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Research Article

Validation of a New Meibomian Gland Dysfunction (MGD) Grading Scale for Rapid Assessment of MGD in Clinical Practice

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Abstract

Meibomian gland dysfunction is an abnormality of meibomian glands and their secretions, resulting in poor quality of tears.

Purpose: To validate the MGD grading combination of telangiectasia plus expressibility against the MGD14 questionnaire and against meibography (measured using the Oculus Keratograph). In addition, the sub-aims of this study are to validate the MGD14 questionnaire against meibography and against OSDI questionnaire.

Methods: Study design is an observational, cross-sectional, single visit study**.** Twenty participants were enrolled into this study, including non-contact lens wearers (14 males and 6 females; mean age ± SD, 30.8 ± 3.5 years). Ocular comfort symptoms were examined using MGD14 and OSDI questionnaires. Telangiectasia, expressibility, meibography and Marx line were each graded from 0 to 3, pouting, orifice plugging and irregular lid margins were scored as present or absent while the number of capped glands and the number of expressible glands were counted.

Results: There was no significant correlation between MGD14 score and TE combination, (Spearman's correlation $r = 0.37$; $p > 0.05$). Meibography scores didn't show correlation with TE combination (Spearman's correlation $r = 0.17$; $p > 0.05$). In addition, the results showed that there was no association between meibography and MGD14 score (Spearman's correlation $r = 0.21$; $p > 0.05$). A strong positive correlation was found between MGD14 scores and OSDI scores (Pearson correlation $r = 0.68$; $p < 0.05$).

Conclusion: This is the first study to validate the combination of TE for evaluating MGD. This study didn't show correlations between TE combination against MGD14 and against meibography. In addition, there was no correlation between meibography and MGD14. Overall, this study displayed poor relationship between symptoms and signs of dry eye, however, these results need to be confirmed in a large sample size with more participants displaying MGD.

Keywords: Meibomian Gland Dysfunction; Abnormality; Meibography

Literature Review

What is meibomian gland dysfunction?

Meibomian gland dysfunction (MGD), as defined by the International Workshop on Meibomian Gland Dysfunction 2011, is "a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/ quantitative changes in the glandular secretion" [1]. MGD can

result in altered tear film, inflammation, ocular surface disease and symptoms of eye irritation and discomfort [1].

Meibomian glands are modified sebaceous glands in the upper and lower eyelid that secrete a complex mixture of lipids, which retard tear film evaporation and promote tear film stability [1,2]. These glands dynamically manufacture lipids and proteins which are secreted from the lower and upper eyelids just anterior to the mucocutaneous junctions. In the upper tarsus, there are around 30-40 glands and fewer in the lower lid (20-40) [3]. Each sebaceous gland made of various secretive acini-containing meibocytes, lateral ductules, a centric duct, and a concluding discharge tube that opens at the backward lid side [4].

Meibomian gland disease is utilized to explain a wide variety of sebaceous gland disorders, comprising pathological growth of tissue and genetic abnormality. MGD has been classified according to its anatomical or physiological alterations or acuteness of the disease. Low-delivery and high-delivery conditions are two main categories of MGD depend on the glands excertion. Low-delivery states are moreover grouped to hyposecretory (decreased meibum delivery owing to abnormalities in meibomian glands without noticeable obstruction) and obstructive (terminal duct obstruction) [4]. High-delivery (hypersecretory) states are recognized by discharging of high amount of lipid into the lid margin [4].

Prevalence of meibomian gland dysfunction

Meibomian gland dysfunction is a leading cause of dry eye and 45-65 % of patients who have dry eye symptoms have MGD [5]. The prevalence of MGD varies geographically with an estimate of 60% among Asian populations but less than 20% in Caucasians [4]. Prevalence is additionally influenced by age, with reports of 33% prevalence in patients aged < 30 years and 72% in patients aged ≥ 60 years among the Asian population [6]. These wide differences in the prevalence of MGD may because of lack of standardized criteria for MGD grading [6].

Clinical assessments of MGD

Clinical assessment of MGD includes grading of meibomian gland appearance and assessment of ocular symptoms. It is unclear whether MGD symptoms start at the commencement of or after meibomian gland impairment and changed meibum delivery or instead arise from subsequent damage to other eye surface tissues [4]. Eye discomfort symptoms associated with MGD are subjectively assessed using questionnaires. OSDI questionnaire is a reliable and valid instrument for assessing dry eye symptoms [7] while the MGD14 is a recently developed questionnaire to assess symptoms of MGD specifically [8]. During development, the MGD14 was found to have moderate to good relationship (Pearson's correlation r = 0.69) with the Schein questionnaire [8]. The MGD14 has not yet been validated against clinical MGD status or the OSDI.

Meibomian gland grading using a slit-lamp involves assessment of meibomian glands and orifices visible on the eyelid margin. This study concentrated on a number of MGD parameters to diagnose MGD as described in table 1. The Korb expressor has been used to apply a constant pressure to examine glands expressibility [9]. Non-contact meibography is a clinical technique that facilitates the diagnosis of obstructive MGD and involves collection and grading of infrared images of the entire meibomian glands [10] and has an advantage of providing information of the morphological features of these glands [11]. Although used frequently in research studies, it's utility in clinical practice has been limited, due to the need for specialized equipment and skills needed for its image analysis and interpretation.

Parameter	Description
Telangiectasia	Abnormal vessels on eyelid margin [12].
Pouting	In pouting meibomian gland orifices do not appear flush with the surface of the eyelid margin anymore and it is considered an early sign of MGD [12].
Capping glands	Capped glands appear as a dome of oil over scattered meibomian orifices. However, this cap may be punctured by a needle tip to liberate abundant oil [4].
Plugging	Plugged glands appear as raised orifices above the surface of the eyelid margin due to a blockage of duct and extrusion of a blend of meibomian lipid and keratinized cell fragments [12].
Irregular lid margin	The abnormality of the lid margin starts from accumulation of tissue (e.g. scarring), or loss of meibomian glands but will occur with more gross distortions of lid architecture in cicatricial and ulcerative lid disease [3].

Marx line (ML)	lissamine green staining line on the inner lid as indicator of meibomian gland function. In assessing MGD, the position of Marx line is on the conjunctival side of the meibomian orifices in normal eyes; however, based on the severity of disease, ML might be completely or partly positioned on the cutaneous side of the orifices [13].
Non- contact meibography	A clinical imaging technique used in quantification of meibomian gland dropout by infrared light [14].
Expressibility	The secretive functions of the meibomian glands are evaluated indirectly, by squeezing the tarsal plate locally in relation to individual groups of orifices. This might be carried out with finger pressure or with Korb expressor to produce a dome of clear oil.
	Over the orifices in normal lids. Absent secretion or obstruction occurs with many of the features of MGD [3].
Expressible glands Number	The score of expressible glands is depend on the number of glands that secrete oil when expressed [12].

Table 1: MGD grading parameters.

Natural history of MGD

There is an absence of proof on the explanation of MGD history, i.e. the order in which signs occur [4]. Different aspects of meibomian gland morphology start to change at different ages. Telangiectasia starts to occur in patients older than 40 [15,16], Marx line (ML) moves more anteriorly in patients aged 41 or older [13], meibomian gland plugging, dropout and the presence of irregular eyelid margins occur over 49 years [17], pouting is evident in patients older than 50 [16], expressibility declines in patients older than 50 [15,17] and meibum quality reduces in patients older than 55 years [15]. Knowledge of when meibomian glands change due to age is important because aging is supposed to play a key role in meibomian gland dysfunction by influencing the structure and/or functions of the meibomian glands. To avoid the influence of age on meibomian gland morphology this study recruited patients aged 18 to 40 which is the age before these meibomian gland parameters change.

There are several factors that may influence on pathogenesis of MGD including ophthalmic, systemic history and medications. Ophthalmic conditions such as contact lens wear, anterior blepharitis, dry eye and Demodex folliculorum [4] as well as systemic factors like androgen deficiency, menopause, Sjogren's syndrome, hypertension, aging, rosacea, cholesterol levels, atopy, psoriasis, and benign prostatic hyperplasia (BPH) may promote MGD [4]. Steroid hormones such as androgens that play a major role in the development, differentiation, and lipid secretion of sebaceous glands. [18] Medications associated with the pathogenesis of MGD include, but are not limited to, anti-androgens, medications used to treat benign prostatic hyperplasia (BPH), postmenopausal hormone therapy (e.g., estrogens and progestins), antihistamines, antidepressants, and isoretinoids [4].

Diagnosis of meibomian gland dysfunction

The investigation of MGD prevalence has been incomplete because of the inconsistent clinical assessment to characterize this disease. Each study uses a different combination of parameters due to the absence of an established set of, routinely used, MGD grading criteria (see table 2) [4].

Paper	MGD grading parameters used
Bron., *et al.* [16]	Telangiectasia, cutaneous hyperkeratinization, increased narrowing of meibomian gland orifices, pouting and plugging, rounding of lid margin, blepharitis, trichiasis, entropion or ectropion, mucocutaneous junction ridging, secretion quantity and quality, tarsal plate abnormality, main ducts and acini abnormality.
Foulks., *et al.* [19]	Evaporimetry, interferometry, meibometry, clinical quantification, expressibility, physical and chemical analysis, meibography, hyperkeratinization, anterior blepharitis, vascularity of lid margin, eyelid irregularity, eyelid rounding and abnormality, lashes disturbed and loss, mucotaneoua junction abnormality, orifices plugging, retroplacement, pouting, main duct and acini abnormality, expressed secretions.
Arita., *et al.* [20]	Lid margin abnormality, non-contact meibography (meibo-score), superficial punctuate keratopathy (SPK), meibum volume and quality and Schirmer's test.
Arita., *et al.* [21]	Telangiectasia, Marx line, lid margin irregularity, plugging, foaming, and thickness. Corneal and conjunctival staining, tear film breakup time (TBUT), Schirmer's test, noncontact meibography (meibo-score) and expressibility.

Alghamdi., *et al*. [22]	The Ocular Surface Disease Index (OSDI), Contact lens dry eye questionnaire (CLDEQ-8), Dry eye questionnaire (DEQ-5), non-contact meibography, MG expressibility, plugged orifice, telangiectasia, Marx line, NIBUT and phenol red thread.
Yeotikar., *et al*. [15]	Tear osmolarity measured by tearlab osmometer, meibography, OSDI, anterior blepharitis, bulbar and limbal redness, telangiectasia, fluorescein tear breakup time (FTBUT), tear film assessment by tearscope, lipid layer appearance, noninvasive tear breakup time (NITBUT), Tear meniscus height and volume and MG expressibility.

Table 2: Combinations of parameters used to grade MGD in published studies.

Multiple combinations of MGD grading parameters have been suggested in the literature [5,8,18,20], however, these are quite lengthy, some including in excess of 20 parameters as seen in Table 2 and none have been decided upon as the gold standard. Our research group has recently developed a concise slit-lamp grading method using a combination of eyelid margin telangiectasia and meibomian gland expressibility ("TE") grading, to rapidly detect changes in MGD with treatment or disease progression [25]. The speed with which TE can be performed (approximately 2 minutes) makes it an attractive alternative to meibography and more complex grading systems, which can take a long time to perform. The combination of TE has not yet been validated.

Aims

This study examined a range of participants who may or may not currently have meibomian gland dysfunction (MGD). The intention was to include participants with a range of MGD signs, in order to achieve the main aim of this study: to validate the MGD grading combination of telangiectasia plus expressibility against the MGD14 questionnaire and against meibography (measured using the Oculus Keratograph). In addition, the sub-aims of this study were to validate the MGD14 questionnaire against meibography and OSDI questionnaire.

Hypothesis

- The MGD grading combination of telangiectasia plus expressibility (TE) scores will be well correlated with non-contact meibography scores.
- A significant correlation will exist between the MGD grading combination of telangiectasia plus expressibility scores and MGD14 questionnaire.
- There will be a good correlation between MGD14 scores and meibography scores.
- The MGD14 scores will correlate with OSDI scores.

Methods

An observational, cross-sectional, single visit study. This study was conducted at The University of New South Wales, Sydney, NSW, Australia. The study was approved by Human Research Ethics Committee at University of New South Wales and the procedures used obey the tenets of the Declaration of Helsinki (approval number: HC17868). All subjects provided written informed consent before entry into the study.

Inclusion and exclusion criteria

The study recruited participants aged 18 to 40 years who understand the English language to complete the questionnaires. The exclusion criteria included diagnosis with Sjögren's Syndrome or other autoimmune disease, recent ocular surgery (within the last 1 month), history of refractive surgery, contact lens wearers, ocular or systemic conditions deemed likely to significantly impact the ocular surface (including thyroid abnormalities, auto-immune disorders, significant liver disease) and current use/use within the last month of medication deemed likely to significantly impact the ocular surface (including current use of anti-acne medication, corticosteroids, immunosuppressants, antihistamines).

Clinical assessment

Participants were required to attend one visit and undergo a number of tests by an Optometrist. MGD symptoms were assessed by OSDI and MGD14 questionnaires. According to the published grading criteria (shown in Table 3), lid margin features including telangiectasia, pouting, capped glands, irregular lid margin, orifices plugging and meibum expressibility (quality and quantity) were evaluated for the lower eyelid of both eyes with the use of a slit-lamp microscope.

A constant pressure by the Korb expressor for a time of 10-15 seconds was used to examine approximately one-third of the central lower eyelid, allowing the simultaneous expression of

approximately 8 meibomian glands [9]. In addition, lissamine green was used to evaluate Marx line for all participants with slit-lamp. Oculus Keratograph software was used to perform the non-contact meibography technique to examine meibomian gland dropout in the lower lid, then pictures were graded according to the Gestalt grading scale as shown in Table 3. Participants were diagnosed using MGD signs according to the following criteria (see Table 3).

Meibomian gland signs	Grading	MGD	Non- MGD
Telangiectasia [21]	Grade 0 = no telangiectasia Grade 1 = single telangiectasis Grade 2 ≥ 2 Grade 3 ≥ 5	Grade ≥ 1	Grade 0
Pouting [21]	Grade 0 = absent Grade 1 = present	Grade 1 = present	Grade 0 = absent
A number of capped glands	(count)	Grade 1 ≥ present	Grade 0 = absent
Orifices plugging [16]	Grade 0 = absent Grade 1 = present	Grade 1 = present	Grade 0 = absent
Irregular lid margin [16]	Grade 0 = absent Grade 1 = present	Grade 1 = present	Grade 0 = absent
Marx line (ML) [13]	Grade 0 = lissamine green line running entirely along the conjunctival side of the meibomian orifices Grade 1 = parts of the ML touching the meibomian orifices Grade 2 = ML running through the meibomian orifices Grade 3 = ML running along the eyelid margin side of the Meibomian orifices	Grade ≥ 2	Grade ≤ 1
Non-contact meibography [14,21]	Grade 0 = no drop out of MG Grade 1 ≤ 33% drop out of MG Grade 2 = 34%- 66% drop out of MG Grade 3 = 67%-100% drop out of MG	Grade ≥ 1	Grade 0
Expressibility [20,21]	Grade 0 = Clear with light pressure Grade 1 = Cloudy with mild pressure Grade 2 = Cloudy with more than moderate pressure Grade 3 = Meibum not expressed even with hard pressure	Grade ≥ 1	Grade 0 = Clear with light pressure
Number of meibomian glands expressible [21]	(Count)	< 5	≥ 5

Table 3: MGD published grading parameters and MGD and Non-MGD grading criteria used in the study.

Statistical analysis

G Power was used to calculate a sample size based on an expected moderate effect size (0.4) for each of the associations tested. For 85% power at alpha = 0.05, effect size = 0.4, a minimum sample size of 34 participants was required. Data was tested for normality using Shapiro – Wilk test. Spearman's correlations have been used to examine associations between the different MGD clinical grading parameters (signs) as well as between signs and symptoms. Mann-Whitney U test was used to examine any significant difference between the right and left eyes.

Results

Twenty participants were enrolled into this study (14 males and 6 females; mean age ± SD, 30.8 ± 3.47 years). Most participants had Middle Eastern background (65%). Shapiro – Wilk test results showed that OSDI, MGD14 and all MGD signs are not normally distributed. Mann-Whitney U test showed that there was no significant difference between right and left eyes. The mean and standard deviations for the average between R and L eye are presented in the following table (Table 4).

Signs and symptoms	Mean ± SD
Telangiectasia(T)	0.25 ± 0.66
Expressibility (E)	0.20 ± 0.66
T+E combination	0.45 ± 1.33
Meibography	1.18 ± 1.01
MGD14	26.10 ± 27.73
OSDI	20.17 ± 14.84

Table 4: Mean and standard deviation for signs and symptoms of all participants for both eyes.

According to MGD and Non-MGD grading criteria used in this study (shown in Table 3), 13 participants (65 %) showed one or more MGD signs. There was no significant correlation between MGD14 score and TE combination scores, (Spearman's correlation $r = 0.37$; $p > 0.05$). Meibography scores didn't show correlations with TE combination scores, (Spearman's correlation $r = 0.17$; $p > 0.05$). In addition, the results showed that there was no association between meibography and MGD14 score (Spearman's correlation $r = 0.21$; $p > 0.05$). A strong positive correlation was found between MGD14 scores and OSDI scores (Spearman's correlation $r = 0.68$; $p < 0.05$).

Discussion

This study shows a strong significant correlation between MGD14 and OSDI questionnaires as discussed at the TFOS 2014 (the tear film and ocular surface) conference that showed 45-65 % of patients with symptoms of dryness would have MGD symptoms [5]. MGD14 didn't display significant correlations with the TE combination scores and with meibography. Although this was not what we hypothesized, these findings agree with the Bartlett., *et al*. (2015) [26] study that demonstrated a weak and inconsistent relationship between signs and symptoms of dry eye.

Meibography scores didn't show correlation with TE combination while Arita., *et al*. (2009) [20] report that vascularity and expressibility signs of MGD would be correlated with meibography scores in MGD group ($P < 0.0001$) [20]. These results are not in line with our hypothesis as it was expected that a group without MGD signs, such as telangiectasia and normal meibum would also have an absence of gland dropout [20].

There are some limitations presented in this study. First and foremost, study sample size was small due to the difficulty to obtain enough participants. The decision to recruit 18-40 was to avoid age related changes. However, The prevalence of MGD is known to be affected by age, with reports of 33% prevalence in patients aged < 30 years and 72% in patients aged ≥ 60 years [27], therefore this study had a lower opportunity of obtaining a high proportion of MGD subjects. More challenging to find people under 40 with MGD.

This project was restricted due to time constraints between receiving ethics approval and the end of the Master's program. Had there been more time, and at a period when there were more potential subjects at the University, participants with more MGD signs may have been found.

As the prevalence of MGD varies geographically with an estimate of 60% among Asian populations but less than 20% in Caucasians [4], 76.1 % in Saudi Arabia [28], this study may be affected by ethnicity distribution factor because of the majority of participants were from the middle eastern background (65%). Future studies are needed to validate TE combination with MGD14 and meibography.

Conclusion

This is the first time of validation MGD14 against TE combination and meibography grading parameters. This study didn't show significant correlations between TE combination against meibography and against MGD14. In addition, there was no significant correlation between meibography and MGD14. In general, this study displayed poor association between symptoms and signs of dry eye, however, these results need to be confirmed in a large sample size with more participants displaying MGD.

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