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A Review on Recent Advances in Meibomian Gland Dysfunction.

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ABSTRACT

We hereby review available literature on Meibomian Gland Dysfunction (MGD) with the perspective of academic and clinical utility. Recent studies have supported increased prevalence of MGD in Asians, and MGD as a major cause for dry eye disease in the elderly. We have discussed the recent advances in the understanding of MGD pathophysiology, including the role of Copper and Zinc-Superoxide Dismutase-1 in quenching free radicals which cause oxidative damage, unsaturated Free Fatty Acids (FFAs), especially linoleic acid, which affect meibum composition, and ectodysplasin A (Eda), in the maintenance of ocular surface health. Diagnostic advancements include newer slit-lamp assisted grading recommendations for MGD with photographic aids, new modalities such as LipiView® to directly visualise and quantify the tear film lipid layer thickness (LLT), In-Vivo Confocal Microscopy (IVCM) for meibomian gland acinar morphology, density and inflammatory cell density, as well as non-invasive infrared meibography. Recent advances in therapy for MGD include emulsion eye drops containing lipids, intraductal meibomian gland probing, the LipiFlow® thermal pulsation system, oral omega-3 fatty acids, topical azithromycin, cyclosporine-A 0.05%, diquafosol 3% and a vitamin-D analog Maxacalcitol as immunomodulatory agents. Several of these are evolving modalities and require further research before they are incorporated in guidelines for optimal management of MGD.

Keywords: Meibomian gland pathology, lipid layer thickness, dry eye disease, Superoxide Dismutase-1, Confocal Microscopy.

INTRODUCTION

The International Workshop on Meibomian gland dysfunction (MGD) defined MGD as "a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease".[1] The present review article describes recent progress and future directions in MGD epidemiology, pathophysiology, diagnosis and treatment.

Epidemiology

Prevalence of MGD in various published studies varies from under 20% to over 70%, the wide range being attributed either to different diagnostic criteria considered in these studies, or to geographic differences.[2-4] The prevalence of MGD is higher in Asians, ranging from 46.2% as found in the Bangkok study to 69.3% in the Beijing Eye Study.[5-8] This contrasts sharply with reports from populations with a majority of Caucasians, which have shown a range from 3.5% in the Salisbury Eye Evaluation study to 19.9% in the Melbourne Visual Impairment Project.[9-14] Prevalence is also affected by age, with a study among army personnel in the United States reporting MGD in 33% of patients aged <30 years and in 72% of patients aged ≥60 years.[15]

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Pathophysiology

The advent of genetic studies have led to better understanding of the pathophysiology of MGD. Ibrahim et al investigated alterations in the meibomian glands in Cu, Zn-superoxide dismutase-1-knockout mice and found an accumulation of large lipid droplets and increased terminal deoxynucleotidyl-transferase (dUTP) nick-end labeling and oxidative stress-marker staining in the meibomian gland acinar epithelium, suggesting the role of reactive oxygen species in the pathogenesis of MGD.[16]

Polyunsaturated fatty acids, particularly linoleic acid play an important role in the development of MGD. Arita et al examined the relationship between the composition of free fatty acids (FFAs) in meibum, and signs and symptoms in patients with MGD and healthy controls. They found that unsaturated FFAs tend to be more abundant in colored meibum.[17] In another study, they reported that the relative amount of linoleic acid in meibum is associated with the

severity of telangiectasia and plugging of gland orifices in patients with MGD.[18]

Dietary deficiency of fatty acids also seems related to the pathogenesis. Miyake et al found that MGD developed in hairless mice fed on a special diet with limited lipid content. In this mouse model, findings characteristic to MGD such as plugging of the meibomian gland orifices, telangiectasia, and toothpaste-like meibum, were observed. Histopathological changes included hyperkeratinization of the ductal epithelium in the meibomian gland with loss of acini and atrophy of the meibomian glands. These findings were similar to those in patients with MGD. In addition, azithromycin treatment decreased the number of plugged orifices.[19]

Meibum composition also seems to be related to the health of the ocular surface. Wang and colleagues showed in Tabby mice, that ectodysplasin A (Eda), via regulation of the epithelial growth factor receptor (EGFR) signaling pathway plays an essential role in the maintenance of ocular surface epithelial homeostasis, and this seems to be related to meibum composition.[20]

These recent studies have provided direct evidence for the hypothesis that alterations in the lipid composition play a crucial role in the development and worsening of MGD. However, the factors affecting the composition of lipids in meibum require further research.

Diagnostics

The International Workshop on Meibomian Gland Dysfunction has diagnosed MGD with the help of symptom questions, tear stability, tear secretion (Schirmer I, Schirmer II, Index of tear volume), ocular surface damage assessed with rose bengal stain, meibometry, interferometry and lid morphology.[21] However the study had not proposed specific diagnostic tests for MGD. Recently, a number of new diagnostic modalities have been introduced:

1. **Slit-Lamp Assisted Grading Recommendations**

Arita et al developed new grading scales for MGD signs that were based on many photographs of lids in patients with MGD and healthy controls. Abnormal lid margin findings of vascularity, plugging of gland orifices, lid margin irregularity, lid margin thickening, partial glands, and gland dropout were assessed. A validation test was performed in another set of patients with MGD to evaluate the efficacy of the proposed grading scales, which showed appropriate inter- and intrarater reliabilities for grading MGD. This suggested the suitability of the grading scales for the standardization of slit-lamp findings in MGD patients.[22]

2. **Measurement of Lipid Layer Thickness**

Previous studies have reported the correlation between a thinner tear film lipid layer thickness (LLT) and fewer expressible meibomian glands. A direct quantification of LLT measurements using an interferometer is useful for the diagnosis of obstructive MGD. Thus, the LipiView® interferometer (TearScience, Inc., Morrisville, NC, USA) has been introduced as a new tool for MGD diagnosis.[23,24]

Finis et al reported that the sensitivity and specificity for MGD diagnosis were 65.8% and 63.4%, respectively, when the LLT cutoff value was ≤75 nm, and 47.9% and 90.2%, respectively, when the LLT cutoff value was ≤60 nm.[24] These values were not high enough, but their clinical utility could be enhanced when the LLT value was combined with other parameters such as symptom scores, lid margin abnormality score, and meibography score. Jung et al investigated the factors related to LLT and found that age, female sex, hyper-secretory MGD, and lid margin inflammation are all associated with increased LLT. Therefore, all of these factors must be considered in the diagnosis of ocular surface diseases.[25]

3. **In Vivo Confocal Microscopy (IVCM)**

Both microscopic (IVCM) and macroscopic (meibography) methods are useful for MGD diagnosis. Building on the works of Messmer et al who observed meibomian gland dilation and obstruction in MGD patients using IVCM, Ibrahim et al measured four confocal microscopic parameters in patients with MGD and healthy controls: Meibomian gland acinar longest diameter, Meibomian gland acinar shortest diameter, Inflammatory cell density, and Meibomian gland acinar unit density. These parameters showed strong and significant correlation with tear function, ocular surface vital staining, meibomian gland expressibility and dropout grades. All parameters showed high sensitivity and specificity for MGD diagnosis, suggesting the potential of IVCM.[26,27]

Matsumoto et al also used IVCM to evaluate the anti-inflammatory treatment response in patients with MGD.[28] Inflammatory cell density was significantly reduced, suggesting inflammatory cell density as a new parameter for evaluation of the treatment response.

4. **Non-contact Infrared Meibography**

Original meibography systems were invasive and therefore not adopted by Ophthalmology clinics. The development of non-invasive methods such as non-contact infrared meibography allowed rapid assessment of meibomian gland morphology. It is an objective and repeatable test. Changes to meibomian gland morphology associated with MGD including dropout, shortening, truncation, distortion, and dilation, can easily be identified using meibography.[29-32]

Using noncontact meibography, Arita et al revealed meibomian gland loss associated with aging, contact lens wear, and long-term topical antiglaucoma

medications.[33-36] Three types of noncontact meibography systems — slit-lamp based, mobile, and topography equipped — are readily available commercially. In addition, interferometry-equipped (LipiView® II; TearScience, Johnson & Johnson, Jacksonville, FL, USA), fundus camera-equipped (Cobra; CSO, Firenze, Italy), combined conventional and noncontact (LipiScan; TearScience), and iPhone-connected mobile (Tearscope; SBM, Orbassano, Italy) meibography systems have been developed.[29]

Therapy

The Japanese Dry Eye Society and Asia Dry Eye Society have recently recommended Tear film-oriented therapy (TFOT), which targets the tear film abnormalities revealed by Tear film-oriented diagnosis (TFOD). If the tear film is abnormal and meibomian gland dysfunction is present, treatment targeting MGD is required.[37]

1. **Emulsion eye drops containing lipids**

   In evaporative dry eye related to MGD, the pathology is thin or abnormal lipid layer in tears, leading to tear film changes.[38] Thus, emulsion eye drops containing lipids have been introduced as optional treatment for MGD.

   Recent studies have shown that that lipid containing meta-stable oil-in-water emulsion might be beneficial to the lipid layer thickness,[39] and has a measurable beneficial effect on tear stability and thereby bringing relief of symptoms.[40,41] Another recent study showed that a specific kind of cationic emulsion eye drops may improve tear spreading, facilitate lipid layer replenishment, and decrease tear evaporation due to better penetration through the membranes, which results in enhanced bioavailability.[42]

2. **Intraductal meibomian gland probing**

   Intraductal meibomian gland probing, proposed by Maskin is a relatively non-traumatic procedure to relieve the symptoms of MGD. In this method, ducts are opened and dilated mechanically to remove abnormal meibum secretions.[43] Following topical anesthesia, patients were treated with 2 mm and subsequently by 4 mm probes; 24 of the 25 cases (96%) had immediate relief of symptoms post-probing, and all the patients had relief by four weeks of probing. This rapid and lasting relief of MGD symptoms may be due to the reestablishment of orifices and central ducts by probing, and removal of the abnormal meibum leading to decrease in the lid congestion and inflammation. The disadvantages of intraductal probing includes discomfort and orifice hemorrhage during the procedure. Orifice hemorrhage resolved without treatment.[43,44]

3. **LipiFlow® thermal pulsation system**

   Expression of the meibum is an effective treatment method for MGD, when combined with lid hygiene and hot compresses.[45] Recently, new treatment methods have been introduced, including the use of the LipiFlow® device which is a temperature- and pressure-controlled device. This novel treatment for obstructive meibomian gland dysfunction has combined the benefits of both heat therapy and physical expression.[46,47] LipiFlow® may also have some adverse effects. In the immediate post treatment period, increased corneal staining was observed in the study, which improved at subsequent follow-up visits. Eyelid pain (three eyes of 138 eyes), moderate conjunctival vascular injection (one eye of 138 eyes) and ocular burning symptoms (two eyes of 140 eyes), were reported to resolve spontaneously within four weeks without treatment.[48]

4. **Oral supplementation with omega-3 essential fatty acids**

   It seems feasible that the lipid composition of the meibomian secretion can be influenced by changing dietary lipid intake to manage MGD. Omega-3 essential fatty acid supplements have been reported to improve some clinical symptoms and signs of MGD, as well as cause changes in meibum content. In a randomized, placebo-controlled, masked trial, omega-3 fatty acid supplementation resulted in improving ocular surface disease index score (OSDI), tear breakup time, and meibum score in patients with MGD.[49] In a daily dose of 1.5 grams, Omega-3 fatty acids improve tear stability and therefore contribute to improvement in dry eye symptoms.[50]

5. **Topical azithromycin**

   Azithromycin is a broad-spectrum macrolide antibiotic. Topical azithromycin is favorable for the antibacterial treatment of MGD, due to great treatment advantages such as high efficacy, favorable tissue penetration in the eyelid, good pharmacokinetics for daily dose, and a sustained delivery mechanism.[51] Besides, azithromycin has been shown to suppress the production of pro-inflammatory mediators by human corneal epithelial cells.[52] This proven anti-inflammatory activity further confirms that it is rational to treat MGD with topical azithromycin.

   Topical azithromycin treatment could suppress tissue or bacterial lipases, which are thought to degrade the lipid in meibum. Thus, azithromycin successfully contributes to correction of the differences in the phase-transition temperature of meibum. Due to this change, relief in meibomian gland orifice plugging and improvement in the lipid properties of the meibomian gland secretion can be demonstrated.[53]

6. **Topical Cyclosporine A 0.05% (tCsA)**

   Perry et al investigated the efficacy of tCsA for the treatment of MGD in a prospective study.[54] Thirty-three patients with symptomatic MGD were randomized to receive either tCsA or placebo twice daily for 3 months. At the 3-months follow-up visit, several objective parameters, including the number of lid margin vascular injections, tarsal telangiectasia, and fluorescein staining scores, showed a significant improvement in the tCsA

group, but not in the placebo group. The most significant finding was the greater decrease in the number of meibomian gland inclusions in the tCsA group than in the placebo group. These results suggest that topical CsA may be helpful in the treatment of MGD.

Rubin and Rao assessed the efficacy of tCsA ophthalmic emulsion versus tobramycin 0.3%/dexamethasone 0.1% in patients with posterior blepharitis.[55] Cyclosporine provided greater improvements in Schirmer's scores ($p<0.001$) and tear break-up time $p=0.018$) than tobramycin/ dexamethasone after 12 weeks of treatment. Eyelid health also improved in both groups, but the mean improvement in meibomian gland secretion quality was significantly greater with cyclosporine than with tobramycin/dexamethasone ($p=0.015$). However, the numbers of subjects in these studies were relatively less, which may have led to some unavoidable contradictions when establishing the role of cyclosporine A.

7. **Topical Diquafosol**

Topical diquafosol, is a P2Y2 purinergic receptor agonist that activates P2Y2 receptors on the ocular surface, including the meibomian glands, to increase lipid production.[56-58] Arita et al used 3% diquafosol ophthalmic solution in patients with obstructive MGD for more than 4 months.[59] Ocular symptoms, lid margin abnormalities, superficial punctate keratopathy score, and meibum grade were decreased, while tear breakup time, tear film meniscus area, and meibomian gland area were increased. These results suggest that topical diquafosol therapy is effective for patients with obstructive MGD.

Amano and Inoue administered topical 3% diquafosol ophthalmic solution for 3 months in patients with MGD.[60] The number of telangiectasis and plugged gland orifices significantly decreased after 1 month of treatment, while the meibum score and meiboscore significantly decreased at 3 months. The increase in the tear LLT at 20 minutes after diquafosol administration became statistically significant at 3 months. Altogether, diquafosol ophthalmic solution has the potential to improve signs and symptoms in patients with MGD.

8. **Topical Vitamin D3 Analog (Maxacalcitol)**

An association between Dry eye syndrome (DES) and vitamin D deficiency has been suggested. In addition, Vitamin D has extensive immunomodulatory effects.[61] Hyperkeratinization is a major cause of obstructive MGD. Maxacalcitol (a noncalcemic analogue of the active form of vitamin D3) is effective for skin hyperkeratosis such as psoriasis and icthyosis. Thus, maxacalcitol is expected to be effective in patients with MGD.[62] Arita et al applied maxacalcitol ointment to the lid margins of patients with obstructive MGD for 2 months. They observed a significant improvement in clinical parameters (scores for plugging of meibomian gland orifices and lid margin vascularity, the tear breakup time, meibum grade, and meibomian gland area).[63]

CONCLUSION

MGD is one of the most common disorders encountered by ophthalmologists, and it may involve inflammation, hypersecretion, obstruction and abnormal lipid secretion of the meibomian glands. The pathophysiological role of oxidative stress needs further research and it provides future direction for development of anti-oxidant treatment for MGD. Previous grading classifications lack specificity for severity of MGD, which needs further work. New diagnostic tools LipiView®, noncontact meibography and in vivo confocal microscopy have been developed, which need standardization of parameters and increased accessibility, as they are costly. Although there are a number of traditional treatment options, such as warm compresses and lid hygiene for alleviating obstructed meibum, and antibiotics and anti-inflammatory agents used to improve the quality of meibum; still the treatment of MGD remains challenging. Intraductal meibomian gland probing could produce lasting rapid relief of MGD symptoms. A novel treatment, LipiFlow® applies heat and pressure as a safe and effective treatment for MGD. Emulsion eye drops containing lipids may be viewed as optional treatments for MGD. Topical azithromycin therapy could lead to clinical control or relief in the symptoms and signs of MGD, and result in improvement in the lipid composition of meibomian gland secretion; thus, it could be a potentially effective and safe treatment for MGD. Nutritional supplementation with omega-3 essential fatty acids and topical immunomodulatory agents such as cyclosporine A, diquafosol and maxacalcitol are also potential adjunctive treatments for MGD. These evolving modalities require further research before they are incorporated in guidelines for optimal management of MGD.

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