Major review

Management of meibomian gland dysfunction: a review

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Abstract

Meibomian gland dysfunction is the leading cause of evaporative dry eye disease and is one of the most common conditions encountered by eye care providers. The disorder is characterized by obstruction of the meibomian gland terminal ducts and/or changes in their glandular secretion, resulting in changes in tear film stability, inflammation, and symptoms of irritation. There is no gold standard treatment for meibomian gland dysfunction, but rather a diversity of options. Conservative measures include warm compresses and lid hygiene, but there is growing interest and need for medical treatments and procedures. Potential medical treatments include antibiotics, nonsteroidal and steroidal anti-inflammatory agents, essential fatty acid supplementation, hormone therapy, and control of Demodex infestation. Procedures include intraductal meibomian gland probing, the use of electronic heating devices, intense pulsed light therapy, and intranasal neurostimulation. We provide an update on meibomian gland dysfunction treatments based on recent studies.

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1. Introduction

Meibomian gland dysfunction (MGD) is the leading cause of evaporative dry eye and one of the most common conditions encountered by eye care providers. It is a type of posterior blepharitis that involves inflammation posterior to the gray line of the lid margin. Symptoms of MGD can have a significant impact on quality of life, causing not only ocular irritation, but also the sequelae of ocular surface inflammation and resultant deficits in visual function.

According to the International Workshop on Meibomian Gland Dysfunction (IWMGD), “meibomian gland dysfunction 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 terminal duct obstruction occurs because of
hyperkeratinization of the ductal epithelium and increased viscosity of meibum and can lead to gland dropout, atrophy, and decreased secretion.98 The development of this obstructive process has been shown to be influenced by numerous factors, both endogenous and exogenous, including age, sex, hormone levels, as well as medications.98 Reduced delivery of lipids to the ocular surface can cause evaporative dry eye disease, hyperosmolarity, and tear film instability.98

The tear film lipid layer consists of an outer nonpolar layer and an inner polar layer at the level of the air-lipid and aqueous-lipid interfaces, respectively.16 The outer nonpolar layer serves as a lubricant, with its water barrier function preventing tear evaporation, whereas the inner polar layer acts as a surfactant that allows the entire lipid layer to spread across the ocular surface and also provides an interface between the aqueous and outer nonpolar lipid layers.51,95 Sphingolipids comprise 30% of the polar lipid layer, levels of which have been shown to increase in the setting of MGD.95,102,110 Elevated meibum concentration of the sphingolipid metabolite ceramide has been shown to cause an increase in meibum melting temperature and resulting tear film lipid layer instability.5,115 Furthermore, sphingolipids have been shown to regulate cellular processes including cell growth, differentiation, migration, proliferation, apoptosis, and inflammation, thus reflecting other potential roles of these lipids in the pathophysiology of MGD.90,55

The goal of treatment for MGD is to improve the flow of meibomian gland secretions and ultimately help reestablish tear film stability.145 In addition to eyelid hygiene and warming, numerous medical and more invasive treatment options have emerged over the years. In 2011, the IWMG released an extensive report on MGD which included an evidence-based summary of management options.44 We shall provide an update on MGD treatments based on studies published since the IWMG report. Medical treatments discussed in this article include antibiotics, nonsteroidal and steroid anti-inflammatory agents, essential fatty acid (EFA) supplementation, hormone therapy, and control of Demodex infestation. Procedures discussed include intraductal meibomian gland probing, the use of electronic heating devices, intense pulsed light therapy, and intranasal neurostimulation.

2. Medical management

2.1. Antibiotics

It is not entirely clear whether bacterial colonization of the lid margin in patients with MGD indicates that infection is the underlying cause of disease or just that the lid environment in patients with MGD is more amenable to colonization by bacteria compared to normal subjects.44 The effects of bacteria on the pathophysiologic processes of MGD are mediated in part by the production of directly toxic products, such as lipases, as well as pro-inflammatory molecules, such as matrix metalloproteinases (MMPs). Regardless of the exact impact of bacteria on the disease process, commensal bacterial species that are found on the lid margins of normal individuals are present in increased numbers in those with blepharitis,69 and thus, antibiotics have been used for years in the management of MGD.

2.1.1. Tetracyclines

Tetracyclines are bacteriostatic antibiotics used in the treatment of MGD primarily for their anti-inflammatory properties rather than their antibiotic effects.44 They have been shown to suppress the production of bacterial lipases as well as the release of pro-inflammatory molecules, particularly free fatty acids, both of which cause instability of the tear film and inflammation within the meibomian glands.26,67,102,123 Furthermore, they modulate neutrophil and lymphocyte function and provide anti-oxidative effects through various mechanisms including the inhibition of MMPs and inflammatory cytokines such as tumor necrosis factor (TNF)-α,33 MMP-8,88 and MMP-9.88 Finally, they may be antiangiogenic and antiapoptotic at the ocular surface.90

There are a multitude of studies on the use of tetracyclines in the treatment of MGD, but very few are classified as level I (randomized, placebo-controlled) studies.80 One randomized controlled trial compared 60 patients with MGD assigned to either artificial tears only or artificial tears plus oral minocycline, and showed a statistically significant improvement in the minocycline group with regards to all clinical signs and symptoms measured, including tear breakup time (TBUT), Schirmer test, corneal and conjunctival fluorescein staining, lid margin appearance, and meibum quality.77 Furthermore, the minocycline group also showed statistically significant reductions in inflammatory cytokines interleukin (IL)-6, IL-1β, IL-17α, TNF-α, and IL-12p70 after two months of treatment, whereas the control group only showed statistically significant reductions in levels of IL-1β and monocyte chemotactic protein-1.

Of note, doxycycline and minocycline are more lipophilic compared to tetracycline or oxytetracycline and are therefore more concentrated in ocular and lid tissues at lower doses (i.e., 50–100 mg dosed at once or twice a day for the former compared to 250 mg once to four times a day for the latter).44 These doses generally allow for only anti-inflammatory rather than antibiotic effects at the ocular surface, except for minocycline, which has been shown to also reduce the population of lid flora in patients with rosacea.6,132 The main side effects of tetracyclines include photosensitivity and gastrointestinal symptoms, and their use is contraindicated in pregnant women and children.146

2.1.2. Azithromycin

Azithromycin is a macrolide antibiotic that is used off-label to treat MGD. Macrolides provide predominantly gram-positive coverage, inhibiting bacterial protein synthesis by binding to the 23S rRNA molecule of the 50S ribosome subunit. Azithromycin has been found to not only reduce the growth of lid bacteria but also suppress bacterial lipases134 and conjunctival inflammation.85 It has been shown that it reduces the expression and release of pro-inflammatory molecules including nuclear factor-kappa B,1 IL-6, IL-8,7 TNF-α,44 IL-18, and MMP-9 mRNA,146 and increases the expression of transforming growth factor-β1, which has anti-inflammatory effects.146 Furthermore, macrolides can influence the functions of neutrophils and phagocytes.146 Azithromycin has been
shown in experimental studies to promote the differentiation of immortalized human meibomian gland cells and stimulate phospholipidosis through the accumulation of cholesterol, neutral lipids, and lysosomes. Moreover, it restores and promotes differentiation of carotenoids in meibum. Azithromycin has been used in both topical and oral formulations for the treatment of MGD.

2.1.2.1. Topical azithromycin. Topical azithromycin is available in the United States as an ophthalmic solution 1% (AzaSite®, Inspire Pharmaceuticals, Inc., Durham, NC, USA). The efficacy of topical azithromycin for treatment of MGD has been shown in a number of studies. A cohort study evaluating the use of topical azithromycin 1% twice a day for one month in 26 patients showed statistically significant improvements in symptoms including lid itching, eye itching, ocular hyperemia, and ocular mucus secretion. Another cohort study examining 26 patients using oral azithromycin results in high drug concentrations in the conjunctival tissue and tear fluid lasting for at least 14 days. The same study showed improvement in signs and symptoms in both groups at 1 week and minimal irritation with use of the drug. Finally, a retrospective study looking at outcomes of 35 patients with MGD treated with topical azithromycin 1.5% twice daily for 2 days then once daily for a total of 30 days in addition to daily lid hygiene with diluted baby shampoo found statistically significant improvements in meibomian gland grading score, Schirmer score, TBUT, and corneal fluorescein staining at 1 month, but no significant change from baseline at 3 months.

2.1.2.2. Oral azithromycin. There has been growing interest in the use of oral azithromycin not only for reasons of effectiveness in treating MGD, but also for improved compliance because oral azithromycin usually involves once daily dosing for several days, sometimes in weekly cycles, as compared to daily use of tetracyclines for weeks or months. It has been shown that a single 1-gram dose of oral azithromycin results in high drug concentrations in the conjunctival tissue and tear fluid lasting for at least 14 days. A cohort study examining 26 patients using oral azithromycin 500 mg per day for 3 days in 3 cycles with 7-day intervals showed statistically significant improvements in lid debris, telangiectasia, and redness. Furthermore, there were statistically significant improvements in symptoms including lid itching, eye itching, ocular hyperemia, and ocular mucus secretion. Another cohort study examining 32 patients with meibomitis found that 75% had improvements in symptoms after using 1 gram of oral azithromycin once a week for 3 weeks in addition to topical steroid treatment. Furthermore, one randomized trial of 110 patients assigned to either oral azithromycin for 5 days (500 mg on day 1 followed by 250 mg on days 2–5) or oral doxycycline 200 mg daily for one month showed that the former resulted in a significantly greater improvement in bulbar conjunctival redness and ocular surface staining. Of note, azithromycin has been reported to cause adverse cardiac events, most notably QT prolongation. The risk of such has been found to be higher in those with a preexisting long QT interval, those on other QT-prolonging medications, or those with baseline cardiovascular abnormalities.

2.2. Anti-inflammator agents

The role of inflammation in the pathophysiology of MGD is not entirely understood; however, patients with blepharitis demonstrate increased meibum levels of phospholipase A2, which plays a role in the synthesis of inflammatory mediators such as prostaglandins and leukotrienes. Local inflammation in turn can cause activation of ocular surface epithelial cells which then produce inflammatory cytokines such as TNF-α and TNF-β. Furthermore, the concentration of IL-1β, mature IL-1β, and MMP-9 is known to be increased in the tear fluid of patients with MGD. The presence of inflammatory cytokines including IL-1β can cause increased epithelial proliferation and keratinization thereby contributing to obstructive meibomian gland disease and is therefore a target of anti-inflammatory agents in the management of MGD.

2.2.1. Cyclosporine A

Cyclosporine A, a calcineurin inhibitor available as a topical 0.05% emulsion (Restasis®, Allergan Inc., Irvine, CA, USA), was the first FDA-approved treatment for dry eye disease. Cyclosporine A is a molecule which induces transcription factors involved in the transcription of IL-2, a cytokine which activates T-helper lymphocytes, and is necessary for their replication. By inhibiting calcineurine, cyclosporine A effectively inhibits T-cell proliferation. In addition to increasing aqueous tear production in inflammatory dry eye disease, cyclosporine A has also been shown to play a role in the management of MGD, contributing to improvements in lid margin redness, meibomian gland inclusions, telangiectasia, and corneal staining, as well as in the quality of meibomian gland secretions.

There are numerous studies evaluating the effectiveness of topical cyclosporine A in managing dry eye disease, but very few assessing its use in the treatment of MGD specifically. A double-masked, randomized controlled trial of 70 patients with symptomatic MGD found that, in comparison to controls treated with preservative-free artificial tears, twice daily dosing of topical cyclosporine A 0.05% for 3 months resulted in statistically significant improvements from baseline in terms of OSDI, TBUT; lid margin inflammation, meibomian gland expressibility, and tarsal injection; furthermore, it resulted in a longer TBUT and a greater change of TBUT from baseline compared to the control group. The most common side effect and reason for discontinuation of cyclosporine A is a stinging sensation. Pretreatment with topical loteprednol 0.5% has been shown to reduce discomfort associated with use of cyclosporine A. Overall, the anti-inflammatory properties of cyclosporine A that have made it an effective treatment option for aqueous-deficient dry eye disease appear to also play a role in tackling the inflammatory contributions to disease in MGD.

2.2.2. Lifitegrast

Lifitegrast is a lymphocyte function–associated antigen-1 antagonist that blocks T-cell binding to intercellular adhesion molecule-1, a ligand expressed on inflamed ocular
epithelial and vascular endothelial cells. This prevents the release of proinflammatory cytokines including interferon-γ, TNF-α, macrophage inflammatory protein 1α, as well as IL-1α, IL-1β, 2, 4, and 6. Topical lifitigrast ophthalmic solution 5.0% (Xiidra®, Shire, Lexington, MA, USA) is the second and most recent drug approved by the FDA for management of dry eye disease. The results of the OPUS-3 phase 3 trial comparing twice daily dosing of lifitigrast ophthalmic solution 5.0% to placebo showed that lifitigrast provided greater improvement in eye dryness score (measured on a visual analog scale) at day 14, 42, and 84. Subjects using lifitigrast experienced greater improvement in itching, foreign body sensation, and ocular discomfort at day 42 compared to placebo. The most common adverse effect of topical lifitigrast is transient, intermittent instillation site irritation or discomfort, primarily at the time of the initial dose. To date, there have been no published studies evaluating the use of lifitigrast specifically in the treatment of MGD.

2.2.3. Corticosteroids
According to the IWMGD report released in 2011, no published study has supported long-term maintenance therapy with steroids. Rather, steroids have proven useful in the setting of acute bouts of inflammatory complications of MGD, such as chalazia or marginal keratitis. Considering the risk of cataract development and elevation of intraocular pressure, the benefits of steroid therapy must be measured against the risks. Several studies have demonstrated the efficacy of short-term treatment with steroids in the management of patients with dry eye disease, however, the literature available on steroid use in the treatment of MGD is limited.

A randomized controlled trial on 70 eyes with MGD showed that treatment with 0.5% lotepredn etabonate ophthalmic suspension four times a day, in addition to the control treatment of eyelid scrubs and warm compresses twice a day, demonstrated more improvement in TBUT, meibum quality, conjunctival fluorescein staining, and meibomian gland expressibility at 1 month compared to controls. Another study randomized 20 patients to either N-acetylcysteine 5% or betamethasone 0.1%-sulfacetamide sodium 10% (a steroid-antibiotic combination) used topically 4 times a day for one month; all patients were instructed to apply lid hygiene once (Xiidra®, Shire, Lexington, MA, USA) is the second and most recent drug approved by the FDA for management of dry eye disease. The results of the OPUS-3 phase 3 trial comparing twice daily dosing of lifitigrast ophthalmic solution 5.0% to placebo showed that lifitigrast provided greater improvement in eye dryness score (measured on a visual analog scale) at day 14, 42, and 84. Subjects using lifitigrast experienced greater improvement in itching, foreign body sensation, and ocular discomfort at day 42 compared to placebo. The most common adverse effect of topical lifitigrast is transient, intermittent instillation site irritation or discomfort, primarily at the time of the initial dose. To date, there have been no published studies evaluating the use of lifitigrast specifically in the treatment of MGD.

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2.2.4. Anakinra
Interleukin-1 (IL-1) is a proinflammatory cytokine produced by inflamed epithelial cells and a key mediator of ocular surface inflammation. IL-1 activates and recruits leukocytes, facilitates T cell differentiation, and promotes the production and activity of other proinflammatory molecules, including IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, MMP enzymes, and TNF-α. IL-1 levels have been found to be elevated in tears of patients with moderate evaporative dry eye disease and MGD and are correlated with severity of ocular surface epithelial disease. IL-1 receptor antagonist (IL-1RA) is a cytokine that suppresses IL-1α and IL-1β activity by competitively binding to the type 1 IL-1 receptor. Anakinra (Kineret™, Amgen Inc.) is a recombinant version of human IL-1RA approved for treatment of rheumatoid arthritis and used off-label for other conditions, including dry eye disease. Although Anakinra has been reported to be efficacious in treating dry eye disease, there are no published studies to date on its use in treating MGD. Of note, it is not currently commercially available in the United States.

2.3. Sex hormones
Androgens, estrogen, and progesterone have been found to regulate a number of meibomian gland genes through their action on local meibomian gland receptors, with variable effects in females and males. Androgens have been found to suppress genes associated with keratinization, stimulate genes associated with lipogenesis, and influence the maturation of acinar cells leading to increased lipid secretion. Androgen deficiency, androgen receptor dysfunction and insensitivity, and the use of anti-androgen medications have been shown to be associated with obstructive MGD. Whereas androgens exert a proinflammatory effect on meibomian glands, estrogens have been found to do the opposite, reducing the size and lipid output of sebaceous glands and negatively influencing lipid secretion from meibomian glands through the inhibition of lipogenesis and upregulation of lipid catabolism. Estrogens, particularly 17β-estradiol, have been found to have a proinflammatory effect on the ocular surface.

The exact relationship between serum sex hormone levels and dry eye disease, including MGD specifically, still remains unclear to date. For example, postmenopausal women on hormone replacement therapy (HRT) have been shown to have a greater risk of dry eye disease compared to those not on HRT; a potential reason for this may be the suppression of the hypothalamic-pituitary-adrenal axis in the presence of exogenous estrogen, thus reducing adrenal androgen production. In contrast, others have found decreased symptoms and increased tear production in patients on HRT. A more recent study showed a statistically significant improvement in TBUT, lid meiboscore, excretion difficulty, and corneal fluorescein staining at 1, 3, and 6 months in perimenopausal women on HRT compared to those not on HRT.

2.3.1. Hormone therapy
A paucity of literature exists with regards to the use of sex hormone therapy in the management of dry eye disease in general and, to an even greater extent, MGD. Feng and coworkers showed improved tear production in postmenopausal patients on HRT who were <50 years old. Connor and colleagues demonstrated an increase in TBUT and a reduction of OSDI in females aged 22-65 years using 5% testosterone cream to the eyelids twice daily for 3 weeks, with greater benefit in perimenopausal and postmenopausal patients. Schiffman and associates showed in a randomized, vehicle-controlled trial that the use of topical 0.03% testosterone ophthalmic solution significantly improved meibomian gland secretion viscosity compared to vehicle after 6 months of treatment. Worda and coworkers had also...
shown that topical androgens enhance meibomian gland function as measured by increased lipid layer thickness and TBUT. With regards to determining which patients are candidates for hormonal treatment of dry eye disease, it has been suggested that age and endogenous hormonal levels are the most important considerations. To date, there has not been an approved topical testosterone product for treatment of dry eye symptoms due to inadequate evidence, similarly, there is currently inadequate evidence to support the use of dehydroepiandrosterone and dehydroepiandrosterone-sulfate for relief of MGD symptoms in postmenopausal patients, in whom these adrenal precursors to estrogen and androgens are naturally deficient. Overall, there is limited literature on the use of topical or systemic sex steroid agents in the treatment of MGD, and further research is needed in this area.

2.4. Essential fatty acids

Essential fatty acids have been found to have anti-inflammatory effects, and oral supplementation with omega-3 fatty acids has been found to be associated with a change in the fatty acid saturation content in meibum. Multiple studies have shown a beneficial effect of oral supplementation with EFAs in dry eye disease. Omega-3 fatty acids have been associated with improved TBUT and Schirmer test scores. There are still few studies examining the effect of EFAs on MGD, however, and their mechanism of action in improving signs and symptoms of MGD is not clearly understood. It has been suggested that omega-3 fatty acids suppress inflammation while omega-6 fatty acids promote inflammation. Another hypothesis is that omega-3 fatty acid supplementation may influence the fatty acid composition and thus lipid properties of meibum.

2.4.1. EFA supplementation

In 2008, Dana and coworkers compared the use of topical 0.2% alpha-linolenic acid (omega-3) to 0.2% linoleic acid (omega-6) as well as a combination of 0.1% alpha-linolenic acid and 0.1% linoleic acid, all used once daily in mice with induced dry eye. This study found a significant decrease in corneal staining, CD11b+ cell number, and corneal IL-1a and TNF-a concentrations in the omega-3 group compared to both the omega-6 and the combined omega-3 and -6 groups; no beneficial effects were found for the latter two groups. With regards to oral supplementation, a randomized controlled trial of 61 patients with MGD compared daily use of an omega-3 supplement (BrudySec® 1.5 g, containing omega-3, glutathione, and vitamin A) to an oral placebo control. The omega-3 group was found to have significant improvements in both Physical Component Summary and Mental Component Summary scores compared to baseline and compared to the control group at 3-month follow-up. In another non-randomized, placebo-controlled study, 60 patients were allocated alternately to either a control group receiving warm compresses, lid massages, and artificial tear substitutes, or a treatment group receiving 1.2 g of omega-3 fatty acid supplement daily in addition to the control group regimen. Significantly greater improvement in contrast sensitivity was found in the treatment group compared to the control group, as was the case with OSDI scores, TBUT, ocular surface staining, meibum quality, and meibum expressibility. Another study randomized 54 patients to receive omega-3 (1680 mg eicosapentaenoic acid/560 mg docosahexaenoic acid) and 51 patients to receive the control omega-6 (3136 mg linoleic acid), both receiving treatment daily for 12 weeks. The omega-3 group showed a statistically significant reduction in tear osmolarity at weeks 6 and 12 compared to the control group, as well as a statistically significant increase in TBUT at week 12. There was a statistically significant reduction in MMP-9 levels as well as OSDI scores in the omega-3 group versus the controls. In contrast to these reports of success using omega-3 supplementation, in 2018, the Dry Eye Assessment and Management (DREAM) Study Research Group published the results of a multicenter, double-blind clinical trial in which patients with moderate-to-severe dry eye disease were randomly assigned to receive either fish-derived omega-3 supplementation (daily oral dose of 2000 mg eicosapentaenoic acid/1000 mg docosahexaenoic acid) or an olive oil placebo (5000 mg daily dose) for 12 months. The primary analysis included 329 patients in the active supplement group and 170 patients in the placebo group. Although both groups improved significantly with respect to mean OSDI score, it was found that the difference between their mean score changes was not statistically significant. There was also no statistically significant difference between the two groups with respect to conjunctival staining score, corneal staining score, TBUT, or Schirmer test results. Note that this study had fewer restrictions on inclusion criteria than the aforementioned studies and did not include only patients with MGD-related dry eye disease. Regardless, considering the conflicting results of these recent studies on EFA supplementation in the management of both MGD-related as well as other forms of dry eye disease, further randomized controlled trials evaluating their effectiveness would continue to provide valuable insight into their utility.

2.5. Demodex treatment

Demodex mites are the most common ectoparasite found on the human skin, many species of which are obligatory commensals of the pilosebaceous unit of mammals. Colonization of Demodex mites in humans has been shown to increase with age, with up to 100% of adults infested beyond the age of 70 years. The most common species identified in humans are Demodex folliculorum, found primarily in lash follicles, and Demodex brevis, found mainly in the sebaceous and meibomian glands of the lids. Although there is no clear evidence of a causal relationship with MGD, a study of 150 patients demonstrated the presence of Demodex in 90% of those with anterior blepharitis and 60% of those with MGD. Demodex is thought to cause blepharitis via several mechanisms. D. folliculorum directly damages cells at the base of the hair follicle, causing reactive hyperkeratinization and resulting in the formation of cylindrical dandruff. D. brevis physically blocks the meibomian glands, resulting in a granulomatous reaction from tissue irritation and thus predisposing to MGD and chalazia. Furthermore, Demodex mites can serve as a vector for certain bacteria, triggering an inflammatory response in the host, and can cause a delayed
hypersensitivity reaction particularly in patients with rosacea.\textsuperscript{15}

2.5.1. Tea tree oil
Tea tree oil (TTO), an essential oil derived from the leaf of the plant \textit{Melaleuca alternifolia},\textsuperscript{135} has been found to be an effective treatment for blepharitis associated with \textit{Demodex}.\textsuperscript{31,42,67} A one-month treatment of weekly 50% TTO lid scrubs in the clinic and 10% lid scrubs daily at home has shown to eradicate ocular \textit{Demodex}.\textsuperscript{42,70} It reduce inflammation of the lid margin, conjunctiva, and cornea,\textsuperscript{41,67} decrease tear concentrations of IL-1\& and IL-17,\textsuperscript{68} and improve ocular surface irritation.\textsuperscript{41,67,70} More recently, home therapy with daily lid massage and 5% TTO ointment has also been found to significantly decrease mite counts within four weeks and provide significant relief from itching.\textsuperscript{24} Aside from its miticidal effects, TTO may also have antibacterial, antifungal, and anti-inflammatory properties that improve signs and symptoms of blepharitis.\textsuperscript{44} In light of adverse effects such as contact dermatitis and hypersensitivity reactions attributed to certain ingredients found in TTO such as terpinolene, α-terpinene, ascaridole, and 1,2,4-trihydroxy methane,\textsuperscript{23,111,134} it has been suggested that terpinen-4-ol—the most effective ingredient for killing the mites—be used alone for treatment of \textit{Demodex}.\textsuperscript{135} This ingredient has both antimicrobial and anti-inflammatory functions and is what composes the product Cliradex® (Bio-Tissue, Inc.).\textsuperscript{71} Cliradex® is applied to the lids once daily for mild symptoms or twice a day for moderate to severe symptoms, for an initial trial of two months’ duration.\textsuperscript{134}

2.5.2. Other agents used to treat \textit{Demodex}
Other agents such as mercury oxide 1% ointment, or sulfur ointment, pilocarpine gel, and camphorated oil have been used to physically trap the mites as they attempt to emerge from one follicle and move on to the next overnight.\textsuperscript{91,95} Twice-daily topical application of 0.25% povidone-iodine in a dimethylsulfoxide vehicle has been reported to improve signs of anterior and posterior blepharitis attributed to \textit{Demodex}.\textsuperscript{104} In a study of 24 eyes of 12 patients with refractory posterior blepharitis with the presence of \textit{D. folliculorum} in lash samples, treatment with oral ivermectin (200 μg/kg) taken at one dose on day 0 and again on day 7 showed statistical improvement in the absolute number of \textit{D. folliculorum} found in the lashes, as well as statistically significant improvement in Schirmer I test results and TBUT\textsuperscript{96}; no statistically significant improvement was observed in average tear meniscus height or value of corneal fluorescein and rose Bengal staining after treatment with oral ivermectin.

3. Procedures for MGD management

3.1. Expression of meibum
According to the IWMGD definition of MGD, terminal duct obstruction is a key feature of the disease process, and therefore, mechanical opening of the terminal duct as well as meibum expression play an important role in management. Both intraductal meibomian gland probing and electronic heating devices act to assist locally with ease of meibum expression through mechanical opening of the duct orifice and/or heating of meibum to allow for better outflow.

3.1.1. Intraductal meibomian gland probing
Intraductal meibomian gland probing can be performed at the slit lamp. It involves mechanically opening and dilating blocked meibomian gland orifices and ducts through the insertion of probes of varying sizes. The gland orifice is initially penetrated using a 1 or 2 mm Maskin probe (Rhein Medical, Tampa, FL, USA), followed by either a 4 or 6 mm probe, depending on the length of the gland, to achieve ductal patency. Probing can help release accumulated meibum, improve ductal patency, and potentially increase accessibility of the diseased meibomian glands to treatment with topical medicaments.\textsuperscript{87} Probing has been shown to improve both objective signs of disease—including TBUT,\textsuperscript{87,121} meibum lipid levels and viscosity,\textsuperscript{96} lid margin abnormalities,\textsuperscript{87,121} and conjunctival hyperemia\textsuperscript{121}—as well as symptomatic.\textsuperscript{87,121,135} In a retrospective cohort study of 25 patients treated with probing by Maskin,\textsuperscript{93,135} 96% of patients had immediate symptom relief after probing,\textsuperscript{93} and 66.7% of patients required only one treatment during an average follow-up duration of 30.3 months.\textsuperscript{5} Probing improved lid functionality (defined as ≥5 expressible glands in a lid) in 62 of 67 lids (92.5%) over a follow-up range of several days to 7 months (average follow-up of 7.65 weeks).\textsuperscript{5} In a randomized controlled trial of 49 patients with MGD randomized to either probing plus 0.1% fluorometholone or 0.1% fluorometholone alone, 76% of patients experienced immediate symptomatic relief one day after probing before application of topical medicaments.\textsuperscript{87} A recent study has reported an increase in meibomian gland area on meibography at 4.5 to 12 months after probing, suggesting that glandular growth may be promoted through the establishment of a patent duct.\textsuperscript{36}

A modified technique called dynamic intraductal meibomian probing has been described by Syed and Sutula\textsuperscript{31} in which the patient lies supine in a procedure chair under an operating microscope and the lid is grasped with forceps and pulled in the direction opposite to that of the movement of the probe. This offers greater magnification of the duct orifices as well as probing against resistance and has shown good effects in a retrospective chart review, with 92% of 22 patients reporting symptomatic improvement.\textsuperscript{131}

3.1.2. Electronic heating devices
The melting point of meibomian lipids ranges from approximately 19°C to 32°C,\textsuperscript{89} allowing meibum to remain in a fluid state in the setting of ocular surface and eyelid temperatures, that range from approximately 33°C to 37°C.\textsuperscript{10} Meibomian gland dysfunction has been shown to cause an alteration in the composition of meibum which results in an increase in the melting point, thus requiring higher gland temperatures to liquefy materials that otherwise cause obstruction.\textsuperscript{13,65} Increased eyelid temperatures have been shown to decrease meibomian lipid viscosity and increase lipid levels present on the lid margin.\textsuperscript{36} Prior studies have demonstrated that temperatures of greater than 40°C are required for liquefaction of obstructive glandular material in severe MGD.\textsuperscript{13} This concept forms the basis for the role of heat therapy in MGD
management, either in the form of warm compresses or through electronic heating devices, the latter of which will be discussed here.

LipiFlow® (TearScience, Morrisville, NC, USA) is a single-use sterile vectored thermal pulsation system which uses simultaneous application of heat to the palpebral conjunctival surfaces of the upper and lower eyelids along with distal to proximal pulsatile pressure to the outer eyelid surfaces to express meibomian gland contents. A single treatment is 12 minutes in duration. LipiFlow® is currently the only device able to apply heat to the internal lid surface. This treatment has been shown to be effective in improving objective measures of disease including meibomian gland secretion scores, TFBUT, number of expressible glands, lipid layer thickness, bulbar redness, and lid margin parallel conjunctival folds. Studies have also shown significant subjective improvements in dry eye and irritation symptoms as measured by the OSDI questionnaire and the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire. An observational cohort study of 40 eyes showed that a single LipiFlow® treatment resulted in statistically significant improvements in meibomian gland secretion scores, OSDI scores, and SPEED scores at 1 month, and these improvements persisted at 3 years after LipiFlow® treatment. There was also a statistically significant increase in TFBUT at 1 month, but this improvement was not sustained at 3-year follow-up; a similar finding occurred in a study by Zhao and colleagues in which TFBUT was modestly improved at 1 month but was not different from the warm compress control group at 3 months. An open-label randomized controlled trial using 400 eyes showed a greater mean improvement in meibomian gland secretion and dry eye symptoms in patients who had received a single LipiFlow® treatment compared to those using twice daily 10-minute warm compress and eyelid hygiene therapy using the Eye-Giene® Insta-Warmth™ (Eyedetect Medical, Inc. Danville, CA, USA) system and OCuSOFT® Lid Scrub™ Original (OCuSoft, Rosenberg, TX, USA), when measured at 3 months. At 12-month follow-up, 86% of the LipiFlow® group only required a single treatment and sustained a significant mean improvement in meibomian gland secretion and dry eye symptoms. Early treatment was positively correlated with improved outcomes. A recent randomized trial comparing a single 12-minute LipiFlow® treatment to daily doxycycline for 3 months found that the former resulted in significantly better SPEED scores while performing at least as well as doxycycline in terms of improvements in TFBUT, corneal and conjunctival staining, and meibomian gland function. MiBo Thermoflo® (MiBO Medical Group, Dallas, TX, USA) is another electronic heating device using an external paddle heated to 42.2°C (108°F) and applied to the lids with an ultrasound gel buffer. There is currently a paucity of literature on the efficacy of this device in the management of MGD. One case report comparing palpebral conjunctival temperature before and after use of four different heating devices (Bruder mask, Blephasteam®, MiBo Thermoflo®, and LipiFlow®) found that MiBo Thermoflo produced the smallest increase in temperature after a 12-minute treatment—an increase from 36.3°C to 36.5°C for the upper eyelid, and no change from 36.8°C for the lower eyelid. On the other hand, LipiFlow® provided the greatest increase in temperatures, increasing that of the upper eyelid from 36.9°C to 41.1°C and that of the lower eyelid from 37.0°C to 42.0°C.

As the evidence does not clearly point toward one heating device as superior to another, the decision to pursue a specific therapeutic option should involve considerations of patient comfort, cost, ease of follow-up, and individual response to therapy.

3.2. Intense pulsed light therapy

Intense pulsed light (IPL) therapy has been used for years in dermatology practices to improve the appearance of the skin and is a known treatment for rosacea. It uses a high-intensity non-laser light source, producing wavelengths ranging from 500 to 1200 nm. When applied to the skin, the absorption of light by oxyhemoglobin in blood cells traveling within vessels near the skin surface results in heat generation and local coagulation, leading to thrombosis of the blood vessels and therefore decreasing redness caused by abnormal telangiectasias and eliminating this source of inflammatory mediators. Furthermore, IPL has been shown to eradicate bacteria on treated areas of the skin. Because the pathophysiology of MGD involves a combination of microbial overgrowth, inflammation, abnormal blood vessel growth surrounding and causing dysfunction of the meibomian glands, and resultant abnormal meibum production, IPL therapy should theoretically improve MGD. Major mechanisms by which IPL is thought to improve signs and symptoms of MGD include thrombosis of abnormal blood vessels, heating and liquefaction of meibum allowing greater ease of secretion and expression, reduction in epithelial turnover, local photomodulatory effects, activation of fibroblasts, enhancement of collagen synthesis, and destruction of Demodex mites. Studies evaluating the effectiveness of IPL in the treatment of MGD have reported improvements in lid margin edema, redness and vascularity, meibum viscosity and secretion quality, meibomian gland expressibility, oil flow scores, lipid layer grade, tear film osmolarity, corneal fluorescein staining, and conjunctival injection. Of note, however, a randomized controlled trial of 28 patients having undergone IPL treatment on day 1, 15, and 45 showed no difference in tear evaporation rate or tear meniscus height from baseline. A recent cohort study of 35 patients comparing IPL to eyelid hygiene found that IPL induced alterations in meibomian gland structure, with a significant increase in meibomian gland acinar longest diameter and unit density, as well as a decrease in inflammatory cells surrounding the glands. Furthermore, a randomized controlled trial of 88 eyes comparing IPL therapy to sham found that after 3 consecutive treatments 4 weeks apart, IPL significantly reduced tear concentrations of IL-17a and IL-6. Patients have reported significant improvement in ocular surface symptoms after IPL therapy. A retrospective cohort study of outcomes after combination therapy with IPL and meibomian gland expression demonstrated a significant improvement in dry eye symptoms in 89% of 35 patients. No serious adverse events have been reported.
with use of IPL for treatment of MGD, but redness and swelling have been documented in up to 13% of patients.\textsuperscript{136}

3.3. Neurostimulation

Intranasal tear neurostimulation makes use of the nasoacri- mal reflex, connecting neural pathways from the nasal mucosa to cellular structures that are involved in tear film maintenance. Pulsed stimulation of the anterior ethmoid nerve occurring over 3 minutes per day and applied daily for 3 weeks in experimental animals resulted in an increase in tear volume as well as lipid and protein concentrations, and a decrease in tear osmolarity.\textsuperscript{13} A randomized controlled trial in human subjects comparing the Allergan TrueTear® Intranasal Tear Neurostimulator (ITN) to sham found that the former induced degranulation of conjunctival goblet cells.\textsuperscript{52} An open-label, non-randomized study assessing outcomes of intranasal tear neurostimulation performed at least 4 times a day for 180 days found increased Schirmer scores, reduced corneal and conjunctival staining, and improved symptoms after treat- ment.\textsuperscript{20} Pondelis and coworkers found that the Allergan ITN changes meibomian gland morphology after 3 minutes of stimulation, significantly reducing both area and perimeter, suggesting release of meibum.\textsuperscript{2} Furthermore, Green and colleagues found that, after 3 minutes of stimulation, the device significantly increases tear meniscus height while maintaining a similar lipid concentration, suggesting an increase in lipid production as well.\textsuperscript{1} Watson and associates found that use of the ITN significantly increases lower central meibomian gland temperature as well as the lipid layer thickness, further demonstrating the effect of the device on meibomian glands.\textsuperscript{52}

4. Conclusion

There are a multitude of studies evaluating the use of various medical treatment strategies and devices in the management of MGD, but few classify as level 1 evidence; most of the evidence available for this review included retrospective and prospective cohort studies. Antibiotics such as tetracyclines and azithromycin have been shown to effectively decrease signs of eyelid inflammation, but their side effect profiles are not insignificant and must be considered when prescribing to patients on a case-by-case basis. Topical cyclosporine A (Restasis®) has proven to be an effective modality for dry eye disease and MGD; furthermore, lifitegrast (Xiidra®), although to date only approved for aqueous-deficient dry eye, is a promising alternative in the treatment of the inflammatory pathways related to MGD. Omega-3 supplementation has been shown to change the lipid properties of meibum and improve signs and symptoms of MGD. Treatment of Demodex has clear benefits in improving blepharitis and contributes to improvements in eyelid inflammation. The utility of hormone therapy in treating MGD is still an active area of research. With regards to more invasive treatments, meibomian gland duct probing has proven to be an effective measure taken in the office setting but may be limited by time and discomfort. Of the available electronic heating devices, LipiFlow® is the only one that offers vectored thermal pulsation, with directional pressure applied to the heated lids to further facilitate the outflow of meibum from the glands. Intense pulsed light therapy offers an alternative route to decreasing the delivery of inflammatory markers to the lids by targeting telangiectatic vessels and also decreasing bacterial load around the eyelids. Finally, intranasal tear neurostimulation not only increases tear secretion but also stimulates lipid production and the secretion of meibum from meibomian glands. As is evidenced by this review, there are a host of treatment options available for the management of MGD, each of which must be catered to the individual patient based on ease of use, level of comfort with the treatment strategy, cost, side effect profile, and response. Continued efforts to conduct research studies, particularly randomized controlled trials, are necessary to further establish the role and order of escalation of treatment options in the management of MGD.

5. Literature search

This review was compiled using articles identified by searching Ovid MEDLINE from 1946 to the present. The intention of this review was to provide a literature update on evidence behind medical and invasive management strategies for MGD based on studies published since the release of the report by the IWMGD in 2011. Therefore, although some select articles published before this date are included for historical purposes or in the case where only a very limited number of studies are available on a certain discussed topic, the review is based primarily on articles published from 2011 onward. An overall search was conducted using the key- words “meibomian gland dysfunction treatment,” “meibo- mian gland dysfunction management.” To ensure that all studies published on the specific treatments discussed in the review were mentioned, individual searches were conducted for each treatment strategy using terms for the treatment in combination with the following keywords: meibomian glands, meibomian gland dysfunction, meibomian gland disease, dry eye syndromes, and posterior blepharitis. The search terms used for each individual treatment search included the following: tetracyclins* or doxycycline, azi- thromycin, cyclosporin* or Restasis, adrenal cortex hormones or topical* (steroid* or corticosteroid*), interleukin 1 receptor antagonist* or Anakinra or Kineret, sex hormone* or gonadal steroid hormones or dehydroepiandrosterone or estradiol or anabolic agents or androgens or estrogens or progestins, fatty acid* or omega 3 or omega 6, mite or Demodex or mite in- festations, phototherapy or intense pulsed light therapy or pulse* light, thermal pulsation or LipiFlow, probe* or probing. All relevant articles in English were included. Those in lan- guages other than English were considered if English ab- stracts were available.

6. Disclosures

Dr. Saama Sabeti, Dr. Ahmad Kheirkhah, and Dr. Jia Yin have no conflicts of interest to disclose. Dr. Reza Dana serves as a consultant to Dompe, Kala, Novaliq, Santen and owns equity in Claris Biotherapeutics.
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