Ocular Surface Disease and Meibomian Gland Dysfunction

A Clinical Handbook

Théa

Preface

Meibomian gland dysfunction is very likely the most frequent cause of dry eye disease. This is an extremely important and underestimated condition.

Dry eye disease and Meibomian gland dysfunction have many overlapping signs and symptoms and share common ocular, systemic and treatment-related risk factors. The co-existence of these condition sets an unmet clinical need for accurate diagnosis and effective treatment strategy.

This project was designed to provide an illustrated stepwise approach which will assist general ophthalmologists to find their way around the different aspects of ocular surface disease and Meibomian gland dysfunction such as pathophysiology, diagnosis, interaction with dry eye disease and therapeutic options.

We hope this handbook will be a useful tool for healthcare professionals to better understand Meibomian gland dysfunction and to utilize the advice and recommendations given by this guide, in their real-world management of patients suffering with this multifactorial condition.

Enjoy your reading!

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Contents

Introduction to Meibomian Gland Dysfunction (MGD)

1.1 Definition

WHAT IS MGD?

> *MGD is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.*
>
> The International Workshop of MGD, 2011

Meibomian Gland Dysfunction (MGD) is just one form of meibomian gland disease, and a type of posterior blepharitis. The meibomian glands are large, modified sebaceous glands located in the tarsal plates of the upper and lower eyelids [1] (Figure 1).

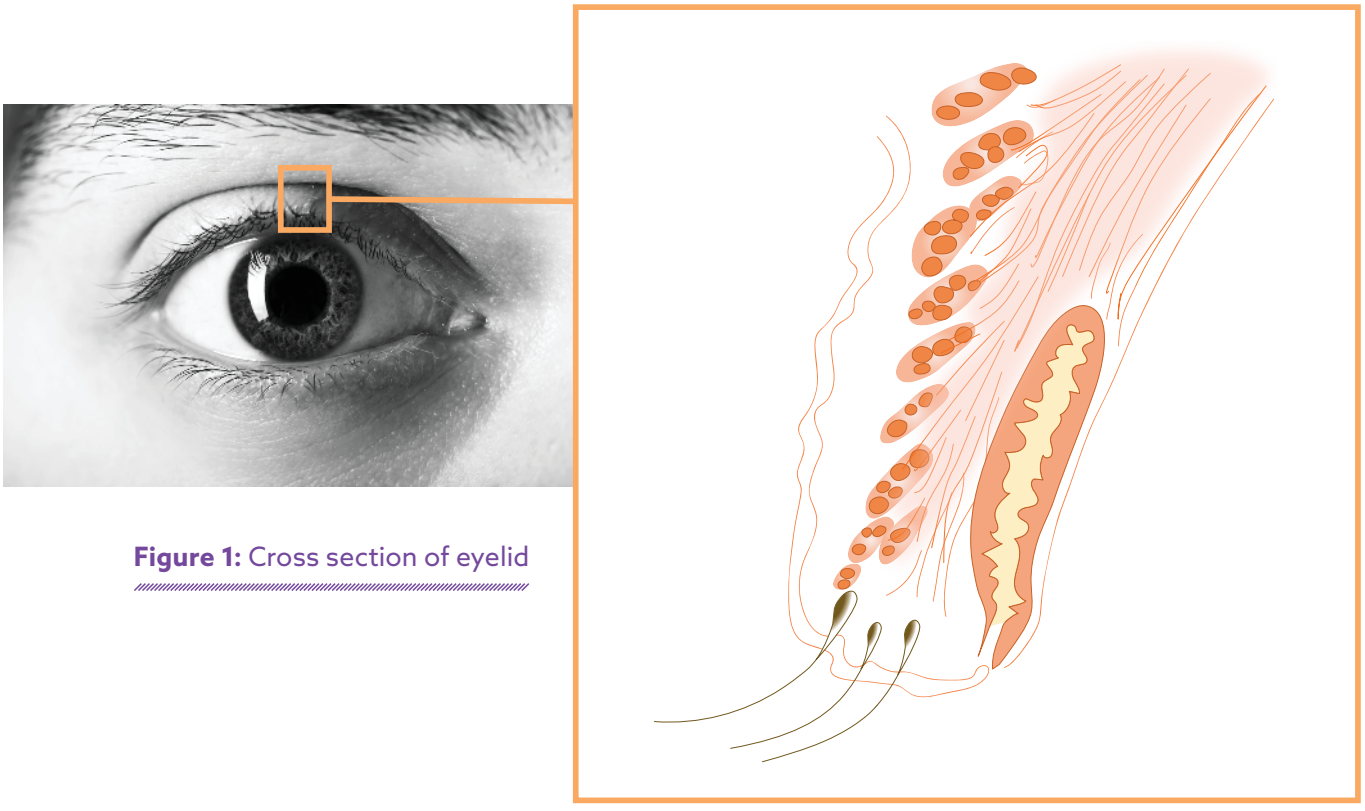


Figure 1: Cross section of eyelid

During a holocrine secretory process, meibum, comprising of polar and non-polar lipids, is continuously produced from the secretory acini and pushed through the ductal system towards a short excretory duct, the MG orifice (Figure 2a). Upon blinking, the meibomian gland is compressed driving the meibum out of the orifice, causing it to excrete into the marginal lipid reservoir provided there is contact of the orifice with the lower tear meniscus. This ultimately forms the tear film lipid layer (TFLL), promoting tear film stability and protecting against evaporation (Figure 2b).[2]

MGD pathophysiology is characterized by compromised meibum secretion due to either or a combination of the following: ductal occlusion of the MG orifice due to lipids or hyper-keratinization, as well as impairment of the mechanical forces responsible for the delivery of meibomian oil onto the margin and tear film, and inadequate tear meniscus for lipid dispersion (Figure 2).[2]

Meibomian Gland Dysfunction (MGD) can present with various degrees of severity (Figure 3) and describes abnormal meibum consistency and/or production, leading to tear film instability, ocular surface disease, ocular and eyelid discomfort, as well as entry to the vicious circle of dry eye disease [3]. It is not a term intended to describe focal abnormalities such as chalazion [1].

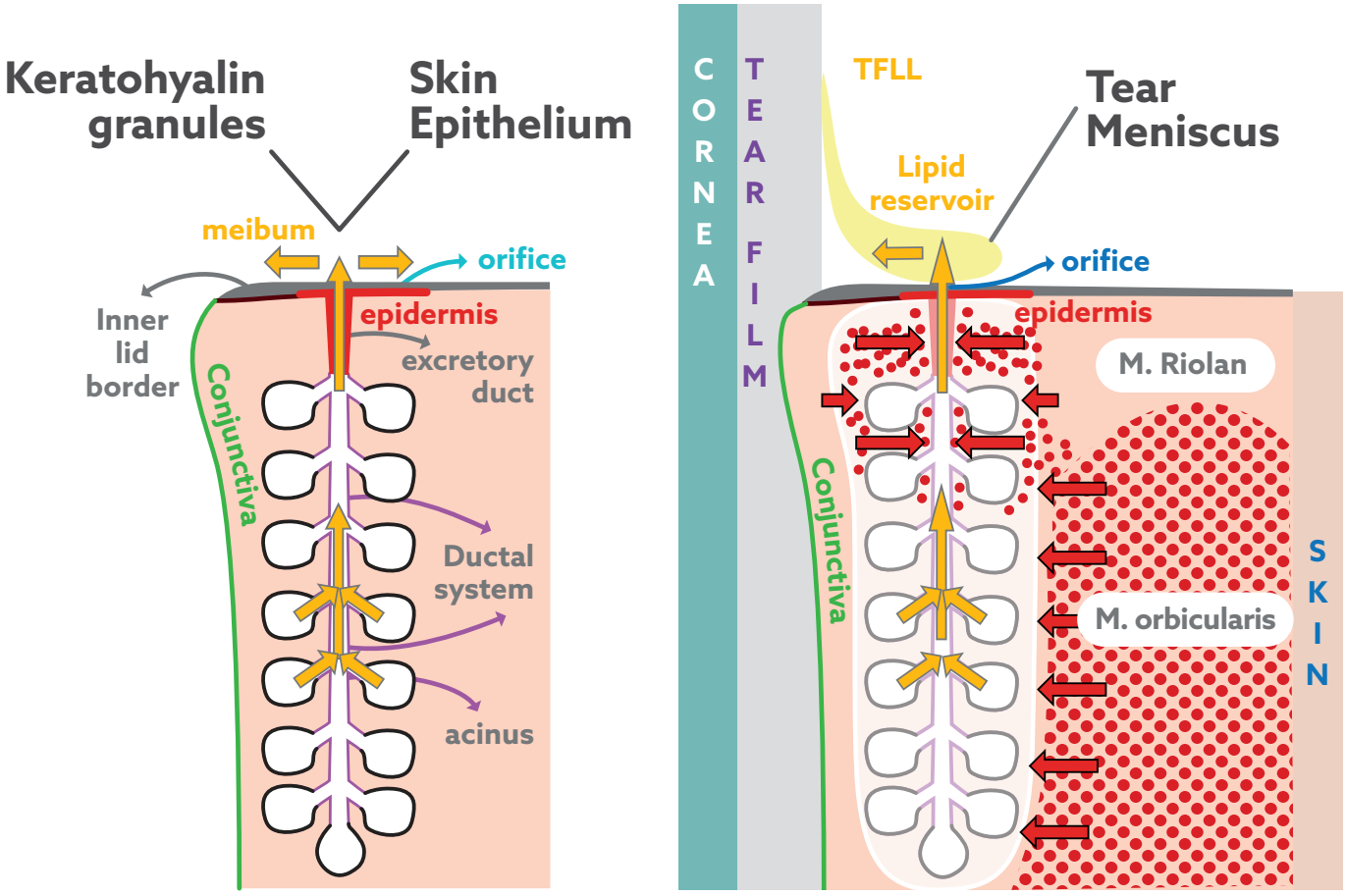


Figure 2: a) Meibum is constantly synthesised by secretory acini and transported through the ductal system toward the MG orifice. Obstruction of the MG orifice from lipids and keratohyalin globules prevents subsequent meibum excretion. b) The mechanical muscular contraction of M. orbicularis and M. Riolan is required for meibum excretion, facilitated further via adequate tear on lid meniscus for lipid dispersion in the lipid reservoir. (Figure adapted from Knop et al, 2011 [2])

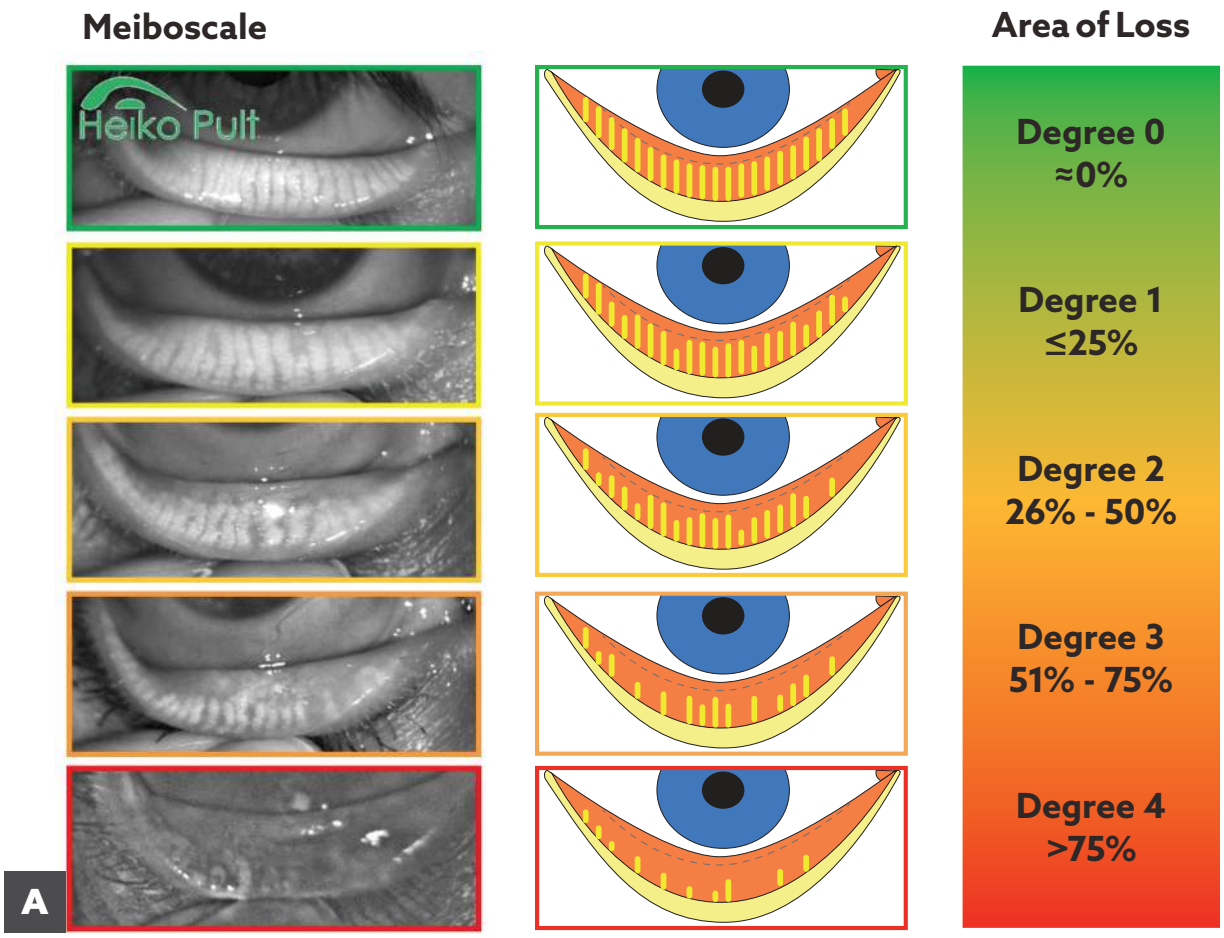


Figure 3: a) Meiboscale depicting severity degrees of MGD [4] , b) stage 3 severity of MGD (courtesy of JM Benitez-Del-Castillo), c) stage 4 severity of MGD (courtesy of JM Benitez-Del-Castillo)

1.2 Classification

HOW IS MGD CLASSIFIED?

MGD is classified according to its pathophysiology, based on the rate of meibum secretion (Figure 4). **Low delivery states**, accounting for the most common forms of MGD, are characterized by meibomian gland hyposecretion or obstruction with cicatricial and noncicatricial categories. Less common are **high delivery states** which are characterized by meibomian gland hypersecretion. All categories are further defined by primary or secondary causes. Overall MGD leads, in all classes, **to alterations of the tear film, symptoms of eye irritation, inflammation, and ocular surface disease including evaporative dry eye disease** [1, 3, 5].

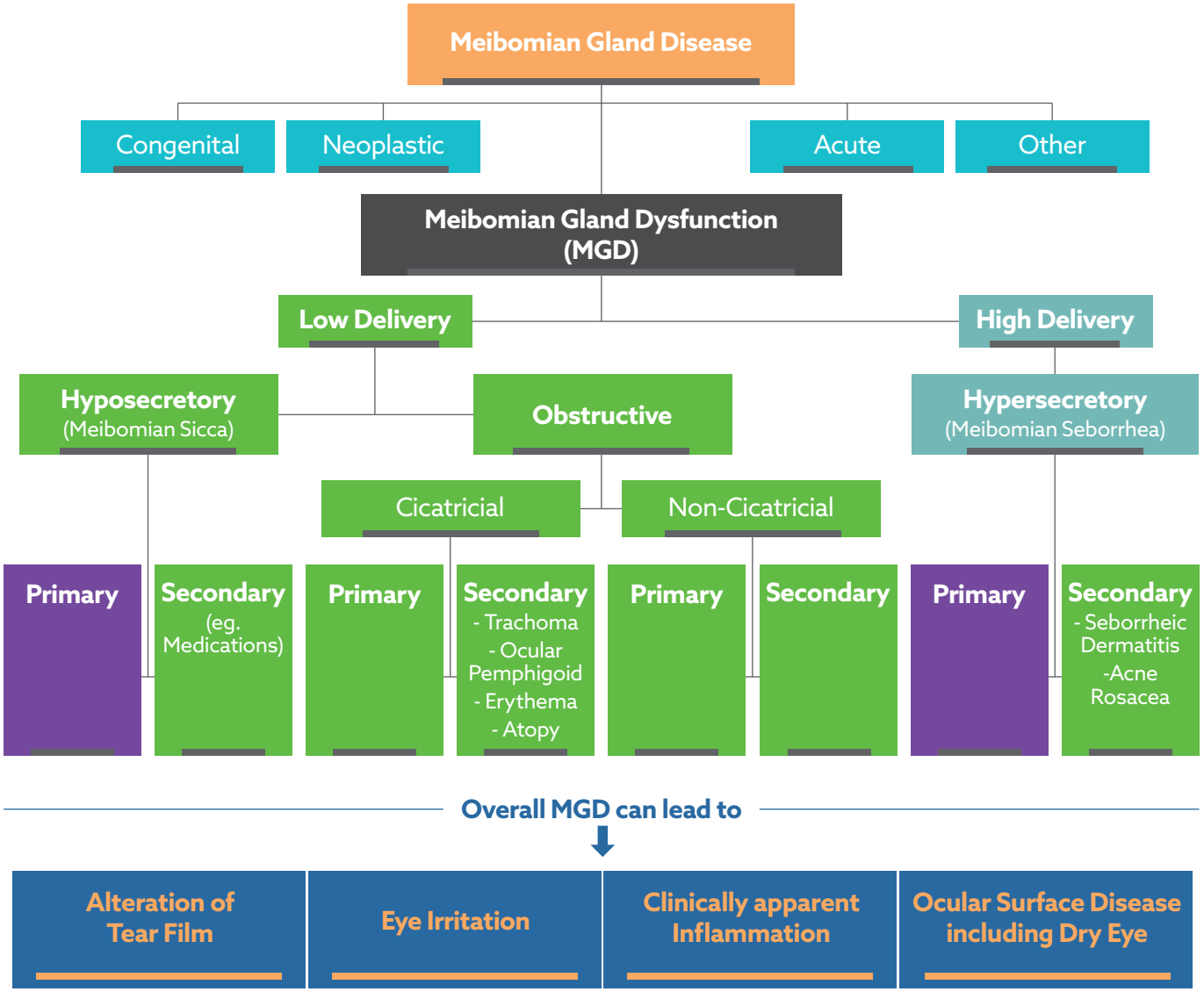


Figure 4: MGD Classification (Reproduced from Nichols et al, 2011 [1])

1.3 Prevalence

HOW MANY PEOPLE HAVE MGD?

Population-based studies have reported a 60% prevalence of MGD in Asian populations and up to 20% prevalence in Caucasian populations [1]. A 37-39% prevalence of MGD has been demonstrated amongst patients randomly selected during routine vision examinations [6, 7].

Patients with clinical signs of MGD demonstrate symptoms of Dry Eye Disease (DED). Remarkably, MGD signs were found in approximately 86% of patients diagnosed with DED in a retrospective general clinic-based cohort study [8]. The prevalence of blepharitis in clinical populations has been estimated as high as 66% [9].

Prevalence increases with age, as demonstrated by the 67.2% of patients aged above 60 years old testing positive for MGD in routine vision examinations [6].

Clinical Impact

At least **4** in every **10** people will have some signs of MGD

Diagnosing MGD

2

2.1 Risk factors

The high prevalence in the general population is explained by a big number of ophthalmic, systemic and medication related risk factors [1, 3, 5].

Ophthalmic

- Chronic anterior blepharitis
- Contact lens wear
- Demodex
- Eyelid tattooing
- Floppy eyelid syndrome
- Giant papillary conjunctivitis
- Trachoma
- Poor blinking
- Dry eye disease

Systemic

- Aging
- Androgen deficiency Menopause
- Parkinson's disease
- Polycystic ovary syndrome
- Psoriasis
- Rosacea
- Hypertension
- Cholesterol levels
- Sjögren's syndrome

Medication Related

- Isotretinoin therapy
- Anti-androgens
- Antidepressants
- Antihistamines
- Medications for benign prostrate hyperplasia
- Postmenopausal HRT

Aging is a major risk factor for MGD. The prevalence of MGD is affected by age [6] with older patients at increased risk of developing MGD. Aging results in atrophy of the meibomian gland acini leading to decreased lipid production and altered lipid composition, linked to decreased meibocyte differentiation, renewal, decreased meibomian gland size and elevated inflammatory cell infiltration [3, 10].

The mechanical forces of muscle contraction during blinking deliver the meibomian gland secreted lipids to the lid margin, increasing the lipid layer's thickness protecting the aqueous layer over the cornea. **Reduced blink rate** leads to decreased lipid delivery, stasis and MGD [11]. Blinking rate is reduced by 60% as people stare on a computer screen, contributing to altered meibomian gland secretion, poor tear film quality and increased evaporation. Prolonged or frequent computer use has been shown to be associated with MGD [12]. In a study amongst individuals who complained of ocular discomfort associated with the use of Video Display Terminals (VDT), 74.3% were found to have MGD [13].

Estrogen and progesterone are implicated in meibomian gland metabolism and regulate gene expression and lipid production in these glands. Hormone Replacement Therapy (HRT) intake has been associated with increased risk of DED and an abnormal meiboscore in postmenopausal women [14].

Chronic primary anterior blepharitis is commonly associated with Staphylococcal bacterial overload, which produce lipases around the lid margin, which in turn destroy meibum secretions (via saponification), resulting in frothy tears and eyelid inflammation. This chronic inflammation in the eyelid results in MGD [2, 5, 15].

Demodex are tiny mites that live in or near the lash follicles and sebaceous glands of mammals. Infestation with either of the Demodex species, Demodex folliculorum and Demodex brevis, has been implicated in the pathogenesis of MGD and its differential diagnosis is essential to the subsequent management of MGD [16]. Remarkably, 46.8% of MGD patients with MGD present with Demodex infestation [3]. D. brevis has been associated with symptomatic MGD and MGD severity has been correlated with infestation from this species [16]. Demodex is also associated with the development of secondary anterior blepharitis [2].

2.2 Symptoms

MGD may be asymptomatic or symptomatic. Asymptomatic MGD is detected by signs alone. It can be symptomatic in its own right or give rise to symptoms through its contributions to ocular surface damage or to dry eye. Most eye care professionals use a dry eye questionnaire that may not distinguish the symptoms of MGD from those of dry eye [17]. Despite the lack of specificity in dry eye questionnaires, what we do know is that MGD is present in 60-86% of symptomatic patients [8, 17].

A specific questionnaire was developed by Kwan and colleagues in 2013 but has not been used extensively. It assessed the frequency and intensity of nine symptoms: dryness, grittiness, burning, vision fluctuation, soreness, scratchy, itch, crusting, sensitive to bright light [18]. A subsequent study reduced these symptom items further to produce a questionnaire evaluating the frequency and intensity of just 7 symptoms: dryness, grittiness, burning, vision fluctuation, soreness, scratchy, itch. The 7 symptoms reported were well fit according to the Rasch model used to evaluate the psychometric functioning of the questionnaire, suggesting they reliably characterize the symptoms of MGD [19]. This questionnaire correlated well with the Schein questionnaire's score, and both Schein questionnaire and this new MGD- specific instrument are able to monitor changes in symptomatology of MGD over time after treatment [19].

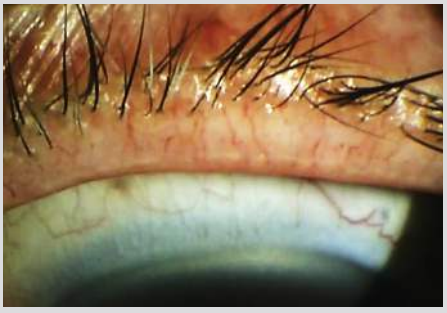
Some specific symptoms are known to be more strongly correlated with meibomian gland (MG) appearance [14] and their severity increases with dysfunction [20]:

- High OSDI (dry eye) score
- Puffy eyelids on waking
- History of hordeolum or chalazion
- Foreign body sensations
- Dry eye symptoms that tend to be worse in the morning

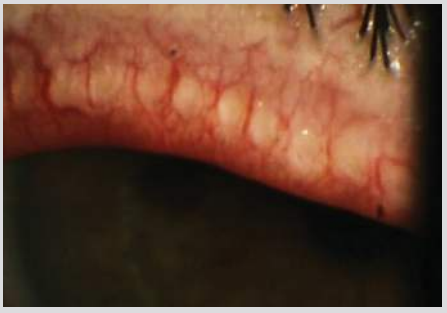
2.3 Signs

There are 2 lines of events in the progression of MGD pathology, described as the fibrotic process and the atrophic process [21], each with characteristic structural and functional lid margin changes (Figure 5).

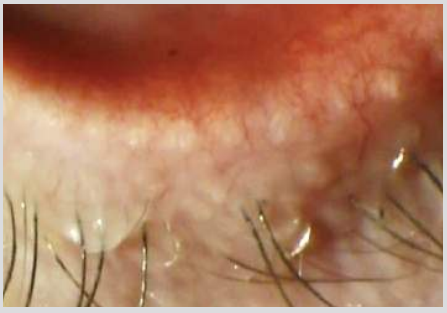
Line 1: Fibrotic process (cicatricial)



Lid margin hyperaemia

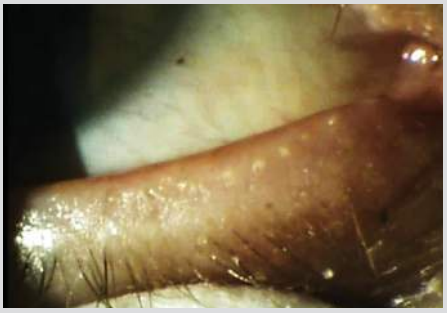


Lid margin hyperaemia orifice opacity with plugging

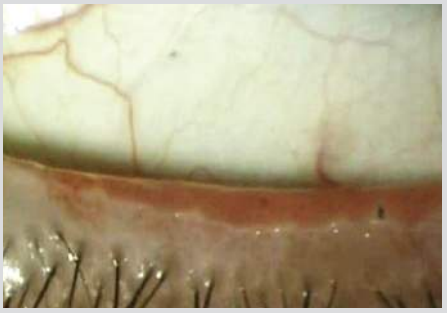


Orifices open onto the marginal conjunctiva

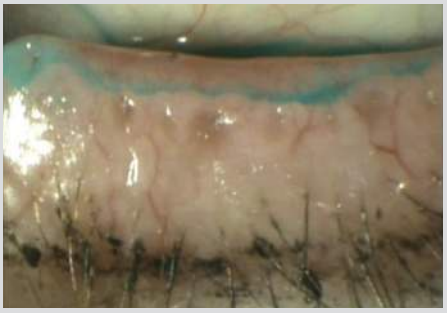
Line 2: Atrophic process (obstructive with gland atrophy)



Orifice opacification with periductal fibrosis



Epithelial ridging between opacified MGs



Notching & absorption of the orifices

Figure 5: Representative images of the fibrosis stage and the atrophic stage of MGD (Images courtesy of Prof Boboridis)

The Key Clinical Signs Of Symptomatic MGD Include:

Signs of lipid layer abnormalities in the tear film

Tear film instability

Lipid layer appearance

Meibomian foam (saponified lipids)

Meibomian gland drop out

Appearance through imaging, or absent expression result

Changes in lid appearance

Hyperaemia

Lid thickening

Notching of lid margin

Uneven tear meniscus

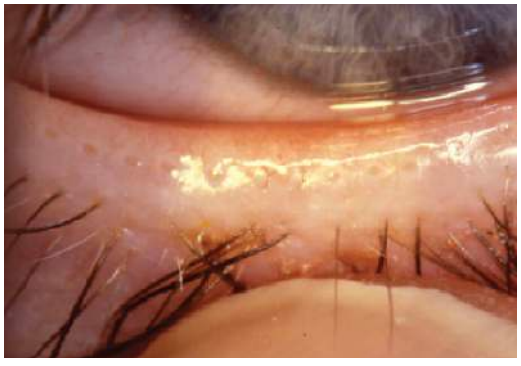
Distortion of the orifices anteriorly and the muco-cutaneous junction

Altered secretion

Thickened secretions under expression

Blocked meibomian gland orifices

Asymptomatic or pre-clinical MGD, also known as non-obvious MGD [22] (Figure 6), may only be detected through gland expression, before further signs develop (Figure 7).



A

B

Figure 6: a) Normal MG expression [22], b) Meibum expression in non-obvious MGD [22]

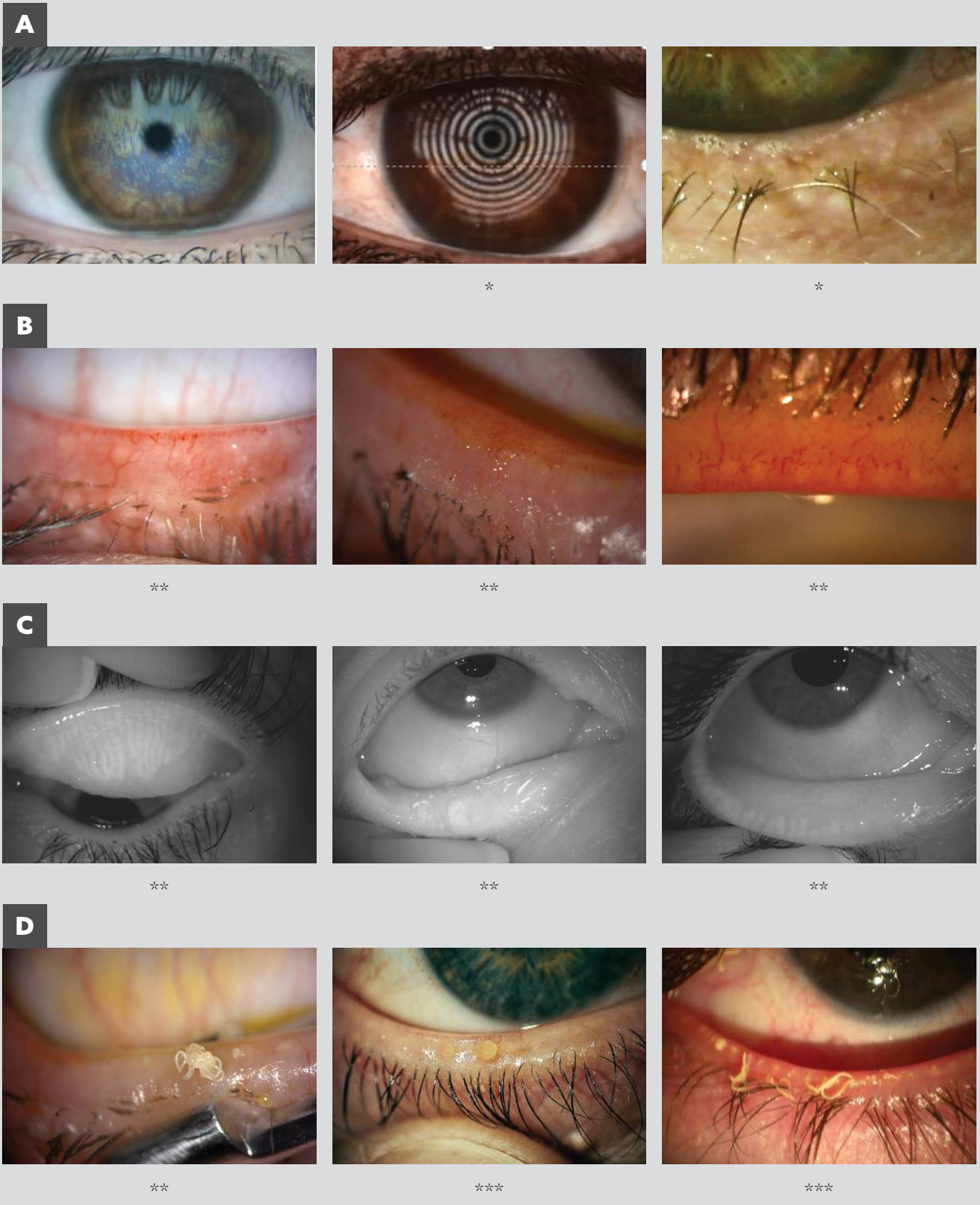


Figure 7: Signs of MGD: a) lipid layer abnormalities (LEFT: full spread on the corneal surface, MIDDLE: insufficient spread on the lower half of the cornea, RIGHT: meibomian foam), b) changes in lid appearance, c) MG dropout on Meibography, d) altered meibum secretion.

Images courtesy of *Prof K. Boboridis, ** S Farrant, *** JM Benitez-Del-Castillo

2.4 Diagnostic Techniques

Slit lamp examination to detect changes in lid morphology & tear film lipid layer

Examination of the eyelid margins at a minimum of 25x magnification is essential to detect clinical signs of changes in lid morphology and tear film lipid layer.

Figure 8: Slit lamp examination of the eyelid margins

MG expression to assess altered meibomian gland secretion

Altered meibomian gland secretion is assessed by applying pressure to the eyelid margins and rating the expressibility and texture of the meibum. Expression of the meibomian glands can be achieved simply, using digital pressure, a method that lacks standardization. Controlled force diagnostic expression can be achieved using a spring-loaded device (KORB device) [20] (Figure 9). This instrument allows the application of standard force for the diagnostic expression of 5 consecutive meibomian gland orifices on each of the temporal, central or nasal sections of the lower eyelid [23]. MGD meibum is difficult to express and has a more viscous and opaque appearance compared to normal meibum that is clear and easily expressed.

Figure 9: KORB device

Meibography to assess partial or total gland drop out

Meibography is performed to assess partial or total gland drop out. It can be achieved via transillumination with white light through everted eyelids, where glands can be seen in silhouette, or more commonly via infrared (IR) imaging where glands appear white against a darker background [24] (Figure 10 [25]). Abnormal glands appear tortuous. Extensive dropout is associated with increasing evaporative water loss from the eye, leading to dry eye symptoms [17].

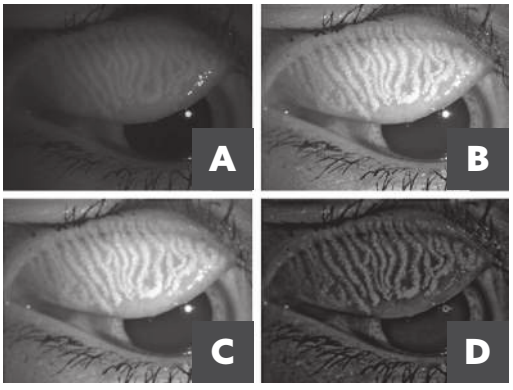


Figure 10: Non-invasive meibography using an IR light source [25].
(A) Raw image
(B) Applying a Wallis filter to the raw image
(C) Applying a Gaussian filter to (B)
(D) Preprocessed image

2.5 Clinical Grading of MGD Signs

Adopting a reliable grading scale for ocular complication in clinical practice can ascertain accuracy and consistency in clinical record keeping, meaningful communication of clinical cases between ophthalmologists and reproducibility of the classification. Clinical grading scales not only are useful for diagnosis and monitoring disease progression but also for monitoring of the effectiveness of an intervention. Two of the most commonly adopted grading scales for ocular complications in clinical practice, are the Brien Holden Vision Institute (formerly CCLRU or IER) and the Efron grading scales [4, 26]. It is advised to always record the grading system used and always refer to the same grading system.

Grading meibomian gland dropout:

Obtaining a reliable meibography for the diagnosis of MGD relies on using an effective grading system. Most of the grading scales proposed for assessing meibomian gland dropout are 4-grade scales [27-29]. The use of a five-grade scale, such as the Pult meiboscale (Figure 11), is recommended to enhance the meibography grading, making it more sensitive to smaller increments and improving the inter- and intra-observer repeatability of the classification [4].

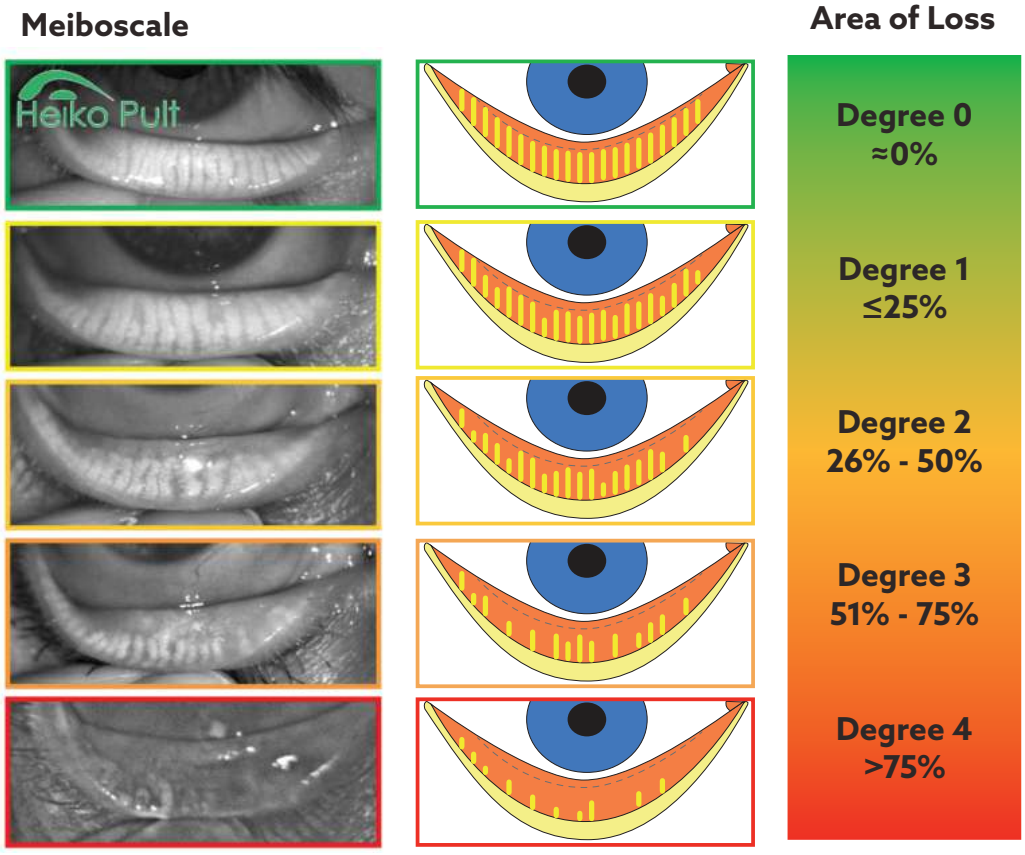


Figure 11: Five-grade meiboscale [4].
2012© Dr. Heiko Pult - Optometry & Vision Research, Germany. www/heiko-pult.de

Grading meibomian gland expression:

The volume of expressed meibum by firm digital pressure is sometimes equated with meibomian gland functionality. An ordinal grading scheme of 4 points (0: normal volume, 1: increased 2-3 times, 2: increased >3 times, 3: increased >10 times) has been proposed [30]. However, expressed meibum volume should not be considered as a reliable surrogate measure of secretory activity [17].

The quality of expressed oil varies and can appear clear (normal), cloudy, cloudy with particles, or impissated, graded by 4-point grading schemes [15, 30].

The expressibility from single or multiple glands, with standard force applied for 10-15 seconds with a specially designed instrument can be measured, scoring the glands that yield liquid secretion (MGYLS score), regardless of its quality [20].

A useful grading scheme for meibomian gland expression, provided by the Report of the Diagnosis Subcommittee of the International Workshop on Meibomian Gland Dysfunction [17] can be found in Appendix A.

Grading morphologic lid changes:

Grading morphologic features of MGD, such as characteristics of eyelid margin, orifices, main duct and acini, offers the opportunity to generate an aggregate MGD score that can be combined with measures of gland expression and dropout [17]. Some of the characteristic changes anticipated have been presented in Figure 5.

Key Diagnostic Feature is Lissamine Green Staining & Observation of:

Relative position of the line of the orifices of the glands in relation to Marx line, to define progression and severity (Figure 12)

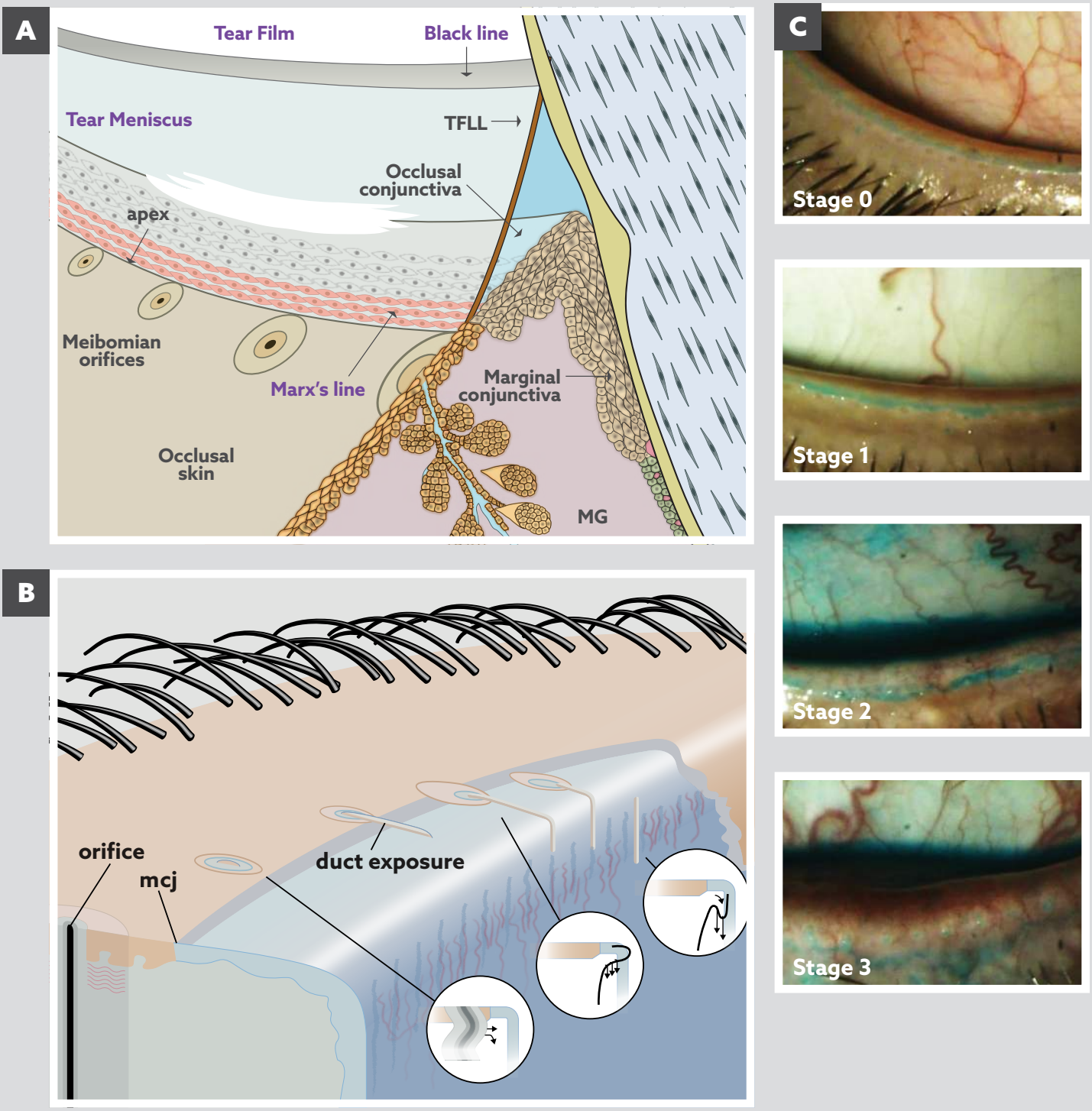
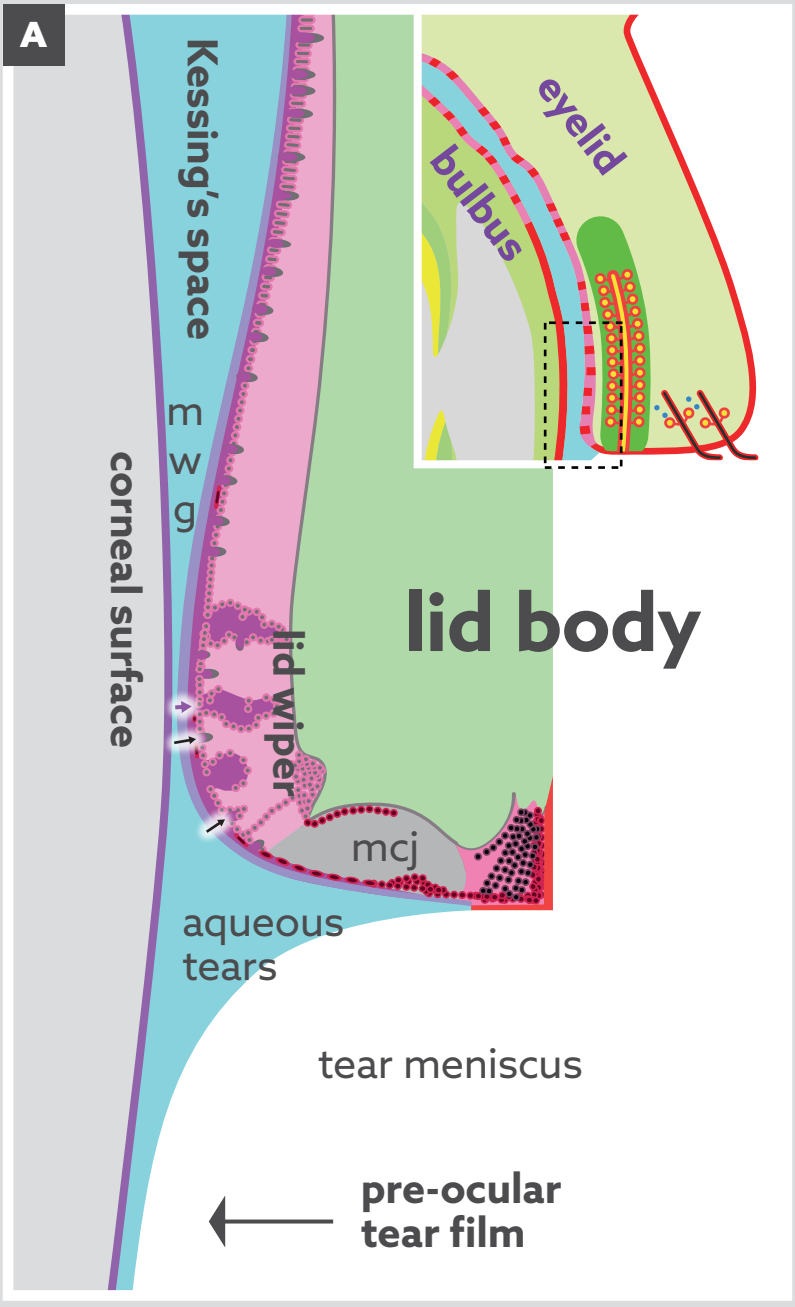


Figure 12: a) Schema depicting the lower tear meniscus and lid margin. Marx's line is a row of stainable epithelial cells lying directly under the apex of the tear meniscus [31] b) Schematic representation of the morphology of progression of cicatricial changes [21] c) Lissamine green staining of Marx line; Stage 0: Normal Marx line staining running along the conjunctival side behind the meibomian orifices, Stage 1: Marx line staining partially in contact with the meibomian orifices, Stage 2: Marx line staining running through the meibomian orifices, Stage 3: The Meibomian orifices are being contracted posteriorly of Marx line indicating cicatricial changes on the palpebral conjunctiva. (pictures courtesy of Prof K. Boboridis).

Lid wiper epitheliopathy

due to causes including but not limited to lipid deficiency (Figure 13)



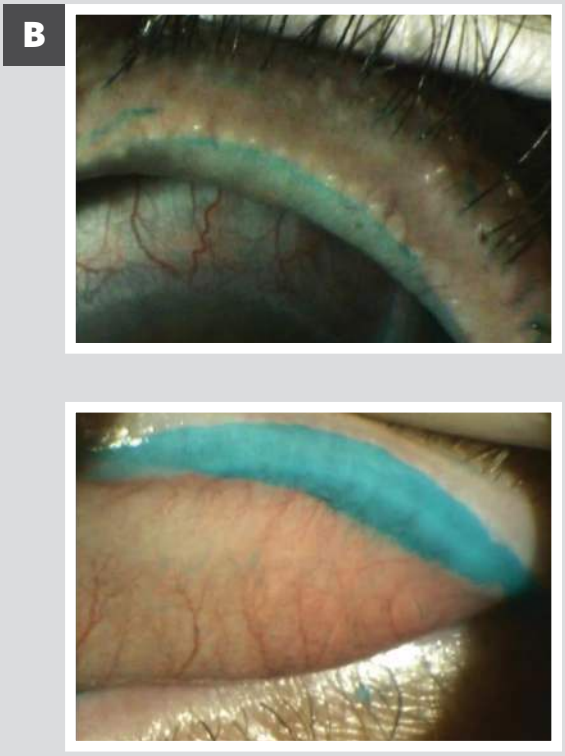
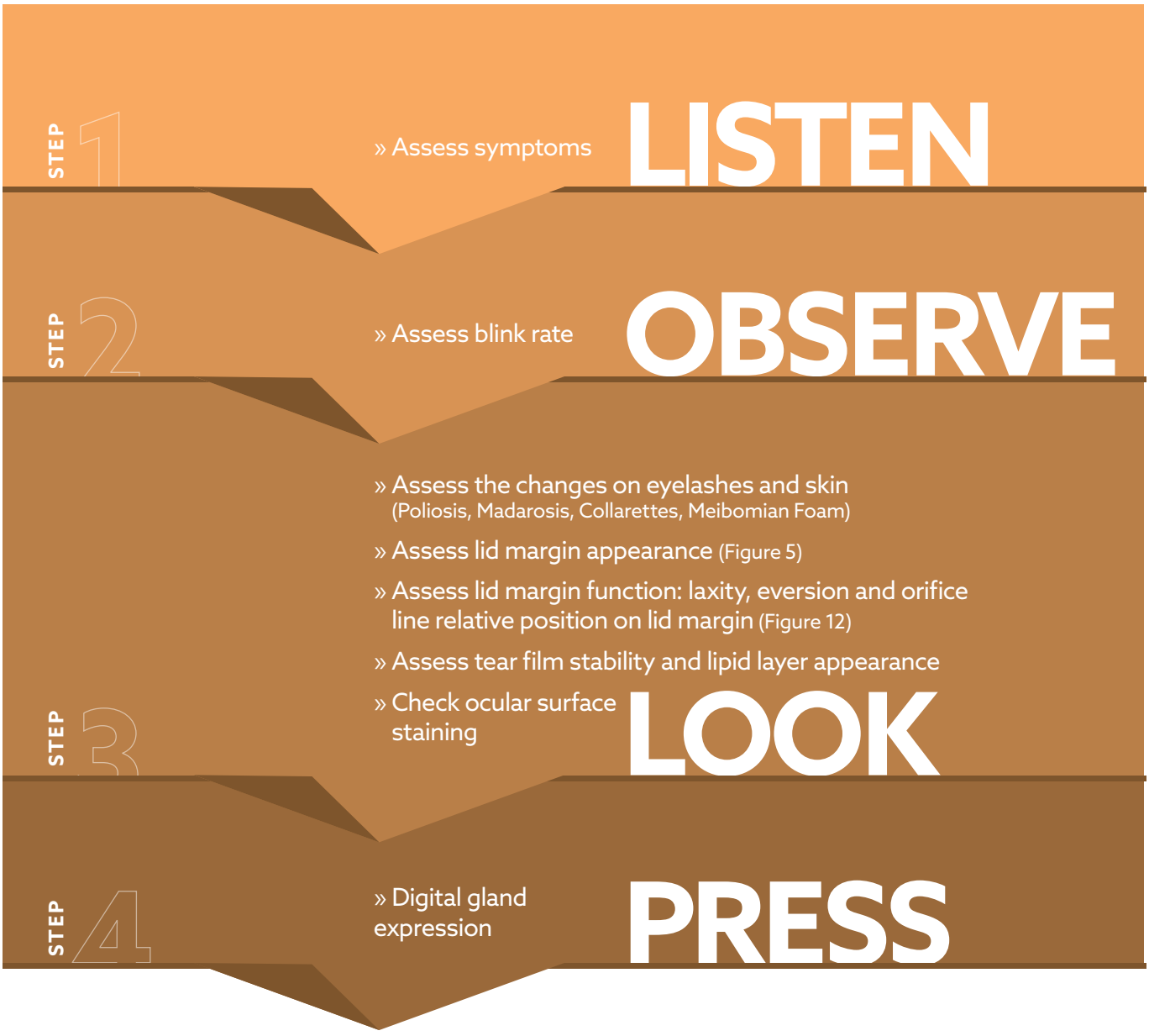


Figure 13: a) Abundance of goblet cells organized in crypts have been identified (black arrows) on the conjunctival surface of the inner corner of the lid margin (lid wiper). They deliver mucin to facilitate adequate lubrication between the eyelid and the ocular surface during blinking, b) Lid Wiper Epitheliopathy as detected by Lissamine green staining indicating frictional tissue damage and subsequent goblet cell death. (TOP: Grade 2, BOTTOM: Grade 3) (Pictures courtesy of Prof K Boboridis)

2.6 Step by Step MGD Diagnostic Routine



Association between MGD and dry eye

3.1 How MGD relates to dry eye

Ocular surface damage resulting from increased tear evaporation, hyperosmolarity, proinflammatory mediators in the tears, may give rise to irritative symptoms of the ocular surface and eyelids. Many of these ocular signs and symptoms are overlapping in MGD and DED, which also share many common ocular, systemic and treatment-related risk factors.

Two types of DED are identified:

Evaporative dry eye or lipid deficient DED caused by water evaporation. This is the most frequent form of DED. MGD is considered to be the most common cause of evaporative DED and is identified as a potential entry point into the vicious cycle of DED.

Aqueous-deficient dry eye caused by lacrimal glands dysfunction, further categorized in Sjögren's and non Sjögren's syndromes. MGD has also been associated with Sjögren's syndrome, which although a form of aqueous deficient DED, may also include the evaporative type, resulting from MGD.

Over **80%** of patients with dry eye symptoms have signs of MGD

3.2 The double vicious cycle of MGD and Dry Eye Disease (DED)

The interacting pathophysiology underlying MGD and DED combine to form the chronic type of MGD-related DED. The meibomian gland changes connect the two vicious cycles of DED and MGD forming a double vicious cycle (Figure 14). The vicious cycle of MGD consists of the following sequential steps:

Stasis of the meibum, caused by obstruction, dropout or inflammation of the meibomian gland, may result in **bacterial proliferation** which may lead to the **release of lipases and esterases**, causing **inflammation, and increased meibum melting temperature and viscosity** responsible for **reduced secretion of meibum**. Reduced volume or abnormal composition of meibum alters the lipid content of the tear film providing an entry point into the DED vicious cycle leading to increased evaporation, hyperosmolarity, and inflammation, all causes and consequences of DED [5].

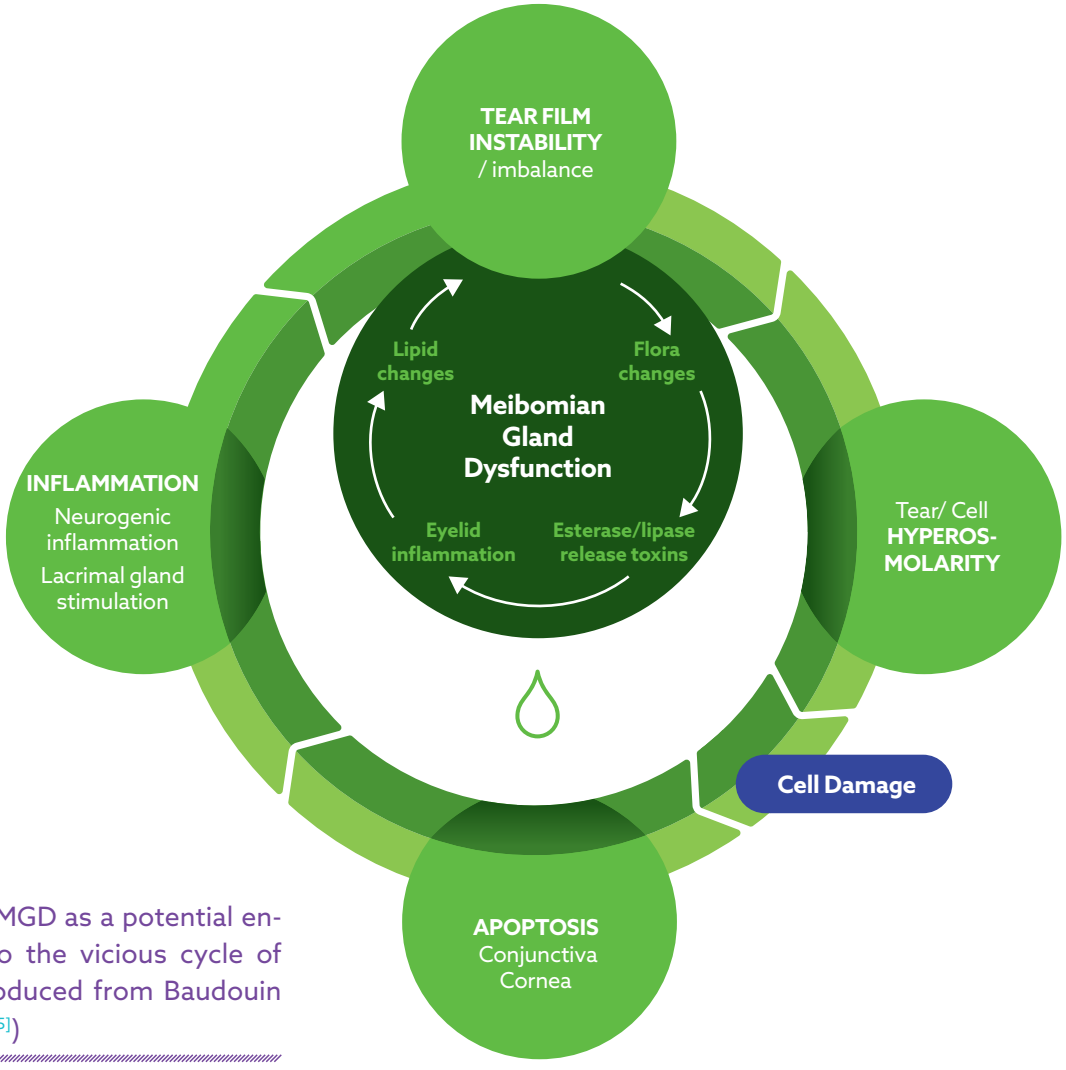


Figure 14: MGD as a potential entry point to the vicious cycle of DED (Reproduced from Baudouin et al, 2016 [5])

Bron and colleagues have proposed that **MGD-related DED** leads to a compensatory increase in tear production, followed by compromised lacrimal function and reduced tear secretion that results in a mixed form of DED comprised of both evaporative and aqueous subtypes [32]. The proposed mixed form DED is supported by clinical evidence in patients with Sjögren's syndrome presenting with increased meibomian dropout score and reduced meibomian gland expressibility [5]. The evaporative and mixed forms of MGD account for 60-89% of patients with MGD [8, 33] (Figure 15).

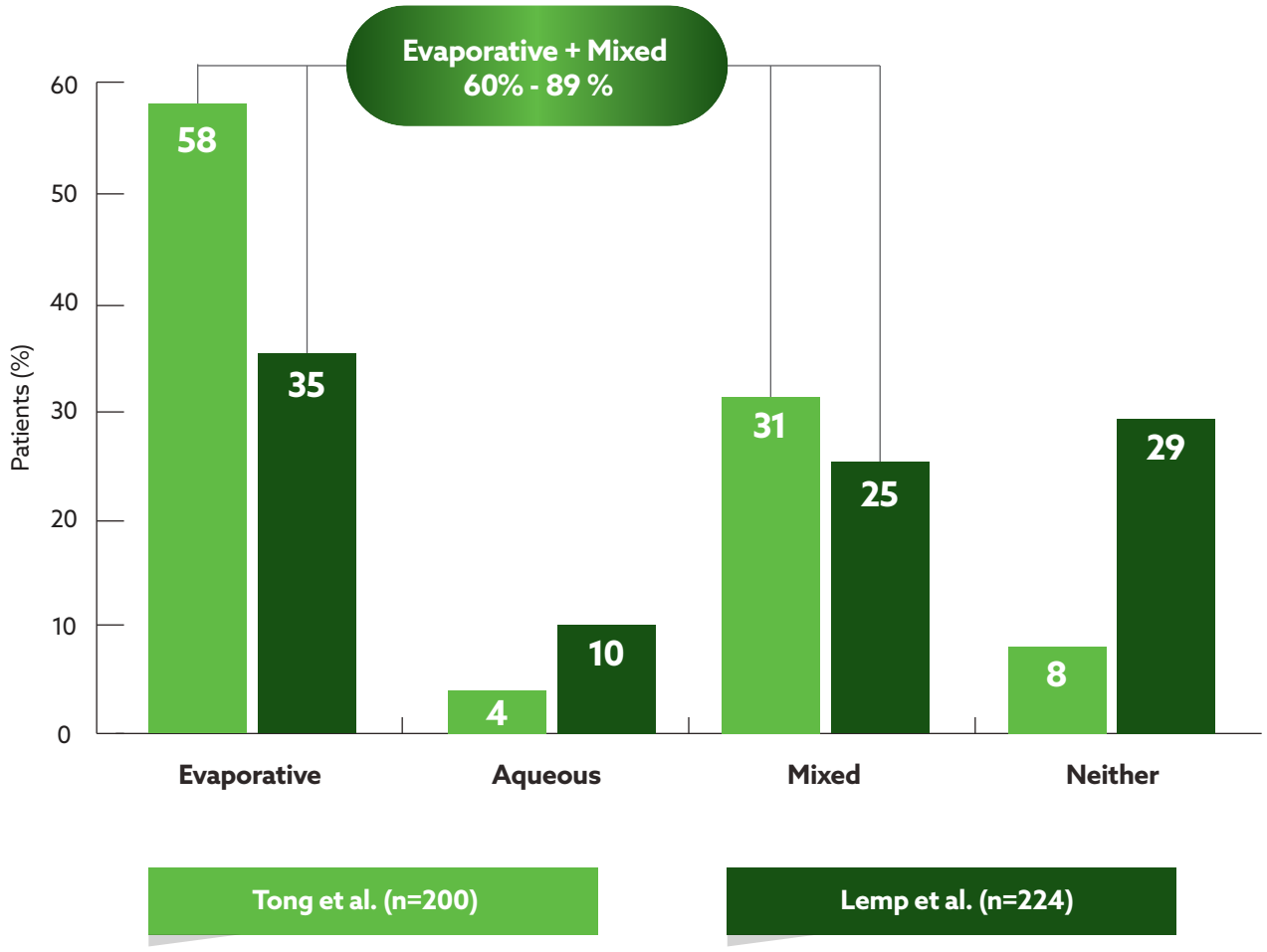


Figure 15: Evaporative and mixed forms of MGD account for the majority of Dry Eye cases. Aqueous deficiency only represents 4-10% of the patients, possibly representing the Sjögren's syndrome sub-group of patients.[8, 33]

Treatment for MGD

MGD treatment ultimately aims in increasing the quantity and quality of meibomian expression and thus improving patient symptoms [1]. Management plans should include an overarching 3 step routine: lid warming, massaging and cleansing.

This routine may be sufficient for some patients but may be supplemented by one-off physical treatments and/or oral and topical medicinal therapies, as required. To break the cycle of chronic MGD, there is a general consensus amongst clinicians that chronic MGD will need more intervention initially, but symptoms can be reduced to manageable levels through the 3-step routine at home.

4.1 Physical Treatments

a. Eyelid warming

Obstructive MGD is characterized by reduced meibomian secretion. Secreted meibum in patients diagnosed with obstructive MGD has a melting temperature of 35°C in contrast to 32°C in healthy subjects and is more stagnant and viscous [34]. Altering eyelid temperature has been reported to impact on meibum secretion in healthy subjects [35]. Consequently, eyelid warming methods can be used to enhance meibum secretion by melting the pathologically altered meibomian lipids. The therapeutic threshold for melting obstructed meibum is 40-45°C [34, 36]. Moist heat application has been associated with increased lipid layer thickness and tear film stability [34, 37].

Warm compresses: Eyelid warming has traditionally been achieved by applying moist warm compresses twice daily for at least 5 min, whereas hot compresses are not recommended as high temperatures may be uncomfortable and risk causing thermal injury to the eyelid skin and visual degradation due to corneal deformation. However, warm compress therapy is a poorly standardized procedure in terms of variable duration of warming, inconsistent temperature and scarce patient compliance.

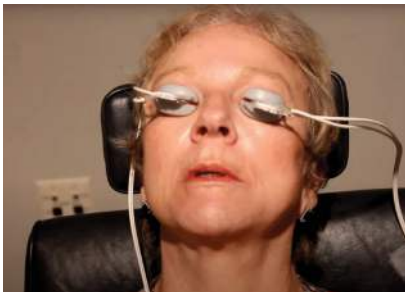
Therefore, dedicated devices that deliver heat therapy consistently and effectively have been developed, such as **EyeBag™**, **Blephasteam®** and **LipiFlow®**.

EyeBag™

EyeBag™ is a silk and cotton device filled with flax seeds heated in a microwave and maintaining temperature for up to 10 minutes. It is reported to be effective and safe with a low risk of corneal deformation and visual changes [38].

Blephasteam®

Blephasteam® is an electrical pair of goggles that delivers warmth and steam. It is not user dependent and it is designed to provide uniform, regulated treatment temperature and duration, without any adverse ocular response [39].



LipiFlow®

Lipiflow® is an automated thermal pulsation system based on vectored thermal pulsation delivering heat (42.5°C) to the inner surface of the eyelid as well as applying mechanical stimulation to the outer eyelid surface to express meibomian lipids [40].

Characteristics of eyelid warming methods

Hot flannel	EyeBag ™ Class I medical device	Lipiflow ® Class II medical device	Blephasteam ® Class IIa medical device
Low tech approach	Dry heat	Dry heat	Moist heat
Variable temperature	Maintains temperature	Consistent temperature to the inner eyelid	Closely regulated
Poor compliance	Closed eyes Lying Down	Closed eyes Requires anesthetic	Can see during treatment
No clinical evidence	Clinically proven	Cinically proven	Clinically proven

b. Gland expression

MGD is manifested by the obstruction of gland orifices leading to stasis of the secretion in the acini causing abnormally thick meibum consistency. Physical expression of meibomian glands is practiced for diagnostic and therapeutic purposes.

Diagnostic expression (expressibility): Assessing the expressibility of meibomian glands describes the ease with which secretion can be released from the gland on physical expression and is required during clinical evaluation of the MG [20].

Therapeutic expression (purging): Forceful expression of the glands to release the obstructive material from the gland, thereby facilitating normal gland function, is a well-established procedure for therapeutic purposes. The force needed to evacuate the contents of obstructed glands can be significant and is limited by the high level of associated pain. Warm compresses before the expression, proper education of the patient regarding the discomfort that will be experienced are precautions recommended to be taken before the procedure [41].

Meibomian gland expression can be achieved using:

Manual expression techniques: These are performed by forceful squeezing the lids against each other or by applying force on the outer lid surface placing a rigid object on the inner lid surface such as a sterile cotton swab (Figure 16a), or an instrument such as the Mastrota paddle (Figure 16c) or by the use of a rigid instrument placed on the inner and outer lid such as the Colins forceps (Figure 16b). The rigid object on the inner lid surface will protect the eyeball from the expression forces and provide the resistance required to increase the force applied to the glands.

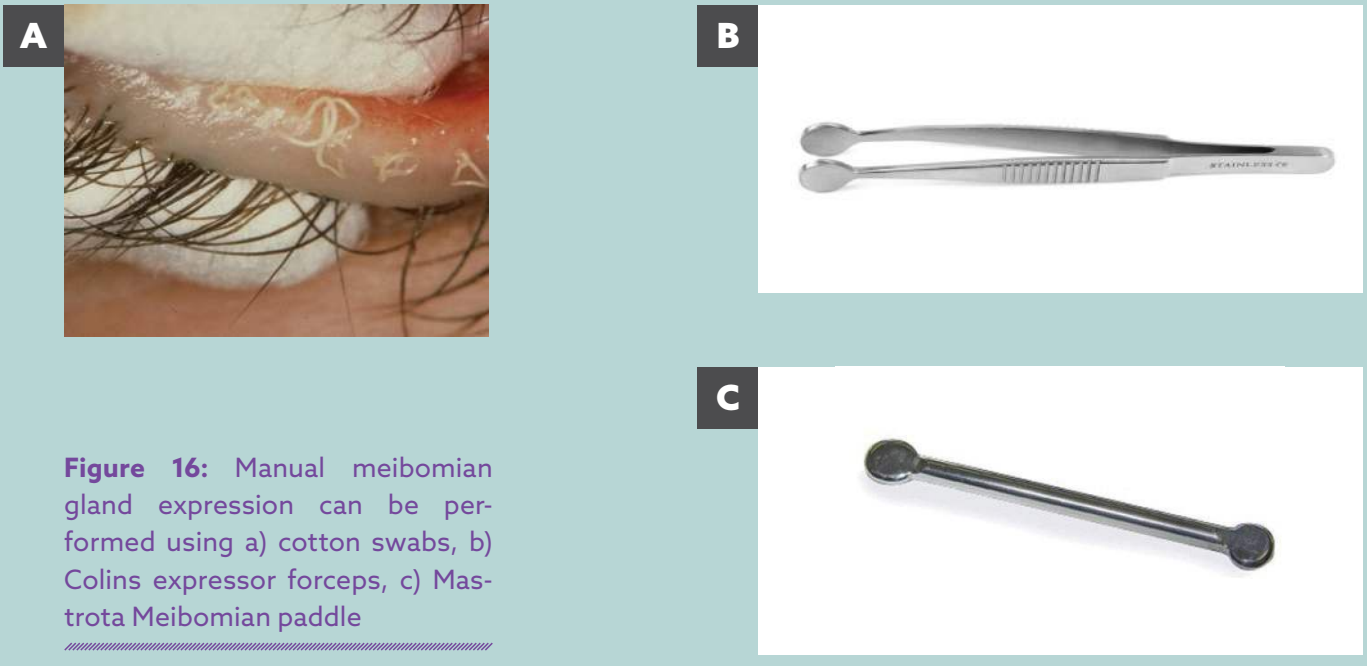


Figure 16: Manual meibomian gland expression can be performed using a) cotton swabs, b) Colins expressor forceps, c) Mastrota Meibomian paddle

Mechanical devices such as LipiFlow®, which combines gland expression at controlled force with eyelid warming (Figure 17).

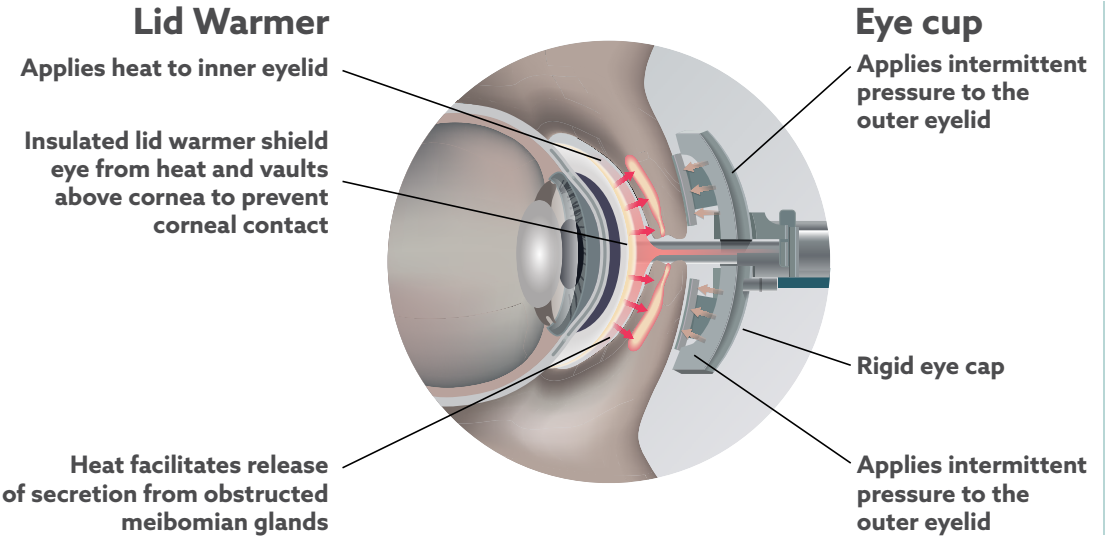


Figure 17: Lipiflow device for obstructed gland expression and eyelid warming

c. Lid margin exfoliation

Hyperkeratinization is a key feature of MGD and contributes to the obstruction of the MG orifice. Internal obstruction and plugging of the MG leads to increased epithelial turnover and accumulation of desquamated epithelial cells near the lid margin. Lid margin exfoliation is a process of debridement that can be used to remove excess keratinized material as well as reduce the bacterial bioburden in the eyelid margin, thereby improving MG function and reducing ocular discomfort [42]. The procedure can be performed using a golf club spud debrider to mechanically exfoliate the cells and debris from the eyelid margin (Figure 18a). Alternatively, a hand piece device can be used, such as the BlephEx™ instrument which contains a hand piece used to spin a medical-grade microsponge along the edge of the eyelids and lashes and to remove keratinized cells, thereby exfoliating the eyelids (Figure 18b).

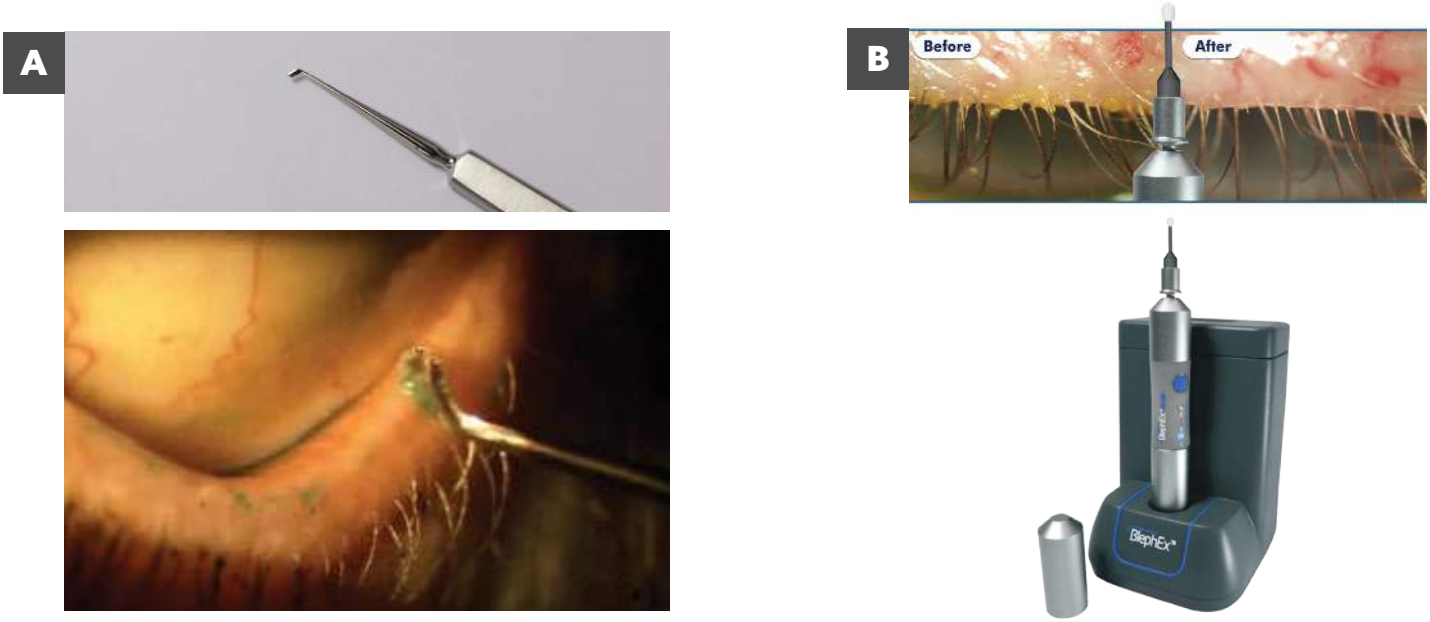


Figure 18: Lid margin exfoliation using a) a club spud debrider, b) the BlephEx™ device

d. Intense Pulse Light (IPL)

IPL treatment has long been used in dermatology to treat acne rosacea, telangiectasias hyperpigmentation and photodamaged skin. IPL treatment is now also proposed as a comprehensive treatment approach in patients with MGD (Figure 19). IPL is a high-intensity light source in the wavelength range of 515 to 1200 nm. The emitted light is applied to the periocular area and is absorbed by oxyhemoglobin in blood vessels on the surface of the skin. The absorption raises skin temperature, the heat coagulates the red blood cells, leading to thrombosis of the blood vessels [43]. Additionally, IPL aims to the eradication of parasitic and bacterial growth on the lids. For instance, the pigmented exoskeleton of Demodex can absorb IPL energy, and IPL treatment induces coagulation and necrosis of mites, thereby contributing to relieving of the chronic inflammation and improving the response of patients with MGD [44].

Figure 19: IPL treatment on a patient with severe MGD with few or no expressible glands.

Clinical studies have proven the effectiveness of IPL in improving the lipid layer and patient symptoms. Combined treatment of gland expression and IPL has been shown to improve meibum quality, increase significantly oil flow score and tear film breakup time and decrease lid margin oedema, facial telangiectasia and ocular surface disease index (OSDI) scoring [43].

There are various IPL devices on the market designed for ocular application. Treatments are recommended 4-6 weeks apart. The Fitzpatrick Scale should be used to determine which level of light energy is safe for various skin types and the patient's physical characteristics and medical condition should determine wavelength, pulse rate, and pulse duration [43].

4.2 Eyelid Cleansing & Massage

Eyelid hygiene, consisting of eyelid warming and eyelid massage, is the cornerstone of MGD treatment. A combination of eyelid warming with eyelid massage and cleansing is recommended. Such practice may improve the TBUT, corneal and conjunctival fluorescein staining, lid margin abnormality, meibum quality, expressibility, as well as ocular irritation symptoms in patients with moderate and severe MGD [45].

Lid massage can dramatically improve symptoms by helping re-establish tear film stability. Care should be given to properly instruct the patient on how to perform lid massage according to the following steps [46]:

Lid warming

Patient should apply traction on the lateral canthus to achieve upper and lower lid immobilization

Patient should compress with the finger of the opposite hand the eyelids downward or upward, beginning at the nasal canthus and moving laterally to the lateral canthus

Lid scrubs help to remove oil, bacteria and debris as well as stimulating the meibomian glands. It is not recommended to use generic methods of lid margin cleansing with products such as baby shampoo and cotton buds since numerous specialized cleansing products have become available. The need for good communication with patients is imperative and patients should be educated on appropriate products and methods to be used for lid cleansing [47-49]. Various products have been reported to be clinically effective for eyelid margin cleansing. Tea-tree containing solutions [34] are the first choice of cleansing agents as tea-tree oil, apart from being a good general antibacterial - disinfectant agent, has also been proven effective against demodex [50, 51]. Other approaches include the use of heated saline solutions and preservative-free artificial tears [46], washing the eyelids with specially formulated cleansers, and eyelid cleansing using wipes which, although involving mechanical wiping, is especially convenient when there is no access to running water [47-49].

BLEPHACLEAN® WIPES Class IIa medical device

High-tolerance, preservative-free cleansing wipes for daily hygiene of eyelids and sensitive skin, Blephaclean are specially formulated to be used for eyelid cleansing associated with massage. The action of Blephaclean wipes on the lid margin is optimized by their specific formulation containing capryloyl glycine and Iris florentina, known to regulate sebum production and sodium hyaluronate, a natural skin moisturizer. Their efficacy has been proven in a 3-month treatment regimen comprising of a 3-week intensive use period (twice daily) followed by a maintenance period (once daily). This clinical methodology demonstrated significant improvement of the signs of MGD and anterior blepharitis, and lead to symptomatic relief and ocular comfort increase, that was maintained over time [47, 48].

4.3 Topical Treatments

General artificial lubricants for dry eye

There is a high coincidence of aqueous tear deficiency and MGD-related DED. Both reduced tear production and increased tear evaporation increase tear osmolarity, a central pathophysiological mechanism in dry eye. Supplementation of the tear film addresses the common pathway in OSD and can reduce tear hyperosmolarity, improve the tear film layer spreading, remove toxins and debris from the ocular surface and dilute the concentration of inflammatory molecules. Regular and repeated doses of high viscosity, preservative-free artificial tears are recommended [46]. Non lipid containing artificial tears, such as sodium hyaluronate, are also very beneficial for the management of MGD providing lid margin lubrication and meibum dispersion [52].

Lipid supplementation of the tear film

Topical lipid supplements may improve signs and symptoms of MGD, by replenishing the lipid layer of the tear film to reduce tear evaporation rate and restore tear film stability. Lipids used in artificial lubricants include, mineral oil, castor oil, polar phospholipid surfactant, glycerin, soy oil, phospholipid liposomes [34, 46, 53]. However, it is difficult to replace the complexity of natural lipids and the healthy lipid bilayer that is why topical current lipid supplements may not be the treatment of choice, with the exception of atrophic MGD. Focus should be turned into restoring the natural lipids. In that sense, lipid-containing eye drops (with phospholipids and triglycerides present in natural tear) might be better in correcting lipid alterations without affecting tear film optimal quality [54].

Topical Demodex treatment

Demodex infestation is related to ocular discomfort, lid margin abnormality and corneal epithelial barrier disruption in MGD [55]. Lid hygiene is recommended, and topical treatment for Demodex with tea tree oil [50], pilocarpine gel [56] and povidone iodine [16] has been investigated for MGD patients. Terpinen-4-ol, the most active ingredient of tea tree oil regarding the killing of Demodex mites [51], can be found in commercially available products such as the preservative-free Blephademodex wipes, which are proven to improve ocular symptoms [57].

Steroid treatment

Topical corticosteroids are recommended only to manage acute flares of inflammation or inflammatory complications related to MGD. Long term use is not advised due to adverse sequalae such as cataractogenesis, intraocular pressure elevation, and they should not be used on MGD-associated cutaneous rosacea lesions [34, 46]. It has been shown that MGD induces inflammation even at the preclinical stages [58]. Therefore using preservative-free, mild, surface acting steroids such as hydrocortisone is advisable along with the anti-inflammatory action of the antibiotics. Hydrocortisone is considered safe for low dose and longer term use as it has been documented to act on the ocular surface only and induce negligible changes on intraocular pressure [59].

Cyclosporine may also be used as an advance line topical anti-inflammatory and immunomodulatory treatment for long term use [60].

Topical antibiotics

Topical antibiotics are commonly used to reduce the bacterial load associated with MGD:

Antibiotics with bactericidal and/or bacteriostatic properties: Bacitracin, Fusidic acid, Metronidazole, Fluoroquinolones [46].

Antibiotics with bactericidal/bacteriostatic, immunomodulatory and anti-inflammatory properties: Macrolides including erythromycin [46], azithromycin [61]. Azithromycin exerts an additional antilipase effect leading to restoration of meibum composition to near normal [34, 46].

4.4 Oral Treatments

Systemic antibiotics

Oral tetracycline and derivatives such as oxytetracycline, minocycline and doxycycline are mainly used in MGD treatment for their anti-inflammatory and lipid-regulating effects rather than for their antibacterial action. Their antimicrobial effect in the lid is limited at the systemic doses, with the exception of minocycline [46]. Their efficacy is manifested by the suppression of microbial lipase production which is subsequently preventing the release of pro-inflammatory free fatty acid and diglycerides at the lid margin and ocular surface. Their action ultimately prevents inflammation induced keratinization of meibomian glands to improve meibum secretion [34, 46].

Oral azithromycin: The combination of systemic and topical azithromycin, rather than oral administration alone, is clinically proven to be more effective in the improvement of MGD associated signs and symptoms [62].

Sex hormones

Androgens regulate meibomian gland gene expression involved in stimulation of lipid production and inhibition of keratinization [46]. Their age-related decline leads to impaired lipid synthesis by the meibomian glands. Preliminary laboratory and clinical data suggest that androgens can improve lacrimal and meibomian gland function. HRT intake in perimenopausal women has been shown to resolve MGD signs to a certain degree [63].

Essential fatty acids

Dietary intake of omega-3 essential fatty acids has anti-inflammatory effects and has been reported to improve the signs and symptoms of DED and the expressibility and quality of meibum in patients with MGD [64, 65]. The exact mechanism is poorly understood but omega-3 and omega- 6 have been shown to directly influence the quantity and quality of lipids produced by meibomian gland epithelial cells [66].

MGD Management plan Summary

Assess patients symptoms

Assess MGD signs

Abnormal secretion

Changes in lid morphology & tear film lipid layer

MG dropout

Establish a management plan

Summary of treatment plan for MGD

Physical treatments	Eyelid hygiene	Topical treatments	Oral treatments
Eyelid warming	Eyelid warming and massage	Preservative free artificial tears	Systemic antibiotics
Gland expression	Eyelid cleansing	Lipid supplements	Sex hormones
Lid margin exfoliation		Demodex treatment	Essential fatty acid supplements
IPL		Topical antibiotics	
		Steroids	

APPENDIX A

Grading Meibomian Gland expression [17]

Technique	Study Details	Lid Region	Grading Scheme
Meibum Characteristics			
Firm digital pressure	Volume of expressed meibum	Central eight glands of lower eyelid	0 = Normal volume. Just covers orifice 1 = increased to 2 to 3 times normal 2 = increased more than 3 times 3 = increased more than 10 times
Firm digital pressure	Viscosity of expressed meibum	Central eight glands of lower eyelid	1 = normal, clear, may have a few particles 2 = opaque with normal viscosity 3 = opaque with increased viscosity 4 = severe thickening (toothpaste)
Firm digital pressure	Volume and viscosity of expressed meibumClinic-based; referred for dry eye or blepharitis *n* = 513 total; *n* = 76 normal women (used to define aqueous deficiency)	Central eight glands of lower eyelid	Obstructive: Viscosity ≥ 3 (1, clear; 2, slightly opaque; 3, thick, opaque; 4, toothpaste Avg. lipid volume: ≤0.3 mm (diameter of expressed lipid in millimeters) Dropout: >0 (presumably examined central eight glands; includes 1/2 and whole glands) Seborrheic: Viscosity: no criteria Avg. lipid volume: >0.7 mm
Meibum Quality and Expressibility			
Firm digital pressure	Quality of meibum	Number of glands not stated	0 = clear fluid 1 = cloudy fluid
		UL or LL	2 = cloudy particulate fluid 3 = inspissated, like toothpaste
Firm digital pressure	Expressility of meibum from five glands	UL or LL	0 = all glands expressible 1 = 3–4 glands expressible 2 = 1–2 glands expressible 3 = no glands expressible

Technique	Study Details	Lid Region	Grading Scheme
Standardized application of pressure	Expression applied to a set of about eight glands	Nasal, central and temporal lid	The MGYLS score is the number of Meibomian Glands out of 8, Yielding Liquid Secretion
Meibum Expressibility			
Variable digital pressure	Gentle or forceful expression	LL	Analysis of expressed secretion
Variable digital pressure	Expressibility of meibum	LL	0 = clear meibum, easily expressed 1 = cloudy meibum, easily expressed 2 = cloudy meibum expressed with moderate pressure 3 = meibum not expressible, even with hard pressure
Variable digital pressure using the Shimazaki schema	Measurement of lid morphology, expression and meibography	See grading box	Lid margin: Irregular Vascular engorgement Plugged orifices Displacement of MCJ, score "1" for each present
	Clinic based *n* = 53 obstructive MGD subjects *n* = 60 age-matched controls		Expressed meibum (upper eyelid): 0 = clear, easily expressed 1 = cloudy, mild pressure 2 = cloudy, > moderate pressure 3 = meibum not expressed, with hard pressure
			Meibography: upper and lower eyelids, meiboscore summed (0, no loss; 1, gland loss < 33% of total area; 2, loss = 33–67%; 3, ≥67% loss)

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