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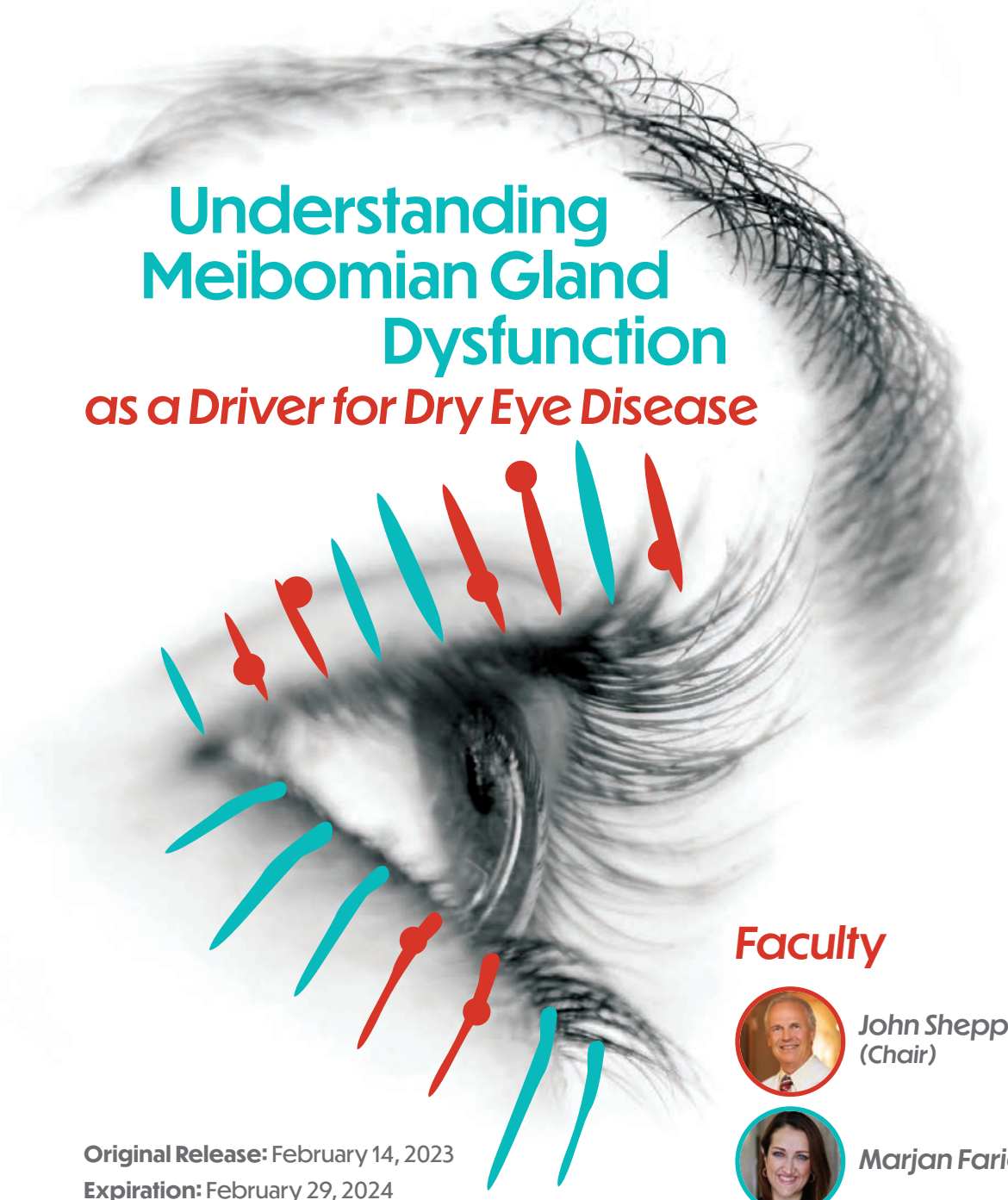
Understanding Meibomian Gland Dysfunction

as a Driver for Dry Eye Disease



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Activity Description and Purpose

Meibomian gland dysfunction (MGD) is a common condition affecting the ocular surface. Changes in the functioning of the meibomian glands result in alteration of oily secretions, or meibum, from the glands that form the outer lipid layer of tear film. Meibum is responsible for helping to lubricate the ocular surface, facilitating the spread of tears, and reducing evaporation. The presence of MGD is a major contributing factor to the development of dry eye disease. Understanding the signs and symptoms of MGD can help ophthalmologists achieve a differential diagnosis and connect the impact of this chronic condition to the development and progression of dry eye disease. The desired results of this educational activity are for ophthalmologists to understand the epidemiology and underlying pathophysiology of MGD, diagnostic techniques, and current and emerging treatments.

Target Audience

This educational activity is intended for ophthalmologists.

Learning Objectives

After completing this activity, participants will be better able to:

- Describe the prevalence of meibomian gland dysfunction
- Describe the pathophysiology of meibomian gland dysfunction–associated dry eye disease
- Implement best practices for diagnosing patients with meibomian gland dysfunction

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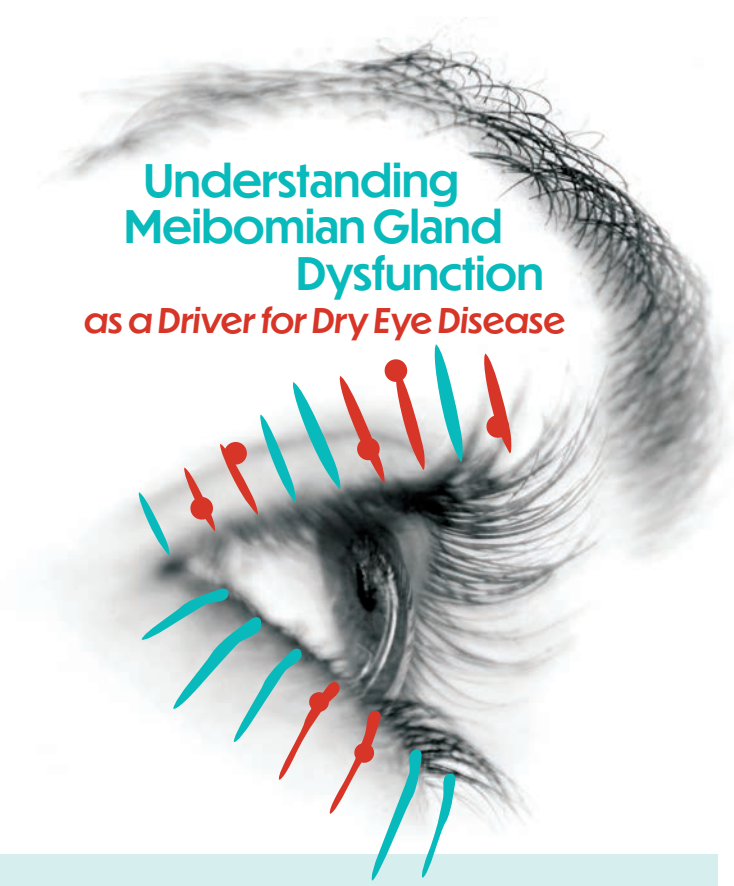

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Introduction

Meibomian glands, located within the upper and lower eyelids, are sebaceous glands responsible for secreting meibum, the principal component of the oily outer layer of the tear film. Meibomian gland dysfunction (MGD) is a chronic condition associated with abnormalities in the functioning of the meibomian glands, involving changes in the quality and/or quantity of meibum.[1] Changes in any of the components of the tear film, including the outer lipid layer, can lead to destabilization and the development of dry eye disease (DED).[1-3] Recently, a group of experts in corneal and external disease participated in a virtual roundtable discussion focused on understanding MGD and its association with DED, with an emphasis on the epidemiology, pathophysiology, diagnosis, and treatment options for patients with MGD. This educational activity presents the highlights of their discussion.

Prevalence and Epidemiology of Meibomian Gland Dysfunction

The reported prevalence rate of MGD varies widely across different patient populations, with estimates ranging from 3.5% to 70% **(Table 1)**.[4] Variations in the characteristics of study populations can significantly affect the apparent prevalence of MGD, particularly with respect to age, ethnicity, and any underlying conditions that may be associated with MGD. The definitions and criteria used to determine MGD in a study population can also result in differences among studies in the estimated prevalence of MGD in a given population.[4-7]

A recent meta-analysis assessing published studies to evaluate the prevalence of MGD found a pooled estimate of 35.8% for a global population.[8] Examination of the pooled analysis indicated that varying prevalence rates for MGD were found across studies, even when age ranges and diagnostic criteria were similar.

The development of MGD has been found to have a high degree of overlap with other conditions that affect the ocular surface, such as DED, anterior blepharitis, forms of conjunctivitis, and rosacea.[6] Ocular surface conditions often affect the tear film, and the presence of MGD can further disrupt the equilibrium and maintenance of the specialized glands and tissues that produce the components of the tear film. MGD is recognized as the most common cause of the evaporative form of DED. Other relevant epidemiologic factors that have been recognized for MGD include a potentially increased incidence in Asian populations and a slightly higher reported estimated prevalence among men, particularly men aged < 60 years.[4,6,8]

Expert Discussions: Meibomian Gland Dysfunction in Practice Populations

Dr Farid: MGD is likely more prevalent than some of the earlier studies indicated, especially at ophthalmic practices that deal with older populations, such as cataract surgery practices. Is MGD more common in men? If you look at DED specifically, we see its prevalence across male and female patients. In fact, the prevalence of DED may be slightly higher among women.[9] Approximately 85% of patients with DED have an evaporative component, which is from underlying MGD.[10] Although some studies may imply a greater prevalence of MGD in men,[8] I think the prevalence is fairly equal for men and women in my practice. I think the number one risk factor of MGD is aging. Unpublished data from my dry eye practice show that aging is the number one risk factor for the meibomian gland dropout that we see on meibography. Similar to DED, there are many risk factors for MGD, which compound one another when considering factors such as hormonal impact on the glands.[4]

Dr Sheppard: We all see specific populations in our individual practices. Surgeons tend to see a higher risk profile in a cataract practice, so our estimates of MGD may be higher. We are also consciously looking for MGD. Even 1 or 2 inspissated glands or a mild degree of keratinization may be relevant enough to indicate a diagnosis of MGD or blepharitis, whereas a comprehensive ophthalmologist or primary optometric practice may just

Table 1. Population-Based Studies Providing Estimates of the Prevalence of Meibomian Gland Dysfunction[4]

Study	Participants	Ethnicity	Parameter	Prevalence (95% CI), %	Age, years
Bangkok Study	550	Thai (various)	Telangiectasia or meibomian gland plugging or collarettes	46.2 (42-51)	> 40
Beijing Eye Study	1957	Mainland Chinese	Telangiectasia (asymptomatic) Telangiectasia (symptomatic for dry eye)	68 (65.6-70.4) 69.3 (64.5-73.8)	> 40
Japanese Study	113	Japanese	Gland dropout, expressibility and nature of meibum secretion	61.9 (52.1-70.9)	> 60
Shihpai Eye Study	1361	Taiwanese Chinese	Telangiectasia or meibomian gland orifice plugging	60.8 (59.5-62.1)	> 65
Melbourne Visual Impairment Project	926	White	TBUT < 1 SD (10 seconds) TBUT < 1.5 SD (8 seconds)	19.9 (17.4-22.7) 8.6 (6.9-10.7)	40-97
Salisbury Eye Evaluation	2482	White	Meibomian gland plugging or collarettes (clinical grades 2, 3)	3.5 (2.8-4.4)	> 65

Abbreviations: CI, confidence interval; SD, standard deviation; TBUT, tear breakup time.

ignore those factors because they are so prevalent. Many patients with MGD are asymptomatic, so in a busy practice, if patients are not complaining about their MGD, most of us are not very likely to go after it unless it is in a preoperative setting, in which you really want to fine-tune the ocular surface. The PHACO (Prospective Health Assessment of Cataract Patients' Ocular Surface) study found that 77% of patients who were expecting to have cataract surgery had signs of dry eye,[11] but most of them were unaware of the disease; this incidence is likely the same for MGD. Regarding the prevalence of MGD in Asian populations, although I do see many patients of Asian descent in my practice, I cannot say that I have looked at MGD as a race, ethnicity-, age-, or sex-specific condition. It is certainly prevalent in virtually all my patient populations.

Dr Wirta: MGD prevalence is directly related to age.[12] I also believe MGD may be exacerbated by having a Western diet, although there are no definitive scientific studies confirming this. Related to this point, in my practice population, men tend to have a less-balanced diet. For instance, if a high-fat diet that is rich in omega-6 oils and poor in omega-3 oils hastens the development of MGD, men might be more at risk. A study by Borrelli et al also reported more symptoms of DED in women, but perhaps more signs of DED in men.[13]

Dr Starr: I agree, as in many eye conditions, age is a leading risk factor for MGD and DED.[2,12] That being said, we are now seeing these conditions more often in younger populations.[14] Partly because we are looking for it more and have better diagnostic tools at our disposal, but the increased prevalence is also likely related, at least partially, to increased computer/digital screen time, earlier contact lens wear, use of eyelid cosmetics, and isotretinoin for acne, among other potential factors in the pediatric population.[9]

Meibomian Gland Dysfunction Pathophysiology and Diagnosis

The International Workshop on Meibomian Gland Dysfunction defined the condition as a *chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease* **(Figure 1)**.[1,15]

The meibomian glands are modified sebaceous glands located within the eyelids.[3,16,17] Meibum is released from the openings of the meibomian glands on the posterior lid margin with each blink. The secreted meibum spreads to form the thin, oily, outer layer of the tear film.

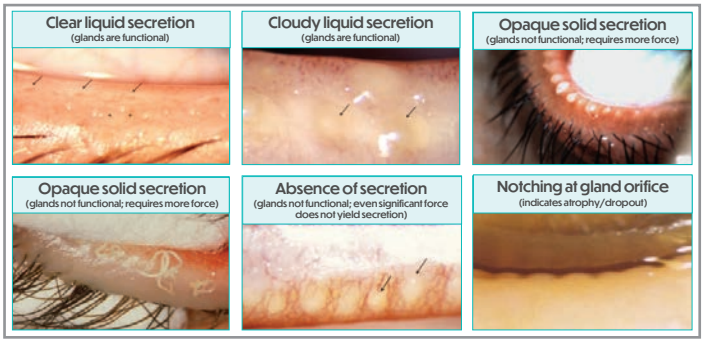

Figure 1. Meibomian gland secretions and lid margin features often associated with meibomian gland dysfunction[15]

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The meibum secreted from the meibomian glands plays a significant role in the homeostasis of the tear film, providing a smooth optical surface for the cornea at the air-lipid interface, enhancing spreading and stability of the tear film, and reducing evaporation of the tear film, among other functions.[17] Lipids secreted from the meibomian glands include a mixture of cholesterols, wax esters, diesters, triacylglycerols, free fatty acids, and phospholipids.[3,16] The lipids in the meibum form the outer layer of the tear film, overlying the bulk muco-aqueous constituents. An even spreading and distribution of the meibum across the ocular surface promotes stability of the tear film and reduces the rate of evaporation.[3,16,17]

Alterations in the composition and quantity of secreted meibum in patients with MGD can destabilize the tear film.[1,3,12,16,17] Clinical presentations of MGD include both hyposecretory and hypersecretory forms. MGD is characterized by a cycle of pathophysiology that contributes to tear film instability. Epithelial cell hyperkeratinization can cause obstruction of the gland orifices, leading to stasis of the meibum within the glands, cystic dilation, and gland dropout. Inflammation within the eyelids and along the lid margin leads to the release of inflammatory agents onto the ocular surface. Bacterial action on the constituents of the meibum can lead to further irritation and inflammation of the ocular surface.

Historically, there has been a lack of a uniform system to grade or categorize the severity of MGD. The International Workshop on Meibomian Gland Dysfunction proposed a grading system that

Table 2. Clinical Summary of Meibomian Gland Dysfunction Staging Used to Guide Treatment[1]

Stage	MGD Grade*	Symptoms	Corneal Staining
1	+ (minimal)	None	None
2	++ (mild)	Minimal to mild	None to limited
3	+++ (moderate)	Moderate	Mild to moderate; mainly peripheral
4	++++ (severe)	Marked	Marked; central in addition
"Plus" disease	Coexisting or accompanying disorders of the ocular surface and/or eyelids		

Abbreviation: MGD, meibomian gland dysfunction.
* Degree of altered expressibility and secretion quality

categorized the clinical severity of MGD according to a combination of patient-reported symptoms, the expression and characterization of the meibomian glands, and other diagnostic techniques to evaluate the condition of the ocular surface, such as corneal and conjunctival staining **(Table 2)**.[1,17]

A comprehensive examination is necessary to achieve a differential diagnosis of MGD, thereby allowing the identification of any other ocular surface conditions that may be present.[15,18] Important steps in an examination for a differential diagnosis of MGD include the following[1,15,18-21]:

- Collection and review of a patient's medical/ocular history
- Assessment of symptoms through the use of standardized questionnaires, including the Ocular Surface Disease Index (OSDI) and Standard Patient Evaluation of Eye Dryness questionnaire, or other methods to help identify asymptomatic and symptomatic patients
- Performance of tests to evaluate the clinical signs of ocular surface diseases (OSDs):
  - Blink rate/interval
  - Tear meniscus height
  - Tear film osmolarity
  - Instillation of fluorescein
    - Measurement of tear film breakup time (TBUT)
    - Ocular surface staining
  - Schirmer tear test
  - Meibomian gland assessment:
    - Eyelid and lid margin morphological characteristics
    - Expressibility and quality of secretions
    - Meibography to determine meibomian gland dropout
    - In vivo confocal microscopy

MGD is a common condition affecting the ocular surface that is frequently underdiagnosed and can be misdiagnosed because of overlap in the clinical presentation with other ocular surface conditions. Early recognition and treatment during routine examinations allows for initiation of basic treatment and referral to a specialist, as needed. A timely diagnosis and initiation of early treatment can help mitigate symptoms and potentially limit the progression of the condition associated with changes in lid morphology and meibomian gland dropout.

Expert Discussion: Best Practices in the Diagnosis of MGD

Dr Sheppard: One simple diagnostic tool I prefer to use when evaluating patients for MGD is a long-handled cotton tip swab. This is much longer than the standard cotton-tipped applicator, and I find it very easy to manipulate the lid margin and to express 2 or 3 specific meibomian glands. By pulling down the lower lids to allow a view of the whole cornea, you can express the glands and get a look at the inferior bulbar conjunctiva. By turning a little harder, you can get a look at the inferior tarsal conjunctiva. You can also use your cotton swab to evert the upper lid and look at the superior tarsal conjunctiva. This tiny, disposable, $0.003 diagnostic tool provides a great deal of information, yet avoids direct clinician finger contact with patient tissues.

Dr Farid: I agree. I have cotton-tipped applicators that are wonderful. We rely on LLPP: look, lift, pull, and push.[22] You want to lift the lids, look, and then while you are there with your cotton-tipped applicator—not your thumb—you can assess both the rapidity and quality of the meibum secretion. How quickly can you express those glands? Do they express rather easily or is there absent expression? Does the meibum have an olive oil consistency or a toothpaste consistency? This will really help you determine the degree of MGD and is a critical part of the diagnosis. I look at results of tests such as TBUT because I think they are a direct assessment of the smoothness of the tear film based on the lipid layer. A healthy lipid layer on the tear film results in better quality vision; conversely, a poor lipid layer on the tear film results in a rapid and irregular TBUT, which contributes to higher-order aberrations of visual quality. Simply put, a poor lipid layer leads to visual degradation, and meibum is really crucial for quality of vision in addition to lubrication of the surface of the eye. If there is a rapid TBUT, I know that there is going to be some degree of MGD.

Rapid TBUT can affect activities, such as reading speed. Many symptoms can be present or indicated on the preoperative questionnaire that will help us decide to do testing and to delve further into the problem. If a patient says, "I just can't read" or "I start reading okay and then after 10 minutes I can't read anymore", that tells me that there is a high likelihood of MGD and lipid-layer deficiency.

Dr Starr: I do not think we can stress that point enough! Interblink precorneal tear evaporation or breakup is the number one cause of visual fluctuations in our patients. This, of course, can negatively affect Snellen visual acuity (VA), which we measure and quantify, but it also has an adverse effect on visual quality, visual performance, and reading speed, which we do not routinely measure objectively and which is easily missed. This impact on vision is a frequent cause of reduced job productivity and reduced quality of life. In children, this may negatively affect their learning and schoolwork. Of course, it can also have a major impact on preoperative surgical measurements and postoperative outcomes and patient satisfaction.

Dr Farid: MGD can be present in the absence of inflammation. I think MGD often starts with obstruction of the terminal glands. Over time, that obstruction and the lack of good quality meibum expression can result in tear film inflammation. I think MGD can start without inflammation, and then inflammation can develop with chronic disease.

Dr Sheppard: When we were trying to educate our colleagues about inflammation and DED 20 years ago, everyone thought patients with dry eye had to have red eyes and that blepharitis only mattered when a patient presented with a red inflamed chalazion. A chalazion is the defining characteristic of grossly, out-of-control blepharitis, but that is truly the tip of the iceberg. Chronic, low-grade destruction of structural integrity will clearly lead to crises of obstruction and secondary infection.

Dr Wirta: When evaluating an ocular surface patient, I always want to have the first look before a technician has applied any topical anesthetic or performed any potentially invasive procedures, such as applanation tonometry. I really need to see the eyelid margin and tear film in its undisturbed state to make the proper diagnosis. I apply a slight amount of fluorescein and examine TBUT and staining, then proceed to use a cotton-tip applicator for meibomian gland evaluation. The applicator-aided expression can also provide a therapeutic trial of expression as a potential to relieve the patient's symptoms if the clinician desires.

Dr Sheppard: MGD is so important and so prevalent, yet it is often overlooked out of convenience or self-selected ignorance. I think every clinician is aware of its existence, but we can educate our

physicians-in-training to adopt a very efficient protocol that can be followed in a very systematic order with every patient so we do not miss something. Dr Farid's very quick protocol at looking at the lids, lid margins, and tarsus adds approximately 20 seconds to the examination, which is time well spent, especially if the protocol becomes habitual. Increased awareness and incorporation of an intelligent ocular surface analysis into the routine examination will allow MGD to be identified and treated sooner, avoiding some adverse consequences, such as visual dysfunction, infection, and decreased tear film integrity.

Are there any other specific diagnostic tests other than lid examination and gland expression that you find particularly useful?

Dr Farid: Meibography is another helpful tool. It is not as cost prohibitive as it used to be in terms of purchasing an imaging device. I think a picture speaks a thousand words, and patients are much more likely to be compliant with treatment when they can see their disease. Meibography has been a great addition to my practice, both for helping me diagnose MGD and for helping patients initiate and continue treatment.

Dr Starr: Noninvasive TBUT is a very useful test that can be performed without drops and was recommended as a key diagnostic tool in the Tear Film & Ocular Surface Society Dry Eye Workshop II Diagnostic Algorithm.[23] Osmolarity and matrix metalloproteinase-9 testing, although not specific to MGD, are fundamental to my workup of all patients with OSD and DED. I agree with Dr Farid that our LLPP examination technique is still my standard of care and can very rapidly help me diagnose most OSD subtypes. The 1 modification I have made to LLPP since we published our American Society of Cataract and Refractive Surgery algorithm paper in 2019[22] is that I now have patients *look* down or sometimes I *pull* the upper lid down, which allows me to better examine the base of the lashes for collarettes and the presence of *Demodex* blepharitis.

Current and Emerging Treatments for Meibomian Gland Dysfunction

The International Workshop on Meibomian Gland Dysfunction developed a staged treatment algorithm as a stepwise approach to management of the condition, beginning with basic, broad-spectrum therapies that are likely to benefit most patients and moving to more specific treatments according to an individual patient's response to therapy and severity of the condition.[24]

Current approaches to treatment of MGD include the following[18,21,24-29]:

- Topical formulations of artificial tears, lubricants, and other supplements to the tear film that are designed to hydrate the ocular surface and reduce the symptoms associated with MGD
- Thermal therapy through the direct application of heat to the eyelids that is intended to soften/liquify the meibum within the glands. Thermal therapy can be conducted by patients at home or through the use of specialty devices as part of an in-office procedure or take-home equipment.
- Mechanical therapy involving lid massage, techniques to remove debris and keratinized tissue along the lid margin, and probing of the meibomian glands to facilitate gland expression
- Combination therapy using the application of heat followed by or with concurrent use of lid massage
- Pharmacotherapy options, including topical/systemic antibiotics, cyclosporine formulations, lifitegrast, varenicline, and corticosteroids
- Nutritional supplements, particularly omega-3 essential fatty acids, including eicosapentaenoic acid, docosahexaenoic acid, and gamma linoleic acid
- Intense pulsed light (IPL) therapy, which uses repeated photon exposure of the tissue along the lid margin, targeting abnormal superficial blood vessels

Current treatment options for MGD are limited because of multiple issues. Artificial tears and lubricants form the mainstay of treatment for many patients with MGD.[24] Despite providing symptom relief, these treatment options do not address the underlying pathophysiology of the condition. Thermal and mechanical therapy can be effective in treating both the signs and symptoms of MGD, but patients are required to adhere to a long-term regimen, and compliance is limited. Currently available pharmacotherapeutic approaches generally target the inflammatory response that can be associated with MGD.[18,21,24,26] There is a need for options that are specifically directed at the abnormalities associated with the meibomian glands and altered meibum that occurs with MGD.

New treatments are currently in development that target MGD through different mechanisms of action.

NOV03

NOV03 is a nonaqueous, preservative-free formulation of 100% perfluorohexyloctane that is currently completing clinical trials for the treatment of MGD.[30,31] The low-surface tension of the topically applied formulation allows the perfluorohexyloctane to spread rapidly across the cornea.[30-32] The perfluorohexyloctane interacts with the lipid layer of the tear film, preventing evaporation and stabilizing the tear film.[30,31,33-35] NOV03 penetrates the meibomian glands following instillation, helping to liquify thickened, abnormal meibomian gland secretions.[30,33,34]

SEECASE was a prospective, multicenter, randomized, double-masked, saline-controlled phase 2 study designed to evaluate the safety, efficacy, and tolerability of NOV03 for the treatment of patients with DED.[30] The study population was selected from patients who had a TBUT of ≤ 5 seconds, abnormal meibum secretions, a total corneal fluorescein staining score between 4 and 11, a Schirmer test score ≥ 5 mm, and an OSDI score ≥ 25. Patients were randomly assigned (2:2:1:1 ratio) to receive NOV03 4 times daily, NOV03 twice daily, saline 4 times daily, or saline twice daily. Significantly greater improvement in signs and symptoms were observed for patients in the NOV03 groups compared with those in the control groups. The total corneal fluorescein staining score (primary end point) significantly improved for both NOV03 groups [$P < .001$ (4 times daily) and $P = .009$ (twice daily)] compared with the control groups, with improvements beginning at the 2-week point after initiating treatment. Improvement of symptoms (secondary end points), assessed by the Visual Analogue Scale for dryness, was demonstrated for both NOV03 groups, with statistically significant improvements from baseline [$P \leq .001$ (4 times daily) and $P = .002$ (twice daily)] at week 8 compared with control groups. NOV03 was well tolerated in both groups, with instillation site reactions < 3%.

The phase 3 development program for NOV03 consisted of the GOBI and MOJAVE multicenter, randomized, double-masked, controlled trials in patients with DED associated with MGD.[36,37] Patients were randomly assigned (1:1) to receive NOV03 or saline 1 drop 4 times daily in both eyes for 8 weeks. The primary end points (sign and symptom) were met in both studies **(Figure 2).** Significantly greater improvements were observed at day 57 (8 weeks) for patients in the NOV03 groups compared with those in the control groups for both total corneal fluorescein staining score and Visual Analogue Scale dryness score ($P < .001$ in each study). Safety assessments indicated NOV03 was well tolerated in the study population, with a low incidence of adverse

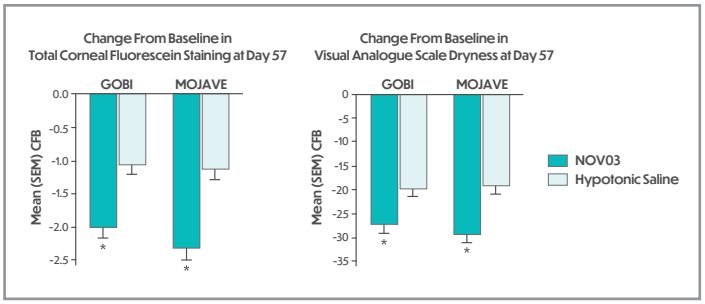

Figure 2. The primary end points (sign and symptom) were met in both the GOBI and MOJAVE studies.[36,37] Significantly greater improvements were observed at day 57 for patients in the NOV03 groups compared with those in the control groups for both total corneal fluorescein staining score and Visual Analogue Scale dryness score (* $P < .001$ in each study).
Abbreviations: CFB, change from baseline; SEM, standard error of the mean.

events reported. The most common adverse events reported with NOV03 in GOBI were blepharitis (1.6%), blurred vision (1.3%), conjunctival hyperemia (1.3%), conjunctival papillae (1.3%), eye discharge (0.3%), and eye pain (0.3%).[36]

Additional clinical studies, including KALAHARI (safety extension), have completed.[38] The US Food and Drug Administration accepted the New Drug Application filing for NOV03 on September 06, 2021.[39] NOV03 has been assigned a Prescription Drug User Fee Act action date of June 28, 2023.

AZR-MD-001

AZR-MD-001 is a novel ophthalmic formulation of selenium sulfide in development for the treatment of ocular disorders affecting the lid margin, including MGD.[40-42] AZR-MD-001 is a keratolytic, targeting abnormal hyperkeratinization that blocks meibomian glands, alters quality of lipids, and prevents secretion of lipids. Additionally, AZR-MD-001 has been shown to break the bonds between abnormal keratin proteins to help soften blockage of the glands and to slow the production of keratin in order to improve the quality of meibomian gland lipids and potentially prevent future blockage.

The AZR-MD-001 phase 2 program consisted of 4 multicenter, double-masked, vehicle-controlled studies that evaluated the safety and efficacy of AZR-MD-001 (0.1%, 0.5%, and 1.0%) in 95 patients with MGD.[43] Results of the integrated analysis of the phase 2 studies indicated that patients treated with AZR-MD-001 showed improvement in the signs and symptoms of MGD. A statistically significant improvement in patient-reported symptoms (OSDI) at 3 months was observed with AZR-MD-001, 0.5%, vs control ($P < .01$). Approximately 47% of AZR-MD-001–treated patients became asymptomatic at 3 months, as measured by OSDI, and approximately 46% had at least 5 more glands opened from a baseline of 1.7, as measured by the Meibomian Glands Yielding Liquid Secretion responder rate.[44] Safety assessments indicated that AZR-MD-001 was well tolerated, with the most common adverse events being stinging and watery eyes.[43,44]

TP-03

TP-03 is an ophthalmic formulation of an isoxazoline agent (lotilaner) in development for the treatment of *Demodex* blepharitis.[45] The isoxazoline compound paralyzes and eradicates *Demodex* mites by targeting parasite-specific γ-aminobutyric acid–chloride ion channels.

TP-03 was evaluated for the treatment of *Demodex* blepharitis in 2 pivotal clinical studies: Saturn-1 (phase 2b/3) and Saturn-2 (phase 3).[46,47] The primary end point, complete collarette cure (defined as collarette grade of 0 or 1), was met. Patients receiving twice-daily TP-03 for 43 days achieved a clinically meaningful collarette cure compared with those receiving control ($P < .0001$) **(Table 3)**. Secondary end points were also met, including mite eradication ($P < .0001$), composite cure (grade 0 for collarettes and erythema) ($P < .0001$), erythema cure ($P = .0001$), and erythema response ($P = .0002$). TP-03 was well tolerated, with a safety profile similar to that of control. All ocular adverse events reported were mild in severity, and no treatment-related discontinuations occurred.

Table 3 indicates the proportion of patients with clinically meaningful collarette cure (grade 0 to 1, ≤ 10 collarettes) in the upper eyelid of the analysis eye in the study and control groups.[46] The study group demonstrated a statistically significant improved collarette grade compared with the control group from day 8 onward. Positive data from the phase 3 Saturn-2 clinical trial have been reported, and a New Drug Application for TP-03 was submitted to the US Food and Drug Administration.[47]

Table 3. Percentage of Patients Achieving a Clinically Meaningful Collarette Cure in Saturn-1[46]

Day	Percentage of Patients		*P* Value
	Lotilaner, 0.25%	Vehicle	
8	23.2	10.6	.0003
15	40.7	16.3	< .0001
22	60.4	18.4	< .0001
43	81.3	23.0	< .0001

AXR-270

AXR-270 is a selective glucocorticoid receptor agonist that is being developed for the treatment of patients with DED associated with MGD.[48] AXR-270 is formulated as a topical cream that is intended for application to the eyelids once daily. Improvement in the signs and symptoms of MGD was observed in a phase 2 study evaluating the safety and efficacy of AXR-270.[48] In the study, 129 patients were randomly assigned to receive either AXR-270, 0.2%, AXR-270, 2%, or vehicle. AXR-270, 0.2%, was associated with statistically significant improvements from baseline to day 22 in eye dryness score ($P < .001$), eye discomfort score ($P <. 001$), TBUT ($P < .01$), and total corneal fluorescein staining ($P < .001$). The drug was well tolerated.

CBT-006

CBT-006 is a topical formulation of cyclodextrin under development for the treatment of MGD associated with DED. CBT-006 dissolves cholesterol and other lipid deposits in the orifice of meibomian glands to improve secretion and function. A phase 2 study was conducted to evaluate topical administration of CBT-006 3 times daily for 3 months in the treatment of MGD associated with DED.[49] Data on CBT-006 have yet to be released.

Treating Meibomian Gland Dysfunction: Current and Future Considerations

Dr Farid: When I am treating a patient with MGD, my choices of available treatment options are limited. At-home hot compresses, which specifically treat MGD but not necessarily DED, and lid hygiene measures are first-line treatment recommendations. Often, the biggest issues with these treatment options are compliance and efficacy. Getting enough heat to the posterior lid margin to be able to effectively melt the thickened meibum and express the chronic obstruction of the meibomian glands is challenging for patients at home, so I am quick to move to the next step in my protocol, which is an in-office thermal pulsation treatment. If patients have ocular rosacea or concomitant significant inflammation of their lids, I will add oral doxycycline or a macrolide to help with inflammation and bacterial load. IPL is another US Food and Drug Administration–approved, in-office procedure to treat MGD.[50] There is definitely a cost to patients associated with these in-office procedures, which can present a challenge. Targeted treatments are also limited. Lotilaner is a target-specific treatment of *Demodex* mite infestation that is currently under investigation.[45] When a mite infestation is part of the diagnosis, I think a treatment option that is more targeted to the specific disease process is going to be an important consideration.

Dr Starr: We use the term "customized ablation" in the laser vision correction realm, but I think it also applies quite nicely in the OSD/MGD realm. For instance, several in-office thermal devices are available, some with automated, manual, or no pulsation. Some patients may benefit from concurrent or isolated blepharoexfoliation or IPL or both, but one size does not fit all and it is important to tailor all available treatments to the individual patient, thereby creating a "customized" treatment approach.

Dr Sheppard: I think it is important to have a broad approach and to eliminate deleterious environmental influences, such as smoke or allergens, and deleterious lifestyle practices, such as excessive use of

digital devices. Dietary alterations—namely, essential fatty acid therapy—also make sense. MGD is a disease of the lipids and the tear film, and improving dietary intake and supplementation of beneficial anti-inflammatory, polyunsaturated fatty acids may be beneficial. This is a first-line regimen for my practice and many other practices. Most of the studies evaluating essential fatty acids show a positive effect on OSD.[24]

Another systemic therapeutic consideration is eliminating medications that might be negatively affecting the eyes, such as drying agents, hypertensive agents, antipsychotics, and antiallergy medicines, which are often given excessively to patients. Working with a patient's internist can be very helpful. Macrolides and tetracyclines, which are very useful systemically,[24] are associated with their own array of toxicities, including upsetting the flora in the gastrointestinal tract and upper gastrointestinal upset. It is very difficult to get a macrolide onto the ocular surface such that it produces a therapeutic concentration in the lids themselves and specifically the meibomian glands; this occurrence is similar for the highly insoluble tetracycline class. Azithromycin is a macrolide that we can use topically, but it comes in a very small bottle and is not entirely cost effective, and there are occasional difficulties in the supply chain. Overall, there are several limitations with respect to treatment of MGD. Several good approaches can be optimized, and we would like to make the most specific treatment recommendation for a given patient's disease. Hopefully, in the future, it will be possible to characterize the nature of the MGD, determine which lipids are actually most out of balance and target those specifically, and thus ascertain if a patient's MGD has an inflammatory component. One of my first-line therapies for severe MGD, red lid margins, ocular allergy, and dry eye is a topical steroid. Steroids can be a great way to induce therapy. Another agent that is more suitable for chronic maintenance therapy can then be used.

Regarding the NOV03 product in development, I think it is exciting to have a new mechanism of action available. Semifluorinated alkanes are water free and therefore preservative-free topical medications with a very small drop size and a very comfortable adverse effect profile.[36] Clinical data have shown that when this drop is administered 4 times daily, improvements in symptoms are seen in as early as 2 weeks.[36,37] The signs and symptoms primary end points were met in a pair of phase 3 trials.[36,37] To have such exciting results with a completely new approach to treating OSD, which is specific for patients with DED who have MGD, could be a game changer. One downside might be the 4-times-daily administration because patients do not always administer treatment as recommended. If the compound is approved at this dosage, the bottle will fortuitously be rather large. If the patient finds that the drug is working at twice daily, the patient will use it twice daily, giving the prescribing physician the off-label privilege of downregulating the dosage frequency for the numerous compliance costs and convenience benefits that would be relevant to individual patients.

Dr Wirta: Treatment options tailored to the clinical examination are ideal. If there is prominent lid margin inflammation with the MGD, then pulse therapy with topical corticosteroids or antibiotic-steroid combinations can be effective. If there is a strong component of aqueous deficiency, then frequent topical lubricants or even punctal plugs will be useful. Mechanical gland expression can be quite effective with or without prior heat therapy, but requires regular/repeated visits to maintain symptomatic benefit. I agree that NOV03 holds promise for patients, particularly for symptom relief.

Case-Based Discussions

Case 1: Blepharitis

From the Files of Marjan Farid, MD

A 42-year-old female software engineer presented with recurrent chalazia, or styes, that she had developed over the last few years, resulting in her inability to use soft contact lenses. She had experienced rapid redness and irritation when putting on her contact lenses, and had difficulty working at the computer. Her eyes were always feeling irritated and gritty. She also had itching that was not relieved with over-the-counter allergy drops. Findings on examination included a VA of 20/20 and a small left upper lid chalazion. When the patient looked down, diffuse collarettes were visible along the upper and lower lash base. The patient had a rapid TBUT and a slow secretion of thickened meibum from her meibomian glands. Meibography images revealed a lot of shortening of her glands as well as thickening dilation of the glands, suggesting that she was likely at a stage 2 meibomian gland dropout in certain areas ***(Figure 3)****.*

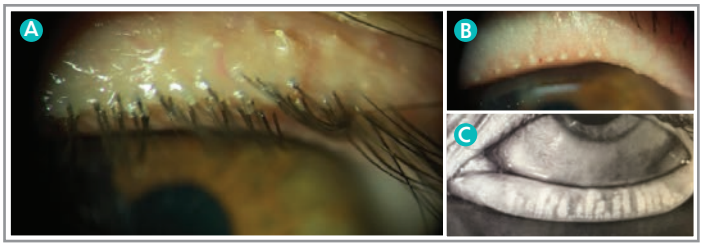

Figure 3. Clinical presentation of the patient in Case 1 showing (A) diffuse collarettes at the base of the lashes, (B) thickened meibomian gland secretions, and (C) meibomian gland dropout

Dr Farid: I find a high correlation among MGD, DED, keratitis, and *Demodex* blepharitis in younger patients. I think one of the hallmarks of this patient's examination findings and her symptoms is eyelid itching that was not relieved with allergy drops. Two factors really cause significant itching: (1) ocular allergies and (2) *Demodex* mite blepharitis. The presence of collarettes is an important indicator in the diagnosis of *Demodex* mite infestation. The collarettes along the lash base are essentially regurgitated, undigested material of the mites, resulting in waxy plugs at the base of the lashes. Two species of *Demodex* harbor in humans: *Demodex folliculorum*, which can be seen along the lash margin, and *Demodex brevis*, which is a shorter, fatter mite that invades the meibomian glands and creates inflammation, resulting in obstruction within the glands. This patient had a *Demodex* blepharitis infestation with secondary MGD.

We tell all our patients with blepharitis to work on lid hygiene. Some lid scrubs have tea tree oil as an active ingredient that is used for cleansing the lashes, but blepharitis requires really aggressive debridement of the lid margin, which may result in a compliance issue. Hypochlorous acid is another option for lid scrubs. Mechanical microblepharoexfoliation can be done in the clinic. The device used in microblepharoexfoliation allows a deeper cleansing or debridement of the lid margin to somewhat debulk some of the collarettes that have formed and to remove biofilm and scurf. In this patient, we initiated microblepharoexfoliation treatment on all 4 lids and started her on some commercial tea tree oil lid scrubs. We then started her hot compresses as an at-home treatment. Preservative-free artificial tears were recommended for her dry gritty eyes as well.

The patient reported some relief of her symptoms. She is doing a few at-home treatments, but it is hard for her to keep up with her lid hygiene recommendation because of a busy lifestyle, so she is coming in every few months to have the in-office microblepharoexfoliation treatment. Her contact lens wear is still limited. This is a case of a patient whose lids can be at least managed with consistent lid margin hygiene practices. Other treatments can be considered, such as oral doxycycline or topical cyclosporine, which can help manage associated eyelid and ocular surface inflammation. What is interesting to me is that *Demodex* mites can be the culprit in many patients with MGD. With improved treatments in this area, I am excited to see how we may be able to better treat patients with MGD.

Dr Sheppard: There is currently a wide variety of sources for tea tree oil treatments, including *Demodex* foam and *Demodex*-specific lid wipes. Chronic application of tea tree oil tends to be associated with toxicities to cutaneous, conjunctival, and corneal epithelium. Therefore, tea tree oil is not something you can use perpetually, but in maintenance regimens, I will have patients use their anti–*Demodex*-specific regimen on a weekly basis, perhaps 1 day a week or 1 week a month, just to keep the

Demodex at bay. The active ingredient in tea tree oil, terpinen-4-ol, has also shown efficacy with reduced adverse effects.[51,52] There is a current lack of other specific treatments to control *Demodex*, although topical hypochlorous acid has shown efficacy in the treatment of blepharitis and ocular infections.[53,54] Treatment of MGD definitely overlaps with the treatment of *Demodex* disease. It is important to note that *Demodex* contributes to anterior blepharitis and MGD is synonymous with posterior blepharitis. We are learning to better differentiate between the 2 as we formulate specific treatment regimens.

Dr Wirta: For eyelids such as these, appropriate debridement of collarettes is very useful, but not all patients are able to achieve this with self-care. In addition to the in-office debridement, I would perform a dissolvable punctum plug trial, particularly because this patient is a contact lens wearer who tends to do well with improved comfort of contact lens wear after punctal plugs.

Dr Starr: I, too, am excited for the possibility or newer and better treatments for *Demodex* blepharitis. Until their availability, I will continue performing in-office blepharoexfoliation and recommending at-home lid wipes to mechanically remove collarettes and biofilms, both sources of nourishment for mites, and I also recommend smothering the base of the eyelashes with ointment before bed, which may impede the nightly migration and mating habits of mites.

Dr Farid: Both topical and oral ivermectin have been used with some success to treat *Demodex* blepharitis.[55,56] Further studies with randomized controlled trials will be needed to assess its efficacy and safety.

Case 2: Surgery and Meibomian Gland Dysfunction

From the Files of Christopher E. Starr, MD

A 71-year-old female sought a second opinion after undergoing cataract surgery on her right eye 5 weeks ago. A multifocal intraocular lens (IOL) was implanted with paired limbal relaxing incisions at 3:00 and 9:00 ***(Figure 4)****. She presented with fluctuating, poor-quality vision in her right eye after surgery, and was experiencing glare, halos, starbursts, and a very mild foreign body sensation. She expressed concern that her right eye was not healing properly after surgery and was further concerned about having cataract surgery on her left eye. The patient reported that she had been promised "perfect vision" and was considering suing the surgeon. Current ocular medications included prednisolone twice daily, a nonsteroidal anti-inflammatory drug once daily, and fluoroquinolone drops 4 times daily.*

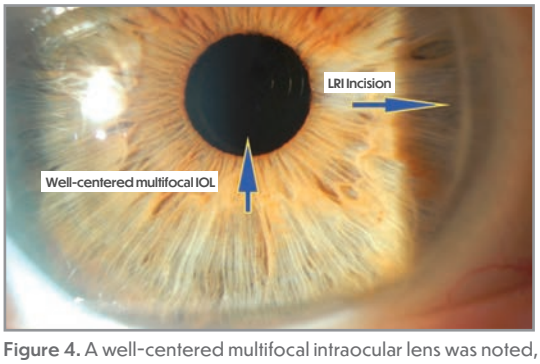

Figure 4. A well-centered multifocal intraocular lens was noted, along with paired limbal relaxing incisions, in the patient in Case 2

Abbreviations: IOL, intraocular lens; LRI, limbal relaxing incision.

On examination, the patient's VA was 20/40, J3 near. Her vision and visual quality fluctuated, and she was blinking rapidly to help improve her vision. Ten minutes after an artificial tear was administered, VA improved to 20/20 but only briefly. Refraction was measured at -0.25 sphere; keratometry was 46.25/46.00. Her corneal sensation was also moderately reduced in the right eye compared with the left eye. Further examination of the patient revealed a rapid TBUT of < 5 seconds, the presence of soapy tears with foam, a low tear meniscus height, thickened meibum on expression of the glands, telangiectasia on the lid margin, punctate epithelial erosions in the central and inferior cornea, elevated tear film osmolarity, and a positive test result for matrix metalloproteinase-9 ***(Figure 5)****.*

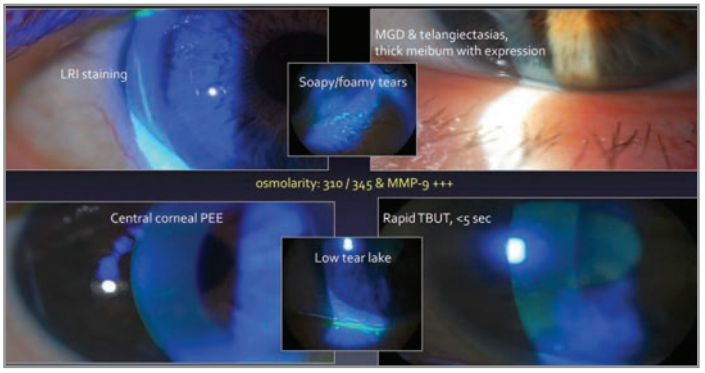

Figure 5. Examination of the ocular surface of the patient in Case 2 revealed signs of meibomian gland dysfunction

Abbreviations: LRI, limbal relaxing incision; MGD, meibomian gland dysfunction; MMP-9, matrix metalloproteinase-9; PEE, punctate epithelial erosion; TBUT, tear breakup time.

Dr Starr: Multifocal or extended depth of focus IOLs are often blamed first when postoperative patients are dissatisfied with their vision, but in this case, and many others, an OSD flare is the culprit. Multifactorial OSD requires a varied and multifaceted treatment regimen, and in perioperative patients, we tend to be more aggressive with our recommendations. The first thing I did with this patient was to discontinue the unnecessary, and potentially toxic, topical medications (fluoroquinolone with benzalkonium chloride preservative and nonsteroidal anti-inflammatory drops). The steroid was maintained twice daily because the matrix metalloproteinase-9 test was strongly positive. Lower lid punctal plugs were placed, and microblepharoexfoliation and thermal pulsation procedures were performed in the office. Hot lid compresses, lid hygiene, lid massage, and use of a humidifier were recommended as home-based treatments. Topical azithromycin drops at bedtime (off-label) and topical cyclosporine A twice daily were also initiated. Preservative-free lipid-based artificial tears were recommended to use 4 to 8 times daily, along with oral supplements of omega-3 essential fatty acids. A similar regimen was started for the left eye as a means of preoperative prophylaxis and surface optimization, knowing that she wanted another multifocal IOL and spectacle independence postoperatively. After 4 to 6 weeks of the preceding treatment regimen, the patient was elated with her vision, surgical outcome, and, ultimately, her surgeon, so much so that she returned to him for surgery on her fellow eye. I recommended a toric multifocal IOL be placed rather than limbal relaxing incisions because the latter are known to have a neurotrophic effect and can exacerbate the corneal signs of preexisting DED/OSD.[57] Topical recombinant human nerve growth factor would have been a reasonable next step if the patient's corneal sensation remained reduced.

Dr Farid: Preoperative diagnosis and treatment of ocular surface conditions is important, even if the patient is asymptomatic. If you do not diagnose MGD and OSD preoperatively in cataract surgery patients, they can do really poorly postoperatively from a visual standpoint and will often blame this on their surgery or the type of IOL that was placed into their eye, especially with premium lenses such as multifocal technology. You really have to make sure that the ocular surface is pristine, specifically the lipid layer that is critical to good quality vision. It is really hard to backtrack and say the poor vision is a result of the patient's DED. Without treatment, an asymptomatic patient becomes symptomatic, which is the last place you want to go. Diagnosing and treating MGD is really critical to good quality vision, good IOL planting, and postoperative patient satisfaction.

Dr Sheppard: I see 3 types of patients with DED: (1) the patient who is there for the DED, with whom you have to be scientific and careful; (2) the patient who presents with DED or MGD and is already on several topical medicines, and who primarily has something else going on and can be treated with heat-based or systemic therapy; and (3) the patient who is a surgical candidate. Even if surgical candidates are asymptomatic, I tell them they have to treat their OSD if they want to have good results and good predictability. The complexity of the disease does not matter. You want to treat the disease before you take measurements or perform surgery. The last thing you want is patients saying you caused their DED as a consequence of your surgery, but it happens all the time.

Dr Wirta: When a patient with OSD presents on so many concurrent medications, the clinical picture can be cloudy. My first step would be to assure the patient that the IOL is well placed and that the corneal incisions are appropriately placed (according to the keratometry readings). Then, I might consider stopping all topical therapy except preservative-free artificial tears for 1 or 2 weeks, followed by a reassessment. After reassessment, I can add on therapies according to the remaining clinical findings.

Case 3: Rosacea and Meibomian Gland Dysfunction

From the Files of David Wirta, MD

A 48-year-old female presented with red/itchy eyes and reported general eye discomfort and burning. The patient stated that the symptoms had begun gradually with redness and itching. She also noted that her eyelids were often swollen and her eyes were watery. She had tried over-the-counter drops to reduce the redness, but they were not very effective.

Mild to moderate flushing/telangiectasia of the cheeks was noted on examination. Ocular findings included eyelid inflammation and telangiectasia along the lid margin. Expressed meibum was cloudy and thickened ***(Figure 6)****. A rapid TBUT and moderate corneal staining was observed during the slitlamp examination* ***(Figure 7)****. The remainder of the slitlamp and fundus examination were normal. The patient's intraocular pressure was in the normal range.*

Dr Wirta: The patient was diagnosed with blepharitis/MGD and DED, and is likely to have ocular rosacea according to the dermatologic findings. The treatment plan included a referral for the dermatologic aspect of the rosacea and treatments for both the blepharitis/MGD and the DED. Daily warm compresses and lid hygiene were recommended, along with an in-office thermal procedure for the lids, followed by manual expression of the meibomian glands. A course of topical corticosteroids or steroid/antibiotic combination drops was recommended. Punctal plugs were considered. Use of the patient's preferred lubricating artificial tear drops was also included in the treatment plan.

The patient showed symptomatic improvement from the thermal treatment and manual gland expression. Further improvement resulted from punctal plug placement in this case.

Dr Farid: Ocular rosacea is an inflammatory condition. I often cycle oral tetracyclines, such as doxycycline, for patients who have chronic ocular rosacea. I will put the patient on treatment for 1 to 2 months, then take the patient off for several months and initiate pulse therapy as needed. I think IPL, which is now on-label,[50] also works well for many patients with

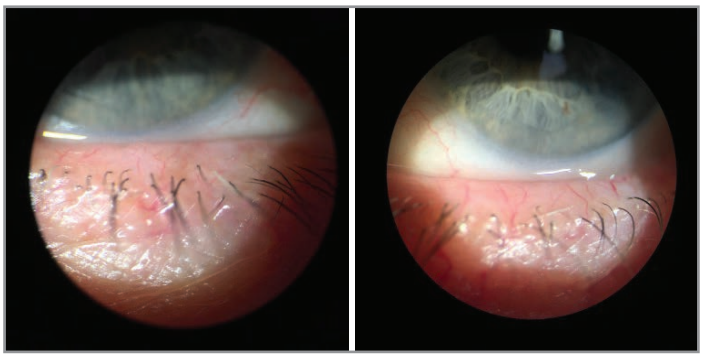

Figure 6. Rosacea and meibomian gland dysfunction of the patient in Case 3. Telangiectasia was observed along the eyelid margin. Thickened, cloudy secretions were expressed from the meibomian glands.

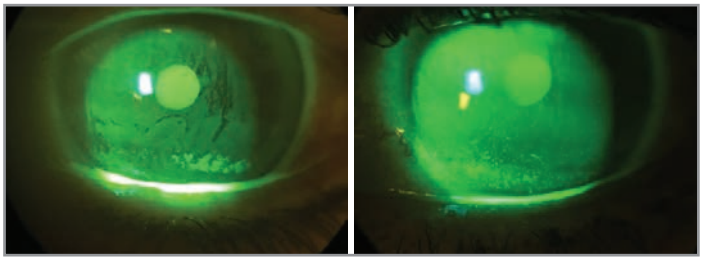

Figure 7. Moderate corneal staining observed in the patient in Case 3 with meibomian gland dysfunction and ocular rosacea

ocular rosacea. I do not have an IPL device in my practice, but I think that targeting the telangiectatic vessels at the lid margin really helps with ocular rosacea specifically. In general, DED tends to be a bit more hyperinflammatory in patients with ocular rosacea, so I use both long-term anti-inflammatories and short-term steroids, that is, low-potency steroids such as loteprednol etabonate, to treat the ocular surface inflammation. It usually helps these patients better tolerate other topical drops that might be used.

Dr Sheppard: Long term is the key for treatment with this patient. You are not going to cure this patient, so you want to give her some lifestyle changes that will aid her tolerance of the medications and look for the least complex and lowest dose possible in a successful maintenance regimen. Once you quiet down the inflammation, my follow-up recommendation is to perform examinations as infrequently as possible. You do not want to see a patient with rosacea/blepharitis every month, and the patient does not want to come into the office daily, so pulse and maintenance therapy is a good strategy. Finally, punctal plugs work well for patients who do not have tears and who have hyposecretory disease with or without rosacea. You make a separate decision on the punctal plugs regardless of whether the patient has ocular rosacea.

Dr Starr: I agree with Dr Sheppard. I have a very low threshold for punctal plugs in patients with both forms of DED. For MGD and evaporative DED, having more tear volume and a thicker inferior tear meniscus will provide more tear reserves, which minimize the adverse signs and symptoms of excessive tear evaporation. For aqueous-deficient DED, the benefits of punctal plugs are more obvious, but it never hurts to reiterate how important it is for us to maintain a high level of suspicion for Sjögren syndrome and other autoimmune diseases when encountering these patients.

Complete the CME posttest online at
https://tinyurl.com/MGDDEDMD

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1. MGD is an underlying component for approximately 85% of patients with the _____ form of DED.
    a. Aqueous deficient
    b. Sjögren syndrome
    c. Evaporative
    d. Autoimmune

2. Healthy meibomian gland secretions are essential for:
    a. Enhancing the stability of the tear film
    b. Providing a smooth optical surface for the cornea at the air-lipid interface
    c. Reducing evaporation of the tear film
    d. Enhancing the spreading of the tear film
    e. All the above

3. Clinical signs often associated with MGD include:
    a. A prolonged TBUT, thickened meibomian gland secretions, and inflammation along the lid margin
    b. Rapid TBUT, thickened meibomian gland secretions, and inflammation along the lid margin
    c. Rapid TBUT, clear meibomian gland secretions, and swelling of the eyelids
    d. Rapid TBUT, clear meibomian gland secretions, and inflammation along the lid margin

4. Meibography is a technique used in the diagnosis of MGD to:
    a. Evaluate the mucin layer of the tear film
    b. Test for corneal staining
    c. Check for symptom severity
    d. Visualize the meibomian glands within the lids