Curr Ophthalmol Rep (2014) 2:65–74
DOI 10.1007/s40135-014-0039-3

MGD Diagnosis and Treatment

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Published online: 1 June 2014

Abstract The identification of the starting cause or main pathogenic factors of dry eye can be of great help for planning an appropriate therapy. DED can be divided into conditions in which the production of the aqueous component of tears is inadequate [aqueous deficient dry eye (ADDE)] and conditions in which this is not the case. Unfortunately, standard DED symptom questionnaires are not designed to differentiate between ADDE and EDE; however, if the symptoms described are more frequent in the morning or are associated with the lids rather than the eye in general, this could be indicative of some form of blepharitis or meibomian gland dysfunction (MGD). The recollection of personal habits, such as lid rubbing, is also of interest, and a history of chalazion or hordeolum or of skin diseases is also suggestive. In clear-cut cases, a normal tear secretion with thick meniscus but low break-up time (BUT) and/or bad dynamic behavior of the lipid layer should suggest increased evaporation as the main source of dysfunction, while a thin, scanty meniscus or a Schirmer's test score <5 mm per 5 min associated with a low BUT or poordynamic lipid behavior makes us think of aqueous deficiency. Unfortunately, the clinical picture frequently is not so sharp. Nevertheless, the combination of the results of the different clinically available tests and the addition of one or more other tests, such as interferometry, meibometry, meniscometry and meiboscopy as well as direct evaporimetry, if available, will allow us to address the therapy toward the particular dysfunction active on the ocular surface or ameliorate the vicious cycles that are the basis of the problem, correcting, if possible, the failures that cause the disease.

Keywords Meibomian gland dysfunction (MGD) · Dry eye · Blepharitis · Ocular surface · Tear film · Lipid layer

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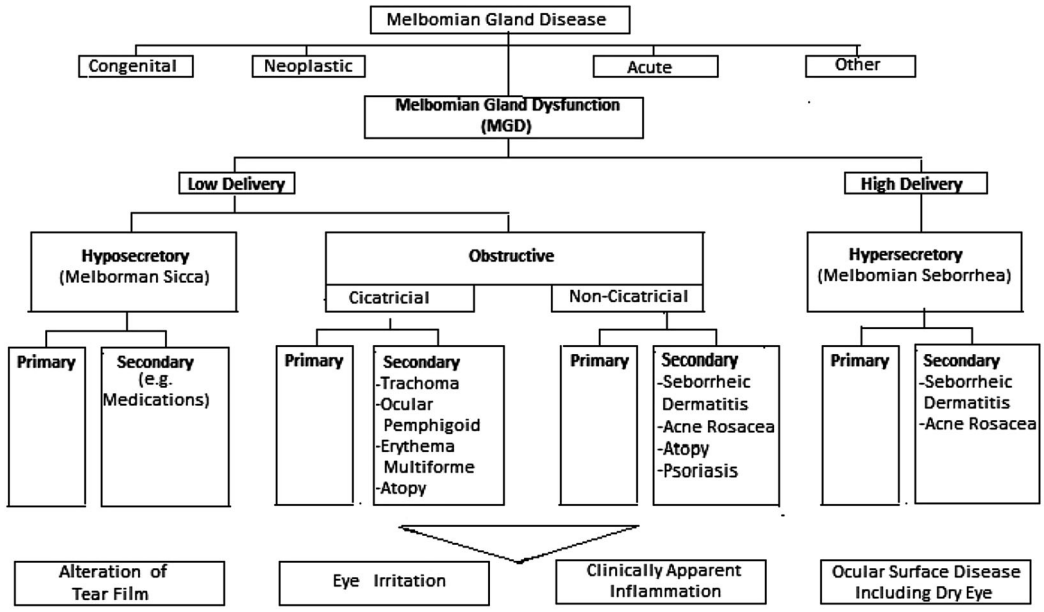
MGD Diagnosis

Meibomian gland dysfunction (MGD) represents a significant risk factor for posterior blepharitis and dry eye, but also for any surgery involving the ocular surface. History, clinical features, an accurate slit lamp examination, and specialized and non-specialized tests are important for the accurate diagnosis.

History

MGD can be classified as primary and secondary: in the first case, it is not connected to other local or systemic diseases, while secondary MGD may rely on a range of systemic disorders, above all some common skin diseases, such as acne rosacea, atopic dermatitis and seborrhoea sicca. It is associated with cicatrizing conjunctival disorders (trachoma, Steven-Johnson syndrome and ocular pemphigoid [1••], [2••], [3•]. Clinically, drug and toxin exposure can also generate this condition.



The new classification system proposed by the International Workshop on MGD
From: J.Daniel Nelson et al: "The International Workshop on Meibomian Gland Dysfunction: Report of the Definition and Classification Subcommittee" by Invest Ophthalmol Vis Sci. 2011 March; 52(4): 1930–1937.

Clinical features

The classification of MGD's clinical features [1••] is shown below.

MGD Alone

Asymptomatic MGD (preclinical) The only detectable clinical aspect may be the meibomian gland expression, which might be absent, decreased and/or altered in quality. Afterwards, MGD probably becomes symptomatic, and additional lid margin signs (e.g., hyperemia) appear on slit lamp examination.

Symptomatic MGD Patients show the presence of sensory symptoms referable to the lid margins (itching, irritation and soreness) and morphological features, such as visible lid margin changes (e.g., redness and swelling) when crusts or flakes are absent.

Evident signs of MGD are meibomian gland dropout, altered meibomian gland secretion and changes in the lid morphology, for which existing grading schemes have been applied in the clinic or clinical trials [3•, 4, 5].

Meibomian gland dropout This is the partial or total loss of acinar tissue detected by meibography. Loss may be proximal, at the attached border of the lid or involve the whole gland. Meibomian gland dropout increases with age in subjects not affected by obstructive MGD [6], but it is hypothesized that measurable dropout is an MGD feature and increases with MGD severity. Extensive dropout is associated with increasing evaporative water loss from the eye [7–9].

In *altered meibomian gland secretion*, both the material quality and expressibility are altered. The expressed lipid quality turns from clear to cloudy and can be viscous, containing particulate matter, densely opaque, inspissated and toothpaste-like.

Changes in lid morphology Other morphological features have been included in the grading schemes, such as the *meibomian orifice pluggins*, because of the terminal duct obstruction and extrusion of the meibomian lipid mixture and keratinized cell debris, which is a clinical pathognomonic sign of MGD. Another morphological feature affects the *meibomian orifices and the mucocutaneous junction (MCJ)*. In addition, further important changes affect the location of the meibomian orifices in relation to the MCJ and the anteroposterior position of the MCJ itself. This junction is important because it forms the watershed between the lid margin lipid-wettable skin and the water-wettable mucosa. Marx's line is a line of conjunctival epithelial staining placed right behind the MCJ, indicates the MCJ location and is shown by dyes such as rose bengal and lissamine green [10–13]. The correlation between the anterior migration line and presence of MGD has been demonstrated by Yamaguchi et al. [14•].

Symptomatic MGD can be distinguished as:

Noncicatricial MGD where initially the orifices retain their position anterior to the MCJ. In this case, restoring

the meibum delivery will permit taking up oil into the tear film lipid layer (TFLL) once again.

Cicatricial MGD in which gland terminal duct stretching, with its exposure, and thinning of the overlying conjunctival mucosa are caused by submucosal connective tissue scarring. It can be isolated or associated with different forms of cicatricial conjunctivitis (e.g., trachoma, erythema multiforme and pemphigoid).

Other MGD characteristics are rounding, notching, dimpling, telangiectasia, increased posterior lid margin vascularity, epithelial ridging between gland orifices, orifice architecture loss, gland cystoid changes and the presence of concretions inside the acini with increasing chalazia.

MGD Associated with Ocular Surface Damage (OSD)

OSD may be associated with MGD, and its most advanced form is meibomian keratoconjunctivitis (MKC), characterized by positive vital dye staining in the lower part of the exposed cornea and conjunctiva. Different methods to quantify the ocular surface damage consist of grading the cornea and conjunctival staining using selected dyes, immunohistochemistry or flow cytometry on impression cytology specimens and the direct biochemical measurement of inflammatory mediators in tears using multiplex bead technology or MALDI-TOF and proteomic techniques [15].

MGD-Related Evaporative Dry Eye

When MGD is present, the affected orifices are malpositioned, and the stretched and narrowed ducts cause a decrease in the amount of oil transferred to the reservoir and/or a composition change after meibomian inflammation, obstruction or gland atrophy and cicatricial MGD. As MGD proceeds, the global oil quality, amount in the reservoir and its distribution along the lid margins can no longer maintain a normal TFLL, so the TFLL functionality is compromised.

MGD Associated with Other Ocular Disorders

The existing literature has reported different analyses to examine the relationship between MGD and other ocular and systemic disorders.

Meibomian Keratoconjunctivitis (MKC) is a condition observed in patients affected by chronic blepharitis that presents as tear film instability, ocular inflammation and ocular surface damage [16]. Often in these patients, the lower interpalpebral globe and cornea present obstructive MGD associated with conjunctival injection and superficial punctuate keratitis (SPK). MKC always presents in the form of a skin disease, such as seborrhoea sicca, (11.5 %), acne rosacea (34.6 %) or seborrheic dermatitis, on its own (38.5 %) or combined with atopy (15.4 %).

MGD and wearing contact lenses MGD can often be observed in patients intolerant to wearing contact lenses (CL) [17, 18], and several clinical reports associated MGD with giant papillary conjunctivitis (GPC). Anyway, the role of wearing contact lenses needs to be studied thoroughly in order to define MGD's development and/or progression.

Mixed Anterior Blepharitis and MGD Mixed anterior blepharitis in patients affected by MGD disease is quite common and often shows up clinically in seborrheic blepharitis [19], atopic blepharitis [20, 21] and as a specific systemic complication of retinoid therapy [22].

Slit Lamp Examination

During slit lamp examination, the following steps are recommended:

- Lid and lid margin examination.
- Seeking signs of inflammation. The lid margin may be thicker and rounded, and there may be notching. Address attention to the lid margin vascularity (e.g., the presence of vessels bridging the lid margin is typically associated with rosacea), the presence of lash loss or alteration (trichiasis, districhiasis) and mucocutaneous junction displacement or hyperkeratinization.
- Attentively examine the acini, especially their morphology (e.g., enlargement), visibility, concretions and lipid inclusions.
- Carefully observe the secretions. Excessive foam reveals a meibomian gland disorder. Anterior blepharitis is frequently accompanied by scales and collarettes. Tubules may denote *Demodex folliculorum* infection. The volume, quality [23] and expressibility [24] are the parameters for evaluating the expressed secretion.
- Also examine gland orifices well for both the existing orifice number and orifice patency [25]. Analysis of capping, pouting, epithelial plugging and the degree of obliteration (narrowing, cuffing loss, scarring) is recommended. Vascular invasion or fibrotic signs (e.g., glands retroplacement) and main duct exposure and cystoid dilation also need to be considered.
- Conjunctival injection examination. Usually in the early disease phases conjunctival injection can be found in the inferior third of the exposed interpalpebral area; the more the disease advances, the more it expands toward the surrounding areas.

- Corneal change observation. Blepharitis typically presents with infiltrates, ulcers and keratitis in the interpalpebral zone. Some immunomediating reactions forming in lid or meibomian gland disorders are strictly related to the vessel branches invading the cornea in the lower limbal area.
- Recognition of changes in the fornix. An extensive eye inflammatory response and cicatricial reaction are characterized by symblepharon or ankyloblepharon.

Specialized and non-specialized tests

(e.g., orifice plugging and other orifice or lid margin signs), it is possible to verify meibomian gland functionality by applying digital pressure over the central (± nasal) third of the lower/upper lids. Assessment is suggested to determine the ocular surface damage and evidence of dry eye.

MGD-Related Dry Eye Diagnosis

(1) Identifying the particular features allowing discrimination between MGD dry eye and generic dry eye patients.

Testing category	Specific test (s)	Tests for general clinics	Tests for specialized units
Symptoms	Questionnaires	M cMonnies, Schein,OSDI, DEQ, OCI,SPEED, etc.	McMonnies, Schein, OSDI, DEQ, OCI, SPEED, etc.
Signs			
Meibomian function	Lid morphology	Slit lamp microscopy	Slit lamp microscopy, confocal microscopy
	Meibomian gland mass	–	Meibography
	Gland expressibility	Slit lamp microscopy	S lit lamp microscopy
	Expressed oil: quality		
	Expressed oil: volume		
	Lid margin reservoir	–	Meibometry
	Tear film lipid layer		
	Thickness	Interferometry	Interferometry
	Spread time	Slit lamp	Slit lamp
	Spread rate	–	Video interferometry
Evaporation	Evaporimetry	–	Evaporimetry
Tears			
Osmolarity	Osmolarity	TearLab device, other	TearLab device, other
Stability	Tear film	TFBUT; OPI	T FBUT; OPI
	TFLL	Spread time	Int erferometry; spread rate; pattern
Indices of volume and secretion	Tear secretion	Schirmer 1	Fluorophotometry/FCR
	Tear volume	Not available	Volume by fluorophotometry
	Tear volume	Meniscus height	Meniscus radius of curvature; meniscometry

Specialized and Nonspecialized Tests for MGD and MGD-Related Disease

From: Tomlinson et al: "The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. Invest Ophthalmol" Vis Sci. 2011 Mar 30;52(4):2006-49.

MGD Diagnosis

In asymptomatic adults, routine workup considering the gland expression (e.g., applying moderate digital pressure to the central lower lid) helps to detect asymptomatic, non-obvious MGD.

(1) In order to diagnose MGD, patients must be further observed by appropriate diagnostic techniques to identify ocular surface damage and dry eye.
(2) To evaluate MGD's extent and severity (expressibility and secretion quality) in patients with ocular surface symptoms or morphological MGD lid signs

(2) Differential MGD diagnosis to distinguish MGD-related evaporative dry eye from aqueous-deficient dry eye.

Practitioners working in a general clinic and investigators working in specialized units can follow the two different approaches proposed below.

MGD Diagnosis in a General Clinic

In a general clinic, patients presenting ocular surface disease symptoms should undergo the following test sequences:

(1) Performing a symptom questionnaire.
(2) Blink rate measurement and blink interval (BI) calculation.
(3) Lower tear meniscus height assessment.
(4) Tear osmolarity measurement if available
(5) Fluorescein instillation and tear film breakup time (TFBUT) assessment: a blue exciter filter and a yellow barrier filter help for measurement and viewing. The instilled volume affects the cutoff value for the diagnosis of dry eye. The Ocular Protection Index [26] can be calculated as the TFBUT:BI (blink interval) ratio. A value corresponding to <1 indicates pathology and implies that tear breakup is occurring in the waking state; on this basis, the lower the value is, the greater the degree of tear film instability.
(6) Right after TFBUT evaluation, fluorescein staining can be graded on both the exposed cornea and conjunctiva. Lacking a yellow barrier filter, lissamine green must be used to measure the conjunctival staining independently. This grading can be performed after Schirmer's test.
(7) Schirmer's test or phenol red thread test. A positive, even if abnormal, result from the tests described in (1), (4), (5) and (6) provides partial evidence of the presence of generic dry eye, without specifying whether it is aqueous-deficient or evaporative. Tear meniscus height or Schirmer's test allows measuring the tear flow or aqueous volume assessment, which indicates aqueous-deficient dry eye.
(8) If a previous visit did not define MGD (symptomatic/asymptomatic), then it can be determined after the following sequence:
    (a) Morphological lid feature quantification.
    (b) Expression: meibum expressibility/quality quantification.
    (c) Meibography: dropout quantification.

If generic dry eye is diagnosed and the tear flow tests and volume are normal, then evaporative dry eye is suspected, and MGD quantification will suggest the contribution of the meibomian gland.

The above sequence allows diagnosing symptomatic MGD, too (with or without ocular surface staining and with or without dry eye). Thanks to each test result, the disease can be monitored during treatment.

MGD Diagnosis at a Specialized Unit

Corneal specialists or investigators employed in clinical trials, having a wider range of diagnostic equipment, can take advantage of other alternative comprehensive test series. The suggestion again is to make the diagnosis into two steps:

1. Diagnose generic dry eye and then subtype it by the MGD grade. This test series allows: symptom identification, tear measurement, osmolarity analysis, the tear secretion test (fluorophotometry or fluorescein clearance rate), measurement of tear volume in the eye (by fluorophotometry and meniscometry), stability test (TFBUT or non-invasive TBUT, or interferometry) and tear evaporation quantification by evaporimetry. In order to quantify the quality of the behavior of the oily layer of the tear film, the the dynamic lipid layer interference pattern (DLIP) test can be used [27].
2. The ocular surface damage test series also includes corneal and conjunctival staining. Using inflammatory mediator tests, inflammatory cell marker presence and other proteomic and lipidomic mass spectrometry analyses, it is also possible to obtain information on the overall inflammatory status of the ocular surface, although at this time the link to MGD is not specifically known. Specific tear production measurements are also recommended to diagnose aqueous-deficient dry eye.

MGD Treatment

Although generally clinical handbooks agree on how to manage MGD, across the world substantial differences exist regarding its practical treatment due to the availability of therapeutics as well as the commonly used clinical manuals. Specifically, Moorfield's Manual of Ophthalmology (2nd edition) and The Wills Eye Manual (3rd edition) recommend [28••]:

> Lid hygiene: warm compresses and lid massage up to four times a day for 15 min;
> Tear substitutes: additional lubricants also for dry eye disease;
> Topical antibiotic ointments: for both moderate and severe cases;
> Systemic antibiotics: tetracycline derivatives for 6 weeks to several months in recurrent cases, and/or
> Topical steroids: for a short time, in severe cases, incision and curettage with optional steroid injection in the chalazion.

Lid Hygiene

Lid hygiene also has a fundamental role in reducing potentially toxic lipids caused by tear film spoilage provoking products (free fatty acids) and decreasing the lipolytic bacteria load.

These procedures include the application of warm compresses on the eyelids for several minutes in order to liquefy thickened meibomian secretions and soften adherent incrustations on the eyelid margins. After heat

application, it is advisable to massage the eyelids gently to spill the retained meibomian secretions.

The following procedures improve meibomian gland secretion turnover:

1. *Secretion melting* Temperature significantly influences the delivery of meibomian gland secretions [29]. The closed eyelid temperature can be increased by applying a warm (around 40–45 °C), water-soaked wash cloth, cotton or gauze (using microwaved damp cloths is convenient) for 3–10 min. This procedure can improve the tear film lipid layer thickness proportionally to the application length, increasing it by more than 80 % in patients affected by MGD [30].
2. *Forced expression of secretions* Once the excretions are in a more liquid state, lid massage pressing the gland body may help to evacuate the meibomian glands and normalize the oil flow into the tear film by removing keratinized cells plugs and thickened lipids.
3. *Lid scrubbing* Afterwards, the eyelid margin has to be washed and scrubbed to remove the adherent debris, such as collarettes and crusting, and to clean the gland orifices. Through the tensio-active and detergent soap action, for example diluted baby shampoo or a commercially prepared eyelid cleansing solution, the bacterial membranes can be lysed, reducing the bacterial load. Non- or very low tension-active preparations are preferred, as they are less irritating to the eye than common shampoos [31].

The frequency of lid hygiene depends on the disease severity: generally, during the acute phase, therapy has to be performed several times a day, while it is needed less frequently (from once a day to twice a week) after the symptomatic disease phase.

Tear Substitutes

Topical tear substitutes (eye drops, gels and ointments) are key preparations for treating MGD; patients who use them often are strongly recommended to employ preservative-free tear substitutes in order to avoid toxicity.

The usefulness of tear substitutes is reconstituting an adequate fluid volume in front of the ocular surface, easing good lipid spread, protecting against thickened, inflamed lid friction, helping to clean the surface from the stagnation of the disease's toxic and inflammatory by-products and reducing elevated tear film osmolarity or its activity on the epithelia. In order to prevent the excessive tear water evaporation typical of MGD, lipid-containing tear substitutes have been suggested to provide possible improvement for these patients.

Topical Antibiotic Ointments

No proof exists showing that bacterial infection is the primary pathophysiological process in MGD, even though various clinical findings often observed in this disease may be related to the effects of the eyelid colonizing bacteria. Bacteria may have both direct and indirect effects on the ocular surface and on meibomian gland function. However, the demonstration of bacterial presence on the lid margin of patients suffering from MGD does not imply its causality. It is likely that the excessive lid colonization, demonstrated in patients affected by blepharitis [32, 33], coagulase-negative staphylococcus (*Staphylococcus epidermidis*), *Staphylococcus aureus*, *Propionibacterium acnes* or other microbes, is an epiphenomenon, suggesting the possibility that microbes find the altered eyelid environment in MGD more hospitable than that in the normal eyelid.

Short-term use of antibiotic ointments (tetracycline, bacitracin and erythromycin, as well as tobramycin or gentamicin) can lower the bacterial load on the eyelid margin.

Tea tree oil scrubs have been suggested as efficacious in Demodex-related lid margin inflammation.

Systemic Antibiotic Treatments

Systemic tetracyclines can be very effective if eyelid hygiene fails to keep MGD signs and symptoms properly under control.

However, only 30–50 % of staphylococci are sensitive to tetracycline, and its salutary effect probably, at least in part, is different from the antimicrobial one. Systemic tetracycline seems to have other activities besides its antimicrobial action, allowing a reduction of the vital bacterial number: production of extracellular enzyme inhibition caused by the ocular flora in fact represents an alternative mechanism. Toxic hydrolysis products, i.e., free fatty acids, which may exacerbate the disease process, at lower levels result in inhibition of lipase production.

In the first 3–4 weeks, patients can be treated with tetracycline (250 mg), to be ingested every 6 h; then, according to the clinical response, the dose can usually be reduced to 250–500 mg daily, but due to the posology (to be taken on an empty stomach and more frequent dosing), doxycycline and minocycline are now being increasingly prescribed. Their doses are 100 and 50 mg, respectively, every 12 h for 3–4 weeks, tapering to 50–100 mg per day. Patients or children with known hypersensitivity can be treated with erythromycin.

Topical Steroids

Steroids are suggested to treat MGD, as they are associated with inflammatory changes on the ocular surface. Topical corticosteroids, such as dexamethasone and loteprednol etabonate, have proven efficacity in reducing at least some signs and symptoms related to more severe forms of dry eye and ocular surface disease, including blepharoconjunctivitis [34, 35]. Topical corticosteroids are also useful:

- To treat moderate to severe inflammation for short periods
- During acute phases, for a long time
- During non-acute inflammatory phases in pulsed or minimal doses (smart)
- Together with steroid use to overcome MGD inflammatory complications.

Other Main Treatments

Cyclosporin A

Many inflammatory ocular conditions, such as uveitis, atopic keratoconjunctivitis and vernal keratoconjunctivitis, can be treated with calcineurin inhibitors such as cyclosporine. The FDA has approved topical cyclosporine A 0.05 % to manage the inflammatory features of dry eye. Lacrimal acini destruction and neural responsiveness can be lowered and increased, respectively, improving lacrimal secretion (Figs. 1, 2, 3).

Compared to placebo [36], cyclosporine A 0.05 %, administered over a 3-month period to patients suffering from symptomatic MGD, significantly reduced lid margin vascular injection, tarsal telangiectasis, fluorescein staining and the meibomian gland inclusion number. In ocular rosacea patients, another study compared cyclosporine A to artificial tear treatment over a 3-month period: as a result, in the cyclosporine A group, the Schirmer's test value, TFBUT and staining were all improved to a greater extent [37].

Essential Fatty Acid Supplementation

As studies have demonstrated, ocular surface inflammatory activation in dry eyes may be reduced by using a systemic polyunsaturated fatty acid associated with long-term nutraceuticals containing balanced proportions of omega-3 and omega-6 polyunsaturated fatty acids [38].

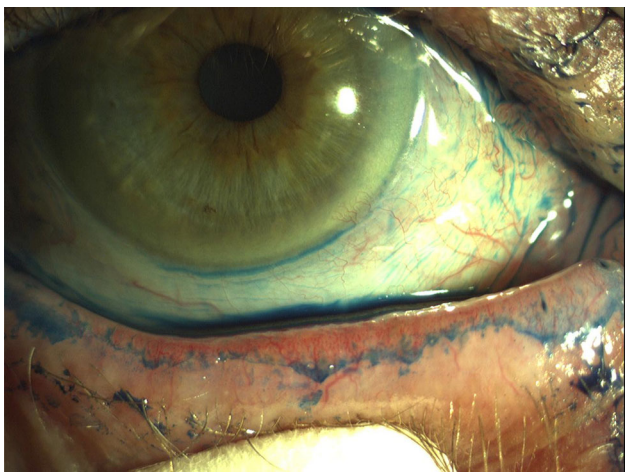


Fig. 1 Lissamine green staining outlines the irregular shape of the muco-cutaneous junction in this eye with chronic MGD

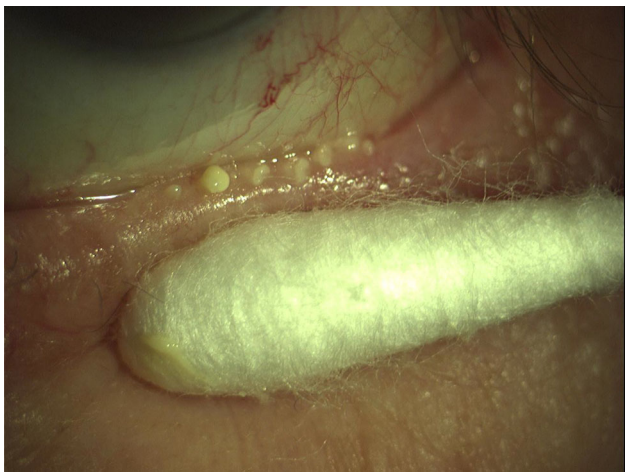


Fig. 2 Mild compression on the lid margin shows the thick, altered MG secretion in an apparently calm ocular surface of a symptomatic eye

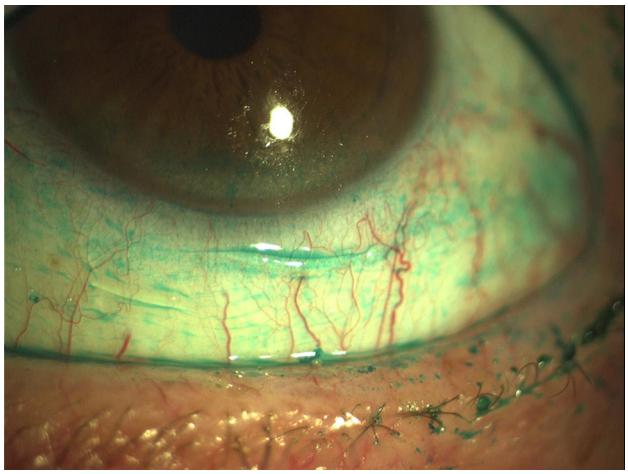
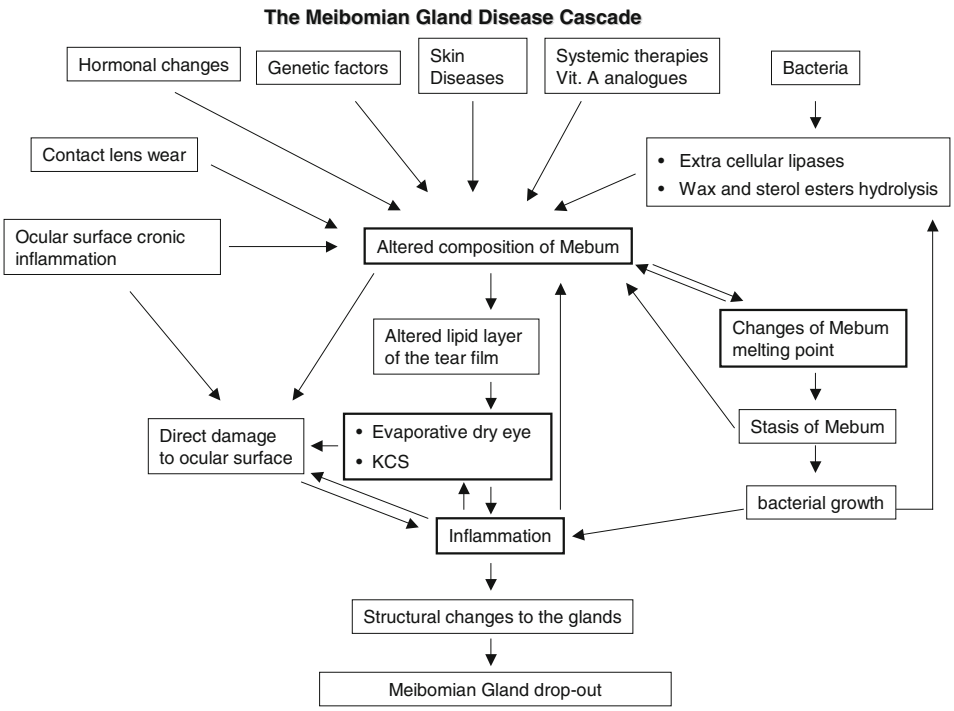


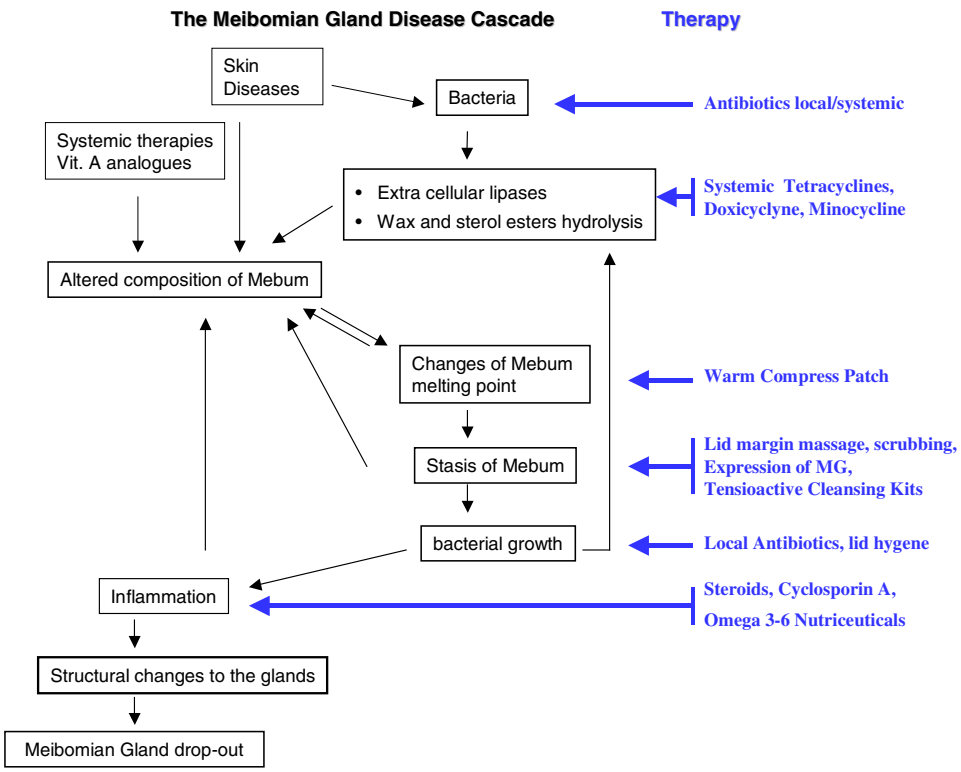
Fig. 3 In the same eye lissamine green shows a very thin meniscus and vital staining of both the cornea and conjunctiva

Topical and Systemic Sex Hormones

In mice, meibomian gland gene expression was influenced by androgenes, especially to suppress the genes associated with keratinization and stimulate genes related to lipogenesis [39, 40]. Marked clinical abnormalities in meibomian gland function [41] have been considered related to clinical improvement of MGD depending on androgen receptor dysfunction and systemic androgen (0.03 % testosterone) medication use [42–45].



From: M. Rolando "*Lids and ocular surface disease-diagnosis and management*" in "Dry Eye Disease" by Penny Asbell and Michael Lemp eds. Thieme Publishers, New York.



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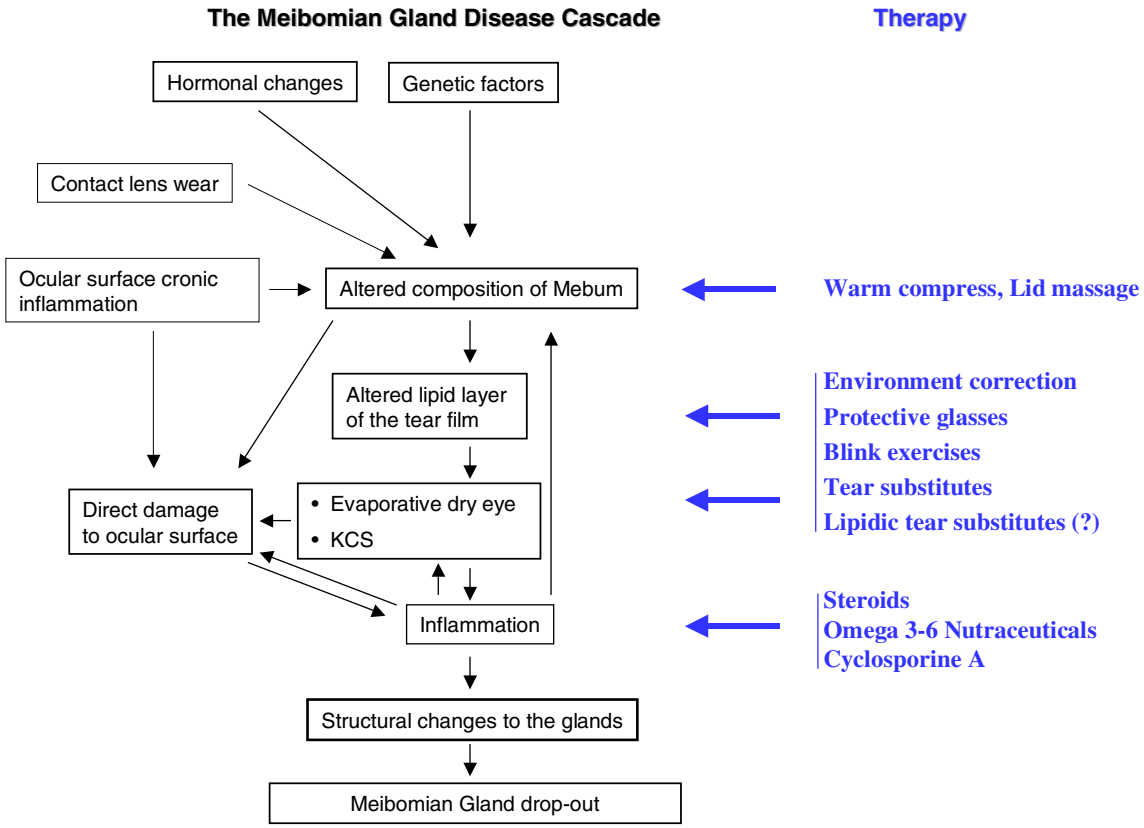

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Disclosure Prof. M. Rolando is or has been in the last 3 years a consultant for Allergan, Bausch & Lomb, Thea, Farmigea and Santen. Dr. Vagge has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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