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Meibomian Gland Disease

The Role of Gland Dysfunction in Dry Eye Disease

Priyanka Chhadva, MD,[1] *Raquel Goldhardt, MD,*[2,3] *Anat Galor, MD*[2,3]

Topic: To discuss the pathology, causes, and ocular surface impact of meibomian gland disease (MGD), as well as its relationship to dry eye.

Clinical Relevance: MGD is a common disorder with various contributing mechanisms and clinical manifestations. Understanding MGD pathophysiology and its relationship to dry eye is important in order to optimize diagnosis and treatment algorithms.

Methods: A review of current literature was performed to discern MGD in terms of pathophysiology, risk factors, and ocular surface impact, and the relationship to dry eye.

Results: Meibomian gland obstruction and meibocyte depletion are important components of MGD. Many pathologies can disrupt function of meibomian glands, 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, increased inflammation, symptomatic irritation of the eyelid and globes, as well as decreased visual acuity have all been observed.

Conclusion: 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. *Ophthalmology 2017;124:S20-S26 Published by Elsevier on behalf of the American Academy of Ophthalmology*

The meibomian gland is a type of sebaceous gland with tubuloacinar 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 Meibomian Gland Dysfunction

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 noncicatricial), 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 noncicatricial 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 production[9] 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 (PPARγ). PPARγ is a nuclear receptor protein involved in regulating meibocyte differentiation and lipid biosynthesis, contributing to the formation and function of meibomian glands.[13] Downregulation of PPARγ is thought to underlie the decreased meibocyte

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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-to-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-to-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 and 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, whereas 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 Meibomian Gland Dysfunction 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, whereas estrogens increase inflammation.[22] However, androgens regulate the expression of thousands of genes in human meibomian glands, including pathways involved in lipid dynamics and peroxisome proliferator-activated receptor (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 Sjögren 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, Hoffmann-La Roche Limited, Mississauga Ontario, Canada) 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 hyperkeritinization of the duct epithelium, leading to meibomian gland plugging and dilation.[30] Glaucoma medications (e.g., topical β-blockers, prostaglandin analogues, 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 symptoms 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 human leukocyte antigen [HLA-DR]) in