Update in Current Diagnostics and Therapeutics of Dry Eye Disease

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Conflict of Interest

None
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) represents a heterogeneous group of conditions with 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 can be highly variable, with characteristically poor correlation between signs and symptoms. Likewise, there is significant variability and poor correlation between various diagnostic tests of the ocular surface. Thus, the diagnosis of DED is based on a combination of symptoms, signs and clinical tests since any one of these alone would miss a significant number of patients. Similarly, given the varying presentation and pathophysiology, there is no single therapeutic strategy that fits all patients and instead, it is best to individualize the treatment 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.

Diagnostic Testing

While clinical history and examination remain the mainstay of DED diagnostics, available ancillary testing with newer imaging technology has added much to our diagnostic armamentarium. Many of these are available as point-of-care tests, making them widely available to clinicians. An important point to reiterate is that DED is a heterogeneous disease and thus, the tests described below will 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 the patient does or does not have 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 dry eye disease. An insufficient or unstable tear film by definition would 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 samples, and 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 is often used as the threshold in differentiating between normal and early stages of dry eye disease. An important characteristic of tear osmolarity in dry eye disease 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). Additionally, it has been shown to be useful to measure the response to therapy.

Two important points deserve special attention. First, there are patients with symptoms of DED whose tear osmolarity may be measured as normal. Therefore, elevated tear osmolarity should not be considered a pre-requisite for the diagnosis, nonetheless is it is often elevated in many subtypes of DED. Second, it is worth noting that the variability of this test measurement is a reflection of the dynamic
nature of the tear film and thus osmolarity is best not used as a static measure (e.g. it is not like height measurement). Rather, in some ways it is analogous to clinical tests such as blood pressure or 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 clinically 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 (weeks or months) 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, rather than the absolute number of a single measurement, tear osmolarity can offer valuable insights into the status of the tear film and help 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 since the clinical signs are not always sufficient. Biomarkers that can detect subclinical inflammation and ideally provide information about the severity of inflammation can significantly improve our ability to provide more individualized therapies. One key inflammatory biomarker that is now in clinical use is matrix metalloproteinase -9. This endopeptidase is part of the extracellular matrix remodeling after injury and has been found to be an essential part of the inflammatory cycle of dry eye disease.

Quantitative assessment of MMP-9 levels seem to correlate well with dry eye disease. 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. However, qualitative measurements of MMP-9 levels have shown variable sensitivities and specificities, likely reflecting the myriad of etiologies leading to elevated inflammation. While it’s not yet clear whether a negative qualitative test of MMP-9 is a reflection of lack of inflammation, stage of dry eye disease, 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. 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 telangiectasia 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,
infra-red based non-contact imaging modalities of meibomian gland have offered significantly improved
details to guide the diagnosis and treatment of MGD related DED.

Infrared meibography utilizes non-contact method 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.9,10 The commercially available imaging systems in the U.S. utilize automated meibomian gland
grading which further reduces the subjectivity of meibomian gland evaluation. 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.

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

Tear film stability and volume

Traditionally, tear film stability and volume/production are assessed by Schirmer testing and fluorescein
tear breakup time (TBUT). While these tests remain essential components of the ocular surface exam,
several non-invasive tests now provide objective and noninvasive 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 mire reflected from pre-corneal tear layer. Despite its
advantages over fluorescein TBUT, particularly reduced variability and subjectivity, the use of non-
invasive TBUT has not 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. While lipid layer thickness correlates well with symptoms as well as signs of dry eyes,10,11 it does
not necessarily reflect quality of the lipid layer.12 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 newer ocular surface
imaging systems, 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 well with tear breakup time
and corneal fluorescein staining. A meniscus height less than 0.3mm has a 67% sensitivity and 81%
specificity for dry eye disease using the Japanese Dry Eye criteria.13 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.\textsuperscript{14}

**Advances in Dry Eye Therapeutics**

**Anti-inflammatory Therapies**

Inflammation is one of the major DED targets for which treatments have been developed. Breaking the cycle of worsening inflammation is of key importance for effectively treating many subtypes of DED. As noted above, the use of MMP-9 testing can 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 the course of 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 topical steroids can be effective in improving DED and a positive response to steroids can provide further evidence that inflammation likely plays a key role in the patient’s disease.\textsuperscript{15,16} Long term therapy obviously is not an option given the risk of complications such as cataracts or glaucoma. 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.\textsuperscript{17} Despite compelling results in trials, 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 the delayed onset of action and tolerability. Currently, a number of different CsA preparations are in clinical trials for DED, and with improved tolerability and bio-availability, topical CsA is expected to remain as an important non-steroidal option for controlling inflammation in DED.

**Lifitegrast**

The newest addition to the anti-inflammatory armamentarium for DED is lifitegrast. It was designed to block lymphocyte-function associated antigen/intracellular adhesion molecule-1 (LFA-ICAM-1) interaction, thus decreasing T-cell activation and cytokine recruitment. It was FDA approved in 2016 based on three phase III trials that showed improvement in symptoms and signs of DED.\textsuperscript{18-20} All three
trials showed transient instillation site irritation with dysgeusia was the most common non-ocular side effect. 18-20

A notable advantage of lifitegrast appears to be its faster onset of action, with patients reporting improved symptoms within a few weeks to a month. 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 research question that will become apparent with time is whether lifitegrast and CsA have any additive effects or are they 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 break up time, Schirmer score, and OSDI scores. 21-27 Likewise, studies have shown decreased HLA-DR positive cells, another marker of surface inflammation. 21,24 While improved symptoms have been shown in multiple trials, many of these trials lack from standardization of supplements. In particular, there may be significant difference in the various preparations that affect the absorption and bio-activity of Omega-3. For instance, fish-oil based preparations provide different types of poly-unsaturated fatty acid (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 with co-existing MGD. The mechanism of action is generally two-fold, first to reduce/alter the eyelid flora that is contributing to MGD and inflammation on the ocular surface, and second, through a direct anti-inflammatory effect. The two main groups of antibiotics that have been used are tetracycline group and macrolides. Oral doxycycline or minocycline have long been used successfully to improve patient-reported symptoms and signs of meibomian gland dysfunction. However, patients are at risk for side effects, with gastrointestinal disturbance being the most common.

Azithromycin, either topical or oral, is used alternatively. A comparison study of topical azithromycin versus oral doxycycline both showed improved signs and symptoms of MGD but with different compositions of changes in meibum, suggesting different mechanisms of action. 28 A 5-day course of oral azithromycin has also been studied in comparison to daily oral doxycycline and showed similar improvements with less side effects at 2 months. 29

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 and DED showed improved subjective symptoms in both the treatment and placebo eyes, but only the treatment eye had improved lipid layer grade and tear break-up time. 30 Other studies show similar
Improvement in subjective and objective measures.\textsuperscript{31,32} 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.\textsuperscript{33} 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.\textsuperscript{34-38}

Thermal pulsation has also been used in patients with various degrees of meibomian gland dysfunction. A meta-analysis of 13 eligible articles showed improvement in meibomian gland scores up to 3 months. Some studies have showed improvement up to 2 years. However, an interventional study comparing single session of thermal pulsation to warm compresses twice daily for 3 months and found that at 4 months, both groups shows improved symptoms and signs, without any significant difference between the two groups.\textsuperscript{39}

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

**Therapies for Refractory cases of DED**

**Autologous Serum**

Autologous serum tears, as an adjunct or substitute to artificial 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 the human tears. Studies have shown conclusively that they can provide symptomatic relief in a variety of subtypes of DED.\textsuperscript{40-46} One notable effect of serum eye drops appears to be the ability to modulate the corneal nerves and sensory pathways, which can be particularly beneficial in the symptoms of dry eyes. Although it is effective in a many subtype of DED, clinically it appears to be particularly useful in patients with more marked aqueous tear deficiency. At our center, we routinely offer this therapy to every patient who has 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.\textsuperscript{47,48} Overall, it is an essential part of our therapeutic management of refractory cases. The major challenge with this therapeutic is accessibility and cost.

**Contact Lenses**

With advancing technology, contact lenses have become a key therapeutic modality for DED, particularly for the more severe cases. There are two types of lenses that are used. Extended wear soft bandage soft
Contact lenses have been used in patients with severe DED such as ocular graft-versus-host disease and showed improvement in both subjective and objective measures.\textsuperscript{49-51} No infectious complications were noted when antibiotic prophylaxis was used along with extended wear.\textsuperscript{49,50} Although studies in other types of DED are limited, in our clinical experience, in selected patients, this can be an effective option in refractory cases of DED.

The most effective contact lens option for patients with severe DED is scleral lenses. Scleral lenses are typically filled with fluid before being placed on the eye, hence providing the cornea with constant lubrication. The lens vaults the cornea and rest peripheral to the limbus. Several studies have shown improved comfort, decreased dry eye symptoms, decreased artificial tear need, and improved visual acuity in patients with dry eyes from various etiologies with good safety profile.\textsuperscript{52-57} While BostonSight PROSE lenses were the first lenses to be used for this indication, they are available only in select centers in the U.S. Newer scleral lenses are easier to fit, and more readily available commercially, making them more accessible for patients. Despite their efficacy, the use of scleral lenses remains limited partly due to availability and cost, and perhaps due to the fact that many eye care providers may not be aware of their significant therapeutic benefit. One downside of scleral lenses is that they are more difficult to insert and remove and hence not all patients can handle them appropriately. With time, contact lenses are expected to play an increasingly more important role in the management of refractory moderate to severe 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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