MGD: Definition Versus Dry Eye Disease, Risk Factors

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Published online: 1 April 2014
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Abstract Meibomian gland dysfunction (MGD) is defined as any functional disorder of the meibomian glands. While MGD is commonly associated with lipid tear deficiency, patients with MGD may also be asymptomatic and/or may have normal tear film parameters. Although there are no standardized diagnostic criteria for the disease, epidemiologic studies have revealed that MGD is very common, especially in Asian populations. Risk factors for MGD include both ocular and systemic conditions. Ocular conditions specifically found to associate with MGD include contact lens wear and the use of glaucoma medications. Systemically, older age, lower androgen levels, rosacea, and Sjogren's syndrome have all been associated with disease.

Keywords Meibomian gland dysfunction · Lipid tear deficiency · Contact lens wear · Glaucoma medication · Rosacea · Androgen deficiency · Nutrition · Sjogren's syndrome

Introduction

Meibomian Glands (MG)

The meibomian glands (MGs) are a subtype of sebaceous glands located in the eyelid. They differ from other

sebaceous glands as they do not associate with hair follicles. The MGs are composed of clusters of secretory acini connected to a central duct by short ductules. Their central duct openings are found in a single file line in the posterior part of the upper and lower eyelid margins, anterior to the mucocutaneous junction. Meibomian acini, consistent with other sebaceous glands, release lipid by holocrine secretion. That is, the cell membrane of a mature meibocyte disintegrates, and the cell content is released to form a lipid product called meibum [1•]. Meibum is a complex substance consisting of nonpolar lipids (e.g., cholesterol, cholesterol esters, wax esters) and polar lipids (e.g., phospholipids) of varying concentrations [2•]. Meibum comprises the superficial layer of the tear film and protects against its evaporation. Healthy MG function is needed to maintain a healthy tear film and ocular surface.

Meibomian Gland Dysfunction (MGD)

MGD is defined as any functional disorder of the MGs. This includes low delivery states due to hypo-secretion or obstruction and high delivery states due to hyper-secretion [3]. It is challenging to study the epidemiology of MGD as there are no standardized diagnostic criteria to define this entity. MG dysfunction can be evaluated by a combination of static and dynamic tests performed at the slit lamp (Table 1). Static tests include the grading of eyelid margin telangiectasias (Fig. 1), keratinization, MG plugging, and MG foaminess. Dynamic tests include the grading of meibum quality and expressibility. The lipid product in patients with MGD is typically thicker than normal meibum and is more difficult or impossible to express.

In addition to these simple metrics, other tests, both commercially and non-commercially available, can be applied to indirectly evaluate MG function. LipiView (Tear

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Table 1 Commonly used tests to evaluate MGD

Slit lamp-based tests

Static tests

- Lid margin telangiectasias
- Lid margin keratinization
- MG orifice plugging
- MG orifice foaminess

Dynamic tests

- Tear break-up time
- MG expressibility
- Determination of meibum quality

Commercially available tests

- Interferometer (LipiView): quantifies thickness of lipid tear film layer
- Confocal imaging (Heidelberg Retina Tomograph II-Rostock Cornea Module): allows assessment of MG morphology

Non-commercially available tests

- Evaporimetry
- Meibography (may be performed with tranilluminator and visually graded or images may be recorded and subsequently analyzed): allows assessment of MG morphology/dropout

MGD meibomian gland dysfunction, MG meibomian glands

Fig. 1 Slit lamp photograph demonstrating telangiectasias of the lower eyelid margin, one of the many diagnostic tests that can be used to evaluate for the presence of MGD

Science, Morrisville, NC) is a commercially available interferometer that is packaged with the LipiFlow Thermal Pulsation System. LipiView quantifies the thickness of the lipid tear film layer, and information on lipid spreading and stability can also be non-quantitatively evaluated in the generated images. In vivo laser scanning confocal microscopy (Heidelberg Retina Tomograph II-Rostock Cornea Module; Heidelberg Engineering GmbH, Dossenheim, Germany) is another commercially available product that can be used to study the morphology of the MG [4•]. Examined metrics in MGD include the longest and shortest acinar unit diameter, periglandular inflammatory cell density, and acinar unit density.

Evaporimetry is a non-commercially available test that measures tear evaporation from the ocular surface. Estimates of evaporation rates have been generated in the research arena by studying pressure and humidity gradients using a variety of techniques [4•]. Meibography is a technique that can easily be integrated into clinical practice

by applying a transilluminator to the external skin while the lower lid is everted. By retroilluminating the MGs, morphology and dropout can be assessed. A more developed research tool records the images allowing for more detailed structural evaluation of the MGs.

Despite the availability of so many metrics and tests, there is no agreement on which one or combination of findings should define MGD. As such, different studies have used different measures to define the disease and report on its epidemiology. To add to the confusion, abnormalities in any of the above measures can be found with or without ocular surface symptoms, ocular surface damage (i.e., corneal and conjunctival staining) or abnormal tear evaporation. These limitations must be kept in mind when evaluating the literature regarding prevalence and risk factors for MGD.

Epidemiology of MGD

Prevalence of MGD

Various population-based studies have used various clinical measures to study MGD prevalence (Table 2). The Beijing Eye Study, for example, used the presence of telangiectasias at the lid margin (yes/no) to define MGD and found an overall prevalence of 68 % ($n = 1,336/1,957$) [5]. Other studies out of Asia similarly found high frequencies of eyelid abnormalities with 46 % ($n = 254/550$) of Thai individuals >40 years having telangiectasias, MG plugging or collarettes [6], and 62 % ($n = 70/113$) of Japanese individuals >60 years having gland dropout and abnormal MG quality [7]. A USA population-based study, on the other hand, evaluated 2,482 white individuals over the age of 65 in Maryland and found that 3.5 % had grade 2 or higher MG plugging or collarettes. A study out of Spain used a different disease definition, namely viscous, waxy or no secretion upon expression, lid margin telangiectasia or MG plugging and found a 31 % frequency of MGD in their population.

Based on the limitations stated above, however, it is difficult to compare MGD prevalence estimates between studies because of differences in the population studied (e.g., different age cutoffs, inclusion methodology) and differences in the clinical definitions of disease.

Prevalence of Lipid Versus Aqueous Tear Deficiency (ATD)

Lipid tear deficiency (LTD) is defined as tear dysfunction in the setting of an abnormal lipid tear layer. It is most commonly assessed by non-invasively measuring the tear break-up time (TBUT), although other tests can also be employed including

Table 2 Frequency of MGD in different populations

	Author	Year	N	Location	Population	Definition of MGD	Frequency (%)
Asia	Lin ^a	2003	1,361	Shihpai, Taiwan	Population-based	Telangiectasia or MG orifice plugging	61
	Lekhanont ^b	2006	550	Bangkok, Thailand	Population-based	Telangiectasia, MG orifice plugging or collarettes	46
	Uchino ^c	2006	113	Near Tokyo, Japan	Population-based	Gland dropout, poor MG expressibility or poor meibum quality	62
	Jie ^d	2009	1,957	Beijing, China	Population-based	Telangiectasia	68
	Siak ^e	2012	3,271	Singapore	Population-based	Telangiectasia or MG orifice plugging	56
	Basak ^f	2012	3,023	West Bengal, India	Clinic-based	Poor meibum quality	32
USA	Schein ^g	1997	2,482	Salisbury, Maryland	Population-based	MG orifice plugging or collarettes	4
	Hom ^h	2005	398	Southern California	Hispanics, Clinic based	Poor meibum quality	39
	Galor ⁱ	2013	263	Miami, Florida	Men, Clinic-based	MG orifice plugging or poor meibum quality	59
Europe	Viso ^j	2011	654	O Salnés, Spain	Population-based	Telangiectasia, MG orifice plugging or poor meibum quality	31

MGD meibomian gland dysfunction, MG meibomian gland

^a Ref. [56]

^b Ref. [6]

^c Ref. [7]

^d Ref. [5]

^e Ref. [46]

^f Ref. [57]

^h Ref. [58]

ⁱ Ref. [59]

^j Ref. [10•]

^k Ref. [60]

interferometry and evaporimetry [4•]. This finding can be seen in patients with MGD, but not all patients with MGD have LTD. LTD must be differentiated from ATD, which is defined as tear dysfunction in the setting of an abnormal aqueous tear layer. Studies have shown that isolated LTD and a mixed pattern of LTD and ATD are more common than isolated ATD [8, 9•]. In a study by Galor et al. [10•], 176 of 263 men were found to have DES by objective tear film parameters. Of these, 22 (8 %) had mostly ATD, 124 (47 %) mostly LTD and 30 (11 %) a mixed pattern.

Symptoms in MGD

It is well known that there is poor correlation between signs and symptoms in DES [10•, 11]. MGD is no exception, and many patients with clinically apparent MGD have been found to be asymptomatic [12•]. In the Beijing Eye Study, 79 % ($n = 1,051/1,336$) with MGD (i.e., presence of lid telangiectasias) had no DES symptoms [5]. Similarly, in the Bangkok Study, 54 % ($n = 136/254$) with MGD (i.e., telangiectasias, MG plugging or collarettes) were asymptomatic [6]. Conversely, in a

US Veterans Administration (VA) eye clinic-based study, only 51 % ($n = 63/124$) with LTD and 57 % ($n = 17/30$) with a mixed pattern complained of severe DES symptoms as assessed by the dry eye questionnaire 5 (DEQ5) [10•].

MGD Risk Factors

Few studies have specifically evaluated for MGD-associated risk factors and have instead focused on DES-associated risk factors, incorporating both the ATD and LTD forms of disease. However, some ocular and systemic risk factors have specifically been associated with MGD, and these will be described below.

Ocular Risk Factors for MGD

Contact Lens (CL) Wear

There is a clinical impression that CL wearers have a higher risk of MGD compared to similarly aged non-CL

wearers. However, limited data are available on the impact of CL wear on the MGs. In one study of 121 individuals, CL wearers had significantly more MG changes than age-matched controls, and these changes increased with longer duration of CL wear [13]. In another, evidence of MGD was found in 8.6 % of 4,064 soft CL wearers in BP Koirala Lions Centre for Ophthalmic Studies in Kathmandu, Nepal [14]. No control group, however, was provided for comparison.

Topical Medications

Epinephrine eyedrops, now no longer clinically utilized, have been described to affect MG function [1•]. Glaucoma medications in general have also been found to affect MG morphology with lower acinar density and area in those using two or more glaucoma medications compared to those not on medications [15]. Patients using any medication also had less homogeneous acinar wall morphology compared to those not on glaucoma drops. Preserved prostaglandin analogs were associated with significantly more morphologic abnormalities in all measured values compared to non-preserved products. Clinically, patients on glaucoma drops were found to have higher meibum scores and lower TBUT than those not on drops [16].

Ocular Surface Microbiome

The ocular surface microbiome may influence the quality of meibum as secreted lipids may be modified by hydrolyzing enzymes from commensal bacteria inside the ductal system and on the ocular surface. These enzymes may have the effect of breaking down triglycerides into free fatty acids [17]. Free fatty acids, subsequently, may be one of the drivers of the hyper-keratinization seen in MGD [1•]. *Demodex* infestation is another ocular factor postulated to affect the MGs. In a study of six patients with *Demodex*, five had evidence of MGD [18]. Additionally, other studies have linked *Demodex* to rocasea, a disease independently associated with MGD [19, 20].

Systemic Risk Factors for MGD

Age

A cross-sectional study demonstrated an increased frequency of eyelid margin abnormalities (e.g., vascularity, keratinization) in older compared to younger individuals [21]. Other studies have supported this observation by demonstrating concomitant changes in meibum quality with both polar and neutral lipid profiles being affected with age [22, 23]. On a cellular level, acinar epithelial cells of the MG have been found to undergo atrophy with age,

with a concomitant decrease in lipid production [1•]. These changes are suspected to occur in the setting of declining hormone levels that occur with age.

Hormones

Androgens are known to affect sebaceous glands throughout the body [1•]. As such, MGs have also been shown to be influenced by hormonal status. Meibomian acini harbor androgen and estrogen receptors [1•, 24•, 25, 26], and they contain the enzymes necessary for the intracrine synthesis and metabolism of sex steroids (5 α -reductase, aromatase, 17-hydroxysteroid dehydrogenase) [1•, 24•, 27]. Schirra et al. found that testosterone influenced the expression of over 1,500 genes in MG tissue from orchiectomized mice. Pathways affected included those of lipid metabolism, sterol biosynthesis, and fatty acid metabolism [28•]. Khandelwal et al. [29] found similar results in an immortalized human MG cell line as 3,000 genes were influenced by the addition of DHT to the culture. Orchiectomy has been shown to change the lipid pattern in rabbit MG with subsequent normalization after administration of 19-nortestosterone [30].

Clinically, MGD has been described in various androgen-depleted states including men receiving anti-androgen therapy (e.g., for prostate cancer), women with congenital androgen insensitivity syndrome, and Sjogren's syndrome [24•, 31–33]. Men on anti-androgen therapy have been found to have abnormal MG secretions with an altered lipid profile [32]. Men and women with MGD and DES have also been found to have lower bioavailable T and dehydroepiandrosterone (DHEA) levels compared to non-MGD dry eye patients and controls [34].

Limited data are available, however, on whether oral or topical hormonal supplementation should be used in patients with MGD and DES. Several trials found that while oral dehydroepiandrosterone (DHEA) improved dry mouth and constitutive symptoms, it did not affect dry eye symptoms in Sjogren's syndrome [35–37]. In one case report, topical androgen therapy improved the tear lipid layer in a patient with MGD [38]. Systemic estrogen, with or without progesterone therapy, on the other hand, has been found to have either no or an adverse effect on DES [1•].

Rosacea

The link between rosacea and MGD has been well described [39•]. In one study, 60,042 rosacea cases and 60,042 controls were identified using the UK-based General Practice Research Database. The overall incidence rate for diagnosed rosacea was 1.65 per 1,000 person-years. Ocular symptoms were documented in 21 % of cases at the

time of diagnosis [40•]. Another study reported that 33 % of 100 rosacea patients in Northern Greece had evidence of ophthalmic involvement in the form of symptoms or signs of disease (e.g., burning, blepharitis, conjunctivitis). Furthermore, patients with rosacea had significantly lower TBUT than age-matched controls [41].

Systemic Medications

Retinoic acid (RA), a metabolite of vitamin A, has been used for the treatment of various dermatologic disorders. MGD has been well described in the setting of systemic 13-*cis* RA (isotretinoin) use [42, 43]. For example, the MGs of 11 patients treated with isotretinoin were assessed before and during treatment. The MGs appeared more atrophic by meibography; meibum thickness increased and meibum volume decreased during treatment [44]. In another study of 40 patients treated with isotretinoin for 2 months, 20 patients (50 %) had a decrease in TBUT to less than 10 s and 22 (55 %) had newly documented blepharitis. Fortunately, all ocular abnormalities disappeared 1 month after cessation of treatment [42]. A recent study shed light on these observations and demonstrated that 13-*cis* RA inhibited proliferation, increased cell death, and increased inflammatory mediator expression in immortalized human MG epithelial cells [45]. Other medications that have been specifically associated with MGD include angiotensin II receptor blockers [46•], anti-androgens, and hormone replacement therapy [39••].

Nutrition

There is much interest in understanding how diet influences MG function and DES. Studies have documented qualitative lipid changes in patients with MGD, including a decrease in monounsaturated fatty acids and polar lipids [1••]. Epidemiological evidence points to the protective effect of essential fatty acids on DES. In a cross-sectional study of over 32,000 women, higher dietary intake of fish oil and omega-3 was associated with a decreased incidence of DES [47]. In clinical trials, oral supplementation of omega-3 improved tear film parameters including TBUT and decreased ocular surface inflammation (as measured by HLA-DR) in patients with DES [48, 49••, 50]. One study of women with Sjogren's syndrome found a difference in polar lipid profiles based on intake of omega-3 [51]. However, a study of patients with blepharitis taking flaxseed oil failed to show a difference in meibum properties (e.g., omega-3 and 6 fatty acids) despite levels of omega-3 being higher in blood [50]. This study, however, reported that the quality of meibum was clinically improved with treatment.

Sjogren's Syndrome

Traditionally, SS has been thought of as a pure ATD form of DES. Studies have demonstrated, however, that patient's with SS have a higher frequency of severe MG obstruction [52] and higher tear evaporation [53] compared to non-SS aqueous tear-deficiency individuals. It is unclear whether these changes are a primary consequence of disease or whether this represents a secondary change. Similar findings have been described in other ATD-specific diseases such as graft versus host disease (GVHD) [54]. GVHD patients have been found to have higher MG dropout [54] and lower MG acinar density and diameter [55] than control patients without GVHD. In general, increased lipid layer spreading abnormalities have been described in patients with increasing ATD severity [39••].

Conclusion

MGD is a common finding in patients with and without symptoms of DES. While much still remains to be elucidated about the pathophysiology and natural history of disease, epidemiological data regarding risk factors suggest that ocular factors (e.g., contact lens use) and systemic factors (e.g., hormonal status and nutrition) play a role in the health of the MGs and in disease.

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