Article Title: Effect of Meibomian Gland Morphology on Functionality with Applied Treatment

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Key Words: Meibomian gland dysfunction, Morphology, Dry Eye, Expression

Purpose: To determine how Meibomian gland (MG) morphology affects MG function by means of gland expression with the effect of treatment.

Methods: Fifteen patients (aged 31.6 ± 13.1 years) from a dry eye clinic diagnosed with MG dysfunction had their 365 lower lid MGs visualised with a slit-lamp biomicroscopy. Using infrared meibography (Oculus K5m), MG length, width and tortuosity were objectively measured. Each MG was expressed and the meibum graded (0=clear fluid, 1=cloudy fluid, 2=cloudy particulate fluid, 3=inspissated, or 4=not possible) to determine functionality. Participants had functionality repeated each time following a sequence of a warm compress, debridement, and forcible expression after 5 minutes.

Results: Just over 10% of complete length MGs gave clear expression, while about 5% did not express at all, with most expressed meibum being particulate in nature. In contrast, the majority of partial length glands gave inspissated expression (38%), with 32% not expressing at all. No MG with <10% length expressed. MG gland length was correlated with gland expression (r=-0.507, $p<0.001$) and MG tortuosity (r=-0.129, $p<0.001$), but not MG width (r=-0.090, $p=0.167$). Regardless of MG length, warm compress increased the quality of expression ($p<0.002$). Debridement further improved expression in partial MGs ($p=0.003$), but not forcible expression ($p=0.529$).

Conclusions: Length is the key functional morphology metric of lower lid MGs. Warm compress and massage increase the quality of expression in all, but the shortest glands and patients with partial length glands also benefit from debridement.

KEY WORDS: Meibomian gland dysfunction, Morphology, Dry Eye, Expression

INTRODUCTION

Management of meibomian gland dysfunction (MGD) typically involves eyelid warming to melt the pathologically altered meibum and eyelid massage to remove obstructed material from within to restore normal functionality [1]. Eyelid warming methods range from simple, hot, wet towels to specially made devices such as eye masks delivering infrared irradiation and moist-air goggles [2, 3]. Likewise, eyelid massage includes manual manipulation and electric, toothbrush-like devices, to in-office, forcible expression procedures [4, 5]. Other procedures include debridement of abnormal tissue from MG orifices to remove any obstruction [6]. While forcible expression and debridement is performed in-office, this can be supplemented by patient self-care using warm compresses and eyelid massage[1, 4]. However, advice regarding these techniques is not standardised, compliance is variable at best, and it remains unclear how they should be tailored for individuals [1].

Diagnosis of MGD is mainly clinical [1] - focussing on detecting signs of altered MG secretions, abnormal eyelid margin morphology, and MG drop-out (atrophy of acinar tissue) [7]. Meibography is a technique used to visualise the MG acini, traditionally utilising a white light source applied to the eyelid skin to detect drop-out in silhouette [8]. More recently, infrared technology has permitted a non-contact method to image the MGs from the mucosal side [9], allowing assessment of MG morphology with respect to shortening, dilatation or tortuosity [10].

Grading or scoring MG drop-out is traditionally based on the proportion of the lower eyelid that exhibits total and/or partial acinar loss [11, 12]. Overall drop-out is considered a major factor in MGD, where significant correlations with altered meibum, tear film stability, tear film lipid layer pattern (a surrogate for thickness) and dry eye symptoms have been reported [10, 13, 14, 15]. Finis et al. (2015) has shown that the meiboscore (a system used to quantify drop-out [9]) significantly, inversely correlates with the proportion of expressible MGs [16]. These studies suggest that where drop-out is observed, MG and tear film function are impaired [16]. MG tortuosity is less well studied, but greater MG bending has been observed in the upper eyelid, which also correlated to tear film stability; while MG bending in the lower eyelid was correlated to dry eye symptoms [10].

Given the important role of MG morphology in MGD diagnosis, it is currently not well understood how affected glands will respond to treatment. Turnbull et al. (2018) show increased tear film lipid layer thickness and stability with a variety of treatments, regardless of MGD severity (based on drop-out extent), but direct MG functionality was not assessed [17]. A case report on the impact of 3 week's treatment in an MGD patient (eyelid warming, massage, and scrubs) showed improved symptoms and ocular signs, but no change in drop-out as measured with meibography [14]. This raises an important consideration of which treatment to advise for MGD patients, as the presence of drop-out may render certain options ineffective. Furthermore, it is unknown which particular treatments, from patient-applied to in-office based, are more or less effective based upon initial MG morphology. The aim of this study was therefore, to investigate the effectiveness of a range of common treatments based on the function of individual MGs glands classified by their morphological appearance and drop-out extent.

MATERIALS & METHODS

The study was designed as an interventional case series. The study was conducted in accordance with the Declaration of Helsinki and the protocol received positive opinion and governance approval from the South East Scotland NHS Research Ethics Committee (REC reference: 15/SS/0113) prior to study commencement.

Inclusion criteria required participants to be aged ≥18 and have a diagnosis of dry eye (based on TFOS DEWS II criteria) [18]. Exclusion criteria were: active ocular disease or systemic disorder known to affect the eye, except for a diagnosis of MGD and self-reported dry eye symptoms (confirmed via prior Dry Eye Clinic assessment); medications known to affect the eye; and contact lens wear (if worn, they were removed 7 days prior to the study visit). Participants were enrolled with

written informed consent following adequate time to read and understand the Participant Information Leaflet.

Eligible participants attended for one visit where the following procedures were conducted on the lower eyelid of the right eye:

1. Video slit lamp examination to determine the location and number of the MG orifices (CSO Phoenix, Firenze, Italy). Each MG was identified at the slit lamp (diffuse white light, x16 mag) by placing a mark on the eyelid skin adjacent to the associated orifice, with a surgical pen, to ensure the same gland was identified each time. The glands were then numbered manually from the captured image.

2. Meibography images were captured [19, 20] (Oculus Keratograph 5M, Wetzlar, Germany) to determine the morphological appearance of MGs detected in step 1. Glands were divided into nasal, central, and temporal locations respectively by dividing the total number of glands into thirds. Visible MG length, calculated as proportion of the vertical length of the palpebral surface on full lid eversion [21] was measured with ImageJ (https://imagej.nih.gov/ij/). They were also classified as either complete (C, 100-75%), partial (P, 75-25%), or minimal/absent (M, <25%). Again, using ImageJ software, the tortuosity of each MG was assessed by measuring the difference between the maximum horizontal width of the MG and the maximum horizontal width of the region bound by the MG, expressed as a percentage.

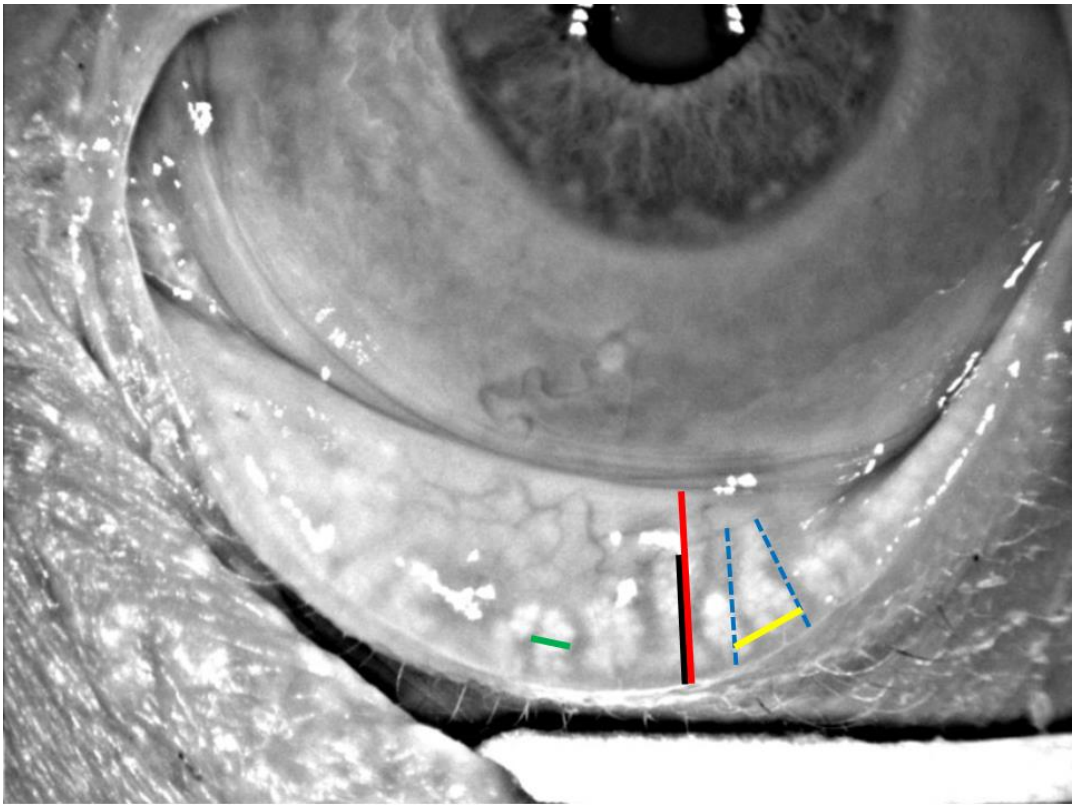

Figure 1: Meibography image to demonstrate ImageJ analysis procedure. Red line = palpebral surface length adjacent to an MG; black line = the MG length; green line = maximum observed width of an MG; blue lines – boundaries of region covered the MG; yellow line = maximum observed width of region covered by the MG.

3. Assessment of meibum quality using the MGD Workshop Meibomian Gland Function scale (quality: 0=clear fluid, 1=cloudy fluid, 2=cloudy particulate fluid, 3=inspissated like toothpaste)[11] following standardised pressure to the lower eyelid margin [22]. If no expression was possible, this was recorded (grade = 4).

Where any MG was identified as having MG function score ≥2 (i.e. abnormal), participants received the following interventions, in sequence of increasing invasiveness:

- **A.** Eyelid warming therapy using the MGDRx Eyebag (5 minutes duration after heating in 800W microwave for 40 seconds on full power followed by manual massage) [2]
- **B.** Debridement of keratinised tissue (stained with lissamine green; GreenGlo, HUB Pharmaceuticals, Iowa, USA) over the MG orifices using a corneal epithelial spatula (Melosa; BVI Medical Limited, Yorkshire, UK) following application of topical anaesthetic (proxymetacaine hydrochloride 0.5%; Bausch & Lomb, UK) to the ocular surface and eyelid margin (brushed with a soaked cotton bud mainly to soften the tissue)
- **C.** Forcible expression of each gland (with movement from proximal to distal end) using MG forceps (Melosa) following application of topical anaesthetic to the ocular surface and eyelid margin

The step **3** evaluation was conducted 5 minutes after each intervention:

Statistical Analysis

Statistical analysis was performed using SPSS for Microsoft Windows (IBM, UK). Data were checked for normality using the Kolmogorov-Smirnov test. Due to the ordinal nature of the grading system applied, data were found to be significantly different from a normal distribution (D=2.50, p<0.001). Thus differences between MG function grade for each MG classification (C, P, or M) with each treatment over time were assessed using the Friedman test. G*Power software (v3.1.9.4) identified a sample size of 24 glands in each group and with this statistic could identify a 0.5 change in grade (with a grade standard deviation of 0.5) with $p \leq 0.05$ and 95% power. Where changes with treatment were determined to be statistically significant (p<0.05), post-hoc analysis was performed using Wilcoxon signed-rank tests with Bonferroni correction applied (6 test pairs per analysis; thus new threshold for statistical significance between treatments = $p \leq 0.008$). Relationships between MG function and morphology metrics was assessed using Spearman's rank correlation analysis due to ordinal nature of MG function grade; with statistical significance at $p \leq 0.05$.

RESULTS

The MGs of 15 participants were assessed (n=9 female; age 31.6±13.1 years; range 18-66), with a combined total of 365 individual MGs identified and examined. Of these, 55.1% (n=201) were classified as complete, 35.9% (n=131) partial, and 9.0% (n=33) minimal/absent. The median number of MGs per participant was 24 (interquartile range: 23 – 26; range: 21 – 28).

Meibomian Gland Function & Morphology

Only just over 10% of complete length MGs gave clear expression, while about 5% did not express at all, with peak expression being particulate in nature (Figure 2,3). In contrast, the majority of partial length glands gave inspissated expression (38%), with one third (32%) not expressing at all. Nearly 70% of glands of <25% length expressed (Figure 2,3). None of those glands with <10% length expressed (Figure 3). MG function was correlated with MG length (r=-0.507, p<0.001; Figure 4, Table 1) and MG tortuosity (r=-0.129 p<0.001; Table 1), but not MG width (r=-0.090, p=0.167; Table 1).

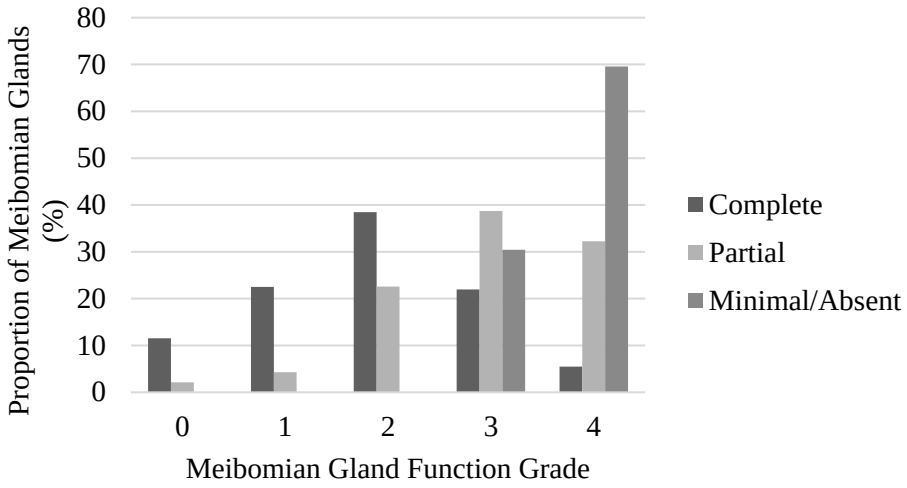

Figure 2: Proportion of meibomian gland classification (complete, partial, and minimal/absent) based on meibomian gland function grade (0 = clear, 1 = cloudy, 2 = particulate, 3 = inspissated, 4 = no expression) at baseline.

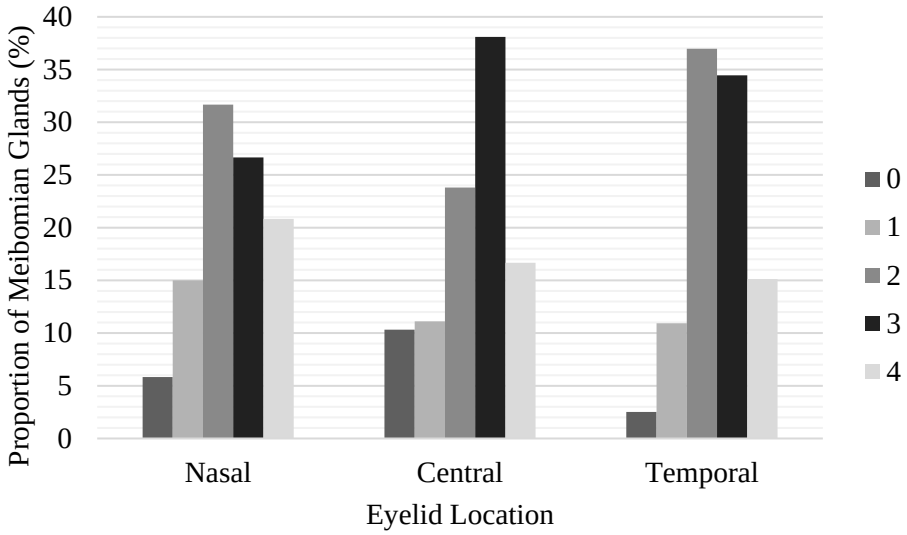

Figure 3: Proportion of meibomian glands at each eyelid location by meibomian gland function grade (see legend). Nasal n = 120 glands, central n = 126, temporal n = 119.

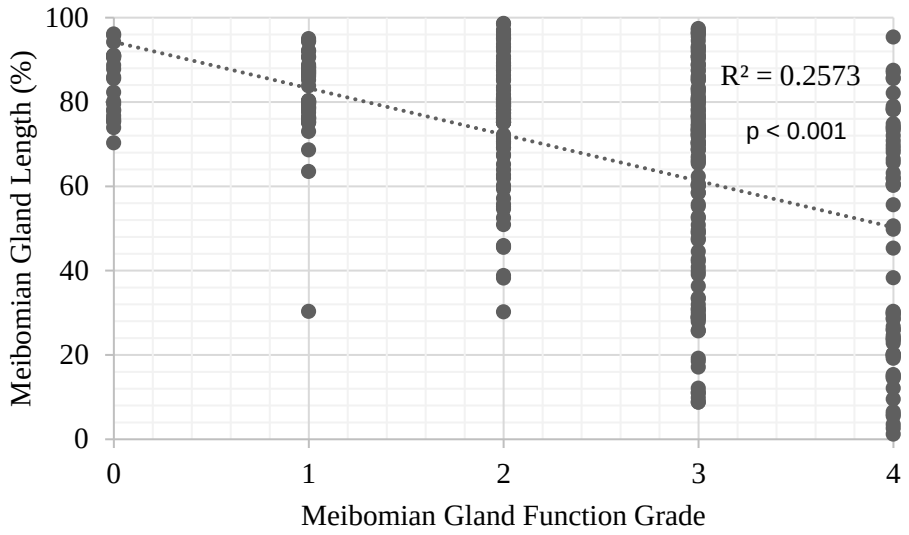

Figure 4: Meibomian gland function grade versus digitally measured meibomian gland length (% = proportion of vertical palpebral length) at baseline. N=365 glands.

Table 1: Correlation between MG Function and MG Morphology			
	MG Length	MG Tortuosity	MG Width
MG Function	r = -0.507	r = -0.129	r = -0.090
	p < 0.001	p < 0.001	p = 0.167

Table 1: Spearman's rank correlation (r) and associated p-values between meibomian gland (MG) function grade and MG length, MG tortuosity, and MG width.

Treatment Effectiveness

Table 2: MG Function - Median, (IQR)				
	Baseline	Warm Compress	Debridement	Forcible Expression
Complete MGs	2 (1 – 3)	2 (1 – 2)	1 (1 – 2)	1 (1 – 2)
Partial MGs	3 (2 – 4)	3 (2 – 3)	2 (1 – 3)	2 (1.5 – 3)
Minimal/Absent MGs	4 (3 – 4)	3 (3 – 4)	3 (3 – 4)	4 (3 – 4)

Table 2: Median (interquartile range; IQR) meibomian gland (MG) function values for complete, partial, and minimal/absent MGs at baseline, and after treatment with warm compress, debridement, and forcible expression.

Complete Meibomian Glands

There was a statistically significant difference in MG function between the different treatments for full length (complete) MGs (χ^2=144.1, p<0.001). There were significant differences between baseline and treatment with warm compress (mean grade reduction: 0.31±0.78 (95% Confidence Interval: 0.19, 0.42); Z=-4.79, p<0.001) and between debridement and forcible expression (0.25±0.62 (95% CI:

0.16, 0.34); Z=-5.05, p<0.001); but not between warm compress and debridement (0.08±0.56 (95% CI: -0.02, 0.16); Z =-1.97, p=0.049).

Partial Meibomian Glands

There was a statistically significant difference in MG function between the different treatment types for partial MGs (χ^2=90.5, p<0.001). There were significant difference between baseline and treatment with warm compress (mean grade reduction: 0.46±0.58 (95% CI: 0.34, 0.39); Z =-6.01, p<0.001) and between warm compress and debridement (0.22±0.68 (95% CI: 0.08, 0.36); Z =-2.92, p=0.003); but not between debridement and forcible expression (0.04±0.61 (95% CI: -0.08, 0.16); Z =-0.63, p=0.529).

Minimal/Absent Meibomian Glands

There was a statistically significant difference in MG function between the different treatment types for minimal/absent MGs (χ^2=14.42, p=0.002). There was a statistically significant difference between baseline and warm compress (mean grade reduction: 0.42±0.51 (95% CI: 0.21, 0.63); Z=-3.16, p=0.002) – but thereafter there was no statistically significant difference between the treatments (warm compress and debridement: Z=-1.73, p=0.083; debridement and forcible expression: Z=-1.07, p=0.285).

DISCUSSION

This study examined how MG morphology, assessed with meibography, affects MG functionality (meibum expression). It also assessed whether this could be improved in the short term by eyelid warming, debridement and forcible expression approaches. As might be expected, at baseline when a patient is first examined, expression is dependent on residual gland length, with no gland <70% of the lower lid length giving clear meibum expression. It should also be noted that even for full length glands, expression can be inspissated or absent (Figure 4). Glands of less than 10% of the lid length did not express and those less than 25% did not express or the meibum was inspissated. It has previously been shown that even 'healthy' MGs do not always express and appear to need time to recharge [23, 24, 25] which will affect the correlation between MG morphology and function.

Regarding calculation of MG length as a proportion of vertical palpebral length, this was chosen, rather than absolute length, due the obvious variation that an MG can extend along the roughly semi-circular inferior tarsal plate. This anatomical feature may also explain the weak correlation between MG tortuosity and MG function (Table 1), where an MG may simply exhibit bending to fit within the physically available space, rather than displaying a pathological change as in MGD [23, 26]. However, this relationship was statistically significant, with more tortuous glands exhibiting reduced functionality with respect to expression. This has also been reported elsewhere – Adil et al. (2019) too found a weak but statistically significant correlation between tortuosity and meibum expression grade (r=-0.107, p<0.05) [27]. However, a recent prevalence study detected 37% of young, asymptomatic participants with measurable MG tortuosity [28]; suggesting this parameter does not influence tear film and symptom measures. In contrast, MG width displayed no significant correlation with MG function (Table 1). Although obstructed material in MGD can lead to dilatation of the central duct, this widening may be offset by acinar atrophy that results from the same process [23, 26, 29]. More recently, Pucker et al. (2019) observed that narrower MGs were associated with worsening expressibility in successful and unsuccessful contact lens wearers; however there was no significant difference in MG tortuosity and width between the two groups [30]. Together with the present results, this suggests that width does not influence MG function, nor correspond to tear film parameters or symptoms and therefore can be ignored as an informative metric by clinicians. Tortuosity, however, requires further study to determine its role in MGD pathogenesis due to the variable presentation between normal and symptomatic patients.

The results demonstrate that despite the extent of MG dropout, warm compresses produce a statistically significant improvement in MG function. This may be explained by the presence of pathologically altered meibomian secretions which result in higher melting temperatures [23, 29] such that even those with significant dropout may still respond to eyelid warming treatment and manual expression. Reduced MG expressibility consistent with MGD diagnosis, has been observed even in the absence of dropout [16]. This abnormal, more viscous meibum is proposed to result from an initial MG obstruction causing changes in lipid composition and subsequently, raised melting temperature [23, 29]. While these improvements were modest and not clinically significant, (mean reduction in grade for all gland classes =0.39±0.64), this effect was observed after only one standardised application, whereas traditional MGD management requires regular long-term use.

Glands with complete/intact acini exhibited the smallest improvement in function, but these glands were initially near normal at baseline (Table 2), so this was not unexpected. Indeed, those glands which were classified as partial length or minimal/absent had a higher proportion of impaired function/reduced meibum quality (Figure 2), supporting the findings observed by Finis et al. (2015) described above [16]. However, glands that are >~10% (of vertical palpebral length) are still able to be expressed without treatment (Figure 4). Thus, unless there is complete loss of the MG acini, improvement in function may still be possible, particularly where the distal portion is intact.

Debridement alone, did not appear to further improve MG function for glands with complete and minimal/absent acini, but did so for glands with partial length acini, although this was not clinically significant. This suggests that occlusion of the orifice may be a precursor to MG acinar tissue atrophy - complete glands have the ability to express normally, while minimal/absent glands do not, such that debridement has no effect on either state. However partial glands, which may be undergoing continued atrophy, responded to debridement; probably because the blockage which can result in dropout has been removed. Indeed, the pathophysiology of obstructive MGD is based on hyperkeratinisation of the orifices and excretory ducts, which in turn may lead to acinar tissue degeneration and atrophy due to increased intra-glandular pressure caused by continually produced meibum [23].

Surprisingly, forcible expression did not further improve MG function in partial length MGs, but this may be due to prior debridement removing the obstruction, releasing meibum and prompting a return to near normal MG function grade (Table 2). Forcible expression was also ineffective for glands exhibiting minimal/absent acinar tissue, which was not unexpected due to the very limited or complete absence of meibum production capability. This corroborates an earlier case report where MG dropout was not affected, even by longer term treatment [14].

A potential limiting feature of this study is the reported observation that a proportion of MGs, whether or not they exhibit dropout, may not be actively secreting at the time of MG function measurement. In a group of young normals, Korb and Blackie (2008) observed that across the entire lower eyelid length, only about 10 MGs yielded liquid secretion at the time of measurement. This temporal variation is accompanied by spatial variation along the eyelid [24, 25]. Further, nasal glands appear more active, and this reduces toward the temporal margin [24, 25]. Thus, individual glands may not have responded to treatment simply because they were not active at the time of measurement, or they were located in a region along the eyelid that is known to be less active. However, Figure 3 reveals that both the proportion of MG function grade and the proportion of expressible glands (nasal = 79.2%, central = 83.3%, temporal = 84.9%) was very similar between eyelid locations. Further, this study examined MG function on an individual basis and in relation to the extent of individual MG dropout detected by meibography; hence it is more likely that a gland did not secrete or respond to treatment due to the reduction or absence of MG acini.

In contrast, a study of the ability of meibography to predict MG function by means of therapeutic expressibility and secretion volume in MGD patients found that while nasal and central MGs had significantly more functional MGs, these regions also exhibited the highest level of dropout; and no correlation was observed between overall dropout and either MG function or secretion volume [31]. However, this group of patients was significantly older (mean age 48.0±12.1 years) and may have developed compensatory mechanisms to maintain meibum secretion in the remaining glands, given

that aging leads to loss of MGs even in healthy asymptomatic patients [32, 33]. In addition, there may have been non-obvious causes of MGD where orifice/ductal obstruction is observed rather than dropout. This study by Murakami et al. (2014) suggests that meibography should not be used alone to determine MG function due to the temporal nature of MG activity and potential non-obvious causes of MGD [31, 34]. Indeed, it is well recognised that morphological examination, such as through meibography, should be used to detect dropout in conjunction with measures of MG function (meibum expression with the force of a blink and lipid thickness over the ocular surface), to help guide therapy [16, 34, 35]. The present study supports this, but adds the importance of individual contribution of MGs to meibum production as well as supporting the use of warm compress therapy and in-office debridement. On the other hand, it questions the role of forcible expression; therapeutic expression seems to excrete similar meibum to diagnostic expression [36], but causes considerable discomfort [37]. A recent randomised controlled trial demonstrated beneficial effects of therapeutic expression alone over a sham treatment [38], but it did not include the less invasive stages of warm compress therapy and in-office debridement which were just as effective without forcible expression in this study.

Using meibography to examine dropout of individual glands is an important tool to help target appropriate therapy (based on MG length rather than width or tortuosity), as well as to communicate to patients the damage sustained that contributes to their dry eye. Eyelid warming therapy, after a single application, significantly improves meibum expression quality, regardless of the extent of MG dropout. This effect may be further enhanced with long-term patient usage, and so clinicians should encourage this treatment in all patients with MGD and check compliance at all subsequent visits. In addition, it is useful to perform in-office debridement in patients with MG drop-out, to help remove orifice and/or excretory duct obstruction, as a preventative measure of MGD progression. There is however, little additional benefit of forcible expression.

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