

# Dry Eye Diagnostics

Join the renaissance!

BY JOHN D. SHEPPARD, MD, MMSc

Traditionally, clinicians have made the diagnosis of dry eye disease (DED) based on a patient's history, slit-lamp examination, Schirmer testing, tear breakup time, and conjunctival and corneal staining. Since the revolutionary introduction of standardized osmolarity testing in 2008, there has been a renaissance in the development of objective diagnostic tools with improved sensitivity and specificity that allow clinicians to better monitor patients for signs of clinical improvement and treatment efficacy. In addition to osmolarity, these tests include the detection of ocular surface matrix metalloproteinase 9 (MMP-9), measurement of tear lipid layer thickness, meibomography, meniscometry, and measuring lactoferrin and lysozyme. It should also be noted that having DED predisposes patients to ocular infection, thus warranting lid, conjunctival, or corneal cultures when clinically indicated.

## HISTORY

A patient presenting with DED may complain of any combination of ocular dryness, pain, redness, irritation, discomfort, burning, itching, fatigue, blurred vision, and variable visual compromise. Alternatively, he or she may paradoxically verbalize no specific ocular complaints. Ocular symptoms vary tremendously from patient to patient and throughout the day or year for each individual. Furthermore, there may be no correlation between the severity of signs and the intensity or frequency of symptoms. Thus, this highly heterogeneous clinical syndrome challenges even the most astute eye care practitioner.

Patients with DED often describe a number of environmental factors that exacerbate their symptoms such as wind, dryness, smog, tobacco smoke, industrial surroundings, chemical fumes, dirty work spaces, fans, open windows, heat exposure, ultraviolet light exposure, deficient



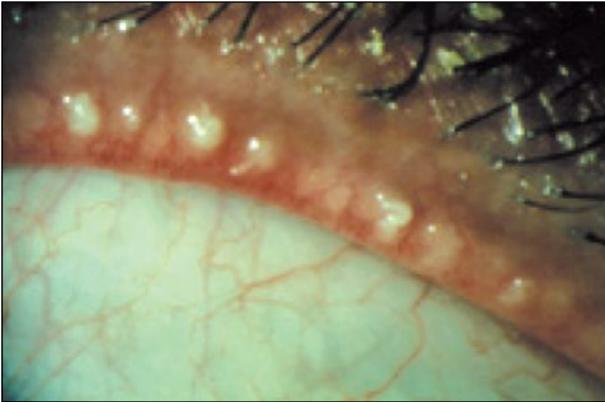
Figure 1. Conjunctival erythema in a patient with DED.

air conditioning and heating systems, contact lens use, drying or toxic topical ocular medications, or drying systemic medications. It is essential to quantify these factors to formulate a diagnosis and a treatment plan.

A number of useful symptom questionnaires have been developed to assist in the longitudinal quantification of dry eye symptoms over time. These include the Standard Patient Evaluation of Eye Dryness or SPEED<sup>1</sup> Questionnaire and the Ocular Surface Disease Index or OSDI.<sup>2</sup> Many clinicians as well as researchers use these tools to take an inventory of patients' complaints (Figure 1).

## SLIT-LAMP EXAMINATION

A careful slit-lamp examination of the anterior segment is critical for making the diagnosis of keratoconjunctivitis sicca; however, the patient should also be examined for gross cognitive impairments, facial or bodily rash, cranial nerve palsies, joint deformities, and xerostomia. The eyelids should be examined for the presence of tel-

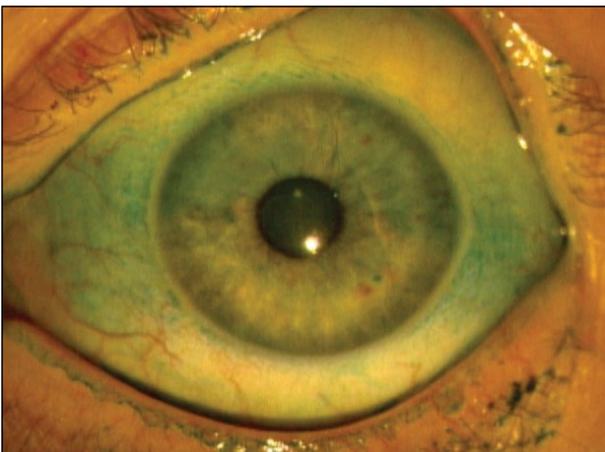


**Figure 2.** MGD with significant lipid inspissation in the superior tarsus and lid margin telangiectasia.

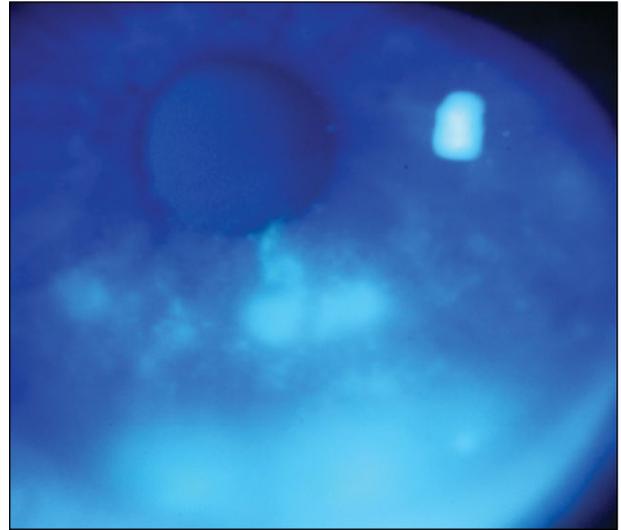
angiectasia, lagophthalmos, poor apposition, trichiasis, meibomian gland dysfunction (MGD), and blepharitis. The conjunctiva should be examined for injection, abnormal vasculature, conjunctivochalasis, pallor, limbal flush, and Bitot spots, as seen in patients with vitamin A deficiency. Clinicians should perform lid eversion on every patient to look for foreign bodies, papilla, tarsal scarring, and follicles (Figure 2).

Practitioners should pay close attention to the cornea and look for the presence or absence of epithelial erosions, neovascularization, epithelial defects, ulceration, scarring, and pannus formation. They should also examine the cornea for the presence of filaments, which represent strands of epithelial cells that are firmly adherent to the corneal surface. In many cases, these often painful corneal filaments require manual removal at the slit lamp (Figure 3).

A variety of corneal and conjunctival stains may help in the diagnosis of DED. Fluorescein stains areas of epithelial erosion and exposed basement membrane. If present, the pattern of corneal punctate epithelial erosions (PEE) may



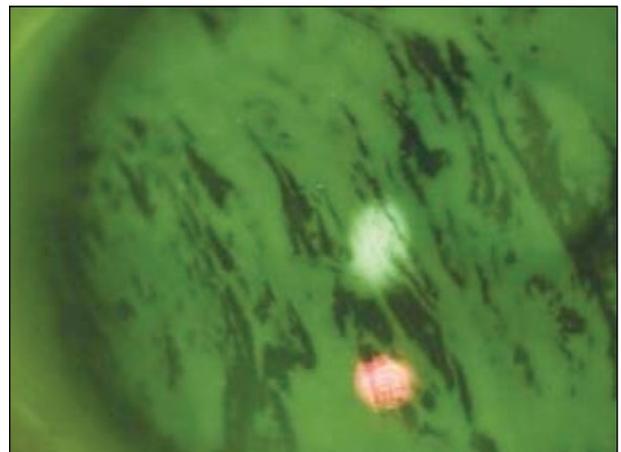
**Figure 4.** Conjunctival staining with lissamine green.



**Figure 3.** Diffuse and confluent superficial punctate keratopathy with fluorescein staining.

help determine the etiology of the disease. For example, inferior PEE has been associated with exposure keratopathy, superior PEE with superior limbic keratoconjunctivitis, and contact lens-associated PEE with disease at the 3- and 9-o'clock positions. Rose bengal and lissamine green can be used to evaluate the cornea and conjunctiva and to stain devitalized epithelial cells as well as cells that lack adequate mucin coverage. Lissamine green (Figure 4) causes less ocular irritation and is thus often the preferred choice of stain.<sup>3</sup>

Clinicians should examine the anterior chamber for angle abnormalities, the presence of iris synechiae, and anterior uveitis. They should also perform a fundus examination to look for posterior uveitis, diabetic retinopathy, vasculitis, and other retinal pathology, findings that may help determine the etiology of anterior segment disease.



**Figure 5.** Rapid tear breakup time in a DED patient.

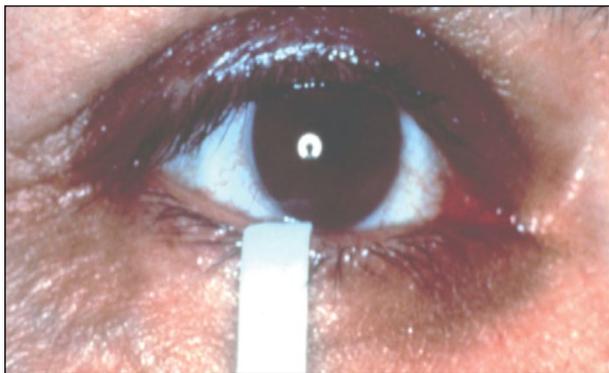


Figure 6. Schirmer test.

### TEAR BREAKUP TIME

The tear film should be closely examined for meniscus height, tear debris, and the presence of an especially oily or “foamy” tear film. TBUT is also commonly used; it measures the length of time that it takes for “dry spots” to appear on the cornea following the instillation of a drop of fluorescein. TBUT is thought to be a direct measure of tear film stability. A TBUT of less than 10 seconds is considered abnormal and should alert the physician to the likelihood of DED (Figure 5).

### SCHIRMER TEST

Although its clinical significance and reliability have been questioned, the Schirmer test is commonly used in the assessment of DED. The test can be performed using various methods, each of which is meant to provide slightly different information. No matter the exact method, each uses a small strip of filter paper that rests in the patient’s inferior fornixes for a given length of time (typically 5 minutes), and the amount of “wetting” of the paper is measured with a ruler. Filter paper strips premeasured and marked in millimeters are also available (Figure 6).

The basic secretion test consists of placing a topical drop of anesthetic on the eye and blotting the excess agent out of the fornix before placing the filter paper into the eye. In theory, the topical anesthetic is meant to prevent reflex tearing, and thus, the measured amount of paper wetting will be from basal tear secretion alone. Wetting of less than 5 mm is considered to be suggestive of aqueous tear deficiency; some physicians use a cutoff of 10 mm.

The Schirmer I test is similar to the basal secretion test, with the only difference being that no anesthetic is given before the measurement. The thought is that both basal and reflex tearing will be measured. Wetting of less than 10 mm with Schirmer I testing is considered to be abnormal. Although the Schirmer I test is relatively specific, it lacks sensitivity.<sup>4</sup> The Schirmer II test, meant to assess pri-



Figure 7. The dry eye severity scale.

marily reflexive tearing, consists of placing filter paper into the eye without anesthetic and then irritating the nasal mucosa with a cotton swab.

These tests of tear production are quick and relatively noninvasive, but false positives are common.<sup>5</sup> The results must therefore be considered in the context of the entire clinical picture.

### TEAR OSMOLARITY MEASUREMENT

Tear osmolality evaluation has quickly moved into the mainstream of clinical point-of-service testing worldwide. This objective test can be performed at initial evaluation and at follow-up visits to help stratify patients and to follow therapeutic efficacy. Hyperosmolality and ocular surface damage have been strongly correlated.<sup>6,7</sup> Several devices in development are used to measure tear osmolality, and the TearLab



Figure 8. Trained office staff can perform the osmolality test. They lightly touch the tear meniscus at the lateral canthus in each eye with the handheld portable lab-on-a-chip reporter and then insert the device into a nearby digital reading station.

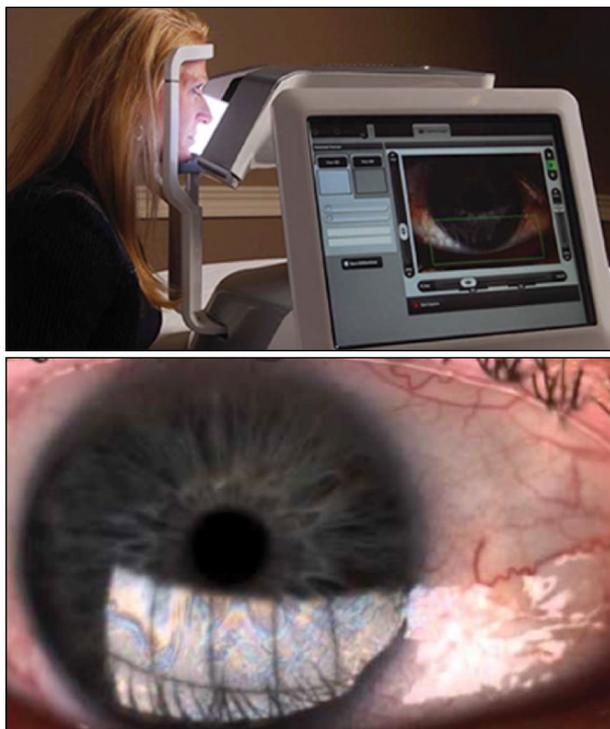


Figure 9. The LipiView monitor screen (A) with lipid breakup patterns undergoing digital analysis (B). Both tear film lipid layer thickness and blink analysis are reported.

Osmolarity System (TearLab) is currently available. The use of this device by trained technicians and staff takes about 2 to 3 minutes, and it represents the first objective, repeatable, and quantifiable test for DED. Significant DED is characterized by an osmolarity of 308 mosm/L or more and a difference of 8 mosm/L or more between eyes.<sup>8</sup> This technology applies to the diagnosis and therapeutic monitoring of a wide variety of ocular conditions, including DED, MGD, environmental ocular surface disease, neurotrophic keratitis, post-LASIK neurotrophic keratopathy, and malingering as well as in preparation for elective anterior segment procedures such as cataract and LASIK surgery (Figures 7 and 8).

### LACTOFERRIN AND LYSOZYME

There has also been interest in using laboratory assays to measure various components of the tear film in the DED patient. Lactoferrin is a glycoprotein secreted by the lacrimal glands. It has natural antimicrobial and antiallergenic properties that are found in decreased levels in keratoconjunctivitis sicca.<sup>9</sup> Lysozyme is a major tear film protein with antimicrobial properties that has the ability to cleave peptidoglycans found in bacterial cell walls.<sup>10</sup> Immunoassays are available to measure the quantity of both of these enzymes in the tear film.<sup>11,12</sup>



Figure 10. Positive MMP-9 assay on the left with a positive red result line and with a positive blue control line. Negative test on the right with the blue control line only, indicating that the test was valid and run correctly.

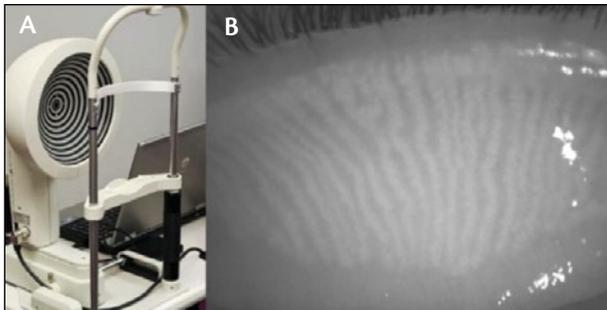
### TEAR FILM LIPID LAYER INTERFEROMETRY

The LipiView Ocular Surface Interferometer (TearScience) measures the thickness, variability, and stability of the lipid layer in the tear film and the completeness of the blink response. For the first time, the eye care professional can diagnose and monitor the responses to the treatment of patients with tear lipid disorders, the most common of which by far is MGD. Furthermore, treatment response to thermal pulsation with the LipiFlow Thermal Pulsation System (TearScience) can be followed and presented to the patient and clinician.<sup>13</sup>

The LipiView test is noninvasive and reproducible. It requires only 2 minutes to complete and is well received by my patients, with no complaints of discomfort or photophobia from the device. The technology employs infrared interferometry to differentiate reflectivity between the anterior and posterior aspects of the tear lipid layer (Figure 9).

### MMP-9 TESTING

The InflammDry test (Rapid Pathogen Screening) for the detection of elevated MMP-9 in tears is now FDA cleared and was submitted to the agency for a Clinical Laboratory Improvement Amendment or CLIA waiver designation, which the company anticipates receiving at the end of the first quarter of this year.



**Figure 11.** The Keratograph 5M (A) and noncontact meibomography image processing (B) demonstrating the entire superior tarsal glandular architecture.

Matrix metalloproteinases are proteolytic enzymes that are produced by stressed epithelial cells on the ocular surface. Specifically, MMP-9 is an inflammatory marker that has consistently been shown to be elevated in the tears of patients with DED.<sup>14</sup> Symptoms alone are inadequate for the differential diagnosis of DED, because the same symptoms can arise in a range of ocular surface conditions and tear film disorders.<sup>15</sup>

Elevated MMP-9 levels in patients with moderate to severe DED correlate with clinical examination findings.<sup>14</sup> Altered corneal epithelial barrier function causes ocular irritation and visual morbidity in patients with DED.<sup>14</sup> The increased MMP-9 activity in dry eyes may contribute to deranged corneal epithelial barrier function, increased corneal epithelial desquamation, and corneal surface irregularity.<sup>14,16-22</sup> The InflammADry test detects elevated levels of MMP-9 ( $\geq 40$  ng/mL) in tears to aid in the diagnosis of DED.<sup>20</sup>

In addition, MMP-9 is instrumental to the healing and remodeling process after LASIK surgery (Figure 10). It may also provide a target for the therapeutic manipulation of various potential post-LASIK complications.<sup>21,22</sup>

## ADDITIONAL TESTING

Although not widely used in clinical practice, a host of other noninvasive methods can be incorporated into the diagnosis of DED. These include impression cytology,<sup>23</sup> confocal microscopy,<sup>24,25</sup> meniscometry,<sup>26</sup> videokeratoscopy,<sup>27</sup> and the measurement of tear viscosity.<sup>28</sup>

The recent introduction of the Keratograph 5M (Oculus; Figure 11) brought previous research tools such as meibomography and meniscometry into the comprehensive eye care practitioner's office.<sup>29</sup>

Sjö, an advanced diagnostic panel for the early detection of Sjögren syndrome (Nicox), is now available as a point-of-service office test capable of detecting proprietary serum antibodies expressed up to 4 years earlier than traditional Sjögren's testing. Earlier identification can prevent

potentially devastating systemic manifestations of the disease including pulmonary fibrosis and vasculitis.<sup>30</sup> ■

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