Supplement to November/December 2021 Sponsored by Azura Ophthalmics

CRST
Cataract & Refractive Surgery Today

MILLENNIALEYE

MEIBOMIAN GLAND DYSFUNCTION:

A Dermatologic Perspective


PREEYA GUPTA, MD


LAURA M. PERIMAN, MD


EDWARD LAIN, MD


ERIC D. DONNENFELD, MD


JOHN A. HOVANESIAN, MD


TERRY KIM, MD


SHERI ROWEN, MD, FACS


WILLIAM B. TRATTLER, MD


ELIZABETH YEU, MD


EDWARD HOLLAND, MD

This is a summary of a paper recently published in *Clinical Ophthalmology* by the featured authors.

Meibomian gland dysfunction (MGD) was first named as a key contributor to evaporative dry eye in the first formal attempt to define and classify dry eye in 1995.[1] Despite this initial mention, MGD wasn't clearly defined until 2011 when the International Workshop on Meibomian Gland Dysfunction proposed the following definition: "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 secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease."[2] The significant negative impact of MGD and its high prevalence make it worthwhile to better understand the underlying etiology and pathogenesis (Figure 1).

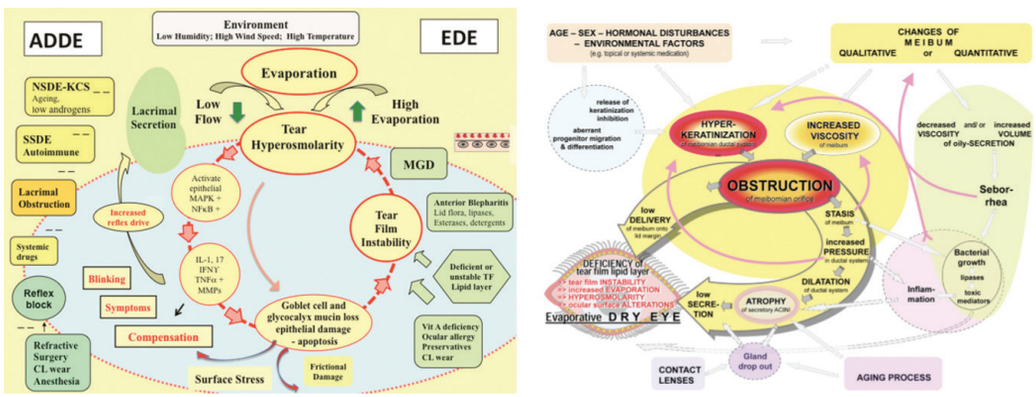

Figure 1. The negative impact of MGD and its high prevalence make it worthwhile to better understand the underlying etiology and pathogenesis.

UNDERSTANDING THE MEIBOMIAN GLAND

An individual meibomian gland consists of multiple acini, which are continuously synthesizing hundreds of different lipids in addition to various proteins and forms of keratin which make up meibum (Figure 2).[3-5] This meibum, moved by the mechanical pressure of blinking, is driven into the central duct of the gland and out of the gland orifice to become a key component of the tear film. The central duct of the meibomian gland is lined with modified keratinized epithelial cells.[6]

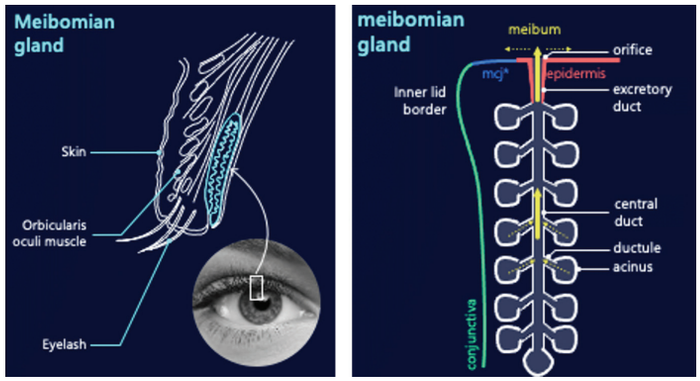

Figure 2. The meibomian gland.

MGD occurs when there are pathological alterations to the quantity and composition of the meibum. This may be an increase in heavier wax and saturated cholesteryl esters, or an alteration of the keratin proteins within the meibum. Incorporation of keratin into the meibum can make it more rigid and unable to incorporate into the lipid layer of the tear film and can raise its melting point so that it is a solid at body temperature.[7-10]

OXIDATIVE STRESS

In healthy tissue, disulfide bonds form between keratin when a single healthy protein has reached its final location. In oxidizing conditions, there is significantly less control in the formation of disulfide bonds that leads to aggregates in uncontrolled locations (Figure 3). Reactive oxygen species that are present in MGD may be promoting this formation of disulfide bonds.[11]

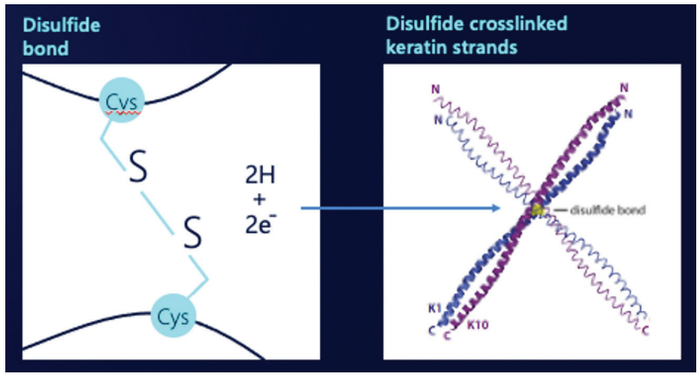

Figure 3. Oxidative stress contributes to the pathology of MGD[11] and the formation of aberrant disulfide bonds.

THE PROCESS OF HYPERKERATINIZATION

Meibomian glands are similar to sebaceous glands, in that they both involve a process that requires continual cell turnover. In meibomian glands, epithelial cells transform to become keratinocytes, and dead keratinocytes are bound together by an intracellular lipid bilayer that includes keratin filaments to allow the skin to function as a barrier. Healthy epithelial cells shed at regular intervals. When these cells do not shed at a sustainable rate, it results in an excess of keratin formation and cell accumulation known as hyperkeratinization.[12] Hyperkeratinization is a fundamental cause of acne and a common finding in other dermatologic diseases, such as psoriasis and atopic dermatitis (Figure 4).

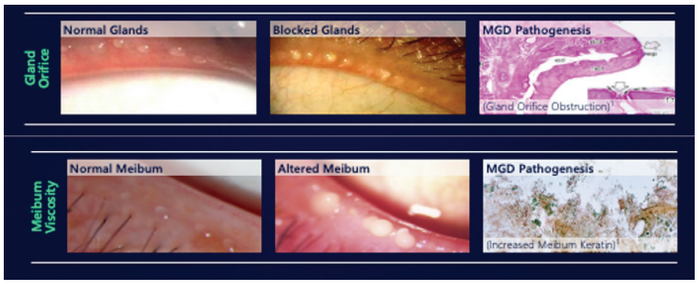

Figure 4. Hyperkeratinization in the gland orifice (top) and central duct (bottom).

Significant study has led to our current understanding that both hyperkeratinization within the meibomian glands and excess protein within the meibum itself are present in patients with MGD.[7,13] Blackie and colleagues published a review of the data and stated, "Despite the potentially coexisting roles of bacteria, tear film osmolarity, and inflammation, it is critical to recognize that the primary mechanism for obstructive MGD is keratinization of the meibomian gland ducts. Thus, the success of any therapy for all forms of obstructive MGD is primarily dependent upon relief of the obstruction and secondarily upon the management of other factors such as inflammation and/or infection."

SELENIUM SULFIDE: A KERATOLYTIC AGENT

Keratolytic agents (agents that soften keratin) are commonly used in dermatology, both water-soluble alpha hydroxy acids (AHAs) and lipid-soluble beta hydroxy acids (BHAs). Selenium sulfide is one potent keratolytic agent that slows the production and development of keratinocytes. It is used as an antifungal for the treatment of dandruff, seborrheic dermatitis, and a fungal skin infection called tinea versicolor. The pathogenesis of dandruff involves hyperkeratinization,

Selenium sulfide has also been found to decrease hyperkeratinization of the meibomian gland ducts by retarding the proliferation of keratinocytes and the production of keratin. It may also break down disulfide bonds, further loosening meibomian gland blockages.

resulting in corneocytes that clump together and manifest as large flakes of skin.[14] Keratolytics, such as selenium sulfide, loosen the attachments between the corneocytes and allow them to be washed off.

Selenium sulfide has also been found to decrease hyperkeratinization of the meibomian gland ducts by retarding the proliferation of keratinocytes and the production of keratin. It may also break down disulfide bonds, further loosening meibomian gland blockages. Furthermore, selenium sulfide has a potential lipogenic effect, stimulating an increase in the quantity of lipids secreted by the meibomian glands.[15] Selenium sulfide has also been applied to the lid margin as a successful treatment for seborrheic blepharitis.[16,17]

RETHINKING MGD TREATMENT

Current therapies for MGD focus on removing blockages in the glands to restore a normal flow and quality of meibum. The most common methods for achieving this include warm compresses and gentle lid massage, gland probing, thermal pulsation, and microblepharoexfoliation. While all of these approaches aim to clear out the hardened meibum that is obstructing the gland, none of them attempt to address the underlying cause for the altered composition of the meibum. Research was recently presented that addresses hyperkeratinization as a core mechanism of the pathophysiology of MGD, demonstrating successful treatment with a keratolytic agent.[15] An ophthalmic preparation of selenium sulfide applied to the meibomian glands over several weeks caused blocked glands to reopen and lipid quality to improve. It is thought that selenium sulfide opens obstructed meibomian glands, stimulates lipid production, and prevents further keratin deposits. Selenium sulfide has also been applied to the lid margin as a successful treatment for seborrheic blepharitis.[16,17] (It should be noted that dermal keratolytics tested in a rabbit toxicology study caused extreme chemosis, redness, corneal clouding, and edema).[18]

Similar to acne, MGD may be the result of hyperkeratinization that alters the flow of meibum and allows the creation of a plug in the central duct of the meibomian gland. Modifying the keratin is a novel approach to the treatment of MGD which may address the underlying pathophysiology of the disease. ■

1. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. *CLAO J.* 1995;21(4):221-232.
2. Nichols KK. The international workshop on Meibomian gland dysfunction: Introduction. *Invest Ophthalmol Vis Sci.* 2011;52:1917-1921.
3. Green-Church KB, Butovich I, Willcox M, et al. The international workshop on Meibomian gland dysfunction: report of the subcommittee on tear film lipids and lipid-protein interactions in health and disease. *Invest Ophthalmol Vis Sci.* 2011;52(4):1979-1993.
4. Butovich IA. The Meibomian puzzle: combining pieces together. *Prog Retin Eye Res.* 2009;28(6):483-498.
5. Tsai PS, Evans JE, Green KM, et al. Proteomic analysis of human Meibomian gland secretions. *Br J Ophthalmol.* 2006;90(3):372-377.
6. Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification, and grading. *Ocul Surf.* 2003;1(3):107-126.
7. Shine WE, McCulley JP. Meibomianitis: polar lipid abnormalities. *Cornea.* 2004;23:781–783.
8. Ong BL, Hodson SA, Wigham T, et al. Evidence for keratin proteins in normal and abnormal human Meibomian fluids. *Curr Eye Res.* 1991;10(12):1113-1119.
9. Obata H. Anatomy and histopathology of human Meibomian gland. *Cornea.* 2002;21(7 Suppl):S70-S74.
10. Blackie CA, Korb DR, Knop E, et al. Nonobvious obstructive Meibomian gland dysfunction. *Cornea.* 2010;29(12):1333-1345.
11. Ibrahim OM, Dogru M, Matsumoto Y, et al. Oxidative stress induced age dependent Meibomian gland dysfunction in Cu, Zn-superoxide dismutase-1 (Sod1) knockout mice. *PLoS One.* 2014;9(7):e99328.
12. Deo PN, Deshmukh R. Pathophysiology of keratinization. *J Oral Maxillofac Path.* 2018;22(1):86-91.
13. Baudouin C, Mesmer EM, Aragona P, et al. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. *Br J Ophthalmol.* 2016;100(3):300-306.
14. Ranganathan S, Mukhopadhyay T. Dandruff: the most commercially exploited skin disease. *Indian J Dermatol.* 2010;55(2):130-134.
15. Gleeson M. Taking a dermatological approach to treating ocular surface disease. Presented at Ophthalmology Innovation Summit at American Academy of Ophthalmology. October 2019. San Francisco, CA. https://ois.net/wp-content/uploads/2019/10/Azura-Ophthalmics.pdf
16. Bahn GC. The treatment of seborrheic blepharitis. *South Med J.* 1954;47(8):749-753.
17. Thygeson P, Vaughan DG Jr. Seborrheic blepharitis. *Trans Am Ophthalmol Soc.* 1954-1955;52:173-188.
18. Rosenthal JW, Adler H. Effect of selenium disulfide on rabbit eyes. *South Med J.* 1962;55:318.

PREEYA GUPTA, MD
- Managing Director, Triangle Eye Consultants, Durham, North Carolina
- Member, *CRST* Editorial Advisory Board
- preeyakgupta@gmail.com
- Financial disclosure: Consultant (AbbVie/Allergan, Alcon, Azura, Johnson & Johnson Vision, Kala Pharmaceuticals, New World Medical, Novartis, Oyster Point Pharmaceuticals, ReGenTree, Sight Sciences, Sun Pharmaceuticals, Surface Ophthalmics, TearLab, Carl Zeiss Meditec)

LAURA M. PERIMAN, MD
- Director of DryEye Services and Clinical Research, Periman Eye Institute, Oracle Eye Institute, Seattle, Washington
- dryeyemaster@gmail.com; Twitter, Instagram, and YouTube @DryEyeMaster
- Financial disclosure: Consultant or speaker (AbbVie/Allergan, Alcon, Azura, Eyevance, Eyedetec, Johnson & Johnson Vision, Lumenis, Novartis, Olympic Ophthalmics, Quidel, ScienceBasedHealth, Sight Sciences, Sun Pharmaceuticals, TearLab, Visant)

EDWARD LAIN, MD
- Chief Medical Officer, Sanova Dermatology, Austin, Texas
- Executive Director & Principal Investigator, Austin Institute for Clinical Research, Austin, Texas
- ted.lain@gmail.com
- Financial disclosure: Consultant and Advisor (Azura)

ERIC D. DONNENFELD, MD
- Founding Partner, OCLI Vision, New York
- Professor of Ophthalmology, New York University, New York
- Trustee, Dartmouth Medical School, Hanover, New Hampshire
- *CRST* Editor Emeritus
- ericdonnenfeld@gmail.com
- Financial disclosure: Consultant (AbbVie/Allergan, Azura, Bausch + Lomb, Glaukos, Novartis, Tarsus)

JOHN A. HOVANESIAN, MD

- Private practice, Harvard Eye Associates, Laguna Hills, California
- Clinical Instructor, Jules Stein Eye Institute, University of California, Los Angeles
- Member, *CRST* Editorial Advisory Board
- jhovanesian@mdbackline.com; Twitter @DrHovanesian
- Financial disclosure: Consultant (Azura), Founder (MDbackline)

TERRY KIM, MD

- Professor of Ophthalmology; Chief, Cornea and External Disease Division; and Director, Refractive Surgery Service, Duke Eye Center, Duke University, Durham, North Carolina
- terry.kim@duke.edu
- Financial disclosure: Consultant (Azura, Kala Pharmaceuticals, Ocular Therapeutix, Omeros)

SHERI ROWEN, MD, FACS

- Medical Director, NVision Eye Centers, Newport Beach, California
- Member, *CRST* Editorial Advisory Board
- srowen10@gmail.com
- Financial disclosure: AbbVie/Allergan, Alcon, Azura, Bausch + Lomb, Johnson & Johnson Vision, Kala Pharmaceuticals, Novartis, Orasis

WILLIAM B. TRATTLER, MD

- Director of Cornea, Center for Excellence in Eye Care, Miami
- Member, *CRST* Executive Advisory Board
- wtrattler@gmail.com
- Financial disclosure: Consultant, speaker, or financial interest (AbbVie/Allergan, Alcon, Azura, Bausch + Lomb, CXL Ophthalmic, Glaukos, Johnson & Johnson Vision, Kala Pharmaceuticals, Novartis, Novabay, Oculus Optikgeräte, Oyster Point Pharmaceuticals, Sight Sciences, Sun Pharmaceuticals, Tarsus, Visus, Carl Zeiss Meditec)

ELIZABETH YEU, MD

- Cataract, corneal, and refractive surgeon, Virginia Eye Consultants, Norfolk, Virginia
- Member, *CRST* Executive Advisory Board
- eyeulin@gmail.com
- Financial disclosure: Consultant (Azura)

EDWARD HOLLAND, MD

- Director of Cornea, Cincinnati Eye Institute
- Professor of Ophthalmology, University of Cincinnati
- eholland@holprovision.com
- Financial disclosure: Consultant (AbbVie/Allergan, Alcon, Azura, Johnson & Johnson Vision, Kala Pharmaceuticals, Oyster Point Pharmaceuticals, ReGenTree, Sight Sciences, Surface Ophthalmics)

CRST
Cataract & Refractive Surgery Today

MILLENNIALEYE