assessing tear film stability is the lipid layer thickness. Interferometry can offer a quantitative value of lipid layer thickness, providing insight into the health of the meibomian gland secretions Although lipid layer thickness correlates well with symptoms as well as signs of dry eyes,[9,15] it does not necessarily reflect quality of the lipid layer.[16] More studies are needed to determine the precise role of this measure in the diagnosis and follow-up of patients with DED.

Tear Meniscus Height. Anterior segment OCT, as well as some interferometry based imaging systems provide a noninvasive measure of the tear volume by quantifying the tear meniscus height. It has been shown to be a good proxy for tear volume and correlates with TBUT, corneal fluorescein staining, and diagnosis of DED.[17] Despite its noninvasive nature, quantitative measurement of the tear meniscus height is generally not a part of the routine ocular examination in DED. Anterior segment OCT, however, may be particularly useful for assessing and measuring conjunctivochalasis, a common finding in patients with ocular surface disease.[18]

Advances in Dry Eye Therapeutics

Treatment of DED is based on minimizing inflammation and optimizing various components of the tear film. Artificial tears remain an essential part of patient comfort, with many lipid- and gel-based formulations holding promise in better simulating a healthy ocular surface.[19] Other key interventions are listed below.