Special Issue

The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on the Epidemiology of, and Associated Risk Factors for, MGD

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Scientists have been interested in studying the secretions of the meibomian glands for many years,[1–8] and diseases associated with the meibomian glands (e.g., cancers, posterior blepharitis) have been noted in the medical literature since at least the early part of the 20th Century.[9–13] However, the term "meibomian gland dysfunction" (MGD) was only introduced by Korb and Henriquez in 1980.[14] The terminology "meibomian gland disease" was later introduced by Bron et al.[15] as an umbrella term to indicate any disease affecting the meibomian glands (see Definition and Classification).

Although the etiology of MGD may differ from that of aqueous-deficient dry eye disease (which is due to insufficient lacrimal gland production), the two conditions share many clinical features, including symptoms of ocular surface irritation and visual fluctuation, altered tear film stability, and potential ocular surface compromise. When MGD is of sufficient degree, it may give rise to the second major subtype of dry eye disease, evaporative dry eye.[16] These subtypes are not mutually exclusive, as has been acknowledged.[16]

Methods of Assessment for Epidemiologic Studies

Epidemiologic investigation has been limited by the lack of agreement regarding definition or a standardized, clinician-based assessment that characterizes MGD. In light of that, it is useful to consider which methods of assessment, incorporating both objective and subjective outcomes, would be most valuable for future studies of MGD.

We consider a purely objective outcome to be one that is obtained without the influence of the examining clinician or the patient's perceptions. In contrast, measures assessed by a clinician or patient each have components of subjectivity. For example, a grading assessment made by a clinician is associated with a subjective aspect and therefore has an inherent within and between-examiner variability that affects study design and planning. Such variability is also inherent in patient-reported subjective outcomes, such as symptoms and standard visual acuity measures. In general, this committee agreed that the most valuable outcomes for assessment of clinical disease demonstrate the attributes of validity, reliability (low variability), sensitivity (to differences between patient groups), responsiveness (to change in disease status over time), feasibility, and practicality.

There is a lack of clarity on the objective and subjective measures for classification and outcomes of MGD in both clinical care and clinical trials. In part, this ambiguity is due to the paucity of evidence on the time course of the disease and its symptoms or the actual processes that cause them—for example, when symptoms associated with MGD actually develop in the disease process. Is it at the onset of meibomian gland damage or altered meibum production and/or secretion or after a certain level of damage or alteration has occurred? Further, the symptoms may not be due to actual meibomian gland damage or altered meibum secretion at all, but instead may arise from subsequent damage to other ocular surface tissues associated with secondary alterations in physiological processes. Therefore, there has been no consensus on the use of patient-reported or clinician-based assessments in MGD or on the relationship between different measures.

In considering the various objective and subjective clinician-assessed approaches used in the evaluation of MGD, it is important to differentiate between those approaches that evaluate some aspect of the meibomian glands or their secretions (primary assessments) and those that assess other physiological consequences related to gland injury or secretory alteration (secondary assessments). We propose that such secondary assessments be considered surrogate markers of MGD.

Objective Approaches

At present, objective approaches require specialized scientific equipment and are currently applicable for small-scale studies, but are not feasible for use in large epidemiologic studies. For the most part, emerging technologies are being used in these small-scale studies. Primary objective assessments include biochemical analyses of the meibomian glands or secretions (e.g., assays, chromatography, mass spectrometry, and spectroscopy). These approaches evaluate the meibum directly in terms of lipid and/or protein components. Secondary objective approaches that might be considered in the evaluation of MGD include evaporimetry (a measure of the consequences of an altered lipid layer), lipid layer interferometry augmented with computerized assessment in lieu of clinician assessment, and osmolarity (a measure of the consequences of evaporation).

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Subjective, Clinical Approaches

Subjective clinical approaches for the evaluation of MGD include biomicroscopy of the lid margins in terms of telangiectasia and overall lid margin injection (dilated blood vessels at the surface of the skin or mucous membrane) or lid margin keratinization; evaluation of capping or plugging of the meibomian gland orifices and evaluation of the expressibility and quality of the meibum from the glands; and in vivo analysis of the meibomian glands themselves (atrophy or loss) through meibography. The latter technique captures images of the lids illuminated by near infrared or infrared light, allowing visualization of the glands. To date, this method has been assessed subjectively by a clinician or reader, but may lend itself to more objective methods of computerized image analysis.[17–19] Some secondary, subjective, clinician-assessed approaches include corneal and conjunctival staining (due to excessive evaporation and subsequent desiccation), Schirmer or phenol red testing (again, due to excessive evaporation and subsequent aqueous tear loss), and measures of tear film stability, such as noninvasive and invasive tear film breakup times.

Subjective, Patient-Reported Approaches

MGD may be associated with symptoms and signs of ocular surface discomfort, such as eye itching, eye burning, heavy/puffy eyelids, eye dryness, eye irritation, watery/teary eyes, crust on lashes (particularly in the morning), eyelids being stuck shut (particularly in the morning), and eyelid and ocular redness, among others. Notably, these symptoms are the same or very similar to those reported in dry eye disease and/or in anterior blepharitis.[20–24] Based on available evidence, since there is broad overlap in these symptoms and those for aqueous deficient and evaporative dry eye patients, we cannot be certain whether a symptom survey that is specific to MGD can be developed. A concerted effort is needed to identify specific symptoms or develop instruments that would separate patients with MGD from those with other ocular surface problems. This is particularly important because patient-reported outcome measures have been described for dry eye disease, but these were validated across dry eye subtypes and were not specific to MGD.[20–24] As more is learned about MGD and dry eye disease, such an approach might gain a foothold if evidence emerges to link specific features or patient symptoms to objective measures of MGD, ocular surface damage, and measures of tear dynamics.

Currently, defining MGD based on symptoms alone is not ideal, and instruments that are specific for MGD are not available and will be challenging to develop, because symptoms that researchers use are associated with more broadly defined conditions such as dry eye disease and blepharitis. For example, eyelid symptoms that include puffiness and morning "stickiness," which have been used for assessment of MGD in some studies,[20–24] may be common to both anterior and posterior types of blepharitis (see Definition and Classification of Meibomian Gland Dysfunction). Recently, a telephone survey of 5019 adults (at least 18 years of age) in the United States found that 15% of the respondents recalled at least one of the symptoms traditionally associated with anterior blepharitis (crust or flakes on eyelashes on waking, eyelids sticking together on waking, and redness of the eyes or eyelids on waking) at least half of the time in the last 12 months, with 1% having experienced all three symptoms in that same period.[25] However, the authors noted that eye care practitioners did not examine participants, and so the reported symptoms cannot be extrapolated to diagnosis. Clinically significant cases of MGD can occur with or without significant anterior blepharitis or aqueous-deficient dry eye. Thus, making specific symptoms a prerequisite in the definition of MGD may underestimate the prevalence of clinically relevant disease.

The difficulty of specifically identifying MGD is supported by the fact that the same telephone survey found that 40% of the respondents who had a diagnosis of blepharitis also had dry eye disease, and the symptom responses were quite similar between these two groups, except that symptoms of "eyelids stuck together on awakening," "eyes or lids red on awakening," and "thinning of the lashes" were more frequent in the blepharitis group.[25]

The clinical picture of patients with ocular surface disease is often complicated. Clinically significant cases of MGD may have anomalies of the lipid component of the tear film and symptoms resulting from evaporative dry eye. Symptoms may also arise from the lid disease itself, with accompanying inflammatory events, or ocular surface damage (e.g., secondary to the release of inflammatory mediators from the lid into the tear film). These symptoms and the associated functional difficulties that arise are a significant concern in people with MGD; the importance of their assessment is clear. That these symptoms cannot be distinguished from those of aqueous-deficient dry eye or other conditions complicates this task, however.

We must also consider that symptoms may vary by both frequency and severity, with most studies so far concentrating on the former. There may also be subjective, patient-reported factors other than ocular surface or eyelid symptoms that are important to quantify, such as climate, humidity, or activity level (e.g., computer use). Understanding and quantification of these subjective, patient-reported aspects of MGD, as well as the perceived impact of the disease on an individual's life, are needed, so that valid techniques can be used for assessment of MGD. Scientifically proven validation techniques should be used in the future development of these assessments.

To the best of our knowledge, there has been no attempt to determine whether ocular surface and/or eyelid symptoms can differentiate between cases of anterior blepharitis or aqueous-deficient dry eye disease and cases of MGD. Nor has the extent to which these conditions occur together, or whether they are separate entities, been well documented.

Combination (Correlative) Approaches

Combination approaches would entail the integration of symptomatic assessment of MGD with measures derived both from clinical evaluation and by purely objective means. We advocate that such an approach could hold the greatest promise for moving the field forward. The inclusion of a clinical assessment could alleviate problems encountered when trying to define MGD based on symptoms alone, and consideration of symptoms could help identify the most clinically relevant cases. Thus far, the Beijing Eye Study comes closest to this type of construct by reporting the prevalence of eyelid telangiectasia (as a clinical sign of MGD) in the presence of symptoms of dry eye.[26] At 69%, the reported prevalence was relatively high when compared to other studies that did not include symptoms in the definition. Future studies using this type of approach would probably succeed best if a set of MGD-specific symptoms can be identified.

Since the severity of MGD can be graded by standard techniques, such measures can form the basis for identification of MGD symptoms and their correlation with clinical disease parameters. Natural history and/or treatment studies using such measures could then advise on which grade (symptomatic or nonsymptomatic) is most predictive of progressive disease, as well as how treatment affects various MGD parameters and how various symptoms and signs affect a patient's quality of life.

It is worth noting that an epidemiologic definition of MGD may not correspond to the threshold used by clinicians for

treatment. For example, whereas symptoms would be expected to develop during the progression of MGD, in some cases intervention may be more effective if initiated before symptom onset. Although worth the effort, it may prove impossible to identify a set of symptoms that are specific to MGD. Last, signs and symptoms of MGD may not themselves show a high correlation, as with dry eye.[26] These problems are common to epidemiologic studies in general and so should not preclude efforts to study MGD in particular. Care should be given to the choice of definition in various settings, taking into account not only factors such as the sensitivity and specificity of a particular definition, but also its cost and feasibility and the burden on study participants when applied on a large scale. Definitions and diagnostic criteria should be documented in sufficient detail to permit comparisons with future work.

Prevalence of MGD

Population-Based Studies

Most population-based studies that have estimated the prevalence of MGD have included a patient-reported symptom outcome that is developed for the study of dry eye disease, but is not specific to MGD. However, there are now several studies that have also evaluated concurrently measured clinical correlates including lid telangiectasia, gland orifice capping, gland dropout, gland expressibility, and tear breakup time. For analysis of these studies, the clinical correlates chosen were evaluated either independently or grouped together with patient symptoms, to serve as an indicator of MGD.

The prevalence of MGD reported in published studies[20,27–31] varies widely, from 3.5% to almost 70% (Table 1). A striking feature in looking across these publications is that the prevalence of MGD appears to be higher in reports arising from Asian populations. The 46.2% found in the Bangkok study,[27] 60.8% in the Shihpai Eye study,[28] 61.9% in a Japanese study,[29] and 69.3% in the Beijing Eye Study[30] contrast sharply with reports from populations with a majority of Caucasians which, in turn, range from 3.5% in the Salisbury Eye Evaluation study[20] to 19.9% in the Melbourne Visual Impairment Project.[31] As the definitions of MGD differed among these various studies, caution is advised in making direct comparisons between studies or drawing overarching conclusions.

Discussing symptoms consistent with MGD, 33.7% (459/1361) of subjects in the Shihpai Eye Study had one or more symptoms often or all the time, whereas 61.7% (283/459) had MGD defined by clinical signs of telangiectasia or orifice plugging.[28] The symptom survey used in this study consisted of eight questions that addressed the frequency of eye dryness, gritty/sandy sensation, burning sensation, sticky sensation, watering/tearing, redness, crusting/discharge, and eyes stuck shut. The group did not report on the relative frequencies of the symptoms reported by the subject sample, and symptom intensity was not assessed. Lekhanont et al.[27] reported a similar study (the Bangkok study) that used a modified version of the symptom survey developed for the Salisbury Eye Evaluation. They showed that of the 187 participants (34%) with "significant symptoms" (one or more of six "dry eye" symptoms, often or all the time), 63% had clinical signs of MGD defined by telangiectasia, collarettes (a sign of anterior blepharitis, not MGD), and gland plugging.[27] In contrast, Jie et al.[30] showed in the Beijing Eye Study that two clinical indicators of MGD (orifice plugging and lid telangiectasia) were not associated with patient-reported symptoms. Further details of these and other studies are summarized in Table 1.

There were substantial differences in the exact clinical signs used to define MGD across those studies. The Beijing Eye Study used telangiectasia of the lid margin as the criterion for MGD, the Shihpai Eye Study considered telangiectasia or plugging of meibomian glands to be MGD, whereas the Melbourne Visual Impairment Project reported only the tear film breakup time (TBUT), which is a secondary or surrogate measure of MGD and therefore a less specific indicator of disease status.[28,30,31] Given the paucity of information on the natural history of MGD as well as the lack of consensus on how to define the disease or its severity, it is difficult to predict how these different definitions will affect MGD prevalence. An additional problem is that there are no universal standards for the assessment of MGD symptoms and clinical signs. For example, there is no universal standard set of criteria for grading eyelid telangiectasia or meibomian gland plugging to indicate clinical significance. In the absence of standards, the inherent subjectivity of assessment contributes to the variability between different studies. Finally, many of the signs or symptoms of MGD may be affected by factors other than MGD, such as contact lens wear,[30,32–36] anterior blepharitis,[37–40] and possibly other symptomatic ocular surface conditions such as ocular allergy.

Another factor to consider in comparing prevalence across studies is the potential impact of the age distribution of the various study groups. If, as in dry eye disease, the prevalence of MGD increases with age, older populations would predictably give higher prevalence estimates than studies with a lower average age. Of the studies summarized herein, Uchino et al.[29] recruited only Japanese participants older than 60 years, whereas the Bangkok study involved participants older than 40 years.[29] The Japanese study found a higher prevalence rate of MGD than did the Bangkok study, as would be expected if the prevalence of MGD increases with age.[27] There has been no published report on the age-specific prevalence of MGD.

There are other methodologic discrepancies that are worth mentioning. For example, the Bangkok study invited 550 volunteers from the population (above 40 years of age) to undergo annual eye screening.[27] This method differs considerably from the random sampling used in many other population-based studies, and as a result, subjects with more severe MGD may have been overrepresented because they may be more likely to volunteer for screening. Likewise, the Japanese study by Uchino et al. could be limited by a similar type of bias because of the disadvantage of recruiting a very small number of the targeted population.[29] Of 12,000 letters sent out to retirees, only 113 consented to the protocol and were recruited. This low participation rate makes it unlikely that the result is representative of the actual population prevalence.

Clinic-Based Studies

Clinic-based studies with smaller sample sizes (Table 2) have also been conducted. As there are still relatively few population-based surveys available, these studies may provide a limited amount of information regarding the prevalence of MGD and the distribution of certain clinical signs and symptoms, but the accuracy with which such studies can estimate true prevalence is questionable. To illustrate, the prevalence of MGD observed in two such studies ranged from 20% in British non–contact-lens (CL) wearers,[32] to approximately 60% in two Japanese studies of patients with or without Sjögren's syndrome.[32,44] It is clearly difficult to make comparisons between these studies, as they involve special, highly selected patient cohorts.

We conclude that the value of this type of clinic-based approach to estimating the prevalence of MGD in the population at large is quite limited. In the future, however, clinic-based approaches may be better suited for study of the risk factors for MGD. Provided that a suitable control population can be identified, such studies may be able to include more detailed clinical assessments and diagnose MGD with a higher degree of specificity than can large epidemiologic approaches.

Clinical Correlates and Possible Risk Factors for MGD

Systematic, epidemiologic evaluation of candidate risk factors for MGD remains in its infancy and is an emerging area of research. Nonetheless, decades of experience, some clinical studies and case series, and expert clinical impressions have suggested several factors that may co-exist with MGD, as well as others that may contribute to its pathogenesis. Moreover, given the highly integrated nature of the ocular surface system and the key role of the meibomian secretions in its maintenance, it is worth considering the strong possibility that the same factors implicated in dry eye disease play a role in MGD as well. In the following section, we summarize some conditions or factors that have been suggested to occur at increased frequency in patients with MGD. Whereas the association be-

Table 1. Population-Based Studies Providing Estimates of the Prevalence of MGD

Study	Participants	Ethnicity	Parameter	Prevalence	Age (y)	Reference
Bangkok Study*	550	Thai (various)	Telangiectasia or meibomian gland plugging or collarettes	46.2% (95% CI, 42–51)	>40	Lekhanont et al.[27]
Beijing Eye Study	1957	Mainland Chinese	Telangiectasia (asymptomatic) Telangiectasia (symptomatic for dry eye)	68.0% (95% CI, 65.6–70.4) 69.3% (95% CI, 64.5–73.8)	>40	Jie et al.[30]
Japanese study	113	Japanese	Gland dropout, expressibility and nature of meibum secretion	61.9% (95% CI, 52.1–70.9)	>60	Uchino et al.[29]
Shihpai Eye Study	1361	Taiwanese Chinese	Telangiectasia or meibomian gland orifice plugging	60.8% (95% CI, 59.5–62.1)	>65	Lin et al.[28]
Melbourne Visual Impairment Project	926	Caucasian	Tear break up time < 1 SD (10 s) Tear break up time < 1.5 SD (8 s)	19.9% (95% CI, 17.4–22.7) 8.6% (95% CI, 6.9–10.7)	40–97	McCarty et al.[31]
Salisbury Eye Evaluation	2482	Caucasian	Meibomian gland plugging or collarettes (clinical grades 2, 3)	3.5% (95% CI, 2.8–4.4)	>65	Schein et al.[20]

* Not a true population-based study because the sampling methods were inappropriate.

Table 2. Frequency of MGD in Selected Clinical Populations

Study	*n*	Parameter	Frequency	Reference
Austria	97	Meibomian gland dysfunction	32.9% (95% CI, 23.8–43.5)	Horwath-Winter et al.[41]
California	398	Cloudy or absent secretion of meibum in lower lid	38.9% (95% CI, 34.0–44.0)	Hom et al.[35]
China	115	Meibomian gland dysfunction	34.8% (95% CI, 26.2–44.4)	Zhang et al.[42]
Japan	Sjögren's 19 Non-Sjögren's 27	Meibomian gland dropout in more than one half of inferior tarsus	57.9% 18.5%	Shimazaki et al.[43]
Japan	Asymptomatic 54	Meibomian gland dysfunction	61.0% (95% CI, 46.6–73.9)	Shimazaki et al.[44]
Kuala Lumpur	231	Meibomian gland dysfunction	43.0% (95% CI, 36.7–50.0)	Ong[45]
United Kingdom	N/A	Meibomian gland dysfunction	30% Contact lens wearers 20% Non-contact-lens wearers	Ong and Larke[32]

Table 3. Population-Based Studies that Have Evaluated the Relation between Ocular Surface Symptoms and Clinical Signs of MGD

Study	Subjective Dry Eye Outcome/Classification	Symptoms Assessed (All Frequency)	Clinical Evaluation	Results (Outcome Association)
Bangkok Study (Lekhanont et al.)[27]*	Dry eye by questionnaire (≥1 symptom, at least often)	Eye dryness; foreign body sensation; burning; discomfort; sticky; tearing	Telangiectasis, collarettes, and plugging were graded (no further definition of MGD provided)	63.6% of those with dry eye had MGD ($P = 0.006$)
Beijing Eye Study (Jie et al.)[30]	Dry eye by questionnaire (≥1 symptom, often or all the time)	Eye dryness; gritty/sandy; burning; redness; lash crusting; eyes stuck shut (in the morning)	No definition, independent signs evaluated	Orifice plugging ($P = 0.51$) Lid telangiectasia ($P = 0.60$)
Shihpai Eye Study (Lin et al.)[28]	Dry eye by questionnaire (≥1 symptom, at least often)	Eye dryness; gritty/sandy; burning; sticky; watery/tearing; redness; lash crusting; eyes stuck shut (in the morning)	Telangiectasis ≥ G1 or gland plugging ≥ G1	61.7% of those with dry eye had MGD; (no *P*-values reported)

G1, Grade 1.

* Not a true population-based study because sampling methods were inappropriate.

tween many of these and MGD may simply be correlative, others can reasonably be hypothesized to constitute risk factors for the disease.

We have organized the discussion by breaking risk factors down into the three broad categories: ophthalmic, systemic, and therapeutic. We separately summarize the available evidence relating CL wear and MGD, for which there have been a few investigations. Although we think it is a useful strategy to classify risk factors on the basis of the strength of the evidence, as was done in the 2007 report on the Epidemiology of Dry Eye Disease by the International Dry Eye Workshop,[46] at present, there are generally few studies available for any particular factor's possible association with MGD. Table 3 identifies the population-based studies to date that have attempted to quantify the relationship (if any) between dry eye symptoms and MGD. Consequently, the evidence that can currently be called on is insufficient to reliably classify the strength or likelihood of the hypothesized associations using such an approach.

Ophthalmic Risk Factors

Maintenance and protection of the smooth refractive surface of the cornea is the function of the ocular surface system, which includes the surface and glandular epithelia of the cornea and conjunctiva; the lacrimal, accessory lacrimal, and meibomian glands, together with their apical (tears) and basal (connective tissue) matrices; the eyelashes with their associated glands of Moll and Zeis, and those components of the eyelids responsible for the blink and the nasolacrimal duct.[47] All components of the system are linked functionally by continuity of the epithelia, innervation, and the endocrine, vascular, and immune systems. In theory, chronic insult to any component of the ocular surface system can lead to clinically relevant sequelae. Given the central role played by the meibomian gland, it is feasible that the development of problems in this tissue (i.e., MGD) could be influenced by factors acting elsewhere within the system. Indeed, such factors may underlie the difficulty encountered when attempting to define and classify chronic afflictions such as dry eye disease, blepharitis, and MGD and may help explain the very large degree of overlap observed among this group of disorders. Table 4 lists factors thought to be associated with MGD. Some of the studies identifying higher risk factors are discussed below.

Table 4. Ophthalmic Factors Hypothesized to Correlate with MGD

Factor	Reference
Aniridia	Jastaneiah and Al-Rajhi[48]
Chronic blepharitis (anterior or posterior)	Auw-Haedrich and Reinhard[40] Jackson[38] Mathers et al.[37] McCulley et al.[39] McCulley and Shine[49]
Contact lens wear	Arita et al.[36] Marren[33] Molinari and Stanek[34] Ong and Larke[32]
Demodex folliculorum	Czepita et al.[50] Kheirkhah et al.[51]
Eyelid tattooing	Kojima et al.[52]
Floppy eyelid syndrome	Gonnering and Sonneland[53]
Giant papillary conjunctivitis	Mathers and Billborough[54] Martin et al.[55] Molinari and Stanek[34]
Ichthyosis	Baden and Imber[56]
Salzmann's nodular corneal degeneration	Farjo et al.[57]
Trachoma	Bron and Tiffany[58]

For example, dry eye disease has traditionally been divided into the two main subtypes: aqueous deficient and evaporative.[16] Under this classification, the most common primary etiologic factor thought to underlie the classic evaporative dry eye subtype is MGD. More recently it has come to be recognized that patients are likely to have (or develop over the longer term) elements of both aqueous-deficient and evaporative dry eye. For example, in a case series of dry eye disease characterized by a primary deficit in aqueous secretion such as in Sjögren's syndrome, MGD is frequently present as well.[43] The MGD in Sjögren's syndrome may represent a second primary defect of the disease (i.e., in addition to the known effects on the lacrimal gland). However, even in the case of aqueous-deficient dry eye with no identifiable primary cause of MGD, MGD may develop as a consequence of long-term changes brought about in the ocular surface system. In this regard, research has shown tear film lipid layer defects in patients with severe, aqueous-deficient dry eye disease and progressive reductions in tear film lipid layer spreading with increasing severity of aqueous-deficient dry eye. Whether such disturbances of the lipid layer and evaporative dry eye are due to MGD specifically, or alternatively, occur in the presence of completely normal meibomian glands have yet to be elucidated. An excellent review of such concepts, including the phenotypes of dry eye, was recently published by Bron et al.[59]

Blepharitis is a generic term used to indicate the presence of inflammatory changes with diverse etiology and presentation that affect the eyelid as a whole. It is one of the most common ocular disorders encountered in clinical practice, and it overlaps substantially with MGD, as MGD is considered to be one cause of posterior blepharitis. Attempts to classify this disorder have been difficult, at least in part due to the complex and incompletely understood mechanisms thought to underlie its pathogenesis, its heterogeneous presentation, and the lack of information on its natural history. Clinical and laboratory investigations of patients with chronic anterior blepharitis have suggested an increased frequency and heavier colonization with certain common bacteria (e.g., *Staphylococcus epidermidis* and *Staphylococcus aureus*).[40,60] Posterior blepharitis is a term used to describe inflammatory conditions of the posterior lid margin, including MGD. Some forms of posterior blepharitis appear to have a seborrheic etiology that can initially be associated with excess meibomian lipid production. Pure subtypes of blepharitis are probably the exception rather than the rule. In one study of 57 patients with various clinical signs and symptoms of chronic blepharitis (presumably of various types), 42 (74%) had evidence of meibomian gland loss shown by gland expression and meibography, whereas only 4 (20%) of 20 normal patients had any gland dropout.[37]

Another ocular factor worth considering for a role in MGD is *Demodex* infestation of the eyelids (see Anatomy, Physiology and Pathophysiology of the Meibomian Gland). Authors of a recent small study observed MGD in five of six patients with this condition.[51] However, additional studies have shown limited to no correlation.[50] Moreover, *Demodex* infestation in the facial skin has been implicated in causing rosacea, a chronic skin condition of presumed inflammatory origin that frequently affects the eye, discussed below.[61]

Aging and Other Systemic Risk Factors

Age-related and other systemic factors or processes may influence the structure and/or function of the meibomian gland. Regarding the possible effects of aging, Den et al.[62] reported a cross-sectional study in which evaluation of lid margin anatomy, meibomian gland, ocular surface epithelium, and tear function was conducted in 354 eyes of 177 subjects. These authors observed that whereas only a few patients aged 50

years and younger showed notable abnormalities in the lid margin or meibomian glands, the frequency of such abnormalities increased dramatically in those older than 50 years. Hykin and Bron[63] have reported in a cross-sectional study with 80 subjects between 5 and 87 years old that an increase in eyelid margin vascularity, keratinization, telangiectasia, and opacity of meibomian gland secretions was observed with aging. Sullivan et al.[64] also showed significant alterations in older versus younger individuals' polar and neutral lipid profiles derived from meibomian gland secretions by high-performance liquid chromatography or mass spectrometry. Such findings appear to coincide with a documented increase in the incidence and prevalence of dry eye disease with aging.[46] The clinical significance of such apparent changes and whether they result directly from aging, are secondary to other age-related biological effects such as the well-known decline in production of sex-steroid hormones or some other mechanism, all of which have yet to be determined.

Sex steroid hormones, such as androgens, are known to control the development, differentiation, and lipid production of sebaceous glands throughout the body, and there is evidence that they have similar effects on the meibomian glands.[65] Accordingly, androgen–meibomian gland interactions may comprise an etiologic factor in the pathogenesis of MGD. Consistent with this idea, Sullivan et al.[65] observed that androgen deficiency, in patients receiving antiandrogen therapy, is associated with MGD, tear film instability, and dry eye symptoms. In a further study in which mass spectrometry of meibomian gland secretions was used in patients with complete androgen insensitivity syndrome, the authors identified significant alterations in the appearance of numerous molecular species in the neutral and polar lipid fractions. These biochemical changes were associated with the observation of clinically apparent MGD and functional dry eye due to tear film lipid layer instability. Mathers et al.[66] measured levels of several sex steroid hormones and performed tear function tests in a group of 110 pre- and postmenopausal women. They observed a positive correlation between higher testosterone levels and better tear function among postmenopausal women, but a negative association in the premenopausal group. Although measures of meibomian gland dysfunction were not reported, this may point to the importance of the balance of different hormones.

Sjögren's syndrome (SS) is an autoimmune disorder that affects exocrine glands, including the salivary and lacrimal glands, and leads to aqueous-deficient dry eye. The annual incidence of physician-diagnosed Sjögren's syndrome has been estimated at 3.9 per 100,000, with a significantly higher incidence in women (6.9/100,000) than in men (0.5/100,000).[67] Using a semiquantitative assessment of the meibomian glands, Shimazaki et al.[43] reported that the frequency of severe gland obstruction was also higher in patients with SS (38.9%) than in dry eye patients without SS (non-SS) (11.1%). This clinic-based study comparing SS (n = 19) and non-SS (n = 27) dry eye patients was among the first to draw attention to the evidence of frequent meibomian gland involvement in SS, a condition that has been regarded as yielding an almost pure form of aqueous-deficient dry eye. Goto et al.[68] reported that tear evaporation rates were higher in the eyes of the SS aqueous tear-deficiency group than in the non-SS aqueous tear-deficiency group. Tear evaporation assessed in conjunction with tear lipid layer findings and meibomian gland expressibility suggested that both entities were associated with MGD, but to a greater extent in SS patients. Pflugfelder et al.[69] documented keratinization of the ocular surface epithelia in patients with SS, and hypothesized that this may play a role in SS-associated MGD. Further study is needed to elucidate the mechanism of MGD in patients with SS and determine whether it represents a primary effect of the disease, develops as a consequence of chronic aqueous deficiency and/or ocular surface damage, or is due to some other factor.

Other systemic conditions may also influence the development of MGD (Table 5). For example, it has been estimated that as many as 13 million Americans have rosacea, but estimates of the proportion with ocular involvement vary from 8% to 50%.[87,88] There have been several clinical reports of MGD in rosacea patients,[83,84] and Alvarenga and Mannis[85] have best summarized the literature on rosacea and report that eyelid changes, including MGD, are present in up to 90% of cases of ocular rosacea, and anterior blepharitis is present in 50%. These authors rightly note, however, that such estimates are not conclusive, because data from general population studies (summarized in Table 1) show similarly high rates of meibomian gland abnormality. Further study of possible links between *Demodex*, rosacea, and MGD may be warranted.

Sotozono et al.[90] evaluated and graded the extent and severity of chronic ocular manifestations in patients with Stevens-Johnson Syndrome (SJS) and observed meibomian gland involvement in 111 (80.4%) of the 138 eyes. Ogawa et al.[78] showed in a prospective study of 53 patients undergoing allogeneic or autologous stem cell transplantation, that those with

TABLE 5. Systemic Factors Hypothesized to Correlate with MGD

Factor	Reference
Aging	Den et al.[62]
	DEWS[46]
	Hykin and Bron[63]
	Schaumberg et al.[70]
	Schaumberg et al.[71]
	Sullivan et al.[64]
Androgen deficiency	Krenzer et al.[72]
	Sullivan et al.[73]
	Sullivan et al.[65]
Atopy	Bron et al.[15]
Benign Prostate Hyperplasia	Schaumberg et al.[70]
Cicatricial pemphigoid	Bron and Tiffany[58]
Complete androgen-insensitivity syndrome	Cermak et al.[74]
	Sullivan et al.[75]
Discoid lupus erythematosus	Ena et al.[76]
Ectodermal dysplasia syndrome	Kaercher[77]
Hematopoietic stem cell transplantation	Ogawa et al.[78]
Hypertension	Schaumberg et al.[70]
Menopause*	Mathers et al.[66]
	Sullivan et al.[65]
Parkinson's Disease	Tamer et al.[79]
Pemphigoid	Iovine et al.[80]
Polycystic ovary syndrome	Yavas et al.[81]
Psoriasis	Horwath-Winter et al.[82]
	Zengin et al.[83]
Rosacea	Akpek et al.[84]
	Alvarenga and Mannis[85]
	Zengin et al.[86]
	Zuber[87]
	Zuber[88]
Sjögren's syndrome	Goto et al.[68]
	Krenzer et al.†
	Pflugfelder et al.[69]
	Shimazaki et al.[43]
	Sullivan et al.[65]
	Sullivan et al.[89]
Stevens-Johnson syndrome	Sotozono et al.[90]
Toxic epidermal necrolysis	Di Pasquale et al.[91]
	Sotozono et al.[90]
Turner syndrome	Bron and Tiffany[58]

* The largest study of 39,876 women showed no association between menopausal status and dry eye disease.[71]

† Krenzer KL, et al. *IOVS* 1999; 43:ARVO Abstract 2864.

dry eye secondary to chronic graft versus host disease (GVHD) are also likely to exhibit coincident severe MGD.

Ectodermal dysplasia syndrome is a group of fairly rare genetic disorders identified by the absence or deficient functioning of at least two derivatives of the ectoderm, such as teeth, hair, nails, and sweat glands. In a report by Kaercher,[77] alterations in the meibomian glands were observed in 21 (95.5%) of 22 patients and included partial loss of the glands, coarsening of the acini, or complete absence of meibomian glands when observed with transillumination. Under the Foulks and Bron[92] classification scheme published in 2003, as well as the classification scheme presented in the Definition and Classification Report, congenital meibomian gland disease is considered separate from MGD. It is important to confirm whether the glandular change in ectodermal dysplasia syndrome is MGD, as opposed to a variable degree of MG agenesis, as the gene responsible for ectodermal dysplasia controls development of the sebaceous glands, among others.

Medication Risk Factors

Studies have been conducted specifically to look into possible effects of drugs on meibomian gland structure and function have not, to our knowledge, been conducted, with the exception of studies assessing 13-*cis* retinoic acid (Accutane; Hoffman LaRoche, Nutley, NJ; removed from the market in 2009) therapy for acne. Clinically, 13-*cis* retinoic acid administration has been shown to result in abnormal meibomian gland secretions, meibomian gland atrophy, decreased TBUT, increased tear film osmolarity, and dry eye symptoms[93–95] and is further detailed in the Report on the Anatomy, Physiology, and Pathophysiology of the Meibomian Gland. In effect, the retinoic acid derivatives may promote MGD and evaporative dry eye; however, the small sample size and clinical nature of those studies warrants further investigation of 13-*cis* retinoic acid as an associated or causal risk factor for MGD and evaporative dry eye.

There have been several studies that have evaluated the effect of medications on the risk for dry eye in general, and this information may be germane, given the overlap between dry eye and MGD (see Table 6 for medications hypothesized to be correlated with MGD). Postmenopausal hormone therapy (PMH) is associated with a higher prevalence of dry eye disease. A large cohort study of more than 25,000 women showed an approximately 70% increased risk among those who used estrogen alone, as well as an approximately 30% higher risk in women who used estrogen in combination with progesterone or progestins.[107] The most biologically plausible explanation for this association involves a possible effect of PMH on the meibomian glands leading to MGD and evaporative dry eye. Results of other studies are mostly consistent with the suggestion that PMH exerts an adverse effect on the ocular surface.[28,96] Erdem et al.[107] conducted a prospective study on 40 postmenopausal women, including 20 with, and 20 without, dry eye, and evaluated its development and progression after initiation of PMH. After 3 months of PMH, all patients with dry eye at baseline still had dry eye, and the condition developed in a further 11 (61.1%) patients ($P = 0.003$). Although these findings cannot be viewed as conclusive, given the unmasked and nonrandomized design, the data support the hypothesis that PMH increases the risk of dry eye while simultaneously refuting the alternative hypothesis that PMH could be beneficial in this circumstance. Further supporting evidence comes from the Blue Mountains Eye Study of 3500 residents, which showed that current PMH use was associated with a statistically significant, 60% higher prevalence of dry eye.[96]

Other medications may also impact the risk of dry eye, including evaporative dry eye. For example, in a recently analysis of data from men participating in the Physicians' Health Studies, the use of medications to treat benign prostatic hyperplasia was observed to be associated with a significantly increased risk of dry eye (OR 1.35; 95% CI, 1.01–1.80). On the other hand, the Physicians' Health Studies showed the statin and antihypertensive drugs were not associated with dry eye, and antidepressants may increase the risk of dry eye.[70] Among 6034 participants in the Physicians' Health Studies for whom information on medication use was available, there was a nearly twofold increased prevalence of dry eye among men who used antidepressants.[70] An analysis from the Beaver Dam Eye Study (age range, 43–86 years, 5924 subjects) showed that antidepressant use was a risk factor for incident dry eye over 10 years of follow-up (OR, 1.54; 95% CI, 1.05–2.27).[109] Similarly, in the Blue Mountains Eye Study, there was a significant increase in the prevalence of dry eye among people who used antidepressants.[96]

Antihistamines are another class of medications whose use appears to be associated with ocular dryness. Systemic use of antihistamines has been associated with increased risk of dry eye in a prospective analysis from the Beaver Dam Eye Study,[97] as well as in an open label, short-term trial of loratadine, 10 mg once daily, among 18 adults with seasonal allergic conjunctivitis. However, it should be noted that no changes in TBUT were observed in the latter study.[110]

Research has shown that dietary intake of ω-3 fatty acids (FAs) and the ratio of their consumption to that of ω-6 FAs affects the overall amount of inflammatory activity in the body.[111] Miljanovic et al.[103] observed that a higher dietary intake of ω-3 FA was associated with a decreased risk of dry eye, whereas a higher ratio of ω-3 to ω-6 FA reduced the risk of dry eye in a large cross-sectional study of 39,876 women in the Women's Health Study. Small randomized trials of ω-3 to ω-6 FAs, as well as animal data, also suggest beneficial effects of essential FAs on the ocular surface in dry eye.[99–101,105,106] More recently, Macsai[102] presented a randomized placebo-controlled double-masked trial of 38 patients with blepharitis and simple obstructive MGD. After 12 months of intake, the group assigned to ω-3 FA had an improvement in TBUT, Ocular Surface Disease Index (OSDI) score, and meibum score, when

Table 6. Medications Hypothesized to Correlate with MGD

Medication	Reference
Isotretinoin (13-*cis* retinoic acid) therapy*	Caffery and Josephson[94] Egger et al.[95] Mathers et al.[93]
Antiandrogens	Krenzer et al.[72] Sullivan et al.[73] Sullivan et al.[65]
Antidepressants	Chia et al.[96] Moss et al.[97] Schaumberg et al.[70]
Antihistamines	Moss et al.[97] Ousler et al.[98]
Medications used to treat benign prostate hyperplasia	Schaumberg et al.[70]
ω-3 Fatty acids (possibly protective)	Barabino et al.[99] Creuzot et al.[100] Kokke et al.[101] Macsai[102] Miljanović et al.[103] Pinna et al.[104] Rashid et al.[105] Viau et al.[106]
Postmenopausal hormone therapy	Chia et al.[96] Erdem et al.[107] Lin et al.[28] Schaumberg et al.[108]

* Accutane; Hoffman-LaRoche, Nutley, NJ; withdrawn from the market in 2009.

compared with the placebo group. Changes in meibum composition were observed in the ω-3 group ($P = 0.04$ compared with baseline); the level of meibum saturated FAs decreased when measured by chromatography.[102] See Clinical Trials for more details on ongoing ω-3 studies.

Environmental Factors

Environmental factors such as geography, temperature, humidity, and visual task may play a role in MGD and/or its impact on patients. For example, as already noted, there may be an increased frequency of MGD in Asian populations, and this may be related to differences in geography (or temperature, humidity, and air quality). Likewise, computer users often complain of eyestrain, eye fatigue, burning, irritation, redness, blurred vision, and dry eyes. This constellation of ocular complaints resulting from video display terminal (VDT) viewing and sustained attention to a computer monitor is frequently associated with a decreased blink rate and can be regarded as a type of repetitive strain disorder, often referred to as computer vision syndrome.[112] Fenga et al.[113] reported a clinical study of 70 VDT users and found that 52 (74.3%) had MGD. There was also a significant correlation between the severity of symptoms of ocular discomfort and hours spent on VDT work, both in the total population ($r = 0.36$; $P = 0.002$; 95% CI, 0.13–0.54) and in the group of subjects with MGD ($r = 0.37$; $P = 0.009$; 95% CI, 0.10–0.58). It remains unclear whether such factors might contribute to the development of MGD itself or just exacerbate symptoms in preexisting MGD.

MGD and CL Wear

There is a longstanding clinical impression that CL wear increases the risk of MGD. It is thus perhaps surprising to find that relatively few studies have addressed this question directly. The peer-reviewed literature relating to CL wear and MGD falls into three areas, discussed in turn in the following section (Table 7).

CL Wear as a Risk Factor for MGD

Korb and Henriquez[14] and Henriquez and Korb[114] elegantly described the tissue changes that accompany MGD. In these studies, they showed a series of micrographs illustrating how stagnation of the sebaceous meibomian secretion occurs due to obstruction of the excretory duct by accumulations of epithelial cells desquamated from the ductal lining. These keratotic clusters of material cause the duct to dilate, and its ability to deliver a normal secretion is impaired or obliterated. This is consistent with mechanisms of duct obstruction, atrophy, and secretion proposed in the Report on Anatomy, Physiology, and Pathophysiology of the Meibomian Gland.

Korb and Henriquez[14] reported on 38 symptomatic and 40 asymptomatic CL wearers. In the former group, 90.1% of eyes had some MGD on the basis of the ability to express meibum using gentle manual expression, decreasing to 79.7% with forcible expression. The corresponding numbers in the asymptomatic group were 42.5% and 24.2%. Intergroup differences were reported as statistically significant, and the authors concluded that MGD is associated with CL intolerance. However, the likelihood of a spuriously significant result was inflated in this study due to the known correlation between fellow eyes and consequent violations of the assumptions underlying the statistical tests performed.

Ong and Larke[32] reported that 30% of CL wearers developed MGD after 6 months, compared with only 20% of the non–lens-wearing population. This difference was statistically significant, but neither lens type (hard, rigid gas permeable, or soft) nor sex was a factor. Most other studies have failed to replicate this finding, as discussed below.

The largest study was that of Hom et al.,[35] who specifically compared the frequency of MGD among CL wearers and non-CL wearers. The criterion for MGD was cloudy or absent gland output on one or two expression attempts, with firm digital pressure on the lower lid margin under the lashes. Although there was a small excess of MGD in the CL wear (41%) versus non-CL wear (38%) group, it was not statistically significant or likely to be relevant clinically. Based on a much smaller sample, Marren[33] was similarly unable to find a significant difference, although the actual overall frequency of MGD in that patient group was higher in both CL wear (60%) and non–CL-wear (57%) groups. Her definition of MGD was any blocked gland orifices on gentle digital pressure below the lower lid orifices. Ong[45] reported that 43% of CL wearers in his sample had MGD, compared with 35% of non-CL wearers. Once again, the difference was not significant.

A clear excess of MGD in CL wear was reported by Molinari,[115] who found that 100% of his young, predominantly male CL-wearing sample was affected. Unfortunately, the reported details of the study population are incomplete, and so it is not possible to know how many subjects were actually involved. Furthermore, the rate of MGD in this group was reported to be only 5%, which is much lower than that in all the other studies mentioned up to this point. Therefore, Molinari's results should be viewed with caution.

In an effort to form a consensus from the available literature, we conducted a subanalysis using data from the more completely characterized studies. To be included, studies had to have reported the total number of CL wearers and non-CL wearers, together with the number in each group displaying MGD. The result is summarized in Table 7 and yields an overall frequency rate estimate for MGD in CL wear of 37.7% ± 5.4% and 32.1% ± 4.3% in non-CL wearers (errors are 95% CIs). This difference is not statistically significant, suggesting that CL wear may not increase the risk for MGD. However, as noted, most of these studies have limitations in size, design, and analysis that preclude any sort of conclusive statements in this regard.

Table 7. Summary and Meta-analysis of Studies Reporting Prevalence of MGD in CL and Non-CL Wearers

Study	Total Subjects	CL Wearers	Non-CL Wearers	CL Wearers with MGD *n* (%)	Non-CL Wearers with MGD *n* (%)	Difference in % MGD between CL and Non-CL Wearers
Hom et al.[35]	398	162	236	66 (40.7)	89 (37.7)	3.0
Marren[33]	50	20	30	12 (60.0)	17 (56.7)	3.3
Ong and Larke[32]	140	70	70	21 (30.0)	14 (20.0)	10.0
Ong[45]	181	53	128	16 (30.2)	29 (22.7)	7.5
Aggregate	769	305	464	115 (37.7)	149 (32.1)	5.6
95% CI				(32.3–43.1)	(27.9–36.4)	
Two-tailed *P*-value				0.11		

A recent study by Arita et al.[116] offers direct evidence that CL wear may affect the morphology of the meibomian glands. Using meibography to view the glands in the everted eyelid, they graded MG loss on an ordinal scale (0–3) referred to as the meiboscore. Higher meiboscores indicate more severe degrees of loss. Wearers of CLs of any type (rigid or soft) had significantly higher meiboscores (1.72 ± 0.24, mean ± 95% CI) than non-CL wearers (0.96 ± 0.23). The duration of CL wear was weakly associated with the meiboscore. Based on this result and the observation that the upper eyelid showed more of a difference between CL wearers and non-CL wearers than did the lower lid, the authors suggest that irritation of the glands through the eyelid by the lens may be responsible for the observed morphologic changes.

Reconciling the findings of Arita et al.[36] with those of the studies in Table 1 requires further work. One obstacle is that differences in interpretation and definition of what constitutes MGD and/or gland loss exist across the various studies. For example, it is not clear to what extent subjects exhibiting low meiboscores, as defined by Arita et al., would respond to the diagnostic criterion, common in other studies, of gentle to forcible meibomian gland expression. Also of interest is the relationship between the degree of meibomian gland loss and symptoms in CL wear, more generally.

MGD and Symptoms in CL Wearers

The question of the relationship between CL wear, symptoms, and MGD has received relatively little attention in the literature to date. Korb and Henriquez[14] and Henriquez and Korb[107] described a syndrome characterized by deficient or inadequate meibomian gland secretions, minimal or transient symptoms suggestive of ocular dryness, fluorescein staining of the cornea, and CL intolerance. Of 71 eyes of affected subjects, 36% showed no secretion from the lower lid glands on gentle expression. Only 2.5% of the 80 asymptomatic, control, CL-wearing eyes were similarly affected. Based on these findings they suggest that asymptomatic CL wearers are five times more likely to show normal meibomian gland expression than are those intolerant of CL wear.

Supporting evidence comes from Paugh et al.[117] who studied the effect of lid scrubs and massage on TBUT and subjective comfort in 21 CL wearers with MGD. They defined MGD as an absent or cloudy meibomian gland secretion on repeated expression. Treatment was applied unilaterally for 2 weeks and showed a significant increase (4 seconds) in TBUT relative to pretreatment in the treatment eye and subjective reductions in discomfort and dryness, assessed on 10-point scales, of approximately 1.7 and 1.1 points, respectively. These latter assessments were made bilaterally, as the subjects could not, in general, distinguish differences in symptoms between the eyes. Control eyes did not change on average. No statistical tests are reported in the paper but, judging from the standard deviations quoted, these differences are probably near the level of statistical significance. These data suggest that discomfort and dryness symptoms in CL wear can be associated with MGD, since the application of treatment brings improvement in the symptoms. However, the study does not provide evidence to suggest that CL wear was a cause of the MGD in these patients.

A somewhat contrary view emerges from Nichols and Sinnott,[118] who conducted an extensive study of 360 CL wearers to look for risk factors associated with CL-related dry eye (CLDE). They were unable to find any significant association between meibomian gland drop out and CLDE symptoms. They did show a reduced lipid layer thickness and corresponding faster pre–lens tear film thinning times and increased osmolarity in the symptomatic CL wearers, suggesting that the outcome of symptoms may be derived from mechanisms other than gland loss. The contrast between this finding and those of Paugh et al.[117] and Korb and Henriquez[14,107] is striking and may be due in part to the differences in diagnostic criteria used. Nichols and Sinnott used meibography to quantify gland loss, similar to that of Arita et al.[116] (who did not report on symptomatology), whereas, in the other two studies, the diagnosis of MGD was founded on the characteristics of material digitally expressed from the gland openings. How these two criteria may be related is not clear, though it is evident that some degree of observable meibomian gland loss can occur without the accompaniment of symptoms. Establishing where this threshold lies, together with the nature of the link between MG loss and the kinetics of gland secretion, would be fruitful areas of research.

MGD and CL-Related Papillary Conjunctivitis

The question of a link between CL-related papillary conjunctivitis (CLPC), or giant papillary conjunctivitis (GPC) as it is also known, and MGD has been addressed by only a few studies, with equivocal results (Table 4). Reporting on 42 contact lens wearers, Mathers and Billborough[54] found that the 27 subjects with clinical signs of GPC had significantly greater meibomian gland dropout than the remainder. Martin et al.[55] found evidence of MGD in each of their 42 subjects with GPC. Molinari and Stanek[34] on the other hand, found that, although 23 of 105 subjects in their study had MGD, none had co-existing GPC.

In reconciling these findings, it may be that the link between MGD and CLPC/GPC is not causal. Rather, the factors in contact lens wear that result in the clinical presentation of CLPC/GPC can produce simultaneously manifesting MG effects without any substantial etiologic connection.

Future Directions for Understanding the Epidemiology of MGD

Although there are several studies that have provided frequency estimates for MGD, these studies have been limited in that they have provided simple frequency or prevalence, rather than incidence, estimates. Further, the studies have generally used nonstandardized definitions of MGD, making it difficult to directly compare the frequency estimates. Future population-based studies should be conducted with standardized classification criteria to better delineate the frequency of MGD, including both prevalence and incidence. Likewise, prior studies that have evaluated potential risk factors for MGD have been nonexistent, or limited by small size, cross-sectional design, and other methodological shortcomings. Virtually none of the studies has evaluated incident (new) cases, and therefore, the temporal relation between the factor of interest and disease status has not been properly determined. At the present time, we consider the prior studies as providing some evidence of concurrent factors or correlates of MGD, rather than as providing true risk factors for MGD. That being said, we reiterate that there appears to be some consistency for certain ophthalmic, systemic, and environmental factors associated with MGD. Possible demographic differences in MGD rates such as by age, sex, and race or ethnicity still need better delineation, especially relative to the undetermined incidence of the disease. There is evidence that CL wear may be associated with certain aspects of MGD, but this, too, needs much better delineation. For instance, it is well known that approximately 50% of contact lens wearers have frequent dry eye symptoms,[119] but it is not known how much of this may be due to MGD.[116] The effects of CL wear on the health of meibomian glands (atrophy), the excretion of the meibomian glands, or function of the lipid layer itself in terms of retarding evaporation need further study.

As summarized herein, There are several commonly used clinician-based assessment methods in addition to reporting symptoms that are generally used in the evaluation of MGD for outcome purposes. Each of these methods is limited by their subjectivity (and therefore, variability), which may lead to a lack of responsiveness as the disease progresses, with time or sensitivity between disease states (i.e., dry eye and MGD). Further, it is unclear how several of these outcomes truly relate to the nature of the disease. For instance, meibography is commonly used to image the meibomian glands (to determine atrophy), but it is unclear how this relates to the gland excretion or symptoms experienced by the patient. Yet, it is hard to argue that atrophy of the meibomian glands is not important in the disease process in some way. It is recommended that the community focus into the relation between the meibomian gland status (through meibography) and other clinical correlates and symptoms of MGD.

Similarly, it is well known that symptoms are a major component of MGD, but there is a paucity of data on the relative importance, including frequency and severity, of specific symptoms associated with the disease. Specific subjective outcome measures for MGD have not been properly established or validated. Related to this, it is unclear what role MGD has in the overall quality of life of an individual. It is recommended that the community focus attention on these patient-reported aspects of outcome development.

It is not entirely understood how the truly objective, analytical measures associated with the assessment of MGD relate to the disease in terms of its incidence (a biomarker, perhaps), clinical correlates (meibomian gland plugging, expressibility, and meibum quality), or subjective outcomes. This uncertainty is particularly true of the biochemistry of the lipid excretion of the meibomian gland in relation to other outcomes. It is recommended that the community try to focus more attention on better understanding these relationships (e.g., the relation between tear osmolarity and symptoms of MGD), in addition to developing a better understanding of potential biomarkers in MGD that may either help diagnostically or track changes in MGD with time or with treatment.

Finally, it is critically important that studies be undertaken that begin to establish the natural history of MGD and associated risk factors. There are many questions that could be answered in this regard. For instance, the time course of disease progression is uncertain, including the relation between true etiologic factors and the development of symptoms of disease. As mentioned, the relation between meibomian gland atrophy (gland loss) and symptom development is uncertain; for instance, it could be that some atrophy of the glands is normal and may not lead to patient symptoms or ocular surface damage. In addition, the actual source of the symptoms of MGD is not known (e.g., do they derive from the meibomian glands or the ocular surface?), nor has the primary contributing factor leading to their development been identified. Once atrophy is present and the patient develops symptoms, it may also be possible for the glands to return to their normal state (for instance, if gland loss is due to CL wear and the individual discontinues from CL wear), but this has not been studied to our knowledge. Further, associated morbidities that may occur after the onset of MGD have not been established with quantitative estimates. This includes, for example, correlates such as the visual impact of the disease or the potential susceptibility of patients with MGD to ocular surface infection. Even the relation and cross-correlation between MGD and dry eye disease is not well understood. For instance, is MGD a risk factor or cause of dry eye disease? Or might dry eye disease be a risk factor or cause of MGD? What is the time course (temporal relation) for the development of these common comorbidities? As noted by Lemp and Nichols[120] in their study of those individuals who had been diagnosed with either MGD or dry eye disease, 40% had been diagnosed with both MGD and dry eye disease. Further, the patient-reported symptoms between those with MGD or dry eye disease were correspondingly similar, with limited exceptions.

SUMMARY

In summary, MGD appears to be a prevalent problem with potentially severe detriments to well-being. Nonetheless, even basic information regarding its prevalence, demographic and geographic distribution, risk factors, and impact on ocular health and quality of life are only beginning to emerge. The same was said of dry eye disease more than a decade ago, and since that time, research efforts have grown exponentially. We are confident that the time has now arisen to embark on the systematic study of MGD as well. It is through such efforts that a better understanding of the disease will be gained, and strategies for prevention and treatment will begin to be developed.

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