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Comprehensive Assessment of the Meibomian Glands by Meibography: Why the Upper Eyelids Matter

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Abstract: The clinical value of upper eyelid meibographic imaging remains relatively underexplored; consequently, it is not commonly used in clinical assessments. However, its significance could be particularly important for the early detection of various ocular diseases and systemic conditions related to the eyes. An analysis of the current literature from the PubMed database, covering the years 2005 to 2023, with additional relevant papers added from cited references was conducted. Failure to diagnose dry eye disease and meibomian gland dysfunction associated with conditions such as Sjögren syndrome or thyroid eye disease in the early stages and taking appropriate action may result in persistent signs and symptoms. This could potentially lead to the development of chronic conditions that directly affect a patient's visual quality, functionality, and overall well-being. Therefore, this review aimed to demonstrate the potential clinical significance of upper eyelid examination as an integral component of comprehensive meibomian gland evaluation.

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TECHNOLOGICAL DEVELOPMENTS IN MEIBOGRAPHY AND CHALLENGES OF THE MEIBOMIAN GLAND EXAMINATION

The diagnostic significance of meibography has undergone extensive scrutiny, establishing it as a fundamental component in managing meibomian gland dysfunction (MGD) and dry eye disease (DED). Its integration into ophthalmic practice has provided deeper insights into the role of meibomian glands (MGs) in ocular and systemic conditions that contribute to ocular surface disease.

Various modalities of meibography, including contact and noncontact infrared techniques, keratography, in vivo confocal microscopy, and optical coherence tomography meibography, offer distinct advantages and drawbacks. Although some modalities offer rapid examination, digital quantification, and noninvasive assessment, they may be accompanied by high costs, time-consuming procedures for image acquisition or analysis, and limitations in capturing the entire eyelid. Expertise is also required for data interpretation, particularly for in vivo confocal microscopy and anterior segment optical coherence tomography.[1]

As with many ophthalmic imaging procedures, several factors can influence meibography outcomes, including illumination, head positioning, eye gaze, and imaging of the upper or lower eyelids. Notably, proper eyelid eversion is crucial for ensuring image quality and accurate assessment (Fig. 1), especially for long-term monitoring.

However, as Daniel et al highlighted in their study, the upper eyelid is more difficult to evert than the lower eyelid, as demonstrated by the higher percentage of upper lid images that were not obtained or had insufficient lid eversion.[2] Notably, this was not the first study to highlight the clinical consequences of improper lid eversion. Different eyelid eversion techniques can yield significantly different results for the exposed area, as demonstrated by Wolffsohn et al[3]. Inadequate eversion may distort perceptions of MG health, leading to erroneous conclusions, with excessive eversion potentially causing glands to seem shorter than their actual length.

Meibographic interpretations use various grading schemes and quantification methods. Although semiautomated algorithms have certain flaws,[4–9] recent advancements in artificial intelligence have attracted attention,

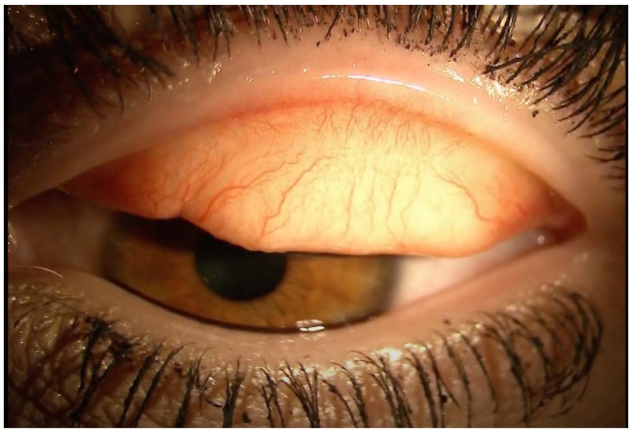

FIGURE 1. Proper upper eyelid eversion technique. With the permission of Dr P. Karpecki.

demonstrating superior performance.[10,11] Thus, meibography has transitioned from a tool primarily for monitoring MG dropout to an AI-supported platform capable of comprehensively assessing the morphometric parameters of the glands.

THE SIGNIFICANCE OF MG MORPHOLOGICAL CHANGES IN CLINICAL PRACTICE

The MGs, situated within the tarsal plates, are modified sebaceous glands crucial for ocular lubrication. In a healthy state, the orifices are evenly dispersed along the lid margins anterior to the mucocutaneous junction. The lipid secretion of the meibum plays a pivotal role in preventing tear evaporation and protecting the cornea and ocular surface from dehydration and external factors.[12,13]

Typically, the upper eyelid contains 24 to 40 glands, whereas the lower lid contains 20 to 30 glands. Notably, the glands in the upper eyelid are longer and thinner, with central measurements of approximately 5.5 mm compared with an average of 2 mm in the lower eyelid.[12]

MGD presents with morphological changes such as gland shortening or truncation, tortuosity, atrophic tissue loss, bifurcation, and gland dropout, each of which is significant in various ocular conditions.

MGD remains the leading cause of evaporative DED, accounting for 65% to 86% of cases.[14,15] It commonly presents with an increased degree of MG dropout, particularly in the lower lid.[16–21] This dropout correlates with reduced lipid layer thickness, noninvasive tear film break-up time (NIBUT), tear film break-up time (TBUT), meibum expression, and abnormal tear film osmolarity.[8,19,22–24]

MG loss effectively distinguishes individuals with DED, aiding treatment selection.[8,25,26] Furthermore, analysis of morphometric parameters such as gland length, width, and tortuosity contributes to early MGD diagnosis,[2,27] with significant correlations observed between MG width or curvature and the ocular surface disease index score and NIBUT.[8]

In contact lens wearers, the lower eyelid presents with more atrophic glands than the upper eyelid, but other abnormal morphological features are more prevalent in the upper lid glands, with tortuosity being the key characteristic compared with the lower eyelid.[28] Pult et al[8] noted a greater curvature in the MGs of the upper eyelids and a greater degree of MG dropout in the lower eyelids of patients. Gland tortuosity effectively delineates MG morphology and aids in diagnosing MGD, particularly in its early stages,[2,27] whereas narrower lower lid glands are associated with decreased meibum expression.[28]

Interestingly, observations among healthy asymptomatic subjects revealed a higher prevalence of tortuous glands in the upper eyelids of asymptomatic individuals, irrespective of the age group. Hence, the correlation between tortuous glands and MGD should be carefully considered and potential physiological variations should be scrutinized.[29]

Although it is believed that atrophic-like changes in MGs are irreversible, recent attention has shifted toward evaluating these changes, considering emerging treatments thought to potentially reverse them. One such treatment is intense pulsed light (IPL) therapy.[30] Studies have shown significant improvements in the acinar unit density and diameter with IPL therapy, suggesting its potential for modulating acinar cell activity and regeneration. This implies that IPL's thermal and photobiomodulation effects are responsible for improvements in the MG macrostructure, microstructure, and inflammation.[30,31]

Early research indicates that IPL therapy, when used as an adjunct treatment, may lead to significant improvements in MG morphological aspects, especially in patients with mild to moderate MGD.[30,32,33] However, the mechanisms underlying these improvements remain unclear. In addition, some of these studies report an "MG dropout score improvement," where the dropout score refers to the partial loss or truncation of the MG. This raises the question of whether we are observing MG regrowth or tissue regeneration in what seems atrophic tissue in meibography images.

Despite this uncertainty, our findings highlight the importance of early diagnosis and appropriate intervention. Morphological changes in MG are key indicators of MGD.[13,17] Understanding the differences in morphology between the upper and lower eyelids and recognizing their clinical significance are critical for the early diagnosis and treatment of various ocular surface conditions.

Method of Literature Selection

This literature review explored the clinical significance of upper eyelid examination in comprehensive MG evaluation. We searched PubMed.gov for publications from 2005 to 2023 using the terms: "MG" or "MGD," and combined with: "meibography," "cataract surgery," "contact lenses," "Sjögren," "thyroid eye disease." Only English-language studies were considered. Additional papers were identified from the reference lists of retrieved articles. The final reference list was refined by removing duplicates and excluding studies not focused on the upper eyelid or deemed irrelevant.

The literature relevant to upper eyelid meibography includes observational studies, clinical trials, and review and methodological papers, each with its own limitations. The

authors' expertise guided the evaluation of references, ensuring relevance and quality while adhering to the preestablished criteria. A significant challenge in comparing findings across studies is the lack of consensus in terminology and the wide range of clinical tests used for the eyelids and MGs. To provide a more comprehensive and nuanced perspective, a narrative review was chosen over a systematic approach. This approach allows for the inclusion of a broader range of studies, offering a holistic overview and identifying areas where further research is needed.

The Clinical Implications of the Upper Eyelid Assessment

The clinical value of upper eyelid meibographic imaging remains relatively underexplored; consequently, it is not commonly used in clinical assessment.

In 2018, Dogan et al[34] studied the interexaminer reliability of meibography in establishing a preferred eyelid. Their research revealed that owing to the correlation with TBUT and better interexaminer agreement on dropout by grading, the upper lid might be considered the preferred lid for evaluation. Interestingly, Maskin and Testa suggested that the upper eyelids are better for longitudinal follow-up studies because the dense tarsus provides a firm, sturdy structure to evert. The authors also argued that lower lid meibography may be unreliable and less accurate because the tarsus is less dense and allows the lid and MGs to easily distort.[35,36]

Before exploring this further, it is important to note that the diagnostic criteria for MGD are not uniform across studies. The use of different meibography equipment results in images that are difficult to compare, leading to reproducibility issues. Without a clear understanding of the histological and morphological changes observed in MG dropouts, some conclusions remain open to interpretation. However, as we are about to reveal, evidence suggests that assessing the upper eyelid regularly may be important in cases of MGD secondary to contact lens use, ocular surgery, or systemic conditions.

The Role of Upper Eyelid Assessment in Contact Lens Fitting

Upper eyelid MG tortuosity is associated with increased odds of contact lens dropout.[37] The *CLASS* or the *Contact Lens Assessment of Symptomatic Subjects* Group explored the role of the upper eyelid in the etiology of contact lens discomfort and published the work in 2019. The investigators studied 56 matched pairs of contact lens wearers, dropouts, and successful wearers across the 5 centers. The authors concluded that the odds of contact lens dropout significantly increased with each worsening grade of upper eyelid meibum quality, upper eyelid gland tortuosity, and upper or lower eyelid gland plugging.[28] The same investigators also examined the impact of gland width on successful contact lens use.[37] MG width was calculated based on an automatic assessment of the mean width of the 7 central upper eyelid MGs and 4 selected central lower eyelid MGs. Although successful contact lens wear did not seem to be clinically influenced by the width of the glands, the study revealed interesting findings in the differences between the upper and lower eyelid glands in contact lens wearers. The MGs were significantly wider on the lower eyelids than on the upper eyelids. The gland tortuosity was significantly worse in the upper eyelid than in the lower eyelid, and significantly more blepharitis was observed in the upper eyelid than in the lower eyelid. There was a lack of association between gland atrophy, meibum expression, and meibum quality in the upper and lower eyelids. Of the above variables between the eyelids, the only clinically significant difference was for MG tortuosity, with an approximately one-grade difference. Logically, for a comprehensive clinical understanding of the patient, investigators recommend MG evaluation of both eyelids in practice.[28,37]

MG modifications in contact lens wearers have also been compared with those in nonwearers. Ucakhan and Arslanturk-Eren examined the MGs of 173 eyes of 87 soft contact lens wearers, age matched with 103 healthy eyes. They analyzed the MG width by subjectively counting the number of "thickened" MGs that is MGs at least twice the width of other glands within the same study subject and assigning to each subject a severity score. Contact lens wearers had significantly worse MG thickening scores on their upper eyelids than on their lower eyelids. They also found that the upper and lower eyelids of contact lens wearers had worse MG thickening scores than the corresponding eyelids of noncontact lens wearers. MG thickening was the only meibography finding that had the highest diagnostic ability for MGD.[38]

Both upper and lower eyelids differed in gland tortuosity, width, atrophy, and even blepharitis grade (Figs. 2A, B).

Furthermore, the lack of association between the upper and lower eyelids suggests that additional and useful information can be gathered by grading both upper and lower eyelids. These findings continue to be an affirmation in general of the work done by Yin and Gong,[39] McCann et al,[40] and Eom et al,[19] further supporting the idea that evaluating each eyelid to gain a better clinical picture of the patient is worth the patient chair-time.

Practitioners should screen for and educate especially contact lens patients about the importance of maintaining healthy MGs, which may potentially allow them to maintain comfortable contact lens use and increase their time wear.[37] Such revelation can be crucial in ensuring that contact lens wearers are properly monitored through meaningful workups, and a proactive approach is taken to ensure optimal outcomes and long-term contact lens wear.

The Role of Upper Eyelid Assessment in Reducing the Risk of Cataract Surgery–Induced DED

Although cataract surgery is one of the safest and most successful anterior segment surgeries, postoperative abnormalities of the tear film leading to surgery-induced DED have been commonly reported.[41] According to previous reports, the prevalence of dry eye after cataract surgery varies from 37.4% to 55.7%.[42,43] The incidence of dry eye after surgery in previously nondry eye patients was 31.3%.[43] Identifying the ocular risk factors associated with early-onset cataract surgery–induced dry eye is essential for early intervention and prevention. Previous reports have indicated that elevated preoperative ocular surface disease index scores and low tear meniscus height after surgery are significant risk factors for cataract surgery–induced dry eye.[44] MG function is altered

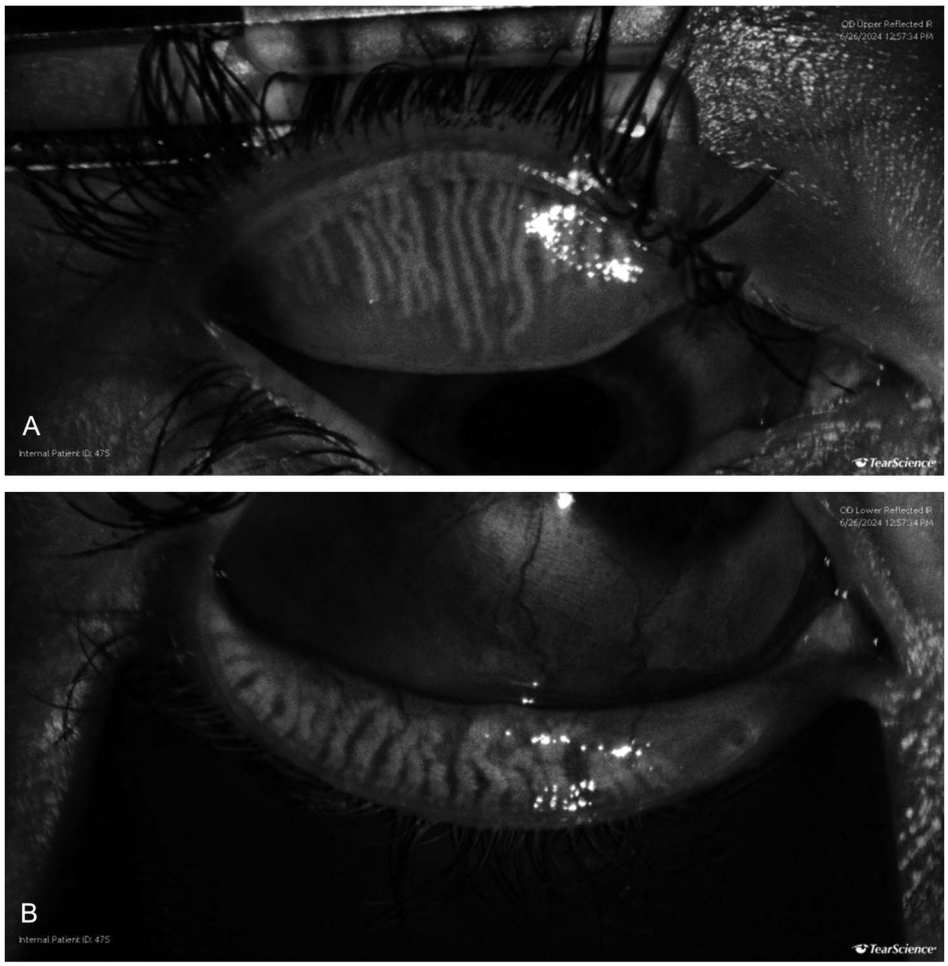

FIGURE 2. A, Upper eyelid meibography showing thinner MGs. With the permission of Dr P. Karpecki. B, Lower eyelid meibography showing mild tortuosity. With the permission of Dr P. Karpecki.

after cataract surgery, resulting in dry eye symptoms induced by excessive evaporation of the tear film.[45]

Fujimoto et al[44] studied 82 eyes of 43 patients who had undergone cataract surgery. These patients did not report any subjective dry eye symptoms before surgery and did not use artificial tears or allergic eye drops. The authors confirmed that cataract surgery shortened TBUT and increased the fluorescein ocular surface staining score, leading to dry eye–related symptoms in 25.6% of patients. Among the preoperative baseline parameters, the area of upper eyelid MG loss was significantly greater in eyes with cataract surgery–induced dry eye symptoms than in those without; however, the area of lower eyelid MG loss was not significant. The significant and detectable risk factors for subjective dry eye symptom development after cataract surgery were preoperative upper eyelid MG loss area (%) [odds ratio (OR) 6.72, $P = 0.012$] and female. Interestingly, a previous study examined MGD involvement in DED development after cataract surgery and reported lower eyelid MGD to be a prominent risk factor, with an OR of 1.145; however, the investigators did not examine the upper eyelid.[46] Although the Fujimoto study was retrospective in nature and included a small population sample, it revealed that the onset of subjective dry eye symptoms after cataract surgery was associated with baseline upper eyelid gland loss. Furthermore, the study suggests that in addition to lower eyelid meibography, monitoring of the upper eyelid meibography before cataract surgery may help identify patients at high risk for dry eye symptoms induced by surgery and that the involvement of the upper eyelid is perhaps an earlier finding than the involvement of the lower eyelid glands in patients with DED.

By incorporating meibography for both upper and lower eyelids into precataract surgery evaluations alongside therapeutic interventions where necessary, surgeons can proactively mitigate surgery-induced dry eye symptoms. They should implement the monitoring of both eyelids before and after the cataract surgery. Careful and active management of MGD in patients with high-risk factors for DED after cataract surgery is warranted to prevent newly raised symptoms and ensure optimal surgical outcomes.

The Role of Upper Eyelid Assessment in Ocular Diseases Related to Autoimmune Conditions

Dry eye symptoms are common in systemic conditions, such as Sjögren syndrome (SS), systemic lupus erythematosus (SLE), and rheumatoid arthritis. The MGs seem to be affected by systemic and local changes associated with these diseases. Individuals with primary SS, secondary SS,

systemic lupus erythematosus, and/or rheumatoid arthritis have symptomatic MGD and suffer from both aqueous-deficient and evaporative DED.[47–49]

Historically, the lack of aqueous tear production resulting from lacrimal changes in SS has been the focus of many studies. Research indicates that MGD is associated with SS,[50] and MG dropout in SS is more severe than that in healthy individuals or patients with non-SS dry eye.[51,52]

However, the role of the upper eyelid in MGD-related SS has not been investigated extensively. The first published work was by Zang et al[53] who examined the differences in ocular symptoms and signs between patients with SS and non-Sjögren syndrome (non-SS) aqueous-deficient dry eye. They reported that the noninvasive keratography tear break-up time (NIKBUT) and MG dropouts of the upper eyelid significantly differed between the 2 groups. In the SS group, NIKBUT were significantly shorter, with more severe MG dropout in the upper eyelid than in patients with non-SS. Lower eyelid MG dropout was much more severe; however, there was no significant difference between the 2 groups. Although the study was small, this is the first report to demonstrate that MG dropout in the upper eyelid was significantly greater in patients with SS than in other patients with dry eye. Changes in the upper eyelid are probably responsible for the differences between SS and non-SS subjects, and these changes could be of great diagnostic importance, and early therapeutic intervention.

The Role of Upper Eyelid Assessment in Thyroid Eye Disease

Thyroid eye disease (TED) is an autoimmune inflammatory disorder that affects the orbital fat, extraocular muscles, and lacrimal gland, resulting in tissue expansion from glycosaminoglycan deposition and edema and, in some cases, fibrosis from collagen production. Symptoms and signs include proptosis, eyelid retraction, eyelid edema, extraocular movement limitation, and exposure keratitis. Ocular symptoms are present in 30% to 45% of patients with TED, but only 5% to 10% of patients have orbitopathy.[54] Dry eye remains the most common cause of ocular discomfort in patients with TED.[54] It has also been suggested that incomplete blinking because of proptosis and eyelid retraction in patients with TED can cause obstructive MGD, and this obstructive MGD can be one of several meaningful factors causing dry eye in patients with TED. Park and Baek[54] investigated the structure and function of MGs and eyelid blinking patterns in patients with TED and DED. They reported that structural loss of the MG in the upper eyelids, but not in the lower eyelid, was greater in patients with TED than in those with DED. The authors assumed that incomplete blinking because of proptosis and increased palpebral fissure height in patients with TED was the cause of obstructive MGD, and their finding could have been explained by their hypothesis because the upper eyelid is relatively more affected by blinking than the lower eyelid. However, another reason for increased structural loss of the MGs only in the upper eyelid may be that the upper eyelid is more likely to be exposed to inflammatory mediators on the ocular surface, including the conjunctiva. The area of the upper eyelid is larger, and more movements are performed. Although Park and Baek's findings are very important, they fell short in the interpretation of patients with TED not showing any significant difference in MG function despite the structural loss of the glands compared with the DED group. Further research is warranted to determine whether ocular surface inflammation directly affects the structural loss of MGs in patients with TED and whether it is the structural loss of the glands that causes clinically significant dry eye symptoms.[54]

The relationship between Graves ophthalmopathy (GO) and the ocular surface, including both MGD and DED, was investigated in a prospective comparative control-matched study.[55] Morphological changes were observed using a non-contact meibography system, and the meiboscore was calculated on a scale of 0 to 6 for each eye. The central region was defined as the middle 1/3 part of the lid. Although all patients had obstructive MGD, the meiboscore of the upper lid was significantly different between patients with GO and healthy controls. The total meiboscore of patients with GO was significantly higher than that of healthy controls. Furthermore, patients with GO exhibit MG changes in the central region of the eyelid, particularly in the upper lid. One possible explanation for this could be the enlarged *levator* muscle characteristics in these patients, which may have affected the morphology of the upper central MG. By contrast, patients with central meibographic changes may experience more inflammation and friction caused by GO. In addition, the oxidative stress, much part of GO, results in alterations in the MGs and meibum composition.[56] Prolonged GO duration might lead to changes in the center of the eyelids, and it is possible that changes in the central region of the upper eyelids are characteristic signs in patients with dry eye symptoms. Moreover, there is a strong association between dry eye symptoms in patients with GO and MG dropout at the center of their eyelids, particularly in the upper lid, eyelid margin vascular engorgement, and ocular inflammation. Both ocular surface inflammation and morphological changes in the MGs may be characteristic findings of patients with GO. Although further investigation is required to elucidate the mechanisms underlying the association between ocular surface condition, MGD, DED, and GO, the findings indicate that MGD is a possible causal factor for eye discomfort and other typical dry eye symptoms in patients with GO.[55]

The findings of Inoue et al[55] are consistent with those reported by other investigators who also studied the role of MGD or MG function in similar patients.[54,57–60] Some of these studies found a higher prevalence of obstructive MGD but mild or no loss of MG, which could suggest that although some MGs may be obstructive and atrophic, others may continue to secrete meibum at normal or increased levels to compensate for such dysfunction.[60] Therefore, thorough and complete assessment of the upper and lower lids is imperative for patients with GO.

Overall, the evidence supports that the obstruction and fewer MGs in patients with GO correlate with objective and subjective dry eye findings. Although we may not fully understand why the structural change in the upper lid glands is greater, its particular involvement in patients with TED

could play a determining role in their diagnosis and management. Clearly, gland obstruction and dropout are contributing factors to dry eye in TED and are related to patients' perception of disease severity. In patients with TED, dry eye management should always include a complete MG assessment to establish the role of MGD.

The Assessment of Upper and Lower Eyelid is Essential for the Complete Evaluation of MGs

Examination of both upper and lower eyelids is key for a thorough assessment of MG function.[61] Research findings underscore significant morphological discrepancies between eyelids, with the upper lid glands being more numerous, thinner, and longer than the lower lid glands.[2,62] Although abnormal morphological features are more frequently observed in the upper eyelid, a higher prevalence of gland dropout has been reported in the lower eyelid of patients.[2,4,19,63]

Crespo-Treviño et al[64] corroborated these findings, noting that morphological alterations were more prevalent in the upper lid, although lower lid alterations were twice as common in their study than in previous reports by Daniel et al.[2] This discrepancy could be attributed to their focus on patients with evaporative DED only, whereas Daniel et al included various DED types including those related to autoimmune diseases. In addition, Crespo-Treviño et al found no significant differences in morphological alterations in the upper lid between healthy and DED subjects, suggesting that lower eyelid MG changes may exert a greater influence on MGD development.

Although the study by Crespo-Treviño et al provides valuable insights, it is crucial to consider certain factors that might have influenced the conclusions, such as sample size, the advanced age of the DED group compared with the healthy group, and the focus of the meibography evaluation protocol solely on the central glands. Nevertheless, their study highlighted significant morphological disparities between the upper and lower lid MGs, emphasizing the importance of assessing both eyelids for a comprehensive understanding of the patient's condition and its severity.

Notably, the CLASS study group, in contrast to the emphasis on the importance of the lower lid glands among patients with DED, revealed a significant increase in the odds of contact lens dropout with each worsening grade of upper eyelid meibum quality, gland tortuosity, and upper/lower eyelid gland plugging. Interestingly, no other analyzed factors were found to increase a subject's odds of contact lens dropout.[37] Based on these findings, clinicians should clearly screen for changes in the upper and lower MGs to prevent contact lens dropout.

The clinical significance of MG morphological changes remains highly controversial,[27,29,65,66] with studies suggesting that some morphological characteristics are present in healthy individuals. Srivastav et al[29] conducted a study on the distribution of various MG morphologies across different age groups in healthy asymptomatic individuals. Their analysis of age-wise prevalence data revealed no clear difference in the morphological features of the MGs in normal individuals with increasing age. The authors emphasized that in addition to severely short glands, various other MG morphological characteristics may also be present in normal individuals. Consequently, interpreting these findings necessitates consideration of other clinical signs and symptoms.

Pult[20] investigated the relationship between the upper and lower lid MG morphology, tear film, and dry eye. The authors assessed the MG thickness and bending or curvature based on the morphology of the "worst case" gland—the width of the most prominent MG (ImageJ units), and the curvature angle in degrees. The authors concluded that specific changes in the upper lid, such as MG thickness and curvature, correlate with noninvasive tear break-up time (NIBUT). They further emphasized that the combination of MG loss in both eyelids showed the best predictability for dry eye.

Similarly, Shirakawa et al[67] stressed the significance of observing both upper and lower eyelids for adequate evaluation of MG morphology and its correlation with tear film parameters in patients with MGD.

By observing and monitoring MG morphological changes in both upper and lower eyelids, beyond just gland dropout, clinicians are likely to improve their ability to predict or diagnose MGD, DED, and other ocular surface–related conditions earlier. Although MG dropout is often significantly correlated with other signs and symptoms of MGD and DED, it represents an advanced stage of MGD.

CONCLUSIONS

Evaluation of the upper eyelid is important in detecting and addressing various ocular conditions early on, and for optimizing outcomes in contact lens fitting and mitigating dry eye after cataract surgery. Evidence underscores the importance of upper eyelid assessment in patients with DED and MGD, especially in the presence of systemic conditions, such as SS or TED. Variations in upper eyelid morphology between patients with and without Sjögren's suggest diagnostic implications and therapeutic opportunities. Structural changes in the upper lid glands are predominant, and their involvement in TED could play a determining role in their diagnosis and management. Upper lid gland evaluation can predict potential contact lens issues and dry eye postcataract surgery. Despite challenges, such as eversion difficulty and chair-time, integrating upper eyelid assessment into MG evaluation is essential. Innovative technologies now available to clinicians can facilitate adequate eyelid exposure for accurate image capture, interpretation, and diagnosis. Morphological changes in the MG must be interpreted along with other clinical indicators for comprehensive assessment. Thorough evaluation of both upper and lower eyelids is necessary when assessing the relevance of MG function to ocular surface health.

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