

Meibomian gland dysfunction

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“The mere formulation of a problem is far more essential than its solution ... To raise new questions, new possibilities, to regard old problems from a new angle requires creative imagination and marks real advances in science.”

—Albert Einstein

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Over the last several decades, we have developed a greater understanding of the tear film and ocular surface disease and a higher level of appreciation of the tear film’s impact on all aspects of ocular health, be it surgical outcomes or day-to-day visual performance. We owe in large part this elevated level of awareness on the topic to the collaborative and invaluable work of the Tear Film and Ocular Surface Society (TFOS, www.tearfilm.org). TFOS was incorporated in 2000 as a non-profit international organization “committed to advancing the research, literacy and educational aspects of the scientific field of the tear film and ocular surface.” Its members have been involved with innumerable collaborative research projects, educational symposia, and peer-reviewed publications. They sponsored the 2007 International Dry Eye Workshop (DEWS) comprised of an international team of experts who gathered over a 3-year period and published an evidence-based review of classification, epidemiology, diagnosis, and management of dry eye disease.¹ The DEWS report highlighted the importance of inflammation in the development of dry eye disease. In that publication, they also offered a road map for developing further research and understanding of the ocular surface and tear film.²

It was emphasized that it is the interplay between the three layers of the tear that allows for most optimal ocular surface health and visual performance. The meibomian glands producing the lipid layer, the lacrimal glands as the source for aqueous tear and vital proteins, and the goblet cells producing the mucin layer are all critical and interact with each other in maintaining a healthy tear film, corneal and conjunctival anatomy. With that said and with the understanding that meibomian gland dysfunction is “underestimated and very likely the most common cause of dry eye disease,” TFOS launched the International Workshop on Meibomian Gland Dysfunction.³⁻¹¹ This MG Workshop was created with the intention to “develop a consensus understanding of the meibomian gland in health and disease” and to “disseminate the knowledge broadly to further the field” through an evidence-based critical evaluation of contemporary science and knowledge.³

Through the sponsorship of TFOS and unrestricted industry grants, more than 50 international experts on the topic of tear and meibomian gland dysfunction gathered and deliberated over a 2-year period. A steering committee led by Kelly Nichols, Ph.D., and Gary Foulks, M.D., created seven subcommittees

to focus on subject categories of interest: definition and classification of MGD; anatomy, physiology, and pathophysiology of MGD; tear film lipids and lipid-protein interactions in health and disease; epidemiology and associated risk factors for MGD;

diagnosis of MGD; management and therapy of MGD; and clinical trials and recommendations for future research. These subcommittees created a thorough summary of all pertinent peer-reviewed research and publications on their assigned topic, which

was then critically evaluated by all members of the Workshop. Their work has culminated in the recently published special issue of *Investigative Ophthalmology and Visual Science (IOVS)*⁴ likely to be widely read and referenced on this important topic

Table 1. Specialized and non-specialized tests for MGD and MGD-related disease⁹

Testing category	Specific test(s)	Tests for a general clinic	Tests for a specialized unit
Symptoms			
	Questionnaires	McMonnies, Schein, OSDI, DEQ, OCI, SPEED, and others	McMonnies, Schein, OSDI, DEQ, OCI, SPEED, and others
Signs			
Meibomian function	Lid morphology	Slit lamp microscopy	Slit lamp microscopy, confocal microscopy
	Meibomian gland mass		Meibography
	Gland expressibility, expressed oil quality and volume	Slit lamp microscopy	Slit lamp microscopy
	Lid margin reservoir		Meibometry
	Tear film lipid layer, thickness, spread time, spread rate	Interferometry, slit lamp	Interferometry, slit lamp, video interferometry
Evaporation tears	Evaporimetry		Evaporimetry
Osmolarity	Osmolarity	TearLab device, other	TearLab device, other
Stability	Tear film	TFBUT, ocular protection index	TFBUT, ocular protection index
	Tear film lipid layer	Spread time	Interferometry, spread rate, pattern
Indices of volume and secretion	Tear secretion	Schirmer 1	Fluorophotometry/fluorescein clearance rate
	Tear volume	Not available	Volume by fluorophotometry
	Tear volume	Meniscus height	Meniscus radius of curvature, meniscometry
	Tear clearance	Tear film index	Tear film index
Ocular surface	Ocular surface staining	Oxford scheme, NEI/industry scheme	Oxford scheme, NEI/industry scheme
Inflammation	Biomarkers		Flow cytometry, bead arrays, microarrays, mass spectrometry, cytokines and other mediators, interleukins, matrix metalloproteinases

of interest for ophthalmic clinicians and scientists alike. This report has the potential to encourage a more standardized approach to treating dry eyes and MG dysfunction and in turn optimize the health of the ocular surface. As members of the ASCRS cornea clinical committee, we applaud and praise the work of TFOS and the MG Workshop and have summarized what we feel are the essential points of each subcommittee report. Ocular surface disease is the most common reason patients visit an eyecare professional and impacts greatly on quality of vision and surgical outcomes. We hope that this will encourage colleagues to reference and read the special *IOVS* issue written by the TFOS-sponsored International Workshop on MG dysfunction.

1. Definition and classification of MGD⁵

The recommended definition by the subcommittee is: *“Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretions. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.”*⁵

It became clear early in the meetings that there is a lack of consensus regarding terminology used describing meibomian gland dysfunction (MGD). Posterior blepharitis, meibomian gland disease, meibomian gland dysfunction, meibomitis, and meibomianitis have all been used interchangeably in literature and in practice. To most clearly define MGD is the first step in standardizing the approach to diagnosis

and treatment. Posterior blepharitis can indeed occur as a result of MGD, but one can have MGD without frank inflammation of the posterior lid margin. In its early phase, MGD could be demonstrated simply by an alteration of the meibomian gland secretions with abnormal quality of the expressant or by decreased or absent expressibility. As the dysfunction progresses, inflammation may indeed occur with related changes such as vascularization of the posterior lid margin. Meibomian gland dysfunction and not disease is the preferred terminology as it is the *function* of the meibomian gland that helps define the condition and can lead to tear film instability, as an example often evidenced by rapid evaporation and related symptoms.

The classification of meibomian gland dysfunction based on pathophysiology is also described with two main subcategories: low delivery and high delivery (Figure 1). Low delivery can occur as a result of hyposecretion or obstruction of the glands. Obstructive MGD, as a result of terminal gland obstruction or altered secretions, is thought to be the “most common form of MGD.” Evaporative dry eye is ultimately the consequence of meibomian gland dysfunction in which the quality and/or quantity of the protective lipid top layer of the tear film is compromised.

2. Anatomy, physiology, and pathophysiology of MGD⁶

The meibomian glands are sebaceous glands in the tarsal plates of the upper and lower lids, more densely populating the upper lid than the lower. The glands produce lipids and proteins that are spread onto the tear film, protecting

against evaporation and helping with tear film stability. The terminal excretory ducts of the meibomian glands open at the posterior lid margin and deliver the meibum onto the tear film with muscular contraction of the lids.

As described above, the most common reason for MGD is terminal duct obstruction as a result of thickened opaque meibum or hyperkeratinization of the ductal system. This may occur in the setting of acne rosacea, hormonal changes, contact lens use, advancing age, or medications. Deficiency of the tear film lipid layer causes symptoms due to tear film instability, increased evaporation, hyperosmolarity, bacterial overgrowth, and ocular surface inflammation and damage.

3. Tear film lipids and lipid-protein interactions in health and disease⁷

This subcommittee’s goal was to understand and summarize the current knowledge of the molecular components of the tear film and the meibomian gland’s contribution to the tear film lipid in health and disease. A model of the tear film is described with the lipid top layer consisting of two forms of lipid: a non-polar hydrophobic top layer and an inner polar hydrophilic layer consisting of very long chain fatty acids. This inner hydrophilic lipid layer may act as a surfactant stabilizing the surface tension between the lipid top layer and the aqueous layer of the tear film. Proteins, whether intercalated or associated with the lipid layer, also play an important role in the healthy tear film.

Meibum lipid changes in disease are varied and not understood in

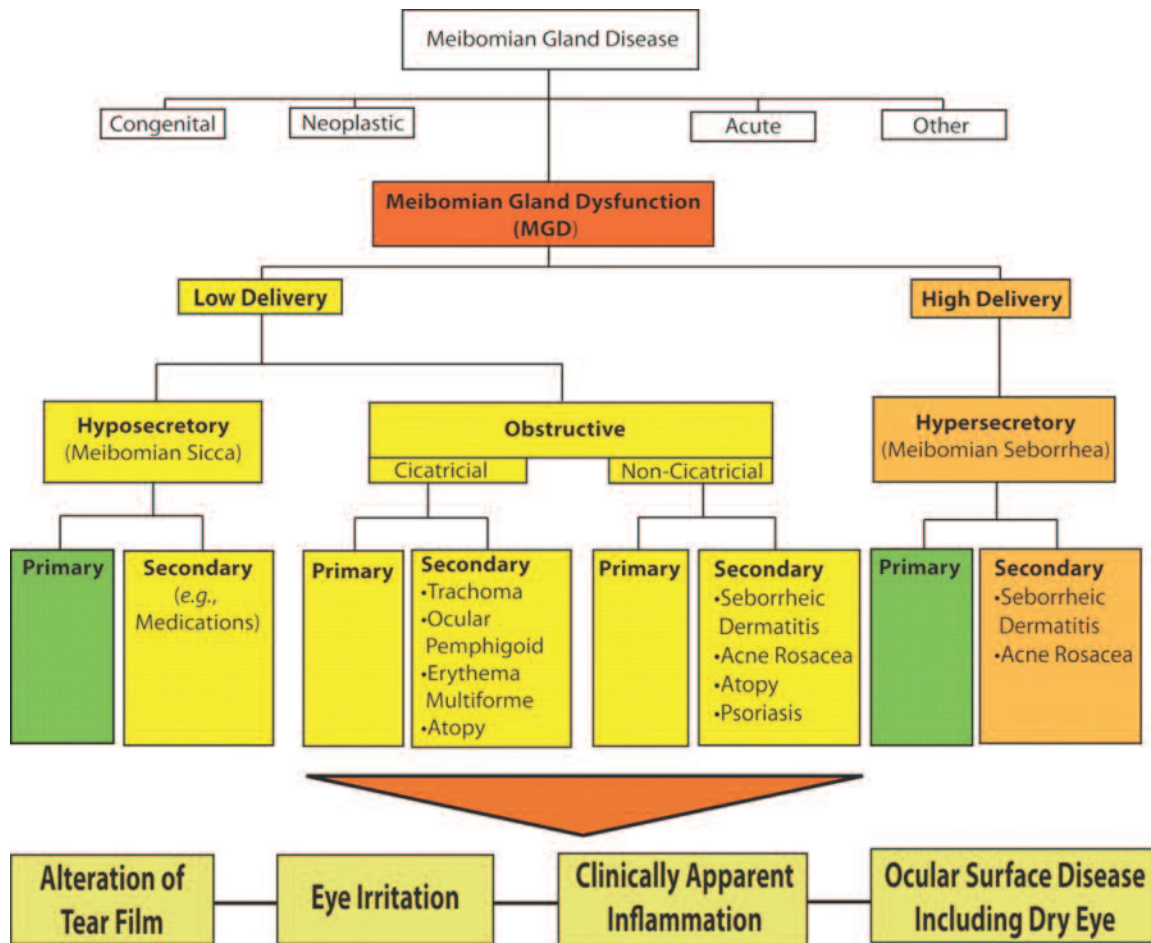


Figure 1. Classification of MGD as described by the TFOS International Workshop on MGD⁵

their full spectrum. There indeed are differences in lipid composition seen in conditions resulting in MGD. As an example, meibomian seborrhea often occurs in the setting of an overgrowth of coagulase-negative *Staphylococcus* strains on the lid margin capable of hydrolyzing cholesteryl oleate. Analysis of lipid components in patients with MGD generally shows a significant decrease in triglycerides, cholesterol, and monounsaturated fatty acids. This in turn increases the melting point resulting in more viscous meibum. The altered fatty acids result in a more rapid evaporation of the tear film, hyperosmolarity, and activation of an inflammatory re-

sponse that can damage the ocular surface. Also, lipases produced by bacteria residing at the lid margin often seen in rosacea patients can disrupt the lipid layer and activate this cascade.

It is also apparent that a healthy lipid profile in the meibum is necessary for contact lens tolerance. Ironically though, long-term contact lens wear may result in meibomian gland atrophy and/or dropout and hyposecretion of meibum. There is a great deal of work done trying to determine factors that may lead to contact lens intolerance. An interesting finding was that tear film stability is decreased in those intolerant of con-

tact lenses as compared to contact lens tolerant individuals even though the number of blocked meibomian glands was equal between the two groups. Indeed the functional quality and not the quantity of the meibum are compromised in these cases.

4. Epidemiology and associated risk factors for MGD⁸

The etiology of meibomian gland dysfunction as has been discussed above differs from aqueous-deficient dry eye, which occurs due to insufficient or poor quality lacrimal gland secretions. Aqueous deficient dry eye syndrome often does coexist with evaporative dry eyes as a result

of MGD, and symptoms related to the two frequently overlap with patients complaining of ocular irritation and visual disturbance whether or not they have combined disease. Epidemiological studies of MGD have been limited due to the lack of consensus on definition, classification, and methods of assessment of MGD. Objective approaches include biochemical analysis of the meibomian glands and the secretions using assays and spectroscopy. Other objective assessments evaluate the function of the lipid layer such as assessing the rate of evaporation of the tear film using evaporimetry. Subjective measures include clinician- or examiner-derived assessment such as biomicroscopic evaluation and grading of the quality and quantity of the tear film and the degree of visible abnormalities in the meibomian glands and orifices. There are also subjective patient-reported symptoms that can help in assessing MGD. Given the degree of overlap in symptoms related to MGD as compared to anterior blepharitis and aqueous-deficient dry eyes, defining MGD based on patient-reported symptoms and signs is limited. It is advocated to adopt a correlative approach evaluating MGD in which results from symptomatic assessment, clinical evaluation, and purely objective measurements of disease are combined in studying and defining the disease.

MGD is believed to be highly prevalent with a wide range of 3.5% to 70% in published reports. The prevalence appears to be highest in Asian populations at nearly 70% in contrast to 3.5% and 19.9% in two studies with Caucasian ethnicity of their subjects. Direct comparisons

cannot be made between most of the studies as clinical signs and symptoms assessed and used to define MGD differed between the studies, as did the demographics and related risk factors of the patients. Risk factors hypothesized to correlate with MGD, some more strongly than others, include anterior or posterior blepharitis, contact lens wear, *Demodex folliculorum*, aging, androgen deficiency, atopy, menopause, rosacea, and some systemic medications such as isotretinoin and anti-androgens.

In evaluating the current available evidence, it became apparent that there are a paucity of studies evaluating the occurrence of new onset MGD, the relationship between objective findings of abnormal meibomian gland function and presence of symptoms, and the natural history of MGD and associated risk factors.

5. Diagnosis of MGD⁹

Diagnostic modalities used in determining MGD and related ocular surface disease are based on demonstrating abnormal anatomy or activity of the glands, abnormal tear film lipid layer, and compromised health of the ocular surface including cornea, conjunctiva, and lids. Symptom assessment is an important part of determining presence of disease, but currently available symptom questionnaires do not help in differentiating MGD-related evaporative versus aqueous-deficient dry eye syndromes. Further studies are encouraged to help to distinguish subjective indicators of each subset of disease. Clinical signs of MGD such as “meibomian gland dropout,” “altered meibomian gland secretions,” “changes in lid morphology,” or

“plugging of the meibomian gland orifices” are more clearly described in association with MGD and used in establishing a grading scale that can be applied to clinical practice.

This subcommittee has subdivided the utility of currently available diagnostic tests both in the general and specialized clinic. Recommendations are made on how to practically approach diagnosing this very common condition with a sequential set of tests such that a consistent approach could be adopted (Table 1). It is recommended to initiate the evaluation by administering an established symptom questionnaire (i.e., the Ocular Surface Disease Index or the Dry Eye Questionnaire), followed by measuring the blink rate, the lower tear meniscus height, tear osmolarity (if testing available), tear film breakup time (TFBUT), and fluorescein or lissamine green staining of the ocular surface. Schirmer’s testing and/or tear meniscus height measurement may help in determining presence of aqueous deficient dry eye alone or, as more commonly seen, concurrently with MGD. At the end of this practical diagnostic sequence, MGD can be characterized by qualifying morphologic lid features, expressing meibum to evaluate its expressibility and quality, and quantifying meibomian gland drop out. If testing and symptoms suggest the presence of “dry eyes” but the tear volume (tear meniscus) and tear flow are normal, then “an evaporative dry eye is implied and quantification of the MGD will indicate the meibomian gland contribution” to the condition. Using a grading scale for each test can help monitor progress and treatment response.

Table 2. Summary of the treatment algorithm as recommended by the TFOS International Workshop on MGD¹⁰

Stage	Clinical description	Treatment
1	No symptoms of ocular discomfort, itching, or photophobia. + Clinical signs of MGD based on gland expression No ocular surface staining	<ul style="list-style-type: none"> • Inform patient about MGD • Discuss diet modification, environmental influences, etc. • Eyelid hygiene • Warming/expression as described below (±)
2	Minimal/mild symptoms of ocular discomfort, itching, or photophobia Minimal to mild MGD clinical signs (scattered lid margin features with mildly altered secretions) None to limited ocular surface staining	<ul style="list-style-type: none"> • Improve environmental influences • Increase dietary omega-3 fatty acid intake • Eyelid hygiene and warming (minimum of 4 minutes, once or twice a day) followed by massage and expression of MG secretions <p>All the above, plus (±)</p> <ul style="list-style-type: none"> • Artificial lubricants (for frequent use, non-preserved preferred) • Topical azithromycin • Topical emollient lubricant or liposomal spray • Consider oral tetracycline derivatives
3	Moderate symptoms of ocular discomfort, itching, or photophobia Moderate MGD clinical signs (increased lid margin features of plugging/vascularity and moderately altered secretions) Conjunctival and peripheral corneal staining , often inferior	<p>All the above treatments, plus</p> <ul style="list-style-type: none"> • 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 (increased lid margin features with MG dropout/displacement and severely altered secretions) Increased conjunctival and corneal staining , including central staining. Increased signs of inflammation: ≥moderate conjunctival hyperemia, phlyctenules	<p>All the above, plus anti-inflammatory therapy for dry eye (+)</p>
“Plus” disease	Specific conditions occurring at any stage and requiring treatment. May be causal of, or secondary to, MGD or may occur incidentally	
	1. Exacerbated inflammatory ocular surface disease	1. Pulsed soft steroid as indicated
	2. Mucosal keratinization	2. Bandage contact lens/scleral contact lens
	3. Phlyctenular keratitis	3. Steroid therapy
	4. Trichiasis (e.g., in cicatricial conjunctivitis, ocular cicatricial pemphigoid)	4. Epilation, cryotherapy
	5. Chalazion	5. Intralesional steroid or excision
	6. Anterior blepharitis	6. Topical antibiotic or antibiotic/steroid
	7. Demodex-related anterior blepharitis, with cylindrical dandruff	7. Tea tree oil scrubs

6. Management and treatment of meibomian gland dysfunction¹⁰

The subcommittee on management and treatment of MGD had the challenge of reviewing traditionally advocated and current practice patterns and all published reports on treatment of MGD. As a result of their extensive and critical evaluation of available evidence for each treatment option, a new algorithm for treatment is presented (Table 2). Their evidence-based recommendations, if implemented in clinical practice, have the potential to cause a paradigm shift in the way we treat meibomian gland dysfunction and in turn help optimize the health of the ocular surface and improve our patients' quality of life.

The treatment algorithm makes recommendations based on clinically evident disease, in both asymptomatic and symptomatic patients. It highlights some traditional approaches such as eyelid warming and expression of the MG secretions as well as increasing dietary omega-3 fatty acids in all cases of MGD. Topical azithromycin with its unique antimicrobial, anti-inflammatory, and lipid-modulating properties is recommended as first-line pharmaceutical treatment for mild, moderate, and severe meibomian gland dysfunction. For moderately symptomatic MGD, it is advised to add anti-inflammatory therapy and possibly oral tetracyclines (minocycline, doxycycline, and rarely tetracycline) to the regimen of topical azithromycin and conservative measures for optimal response. Women in reproductive age need to be advised of the potential contraindication of tetracycline-type antibiotic use during pregnancy. This is summarized in Table 2.

7. Clinical trials and recommendations for future research¹¹

In reviewing clinical trials on the topic of MGD, the members of the subcommittee were faced with the challenge of comparing trial results when, in fact, direct comparison could not be made easily as there was no general consensus in methodology, terminology, or objective measures used in assessing MGD. There were 26 papers published on results of clinical trials involving MGD. In evaluating these papers, the members of this subcommittee have made recommendations on optimizing our research approach in evaluating MGD in the future. They recommend studies on distinguishing and evaluating the association between MGD and dry eye disease. They also suggest developing more standardized, reproducible approaches of assessing and testing MGD.

Conclusion

The current knowledge on the topic of meibomian gland dysfunction is undoubtedly far greater and more advanced than it had been a decade ago, but there are deficiencies and renewed hunger for more knowledge in understanding the pathophysiology, diagnosing and categorizing the dysfunction, and optimizing our treatment and management of this very common ocular condition. We are grateful for the efforts of the TFOS Society and the International Workshop on Meibomian Gland Dysfunction and the impact their work will undoubtedly make on the way we approach and treat our patients with ocular surface disease.

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