

Latest developments on meibomian gland dysfunction: Diagnosis, treatment and management



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Background: Meibomian gland dysfunction (MGD) is one of the leading causes of evaporative dry eye disease and one of the most common ophthalmic conditions found in clinical practice. Meibomian gland dysfunction tends to be overlooked because its signs and symptoms do not cause blindness. Meibomian gland dysfunction is characterised by the obstruction of the meibomian gland terminal ducts resulting in tear film instability.

Aim: The purpose of this article was to provide an update on MGD's diagnosis and treatment.

Method: A literature review was conducted using search engines such as Google Scholar, Medline and ScienceDirect databases. Keywords such as MGD diagnosis and management and treatment of MGD were used to search the databases.

Results: A total of 44 relevant papers were reviewed. These papers were then curated to include only those concerning diagnosis of meibomian gland dysfunction, treatment of meibomian gland dysfunction and management options of meibomian gland dysfunction. The references of individual papers from the curated results were checked to yield a further 13 papers.

Conclusion: Meibomian gland dysfunction is not a single entity but is multifactorial in origin; however, our understanding of the condition is evolving rapidly because of newer imaging technology. There is no gold standard treatment option for MGD, but many options are available that include medications and other procedures.

Keywords: meibomian gland dysfunction; Demodex; dry eye disease; meibum; management and treatment of MGD; diagnosis of MGD.

Introduction

The eye is constantly subjected to drying and stress through the evaporation of the tears but is protected from damage by the tear homeostatic mechanism that regulates tear secretion from the ocular surface.^{1,2,3} Physiologically, homeostasis is the state of equilibrium in the body with respect to its various functions and to the chemical composition of various fluids and tissues. Disruption of homeostasis is considered to be the unifying characteristic that describes the fundamental process in the development of a disorder or disease.

Meibomian glands are essential components of the ocular surface homeostasis. In healthy eyes, the meibomian glands provide the meibomian lipids or meibum onto the ocular surface, which is essential for the maintenance of ocular surface health.^{1,2,3,4,5,6,7,8,9,10,11} They reduce tear evaporation during waking and working hours, seal the lid margins during sleep, function as lubricants for the eyelids during blinking, provide a barrier to prevent bacteria from entering the tear film and help to maintain the smooth optical surface required for good visual acuity.^{3,4,5,6,7,8,9}

Disorders or interruption of the normal function of meibomian glands results in meibomian gland dysfunction (MGD). Meibomian gland dysfunction is one of the leading causes of evaporative dry eye diseases and is one of the most common conditions encountered by ophthalmic clinicians.⁵ Meibomian gland dysfunction is defined as:

[A] chronic, diffuse abnormality involving most of the meibomian glands and is commonly characterised by terminal duct obstruction, retention of thickened opaque meibum with qualitative/quantitative changes, and cystic dilation, shortening, atrophy or loss of meibomian glands.^{1,2}

It is characterised by alterations in gland morphology and location, as well as waning in quality and quantity of gland secretion. Meibomian gland functional abnormalities lead to reduced

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meibum secretion, altered tear film lipid composition, ocular surface disease, ocular and eyelid discomfort and evaporative dry eye disease.^{9,10,11}

Classification

The 2011 International Workshop on MGD represented a significant advance in the understanding and classification of MGD.² This workshop classified MGD as low- and high-delivery status based on the degree of gland meibum secretion. Low-delivery MGD is defined as decreased lipid secretion because of either hyposecretion or obstruction (either as cicatricial or as non-cicatricial). Obstructive MGD is the most commonly seen type of MGD, which presents with reduced lipid secretion combined with highly viscous meibum because of duct orifice inflammation and hyperkeratinisation. High-delivery MGD is characterised by the release of large amounts of meibum at the lid margins and is called meibomian gland hypersecretion. These classifications are further split into primary and secondary causes.^{2,3} Primary hyposecretion of MGD is associated with gland atrophy without signs of gland obstruction. Mucus pemphigoid is a secondary cause of obstructive cicatricial MGD whilst seborrheic dermatitis and acne rosacea are secondary causes of both obstructive and non-cicatricial and hypersecretory MGD.

Pathophysiology of meibomian gland dysfunction

Meibomian gland dysfunction is not a single entity but a heterogenous complex condition associated with multiple pathological mechanisms, arising from any combination of the following separate pathophysiological mechanisms: eyelid inflammation, conjunctival inflammation, corneal damage, microbiological changes and tear film instability associated with dry eye disease.^{4,5}

During the early stages of meibomian gland obstruction, the production of meibum continues but the inability of the meibum to be excreted because of obstruction results in increased pressure within the meibomian glands. This increased pressure causes dilation of meibomian gland ducts and the acini, which may ultimately lead to loss of meibocytes. Stagnation of the meibomian gland lipids causes alterations to the meibomian secretions. Prolonged meibomian gland obstruction can lead to bacterial colonisation. The bacterial colonisation then produces lipolytic enzymes that can cause highly irritating free fatty acids to breakdown the lipids in the tear film contributing to the loss of tear film integrity.⁶ Changes in normal meibomian lipid and the generation of free fatty acids may result in hyperkeratinisation of the meibomian glands.^{1,2,3} Once the epithelium becomes hyperkeratinised, the orifices of the meibomian glands can become obstructed, thus preventing meibum from exiting onto the ocular surface. The loss of tear film stability allows for increased aqueous tear evaporation leading to signs and symptoms of evaporative dry eye.

Obstructive MGD is the most common type of MGD associated with hypertrophy of the duct epithelium and keratinisation

of orifice epithelium.⁴ In obstructive MGD, there is hyperkeratinisation of the epithelium lining of the meibomian gland ducts, which then causes terminal duct obstruction.

Diagnosis

The diagnosis of MGD can be problematic as the symptoms are not specific to the disorder. Meibomian gland dysfunction can be symptomatic or asymptomatic and may develop alone or in association with ocular surface diseases. Ophthalmic clinicians also face a challenge in differentiating MGD from dry eye disease, and so there are challenges to come up with a management approach for symptomatic patients. There are several technologies that are emerging and showing improvement in diagnostic procedures.^{7,12,13,14,15,16,17,18,19,20,21} These include meibography, oculus keratograph 5M, interferometry and *in vivo* confocal laser microscopy.

Non-contact meibography

Meibography is a specialised technology developed exclusively for the purpose of observing the morphology of meibomian glands *in vivo*.^{7,12,13,14,15} The original contact meibography developed in 1977 was uncomfortable for the patient because of heat, brightness and sharpness of the probe. Non-contact meibography is a non-invasive method that allows for the visualisation of meibomian glands without any discomfort to the patient and is performed with a slit-lamp biomicroscope that has an infrared filter and video camera to image the everted eyelid. The meiboscore is an approach to assess areas of partial or destroyed meibomian gland structure as compared with normal regions of the eyelid margins.

The meiboscore is the quantitative analysis of meibomian gland loss and is assigned values between 0 and 3 for the upper and lower eyelid of each eye based on the quantitative analysis of the meibomian gland loss. A score of 0 = lid has no missing glands, 1 = lid area has 33% missing glands, 2 = missing glands involves 33% – 66% and 3 = area of meibomian gland loss is more than 66%. Meiboscores for the upper and lower eyelids are summed to derive a total meiboscore from 0 to 6 per eye.^{3,7} A healthy individual has a score of zero for both upper and lower eyelids, which implies that the lids have no partial or missing meibomian glands.

Optical coherence tomography

Meibography was found not to always be accurate and suffered from reproducibility issues as meibography needed to be interpreted in the context of other clinical parameters, such as tear breakup time (TBUT) and expression of the meibomian glands for the diagnosis of MGD. Optical coherence tomographic (OCT) meibography was then developed to overcome the difficulties of non-contact meibography.^{16,17} The method was developed solely for direct observation of the morphology of meibomian glands *in vivo*, and it became possible to produce an image from the reflection of light off the desired surface being viewed. Optical coherence tomographic meibography is a non-invasive method capable of obtaining 2-D and 3-D tomograms of the meibomian glands *in vivo*.^{16,17}

Optical coherence tomography has an advantage because it can quantify the structure of the meibomian glands volumetrically and the measures can be used to diagnose and follow the progression of MGD.

Oculus Keratography 5M

This represents one of the latest technologies in keratography. Keratography permits visual assessment of the topography of the corneal surfaces, allowing for an analysis of tear film stability.¹² Keratography 5M is a non-contact corneal topography with an integrated keratometer and colour camera (using an inbuilt infrared camera for meibography). The keratography 5M can detect very early tear film changes, which may be an advantage of its use, and thus it has the potential for improving the diagnosis of MGD.

In vivo confocal laser microscopy

In vivo confocal microscopy is another emerging relatively non-invasive imaging method, which is being utilised in many areas of medicine and the procedure has been trialled in ophthalmic field or practice to examine meibomian glands.¹⁸ *In vivo* confocal microscopy is used to evaluate various ocular structures, ocular surface diseases and anterior segment disorders. The technique involves scanning the inverted eyelid and meibomian glands whilst moving the appanating lens of the microscopy along the eyelid. This *in vivo* confocal laser microscopy can obtain multiple images, resolving and characterising the microenvironment and microscopic structures of the meibomian glands. However, the procedure requires an experienced examiner and the use of topical anaesthesia.

Treatment options

The most important goal of MGD treatment is to increase the quality and quantity of meibomian expression and thus to reduce or eliminate the symptoms of the patient. Conventional management of MGD includes eyelid hygiene, topical lubricants, topical and systemic antibiotics with anti-inflammatory properties and topical steroids.^{19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57} However, there are current and emerging treatment approaches such as various devices (see Section Eyelid hygiene)^{54,55,56,57} or topical and systemic therapies.^{19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53}

Eyelid hygiene

Eyelid hygiene is regarded as the cornerstone or mainstay treatment of MGD. It involves eyelid warming or heating and mechanical eyelid massage.^{19,20,21,22,23,24,25,26,27,28} Application of heat to the eyelid results in increased melting temperature of meibum. Meibum in healthy individuals begins melting at 32 °C but for patients with the obstructive form of MGD, the melting temperature is 35 °C.^{19,20,21} Application of warmth to the meibomian glands promotes melting of the altered meibomian lipids and results in unplugging of the meibomian gland orifices, thereby encouraging the meibum to flow more

smoothly. Meibomian gland dysfunction can cause meibomian glands to produce meibum secretion with reduced levels of lipids compared with those produced by normal meibomian glands. Lid hygiene is also important to eliminate microbes that are associated with MGD, such as *Staphylococcus* species and Demodex mites.^{21,22,23,24} These microbes are believed to contribute to the changes in meibum secretion.

After eyelid warming, eyelid massaging can be performed by gently applying a cotton bud to the eyelid, starting from the nasal canthus and moving laterally towards the lateral canthus in circular motions.^{19,20,21} It is recommended that warm compresses should be performed for 5 min in the morning and evening, followed by eyelid massage.²⁰ Lid scrubbing and massage were found to increase tear film stability in patients with MGD by 66.4%.^{19,20,21} Eyelid cleaning products include lid hygiene shampoo and eyelid cleanser. These products are believed to ameliorate ocular symptoms and reduce ocular surface inflammation in patients with blepharitis or MGD and also improve tear film stability.^{19,21,22,23,24} Whilst eyelid warming and eyelid massaging are the mainstay treatment for MGD, they are relatively time consuming and may cause compliance problems in some patients.

LipiFlow, an instrument or device, that produces an intense pulsed light (IPL) therapy is one of the newer technologies to improve on traditional eyelid hygiene approaches.^{25,26,27,28,29,30} The LipiFlow system applies 42.5 °C heat to the eyelid surfaces over the meibomian glands to melt the meibum and increase the number of functional meibomian glands. It uses similar principles as scleral lenses whereby a scleral shell is inserted under the eyelid whilst a second outer shell rests on the outside of the eyelid.²⁵ The inner shell provides heat to the tarsal conjunctiva of both upper and lower eyelids, whilst the outer shell simultaneously applies a massaging pressure for 12 min. A trial study was conducted to compare the LipiFlow with an eyelid warming device for the management of MGD³⁰ and although both techniques were found to be effective by increasing the number of functional meibomian glands at three months of treatment, the LipiFlow treatment showed a rapid improvement within the first month of treatment.^{28,29}

Intense pulsed light therapy is another non-invasive treatment that uses high-intensity light from a broad-spectrum source (0400 nm – 1200 nm)^{31,32,33,34} to excite melanin and haemoglobin in the skin and thereby induce coagulation and ablation of blood vessels. Intense pulsed light therapy is generally administered for the treatment of dermatological conditions, but patients with MGD may benefit from its use. The mechanism of IPL in MGD is putatively related to the thermocoagulation of vascular telangiectasia and antimicrobial effects.^{31,32,33,34} It causes closure of abnormal blood vessels, which are thought to secrete inflammatory mediators that cause malfunction of the meibomian glands. Based on results of a randomised, controlled, double-masked clinical study on long-term effects of IPL combined with meibomian gland expression in the treatment of MGD,³³ it was found that the IPL therapy could be a potential standard treatment option for MGD.

Artificial tears

Artificial tears are believed to replenish and stabilise the lipid layer of the tear film by reducing tear evaporation and ameliorate the signs of MGD.^{35,36} The commonly used artificial lubricants include Optive Plus (Allergan) and Systane (Alcon). Eyelid cleanser and Tears Away lipid-containing eyelid spray have also been shown to relieve symptoms of dry eye disease. The spray is applied to the closed eye and the liposomes enters the tear film via the lid margins.³⁵ It has been shown that a single application of lipid-containing spray significantly increases the tear film stability for up to 90 min.

Artificial tears are recommended to patients with MGD and aqueous-deficient dry eye disease because they reduce hyperosmolality, reduce friction on blinking, improve spreading of the tear film lipid layer and dilution of inflammatory cytokines in the tears, thus reducing pro-inflammatory stimuli.^{20,21}

Antibiotics

Although the role of bacteria in the pathophysiology of MGD is uncertain, antibiotics are commonly used in the treatment of the dysfunction. It is not clear if the bacterial species found on the lid margins in patients with MGD indicates that an infection is because of bacteria colonising the lid margin. So, the use of antibiotics in the treatment of MGD is to reduce the presence of bacterial species associated with MGD. Topical antibiotics that are commonly used to treat MGD include bacitracin, fusidic acid, metronidazole, fluoroquinolones, tetracycline and macrolides (such as azithromycin).^{36,37,38,39} Tetracyclines are bacteriostatic antibiotics often preferred in the management of rosacea and MGD primarily for their anti-inflammatory and lipid-regulating properties rather than their antibiotic effects.³⁶ Tetracyclines suppress the production of bacterial lipase and the release of pro-inflammatory free fatty acid molecules, which can cause instability of the tear film and inflammation within the meibomian glands. The use of tetracyclines is contraindicated in pregnant women and children under the age of 8 years.³⁶ The main side effects of tetracycline include photosensitivity and gastrointestinal symptoms. Other bacteriostatic antibiotics used in the treatment of MGD are doxycycline and minocycline.³⁶ These two antibiotics are more lipophilic compared with tetracycline, but their doses have anti-inflammatory effects on the ocular surface. They tend to be more concentrated in ocular and lid surface at the lower doses of 50 mg – 100 mg once or twice a day, whilst the dosage of tetracycline is 250 mg once to four times a day.

Azithromycin is a broad-spectrum macrolide antibiotic with anti-inflammatory and antibacterial action.^{37,38} However, its mechanism for its anti-inflammatory activity is not clear but is believed to block the activation of the nuclear factor, leading to a decrease in some of the inflammatory cytokines. Azithromycin stimulates the accumulation of intracellular phospholipids and lysosomes, which are important in the

maturation of meibocytes and has been reported to restore the composition of meibum to a near-normal state through an antilipase effect.³⁹ However, the optimal dosage, frequency and duration of its use for MGD is unknown and remains to be established.

Anti-inflammatory agents

The role of inflammation in the aetiology and pathophysiology of MGD is controversial because it is not entirely understood; however, the association between MGD and ocular surface inflammatory diseases (blepharitis, giant pupillary conjunctivitis and Sjogren's syndrome) has been reported. It has been reported that patients with blepharitis have increased meibum levels of phospholipase A2, which contributes to the synthesis of inflammatory mediators and results in the production of inflammatory cytokines.^{40,41,42,43,44} The presence of inflammatory cytokines in the tear fluid of patients with MGD can cause increased epithelial proliferation and keratinisation, thereby causing the obstruction of meibomian glands. Cyclosporine A and corticosteroids are therefore recommended in the management of MGD.

Cyclosporine A is a calcineurin inhibitor agent: a highly specific immunosuppressant agent.⁴⁰ Calcineurin is a molecule that induces cytokines. Topical cyclosporine A inhibits the T-helper lymphocytes proliferation and reduces ocular surface inflammation, which is responsible for the pathophysiology of MGD. Cyclosporine A has been shown to increase aqueous tear production, improve lipid layer parameters, lid margin redness and the quality of meibomian gland secretion.⁴²

Topical corticosteroids have proven to be useful in the treatment of inflammation or inflammatory complications of MGD. It has been reported that corticosteroids demonstrated an improvement in TBUT, meibum quality, improved meibomian gland expression with 0.5% loteprednol ophthalmic suspension four times a day for a month.^{42,43} All participants were requested to practice lid hygiene once daily. However, long-term corticosteroid use is not advisable considering the risk of cataract formation, elevation in intraocular pressure and infections.⁴⁴ Therefore, the use of steroids should be measured against the more serious risks because MGD does not cause blindness.

Essential fatty acids

It has been reported that the essential fatty acids have an anti-inflammatory effect. The anti-inflammatory effect of oral omega-3 fatty acids is associated with a quantitative improvement in fatty acid saturation content in meibum.^{45,46,47,48} Several studies have reported that omega-3 and omega-6 oral supplementation have a beneficial effect with essential fatty acids in dry eye disease and MGD.^{45,47} Omega-3 dietary supplementation was also found to improve overall ocular surface disease index (OSDI) score, TBUT and Schirmer tear

test score.⁴⁶ It is believed that omega-3 fatty acids suppress inflammation and may have an influence on the fatty acids composition and lipid properties of meibum, whilst omega-6 fatty acid promote inflammation.⁴⁵ Further research is needed to fully explain these underlying mechanisms and how they improve the signs and symptoms of MGD.

Microbe treatment

The importance of eyelid hygiene in the management of MGD is highlighted by the potential involvement of microbes in the pathology of MGD. These microbes are reported to contribute to the changes in meibum secretion, increased melting temperature and further inflammation.^{20,21,49} Demodex mite is the most common parasite found on the human skin^{49,50,51,52,53} with the most common species being *Demodex folliculorum* (found primary in lash follicles) and *Demodex brevis* (found mainly in sebaceous and meibomian glands of eyelids).²⁴

Although there is no clear evidence of the causal relationship with MGD, Demodex is believed to cause MGD in several mechanisms. *Demodex folliculorum* has been reported to directly damage cells at the base of the hair follicle, causing reactive hyperkeratinisation resulting in the formation of cylindrical dandruff (debris).^{45,50} *Demodex brevis* is thought to physically block the meibomian glands by their excreta, resulting in irritation, thus predisposing to MGD and chalazia.⁵² Demodex mites trigger an inflammatory response and cause hypersensitivity reaction. The mites and their excreta can directly block gland orifices resulting in MGD.

Diluted tea tree oil (TTO) treatment of the lids has been found to be effective in the treatment of blepharitis associated with Demodex.⁵³ Tea tree oil has been shown to reduce mite counts, reduce inflammation of eyelid and provide significant relief from itching^{52,53} with the adverse effect of contact dermatitis and hypersensitivity reactions attributed to certain ingredients and patient allergens.⁵³ Other agents such as pilocarpine gel, camphorated oil, sulphur ointment and povidone iodine are being investigated to physically trap and eradicate mites as they try to emerge from one follicle to another.^{52,53} Whilst TTOs full mechanism of action against Demodex mites is unknown, it is the most promising option for killing the mites and may be more effective as they are known to have antibacterial, antifungal and anti-inflammatory properties.^{50,51}

Surgical procedures for meibomian gland dysfunction management

As terminal duct obstruction is the key feature of the MGD, mechanical opening of the terminal ducts and expression of the meibum may play an important role in the management of the disease. Intraductal meibomian gland probing involves mechanical opening and dilating blocked meibomian gland orifices and ducts with probes of varying sizes from 1 mm to 6 mm depending on the length of the glands.^{54,55,56,57} Probing can assist in releasing accumulated meibum. This surgical procedure is recommended for chronic MGD, commonly known as meibomianitis or posterior blepharitis.

Conclusion

Meibomian gland dysfunction is one of the most debated topics in eye care but is often overlooked with regard to management. A firm understanding of the role of meibomian gland structure and function is important to address, improve and promote a healthy ocular surface. The traditional approach to dry eye diseases involves the patient's subjective symptoms and the first treatment option that is often given to patient is artificial tears. However, the root cause of the dry eye condition may not have been identified and treated. With firm understanding of both the structure and function of the meibomian glands, clinicians may no longer have to rely only on the patient's subjective symptoms, and the root cause of dry eye disease can be identified and treated. This will leave the patient with a better quality of ocular health.

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S.D.M. is the sole author of this research article.

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