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Update in Current Diagnostics and Therapeutics of Dry Eye Disease

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

[1]Department of Ophthalmology, Emory University, Atlanta, GA, USA

[2]Department of Ophthalmology & Visual Sciences, Illinois Eye and Ear Infirmary, University of Illinois at Chicago, Chicago, IL, USA

Abstract

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, based on the varying presentation and pathophysiology, the treatment must often be tailored to each patient by targeting the specific mechanisms involved in their 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.

Introduction

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 clinical manifestations of DED often have poor correlation between signs and symptoms. 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 since any one of these alone would miss a number of patients. Similarly, there is no single therapeutic strategy that fits all patients and 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.

*Corresponding author thulasip@gmail.com, adjalili@uic.edu, 312-996-8936.

Conflict of Interest

None

Diagnostic Testing

While 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 since 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 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 test device uses micro-electrode technology to measure the number of charged particles in a tear sample provide an estimate of the tear osmolarity. Normal tear osmolarity has a value of 302 mOsm/L, with minimal inter-eye 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 a cutoff for more advanced DED.[1] An important characteristic of tear osmolarity is its variability, both inter-eye as well as repeat measurements in the same eye. The worse the severity 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 two eyes is also considered to be significant and compatible with an unstable tear film.

As noted earlier, given the variability of the results, there are patients with symptoms of DED whose tear osmolarity may be measured as normal. In other words, a normal value does not always rule out DED; and 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 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 the status of 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 whom 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 assessment of MMP-9 levels seem to correlate well with DED. One study showed a level of 7.2 U/mg in controls, compared to 473 U/mg in patients with MGD, and 651 U/mg in patients with Sjogren's 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]While it's 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 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

Meibomian gland disease 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 non-contact imaging modalities of meibomian gland have offered detailed imaging to guide the diagnosis and treatment of MGD-related DED.

Infrared meibography utilizes non-contact methods to image both upper and lower lids. Meibomian gland dropout as assessed by this method correlates well with signs and symptoms of dry eye disease.[8,9] The commercially available imaging systems in the U.S. utilize automated meibomian gland grading which further reduces the subjectivity of meibomian gland evaluation.[10] Spectral domain ocular coherence tomography as well as 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 the 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. While these tests remain essential components of the ocular surface exam, they are subjective and are influenced by many factors, including fluorescein volume.[14] Several non-invasive tests now provide objective measure of these variables.

Non-invasive Tear break-up time—Non-invasive 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 which provide automated measurement of TBUT using the distortion of the mires reflected from pre-corneal tear layer.[9] Despite its advantages over fluorescein TBUT, particularly reduced variability and subjectivity, the use of non-invasive TBUT has not yet become a routine part of the DED exam 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 glands secretions While 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 optical coherence tomography (OCT), as well as some of the other ocular surface imaging systems that use interferometry, provide a non-invasive measure of the tear volume by quantifying the tear meniscus height. It has been shown to be a good proxy for tear volume and correlate with tear breakup time, corneal fluorescein staining, and diagnosis of DED.[17] Despite its non-invasive nature, quantitative measurement of the tear meniscus height is generally not a part of the routine ocular exam in a DED. Anterior segment OCT, on the other hand, 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 the various components of the tear film. Artificial tears remain an essential part of patient comfort, with various lipid- and gel-based formulations holding promise in better simulating a healthy ocular surface.[19] Other key interventions are listed below.

Anti-inflammatory Therapies

Inflammation is one of the major targets in treating DED and breaking the cycle of inflammation is crucial in improving symptoms. As noted above, the use of MMP-9 testing may help identify patients in whom anti-inflammatory therapy should be considered early. Regardless, all patients with DED deserve a trial of anti-inflammatory therapy at some point during their treatment.

Steroids—Corticosteroids are one of the most effective and rapid therapies available for suppressing inflammation on the ocular surface. In the context of DED, steroids are used mainly as pulse therapy. A short course of either commercially available topical steroids or preservative-free methylprednisolone 1% can be effective in improving DED and a positive response to steroids provides further evidence that inflammation likely plays a key role in the patient's disease.[20,21] Long term therapy is obviously not a desirable option given the

risk of complications, nonetheless, steroids are often helpful to “kick start” the anti-inflammatory therapy with transition to the agents outlined below for long term therapy.

Cyclosporine A—One of the mainstays of anti-inflammatory therapy has been cyclosporine A (CsA). A meta-analysis of 12 randomized control trials comparing topical 0.05% to control showed improvement on Ocular Surface Disease Index (OSDI) scores, tear breakup time, Schirmer I scores, corneal fluorescein staining, and goblet cell densities.[22] Despite compelling results in trials with subsequent FDA approval for keratoconjunctivitis sicca, in clinical practice, a large subgroup of patients do not respond to CsA 0.05%. This may be taken as an indication that either inflammation does not play a critical role in many non-responders, or else T cells are not the main bad actors in those patients. Additional contributing factors to the lack of clinical response may be delayed onset of action and tolerability. Currently, different CsA preparations are in clinical trials for DED, and with improved tolerability and bio-availability, topical CsA is expected to remain an important non-steroidal option for controlling inflammation in DED.

Lifitegrast—The newest addition to the anti-inflammatory armamentarium for DED is the recently FDA approved drug, lifitegrast. [23–25] It blocks lymphocyte-function associated antigen/intracellular adhesion molecule-1 (LFA-ICAM-1) interaction, thus decreasing T-cell recruitment. A notable advantage of lifitegrast appears to be its faster onset of action, with patients reporting improved symptoms within a few weeks. Clinical experience with lifitegrast is still quite limited, but with time, it should become another valuable tool for the management of inflammation in DED. An important question that will become apparent with further research is whether lifitegrast and CsA have any additive effects or if they are best used as single agents.

Polyunsaturated fatty acids

Omega-3 fatty acids have been shown to decrease inflammatory markers and ameliorate dry eye symptoms. Multiple trials have shown improved tear production, tear breakup time, Schirmer score, and OSDI scores.[26–32] Likewise, studies have shown decreased HLA-DR positive cells, another marker of surface inflammation.[26,31] While improvements have been shown in these trials, many of these supplements lack standardization to date. In particular, there may be significant differences in preparations that could affect the absorption and bioactivity of Omega-3. For instance, fish-oil based preparations provide different types of polyunsaturated fatty acids (EPA and DHA) compared to plant based preparations (ALA). Nevertheless, omega-3 supplement is a well-tolerated therapy to improve ocular surface health in nearly all forms of DED and is generally recommended to be used for all patients with no medical contraindications.

Antibiotics with anti-inflammatory action

Antibiotics, specifically those with concomitant anti-inflammatory action, play an important role in the management of DED due to MGD. The mechanism of action is generally two-fold, first to reduce/alter the eyelid flora that is contributing to MGD and ocular surface inflammation, and second, through a direct anti-inflammatory effect. The two main groups of antibiotics that have been used are tetracyclines and macrolides. Oral doxycycline or

minocycline successfully improve patient-reported symptoms and signs of MGD.[33,34] However, patients are at risk for side effects, with gastrointestinal disturbance being the most common. Also, given the growing body of research on the role of gut microbiome in modulating the immune system, it is unclear what effects altering the gut flora with doxycycline has in the long term.

Azithromycin, either topical or oral, is used alternatively. A comparison study of topical azithromycin versus oral doxycycline showed that both improved signs and symptoms of MGD but with different compositions of changes in meibum, suggesting different mechanisms of action.[35,36] Research suggests that unlike doxycycline, azithromycin can simulate meibomian gland cell differentiation in vitro.[37] A 5-day course of oral azithromycin has also been studied in comparison to daily oral doxycycline and showed similar improvements but with less side effects at 2 months.[36]

Meibomian gland heating/expression

Intense Pulse Light therapy has been shown to be effective in dermatologic literature but studies in ophthalmic literature are still few. A prospective placebo-controlled study in patients with MGD showed improved subjective symptoms of DED in both the treatment and placebo eyes, but only the treatment eye showed improved lipid layer grade and tear break-up time over a 45-day period.[38] Other studies show similar improvement in subjective and objective measures.[39,40] Combination therapy of intense pulsed light therapy and meibomian gland expression improved dry eye symptoms as well as meibomian gland function in a majority of patients.[41] However, it is not without side effects: uveitis, iris atrophy, pupillary defects, photophobia, pain, and corneal pigment deposition have all been reported in patients who received IPL without appropriate eye protection.[42–46]

Thermal pulsation has also been used in patients with various degrees of MGD and shows improvement in patients,[47–50] in some up to 3 years.[51] However, the effects do fade away with time and an interventional study comparing single session of thermal pulsation to warm compresses twice daily for 3 months found that by 4 months, both groups show improved symptoms and signs without any significant difference between the two groups.[52] Given the arduous nature of daily warm compresses, cost notwithstanding, thermal pulsation may be a good option for those with significant MGD related DED.

Overall, both therapies come with the advantage that they are a single-time intervention with longer lasting effects. While both are very promising, they are still relatively cost-prohibitive and not available as a treatment option for all patients.

Therapies for Refractory cases of DED

Autologous Serum

Autologous serum tears have long been used in a wide variety of ocular surface diseases, including DED. Autologous serum tears provide a natural substitute for the many bio-active proteins, vitamins and lipids that are typically present in human tears. Studies have shown conclusively that they can provide symptomatic relief in many subtypes of DED.[53–59] Clinically, serum tears appear to be particularly useful in patients with marked aqueous tear

deficiency. At our center, serum tears are routinely offered to patients who have failed standard measures. Our preferred starting concentration is 20%, but studies comparing the different concentrations are limited. Platelet rich plasma tears, a closely related therapy, is thought to provide a richer concentration of growth factors, and likely has similar efficacy in this setting, but again studies comparing their efficacies in DED are lacking.[60,61] Overall, autologous serum or plasma is an essential part of our therapeutic management of refractory cases. The major challenge with this therapeutic is accessibility and cost.

Amniotic membrane

Cryopreserved amniotic membrane transplantation has known anti-inflammatory and restorative properties in a variety of ocular surface disorders. It is believed to work through the presence of anti-inflammatory mediators within its stroma as well as its barrier properties by entrapping inflammatory cells. Both cryopreserved and freeze-dried amniotic membrane have been used as sutureless devices in patients with ocular surface disease.[62] Given the limited number of studies its role in the management of DED is unclear.

Contact Lenses

With advancing technology, contact lenses have become a key therapeutic modality for DED, particularly for the severe cases. There are two types of lenses that are used. Soft bandage contact lenses have been studied in patients with a variety of ocular surface diseases with improvement in both subjective and objective measures.[63–65] No infectious complications were noted when antibiotic prophylaxis was used along with extended wear.[63,64] Although studies are limited, in our clinical experience, in selected patients, soft contact lenses (daily or extended wear) can provide significant relief in refractory DED.

The most effective contact lens option for patients with severe DED is scleral lenses. Scleral lenses are typically fluid-filled and vault over the cornea, resting over the limbus, hence providing it with constant lubrication. Several studies using scleral lenses have shown improved comfort, decreased dry eye symptoms, and improved visual acuity with good safety profile in patients with severe ocular surface disease.[66–71] While the PROSE (Prosthetic Replacement of Ocular Surface Ecosystem) lenses were the first lenses to be used for this indication,[71] they are available only in select centers in the U.S. Newer scleral lenses are easier to fit and readily available commercially, making them more accessible to patients. Despite their efficacy, the use of scleral lenses remains limited partly due to availability and cost, and perhaps given the fact that many eye care providers may not be aware of their significant therapeutic benefits. One downside of scleral lenses is that they require more training to use and hence not all patients can handle them appropriately. With time, contact lenses are expected to play an increasing role in the management of refractory DED.

Conclusion

Overall, advances in technologies have significantly improved both diagnostics and therapeutics available for DED. Ongoing and future developments are expected to further enhance our ability to recognize, categorize and provide patient-specific therapies in DED.

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Highlights

This review covers the latest diagnostic and therapeutic strategies in the management of dry eye disease. New diagnostic tests including tear film osmolarity, inflammatory biomarkers and meibomian gland imaging have enhanced our ability to recognize and categorize patients with dry eye disease. Therapeutically, anti-inflammatory therapy, meibomian gland heating and expression, and scleral contact lenses are some of the latest options available for treating dry eye disease.