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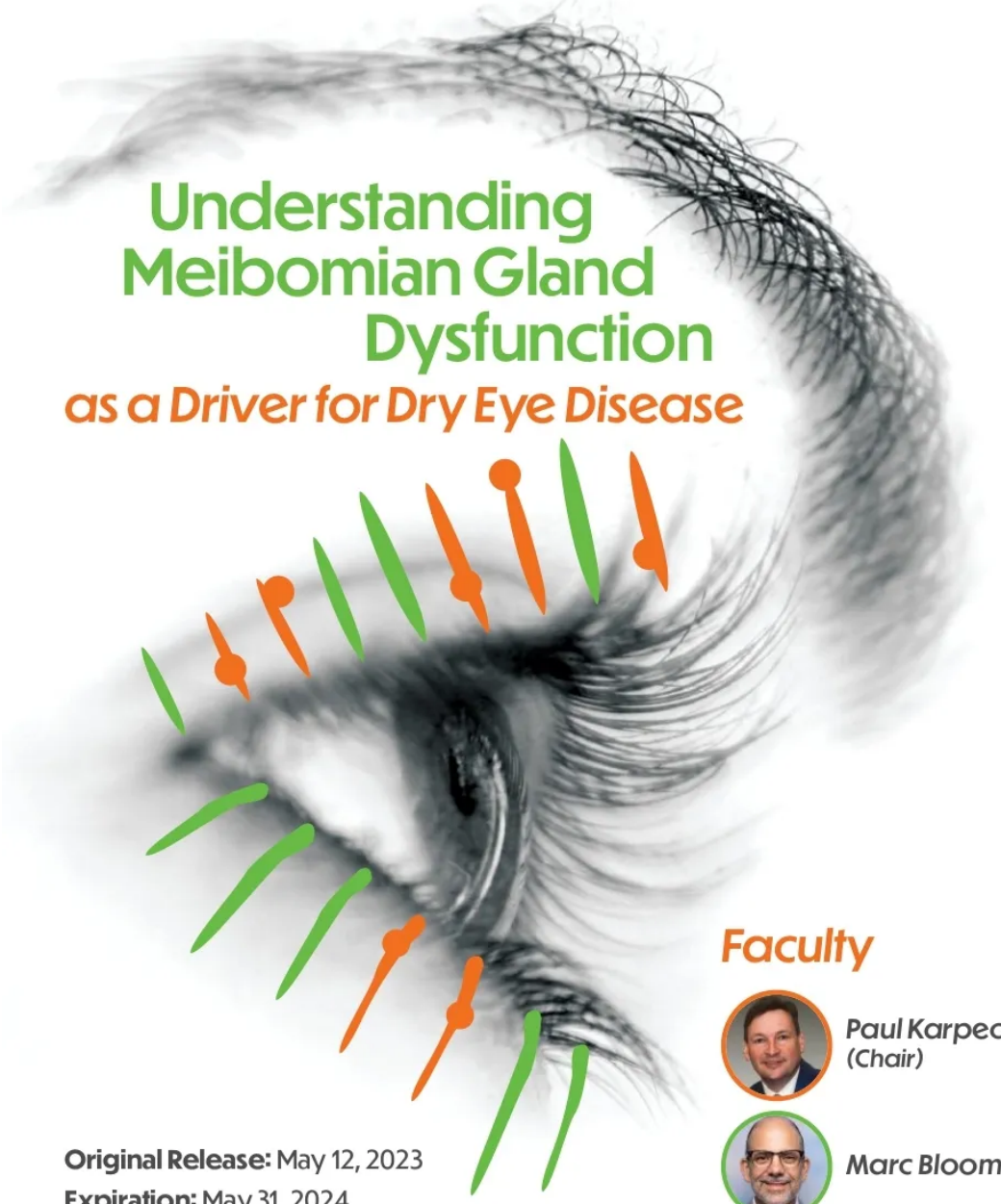
Understanding Meibomian Gland Dysfunction

as a Driver for Dry Eye Disease



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Distributed with REVIEW of OPTOMETRY

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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 meibum from the glands that form the outer lipid layer of the 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 for the development of dry eye disease. Understanding the signs and symptoms associated with MGD can help clinicians achieve a differential diagnosis and connect the impact of this chronic condition as a risk for the development and progression of dry eye disease. The desired results of this activity are to help optometrists understand the epidemiology and underlying pathophysiology of MGD, its diagnostic techniques, and current and emerging treatments.

Target Audience

This educational activity is intended for optometrists.

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
- Identify the current treatments available for patients with meibomian gland dysfunction
- Describe emerging or novel treatment of patients with meibomian gland dysfunction
- Design evidence-based treatment plans for persons with meibomian gland dysfunction–associated dry eye disease

Accreditation Statement

COPE approved for 1.5 CE credits for optometrists.
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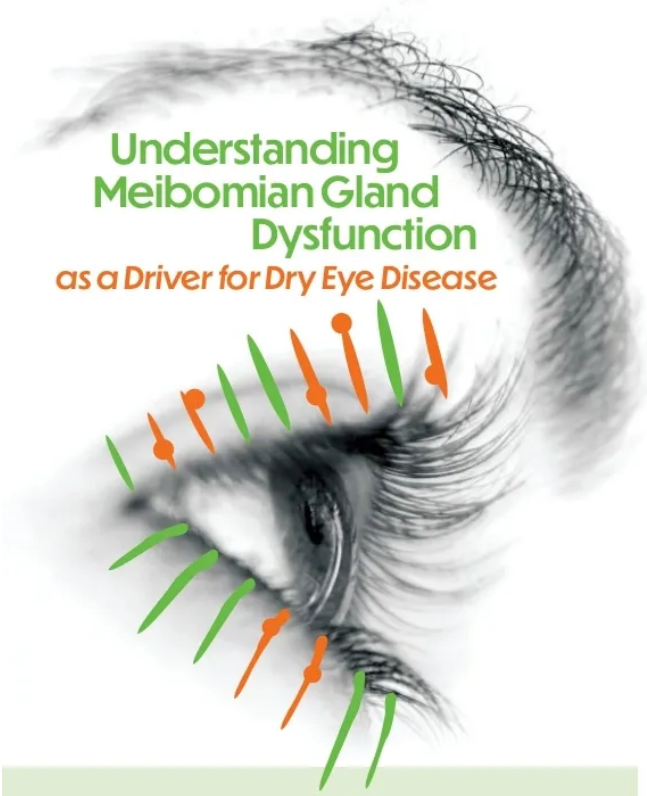

Understanding Meibomian Gland Dysfunction

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Introduction

Meibomian glands are sebaceous glands located within the eyelids responsible for secreting meibum, which forms the oily outer layer of the tear film and acts to promote tear film stability and prevent evaporation.[1] Meibomian gland dysfunction (MGD) is a chronic disease associated with abnormalities in the functioning of the meibomian glands, involving changes in the quality and/or quantity of the meibum. Changes in any of the components of the tear film can lead to destabilization and the development of dry eye disease (DED).[1-3] This educational activity captures the highlights of optometrists discussing MGD and its association with DED, with an emphasis on epidemiology, pathophysiology, diagnosis, and treatment options for patients with MGD.

Prevalence and Epidemiology of Meibomian Gland Dysfunction

The prevalence rate of MGD varies widely, ranging from 3.5% to 70%, even when age ranges and diagnostic criteria are similar across studies.[4-8] The incidence of MGD is also higher in Asian populations.[5,6]

MGD overlaps with other ocular surface conditions, including DED, blepharitis, forms of conjunctivitis, and rosacea.[6] Comorbid MGD exacerbates tear film disruption and is the most common cause of evaporative DED.[9,10]

Expert Discussion: Meibomian Gland Dysfunction in Practice Populations

Dr Karpecki: What is the reason for the wide range in the prevalence of MGD?

Dr Nichols: The wide range is mostly due to a lack of consistent methods, with studies using a combination of different tests, grading, and patient populations.[4-7]

Dr Bloomenstein: A 70% prevalence rate may be realistic if the diagnosis is based only on symptoms, such as burning, fluctuating vision, and irritation.[4,5] Not all patients report the same symptoms. I associate any fluctuation of vision as a guiding factor for MGD.

Dr Nichols: In the MGD report, the clinical group felt there could be MGD without symptoms, that is, asymptomatic or nonobvious MGD.[5]

Dr Mastrota: Yes, many older patients do not generate an optimal consistency of meibum, yet they can be less symptomatic secondary to age-related or other causes of reduced corneal sensitivity.[11,12]

Dr Karpecki: There is also a high degree of overlap among conditions. Dr Michael Lemp's study suggested that 86% of all DED included an MGD component.[10] The overlap with anterior blepharitis, including *Demodex* and staphylococcal blepharitis, needs more research, but overlap makes sense in terms of prevalence estimates.

What are some predisposing factors related to MGD?

A study by Mocan found that 92% of patients with glaucoma on long-term prostaglandin analogue treatment had MGD compared with 58% of patients on non–prostaglandin analogue treatment.[13] Another study by Wu established long-term use of visual display terminals was highly associated with MGD.[14] In addition, a study by Cochener found that 50% of patients who presented for cataract surgery had signs of MGD but were typically asymptomatic.[15]

Dr Nichols: With respect to topical medications, both preservatives and the medications themselves can have an effect.[16]

A recent review on the relationship of contact lens wear and MGD found greater meibomian gland morphology changes in patients with long-term lens wear, as you would suspect.[17] A new Tear Film & Ocular Surface

Society (TFOS) workshop is focusing on lifestyle and the impact of factors such as blink rates, use of digital devices, contact lens wear, smoking, makeup wear, tattooing of the eyelids, and elective surgeries on the ocular surface.[18]

Dr Mastrota: Aside from blink rate, many eyelid disorders are associated with dry eye/MGD, including, but not limited to, poor apposition of the eyelids, ectropion, and floppy or lax eyelids.

Dr Bloomenstein: Optometrists are uniquely situated to identify predisposing factors for MGD. Anything that induces inflammation can be a predisposing factor to MGD. I tend to see patients who are older and may be starting to have some tylosis or those without any prior treatment of the meibomian glands. Once patients are ready for cataract surgery, the challenge is getting the best measurements to provide the best quality of vision. Investigations have demonstrated that having higher tear film osmolarity is correlated with inaccurate K measurements, potentially affecting the choice of the best lens.[19]

Dr Mastrota: While assessing the lid margins, the smoothness of the architecture and undulations or thickening associated with rosacea should be examined. Abnormal blood vessels tend to develop either from rosacea or from chronic inflammation. Patients who have tattooed eyelids can have difficulty with MGD.[20] Watch for meibomian gland orifices that do not follow the lid margin in the appropriate anatomic position; they can be very tight and atrophic in appearance.

Meibomian Gland Dysfunction Pathophysiology and Diagnosis

The 2011 TFOS International Workshop on Meibomian Gland Dysfunction defined MGD 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".[1]

Meibum is released from meibomian gland openings on the posterior lid margin with each blink, spreading to form the thin, oily, outer layer of the tear film.[3] Meibum plays a significant role in tear film homeostasis and function **(Table 1)**.[21]

Table 1. Functions of Healthy Meibomian Gland Lipids[21]

- Provide a smooth optical surface for the cornea at the air-lipid interface
- Reduce tear film evaporation
- Enhance tear film stability
- Enhance tear film spreading
- Prevent spillover of tears from lid margin
- Prevent contamination of tear film by sebum
- Seal apposing lid margins during sleep

Alterations in the secreted meibum associated with MGD can destabilize the tear film and lead to evaporation and incomplete tear film spreading over the eye **(Figure 1)**.[22] Clinical presentations include both hyposecretory and hypersecretory forms.[21] MGD is characterized by a cycle of pathophysiology that contributes to tear film instability. Obstruction of the gland orifices can occur owing to epithelial cell hyperkeratinization, leading to stasis of the meibum within the glands, cystic dilation, and gland dropout.[1,2,23] Insufficient production of meibum or secretion of abnormal lipids can result in a thinning of the tear film lipid layer, an increase in the evaporation rate of the tear film, and a shortened tear breakup time (TBUT).[2,24,25] Inflammation within the eyelids and along the lid margin leads to the release of inflammatory agents onto the ocular surface.[1,2,21] Infestation with *Demodex* mites is also correlated with MGD.[26] *Demodex* mites cause mechanical and chemical damage and release waste products throughout their life cycle, promoting the growth of bacteria.[26] All these factors can lead to inflammation and can increase the viscosity of meibum, which results in its decreased secretion.[2]

The TFOS International Workshop on Meibomian Gland Dysfunction grading system categorizes MGD clinical severity according to a combination of patient-reported symptoms, the expression and characterization of the meibomian glands, and other diagnostic techniques, such as corneal and conjunctival staining **(Table 2)**.[1]

The definition of MGD from the International Workshop on Meibomian Gland Dysfunction still holds up well. The chronic diffuse aspect refers to involvement of > 1 gland. In the MGD report, discussion primarily focused on the obstructive variety because most patients have this disease form. The hypersecretory form is associated with overproduction of clear meibum, typically in a small percentage of younger patients.

–Kelly K. Nichols, OD, MPH, PhD, FAAO

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

Stage	MGD Grade	Symptoms	Corneal Staining
1	+ (minimally altered expressibility and secretion quality)	None	None
2	++ (mildly altered expressibility and secretion quality)	Minimal to mild	None to limited
3	+++ (moderately altered expressibility and secretion quality)	Moderate	Mild to moderate; mainly peripheral
4	++++ (severely altered expressibility and secretion quality)	Marked	Marked; central in addition
"Plus" disease	Coexisting or accompanying disorders of the ocular surface and/or eyelids		

Abbreviation: MGD, meibomian gland dysfunction.

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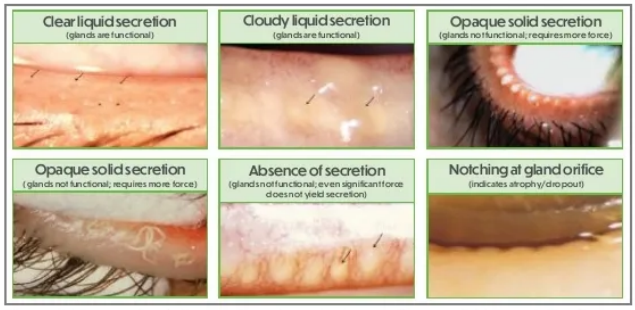

Figure 1. Images depicting meibomian gland secretions and lid margin features often associated with meibomian gland dysfunction.[22] Normal consistency (top left) has an olive oil consistency.

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Diagnosis of Meibomian Gland Dysfunction

A comprehensive examination is necessary to achieve a differential diagnosis of MGD, including identification of any other ocular surface disorder.[22,25] Important steps in an examination for a diagnosis of MGD include the following[1,22,25,27]:

- Collection and review of a patient's medical/ocular history
- Assessment of symptoms via standardized questionnaires, such as the Ocular Surface Disease Index (OSDI) and Standard Patient Evaluation of Eye Dryness Questionnaire, or other methods to identify asymptomatic and symptomatic patients
- Tests to evaluate the clinical signs:
  - Blink rate/interval
  - Tear meniscus height
  - Tear film osmolarity
  - Fluorescein staining score
  - TBUT
  - Ocular surface staining
  - Schirmer tear test
  - Meibomian gland assessment:
    - Eyelid and lid margin morphologic characteristics
    - Expressibility and quality of secretions
    - Meibography to determine meibomian gland dropout

MGD is a common condition that is frequently underdiagnosed or misdiagnosed. Early recognition and treatment can help mitigate symptoms and potentially limit the progression of the disease associated with changes in lid morphology and meibomian gland dropout.[1,22,25]

Expert Discussion: Best Practices in the Diagnosis of Meibomian Gland Dysfunction

Dr Nichols: The TFOS International Workshop on Meibomian Gland Dysfunction helped clarify the terminology used for MGD **(Figure 2)**.[1] Diseases affecting the meibomian glands can be acute, congenital, or neoplastic. One of these diseases is MGD, which includes low- and high-delivery states. We are mainly focused on the low-delivery states. Primary and secondary categories are included beneath those.

Dr Karpecki: What techniques do you use to express the meibomian glands?

Dr Mastrota: I use a finger press for routine expression of the glands. This gives me a sense for how much pressure is necessary to express the glands on a particular patient. I do not apply too much pressure. Using the whole side of my thumb allows for expression of nearly the whole expanse of the lid at once, and I express the lower and upper glands.

Dr Bloomenstein: I ask patients to just blink naturally. I watch them blink at the slitlamp and may request an exaggerated or forced blink. Manual expression with 3.0 psi is a small amount of pressure on the lids. I try to see how much it takes to get something out of the gland and use that as part of my grading system.

Dr Nichols: I use either a cotton swab or my finger to express the glands. In clinical studies, I will use the Korb Meibomian Gland Evaluator device to look at a certain number of glands. I sometimes add a little more pressure by pushing to see what comes out of the glands, and grade according to the worst quality observed. Absence of secretion can occur if the gland has just expressed naturally or if it is blocked or atrophied. A meibography instrument can help determine exactly what you are dealing with if absence of expression occurs.

Dr Karpecki: I prefer the Mastrota Meibomian Paddle and also use my whole thumb on the outside of the lid. I apply pressure gently upwards to express the glands; no anesthetic is required. I express the nasal lower eyelid to central area, expressing 10 to 12 glands. I do not tend

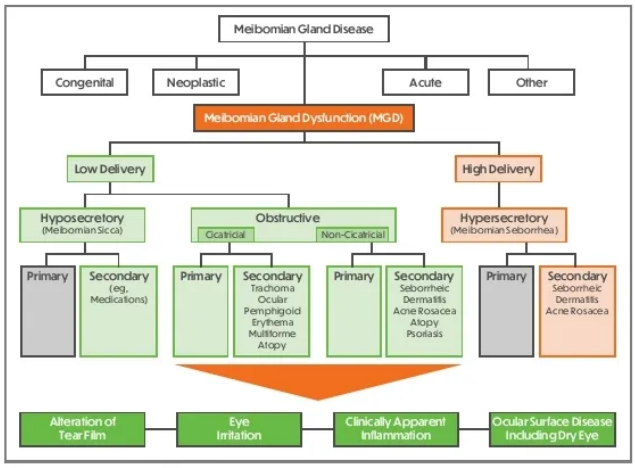

Figure 2. Classification scheme for meibomian gland dysfunction proposed by the Tear Film & Ocular Surface Society International Workshop on Meibomian Gland Dysfunction[1]

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to express the upper eyelid. Normal meibum appears as thin, clear olive oil that is barely visible as it comes out of the glands. Expressing is an easy 5-second technique that provides so much information.

Dr Nichols: I start in the nasal area and move centrally and inferiorly using a finger, holding pressure and giving it some time. I then move to the next set of glands and express there before returning to the original first spot. If you go back to where you were before, then you are more likely to see secretions. I recommend starting in a normal patient to see meibum for the first time if you have not expressed before.

Dr Bloomenstein: The meibomian glands should be expressed on every single patient, not just those you think have problems. This provides a better understanding as to what normal secretions look like compared with abnormal secretions.

Dr Karpecki: Do you use questionnaires for screening patients for MGD or just ask questions when taking the patient's history?

Dr Mastrota: I ask a lot of history questions, including how the patients' eyes feel or if their eyes bother them. I ask them to score these symptoms on a 1 to 10 scale.

Dr Bloomenstein: My questions focus on several points. "How frequently or how much time are you spending on a computer or tablet? Do you feel you can see better after you blink? Do you find yourself wanting to put a drop of artificial tears in your eyes to keep them lubricated?" I find that patients with evaporative DED tend to get more glare at the end of the day. I always ask patients if they have sought any treatment for computer vision syndrome.

Dr Nichols: I check contact lens–wearing patients to see if they mention that their contacts "do not work" or "seem blurrier" at the end of the day and that they have to take them out because they now feel them.

When Drs Begley, Chalmers, Caffery, and I were developing the Dry Eye Questionnaire and the Contact Lens Dry Eye Questionnaire, we did not separate out the patients with MGD.[28,29] All the participating patients had self-reported dry eye. Questions included whether patients stop and close their eyes toward the end of the day, and what time of day bothers them. There was a subgroup of patients that had higher symptom scores later in the day and stopped to close their eyes or blinked to clear their vision. I bet those were the patients with MGD.

Dr Karpecki: I am amazed at how many patients who have morning symptoms have inadequate lid seal (ILS); that is, they do not fully close

their eyes at night. Our eyelids should slightly overlap and seal overnight. These patients do not have lagophthalmos; they simply do not have proper eyelid seal at night, leading to nocturnal evaporative stress and desiccation. Patients not only complain of morning symptoms, but can also sometimes show inferior corneal staining. The Korb-Blackie lid light test, developed by Drs Korb and Blackie, may allow the clinician to confirm the diagnosis of ILS. In this test, you darken the room, have the patients close their eyes—without squeezing them—as if they are sleeping, place the transilluminator light on the upper closed eyelid, and look for light protruding inferiorly between the eyelids. It ties into this very well because they all seem to have meibomian gland issues. Looking at tests to evaluate clinical signs, tear meniscus height can help differentiate the aqueous deficient forms, along with staining.[25]

Do you look at ILS, partial blinking, and blink rate when evaluating patients?

Dr Nichols: A LipiScan or other imaging device can identify patients who do not fully close their lids while blinking.

Dr Mastrota: I wait for a blink at the slitlamp and check the excursion.

Dr Karpecki: Besides meibomian gland expression, what other tests are a little more specific to MGD, or can we even tie to it closely?

Dr Bloomenstein: Evaluation of the quality of the meibum is the best characteristic for this disease state **(Table 2)**.[1] All other tests are downstream from there.

Dr Mastrota: Obtaining fluorescein staining is important to highlight characteristics other than the lid margin and Marx line **(Figure 1)**.[22] I am decreasing my use of lissamine staining.

Dr Karpecki: Using a high-quality number 15 yellow Wratten filter can help visualize the conjunctival staining compared with lissamine green dye.

How often do you see MGD when you express an asymptomatic patient?

Dr Bloomenstein: I think MGD is probably one of the most underdiagnosed conditions in the clinic.[16] There is also a lot of discussion around *Demodex*. The presence of collarettes is pathognomonic for *Demodex*,[30] but the number of asymptomatic patients with collarettes is strikingly high.[31] I question what negative effect the collarettes are having on the glands. Moreover, assessing lid health, including the base of the lashes, is necessary. Secretions other than those with an olive oil texture indicate at least grade 1 MGD. This presents an opportunity and a decision point. Do you talk to patients about treatment strategies or wait until they become symptomatic? We need to manage asymptomatic patients and start doing things differently.

Current Treatments for Meibomian Gland Dysfunction

The TFOS International Workshop on Meibomian Gland Dysfunction developed a staged treatment algorithm for management of MGD, initiating basic, broad-spectrum therapies likely to benefit most patients and moving to more specific treatments according to a patient's response to therapy and severity of the disease **(Table 3)**.[16]

Current approaches to treatment of MGD include the following[16,25,27,32-36]:

- Topical formulations of artificial tears, lubricants, and other tear film supplements
- Thermal therapy via direct application of heat to the eyelids (in office or at home)
- Mechanical therapy involving lid massage (with or without heat), lid hygiene, and debridement
- Topical or systemic antibiotics, cyclosporine formulations, lifitegrast, and corticosteroids
- Nutritional supplements (eg, omega fatty acids)
- Intense pulsed light (IPL) therapy targeting abnormal superficial blood vessels

Table 3. Treatment Algorithm for Meibomian Gland Dysfunction[16]

Stage	Clinical Description	Treatment

1	• No **symptoms** of ocular discomfort, itching, or photophobia
	• **Clinical signs** of MGD based on gland expression
	  ○ Minimally altered secretions: grade ≥ 2 to 4
	  ○ Expressibility: 1
	• No ocular surface **staining**
		• **Inform** patient about MGD, the potential impact of diet, and the effect of work/home environments on tear evaporation and the possible drying effect of certain systemic medications
		• **Consider** eyelid hygiene, including warming/expression as described below (±)

2	• Minimal to mild **symptoms** of ocular discomfort, itching, or photophobia
	• Minimal to mild MGD **clinical signs**
	  ○ Scattered lid margin features
	  ○ Mildly altered secretions: grade ≥ 4 to < 8
	  ○ Expressibility: 1
	• None to limited ocular surface **staining**: DEWS grade 0-7; Oxford grade 0-3
		• **Advise** patient on improving ambient humidity, optimizing workstation, and increasing dietary omega-3 fatty acid intake (±)
		• **Institute** eyelid hygiene with eyelid warming (a minimum of 4 minutes once or twice daily), followed by moderate to firm massage and expression of meibomian gland secretions (±)
		• **All the above, plus** (±)
		  ○ Artificial lubricants (for frequent use, preservative-free preferred)
		  ○ Topical azithromycin
		  ○ Topical emollient lubricant or liposomal spray
		  ○ Consider oral tetracycline derivatives

3	• Moderate **symptoms** of ocular discomfort, itching, or photophobia with limitations of activities
	• Moderate MGD **clinical signs**
	  ○ ↑ lid margin features: plugging, vascularity
	  ○ Moderately altered secretions: grade ≥ 8 to < 13
	  ○ Expressibility: 2
	• Mild to moderate conjunctival and peripheral corneal **staining**, often inferior: DEWS grade 8-23; Oxford grade 4-10
		All the above plus:
		• Oral tetracycline derivatives (+)
		• Lubricant ointment at bedtime (±)
		• Anti-inflammatory therapy for dry eye as indicated (±)

4	• Marked **symptoms** of ocular discomfort, itching, or photophobia, with definite limitation of activities
	• Severe MGD **clinical signs**
	  ○ ↑ lid margin features: dropout, displacement
	  ○ Severely altered secretions: grade ≥ 13
	  ○ Expressibility: 3
	• Increased conjunctival and corneal staining, including central **staining**: DEWS grade 24-33; Oxford grade 11-15
	• ↑ signs of inflammation: ≥ moderate conjunctival hyperemia, phlyctenules
		All the above, plus anti-inflammatory therapy for dry eye (+)

Abbreviations: DEWS, Dry Eye WorkShop; MGD, meibomian gland dysfunction.

Current treatment options for MGD are relatively limited. Artificial tears provide short-term relief for symptoms but do not address the underlying pathophysiology of the condition.[36] Thermal and mechanical therapy requires adherence to a long-term regimen.[16] Pharmacotherapeutic options are needed that are specifically directed at the pathophysiology of MGD.[16,25,27,33]

Expert Discussion: Treating Meibomian Gland Dysfunction

Dr Karpecki: When should you treat patients with MGD? What treatments do you use? Do you treat according to signs or wait for symptoms?

Dr Mastrota: After the examination, I review why the patient came in and what needs to be worked on. I advise the patient on good hygiene and diet. I will also briefly mention the improved aesthetics of healthy eyelids. Early intervention with treatment can optimize outcomes.

Dr Bloomenstein: I discuss findings with patients at the slitlamp during the evaluation while expressing the glands. I explain what I expect to see in contrast to the appearance of their meibum and discuss the ramifications of MGD. If patients are symptomatic or if I see loss of meibomian glands, I let them know there are treatments that might be beneficial and then bring them back to assess how the treatment is working.

I recommend patients apply moist heat for 3 or 4 minutes to improve expression of the glands, followed by massaging of the lids. This can be done in the shower, with warm water on the lids. Patients often report that their vision seems to improve afterward.

Dr Mastrota: I recommend an adaptation of the 20-20-20 rule. After 20 minutes of extended near work or use of a digital device, gaze at something 20 feet away, concentrating on blinking fully and completely 20 times. Then, have 20 sips of water to remain hydrated.

Dr Nichols: It can be difficult for asymptomatic patients with MGD to be compliant with treatments even if you discuss MGD as being chronic and possibly progressive. Showing patients a meibography image can be helpful as a tool to improve patient compliance.

Dr Karpecki: Sharing the consequences of not treating MGD can help some patients. Lid hygiene often has low compliance, and lid massage is not necessarily the right thing because some patients may be massaging a heated-up cornea more than they need to. Some studies have shown good results with warm compresses. One study showed adequate temperature with hydrating compresses, but not with the bundled method.[37] A hydrating compress achieved a sustained temperature of 104˚F to 114˚F.

Dr Bloomenstein: At subsequent patient visits, we talk about the additional benefits of in-office procedures. Optometrists sometimes have a hard time talking to patients about in-office treatments. If patients are not performing their at-home treatments, then this is an opportunity to discuss other treatment options.

Dr Karpecki: Do you recommend the use of omega-3 fatty acid supplements, such as γ-linolenic acid (GLA), eicosapentaenoic acid, and docosahexaenoic acid?

Dr Mastrota: I add nutritional supplements as a low-risk treatment option because there is a suggestion that they (ie, GLA and polyunsaturated fatty acids) may decrease the production of disease-related inflammatory mediators that are implicated in the pathogenesis of chronic dry eye.[38]

Dr Bloomenstein: I explain to patients that inflammation could be driving changes in the quality of the meibum and causing some obstruction of the glands.[3] I recommend cyclosporine or lifitegrast to help control inflammation, especially when patients are getting worse. In that case, I use a low-dose steroid to control flares because allergy or other factors will exacerbate the MGD. In order to improve functioning of the glands, I offer IPL therapy or neurostimulation.[39]

Dr Karpecki: I tell patients I am going to treat their oil glands from the outside in and from the inside out. Outside treatments are topical agents and compresses. Internal treatments are omega fatty acids, such as GLA, eicosapentaenoic acid, and docosahexaenoic acid, and, in rare cases, tetracyclines to help with ocular rosacea. IPL therapy can help treat obstructed glands and inflammation.[40]

Dr Nichols: A stepwise approach is always the best rather than changing all at once, including managing any inflammation you see and other aspects of the lids or contact lenses. We are currently running a placebo-controlled omega fatty acid study that involves patients with MGD who wear contact lenses.

Dr Karpecki: I take a comprehensive approach in each treatment category, starting with a hydrating compress, omega fatty acid supplements, and lid scrubs. If I am not getting results, I perform an in-office procedure. I select a treatment for blepharitis, obstruction of the meibomian glands, inflammation, and even for the tear film, as needed, and advance the nature of the treatments according to the severity of the condition. Microblepharoexfoliation is an in-office procedure that can help, given the the overlap between blepharitis and MGD. Most patients notice how much better their eyes feel after mechanical lid debridement.

Dr Bloomenstein: Stabilization of the glands or getting the glands to be more expressible are important goals of therapy. Positive reinforcement is a good way for patients to be more adherent to therapy in the long run. Try to focus on 1 patient goal, such as a line of visual acuity, making use of a computer or their contact lenses more comfortable, and more stable scans in preoperative cataract patients.

Emerging Treatments for Meibomian Gland Dysfunction

NOV03

NOV03 is a water-free and preservative-free formulation of 100% perfluorohexyloctane designed for the treatment of DED due to MGD.[41,42] It is hypothesized that low-surface tension allows perfluorohexyloctane to spread rapidly across the ocular surface, reducing evaporation and stabilizing the tear film **(Figure 3)**.[43-45] NOV03 can be recovered from the meibomian glands, and may help to liquify thickened, abnormal secretions.[41,42,46,47]

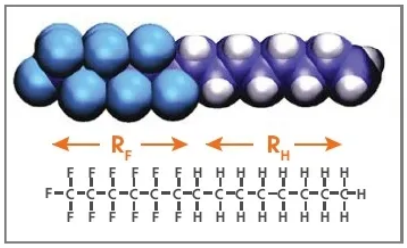

Figure 3. Structure of perfluorohexyloctane[45]
Reprinted from *International Journal of Pharmaceutics*, 538, Agarwal P, Scherer D, Günther B, Rupenthal ID, Semifluorinated alkane based systems for enhanced corneal penetration of poorly soluble drugs, 119-129, Copyright 2018, with permission from Elsevier.

Data on the NOV03 trials have been reported recently. 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.[41] Patients in the study had a TBUT of ≤ 5 seconds, abnormal meibum secretions, a total corneal fluorescein staining score between 4 and 11, a Schirmer tear test score ≥ 5 mm, and an OSDI score ≥ 25. Patients were randomly assigned (2:2:1:1) to receive NOV03 4 times daily, NOV03 twice daily, saline 4 times daily, or saline twice daily, respectively. Significantly greater improvement in signs and symptoms were observed for patients in the NOV03 groups than for 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]; $P = .009$ [twice daily]) compared with the score in the control groups, with improvements beginning at 2 weeks after initiating treatment **(Figure 4A)**. Improvement of symptoms, assessed by the

Visual Analogue Scale for dryness, was demonstrated for both NOV03 groups, with statistically significant improvements from baseline ($P < .001$ [4 times daily]; $P = .002$ [twice daily]) at week 8 compared with control groups **(Figure 4B)**. NOV03 treatment was well tolerated, with instillation site reactions occurring in < 3% of patients.

The phase 3 multicenter, randomized, double-masked, controlled GOBI and MOJAVE trials evaluated NOV03 in patients with DED associated with MGD.[48,49] Patients were randomly assigned (1:1) to receive 1 drop of NOV03 or saline 4 times daily in both eyes for 8 weeks. The primary end points (signs and symptom) were met in both studies. Significantly greater improvements were observed at day 57 (8 weeks) for patients in the NOV03 groups than for those in the control groups for both total corneal fluorescein staining score (signs) and the Visual Analogue Scale dryness score (symptoms) **(Figure 5)**. Onset of effect occurred as early as week 2. The safety assessments indicated that NOV03 was well tolerated in the study population, with a low incidence of adverse events reported. The most common adverse events reported in the NOV03 group (n = 311) in MOJAVE 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%).[49]

Additional clinical studies, including the KALAHARI (safety extension) trial, are ongoing.[50] The US Food and Drug Administration accepted the New Drug Application filing for NOV03 on September 06, 2021.[51] NOV03 has been assigned a Prescription Drug User Fee Act action date of June 28, 2023.

AZR-MD-001

AZR-MD-001 is a selenium sulfide (SeS_2) ointment in development for the treatment of MGD by focusing on the abnormal hyperkeratinization associated with the condition.[52-54] It is a keratolytic agent that breaks the bonds between keratin proteins, which softens the cells blocking meibomian glands and slows the production of keratin. This ultimately decreases the obstruction of meibomian glands, increases quantity and quality of lipids secreted, and improves symptoms.[55]

A phase 2b trial evaluated the safety and efficacy of AZR-MD-001, 0.5%, administered twice weekly to the lower eyelid in 245 patients with MGD.[55] The coprimary end points were the number of glands secreting meibum using the Meibomian Glands Yielding Liquid Secretion score and patient-reported symptoms (measured by OSDI) at 3 months. Patients receiving AZR-MD-001 experienced an improvement in Meibomian Glands Yielding Liquid Secretion score, with an average increase of 1.8 more open glands secreting meibum from baseline ($P = .0004$), and an improvement in OSDI score, with an average improvement of 3.5 from baseline ($P = .0438$), compared with those receiving placebo at 3 months. Improvement with AZR-MD-001 was also noted for key secondary end points: 46.9% of patients became asymptomatic per total OSDI responder rate, 45.7% had ≥ 5 open glands compared with baseline, and meibum quality returned to normal in 68.7% of patients. Safety assessments indicated that AZR-MD-001 was well tolerated, with no serious treatment-related adverse events. The most common adverse events associated with AZR-MD-001 were stinging and watery eyes.[56]

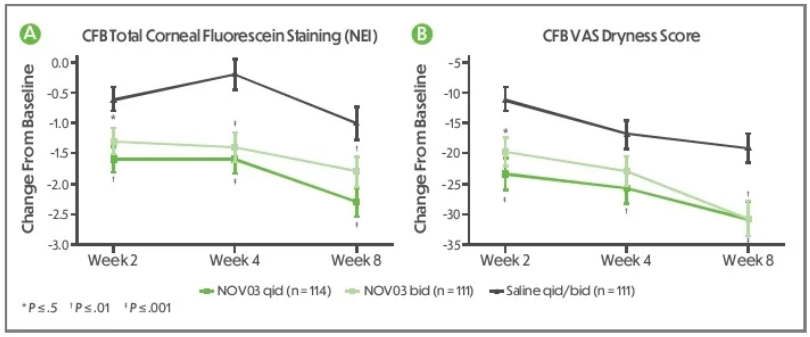

Figure 4. The mean change from baseline in total corneal fluorescein staining (A) and Visual Analogue Scale dryness (B) scores following treatment with NOV03 or saline control in the SEECASE study[41]
Abbreviations: CFB, change from baseline; NEI, National Eye Institute; VAS, Visual Analogue Scale.
Reprinted with permission from Tauber J, Wirta DL, Sall K, et al; SEECASE Study Group. A randomized clinical study (SEECASE) to assess efficacy, safety, and tolerability of NOV03 for treatment of dry eye disease. *Cornea*. 2021;40(9):1132-1140. Copyright 2021 by the Authors.

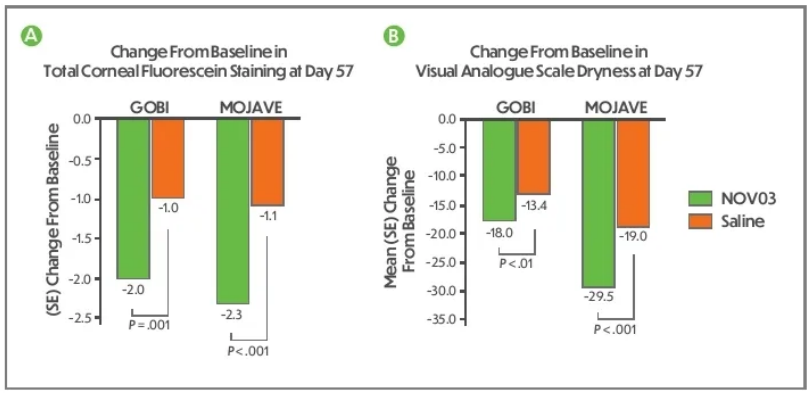

Figure 5. Mean change from baseline in total corneal fluorescein staining (A) and Visual Analogue Scale dryness scores (B) following treatment with NOV03 or saline in the GOBI and MOJAVE studies[48,49]
Abbreviation: SE, standard error.

TP-03

TP-03 (lotilaner) is an ophthalmic solution being developed to treat *Demodex* blepharitis.[26] The isoxazoline compound paralyzes and eradicates *Demodex* mites by targeting parasite-specific γ-aminobutyric acid–chloride ion channels.

TP-03 was evaluated in 2 pivotal clinical studies: Saturn-1 (phase 2b/3) and Saturn-2 (phase 3).[57,58] All prespecified primary and secondary end points were met according to statistically significant improvements observed in the TP-03 group vs the control group, including the primary end point of complete collarette cure, defined as ≤ 2 collarettes ($P < .0001$). Secondary end points included mite eradication ($P < .0001$), a composite of lid erythema and collarette complete cure ($P < .0001$). TP-03 was well tolerated, and all ocular adverse events were mild in severity. A New Drug Application was accepted, and a Prescription Drug User Fee Act target date is set for August 25, 2023.[59]

AXR-270

AXR-270 is a selective glucocorticoid receptor agonist in development for moderate to severe DED associated with MGD.[60] AXR-270 is a topical cream intended for application to the eyelids once daily. In a phase 2 study, AXR-270 improved the signs and symptoms of MGD and was well tolerated.

CBT-006

CBT-006 is a topical formulation of cyclodextrin under development for the treatment of MGD associated with DED.[61] CBT-006 sequesters cholesterol and dissolves lipid deposits at the orifices of the meibomian glands. A phase 2 study was conducted to evaluate topical administration of CBT-006 3 times daily for 3 months. Safety and efficacy data were not available at the time of this publication.

Expert Discussion: Future Considerations in the Treatment of Meibomian Gland Dysfunction

Dr Karpecki: What are your thoughts on the new treatments under development for MGD and evaporative dry eye disease, some of which may be available as early as August 2023?

Dr Nichols: It is exciting that we will have more choices for the treatment of MGD. Each of these clinical candidates has its own unique mechanism of action. There are going to be questions regarding which treatment to use first and payment issues, but the data look really strong.

Dr Bloomenstein: The TP-03 (lotilaner) product is interesting in that it will let us see how eradication of the *Demodex* mites correlates with improvements in our patients with MGD. I also think AXR-270 has the potential to break down the keratin and get the meibomian glands to open up and improve expression. It will be exciting to see what these medications teach us about our patients and MGD.

Dr Mastrota: Modifying keratinization may be beneficial for a number of reasons. The lid margins and the gland ductal system respond to many stimuli, with a tendency to increase keratinization.

It is interesting that NOV03 does not need a preservative because it is water free and has only 1 ingredient in the formulation.[48] Most therapeutic agents are combinations of many ingredients, which can make it difficult to determine allergy issues or other reactions.

Dr Nichols: We will have to see how the expression of the meibomian glands and the quality of meibum are affected by these upcoming medications because some of the study end points in the clinical trials are designed according to dry eye characteristics, such as symptoms and ocular surface staining.

Dr Karpecki: These treatment approaches are novel and could stir up a lot of interest with an MGD or dry eye with MGD indication. A differentiated product may help payers recognize that there are different mechanisms we need to use to treat this disease.

Case-Based Discussions

Case 1: Cataract Surgery With Meibomian Gland Dysfunction

From the Files of Marc Bloomenstein, OD

A 67-year-old male presented with concerns about quality of vision, stating that his vision was blurred and fluctuated. The patient also had concerns of excess tearing, stating that he "cries all the time". Medical history indicated 15 years of diet-controlled non–insulin-dependent diabetes. The patient had no known allergies. He had a history of skin lesion removed from the cheek.

Findings on examination included the following:

- Visual acuity: 20/30 (pinhole 20/20) OD, 20/100 (pinhole 20/70) OS
- Slitlamp examination:
  - Lids: 1+ inspissated glands/turbid expression
  - Trace guttata OU
  - Mild pigment on endothelium OU
  - 1/2+ nuclear sclerotic cataract/trace posterior subcapsular cataract (PSC) OD
  - 2+ nuclear sclerotic cataract/2+ PSC OS

Cataracts were identified in both eyes **(Figure 6)**. Best-corrected visual acuity was reduced, and inspissated meibomian glands and turbid secretions were observed after expressing the glands. There was brunescence in the right eye, and PSC visible in the left eye.

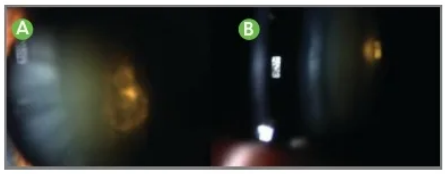

Figure 6. The patient in Case 1 presented with cataracts in both the right (A) and left (B) eyes

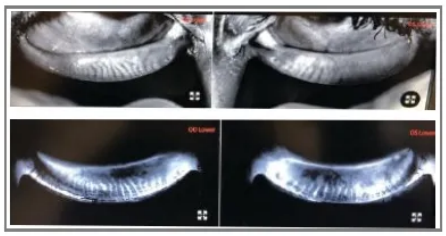

Figure 7. Meibography images were captured of lower lids of right and left eyes of the patient in Case 1 using a LipiScan device

Additional testing was conducted prior to recommending cataract surgery to the patient, with the following results:

- TBUT: 3 seconds OD, 5 seconds OS
- Meibomian Gland Secretion score: 8/45 OD, 3/45 OS
- Schirmer score (with anesthesia): 12 mm/10 minutes OD, 16 mm/10 minutes OS

A LipiScan was performed to visualize the meibomian glands. Significant atrophy was noted in the meibography images **(Figure 7)**. A thermal treatment was performed, and a low-dose topical steroid was prescribed. A-scans were delayed until follow-up.

The patient reported that his vision was more stable at the follow-up visit and felt that his eyelids looked better. Based on the improvement following treatment of the MGD, A-scans were conducted, and the patient was then scheduled for cataract surgery.

Case 2: Postmenopausal Contact Lens Wearer With Meibomian Gland Dysfunction

From the Files of Kelly K. Nichols, OD, MPH, PhD, FAAO

A 53-year-old postmenopausal female presented with concerns regarding her contact lens wear, stating, "I can wear my contacts all day, but they get foggy and less comfortable in the evening." Multifocal daily disposable lenses were used successfully for 1+ years; she previously used monthly disposable multifocal lenses. The patient did not currently use artificial tears or prescription topical medications. She had previously tried cyclosporine and lifitegrast. LipiFlow thermal pulsation therapy was performed 2 years ago. She had no other significant ocular or systemic health history.

Findings on examination included the following:

- Visual acuity: 20/20 OD distance, 20/25 near (-0.75 cyl); 20/25 OS distance, 20/20 near (-1.00 cyl)
- Slitlamp examination
  - Lids: Makeup on eyelashes OU, no collarettes
- Meibomian gland expression: G2 (hazy/turbid) meibum secretion OD, G2 (hazy/turbid) meibum secretion OS
- Contact lens fit: Adequate, minimal movement
- OSDI: 14 (wind/arid/vision/impacts)
- TBUT: 6 seconds OD, 4 seconds OS
- Tear meniscus height: 0.2 mm OD, 0.2 mm OS
- Matrix metalloproteinase-9: Mild positive OU
- Schirmer test (without anesthesia): 9 mm/5 minutes OD, 10 mm/5 minutes OS
- Meibograph: OD 25% loss upper, OD 25% loss lower, OS 25% loss upper, OS 25% loss lower **(Figure 8)**

The following additional test results were obtained **(Figure 9)**:

- Fluorescein staining: Grade 1, inferior cornea OU
- Lissamine green staining: Grade 2, nasal conjunctiva OU
- Lid wiper epitheliopathy: Grade 2, superior OU

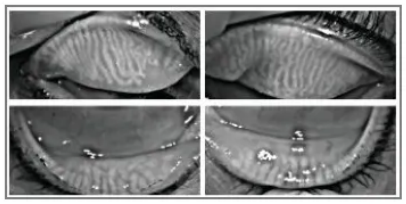

Figure 8. Meibography images of the upper and lower lids of the patient in Case 2 indicated mild gland dropout in both eyes

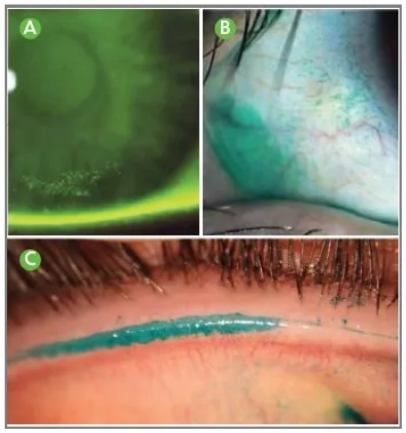

Figure 9. Mild corneal staining in the inferior cornea (A), moderate conjunctival staining in the nasal region (B), and moderate lid wiper epitheliopathy (C) of the patient in Case 2

A management plan was initiated, including maintaining her current contact lenses. Reading glasses (+1.00) for use with computer tasks over contact lens wear, oral omega-3 fatty acid supplements (once daily), and varenicline solution nasal spray (twice daily) were suggested. In-office warming/expression of the eyelids and lid debridement were also recommended. IPL therapy may also be beneficial for this patient.

Dr Karpecki: Often, we may not ask contact lens patients the right questions for MGD or evaporative dry eye. This case is a good example illustrating that clinicians need to look more closely for MGD and manage the condition. Getting at those details, such as uncomfortable lens wear or foggy vision at the end of the day, is important for an accurate diagnosis.

Dr Bloomenstein: Patients want to stay in their contact lenses. Offering a management plan to patients with MGD can enable this option.

Clinical Pearls

- **Expressing healthy meibum to help maintain quality tears directly correlates with quality vision. Look for MGD on every visit to help patients get the best quality of vision.**
- **Look closely at the eyelids for everything from telangiectasia to collarettes and debris. Note any thickening of the lids and capped glands, and then express the glands in the nasal to central area of the lids.**
- **Know who you can refer to within your local optometric community for additional diagnostic testing and in-office procedures to help patients in a stepwise management plan**

Complete the CE posttest online at
https://tinyurl.com/connectingmgd2ded

Imaging and Diagnostic Pearls

Katherine M. Mastrota, OD, MS, EMBA, FAAO, Diplomate ABO

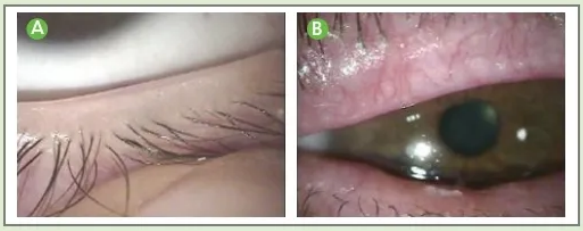

Figure 1. (A) Normal eyelid margin. (B) Eyelid margin with ocular rosacea and meibomian gland dysfunction. Note telangiectasia, loss of lid margin contour, eyelash/lid margin debris, meibomian gland orifice placement irregularity, and watery tear film in the rosacea-impacted eyelid.

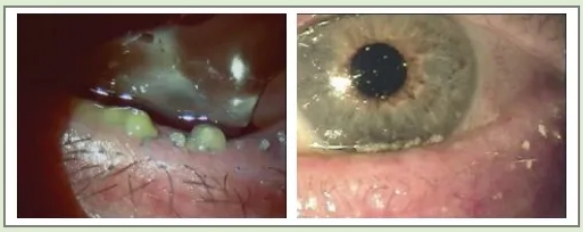

Figure 2. Abnormal lipid composition from the meibomian glands leads to orifice plugging, breakdown into inflammatory components via bacterial lipases, and contributes to *Demodex* infestation

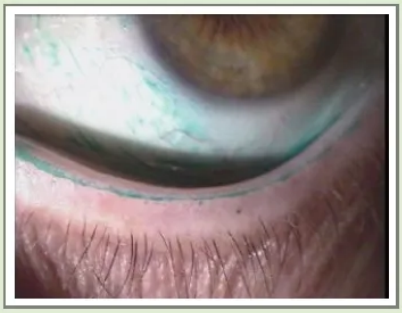

Figure 3. Line of Marx, stained with lissamine green, is an important landmark of the lid margin. In normal patients, the line of Marx lies posterior to the meibomian gland orifices.[1] As meibomian gland dysfunction progresses, it can be seen at the line of the meibomian glands or more anteriorly.

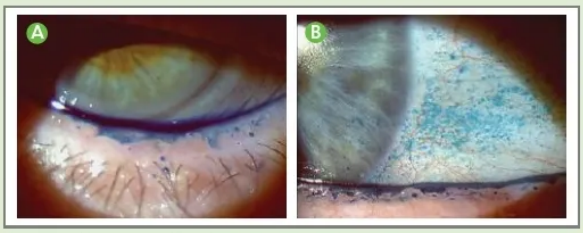

Figure 4. Changes in the Marx line location/staining pattern can occur in ocular surface disease. Abnormalities seen are "teary dry eye", characteristic of tear lipid dysfunction (A), and scant tear film aqueous deficient dry eye (B). Note the irregularity of the lid margin in both images.

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1. The reported prevalence of MGD:
   a. Has been increasing over the past decade to approximately 80%
   b. Is difficult to estimate and varies widely from 3.5% to 70%
   c. Has been decreasing over the past decade to approximately 2%
   d. Is difficult to measure and varies from 75% to 85%

2. MGD has a high degree of overlap with DED and _____.
   a. Choroideremia
   b. Uveitis
   c. Rosacea
   d. Pemphigus

3. A primary pathophysiologic feature of MGD is:
   a. Lateral duct obstruction and alteration of proteins
   b. Hyperkeratinization of the ductal epithelium
   c. Alteration of secretions in the upper eyelid margin
   d. Decreased osmolarity of tears and nerve stimulation

4. Which of the following is commonly associated with chronic obstruction of meibomian gland orifices?
   a. TBUT > 10 seconds
   b. Gland dropout
   c. Conjunctival cysts
   d. Tear osmolarity of 298 mOsm/L

5. If a patient is suspected of having MGD, which assessments can be used to confirm a diagnosis?
   a. Examination of the eyelid characteristics, expression of the meibomian glands, evaluation of TBUT, and corneal staining
   b. Examination of the conjunctiva, expression of the meibomian glands, and measurement of intraocular pressure
   c. Allergen sensitivity testing, corneal staining, and Schirmer tear test
   d. Visual acuity testing, using a questionnaire to assess symptoms, and slitlamp examination of the iris and lens

6. Patients with ocular rosacea and MGD often present with:
   a. Telangiectasia
   b. Eyelash/Lid margin debris
   c. Loss of lid margin contour
   d. All the above

7. A 38-year-old female complains of discomfort while wearing contact lenses and difficulty using her computer for long periods of time, and frequently uses artificial tears with minimal success. She has tattooed eyeliner, rosacea treated with metronidazole, and insomnia for which she takes melatonin, and wears false lashes. Which of the following is her strongest risk factor for MGD?
   a. Computer use
   b. Artificial tears
   c. Tattooed eyelids
   d. Melatonin use

8. What approach was recommended by the 2011 TFOS International Workshop on Meibomian Gland Dysfunction for developing a management plan for patients with MGD?
   a. An aggressive approach, selecting intensive therapy options from each treatment modality to use as a first-line management plan
   b. A limited approach, beginning with the least invasive treatment options and waiting at least 6 months before adding an additional therapy to the management plan
   c. A staggered approach, rotating patients on and off treatments, including drug holidays, to try the most wide-ranging options
   d. A stepwise approach, beginning with basic therapies that are likely to benefit most patients, followed by more specific treatments based on a patient's severity and response

9. Current treatment options recommended for patients with MGD include the following:
   a. Lid hygiene, warm compresses/thermal pulsation, topical lubricants, anti-inflammatory medications
   b. Lid hygiene, warm compresses/thermal pulsation, topical lubricants, prostaglandin medications
   c. Lid hygiene, warm compresses/thermal pulsation, topical allergy medications, anti-inflammatory medications
   d. Lid hygiene, warm compresses/thermal pulsation, beta blockers, anti-inflammatory medications

10. The phase 3 GOBI and MOJAVE trials evaluated NOV03 (perfluorohexyloctane) for DED associated with MGD. Both studies showed significant improvement in _____ after 8 weeks.
    a. Corneal sensitivity
    b. Meibomian gland score
    c. Ocular dryness
    d. Tear osmolarity

11. AZR-MD-001 (selenium sulfide) ointment significantly improved meibomian gland scores and Meibomian Glands Yielding Liquid Secretion scores in patients with MGD and associated DED at ___ months compared with controls.
    a. 3
    b. 6
    c. 9
    d. 12

12. TP-03 (lotilaner) is being studied to treat _____ blepharitis, which is associated with MGD-DED.
    a. Acute viral
    b. *Demodex*
    c. Ulcerative
    d. Staphylococcal

13. What percentage of patients in the GOBI trial of NOV03 (perfluorohexyloctane) experienced eye discharge and/or eye pain?
    a. 0.3%
    b. 1.3%
    c. 3.1%
    d. 13%

14. A 64-year-old female complains of ocular discomfort and fluctuating vision while working on the computer. She has mild thickening of the meibum and limited corneal fluorescein staining. Which is the most appropriate initial treatment plan for this patient?
    a. Lid hygiene and warm compresses at home, topical artificial lubricants, and oral steroids
    b. Lid hygiene and warm compresses at home, bandage contact lenses, and omega fatty acid supplements
    c. Lid hygiene and warm compresses at home, intranasal steroids, and omega fatty acid supplements
    d. Lid hygiene and warm compresses at home, topical lubricant drops, and omega fatty acid supplements

15. DED is often the result of altered secretions of meibum, which has a negative effect on the ____ layer of the tear film and increases evaporation.
    a. Inner
    b. Middle
    c. Outer
    d. Composite