A B S T R A C T

Dry eye disease is one of the most common ophthalmic complaints; it results from the activity of various pathways and is considered a multifactorial disease. An important factor that contributes to the onset of dry eye disease is meibomian gland dysfunction. Meibomian gland dysfunction causes a disruption in the tear film lipid layer which affects the rate of tear evaporation. This evaporation leads to tear hyperosmolarity, eventually triggering the onset of dry eye disease. Dry eye disease and meibomian gland dysfunction are strongly associated with each other, such that many of their risk factors, signs, and symptoms overlap. This review aimed to provide an update on the association between dry eye disease and meibomian gland dysfunction. A stepwise approach for diagnosis and management is summarised.

Introduction

Dry eye disease (DED) is one of the most common ocular surface diseases, which can significantly affect the quality of life of affected patients. The definition of DED has been progressively established in recent decades. The goal of the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) is to create an evidence-based definition, a well-defined classification system, and an appropriate diagnosis and management algorithm for DED.1 In 2007, the TFOS DEWS definition of DED was first published.2 In 2017, the TFOS DEWS II amended the definition of DED to be ‘a multifactorial disease of the ocular surface, characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles’.3 The term ‘multifactorial’ indicates that the disease occurs as a result of multiple influential factors, while the term ‘etiological roles’ suggests the involvement of various pathways in the onset of DED.1 In 2017, the Asia Dry Eye Society also agreed upon a new definition of DED, as ‘a multifactorial disease characterised by unstable tear film causing a variety of symptoms and or visual impairment, potentially accompanied by ocular surface damage’.5

The two main categories of DED are evaporative dry eye and aqueous deficient dry eye.2 Evaporative dry eye is related to conditions that affect the eyelids, such as meibomian gland dysfunction (MGD), poor blinking effort, and lid disorders, or that affect the ocular surface, such as prolonged contact lens wear, frequent use of topical drug preservatives, and immune-related ocular surface disorders (eg, atopic keratoconjunctivitis). Aqueous deficient dry eye is primarily due to conditions affecting lacrimal gland function, such as Sjögren’s syndrome, lacrimal gland duct obstruction or deficiencies, and adverse effects of systemic drugs. Epidemiological evidence suggests that DED is mainly evaporative in nature,4 and is often associated with MGD.5,6

Meibomian glands are found in the upper and lower eyelids, where they secrete lipids (meibum) onto the ocular surface, forming the outermost layer of the tear film. These lipids spread easily, promoting tear film stability and protecting against evaporation. Meibomian gland dysfunction is defined as ‘a chronic, diffuse abnormality of the meibomian glands, commonly characterised 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’.7

This review aims to provide an update on the association between MGD and DED, with particular attention to the diagnosis and management of these conditions. We will discuss the epidemiology,
pathophysiology, risk factors, signs and symptoms, diagnosis, and ancillary imaging of MGD and DED, along with appropriate behaviour, medical, and surgical management.

Methods
A comprehensive literature search on PubMed was performed for studies published between January 2006 and December 2017 with keywords 'dry eye', 'dry eye disease', 'tear film', 'meibomian gland', and 'meibomian gland dysfunction'. Search results were limited to clinical studies published in English. Articles reporting DED and MGD were reviewed. Particular emphasis was placed on papers that investigated the association between DED and MGD. The reference lists of the retrieved articles were also examined for relevant studies.

Epidemiology
The reported prevalence of DED ranges from 5% to 50%, whereas the reported prevalence of MGD varies more widely from 3.5% to nearly 70%. Meibomian gland dysfunction appears to be more prevalent in Asian populations. Meibomian gland dysfunction has been reported to contribute to 60% of all cases of DED; an additional 20% of cases of DED are caused by aqueous deficiency.

Pathophysiology of dry eye disease
All forms of DED primarily occur because of water loss from the tear film, which leads to tear hyperosmolality due to evaporative dry eye and/or aqueous deficient dry eye. In evaporative dry eye, hyperosmolality results from excessive evaporation of tears in the context of normal lacrimal function. In contrast, in aqueous deficient dry eye, hyperosmolality occurs due to an inadequate rate of lacrimal secretion in the context of a normal rate of evaporation. Environmental factors affect the presence of hyperosmolality on the ocular surface, which may trigger the onset of DED, or cause worsening of the condition.

Pathophysiology of meibomian gland dysfunction
Meibomian gland dysfunction is classified according to the rate of gland secretion. A low delivery state is characterised by meibomian gland hyposecretion or obstruction, whereas a high delivery state is characterised by meibomian gland hypersecretion. Of these two categories, the most common mechanism is a low delivery state due to duct obstruction. Epithelial hyperkeratinisation is the most common cause of duct obstruction, leading to meibum accumulation with chronic inflammation and, eventually, gland dropout. Importantly, this results in the quantitative and qualitative abnormalities of glandular secretions. There is a high prevalence of MGD in acne rosacea, which is a chronic cutaneous inflammatory disorder.

Association between dry eye disease and meibomian gland dysfunction
The tear film consists of three distinct layers: the lipid, aqueous, and mucus layers. The lipid layer, a key component of the tear film, is derived from meibomian glands. The lipid layer prevents water evaporation from the ocular surface and is thus crucial in the maintenance of a healthy ocular surface. Dysfunction of the meibomian glands results in unbalanced lipid secretion, thereby increasing the rate of ocular surface evaporation and causing tear hyperosmolality. Patients with MGD reportedly exhibit a higher tear evaporation rate than that of normal subjects. This shows that DED is directly correlated with the integrity and quality of meibum on the ocular surface.

Risk factors
Many risk factors associated with DED also contribute to MGD. Thus, risk factor modifications can likely improve both disease states.

Sex
Female sex is a significant risk factor for the development of both DED and MGD. This may be due to the effect of hormonal changes on meibomian secretion, as androgen and oestrogen receptors are both present within the meibomian glands. Importantly, androgens have been reported to stimulate meibum secretion and suppress inflammation, whereas oestrogens reduce meibum secretion and increase inflammation. Dysfunctional meibomian gland secretion and concurrent alterations in the lipid layer have been
observed in patients with androgen depletion. Additionally, female sex has been identified as a risk factor for the development of autoimmune diseases that lead to DED, such as Sjögren’s syndrome.

Topical medications
Topical medications can cause both DED and MGD; this may be a result of ocular surface disturbances with various aetiologies, including allergic reactions, toxic epitheliopathy, and inflammatory response from chronic chemical irritation. Multiple studies have revealed a clear relationship between the prevalence of dry eye and increasing use of eye drops. The primary factor underlying this relationship is the presence of benzalkonium chloride preservative agent in topical medications. Benzalkonium chloride has been strongly linked with the onset of DED, as it dissolves the lipid tear film layer and has been shown to disrupt tear film osmolarity. Similarly, DED and MGD are commonly reported in glaucoma patients who use topical glaucoma medications, which contain benzalkonium chloride. Use of these medications has been associated with changes in meibomian gland structure, leading to MGD.

Contact lens wear
Contact lens wear is commonly associated with the onset of both DED and MGD. An epidemiological study showed that 50% of contact lens wearers experience dry eye symptoms, whereas only 22% of non–contact lens wearers experience such symptoms. Contact lens wear alters the integrity of the tear film: a thinner lipid layer has been observed in contact lens wearers, which causes an increased tear evaporation rate and tear hyperosmolarity. Environmental factors, such as prolonged usage of visual display devices, as well as air pollution and seasonal changes, further aggravate dry eye symptoms in contact lens wearers. The occurrence of MGD in contact lens wearers is suspected to be a result of chronic inflammation, as well as clogging of gland orifices due to accumulation of desquamated epithelial cells. Contact lens wearers demonstrate a high percentage of meibomian gland dropout and reduction in gland function; these aspects are reportedly directly related to the duration of contact lens wear.

Refractive surgery
Worldwide, laser in situ keratomileusis (LASIK) is the most common corneal refractive surgery currently in use. Dry eye disease is often associated with a history of LASIK, and can be aggravated by both preoperative and postoperative factors. Preoperatively, the risk of DED is significantly increased in patients who are long-term contact lens wearers, as well as in patients whose eyes exhibit pre-existing tear film instability. Greater refractive correction magnitude requires deeper ablation, resulting in a greater extent of sensory nerve damage. This nerve damage results in reduced corneal sensitivity, leading to neuropathic dry eyes. Notably, this mechanism is the most common aetiology of post-LASIK dry eyes. Corneal refractive surgery has also been shown to reduce corneal epithelial integrity, conjunctival goblet cell concentration, and meibomian gland function, resulting in lower ocular surface disease index and ocular surface staining scores.

Demodiosis
Two species of mites, Demodex folliculorum and Demodex brevis, are the only mites that affect human skin; such infestations are known as demodicosis. Reportedly, D folliculorum infests the lash follicles, whereas D brevis infests the meibomian glands. These infestations increase the meibum melting temperature, resulting in a more viscous lipid layer. A recent study showed that a higher D brevis count was associated with more severe MGD. Furthermore, confocal microscopy analysis revealed lower counts of Demodex mites in the glands of healthy subjects than in the glands of patients with MGD-related DED. The role of Demodex mites in the pathology of MGD has not been fully elucidated; however, eradication of Demodex is particularly helpful in relieving related ocular symptoms. Thus, there may be a pathogenic role for Demodex infestation in MGD.

Symptoms
Many signs and symptoms of DED overlap with those of MGD. However, most patients with MGD are largely or entirely asymptomatic; if they are symptomatic, their particular symptoms often do not directly correlate with the severity of ocular surface disturbance. In a population-based study in China, 22% of the study population demonstrated asymptomatic MGD, while 9% showed symptomatic MGD. In cases of symptomatic MGD, patients report a variety of symptoms, including foreign body sensation, dryness, itching, and/or photosensitivity. These manifestations may be linked to chronic inflammation or mechanical friction between the ocular surface and meibum that has accumulated in the gland orifices.

Ocular surface signs and diagnosis
Because DED and MGD are common ophthalmic problems, a clear diagnosis is crucial for suitable management. Appropriate tests should be used to diagnose and monitor DED, in accordance with the revised TFOS DEWS II definition of the disease. For these purposes, the TFOS DEWS II proposed a battery of diagnostic tests for DED.
The diagnostic tests begin with triaging questions and risk factor analysis. These are followed by screening for symptoms using standardised questionnaires, including the five-item dry eye questionnaire or the ocular surface disease index. Markers of homeostasis used in diagnostic testing include measures of tear breakup time, staining of the ocular surface, Schirmer’s test, and tear osmolarity. Tear breakup time is a non-invasive measurement that is defined as the time required for the tear film to break up sufficiently that the patient can no longer refrain from blinking. A tear breakup time of <10 seconds is considered diagnostic for DED (Fig 1). Ocular surface staining is performed by fluorescein staining for corneal damage and lissamine green staining for conjunctival and lid margin damage (Fig 2). Schirmer’s test consists of the placement of a small strip of filter paper inside the lower fornix with the eye closed. After 5 minutes, the amount of moisture is measured as the distance that tear moisture has travelled on the paper, due to capillary action; a value of <5 mm indicates DED. Finally, tear osmolarity should be assessed with a calibrated device; a positive result is defined as ≥308 mOsm/L in the measured eye, or a difference of >8 mOsm/L between two eyes.

The Asia Dry Eye Society recommends diagnosis of DED by using a combination of symptoms assessed by standardised questionnaires (ocular surface disease index, McMonnies questionnaire, women’s health study questionnaire, or five-item dry eye questionnaire), together with a reduced tear breakup time (with a cut-off value of <5 s). The Asia Dry Eye Society recommends diagnosis of MGD by using a combination of symptoms assessed by standardised questionnaires (ocular surface disease index, McMonnies questionnaire, women’s health study questionnaire, or five-item dry eye questionnaire), together with a reduced tear breakup time (with a cut-off value of <5 s).

Clinical diagnosis of MGD is made based on the examination of altered anatomical features, such as meibomian gland dropout, altered meibum excretion, and changes to lid morphology, with plugging or pouting of the gland orifice. Meibomian glands with normal appearance are shown in Figure 3. Gentle gland expression with digital pressure to the central lower lid can evaluate terminal duct obstruction and meibum quality (Fig 4). Subtype classification tests, including identification of MGD features, as well as lipid thickness and tear volume assessment, are then performed to determine whether the disease constitutes evaporative dry eye or aqueous deficient dry eye. Lastly, the severity of disease is evaluated; for this purpose, the International Workshop on Meibomian Gland Dysfunction has provided a grading system that can be used to guide management of MGD.

Role of imaging in diagnosis

In recent years, multiple imaging modalities have been introduced to improve the diagnosis of DED and MGD. These modalities aim to facilitate the evaluation of the structural and dynamic properties of the tear film. In cases of DED with tear film instability, topographic systems have been used to determine changes in the edges of the mires of a Placido disc. Anterior segment optical coherence tomography aims to measure the height of the tear meniscus, while infrared meibography provides an objective evaluation of gland structures. Tear film lipid layer thickness can be measured by interferometry, which allows objective and quantitative measurement of tear film integrity.
Both DED and MGD can lower the ocular surface temperature. In DED, the increased tear film evaporation rate causes heat loss, lowering ocular surface temperature. In MGD, lower tarsal conjunctival temperatures have been observed, increasing the viscosity of meibum; this change in viscosity leads to worsening of gland function. These advancements in imaging modalities have improved accuracy and standardised the diagnosis of DED and MGD.

Management
The aim of all treatment in MGD is to increase the quality and quantity of meibum expression. For this purpose, a stepwise staged approach is necessary to standardise management of the disease. The TFOS DEWS II created an algorithm to implement various management options, on the basis of disease severity. Initially, patients must be educated regarding environmental and dietary modifications, which include essential fatty acid supplements. Patients must also be guided to eliminate factors contributing to the onset of DED, including contact lens wear, as well as both topical and systemic medications. Several lifestyle modifications, such as ensuring sufficient sleep or rest, maintaining appropriate hydration, and discontinuing smoking habits, may help to relieve symptoms. Ocular lubricants are suggested for mild DED; preferably, these should not contain benzalkonium chloride preservatives. Some of these modification approaches are outlined below, along with an overview of the emerging available treatment devices and options.

Eyelid hygiene
In the presence of MGD, eyelid hygiene is the
cornerstone of MGD management. This treatment modality consists of two components: eyelid warming and eyelid massage. Meibum in patients with MGD is more stagnant and viscous and has a higher melting temperature than that in a healthy individual; thus, warming the eyelid to melt pathologically altered meibum can improve its secretion. Warm compression provides further benefits by melting abnormal meibum. Secretions from meibomian glands in patients with MGD exhibit lower levels of lipids, esters, and free sterols. Potential involvement of microbes (ie, Staphylococcus spp, Propionibacterium acnes, Bacillus oleronius, and the Demodex species described above) contributes to the pathology of MGD-associated DED by increasing meibum melting temperature and enhancing inflammation. This illustrates the importance of eyelid hygiene in MGD management.

For patients with MGD who exhibit demodicosis, many treatment options have been described, including the use of topical 2% metronidazole. Recently, the use of tea tree oil has also increased in popularity. Tea tree oil is a natural essential oil that includes 4-terpineol, which is antimicrobial, anti-inflammatory, and toxic to Demodex. Tea tree oil lid scrubs have shown promising results as management for Demodex-related MGD.

Effective eyelid hygiene can be achieved by use of a hot compress (ie, soaking a clean towel in hot water, and applying the towel over the eyelids), which softens the meibum and allows better flow. After the application of the hot compress, lipid-by-products can be removed gently by scrubbing both upper and lower lid margins via mild upward or downward compression of the eyelid, using a moist cotton bud; this compression begins from the nasal canthus and moves laterally. An additional therapeutic approach involves the use of mildly diluted baby shampoo for lid scrubs; this is a widely accepted therapy. Although eyelid warming and eyelid massage are efficacious for the management of MGD, they are often time-consuming and labour-intensive; thus, they encounter patient compliance issues. There are now a wide variety of lid cleansing products, which facilitate standardisation and simplification of treatment. Additional treatment options include warming of the lids and expression of meibomian glands, either manually (similar to above) or with the use of specially designed devices. One such device, LipiFlow (TearScience; Morrisville [NC], United States), is designed to transfer heat through the eyelid tissue to facilitate emptying of gland contents at a therapeutic temperature of 42.5°C. LipiFlow treatment has shown promising results, and may significantly improve symptoms.

Lipid-containing artificial lubricants

The majority of artificial tears are aqueous-based; however, these offer limited and short-term symptomatic relief, partly due to the lack of a lipid component. These artificial tears evaporate at a similar rate to that of natural tears. Addition of a lipid component to the artificial lubricant helps to replenish the lipid layer of the normal tear film. These lipid-containing lubricants exhibit long retention times and can stabilise the tear film lipid layer, reduce tear evaporation, and improve the signs of MGD. Additionally, lipid-containing lubricants have a longer-lasting effect and cause minimal interference of patient vision. Commercially available lipid-containing lubricants include mineral oil, high-purity castor oil, mixtures of light and standard mineral oil, and mixtures of polar phospholipid surfactant and mineral oil. A systematic review found that these lipid-containing eye drops are efficacious and safe alternatives to conventional tear lubricants in their abilities to relieve the signs and symptoms of DED.

Anti-inflammatory medications

Because ocular surface inflammation plays an important role in the development of DED, anti-inflammatory mechanisms must be considered. For patients with moderate to severe DED, low-dose topical steroids have been advocated as a treatment choice, likely because the anti-inflammatory properties of this type of drug can improve ocular inflammation through suppression of inflammatory cytokines. Other anti-inflammatory options include non-glucocorticoid immunomodulatory drugs, such as topical cyclosporine A, which is an immunomodulatory drug that can reduce the expression of inflammatory markers. Notably, topical cyclosporine A has been proven efficacious in the treatment of DED. A randomised trial showed that cyclosporine A is beneficial in the stabilisation of tear film in patients with MGD. However, its anti-inflammatory effect is not as remarkable as that observed in DED, because the main pathophysiology
(epithelial gland hyperkeratinisation) is not clearly resolved.

In severe cases of DED, autologous serum eye drops can be considered. Autologous serum, which is the fluid component of a patient’s own blood that remains after centrifugation, exhibits similar biochemical properties to those of tears. Autologous serum reportedly contains specific factors that enhance epithelial regeneration, and can inhibit the release of inflammatory cytokines.

Another treatment option for patients with severe DED involves scleral contact lenses, which are rigid gas permeable lenses of large diameter that are supported by the sclera and serve as a bridge over the corneoscleral junction. A tear reservoir is maintained between the posterior surface of the scleral contact lens and the anterior corneal surface, improving tear osmolarity and relieving dry eye symptoms.

Omega-3 dietary supplementation

Essential fatty acid supplementation has been proven beneficial in the treatment of DED and MGD, especially when administered by intake of foods rich in omega-3 fatty acids, such as flaxseed and fish oils. There is a speculative association between essential fatty acids and modifications in lipid profile, as well as reductions in the fatty acid content of meibomian gland secretions. In a randomised, placebo-controlled, masked trial, omega-3 fatty acid supplementation resulted in improving ocular surface disease index score, tear breakup time, and meibum score in patients with MGD. Essential fatty acids also enhance the lipid layer, slow tear evaporation, and reduce apoptosis of lacrimal gland cells. Essential fatty acids have been reported to exhibit anti-inflammatory properties, particularly by promoting the production of prostaglandin. These modifications improve the tear secretion rate and tear content. Further research is needed to enhance our understanding of the underlying mechanism by which fatty acid supplementation supports the management of MGD.

Surgical and mechanical treatment options

In cases where medical treatment is insufficient, surgical and mechanical treatment options include tear conservation via punctual occlusion or moisture chamber goggles. Punctal plugs retain tears on the ocular surface by blocking lacrimal drainage through the puncta (Fig 5). Permanent surgical closure may be useful when patients cannot tolerate punctual plugs. Surgical punctual occlusion blocks tear drainage and improves tear retention, and can be performed by cautery or lacrimal canalicul ligation. A systematic review showed that, when combined with other treatment for DED, punctual occlusion improves dry eye symptoms. A less invasive option, moisture chamber goggles provide a humid environment and minimise airflow to the ocular surface, thereby slowing the evaporation of tears.

Severe DED can lead to corneal erosion, persistent epithelial defects, corneal ulceration, and eventual corneal scarring. Amniotic membrane transplant is a reasonable option in such cases. Amniotic membrane has been shown to contain multiple neurotransmitters and neurotrophic factors, which are beneficial for the management of severe DED. For patients with severe DED with persistent epithelial defects that are refractive to medical treatment, tarsorrhaphy may be useful. Notably, tarsorrhaphy is a procedure that achieves partial or total closure of the eyelids, either temporarily or permanently. By reducing ocular surface exposure, the rate of tear evaporation decreases, such that DED can improve. Due to unfavourable aesthetic outcomes, this approach is typically one of the final methods used for management of severe DED.

Suggested treatment guideline for dry eye disease or meibomian gland dysfunction for non-ophthalmologists

Dry eye disease and MGD are two of the most common ocular conditions encountered by medical practitioners. To manage these conditions, risk factors must be identified and modified. Notably, several environmental and lifestyle modifications can help alleviate these conditions. Proper lighting, anti-glare filters, ergonomic positioning of computer monitors, and regular break time from work may...

FIG 5. Appearance of punctal plug (black dot in the circle) after insertion into the lower lacrimal canalicular drainage system
help improve the symptoms.69 A modest increase in relative humidity, achieved by using a desktop-powered humidifier, has been shown to increase subjective comfort.70 Reduction or discontinuation of contact lens use, as well as enhancement of moisture within the surrounding environment, are possible risk factor modifications. Smoking cessation can also improve the ocular surface condition and tear function.71 Lubricants can be prescribed to be used as needed for symptomatic relief. If symptoms do not resolve, benzalkonium chloride–free lubricants should be considered. Low-dose topical steroids should be implemented with particular caution, owing to the risk of steroid-related complications (eg, cataract, glaucoma, and infection). In patients with recalcitrant disease, referral to an ophthalmologist is necessary to ensure regular monitoring. In the presence of MGD-related symptoms, lid hygiene and warm compression are strongly suggested for symptomatic control; careful manual expression of meibum should also be performed. If the above measures fail, or if the DED is secondary to other causes of aqueous deficiency (eg, Sjögren’s syndrome; graft versus host disease; or chronic inflammation in Stevens-Johnson’s disease, toxic epidermal necrolysis, or ocular cicatricial pemphigoid), referral to an ophthalmologist is warranted for further workup (eg, anti-SSA/Ro blood test for Sjögren’s syndrome) and management.

Conclusion

Dry eye disease is a common ophthalmic problem, with a cause that is often multifactorial. Meibomian gland dysfunction is an important contributor to DED, owing to an imbalance in lipid secretion that affects the rate of tear evaporation. When tears evaporate quickly, tear osmolarity increases, resulting in DED. There are many risk factors that contribute to onset of both DED and MGD, many of which may overlap between these diseases. A clear diagnosis is vital when managing DED. Various treatment options are available for DED and MGD, and a stepwise staged approach is often crucial for ensuring appropriate management.

Author contributions

All authors contributed to the concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an epidemiology advisor of the Editorial Board, HKL Yuen was not involved in the peer review process of the article. All authors have disclosed no conflicts of interest.

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