Contact Lens and Anterior Eye 41 (2018) 88–92

Contents lists available at ScienceDirect

Contact Lens and Anterior Eye

journal homepage: www.elsevier.com/locate/clae

Comparison of treatment effect across varying severities of meibomian gland dropout

Philip R.K. Turnbull[a], Stuti L. Misra[b], Jennifer P. Craig[b,*]

[a] School of Optometry and Vision Science, New Zealand National Eye Centre, The University of Auckland, New Zealand
[b] Department of Ophthalmology, New Zealand National Eye Centre, The University of Auckland, New Zealand

ARTICLE INFO

Keywords:
Meibomian gland dysfunction
Dry eye disease
Liposomal spray
Warm compress
Latent heat therapy

ABSTRACT

Purpose: Better understanding of the pathophysiology of meibomian gland dysfunction (MGD) has provided the opportunity to develop treatments which could be tailored for specific presentations of MGD. This study sought to directly compare treatment effectiveness for three current therapies across differing levels of MG dropout.
Methods: Subjects (n = 81), grouped by infrared meibography dropout proportions, into either no (control), mild, or pronounced MG dropout, were randomised to receive treatment with a latent heat device (n = 25), liposomal spray (n = 28), or heated warm compress (n = 28). A battery of tear film measures was performed, pre- and post-application of treatment, and compared by treatment type and MG severity.
Results: Symptoms correlated with MG dropout proportions ($r = 0.618$, $p < 0.001$). Following treatment, non-invasive tear breakup time improved ($p = 0.010$), independent of treatment type ($p = 0.131$). The improvement was significant only in the pronounced MGD group ($+4.32 \pm 1.15$s, $p = 0.008$), however, following treatment, the mild group was no longer distinct from the control group ($p = 0.843$). Lipid layer grade (LLG) also improved following treatment ($p < 0.009$), but again was not specific to treatment type ($p = 0.349$). All three severity groups showed an improvement in LLG, with 49.3% of participants showing an improvement of at least one grade, and none showing decreased LLG.
Conclusions: Increased LLG across all three treatment groups suggests that all methods increase meibum outflow to the tear film, resulting in a thicker lipid layer after treatment. These results suggest that all three treatments are effective in improving tear film quality, independent of MGD severity based either on symptoms or based on gland dropout.

1. Introduction

Meibomian gland dysfunction (MGD) is a leading cause of dry eye, affecting around 33% of people younger than 30 years old, and increasing significantly with age [1]. The early stages of MGD show hyper-keratinisation of the MG duct, and meibum with reduced outflow [2], modified composition [3], and increased melting point. As the disease progresses, meibum outflow further decreases, leading to complete stasis of oils from the gland, and to MG atrophy, observed clinically as loss of the gland (MG dropout). Common treatment paradigms typically focus on either raising the gland temperature or clearing the ducts, to improve meibum outflow, or applying artificial ophthalmic products to supplement the natural tear film [4]. Whether success of these modalities corresponds to different severity stages is not currently known.

Eyelid warming systems, such as latent heat goggles and heated seed or bead pouches aim to increase MG function by raising the local temperature to help liquefy the meibum [5], facilitate output into the tear film [2], and potentially provide a barrier to evaporation. Goggles create a closed microclimate in the periocular area [6], which is believed to further reduce aqueous evaporation [7]. Liposomal sprays work by migration of phospholipids across the lid margin to combine with natural lipids and increase the lipid layer thickness and stability [8], and have previously been shown to be more effective than hyaluronate eye drops and triglyceride gel at restoring tear film stability [9,10].

This study aimed to compare the effectiveness of a single application of three MGD interventions; latent heat device, warm compresses, and liposomal spray, in sex-matched individuals with differing levels of MG dropout.

* Corresponding author at: Ocular Surface Laboratory, Department of Ophthalmology, New Zealand National Eye Centre, The University of Auckland, Private Bag 92019, Auckland, 1142, New Zealand.
E-mail address: jp.craig@auckland.ac.nz (J.P. Craig).

http://dx.doi.org/10.1016/j.clae.2017.09.004
Received 16 July 2017; Received in revised form 23 August 2017; Accepted 8 September 2017
1367-0484/ © 2017 British Contact Lens Association. Published by Elsevier Ltd. All rights reserved.

Table 1
Distribution of three MGD severity groups between the three treatment cohorts: latent heat device, liposomal spray, and heated eyebag. The distribution of McMonnies Dry Eye Questionnaire scores was significantly increased with each MGD severity group ($F = 54.27$, $p < 0.001$). Meibomian gland (MG) dropout was also significantly different between each severity group ($F = 279.38$, $p < 0.001$).

MG dropout group	Age (years)	McMonnies Score	MG Dropout (%)	Latent Heat	Liposomal Spray	Heated Eyebag	Total
Control (≤5%)	36 ± 15	6.76 ± 4.30	3.81 ± 2.18	6	8	7	21
Mild (5–40%)	42 ± 16	17.19 ± 5.43	17.14 ± 8.33	11	8	8	27
Pronounced (≥40%)	55 ± 16	22.45 ± 5.98	75.94 ± 15.05	8	12	13	33
Total	46 ± 18	16.63 ± 8.26	36.91 ± 33.85	25	28	28	81

2. Methods

A total of 81 participants (56% female, age 46 ± 18 years, range 23–89 years) were enrolled in a prospective, single-visit, randomised cohort study of three different MGD treatments. The study was conducted under the principles of the Declaration of Helsinki and was granted local ethical approval (NTY 08/07/070). Informed consent was provided by all participants prior to study commencement. Exclusion criteria included history or evidence of non-dry eye anterior segment disease, previous ocular surgery, trauma, or infection, current contact lens wear, and topical medications other than artificial tear supplements, which were avoided for 2 h prior to study participation.

A battery of baseline measures included non-invasive tear breakup time (NIBUT) measured with the aid of a Tearscope Plus™ with fine grid insert (timed from blink to observation of first distortion in the grid pattern, Keeler, Berkshire, UK), tear meniscus height (TMH) calculated from a calibrated digital image by a masked investigator, and lipid layer grade (LLG), evaluated by tear film interferometry [11] (Tearscope Plus; Keeler, UK) and graded as: 0 (absent), 1 (open meshwork), 2 (closed meshwork), 3 (wave), 4 (amorphous), or 5 (coloured fringes). Meibomian gland drop out was determined by infrared meibography [12,13] (SDZ Electronics, Auckland, NZ), and represents the area covered with glands, as a proportion of the full tarsal area expected to house glands [14]. Corneal temperature variation factor (TVF) was determined with an infrared thermographer (TVS-200, Applied Infrared Sensing, Australia) [15], and tear film evaporation rate was measured with a modified evaporimeter (EP-2, ServoMed, Sweden) [16]. Each participant was randomly allocated to receive one of three treatment modalities; latent heat device (Blephasteam, Spectrum-Théa, UK, n = 25), liposomal spray (TearsAgain®, Optima, Germany, n = 28), or Eyebag® (MGDRx®, Eyebag Company, UK, n = 28), Treatment was applied to both eyes in each case, by an unmasked clinician uninvolved in data collection for the study, to preserve investigator masking. McMonnies Dry Eye Questionnaire symptom scores were calculated before and after treatment.

The pre-heated latent heat device, containing saline-soaked ring inserts, was applied according to the manufacturer's instructions for a period of 10 min. Eyebags were heated, according the manufacturer's guidelines, for 30 s at full power in a 900W microwave, shaken on removal to ensure even heat distribution, then applied immediately to the eyes of the participant, with the silk side adjacent to the eyelids, for a period of 10 min. Participants in the liposomal spray group received one full spray to each closed eye in turn. Once the treatment had been applied, participants were asked to remain seated, blinking normally, for the treatment period of 10-min.

Based on the percentage of meibomian gland (MG) dropout observed by infrared meibography, eligible participants were pooled into one of three groups: control (≤5% MG dropout), mild MG dropout (between 5 and 40%) or pronounced MG dropout (≥40%). Retrospective severity classification ensured masking of the participants MG dropout classification to the researchers.

Ten minutes after the treatment period, the same battery of dry eye tests was repeated, and the results were pooled by treatment. The main outcome measures were the differences in pre- and post-treatment measures, which were compared across treatment groups and MG dropout groups. Only data from right eyes were included in the analysis. Statistical testing was performed in SPSS (V22, IBM, USA). Equivalence of the three treatment groups at baseline was assessed with one-way ANOVA. Paired pre- and post-treatment results were compared with a general linear model for parametric variables, and with Wilcoxon and Kruskal–Wallis (KW) tests for comparisons over time and between groups, respectively, for non-parametric variables. Power calculations indicated that a minimum of 15 participants was required, per group, to detect a clinically significant difference (one lipid layer grade) for the inter-group comparisons at 80% power with an alpha of 0.05. Results were considered significant at $p < 0.05$.

3. Results

3.1. Severity classifications

Eighty-one participants completed the study, with 27 classified with mild gland dropout, 33 with pronounced dropout, and 21 controls. McMonnies Dry Eye Questionnaire symptom scores correlated with the percentage of MG dropout ($r = 0.618$, $n = 81$, $p < 0.001$), increasing with severity group ($F = 54.27$, $p < 0.001$, Table 1). At baseline, there was no difference between treatment groups for McMonnies Dry Eye Score ($F = 0.54$, $p = 0.585$), MG dropout percentage ($F = 0.71$, $p = 0.494$), or sex ($F = 0.24$, $p = 0.942$). Overall, MG dropout showed a positive correlation with age ($r = 0.541$, $p < 0.001$), but the mean ages of participants in each treatment group were not different ($F = 0.22$, $p = 0.801$).

3.2. Clinical measures

Prior to treatment, there was a significant difference in NIBUT between the 3 severity groups ($F = 21.66$, $p < 0.001$, Fig. 1), with the control group (7.14 ± 2.54 s) exhibiting a longer NBUT than both the mild (5.60 ± 1.90s, $p = 0.015$) and pronounced MGD (3.80 ± 1.17 s, $p < 0.001$) groups. Following treatment, there was an overall improvement in NIBUT ($F = 4.85$, $p = 0.010$), with no effect of treatment type ($F = 0.99$, $p = 0.131$). Post-hoc testing revealed that the improved NIBUT after treatment was significant only for the group with pronounced MGD (4.32 ± 1.15 s, $p = 0.008$), with the mild and control groups failing to reach significance (mild: 6.17 ± 2.22 s, $p = 0.057$, control: 6.47 ± 2.06 s, $p = 0.172$). However, a result of this improvement meant that there was no longer a significant difference between the NIBUT of the control and mild MGD groups ($p = 0.843$) following treatment.

At baseline, the lipid layer grade (LLG) was different between MG dropout groups ($\chi^2 = 41.97$, $p < 0.001$), with the control group LLG (Median: 4 (IQR: 2.0–4.0)) higher than both the mild (Median: 2 (IQR: 1.0–2.0), $p < 0.001$) and pronounced (Median: 1.5 (IQR: 0.0–2.0), $p < 0.001$) groups, which were not different from each other ($p = 0.373$). Following treatment, there was an overall improvement in LLG ($\chi^2 = 40$, $p = 0.009$), but again, no effect of treatment type ($p = 0.349$). Post hoc testing revealed a significant difference in the improvement in LLG between the three MGD severity groups ($p < 0.001$) with the mild group LLG increasing from 2.0 (IQR: 1.0–2.0) to 3.0 (IQR: 2.0–3.0, $\chi^2 = 20$, $p < 0.001$), and the

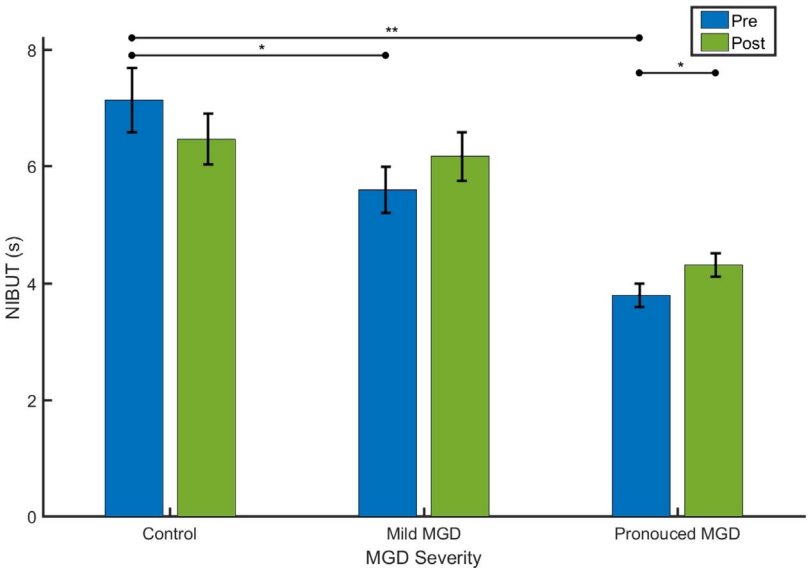

Fig. 1. Comparison of non-invasive tear breakup times (NIBUT) between MGD groups, pre- and post-treatment. The control group had a longer NIBUT than both mild ($p = 0.015$) and pronounced MGD groups ($p < 0.001$). After treatment, there was a significant improvement in NIBUT in the pronounced group ($p = 0.010$), and the post-treatment NIBUT were not significantly different between MGD severity groups. * indicates significance at $p < 0.05$, ** indicates significance at $p < 0.001$.

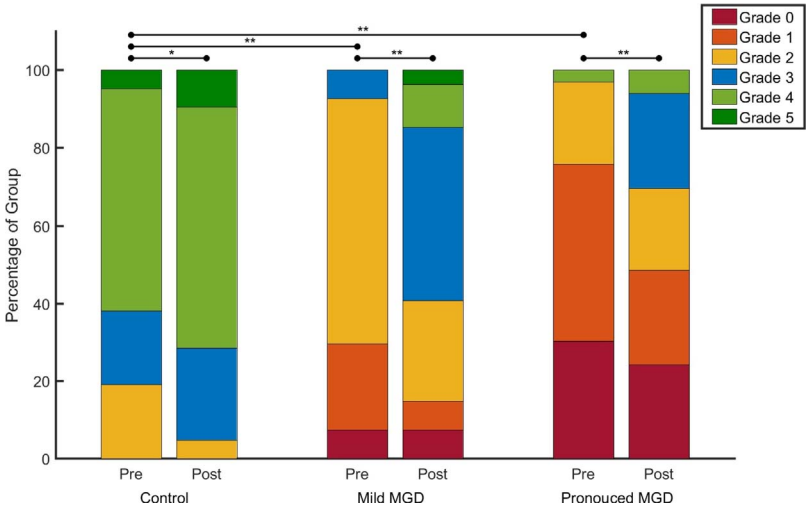

Fig. 2. Lipid layer grade (0 = abnormal colour fringes/worst) across the three severity groups (control, mild MG dropout and pronounced MG dropout), pre- and post-treatment. All three MG dropout groups improved following treatment, with 49% of participants increasing at least one grade, and 51% remaining stable, and none worsening after treatment. * indicates significance at $p < 0.05$, ** indicates significance at $p < 0.001$.

pronounced group LLG increasing from 1.0 (IQR: 0–1.5) to 2.0 (IQR: 0.5–3.0, $\chi^2 = 16$, $p < 0.001$). While the control group also improved slightly ($\chi^2 = 4$, $p = 0.046$), there was no change in the median (4.0) or lower and upper (3.0–4.0) quartiles, but change was most noticeable at the 10th percentile level (Pre: 2.0 to Post: 3.0, Fig. 2). Forty of the 81 participants (49%) improved by at least one lipid layer classification grade, with (11%) improving by 2, and one (1%) improving by 3 grades, while none showed a decreased LLG following treatment. The size of the improvement was not dependent on age in any group ($F = 0.66$, $p = 0.652$).

There was no change in other dry eye metrics following treatment, including TMH ($F = 0.16$, $p = 0.695$), corneal TVF ($F = 0.45$, $p = 0.505$), or tear evaporation rate ($F = 0.61$, $p = 0.439$), in any of the three treatment groups or across MGD severity groups (Table 2).

4. Discussion

As the pathophysiology of MGD becomes better understood [17–19], treatments can potentially be tailored to an individual's presentation of MGD [20,21]. Hyperkeratinization of the MG occurs with both increasing age [22] and MGD [17,18], while atrophy of the gland may be more indicative of underlying MGD [23]. A wider range of effective in-house treatments has become available for MGD. For example, a single treatment of LipiFlow can improve tear breakup time at nine months [24], and improve dry eye symptoms for at least 12 months [25], while a three session course of intense pulsed light can

Table 2
Changes in Tear Meniscus Height (TMH), Non-Invasive Break Up Time (NIBUT), tear evaporation, and corneal Temperature Variation Factor (TVF). Only NIBUT was significantly changed following treatment, and was not related to treatment type. Post-hoc testing showed only the pronounced group had significantly improved NIBUT.

MG dropout group	ΔTMH (mm)	ΔNIBUT (s)	ΔEvaporation (g/cm^2/s)	ΔTVF (°C)
Control (≤5%)	0.02 ± 0.11	−0.49 ± 2.26	0.73 ± 4.66	−0.01 ± 0.29
Mild (5–40%)	0.00 ± 0.05	0.40 ± 1.35	−0.64 ± 5.71	0.01 ± 0.25
Pronounced (≥40%)	−0.02 ± 0.05	0.56 ± 1.07	0.29 ± 4.75	−0.14 ± 0.28
Significance (p)	0.695	0.010*	0.439	0.505

*Indicates significance at $p < 0.05$.

lead to significant improvements in lipid layer thickness and tear breakup times at 45 days [26]. However, patient applied therapies remain the mainstay treatment for MGD, as cost is often a factor, and the chronic nature of the condition requires ongoing therapy.

It had been hypothesised that those with higher MG dropout (and therefore with the least potential to produce adequate meibum) might benefit most from lipid replacement, since both latent heat goggles and warm compresses, in facilitating natural meibum flow, rely on the presence of (non-atrophied) MG. However, we found no difference in the effectiveness of three commonly used home-based MGD treatments, namely liposomal spray, latent heat goggles, and warm compress, across the range of MG dropout severity. This may reflect the relatively small number of participants in the study with very severe drop out ($>$ 75%) in whom treatment encourages the remaining MG to release sufficient meibum to improve the clinical impression of MGD. This was observed through an improvement in LLG, which corresponded to increased non-invasive tear breakup times [16] in both the mild and pronounced MGD groups, which could provide symptomatic relief [27,28]. A poor lipid layer correlates strongly with dry eye symptoms [29,30] therefore increasing the available lipid would be expected to be beneficial.

The results of this study would suggest that an individual's treatment plan can be selected from amongst the three tested treatments according to patient preference, including factors such as cost or ease of use, and thereby encourage optimal treatment compliance in the home environment.

In our study, approximately half of all subjects showed an improvement in LLG of at least one grade while none showed a decrease in LLG quality following treatment. The increase in LLG across all three treatment groups suggests that the methods, whether by effecting expression of natural meibum, or by supplementing the tear fluid with artificial lipid components, contribute similarly to the natural tear lipid layer. In cases where pre-treatment non-continuous lipid layers can be made continuous post-treatment, this may decrease the rate of tear evaporation [16]. The control group ($<$ 5% MG dropout), too, showed an increase in lipid layer thickness, as has been reported in other studies [31,32]. Such universal improvements support the idea that there is considerable redundancy in lipid production [32,33], *via* the number of concurrently active MG [34,35]. While there must be a threshold beyond which remaining MG are unable to maintain a sufficient lipid layer [4], our results demonstrate that even individuals with $>$ 40% MG dropout can benefit from therapies which increase natural meibum release from the remaining glands.

Such a strong relationship between MG dropout and symptoms score was unexpected, as the relationship between clinically measured parameters, and dry eye symptoms, is often poor [36–38]. Due to the investigator-masked nature of this study, only objective measures of dry eye were compared between pre- and post-treatment time periods and, of the range of measures taken, lipid layer thickness and tear breakup times, both important predictors of dry eye symptoms [27,29], showed measurable improvements. Both the single-visit, and in-clinic nature of the study limits conclusions that can be drawn about longer-term and at home benefits of the treatments, and highlights the need for future studies of increased duration that explore optimal treatment application frequency.

Conflicts of interest

None.

Funding

SM was supported by an FDRF grant from the University of Auckland. Product supplies were donated by the respective manufacturers.

References

[1] D.A. Schaumberg, J.J. Nichols, E.B. Papas, L. Tong, M. Uchino, K.K. Nichols, The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD, Invest. Ophthalmol. Vis. Sci. 52 (2011) 1994–2005, http://dx.doi.org/10.1167/iovs.10-6997e.

[2] A. Nagymihályi, S. Dikstein, J.M. Tiffany, The influence of eyelid temperature on the delivery of meibomian oil, Exp. Eye Res. 78 (2004) 367–370, http://dx.doi.org/10.1016/S0014-4835(03)00197-0.

[3] D. Borchman, G.N. Foulks, M.C. Yappert, S.E. Milliner, Changes in human meibum lipid composition with age using nuclear magnetic resonance spectroscopy, Invest. Ophthalmol. Vis. Sci. 53 (2012) 475–482, http://dx.doi.org/10.1167/iovs.11-8341.

[4] D. Finis, P. Ackermann, N. Pischel, C. König, J. Hayajneh, M. Borrelli, S. Schrader, G. Geerling, Evaluation of meibomian gland dysfunction and local distribution of meibomian gland atrophy by non-contact infrared meibography, Curr. Eye Res. 3683 (2014) 1–8, http://dx.doi.org/10.3109/02713683.2014.971929.

[5] M. Mitra, G.J. Menon, A. Casini, S. Hamada, D. Adams, C. Ricketts, E.T. Fuller, J.R. Fuller, Tear film lipid layer thickness and ocular comfort after meibomian therapy via latent heat with a novel device in normal subjects, Eye (Lond.) 19 (2005) 657–660, http://dx.doi.org/10.1038/sj.eye.6701611.

[6] D.R. Korb, J.V. Greiner, T. Glonek, R. Esbah, V.M. Finnemore, A.C. Whalen, Effect of periocular humidity on the tear film lipid layer, Cornea 15 (1996) 129–134, http://dx.doi.org/10.1097/00003226-199603000-00004.

[7] J.P. McCulley, J.D. Aronowicz, E. Uchiyama, W.E. Shine, I.A. Butovich, Correlations in a change in aqueous tear evaporation with a change in relative humidity and the impact, Am. J. Ophthalmol. 141 (2006) 758–760, http://dx.doi.org/10.1016/j.ajo.2005.10.057.

[8] J.P. Craig, C. Purslow, P.J. Murphy, J.S.W. Wolffsohn, Effect of a liposomal spray on the pre-ocular tear film, Contact Lens Anterior Eye 33 (2010) 83–87, http://dx.doi.org/10.1016/j.clae.2009.12.007.

[9] R. Khaireddin, K.-G. Schmidt, Comparative investigation of treatments for evaporative dry eye, Klin. Monbl. Augenheilkd. 227 (2010) 128–134, http://dx.doi.org/10.1055/s-0028-1109686.

[10] D. Dausch, S. Lee, S. Dausch, J.C. Kim, G. Schwert, W. Michelson, Comparative study of treatment of the dry eye syndrome due to disturbances of the tear film lipid layer with lipid-containing tear substitutes, Klin. Monatsblätter Für Augenheilkd 223 (2006) 974–983, http://dx.doi.org/10.1055/s-2006-927266.

[11] J.P. Guillon, Use of the Tearscope Plus and attachments in the routine examination of the marginal dry eye contact lens patient, Adv. Exp. Med. Biol. 438 (1998) 859–867, http://dx.doi.org/10.1007/978-1-4615-5359-5_121.

[12] S. Srinivasan, K. Menzies, L. Sorbara, L. Jones, Infrared imaging of meibomian gland structure using a novel keratograph, Optom. Vis. Sci. 89 (2012) 788–794, http://dx.doi.org/10.1097/OPX.0b013e318253de93.

[13] H. Pult, B.H. Riede-Pult, Non-contact meibography: keep it simple but effective, Contact Lens Anterior Eye 35 (2012) 77–80, http://dx.doi.org/10.1016/j.clae.2011.08.003.

[14] H. Pult, B.H. Riede-Pult, J.J. Nichols, Relation between upper and lower lids' meibomian gland morphology, tear film, and dry eye, Optom. Vis. Sci. 89 (2012) E310–E315, http://dx.doi.org/10.1097/OPX.0b013e318244e487.

[15] J.P. Craig, I. Singh, A. Tomlinson, P.B. Morgan, N. Efron, The role of tear physiology in ocular surface temperature, Eye 14 (2000) 635–641, http://dx.doi.org/10.1038/eye.2000.156.

[16] J.P. Craig, A. Tomlinson, Importance of the lipid layer in human tear film stability and evaporation, Optom. Vis. Sci. 74 (1997) 8–13, http://dx.doi.org/10.1097/00006324-199701000-00014.

[17] C. Baudouin, E.M. Messmer, P. Aragona, G. Geerling, Y.A. Akova, J. Benítez-del-Castillo, K.G. Boboridis, J. Merayo-Lloves, M. Rolando, M. Labetoulle, Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction, Br. J. Ophthalmol. 100 (2016) 300–306, http://dx.doi.org/10.1136/bjophthalmol-2015-307415.

[18] K.K. Nichols, G.N. Foulks, A.J. Bron, B.J. Glasgow, M. Dogru, K. Tsubota, M.A. Lemp, D.A. Sullivan, The international workshop on meibomian gland dysfunction: executive summary, Investig. Opthalmol. Vis. Sci. 52 (2011) 1922, http://dx.doi.org/10.1167/iovs.10-6997a.

[19] A. Tomlinson, A.J. Bron, D.R. Korb, S. Amano, J.R. Paugh, E. Ian Pearce, R. Yee, N. Yokoi, R. Arita, M. Dogru, The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee, Investig. Ophthalmol. Vis. Sci. 52 (2011) 2006–2049, http://dx.doi.org/10.1167/iovs.10-6997f.

[20] A.R. Thode, R.A. Latkany, Current and emerging therapeutic strategies for the treatment of meibomian gland dysfunction (MGD), Drugs 75 (2015) 1177–1185, http://dx.doi.org/10.1007/s40265-015-0432-8.

[21] X. Yan, Emerging treatment options for meibomian gland dysfunction, Clin. Ophthalmol. 7 (2013) 1797, http://dx.doi.org/10.2147/OPTH.S33182.

[22] C.J. Nien, S. Massei, G. Lin, C. Nabavi, J. Tao, D.J. Brown, J.R. Paugh, J.V. Jester, Effects of age and dysfunction on human meibomian glands, Arch. Ophthalmol. 129 (2011) 462–469, http://dx.doi.org/10.1001/archophthalmol.2011.69.

[23] J.V. Jester, G.J. Parfitt, D.J. Brown, Meibomian gland dysfunction: hyperkeratinization or atrophy? BMC Ophthalmol. 15 (Suppl. 1) (2015) 156, http://dx.doi.org/10.1186/s12886-015-0132-x.

[24] J.V. Greiner, Thermal pulsation system treatment improves meibomian gland function and reduces dry eye symptoms for 9 months, Curr. Eye Res. 37 (2012) 272–278, http://dx.doi.org/10.3109/02713683.2011.631721.

[25] J.V. Greiner, Long-term (12-month) improvement in meibomian gland function and reduced dry eye symptoms with a single thermal pulsation treatment, Clin. Exp.

Ophthalmol. 41 (2013) 524–530, http://dx.doi.org/10.1111/ceo.12033.
[26] J.P. Craig, Y.-H. Chen, P.R.K. Turnbull, Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction, Invest. Ophthalmol. Vis. Sci. 56 (2015) 1965–1970, http://dx.doi.org/10.1167/iovs.14-15764.
[27] L.S. Mengher, K.S. Pandher, a J. Bron, Non-invasive tear film break-up time: sensitivity and specificity, Acta Ophthalmol. 64 (1986) 441–444, http://dx.doi.org/10.1111/j.1755-3768.1986.tb06950.x.
[28] N. Yokoi, M. Uchino, Y. Uchino, M. Dogru, M. Kawashima, A. Komuro, Y. Sonomura, H. Kato, K. Tsubota, S. Kinoshita, Importance of tear film instability in dry eye disease in office workers using visual display terminals: the osaka study, Am. J. Ophthalmol. 159 (2015) 748–754, http://dx.doi.org/10.1016/j.ajo.2014.12.019.
[29] N. Yokoi, Y. Takehhisa, S. Kinoshita, Correlation of tear lipid layer interference patterns with the diagnosis and severity of dry eye, Am. J. Ophthalmol. 122 (1996) 818–824, http://dx.doi.org/10.1016/S0002-9394(14)70378-2.
[30] G.N. Foulks, The correlation between the tear film lipid layer and dry eye disease, Surv. Ophthalmol. 52 (2007) 369–374, http://dx.doi.org/10.1016/j.survophthal.2007.04.009.
[31] H. Pult, B.H. Riede-Pult, C. Purslow, A comparison of an eyelid-warming device to traditional compress therapy, Optom. Vis. Sci. 89 (2012) 1035–1041, http://dx.doi.org/10.1097/OPX.0b013e31825c3479.
[32] J.P. Craig, K. Blades, S. Patel, Tear lipid layer structure and stability following expression of the meibomian glands, Ophthalmic Physiol. Opt. 15 (1995) 569–574, http://dx.doi.org/10.1016/0275-5408(95)00071-K.
[33] C.A. Blackie, D.R. Korb, Recovery time of an optimally secreting meibomian gland, Cornea 28 (2009) 293–297, http://dx.doi.org/10.1097/ICO.0b013e31818913b4.
[34] M. Norn, Meibomian orifices and Marx's line studied by triple vital staining, Acta Ophthalmol. 63 (1985) 698–700, http://dx.doi.org/10.1111/j.1755-3768.1985.tb01584.x.
[35] C.A. Blackie, D.R. Korb, The diurnal secretory characteristics of individual meibomian glands, Cornea 29 (2010) 34–38, http://dx.doi.org/10.1097/ICO.0b013e3181ac9fd0.
[36] K.K. Nichols, J.J. Nichols, G.L. Mitchell, The lack of association between signs and symptoms in patients with dry eye disease, Cornea 23 (2004) 762–770, http://dx.doi.org/10.1097/01.ico.0000133997.07144.9e.
[37] M.E. Johnson, The association between symptoms of discomfort and signs in dry eye, Ocul. Surf. 7 (2009) 199–211, http://dx.doi.org/10.1016/S1542-0124(12)70187-8.
[38] B.D. Sullivan, L.A. Crews, E.M. Messmer, G.N. Foulks, K.K. Nichols, P. Baenninger, G. Geerling, F. Figueiredo, M.A. Lemp, Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications, Acta Ophthalmol. 92 (2014) 161–166, http://dx.doi.org/10.1111/aos.12012.