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Meibomian gland disease: the role of gland dysfunction in dry eye disease

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Abstract

Meibomian gland dysfunction (MGD) is an umbrella term that encompasses several meibomian gland disorders, ranging from congenital to acquired. Disruption of meibomian gland function negatively impacts both the quality and quantity of meibum secreted, which in turn affects ocular surface health through changes in tear film composition. Increased tear evaporation, hyperosmolarity, inflammation, and ocular surface damage can subsequently occur. This may cause discomfort, visual disruption, and sensation of dry eye. This review article discusses the pathology, causes, and ocular surface impact of MGD, as well as its relationship to dry eye.

Introduction

The meibomian gland is a type of sebaceous gland with tubulo-acinar structure and holocrine function, located in the superior and inferior tarsal plates.¹ Meibomian glands secrete meibum, a compound made up of polar lipids (phospholipids) and nonpolar lipids (cholesterol, wax esters, cholesterol esters).² Meibum is delivered to the ocular surface where it coats the aqueous layer and provides tear film stability and protects against microbial agents and organic matter. Meibomian gland dysfunction (MGD) is a term used to describe a group of disorders, both congenital and acquired, linked by functional abnormalities of the meibomian glands. MGD can lead to altered tear film composition, ocular surface disease, ocular and eyelid discomfort, and evaporative dry eye.

Pathophysiology of MGD

MGD is traditionally classified by the rate of gland secretion.¹ Low delivery states are defined as those with meibomian gland hyposecretion or obstruction (either cicatricial or

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non-cicatricial), whereas high delivery states are defined as those with meibomian gland hypersecretion. All of these entities are further split into primary and secondary causes; for example, mucus membrane pemphigoid is a secondary cause of obstructive, cicatricial MGD, and seborrheic dermatitis and acne rosacea are secondary causes of both obstructive non-cicatricial and hypersecretory MGD.¹

Within these categories, the most common mechanism for MGD is a low delivery state characterized by gland obstruction. The underlying pathophysiology is reported to be epithelial hyperkeratinization which leads to duct obstruction, meibum stasis, cystic dilation, and eventual disuse acinar atrophy and gland dropout.^{3–5} Newer studies have added to this paradigm and describe meibocyte abnormalities as a contributing mechanism in MGD.^{6,7} Support for the role of the meibocyte in MGD comes from pathophysiologic studies evaluating intrinsic (e.g. aging) and extrinsic (e.g. environmental stress) MGD risk factors on meibocyte differentiation and renewal.

Aging—Aging is a known risk factor for MGD.⁸ With age, meibomian gland acinar epithelial cells atrophy, exhibiting decreased lipid production⁹ and altered meibum composition with changes in neutral and polar lipid profiles.¹⁰ Likely underlying these changes, aged meibomian glands exhibit decreased meibocyte differentiation, decreased meibocyte cell renewal, decreased meibomian gland size, and increased inflammatory cell infiltration, as studied in human and mouse models.^{6,11,12} These changes have been associated with decreased expression of peroxisome proliferator-activated receptor gamma (PPAR γ). PPAR γ is a nuclear receptor protein involved in regulating meibocyte differentiation and lipid biosynthesis, contributing to the formation and function of meibomian glands.¹³ Down regulation of PPAR γ is thought to underlie the decreased meibocyte differentiation and lipid synthesis seen in aging, leading to gland atrophy and a hyposecretory state.^{6,11} Interestingly, hyperkeratinization and gland obstruction were not found to play a role in the development of MGD in this mouse model.⁶

Environmental Stress—Environmental stress also contributes to MGD.^{1,14} Specifically, desiccating stress delivered by low humidity in a mouse model resulted in several meibocyte associated abnormalities including a 3-fold increase in basal acinar cell proliferation, altered meibum protein/lipid ratio, irregular meibocyte differentiation and meibocyte stem cell depletion.⁶ These are likely interconnected; in normal conditions, protein to lipid ratios decrease as meibum travels from the acini to the central duct.⁶ However, this decrease was not observed in mice subjected to desiccating stress, suggesting that the increased cellular proliferation and turnover led to altered meibocyte function and the inability to remove protein from meibum.⁶ In the short term, increased proliferation can result in increased meibum production, with ductal dilation a possible consequence of this phase. In the long term, depletion in the number of functioning meibocytes can occur, with subsequent gland atrophy and hyposecretion.⁶ Additionally, a higher protein/lipid ratio increases the viscosity of meibum with a negative impact on tear film stability.^{15,16}

Stem Cell Renewal—Taken together, these findings suggest that aging and environmental stress eventually lead to the depletion of meibocyte stem cells. Exhaustion of stem cells can

then lead to the loss of acinar meibocytes and meibomian gland dropout seen in MGD. The location and description of meibomian gland stem cells has been debatable; some studies place their location along the central duct while others at the interface between the ductal and acinar basal cells.^{17,18} A recent paper examining several mouse models supported the latter location in the interface between ductal and acinar basal cells.⁶ Furthermore, different stem cell origins were found for different meibomian gland components; acini originated from a single stem cell while ducts originated from progenitor cells of various origins.

Interestingly, a similar correlate has been described in the cornea with aging and stress. Corneal epithelial thickness is in part a measure of the number and regenerative capabilities of limbal epithelial stem cells.¹⁹ Over the course of a lifetime, the eye undergoes many periods of stress, during which time stem cells proliferate and re-establish normal homeostasis. Similar to meibomian glands, with increasing age, the number and proliferative capacity of corneal epithelial stem cells diminishes, leading to an observed decreased epithelial thickness.²⁰

Risk factors for MGD and their potential effect on meibocytes

With the evolving paradigm that meibocyte dysfunction underlies MGD, it becomes apparent that other factors previously associated with MGD can also affect meibocytes including hormones, systemic and topical medications, nutrition, and the ocular microbiome. Meibomian glands can also be altered through external factors such as contact lens wear and be decreased, absent, or replaced in a number of congenital disorders.

Hormonal aspects—Androgen and estrogen receptors are present within meibomian glands, and meibocytes contain the enzymes necessary for the intracrine synthesis and metabolism of sex steroids.^{9,21} Broadly, androgens stimulate meibum secretion and suppress inflammation, while estrogens increase inflammation.²² However, androgens regulate the expression of thousands of genes in human meibomian glands, including pathways involved in lipid dynamics and PPAR signaling.²³ Clinically, MGD has been described in many androgen-depleted states including individuals on anti-androgen agents (treatment of benign prostatic hypertrophy, prostate cancer), individuals with complete androgen insensitivity syndrome, and Sjogren's syndrome.⁹ In all these conditions, alterations in meibomian gland secretion and lipid profiles were observed.^{24–26}

Systemic Medications—Administration of 13-cis-retinoid acid (Accutane, Roche Pharmaceuticals, Switzerland) is associated with severe atrophy of the meibomian glands.²⁷ In hamster models, retinoids caused decreased acinar tissue, thickened ductal epithelium, and reduced mature lipid-laden acinar cells.²⁸ Retinoic acid binds to nuclear receptors, causing changes in gene transcription, which in meibomian glands decreases the volume of acinar tissue and inhibits maturation of lipid-laden meibomian acinar cells.^{28,29} Clinically, these findings have been associated with meibum hyposecretion, effecting evaporation and tear osmolality, leading to dry eye symptoms.²⁹

Topical Medications—Several topical medications have been found to alter meibomian gland function. The use of topical epinephrine caused hyperkeratinization of the duct

epithelium, leading to meibomian gland plugging and dilation.³⁰ Glaucoma medications (e.g. topical beta blockers, prostaglandin analogs, carbonic anhydrase inhibitors) are associated with changes in meibomian gland morphology, including decreased acinar area, acinar density, and homogenous acinar wall morphology.³¹

Dietary Intake—The use of oral fatty acids has been reported to improve dry eye symptom and signs, as well as the expressibility and quality of meibum in MGD.^{32,33} Specifically, the intake of omega-3 fatty acids is associated with alterations in the polar lipid profile and decreases in the saturated fatty acid content of meibomian gland secretions.³⁴ Moreover, supplementation with omegas decreases ocular surface inflammation (as measured by HLA-DR) in patients with dry eye,³⁵ and decreases inflammatory lipid mediator profile in tears.³⁶ Examples of foods potentially rich in omega-3 fatty acids include flaxseed oil, fish oil, and olive oil.³⁴ Moreover, as down regulation of the PPAR pathway is seen in MGD as described above, therapeutically targeting this pathway through agonists such as pharmaceuticals (thiazolidinediones: pioglitazone, troglitazone, and rosiglitazone) or dietary supplements (conjugated linoleic acid [vegetables, fruits, nuts, grains and seeds; linseed oil] or docosahexaenoic acid (DHA) may prove to be beneficial.^{37,38}

Ocular Surface Microbiome—Cholesterol esters present in meibum may stimulate the proliferation of commensal organisms, such as *Staphylococcus aureus*, on the eyelid margin. Such commensal bacteria have lipolytic enzymes that break down neutral fats and esters, releasing glycerides and free fatty acids (polar lipids) into the tear film, altering the composition of meibum.^{21,39} This occurs through the release of bacterial products (e.g. toxins, lipases) in the absence of infection.⁴⁰ The polar lipids can diffuse through the aqueous into the mucin layer, making it hydrophobic.²² This causes the tear film to become unstable. Moreover, the breakdown of triglycerides into free fatty acids can influence hyperkeratinization.^{9,41} Infestation with the Demodex mite has also been associated with MGD, with almost half (46.8%) of MGD patients having Demodex present in one study.⁴² However, as Demodex is also commonly found in the hair follicles of the general population,⁴³ its contribution to MGD is not clear.

Contact Lens Wear—The use of contact lenses is associated with reduced meibomian gland morphology and function. Contact lens wearers have higher degrees of meibomian gland dropout, and the changes seem irreversible.⁴⁴ Moreover, abnormal meibum quality and lid margin abnormalities are positively correlated with the duration of contact lens wear.⁴⁵ While the driving pathophysiology is unknown hypotheses include meibomian gland disruption through mechanical trauma,⁴⁶ plugging due to aggregation of desquamated epithelial cells at gland orifices,⁴⁷ and/or chronic inflammation.⁴⁸

Congenital Decrease—Meibomian glands can be decreased or absent from birth. Congenital absence of glands is seen in Turner syndrome, ectrodactyly with ectodermal dysplasia and cleft-lip and palate (ECC syndrome), and in anhidrotic ectodermal dysplastic syndrome.⁴⁹ Stub-like rudiments can present as yellow streaks on the tarsal conjunctival surface or may be largely absent. The remaining glands are often elongated and enlarged,

with the proximal portion hooked back in a hairpin manner or folded into the horizontal meridian.⁵⁰

Congenital Replacement—Dystichiasis is a congenital disorder in which the meibomian glands are each replaced by eyelashes. This causes meibum deficiency as well as ocular surface trauma due to eyelash misdirection. Dystichiasis can occur secondary to a metaplastic reaction in mucocutaneous disease of the lids or to the autosomal dominant disorder lymphoedema.^{2,51}

Presentation and impact on the ocular surface

Meibomian glands provide key components to the tear film that help maintain a healthy ocular surface. When meibomian glands function correctly, the lipids secreted reduce ocular surface water evaporation and prevent dry eye. When these glands are reduced, absent, or dysfunctional, the impact on the ocular surface can be immense.

Presentation—Clinical signs of MGD are varied and include changes in eyelid morphology, altered secretions, and gland dropout.⁵² Morphological changes are assessed by slit lamp inspection and include meibomian orifice plugging (Figure 1), eyelid margin foaminess (Figure 2), hyperemia/telangiectasias (Figure 3), and changes in orifice position with respect to the muco-cutaneous junction. Meibomian gland secretions are assessed by applying pressure to the eyelid margins and rating the expressibility and texture of the meibum. Normal meibum is clear and easily expressed, while in MGD meibum takes on a more opaque and viscous like form that is difficult to express (Figure 4). Meibomian gland dropout is detected by transillumination through everted eyelids or more accurately, by infrared photography (Figure 5). Not all individuals have all clinical features and in fact, they are often disparate.²¹ For example, blacks rarely have visible eyelid margin telangiectasias but are just as likely as whites to have altered meibum consistency.⁵³

Ocular Surface Signs

Ocular surface damage results from a wide variety of interplaying factors, such as increased tear evaporation, hyperosmolarity, proinflammatory mediators in the tears, and decreased lubrication between the lids and globe.⁵⁴ These may result in irritative symptoms of the ocular surface and eyelids. Many of these ocular signs and symptoms overlap with dry eye disease, and MGD is thought to be a key contributor to evaporative dry eye.⁵⁵

Tear Evaporation—The tear film lipid layer is derived from meibomian glands and functions to prevent water evaporation from the optical surface.⁵⁶ In a rabbit model, meibomian glands were completely occluded by squeezing out their contents and cauterizing the lid margin. A protective film layer subsequently did not form over the eye, and rapid evaporation resulted. Meibum was subsequently smeared over the ocular surface, and the lipid film reformed.⁵⁷ In human studies, patients with obstructive MGD (defined as meibomian gland dropout, poor meibum expression, and lack of signs of inflammation) had increased tear evaporation rates compared to controls as measured by a high-sensitivity microbalance sensor.⁵⁸ The rate of tear evaporation increased proportionally with the

severity of MGD. These studies provide evidence that tear evaporation rates correlate with meibum quality and quantity on the ocular surface.

Tear Osmolarity—Tear hyperosmolarity occurs as a consequence of an increased rate of tear evaporation.^{2,54} In a rabbit model, meibomian gland orifices were closed using light cautery, inducing MGD in the setting of normal lacrimal function. These rabbits were observed over 20 weeks, and increased tear osmolarity, decreased corneal epithelial glycogen levels, and decreased conjunctival goblet cell density were noted.⁵⁹ In a mouse model, hyperosmolar stress via instillation of hyperosmotic saline solution caused ocular surface inflammation via the expression and production of numerous inflammatory cytokines (e.g. TNF-alpha, MMP9, IL-1 β).⁶⁰ In humans, the association between MGD and tear osmolarity (measured via the TearLab instrument, San Diego, CA) is less clear. In 233 most male veterans living in South Florida, mean osmolarity values in the more severely affected eye were lower (300 mOsm/L standard deviation (SD) 17) in those with grade 2 or higher eyelid margin telangiectasias compared to those with normal eyelid vascularity (307 mOsm/L SD 18). Those with a meibum quality grade of 2 or higher had similar mean osmolarity levels (305 mosm/ml SD 16) compared to those with normal meibum quality (306 mosm/ml SD 20).⁵³ These findings need to be interpreted with caution, however, as a single osmolarity measure is less informative than multiple measures, given the dynamic nature of the tear film. Moreover, in the setting of dry eye, intereye variability of osmolarity exists.^{61,62} In humans, large fluctuations in osmolarity values over a short time are a more robust indicator of tear film instability than one static measure.

Ocular Surface Damage—Taken together, abnormal meibum quality and quantity can lead to a decreased tear film lipid layer, tear hyperosmolarity, mechanical irritation through increased friction, and the onset of inflammatory cascades, all of which can lead to ocular surface damage. In humans, patients with MGD (defined as obstruction of meibomian orifices, absence of gland structure, or both) seen in a university-based referral practice in Japan were found to have higher staining with fluorescein and rose bengal compared to patients without MGD.⁶³ In a similar manner, in a population of predominantly male South Florida veterans, those with abnormal meibum quality had higher fluorescein corneal staining scores (2.3 SD 2.3) compared to those with normal meibum quality (1.5 SD 2.1, $p<0.05$).⁵³

Reflex Tearing—Increased tear evaporation causing hyperosmolar surface damage is hypothesized to cause a compensatory, reflex increase in aqueous tear secretion in evaporative dry eye.²² Interestingly, a study in humans demonstrated increased tear production (measured with Schirmer's test) in patients with MGD. This is thought to be due to compensatory reflex tearing in the setting of ocular surface abnormalities and discomfort.⁶³

Ocular Symptoms

In humans, as with other aspects of dry eye, signs of MGD often do not correlate with symptoms of discomfort and in fact, most patients with MGD are asymptomatic.^{64–66} In a study of 619 randomly selected individuals from a population based study in northern China,

21.9% were found to have asymptomatic MGD and 8.6% symptomatic MGD.⁶⁵ This study showed asymptomatic MGD to be twice more common than symptomatic MGD, and that symptomatology did not correlate with the severity of damage to the ocular surface (tear break up time and staining).⁶⁴ In another study of 263 men from the Miami Veterans Affairs eye clinic, no correlations between dry eye signs/symptoms and meibomian gland parameters (meibomian gland quality, orifice plugging, lid vascularity) were established.⁶⁷

However, some patients with MGD do report dry eye symptoms and ocular pain (e.g. foreign-body sensation, photophobia, and conjunctival injection).^{53,63} In one clinic based study of 299 individuals with aqueous and evaporative dry eye, dry eye symptoms (e.g. pain, photophobia, blurry vision, problems with reading/driving/watching TV measured by OSDI) were higher in aqueous and/or evaporative dry eye patients compared to normal controls (normal controls: mean OSDI 5.5; aqueous dry eye: OSDI 26.7; evaporative dry eye: OSDI 39.8; mixed dry eye: OSDI 20.2).⁶⁸

Inflammation likely drives symptoms in some individuals with MGD. Several downstream effects of MGD contribute to inflammation including hyperosmolarity and mechanical friction between the eyelids and globe.⁹ Hyperosmolarity, for example, activates mitogen-activated protein kinases and the nuclear factor-kappa B signaling pathway, leading to the generation of inflammatory cytokines and recruitment of inflammatory cells.^{2,69} A study examining the inflammatory cytokines IL-17 and IL-22 found that they were increased in patients with dry eye and positively correlated with dry eye questionnaire and keratopathy scores.⁷⁰

In addition to ocular symptoms of discomfort/pain, visual acuity and bulbar hyperemia can be manifestations of MGD,² and can occur in the absence or presence of tear abnormalities.²² As the tear film lipid layer provides a smooth optical surface for the cornea,⁵⁶ it is not surprising that alterations in this layer can have implications for visual quality.⁹

The above information is as an overall summary of alterations in lipid composition and behavior in MGD. For a complete discussion, we refer you to the International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Tear Film Lipids and Lipid-Protein Interactions in Health and Disease.⁷¹

Summary

Meibomian glands are important contributors to the maintenance of a healthy ocular surface. MGD is a broad term referring to any functional abnormality of the meibomian glands. Many pathologies can disrupt their function ranging from congenital to acquired causes. Once gland disruption occurs, the quality and quantity of meibum is altered with a negative impact on the ocular surface. Increased tear evaporation, tear hyperosmolarity, increased ocular surface staining, and increased inflammation have all been observed. Symptomatic irritation of the eyelid and globes as well as decreased visual acuity has been reported in some cases.

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Highlights

Meibomian gland obstruction and meibocyte depletion are important components of meibomian gland dysfunction. Many risk factors for MGD influence meibocyte function including aging, desiccating stress, androgen depletion, diet, microbiome alterations, and contact lens wear. MGD leads to changes in meibum quality and quantity that can cause evaporative dry eye and ocular surface disruption, leading to dry eye symptoms in some individuals.

Figure 1.
Slit lamp photograph of meibomian orifice plugging.

Figure 2.
Slit lamp photograph of eyelid margin foaminess.

Figure 3.
Slit lamp photograph of eyelid margin telangiectasias..

Figure 4.
Slit lamp photograph of abnormal meibum which is opaque, viscous, and difficult to express.

Figure 5.
Infrared photography detailing meibomian gland architecture.