CME Monograph

Original Release: September 1, 2019 | **Expiration:** September 30, 2020

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DRY EYE DISEASE AROUND THE WORLD

PREVALENCE, AWARENESS, AND MANAGEMENT

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This continuing medical education activity is jointly provided by **New York Eye and Ear Infirmary of Mount Sinai** and MedEdicus LLC.

This continuing medical education activity is supported through an unrestricted educational grant from Shire.

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ACTIVITY DESCRIPTION

Dry eye disease (DED) is increasing in prevalence and affecting younger individuals. There are global variations in tools for diagnosing and treating DED. This activity will provide an update on the epidemiology of DED and highlight the consequences of untreated DED. The desired results of this activity are for ophthalmologists to better identify and manage affected patients through appropriate use of screening, diagnostic testing, and treatment modalities.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Review the global prevalence of DED
- Explain the role of inflammation in DED pathophysiology
- Appraise the consequences of underdiagnosis in patients presenting with signs and symptoms of DED

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DRY EYE DISEASE AROUND THE WORLD
PREVALENCE, AWARENESS, AND MANAGEMENT

INTRODUCTION

Dry eye disease (DED) is a common problem worldwide,[1] and its prevalence is increasing.[2] Diagnosis and treatment of DED is of significance because the disease can adversely affect daily function, quality of life (QOL), and outcomes of ocular surgery.[3,4] Knowledge of the epidemiology and pathophysiology of DED provides a foundation for implementing strategies that can improve DED detection and management, although access to diagnostic and treatment modalities for DED differs in countries around the world. This CME monograph presents the proceedings of a roundtable discussion and case-based reviews from an international faculty of dry eye experts, providing readers an update on the epidemiology and pathophysiology of DED and approaches for patient evaluation and care.

EPIDEMIOLOGY

Dr Messmer: How would you describe the patients you typically see with DED?

Dr Wu: Dry eye disease is often thought of as a condition that occurs mostly in postmenopausal women, but in recent years, I have been diagnosing it more in patients who are younger and in men. I think the changing epidemiology is explained by time spent looking at digital screens. Significant changes in meibomian gland (MG) morphology and function as well as shortened tear break-up time (TBUT) and corneal staining have been found in workers who spend a prolonged time using video display terminals.[5,6] The DED I see in younger patients tends to be related to MG dysfunction (MGD).

Dr Pflugfelder: I am also seeing more men and younger patients with DED. I agree that it is a consequence of today's digital lifestyle.

Dr Calonge: My experience is the same. I estimate that males now account for approximately one-third of my patients with DED.

Dr Messmer: I, too, am seeing more men and more younger patients with DED. Men often have a very low Schirmer score in addition to MGD, but I do not know if this finding represents a change from the past because I did not consider this before.

Have you changed how you screen for DED according to the shifting epidemiology?

Dr Calonge: Ten to 15 years ago, I did not look for DED in younger patients, but now I consider that it can be present regardless of patient age or sex. I am particularly careful about looking for MGD in younger patients.

Dr Wu: I have changed my diagnostic approach. In the past, I relied on ocular surface staining and a Schirmer test. Now, I include a careful lid evaluation, including MG expression and meibography, to look for MGD. Not only do I see MGD more often in younger patients, but also in the large Asian segment of my practice; studies in Asian populations show a high prevalence of MGD.[7,8]

Dr Pflugfelder: I am paying more attention to symptoms of DED, how they correspond with signs, and if the DED is aqueous sufficient, aqueous deficient, associated with a condition causing altered distribution of tears on the ocular surface (eg, conjunctivochalasis and pterygium), or of a mixed etiology.

Dr Messmer: Published studies report that DED prevalence ranges from 5% to 50% **(Figure 1)**.[1]

How do you explain this wide-ranging variation?

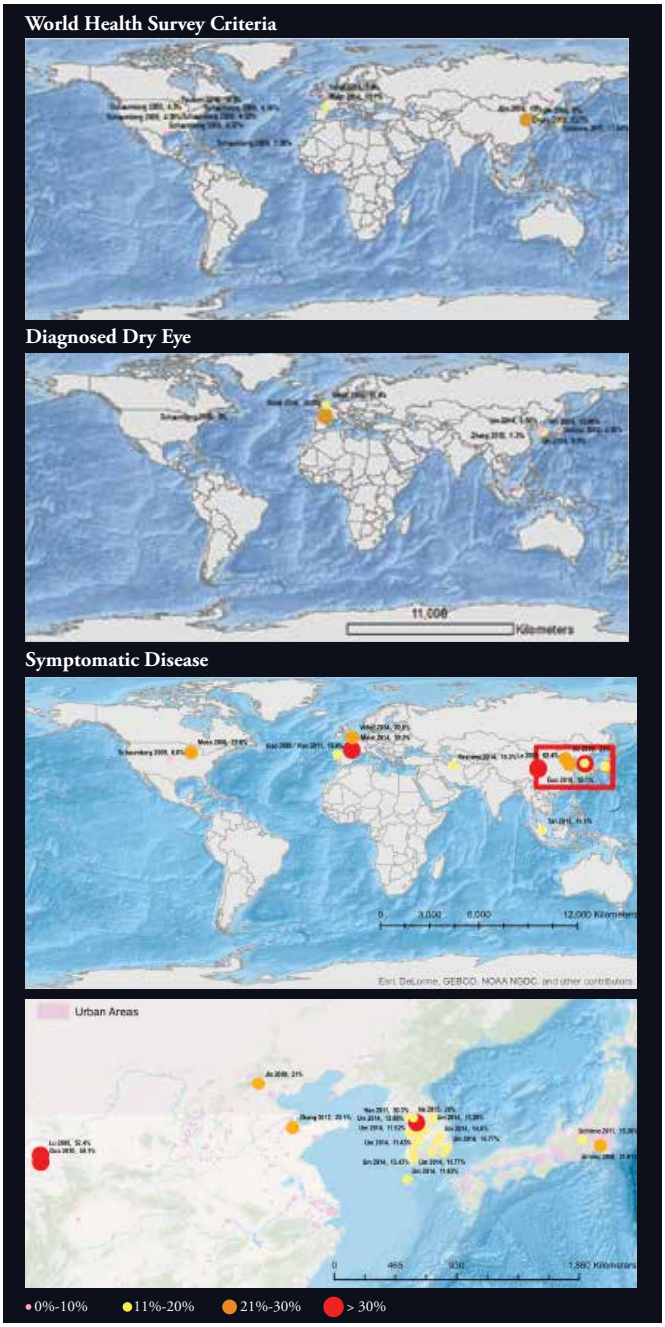

Figure 1. Global prevalence maps of dry eye disease according to diagnostic criteria and symptomatic disease[1]

Abbreviations: GEBCO, General Bathymetric Chart of the Oceans; NGDC, National Geophysical Data Center; NOAA, National Oceanic and Atmospheric Administration.

Reprinted from *Ocular Surface,* 15, Stapleton S, Alves M, Bunya VY, et al, TFOS DEWS II epidemiology report, 334-365, Copyright 2017, with permission from Elsevier.

Dr Pflugfelder: Prevalence varies according to the population studied. Published studies show DED prevalence is similar in the United States and Europe, and higher in Asia.[1] This is consistent with what I see in my practice.

Of note, there is no gold standard test for diagnosing DED; the criteria used in some studies set a fairly high bar. For example, they might require the presence of corneal staining, which might develop later than symptoms. Consequently, the prevalence of dry eye symptoms is very likely higher than the prevalence of diagnosed DED.[1]

BURDENS OF DRY EYE DISEASE

Dr Messmer: It is important to recognize that DED has detrimental effects on daily activities and on QOL, including work productivity and psychosocial functioning.[3] My patients often complain about fluctuating vision and problems with vision when they are reading, driving, or working at the computer. Problems using the computer can interfere with the ability to work. I have seen patients with DED who are just 30 years old who say they cannot work anymore, and others who are in severe pain when their eyes are open.

Dr Wu: I also see patients who complain about problems with dry eye, contact lens intolerance, and fluctuating vision with computer use on days when they are working. Patients describing these problems usually have mild-to-moderate DED, whereas those with a more severe condition might complain about pain, even from a minimal stimulus, such as a draft from heating or air conditioning vents.

Dr Pflugfelder: I too have had patients who are disabled by DED at a young age. Those who complain about fluctuating vision tend to be younger and have excellent visual acuity. They might have a rapid TBUT, and, consistent with this, they will complain about increased blink frequency. In fact, I see patients referred for blepharospasm who turn out to have DED with an unstable tear film.

Dr Calonge: Most of my patients with DED suffer from a negative effect on QOL. Patients with significant ocular surface staining experience the greatest effect, but QOL consequences also occur in patients who have MGD with no corneal staining and a normal Schirmer score. Environmental conditions affect tear film stability.[9] Therefore, it is not surprising that patients with DED suffer more when they are exposed to adverse conditions such as increased air flow and low humidity and that those who work long hours at a computer in air-conditioned offices are particularly affected. Some of my patients complain about photophobia, which is sometimes hard to understand because they do not always have corneal staining.

Dr Messmer: What are the implications of DED for contact lens wearers?

Dr Wu: By acting as a barrier to the environment, contact lens wear can mask some DED symptoms. For example, patients might be protected from symptoms caused by wind exposure when they are wearing their contact lenses. On the other hand, contact lens wear can disrupt ocular surface homeostasis through a variety of mechanisms and thereby cause or worsen DED.[10] In fact, many patients seeking refractive surgery are interested in the procedure because of DED-related contact lens intolerance.

Dr Messmer: Does DED affect the outcome of refractive surgery?

Dr Wu: Preexisting DED is an important risk factor for having more prolonged and more severe DED after laser vision correction.[11] Therefore, I treat DED very aggressively before surgery. I will not perform laser vision correction on anyone who has corneal staining. If the staining cannot be resolved, I default to phakic intraocular lens (IOL) surgery. Although similar to cataract surgery, phakic IOL surgery can potentially worsen DED temporarily. One of the most severe cases of neuropathic pain I have seen occurred in a patient who had worsening of preexisting DED after phakic IOL surgery.

Dr Pflugfelder: Dry eye disease can particularly affect the visual outcome with a multifocal IOL that might be used in a patient undergoing refractive lens exchange.[12] I consider an unstable tear film, epitheliopathy, or conjunctivochalasis a red flag for implanting a multifocal IOL.

Dr Messmer: Many patients presenting for cataract surgery have DED with a low Schirmer score, MGD, increased tear film osmolarity, and a positive matrix metalloproteinase-9 (MMP-9) test preoperatively.[13-15] It is very important to look for DED in patients needing cataract surgery and then to treat the condition both before and after surgery because DED can affect surgical planning and the functional outcome.[4]

ROLE OF INFLAMMATION IN DRY EYE DISEASE PATHOGENESIS, DIAGNOSIS, AND TREATMENT

Pathogenesis

Dr Messmer: Dry eye disease is categorized into 2 major subtypes: aqueous deficient and evaporative.[16] Aqueous-deficient DED is related to insufficient lacrimal gland production of the aqueous tear component. There are many causes for evaporative DED, but MGD that affects the quality and/or quantity of the lipid component of tears is the most common.

Inflammation and damage of the ocular surface, along with tear film instability and hyperosmolarity and neurosensory abnormalities, are etiologic factors in the pathogenesis of DED, regardless of subtype.[17] In addition, these features interact with and perpetuate one another in a "vicious circle" that maintains the pathogenic state and can lead to disease progression **(Figure 2)**.

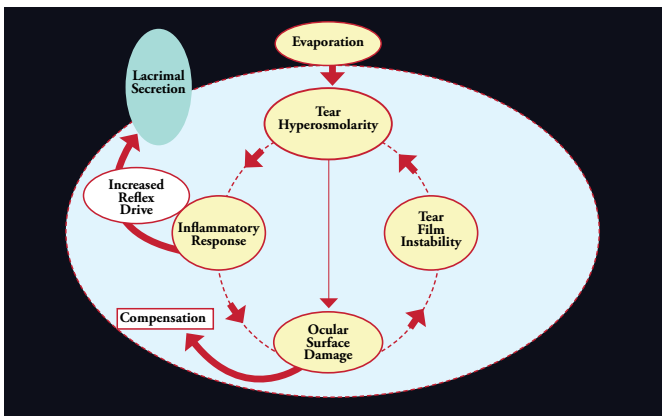

Figure 2. Tear hyperosmolarity is the core mechanism of dry eye disease, causing an inflammatory response that leads to tear film instability or damaging the ocular surface directly. This repetitive cycle maintains a pathogenic state and might result in the progression of dry eye disease.

Understanding DED pathogenesis provides the foundation for controlling inflammation as part of successful management of DED. Do you think that eye care providers in your country adequately appreciate the importance of inflammation in DED pathogenesis and the need to control inflammation as part of the treatment strategy?

Dr Pflugfelder: I think there is increasing awareness that inflammation plays a role in the development and progression of DED, and the majority of clinicians in the United States accept that there is a component of inflammation in most DED. It is my observation that if artificial tears are not effective, corticosteroids are frequently prescribed for DED in this country, which suggests that US clinicians recognize the need to treat inflammation.

Dr Wu: My clinical impression is that in the United States, many eye care providers reserve the anti-inflammatory medications that are indicated for DED as their "big guns", suggesting they mistakenly consider inflammation as something that is important only later in the disease process.

Detection

Dr Messmer: It seems that clinicians in Europe are slowly accepting that inflammation is important in the pathogenesis of DED. MMP-9 and tear film osmolarity tests can be used to identify inflammation.[18]

In Germany, however, these tests are not reimbursed and are typically not done. What is the situation where you practice?

Dr Calonge: In Spain, we do not usually perform the MMP-9 test, and the tear film osmolarity test is not reimbursed. I do not measure tear film osmolarity. Although I believe that a difference in tear film osmolarity can be seen when comparing larger populations of patients with DED with unaffected controls, the result in an individual is not necessarily meaningful. Furthermore, because I believe that inflammation is involved in the pathogenesis of DED, I assume that inflammation is present and treat it routinely.

Dr Wu: Reimbursement is available in the United States for both the MMP-9 and tear film osmolarity tests, but they are not widely done, probably for logistical reasons.

Anti-Inflammatory Treatment

Dr Messmer: Many of the agents that are used for treating DED, including omega-3 fatty acid supplements, topical and oral azithromycin, oral tetracyclines, and tea tree oil, have anti-inflammatory properties.Topical corticosteroids are also used, but only topical cyclosporine products and lifitegrast are approved for the treatment of DED, and their availability varies among countries **(Table)**.[19-22]

What do you use to treat inflammation?

Dr Calonge: I start with a short-term corticosteroid and switch the patient to cyclosporine once I see that the ocular surface condition and MG function have improved. In some patients, I start both together. If the patient relapses on cyclosporine, I restart the corticosteroid and continue or even increase the dose of cyclosporine. We do not have lifitegrast in Europe. I also use oral doxycycline, which is inexpensive in Spain, along with lid hygiene if I see a significant MGD component.

Table. Commercial Availability of Topical Cyclosporine Products and Lifitegrast

Product	FDA Approved	EMA Approved
Cyclosporine cationic ophthalmic emulsion, 0.1% (Ikervis)[19]		X
Cyclosporine ophthalmic emulsion, 0.05% (Restasis)[20]	X	
Cyclosporine ophthalmic solution, 0.09% (Cequa)[21]	X	
Lifitegrast ophthalmic solution, 5% (Xiidra)[22]	X	

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration.

Dr Pflugfelder: I try to stratify patients according to type of DED. Studies show that patients with aqueous-deficient disease tend to have goblet cell loss.[23,24] In these patients, I start a corticosteroid for short-term intervention concurrently or followed by cyclosporine or lifitegrast because these 2 medications act on T cells that produce cytokines that cause goblet cell loss.[25] I like to use lifitegrast for patients who are particularly symptomatic and cyclosporine for those who have less severe symptoms but worse conjunctival lissamine green staining. My choice, however, might be determined by which medication is covered by the patient's prescription insurance.

Patients who have sufficient production of aqueous component tears, including those with pure MGD, have normal goblet cell density.[23,24] The anti-inflammatory medications I use in these patients suppress innate inflammatory mediators and include nutritional supplements containing essential fatty acids, such as fish oil and gamma linolenic acid, topical corticosteroids, oral doxycycline, or oral azithromycin.

Dr Wu: I will start cyclosporine or lifitegrast, sometimes in combination with a topical corticosteroid, in anyone with moderate-to-severe DED who is still complaining about symptoms while using artificial tears a few times a day. My choice of cyclosporine or lifitegrast is often dictated by the patient's prescription insurance. I like to start with lifitegrast for refractive surgery patients because it has been shown to improve the signs and symptoms of DED within 2 weeks.[26-28] I like to use the corticosteroid as a short-term bridge, but in patients who have more severe DED, particularly when their condition is associated with autoimmune disease, the topical corticosteroid might need to be continued long term. I recommend omega-3 fatty acids to nearly all patients, and review their medication history to see if they are using anything that could exacerbate the DED, such as an antihistamine.

Dr Messmer: Studies in glaucoma show high rates of treatment nonadherence and that only approximately 50% of patients persist with therapy after 1 year.[29,30]

How well do patients adhere to and persist with treatment for DED?

Dr Wu: To my knowledge, there is a lack of formal studies investigating adherence and persistence with treatments for DED. There was a study of patients who were told to do lid hygiene for MGD that found a compliance rate of only 55% after 6 weeks.[31] In addition, instillation site burning and stinging and delayed onset of benefit can underlie early discontinuation of topical cyclosporine.[32]

Cost can also be an issue for some patients in the United States. Individuals who cannot afford prescription medications might still use artificial tears, and those with moderate-to-severe DED might overuse preserved artificial tears.

Dr Calonge: Patients pay little for prescription medications in Spain because the government subsidizes the cost, so there is no barrier to receiving treatments. To get reimbursement for the commercially available topical cyclosporine, however, patients need to have the indication for which topical cyclosporine was approved by the European Medicines Agency—severe keratitis in the context of DED.[19] We also use a lot of compounded cyclosporine here.

I think that the number of physicians a patient has seen is a factor that is associated with adherence. My patients are referrals who have already seen several physicians, and I think they are motivated by the thought that if they do not follow instructions, they will not get better.

Dr Messmer: Adherence and persistence seem to be better among patients with DED than among those with glaucoma because DED can be very symptomatic in contrast to glaucoma.

CASE 1: CLINICAL COURSE AND TREATMENT OF CHRONIC DRY EYE DISEASE

From the Files of Helen K. Wu, MD

A 51-year-old female was referred 5 years ago for severe DED related to Sjögren syndrome. She presented with a flare of DED and salivary gland inflammation. Her medications included an omega-3 fatty acid supplement 4 times daily, flaxseed oil 2000 mg daily, over-the-counter ocular lubricant gel twice daily, and over-the-counter preservative-free artificial tears hourly. She was on cyclosporine, but stopped using it after several weeks because of intolerable burning. On examination, she had a low tear meniscus, mild inferior superficial punctate keratopathy, MGD with many blocked glands, and mild facial rosacea.

She was started on loteprednol etabonate ophthalmic gel, 0.5%, 4 times daily, and cyclosporine was restarted after she had been on the corticosteroid for 1 month. Although her symptoms improved with the corticosteroid, she did not improve after starting cyclosporine and developed reddish nodular lesions around her lids. Cyclosporine was stopped and the lesions slowly resolved. The patient also developed liver issues and was told by her rheumatologist to stop the omega-3 fatty acid supplement.

The patient's intraocular pressure (IOP) became elevated, and she developed nerve fiber layer damage and a visual field defect. Loteprednol etabonate was discontinued, and she was referred to a glaucoma specialist. Her ocular inflammation worsened, and she was started on oral doxycycline for ocular rosacea. After her IOP was controlled with brimonidine twice daily, the patient was started on loteprednol, 0.5%, once daily. The IOP in her left eye increased again, and she was switched to loteprednol, 0.2%, with the addition of brinzolamide, 1%, twice daily in the left eye. Brinzolamide was stopped after several months because of stinging. The patient was also started on serum tears every 2 to 4 hours, which she stated provided some temporary relief but not long-term comfort.

Azithromycin, 1%, was added to treat the patient's MGD, but was discontinued because of burning. Doxycycline was causing gastrointestinal distress, so the patient used it only for short-course therapy when her facial rosacea flared.

Approximately 2 years ago, the patient's symptoms worsened. At that time, her Schirmer score was 0 to 1 OU. She stopped using the serum tears because of cost and because she felt they were not helping. The patient was started on lifitegrast, 5%, twice daily. Her ocular and lid inflammation improved, and she has remained on lifitegrast.

Intense pulse light therapy (IPL) was recommended because of her MGD and rosacea. After 4 monthly treatments, the patient had minimal symptom improvement, but her lid margins and telangiectasias looked slightly better. Topical testosterone was tried for a few months, followed by amniotic cytokine drops for several weeks. Initially, the patient reported no benefit from those treatments, but later said they were a little helpful.

The patient's rheumatologist prescribed oral cevimeline, which she did not tolerate. She started oral hydroxychloroquine 1 year ago for Sjögren syndrome and has stayed on it without improvement of her symptoms. Her current treatments also include loteprednol, 0.2%; brimonidine twice daily; lifitegrast twice daily; omega-3 supplement 2000 mg twice daily; and IPL every 6 months. She still has no aqueous tear production.

Dr Wu: This case describes a very challenging patient, but I was gratified that she said she felt able to function while on the regimen she has been using for the past few years. I believe she might have gotten more benefit if she could have continued using the higher-strength loteprednol. The fact that I tried so many treatments did not make this patient question if I knew what I was doing. Rather, she seemed happy that I was willing to try so many new options to find something that might help.

Dr Messmer: Would you have treated her differently if she did not have Sjögren syndrome?

Dr Wu: No, except that cevimeline is usually not used to treat DED in patients without Sjögren syndrome. I participated in a clinical trial in which patients with post-LASIK (laser in situ keratomileusis) dry eye were treated with cevimeline. The results were never published, but treatment with cevimeline was found to stimulate tear production.

Some of the side effects she reported after starting several treatments are not unique to patients with Sjögren syndrome. Stinging and burning are common side effects of topical drops. The development of lid lesions known as xanthelasma palpebrarum has been associated with hyperlipidemia, diabetes, and the use of some drugs, such as cyclosporine,[33] and this patient's lesions resolved after discontinuing cyclosporine. Although her rheumatologist discontinued omega-3 supplementation due to her liver issues, there is little evidence that links omega-3 fatty acids to liver injury,[34] and the patient later resumed taking omega-3 supplements. The little to no response of her disease to topical testosterone might be related to Sjögren syndrome because the tear deficiency of patients with this syndrome is too severe to show much benefit from androgen treatment.[35]

Dr Messmer: Did you consider punctal plugs?

Dr Wu: Her optometrist had placed punctal plugs, but they worsened her symptoms. I sometimes cauterize the puncta in patients such as this one, and I close all 4 puncta, but only after the inflammation is controlled because otherwise symptoms can worsen.

Dr Messmer: Dr Pflugfelder, is there anything you would have added?

Dr Pflugfelder: I use a scleral contact lens for patients with severe DED if they have pure aqueous-deficient DED. Patients do not do as well with the scleral lens if they also have MGD because they have normal or heightened corneal sensitivity.[36] Therefore, I would probably not use a scleral lens in this case.

Dr Wu: A scleral lens was discussed with this patient, but she rejected the idea. According to Dr Pedram Hamrah, scleral lenses might mask the symptoms of neuropathic pain (personal communication). Still, scleral lenses might be useful for some patients who have neuropathic pain and can be very helpful post-LASIK because it solves both the vision problem and helps with DED symptoms.[37,38]

Dr Calonge: Hematic derivatives (autologous serum, platelet-rich plasma, or plasma rich in growth factors) are reimbursed in Spain for patients with severe DED. I would especially recommend plasma rich in growth factors for this patient. I typically consider the hematic derivatives to treat patients who have not responded sufficiently to a corticosteroid and cyclosporine. I usually use a 20% concentration for autologous serum, but it can be prepared up to 50%.[39]

CASE 2: MEIBOMIAN GLAND DYSFUNCTION AND INFLAMMATION

From the Files of Margarita Calonge, MD, PhD

A 72-year-old male was seen with complaints of constant foreign body sensation, red eyes, tearing with simultaneous dryness, photophobia, and puffy eyes that he said had been present for 15 years. He had a history of hordeola. Current treatments included lid hygiene and topical prednisolone acetate, 1%, twice daily. The patient had previously used the topical fluorometholone, 0.1%, corticosteroid with benefit, but his problems recurred when it was stopped.

Figure 3 *shows images from the patient's clinical examination. He had facial rosacea, but no other medical issues. Findings on examination were visual acuity of 20/60 OU, IOP of 25 mm Hg OU, thickened eyelid margins with telangiectatic vessels, and barely visible MG orifices with some inspissated secretions, but mostly obstruction. Tear film meniscus was foamy, and he had conjunctival hyperemia and mild pterygium OS. TBUT was 3 seconds OD and 2 seconds OS. Schirmer score was 7 mm/5 min OU, fluorescein corneal staining was +2 OU inferior, and rose bengal conjunctival staining was negative OU. The patient had +2 cataracts OU and no evidence of glaucoma. His Ocular Surface Disease Index (OSDI) score was 64.58.*

The patient is diagnosed with evaporative-type DED due to rosacea-associated MGD. He was educated on the technique for lid hygiene and told to increase the frequency to twice daily. Prednisolone was tapered to discontinue over a period of 2 weeks because of his elevated IOP. He was started on oral doxycycline, which he had never tried before, with instructions, according to Dr Calonge's clinical experience,

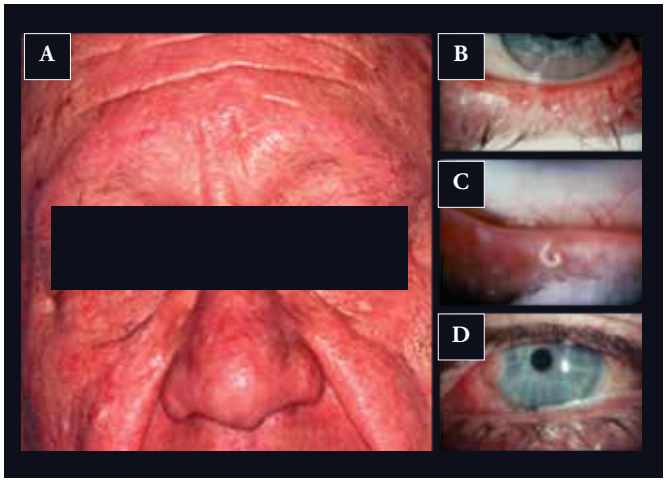

Figure 3. Clinical examination of the patient presented in Case 2 showed facial rosacea (A), thickened eyelid margins with telangiectatic vessels (B), barely visible meibomian gland orifices with some inspissated secretions (C), and conjunctival hyperemia with foamy tear meniscus (D)

to begin taking 100 mg once daily for 2 months and then to taper to discontinue by using each of the following doses for 2 months: 50 mg once daily, 50 mg every other day, 50 mg twice a week, and 50 mg once a week.

After 2 months, the patient's lid appearance was unchanged ***(Figure 4A)****, but his OSDI score was 37.50 and IOP was 17 mm Hg. OSDI score further improved to 29.16 at 4 months. At 6 months, the patient was asymptomatic, his OSDI score was 16.66, and the appearance of his lid margins and MG secretions had improved, although there was still some MG obstruction* ***(Figure 4B)****. At 12 months, the patient's condition was stable while using only lid hygiene. Thereafter, he experienced a mild flare approximately once a year that was usually controlled with doxycycline but sometimes required a topical corticosteroid.*

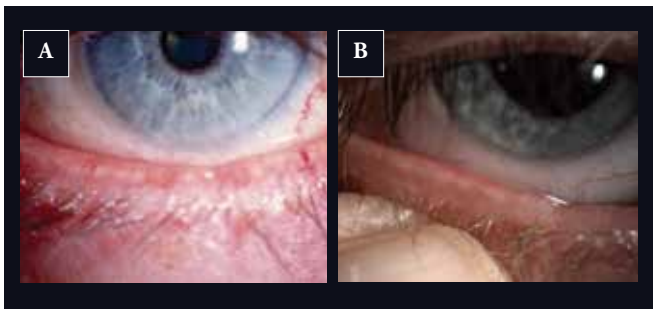

Figure 4. Lid appearance of the left eye at 2 months (A) and the right eye at 6 months (B) of the patient presented in Case 2

Dr Messmer: How do you evaluate symptoms of DED? Do you have patients complete a questionnaire, or do you personally question them informally?

Dr Calonge: Each of my patients completes the OSDI, the SANDE (Symptom Assessment in Dry Eye) visual analogue scale, and DEQ-5 (5-item Dry Eye Questionnaire) at the first visit.

Dr Wu: All my patients are asked about their symptoms, but I tend to use questionnaires only for those being treated with IPL.

Dr Pflugfelder: Every new patient coming in for an ocular surface evaluation is given the OSDI and SANDE. I particularly like the SANDE because it is a sensitive tool that has only 2 questions and so can be completed very quickly[40]; it seems more sensitive than the OSDI. Only patients participating in a clinical study will be asked to fill out the questionnaires again at follow-up visits.

Dr Messmer: I also have my patients fill out a questionnaire at their first visit only. Because it contains very few questions, I prefer the SPEED (Standardized Patient Evaluation of Eye Dryness) questionnaire over the OSDI or DEQ-5. It is my impression that general ophthalmologists in Germany overlook rosacea unless it is very obvious, and then they send the patient to a dermatologist, but do not consider using doxycycline.

Dr Calonge, what is the situation in Spain?

Dr Calonge: I think it is the same. I have seen patients referred from general ophthalmologists who might have very mild facial signs of rosacea and more significant ocular changes. I do not refer patients to a dermatologist unless they have significant facial disease.

Dr Messmer: Do you typically use interferometry to look at the lipid layer or meibography to evaluate the anatomy of the meibomian glands?

Dr Calonge: I do, only if doing so is part of a clinical trial protocol, but not in daily practice because there is not enough time and I do not consider those tests necessary for diagnosing MGD.

Dr Messmer: Are those instruments widely used in the United States?

Dr Pflugfelder: I think most ophthalmologists rely on a clinical examination to diagnose MGD, but some practitioners like to use the images from those devices for patient counseling. There is no evidence to show that serial interferometry or meibography is useful for monitoring response to treatment for MGD, although it is likely that patients with functioning MGs, as documented by meibography, will respond better than those with atrophied glands.

Dr Wu: I have the multipurpose instrument that provides meibography, lipid layer thickness, and a noninvasive TBUT, but only because it is being used in a clinical trial. It is nice to be able to show patients what their glands look like, but I have not used the device long enough to know if the findings change over time after patients start treatment. The imaging devices are expensive, and although they can help with patient education, I agree with Dr Pflugfelder that they do not necessarily change our approach to treatment.

When patients with rosacea have *Demodex* infestation, I like to show them pictures of the mites that I take with a confocal microscope. These pictures make a strong impression, and I think they motivate patients to be compliant with the treatment I recommend, which includes tea tree oil and sometimes ivermectin.

Dr Messmer: I also think the images from interferometry and meibography are great to use in patient counseling and can increase adherence and persistence with treatment, especially regarding lid hygiene. I use these tests only when patients request them because they are generally not reimbursed by health insurance companies in Germany.

Dr Calonge: I show patients the slit-lamp examination image of their lids, in which they can easily see telangiectatic vessels or thickened secretions.

CASE 3: DRY EYE FOLLOWING CATARACT SURGERY
From the Files of Elisabeth M. Messmer, MD, FEBO

A 68-year-old female presented with complaints of severe foreign body sensation and fluctuating vision in her left eye that started after she had cataract surgery 2 years prior. Her right eye had a cataract and was mildly symptomatic, if at all. She was using artificial tears OU twice daily.

Examination of the right eye showed mild corneal staining ***(Figure 5A)****, normal conjunctiva, and best-corrected visual acuity of 20/20. The left eye had 3+ corneal staining* ***(Figure 5B)****, 1+ conjunctival injection, filamentary keratopathy, and best-corrected visual acuity of 20/25. Intraocular pressure was within normal limits OU.*

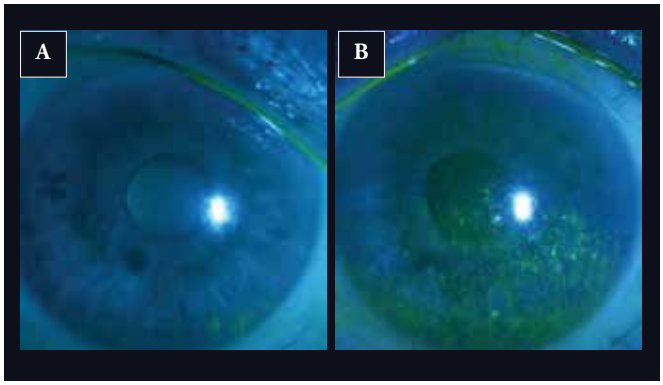

Figure 5. Staining with fluorescein showed mild corneal staining of the right eye (A) and 3+ corneal staining of the left eye (B) in the patient presented in Case 3

The patient had normal meibomian secretions, TBUT was 8 seconds OU, Schirmer test without anesthesia was 8 mm/5 min OD and 15 mm/5 min OS, and Schirmer test with anesthesia was 6 mm/5 min OD and 4 mm/5 min OS.

The patient was diagnosed with moderate-to-severe DED OU related to aqueous deficiency. She was told to use nonpreserved artificial tears 6 times daily. In addition, she was started on a nonpreserved soft corticosteroid 4 times daily (to be tapered over 4 weeks) along with cyclosporine, 0.1%, once daily as long-term treatment. Because of her low Schirmer scores, punctal plugs were inserted in both inferior puncta, but only after inflammation and corneal staining were decreased. Over a period of 3 months, the patient's signs and symptoms improved. Cyclosporine will be discontinued after 6 to 12 months, but will be restarted if the patient's condition worsens.

Dr Messmer: It is my impression that there is still a lack of awareness among eye care practitioners that DED is common in patients with cataracts, can be worsened by surgery, and should be addressed prior to surgery because it can affect the surgical outcome.[4,13,15,41]

What do you think?

Dr Pflugfelder: I agree. I find that in the United States many patients come on referral to the cataract surgeon without having undergone a thorough evaluation for dry eye. There is also a need to educate the technical staff who are doing the preoperative evaluation. Inability to get a good topography reading is a clue to the diagnosis of DED, but technicians who are doing the measurement might just put artificial tears in the patient's eye so they can capture the image. Instead, they should inform the physician that they cannot get a quality reading.

Dr Wu: I think the importance of identifying DED and optimizing the ocular surface prior to cataract surgery is becoming more widely recognized, but at the same time, I think greater awareness is needed that optimizing the ocular surface is particularly critical for patients who are paying for an advanced technology IOL and for getting the best possible result after standard cataract surgery.

Dr Messmer: How long does it take to improve the ocular surface before a cataract surgeon can begin planning the procedure?

Dr Wu: The severity of the DED and the type of patient are determining factors. For example, if I am doing a refractive procedure in a younger patient, I will wait until corneal staining is resolved; but I am less strict if I am operating on an older patient who is getting a monofocal IOL. Ideally, one should take as much time as needed to optimize the ocular surface, although realistically, this is not always possible.

Dr Messmer: Do you consider stopping cyclosporine in patients whose DED has responded to the treatment?

Dr Calonge: To my knowledge, there are no published data to guide decisions on discontinuing cyclosporine when it has been effective for treating DED, so there is a need for a prospective, multicenter study to provide scientific evidence on this issue. In my clinical practice, I recommend stopping cyclosporine only if a patient no longer has symptoms or ocular surface staining, but I always keep patients on cyclosporine for at least 1 year and usually for 2 or 3 years before stopping it. Some patients need to resume cyclosporine, but many patients who stop the treatment have been able to stay off for years.

CASE 4: DRY EYE DISEASE IN A PATIENT WITH SYSTEMIC AUTOIMMUNE DISEASE
From the Files of Stephen C. Pflugfelder, MD

A 45-year-old female with a 20-year history of rheumatoid arthritis presented with worsening eye irritation over the past 5 years. She complained of constant foreign body sensation, photophobia, and blurred vision, and she noted that she sometimes felt like there was glass in her left eye, especially at the end of the day. She had lost the ability to reflex tear. Because her vision was so bad at the end of the day, she sometimes had a hard time driving home from work at night. She had no improvement with artificial tears and punctal plugs.

Figure 6 *shows images from diagnostic imaging. On optical coherence tomography, the tear meniscus was barely detectable OU. With lissamine green, she had severe exposure zone staining OU and superior limbic keratoconjunctivitis OS. Corneal fluorescein staining was severe OU (7/15 OD and 12/15 OS using the National Eye Institute scale) and included the central cornea, and there were filaments OS. Topography showed surface irregularity. Impression cytology showed loss of goblet cells in the bulbar conjunctiva OU.*

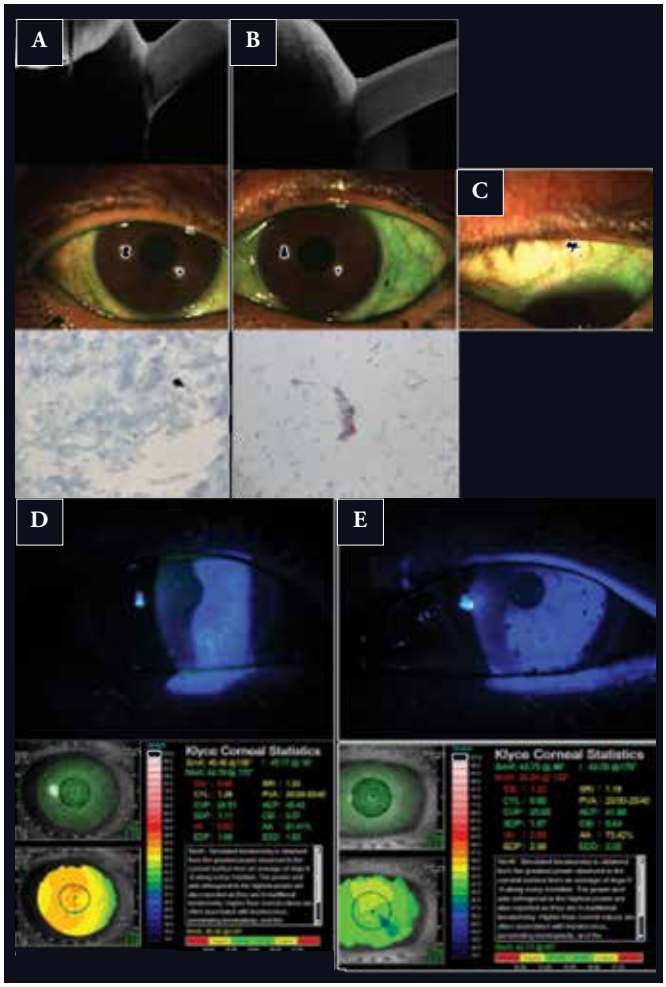

Figure 6. Optical coherence tomography scan showing a barely detectable tear meniscus OU in the patient presented in Case 4 (A). Conjunctival lissamine green staining reveals severe exposure zone staining OU and superior staining OS (B). Impression cytology shows loss of goblet cells in both eyes (C). Severe corneal fluorescein staining bilaterally with filaments OS (D). Topography shows bilateral corneal irregularity (high surface regularity index) (E).

Dr Pflugfelder: I use optical coherence tomography fairly often to examine the inferior tear meniscus, and I think it is very valuable procedure. The tear meniscus will usually be normal or elevated in patients with MGD or conjunctivochalasis.[42,43] The tear meniscus was barely detectable in this patient.

The patient's serology was consistent with rheumatoid arthritis, but she did not fulfill the American College of Rheumatology criteria for diagnosing Sjögren syndrome.[44] According to the criteria, patients must have at least 2 of the following 3 findings: (1) positive serum anti–Sjögren-specific antibody A and/or anti–Sjögren-specific antibody B or positive rheumatoid factor plus antinuclear antibodies (≥ 1:320); (2) ocular staining score ≥ 3 (cornea and conjunctiva combined); and (3) presence of focal lymphocytic sialadenitis with focus score ≥ 1 focus/4 mm^2 in labial salivary gland biopsy.

Patients who have DED associated with a systemic autoimmune disease usually have a greater reduction of tear volume with loss of reflex tearing, more severe ocular surface disease, greater conjunctival goblet cell loss, greater alteration of corneal nerve plexus and reduction of corneal sensitivity, and recurrent filamentary keratitis.[24,36,45] The loss of goblet cells seems to separate patients who have mild-to-moderate DED associated with MGD or aqueous-tear deficiency from those with a more severe condition associated with autoimmune disease.[24] For this reason, I tend to treat the latter patients with therapies that can increase goblet cell density—cyclosporine,[46] lifitegrast,[47] autologous serum,[48] punctal occlusion,[49] vitamin A or retinoic acid.[50,51]

Treatments for filamentary keratitis include punctal occlusion or placement of a hydrogel or scleral contact lens.[49] Injection of botulinum toxin to relax lid pressure on the globe can be considered if the patient is refractory to other treatments.[52]

Dr Messmer: It is an important fact—but not well known—that DED can be associated with goblet cell loss, especially when DED is related to autoimmune- or immune-mediated disease.[17]

Dr Pflugfelder: I agree. Unfortunately, we do not have an easy test to measure goblet cells or mucin in tears that would allow us to identify this problem. Therefore, we have to assume there is goblet cell loss in patients with autoimmune- or immune-mediated DED. In addition to mucin production, there is growing evidence that goblet cells produce immunomodulatory factors that help to suppress inflammation in the eye and that cytokines produced by T cells, particularly interferon-γ, cause goblet cell loss.[24,53] So there is a vicious cycle in which loss of goblet cells perpetuates inflammation that leads to further loss of goblet cells.

There is also evidence that goblet cell density might return to normal within 6 months or even sooner in patients treated with topical cyclosporine.[22,24,54] There is no published information on change in goblet cell density in patients treated with lifitegrast. In a mouse model of dry eye that was similar to Sjögren syndrome, we found that after 5 days, animals treated with lifitegrast had greater conjunctival goblet cell density than control animals treated with vehicle.[47] Interestingly, we have observed that patients can remain symptomatic even when the goblet cells come back.

Dr Calonge: Perhaps the explanation is that these patients have permanent nerve damage.

Dr Messmer: Have you been using medications such as diquafosol that stimulate tear and mucin secretion in patients with goblet cell loss?

Dr Pflugfelder: There are no secretagogue medications approved in the United States, but I know that diquafosol and rebamipide are used in Japan to treat patients with goblet cell loss.

Dr Messmer: In Germany, only patients with a definitive diagnosis of Sjögren syndrome can get artificial tears reimbursed, so a salivary gland biopsy is now often done to confirm the diagnosis.

Dr Calonge, would you have ordered a salivary gland biopsy to evaluate this patient for Sjögren disease?

Dr Calonge: There is a tendency now in Spain to avoid the biopsy by doing salivary scintigraphy to evaluate salivary gland function, but many rheumatologists are strict about using the diagnostic criteria and so do the biopsy. In Spain, artificial tears are reimbursed only for patients with a diagnosis of Sjögren syndrome, and many rheumatologists will not make the diagnosis without having a positive biopsy result.

TAKE-HOME MESSAGES

Dry eye prevalence is increasing.

- It is increasingly being diagnosed in men and in younger patients
- Published prevalence estimates vary depending on the population studied, but seem highest in Asians

Dry eye disease can have a negative effect on daily function, work productivity, QOL, and outcomes of ocular surgery.

- All patients undergoing corneal refractive surgery or cataract surgery should be evaluated for DED and treated prior to surgery

Inflammation plays an etiologic role in the development and progression of DED and is therefore an important therapeutic target.

- Options for mitigating inflammation include corticosteroids, cyclosporine, lifitegrast, omega-3 fatty acids, and certain antibiotics with anti-inflammatory properties (doxycycline, azithromycin)

Dry eye disease associated with an autoimmune disease is usually severe and associated with advanced goblet cell loss.

- Cyclosporine, lifitegrast, autologous serum/platelet-rich plasma, and vitamin A/retinoic acid can increase goblet cell density
- Scleral lenses can help relieve symptoms and improve vision

Diagnostic evaluation, therapeutic decisions, and patient compliance with treatment for DED can all be affected by reimbursement.

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See detailed instructions at **To Obtain *AMA PRA Category 1 Credit*™** on page 2.

1. Findings from population-based studies indicate the prevalence of DED is highest in:
   a. Asia
   b. Europe
   c. South America
   d. United States

2. Rising prevalence of DED in younger patients is attributed to increased:
   a. Time spent indoors
   b. Digital screen viewing
   c. Autoimmune disease prevalence
   d. Allergy prevalence

3. Diagnostic tests for identifying inflammation related to DED include:
   a. MMP-9
   b. TBUT
   c. Osmolarity
   d. a and c

4. Goblet cell loss is a feature of DED related to _____.
   a. Aqueous deficiency
   b. Conjunctivochalasis
   c. Seasonal allergic conjunctivitis
   d. MGD

5. Which of the following is a true statement about DED progression?
   a. DED always worsens if untreated
   b. Cyclosporine has been shown to stop DED progression
   c. Corticosteroids have been shown to stop DED progression
   d. Topical anti-inflammatory treatments have been shown to stop DED progression only in patients with autoimmune-mediated disease

6. A scleral lens is particularly helpful for patients with severe DED associated with:
   a. Aqueous deficiency
   b. MGD
   c. Prior LASIK
   d. All the above

7. Which dry eye questionnaire includes only 2 questions?
   a. DEQ-5
   b. OSDI
   c. SANDE
   d. SPEED

8. Untreated DED in a patient undergoing cataract surgery can affect the visual outcome after implantation of a _____ IOL.
   a. Monofocal
   b. Multifocal
   c. Toric
   d. Any

9. All the following treatments have been shown to increase goblet cells, EXCEPT:
   a. Cyclosporine
   b. Lifitegrast
   c. Omega-3 fatty acid supplementation
   d. Punctal occlusion

10. Which treatment for DED is NOT used to control inflammation?
    a. Oral doxycycline
    b. Punctal occlusion
    c. Topical azithromycin
    d. Topical lifitegrast