Effects of Eyelid Warming Devices on Tear Film Parameters in Normal Subjects and Patients with Meibomian Gland Dysfunction

REIKO ARITA, MD, PHD,[1,2,3,4] NAOYUKI MORISHIGE, MD, PHD,[4,5] RIKA SHIRAKAWA, MD, PHD,[2,4] YOICHI SATO, CO,[6] AND SHIRO AMANO, MD, PHD[7,8]

ABSTRACT **Purpose: To evaluate the effects of commercially available eyelid warming devices on ocular temperatures, tear film function, and meibomian glands in normal subjects and patients with meibomian gland dysfunction (MGD). Methods: Ten healthy volunteers were enrolled to evaluate the effects of a single warming and of repeated warming for 2 weeks. Ten MGD patients were enrolled for evaluation of repeated warming over 1 month. Two non-wet (Azuki no Chikara, Eye Hot R) and three wet (hot towel, Hot Eye Mask, Memoto Este) devices were compared in a masked manner. Visual analog scale (VAS) score for ocular symptoms, tear film breakup time (TFBUT), meibum grade, temperatures (eyelid skin, tarsal conjunctiva, central cornea), Schirmer test value, and meibomian gland area were measured before and after warming application. Results: The single application of the five warming devices improved the VAS score, TFBUT, and ocular temperatures. In the repeated warming application, Azuki no Chikara as a representative non-wet warming device induced a stable and significant improvement in TFBUT and increased the tarsal conjunctival temperature and meibomian gland area in both normal subjects and MGD patients. It also improved meibum grade in MGD patients. Conclusion: Our results suggest that repeated eyelid warming with a non-wet device improves tear film function in normal individuals and may have beneficial effects on both tear film and meibomian gland function in MGD patients.**

KEY WORDS **dry eye, eyelid warming, meibomian gland, meibomian gland dysfunction, meibography, tear film**

I. INTRODUCTION

Meibomian gland dysfunction (**MGD**) is a chronic abnormality of the meibomian glands characterized by terminal duct obstruction or qualitative or quantitative changes in glandular secretion.[1] It can result in changes to the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.[1] MGD is common and yet is often overlooked in ophthalmic practice. Population-based studies have suggested that the prevalence of MGD is higher in Asian than in other populations, with reported prevalence of 46.2% in Thailand,[2] 60.8% in Taiwan,[3] 61.9% in Japan,[4] and 69.3% in China.[5] In a study performed in the U.S.A. and Europe, more than 80% of patients with dry were found to have MGD.[6]

The application of a warm compress to the eyelids is a standard treatment for obstructive MGD.[7] The surface temperature of the eyelids ranges between 33° and 37°C, whereas the melting range of expressed meibum is between 19.5° and 33.8°C in normal individuals[8-11] and between 32.2° and 35.3°C in patients with MGD.[9,11-14] In individuals with MGD, meibum consists of a mixture of melted lipid and desquamated, keratinized epithelial cells, which probably explains the difference in melting range between normal individuals and MGD patients.[9,15] Nuclear magnetic resonance analysis has revealed that lipid phase-transition temperatures of meibum are substantially higher (+4°C)

Accepted for publication April 2015.

From the [1]Department of Ophthalmology, Itoh Clinic, Saitama, [2]Department of Ophthalmology, The University of Tokyo, Tokyo, [3]Department of Ophthalmology, Keio University, Tokyo, [4]Lid and Meibomian Gland Working Group, Japan, [5]Department of Ophthalmology, Yamaguchi University Graduate School of Medicine, Yamaguchi, [6]Yamaguchi University Hospital, Yamaguchi, [7]Inoue Eye Hospital, Tokyo, and [8]Miyata Eye Hospital, Miyazaki, Japan.

Financial support: None.

The authors have no commercial or proprietary interest in any concept or product discussed in this article.

Single-copy reprint requests to Reiko Arita, MD, PhD (address below).

Corresponding author: Reiko Arita, MD, PhD, Department of Ophthalmology, Itoh Clinic, 626-11 Minami-Nakano, Minuma, Saitama, Saitama 337-0042, Japan. Tel: (814) 86865588. Fax: (814) 86868485. E-mail address: ritoh@za2.so-net.ne.jp

 The Ocular Surface ISSN: 1542-0124. Arita R, Morishige N, Shirakawa R, Sato Y, Amano S. Effects of eyelid warming devices on tear film parameters in normal subjects and patients with meibomian gland dysfunction. 2015;13(4):321-330.

in patients with MGD than in age-matched normal controls.[16] Eyelid temperature influences not only the secretion but also the delivery of meibum to the ocular surface.[16]

Previous studies have assessed the effects of various warming devices, including infrared devices,[17,18] a disposable eyelid warming device,[19] warm moist air devices,[20-22] and an Orgahexa fiber eyemask,[23] on tear function and the ocular surface. However, no study has previously compared the efficacies of such devices based on different warming mechanisms. We have compared the efficacies of five commercially available warming devices with regard to their effects on tear film function, meibomian glands, and the ocular surface in normal subjects. On the basis of the results obtained for a single warming application in normal subjects, we examined the effects of repeated warming over 2 weeks or 1 month with representative devices in normal subjects and patients with MGD, respectively.

II. METHODS

A. Subjects

Ten eyes of 10 healthy volunteers (5 men and 5 women; mean age ± SD, 33.9 ± 11.4 years) were enrolled for evaluation of a single warming application (for 5 minutes), and 10 eyes of 10 healthy volunteers (5 men and 5 women; mean age ± SD, 32.3 ± 11.7 years) were enrolled for evaluation of repeated warming (5 minutes twice a day for 2 weeks). Eight out of 10 subjects overlapped in the single and repeated warming evaluations. Ten eyes of 10 patients with obstructive MGD (2 men and 8 women; mean age ± SD, 75.6 ± 6.7 years) were also enrolled for evaluation of repeated warming (5 minutes twice a day for 1 month). These subjects were diagnosed with obstructive MGD on the basis of our previously applied criteria,[24] including the presence of ocular symptoms, at least one lid margin abnormality (irregular lid margin, vascular engorgement, plugged meibomian gland orifices, and anterior or posterior displacement of the mucocutaneous junction) as evaluated from edge to edge in upper and lower eyelids, and impaired meibum expression. These inclusion criteria enabled us to exclude the subjects with age-related meibomian gland changes as opposed to patients with MGD. Exclusion criteria for subjects included ocular allergies, contact lens wear for more than 1 year, a history of eye surgery, and systemic or ocular diseases (other than MGD for MGD patients) that might interfere with tear film production or function. Patients whose eyes showed excessive meibomian lipid secretion were also excluded.

Data were obtained from the right eye of each subject unless this eye did not meet the enrollment criteria, in which case data were obtained from the left eye. Written informed consent was obtained from all subjects before examination. The study was approved by the institutional review boards of Itoh Clinic, The University of Tokyo Hospital, and Yamaguchi University Hospital, and it adhered to the tenets of the Declaration of Helsinki.

B. Warming Devices

We evaluated five warming devices, including a hot towel (conventional towel widely available commercially), a disposable eyelid warming device (Hot Eye Mask; Kao, Tokyo, Japan), an electrical warming and massaging device (Memoto Este; Panasonic, Osaka, Japan), a warming eye pillow (Azuki no Chikara; Kiribai Chemical, Osaka, Japan), and an infrared eyelid warming goggle (Eye Hot R; Cept, Tokyo, Japan). On the basis of a subjective sense of skin wetness during or after warming, we divided these devices into two groups designated “wet warming” and “non-wet warming” (Table 1). This categorization was verified by measurement of the amount of residual water on the lid surface after removal of each device. Hot Eye Mask is a disposable sheet with a warming mechanism based on the oxidation of iron[19]; Memoto Este is an electrical massage and warming device equipped with a wet water sponge; Azuki no Chikara is a small pillow containing red beans that are warmed in a microwave oven; and Eye Hot R is equipped with a source of near-visible red light (wavelength of 700 nm) and is an improved version of the infrared-based Eye Hot device.[18,25]

The hot towel was microwaved at 500 W for 30 seconds before application. It was wrung sufficiently before application so that it did not leave obviously wet skin after eyelid warming. Hot Eye Mask was applied immediately after opening of each individual package. Memoto Este was applied after turning on the device. Azuki no Chikara was microwaved for 30 seconds at 500 W. Eye Hot R was applied immediately after turning on the light source. Non-warmed devices were applied as a control procedure for the measurements in the single warming protocol.

The surface temperature of the devices was measured with the use of an ocular surface thermographer (TG-1000; TOMEY, Nagoya, Japan) before and 5 minutes after microwaving or activation, and the temperature change

Table 1. Warming devices and mechanisms

Type	Device	Subjective wetness	Moisture supply (g/5 min)	Temperature change (°C/min)	Warming mechanism
Wet warming	Hot towel	Most	1.57 ± 0.76	−4.1 ± 0.7	Microwave-warmed wet towel
	Hot Eye Mask	Yes	0.08 ± 0.02	−2.7 ± 0.3	Oxidation of iron
	Memoto Este	Yes	0.07 ± 0.03	−0.7 ± 0.2	Electrical massaging and warming
Non-wet warming	Azuki no Chikara	No	0.00 ± 0.00	−1.2 ± 0.1	Microwave-warmed red beans
	Eye Hot R	No	0.00 ± 0.00	2.2 ± 0.2	Near-visible red light

Quantitative data are means ± SD from independent experiments for values obtained on three separate days.

is shown in Table 1. The temperature of each device was determined as the warmest temperature obtained from the measured area. The residual moisture left on the surface of the eyelid by each device after 5 minutes was also collected with conventional facial tissue paper (Kawano Seishi, Kochi, Japan) and measured by weight determination with an electric balance (Table 1). The temperature and moisture value for each warming device were determined as the mean ± SD for measurements obtained on three different days.

C. Study Protocols

1. Application of Warming Devices

The examiners (R.A., R.S., N.M., and Y.S.) were masked with regard to the warming device applied. For evaluation of the effects of a single application of the five devices in normal subjects, each warmed device was applied to each individual for 5 minutes on different days. The sequence of device application was determined in a pseudo-random manner by each subject. The examiner was waiting in an adjacent room during the warming application. A nurse or clinical research assistant removed the warming device, and the examiner then entered the subject's room to carry out the clinical evaluation immediately. Parameters related to the ocular surface, tear film, and meibomian glands were measured before as well as immediately after and 10 and 30 minutes after the removal of each device. Measurement of each ocular surface temperature was performed within 5 seconds, and tear film breakup time (**TFBUT**) was measured within 10 seconds. All examinations were completed within 1 minute.

After single application of the warmed devices, evaluation of the application of non-warmed devices was performed in a device-masked manner as described above. For evaluation of the effects of repeated warming in normal subjects, the subjects were instructed to apply Azuki no Chikara as a non-wet warming device for 5 minutes twice a day for 2 weeks. Two weeks after termination of this treatment, the subjects were instructed to apply a hot towel as a wet warming device for 5 minutes twice a day for 2 weeks. For evaluation of the effects of repeated warming in patients with MGD, the patients were instructed to apply Azuki no Chikara for 5 minutes twice a day for 1 month. Treatment with artificial tears that had been instituted before the study was not changed during this 1-month period.

2. Assessment of Ocular Symptoms

Ocular discomfort symptomatology was evaluated with the use of the visual analog scale (**VAS**), with the questionnaire addressing symptoms such as dryness sensation, foreign body sensation, and other ocular discomfort, and the scale ranging from 0 (no symptoms) to 100 (severe symptoms) points. The VAS was presented as a series of 10-cm lines, and the subjects were asked to check a point on each line corresponding to the extent of their symptoms both before and after eyelid warming.

3. Measurement of Eye Temperatures, Tear Film Parameters, and Meibomian Gland Morphology and Function

Examinations were performed sequentially both before and after eyelid warming for the single warming evaluation in normal subjects. Superficial punctate keratopathy (**SPK**) of the cornea was scored from 0 to 3 on the basis of fluorescein staining. TFBUT was measured three times consecutively after the instillation of 1 μl of 1% fluorescein with a micropipette, and the mean value was calculated. Eyelid skin, tarsal conjunctival, and central corneal temperatures were measured with the use of an ocular surface thermographer in a standard clinic room maintained at a relatively constant temperature (25.3° ± 1.2°C), humidity (41.2 ± 6.3%), and brightness (300 lux). The subjects were positioned in a standard ophthalmic chin- and head-rest and were instructed to look forward. The eyelid skin temperature was measured with both eyes shut, the tarsal conjunctival temperature was measured immediately after

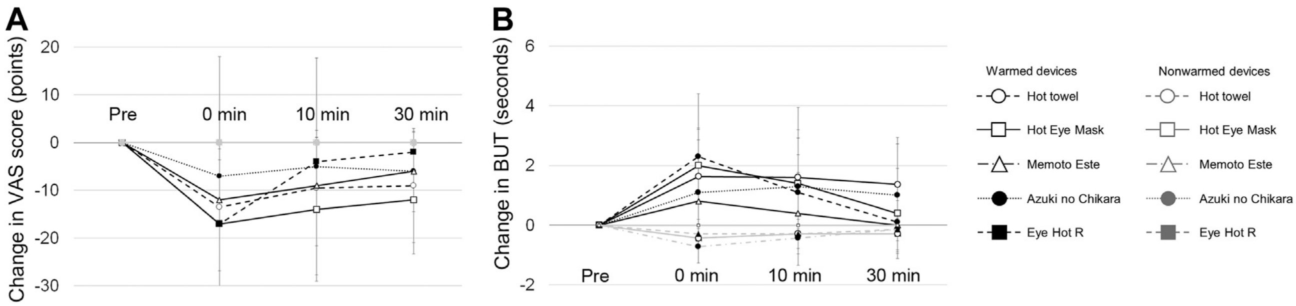

Figure 1. Time course of changes in VAS symptom score (A) and TFBUT (B) after a single application of warming devices for 5 minutes. Data are means ± SD for 10 eyes of 10 normal subjects.

the eyelid was turned over, and the central corneal temperature was measured under the condition of normal blinking. The surface temperature was not displayed until after the region for evaluation had been determined. The measurement was thus performed automatically and not subject to any bias.

For evaluation of repeated warming, the upper and lower eyelids were turned over and the meibomian glands were observed by noncontact meibography with a BG-4M instrument (TOPCON, Tokyo, Japan). The noncontact meibography system we developed allows us to observe all areas from the nasal to the lateral edge in both upper and lower eyelids.[26] Quantitative analysis of meibomian gland area was performed with the use of a newly developed program.[27] SPK score, TFBUT, meibum grade (MGD patients), Schirmer test value (for evaluation of tear film production without topical anesthesia), and eye surface temperatures (eyelid skin, tarsal conjunctiva, and central cornea) were also measured. For patients with MGD, digital pressure was applied to the upper tarsus, and meibum expression was evaluated semiquantitatively according to the following grades[4]: 0, clear meibum easily expressed; 1, cloudy meibum expressed with mild pressure; 2, cloudy meibum expressed with more than moderate pressure; and 3, meibum not expressed even with strong pressure. All analyses were performed both before (at least 1 day) the initial application of

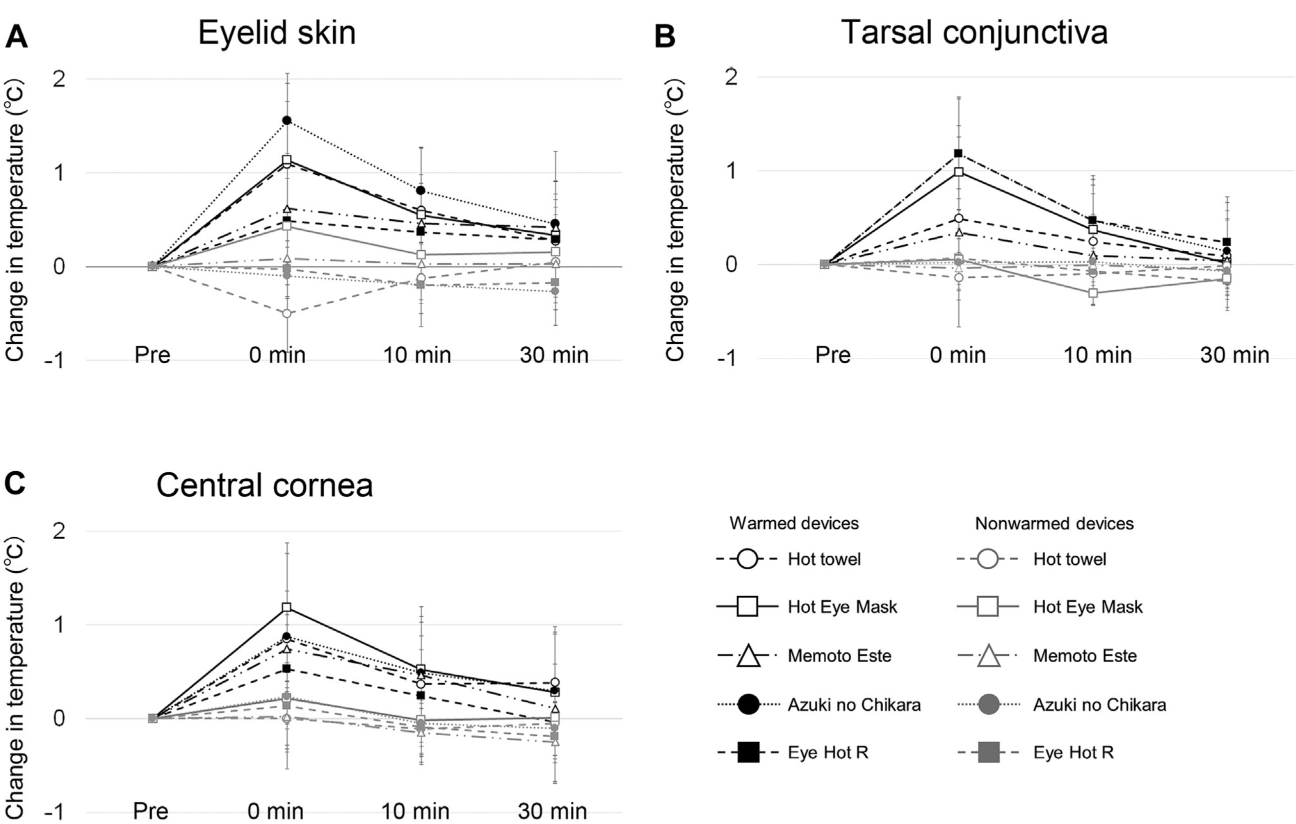

Figure 2. Time course of changes in surface temperature for eyelid skin (A), the tarsal conjunctiva (B), and the central cornea (C) after a single application of warming devices for 5 minutes. Data are means ± SD for 10 eyes of 10 normal subjects.

warming as well as during the daytime at least 8 hours after the final warming period in order to avoid an immediate effect of warming.

To minimize the effects of measurements on ocular surface parameters, we performed the clinical examinations in the following orders. For single warming, the order was: 1) SPK score, 2) TFBUT, 3) eyelid skin temperature, 4) central corneal temperature, and 5) tarsal conjunctival temperature. For repeated warming in normal and MGD subjects, the order was: 1) SPK score, 2) TFBUT, 3) eyelid skin temperature, 4) central corneal temperature, 5) tarsal conjunctival temperature, 6) noninvasive meibography, and 7) Schirmer test. In addition, as a final examination for repeated warming in patients with MGD, we assessed meibum grade.

D. Statistical Analysis

Data are presented as means ± SD. For evaluation of single warming application, changes in VAS score, TFBUT, or eye (eyelid skin, tarsal conjunctiva, or central cornea) surface temperatures between before and either immediately or 10 or 30 minutes after the warming period were assessed with the Wilcoxon signed rank sum test. Differences in the effects of the five devices were evaluated with the Friedman test. For evaluation of repeated warming, changes in SPK score, TFBUT, meibum grade, eye (eyelid skin, tarsal conjunctiva, or central cornea) surface temperatures, Schirmer test value, or meibomian gland area were assessed with the paired Student's t test. A P value of $<.05$ was considered statistically significant.

III. RESULTS

A. Evaluation of Single Warming Application

The VAS score showed significant ($P<.05$) improvement immediately after application of each warmed device for 5 minutes (Figure 1A). Hot Eye Mask and Azuki no Chikara also significantly ($P<.05$) improved the VAS score at 30 minutes after warming.

No corneal staining was apparent before or after application of any of the warmed devices. TFBUT was significantly ($P<.05$) prolonged immediately after the application of warmed Hot Eye Mask, Azuki no Chikara, or Eye Hot R for 5 minutes as well as at 10 minutes after the removal of Hot Eye Mask (Figure 1B).

The surface temperature of eyelid skin was significantly increased immediately after the application of each of the five warmed devices for 5 minutes ($P<.01$) as well as at 10 minutes after the removal of the hot towel ($P<.05$), Hot Eye Mask ($P < .01$), Azuki no Chikara ($P<.01$), or Eye Hot R ($P<.05$) and at 30 minutes after the removal of Azuki no Chikara ($P<.01$) (Figure 2A). The surface temperature of the tarsal conjunctiva was significantly ($P<.01$) increased immediately after application of Hot Eye Mask, Azuki no Chikara, or Eye Hot R for 5 minutes as well as at 10 minutes after the removal of Azuki no Chikara or Eye Hot R (Figure 2B). The surface temperature of the central cornea was significantly increased immediately after application of the hot towel, Hot Eye Mask, Memoto Este, or Azuki no Chikara for 5 minutes ($P<.01$), and it was significantly increased at 10 minutes after the removal of Hot Eye Mask, Memoto Este, or Azuki no Chikara ($P<.01$, $P<.05$, and $P<.05$, respectively) as well as at 30 minutes after the removal of Hot Eye Mask ($P<.05$) (Figure 2C). Figure 3 shows representative images of the changes in eye surface temperatures apparent immediately as well as 10 and 30 minutes after the application of warmed Azuki no Chikara for 5 minutes. Compared with the preapplication image, the image obtained immediately after warming shows an increased temperature of eye tissue, including the eyelid skin, tarsal conjunctiva, and cornea. The images obtained at 10 and 30 minutes after warming reveal a gradual cooling of surface temperatures.

Non-warmed devices examined as a control had no significant effects on either TFBUT (Figure 1B) or eye temperatures (Figure 2) compared with baseline for each device application. There was no significant difference among the effects of the five warmed devices on the VAS score, TFBUT, or eye surface temperatures. Warmed device applications were significantly more effective in some parameters than non-warmed devices applications (Table 2).

B. Evaluation of Repeated Warming in Normal Subjects

The application of Azuki no Chikara as a representative non-wet warming device to normal subjects for 5 minutes twice a day for 2 weeks resulted in a significant improvement in TFBUT, as well as a significant increase in the temperature of the tarsal conjunctiva measured at ∼8 hours after the last warming period (Table 3). It also resulted in a significant increase in meibomian gland area (Table 3). In contrast, similar application of a hot towel as a representative wet-warming device for 2 weeks did not significantly affect any of the measured parameters (Table 4).

C. Evaluation of Repeated Warming in Patients with MGD

Our results for single and repeated warming indicated that repeated application of a non-wet warming device resulted in a stable improvement in the condition of the tear film. We therefore selected Azuki no Chikara as a representative non-wet warming device for application (5 minutes twice a day for 1 month) to patients with MGD. This procedure significantly improved SPK score, TFBUT, and meibum grade, and it significantly increased the temperature of the tarsal conjunctiva measured at ∼8 hours after the last warming period (Table 5). The Schirmer test value was significantly reduced after the 1-month treatment period (Table 5), whereas the meibomian gland area was significantly increased (Table 5, Figure 4).

IV. DISCUSSION

We evaluated the effects of eyelid warming devices on clinical parameters related to the tear film. A single application of each warming device to normal subjects induced a transient improvement in VAS score, TFBUT, and eye surface temperatures, with most of these effects not persisting

Table 2. Statistical analysis comparing between warmed and nonwarmed devices

	VAS score			TFBUT		
Devices	**0 min**	**10 min**	**30 min**	**0 min**	**10 min**	**30 min**
Hot Towel	0.011	0.035	0.041	0.182	0.955	0.885
Hot Eye Mask	0.003	0.016	0.009	0.001	0.005	0.223
Memoto Esthe	0.074	0.041	0.111	0.216	0.240	0.701
Azuki no Chikara	0.398	0.504	0.051	0.011	0.070	0.071
Eye Hot R	0.008	0.037	0.168	0.028	0.066	0.847
	Eyelid skin temperature			Tarsal conjunctival temperature		
Hot Towel	<0.001	0.013	0.382	0.018	0.117	0.042
Hot Eye Mask	0.062	0.042	0.260	0.002	0.003	0.029
Memoto Esthe	0.085	0.198	0.248	0.002	0.028	0.362
Azuki no Chikara	<0.001	0.001	0.008	0.169	0.079	0.187
Eye Hot R	0.013	0.031	0.052	0.139	0.101	0.374
	Central corneal temperature					
Hot Towel	0.050	0.163	0.453			
Hot Eye Mask	<0.001	0.002	0.438			
Memoto Esthe	0.034	0.594	0.563			
Azuki no Chikara	0.012	0.106	0.216			
Eye Hot R	<0.001	<0.001	0.025			

Data are *p* value compared between the applications of warmed devices and that of nonwarmed devices.

for longer than 30 minutes. Repeated warming with Azuki no Chikara as a non-wet warming device significantly improved TFBUT and increased tarsal conjunctival temperature and meibomian gland area in normal subjects. These effects were still apparent at ∼8 hours after the last application, whereas repeated application of a hot towel as a wet-warming device had no such beneficial effects compared with baseline values. Furthermore, repeated warming with Azuki no Chikara in patients with MGD also resulted in a significant and lasting improvement in SPK score, TFBUT, meibum grade, tarsal conjunctival temperature, and meibomian gland area compared with baseline values. Our results

Table 3. Comparison of tear film—related parameters and eye surface temperatures between before and after repeated non-wet warming with Azuki no Chikara for 2 weeks in normal subjects

Parameter	Before	After	*P*
TFBUT (seconds)	4.0 ± 1.5	7.1 ± 1.9	<.001*
Eyelid skin temp. (°C)	33.7 ± 0.6	33.8 ± 0.6	.312
Tarsal conjunctival temp. (°C)	33.2 ± 0.7	34.2 ± 0.7	<.001*
Central corneal temp. (°C)	33.7 ± 0.5	33.7 ± 0.7	.394
Schirmer test value (mm)	19.6 ± 11.3	20.2 ± 11.5	.647
Meibomian gland area (%)	72.0 ± 17.8	79.1 ± 17.2	.009*

Data are means ± SD for 10 eyes of 10 subjects. *P* values were determined with the paired Student's *t* test, and those of <0.05 are indicated with an asterisk. Temp., temperature.

Table 4. Comparison of tear film–related parameters and eye surface temperatures between before and after repeated wet warming with a hot towel for 2 weeks in normal subjects

Parameter	Before	After	*P*
TFBUT (seconds)	6.4 ± 2.0	5.6 ± 2.0	.281
Eyelid skin temp. (°C)	33.9 ± 0.8	33.6 ± 1.5	.103
Tarsal conjunctival temp. (°C)	33.6 ± 0.9	33.6 ± 1.1	.670
Central corneal temp. (°C)	33.9 ± 1.0	33.9 ± 1.1	.842
Schirmer test value (mm)	21.0 ± 11.3	18.2 ± 9.0	.251
Meibomian gland area (%)	68.0 ± 18.4	68.4 ± 19.1	.788

Data are means ± SD for 10 eyes of 10 subjects. *P* values were determined with the paired Student's *t* test.

have thus revealed that repeated warming, in particular non-wet warming, improves the condition of the tear film both in normal subjects and in patients with MGD.

Our evaluation of a single warming application in normal subjects revealed that all five warming devices induced a temporary improvement in ocular conditions, consistent with the widespread use of a warm compress to treat MGD. However, the effects of a single application of each of the devices examined in the present study tended to have diminished by 10 minutes after device removal and had largely disappeared at 30 minutes, indicating that a single warming episode is insufficient for lasting improvement in the condition of the tear film. Interestingly, the VAS score for ocular discomfort decreased in normal subjects after device application, indicative of a change in subjective symptoms between before and after the procedure. Warming provides a sense of comfort and may thus improve the score even in normal subjects.

Our evaluation of repeated warming in normal subjects revealed that non-wet warming with Azuki no Chikara increased meibomian gland area, suggesting that this procedure may stimulate meibum production and thereby promote formation of the oily layer on the surface of the tear film and prolong TFBUT. Given that measurements for repeated warming were performed during the daytime at ~8 hours after the last device application, the observed effects of the repeated warming were relatively stable. Our results thus suggest that non-wet warming at least twice daily for 2 weeks may be required to improve the oily layer of the tear film.

On the other hand, repeated wet warming with a hot towel did not improve TFBUT, eye temperatures, or meibomian gland area in normal subjects. The categorization of warming devices as wet or non-wet was based on the subjective sensation of wetness during or after the warming procedure and was confirmed by measurement of the moisture supplied by each device to the eyelid. Wetness of the surface of the eyelid skin may result in evaporative cooling and thereby limit the beneficial effects of warming. In addition, we found that the temperature of the hot towel itself decreased at a rate of 4.1°C/minute over the initial 5 minutes after its removal from the microwave oven. It was previously shown to be difficult to maintain the temperature of a hot towel at >32°C (the melting point of meibum in

Table 5. Comparison of tear film–related parameters and eye surface temperatures between before and after repeated non-wet warming with Azuki no Chikara for 1 month in patients with MGD

Parameter	Before	After	*P*
TFBUT (seconds)	2.3 ± 0.7	4.8 ± 2.4	0.014*
Meibum grade	2.2 ± 0.4	1.0 ± 0.7	<.001*
Eyelid skin temp. (°C)	33.5 ± 0.5	33.5 ± 0.5	.833
Tarsal conjunctival temp. (°C)	33.0 ± 0.8	33.6 ± 0.8	.004*
Central corneal temp. (°C)	33.7 ± 0.6	33.7 ± 0.5	.874
Schirmer test value (mm)	11.1 ± 7.4	9.9 ± 6.3	.024*
Meibomian gland area (%)	54.5 ± 9.6	64.1 ± 9.3	<.001*
SPK score	1.3 ± 0.5	0.5 ± 0.7	.003*

Data are means ± SD for 10 eyes of 10 subjects. *P* values were determined with the paired Student's *t* test, and those of <.05 are indicated with an asterisk.

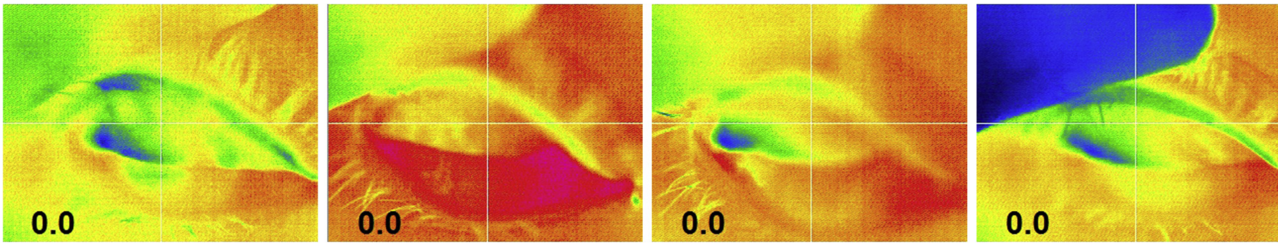

Figure 3. Representative ocular thermography images obtained before (left) as well as immediately (middle left), 10 minutes (middle right), and 30 minutes (right) after a single application of the Azuki no Chikara warming device for 5 minutes in a normal subject. Color scale from red to blue corresponds to warm and cool temperatures, respectively.

many normal individuals) for at least 5 minutes.[12] Conventional warm compress therapy maintains an increased eye temperature by repeated changing of the towel.[28-30] At a temperature of >42°C, a hot towel was shown to induce the Fischer-Schweitzer polygonal reflex,[28] which is the same as anterior corneal mosaic described by Bron.[31-33] Moreover, warm compress therapy with a towel and massage is associated with the risk of an elevated corneal temperature.[34] Together, these various observations suggest that wet warming may be less effective than non-wet warming for warming of the eyelids.

Our data suggest that repeated application of a non-wet warming device is effective for eyelid warming. For daily use, a warming device that warms eyelid skin through to the tarsal conjunctiva without corneal heating is preferred. Although the tarsal conjunctiva and cornea are positioned close to each other, we found that repeated application of Azuki no Chikara resulted in an increase in tarsal conjunctival temperature without an increase in the central corneal temperature. We have previously shown that the conjunctival temperature was significantly lower in MGD patients than in normal subjects, whereas the corneal temperature did not differ between the two groups, indicating that blood flow in the eyelids of patients with MGD is subclinically decreased compared with that in normal subjects.[35] In this previous study and in our present study, we applied an ocular surface thermographer (TG-1000) to measure ocular surface temperatures. We thus speculate that the tarsal conjunctiva may be able to maintain an increased temperature as a result of blood circulation, whereas the avascular cornea cannot. Our present data obtained with healthy subjects suggest that repeated eyelid warming may be beneficial as a prophylactic approach to improve the condition of the tear film and to prevent meibomian gland disease. Given that the risk factors for MGD remain unknown, however, it is difficult to predict the occurrence of MGD. Population-wide prevention of cardiovascular diseases is possible with a well-controlled prevention program.[36] The development of similar programs for prevention of MGD warrants further study.

We selected the sequence of clinical examinations performed after warming device application so as to minimize the effects of the procedures themselves on the measured parameters. Given that contact with the eyelid may have a massage-like effect and thereby prolong TFBUT, we measured TFBUT before we measured ocular surface temperatures. Furthermore, the subjects held the fluorescein solution in a 1.5-ml tube before its instillation in order to ensure that it was at body temperature rather than room

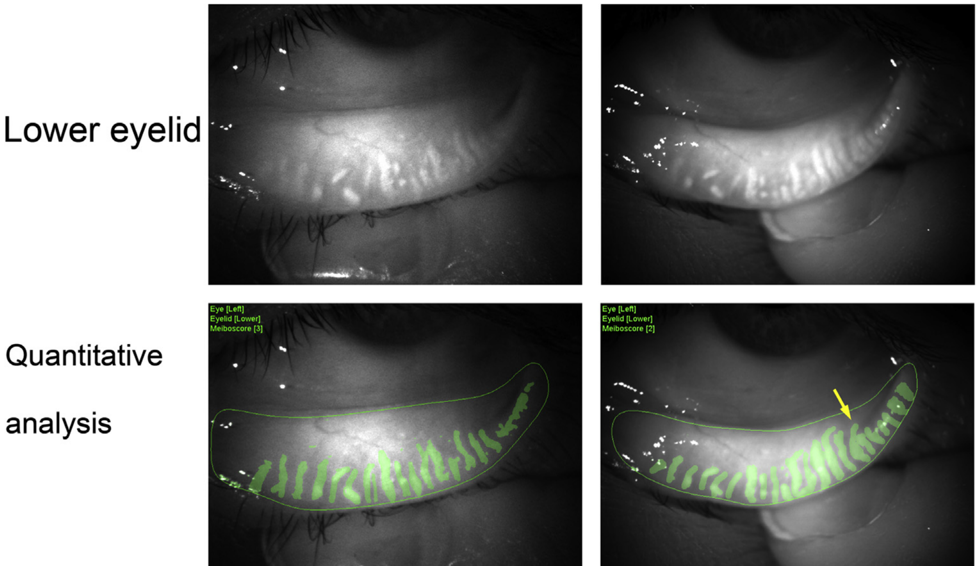

Figure 4. Representative images of a patient with MGD obtained by noninvasive meibography before and after repeated application of Azuki no Chikara for 1 month. Quantitative analysis revealed that warming increased the meibomian gland area of the lower eyelid from 19.5% to 28.2%.

temperature. We measured the central corneal temperature before the tarsal conjunctival temperature, because measurement of the latter requires that the eyelid be flipped over, possibly affecting tear distribution as well as the central corneal temperature. Noninvasive meibography was performed after measurement of ocular temperatures.

The enrollment of normal subjects in the present study did not exclude individuals who had worn disposable contact lenses for less than 1 year. During enrollment of such subjects, we attempted to exclude individuals with suggestive abnormalities of meibomian glands by checking for subjective symptoms, lid margin defects, reduced secretion of meibum, and qualitative changes to meibum. We did not detect any such abnormalities in any of the enrolled normal subjects, including the one individual who wore disposable contact lenses. We previously showed that contact lens wear affected meibomian gland morphology and that changes to meibomian glands were related not to the type of contact lens worn but to the wearing time. The meibomian gland area in wearers of hard contact lenses tended to be smaller than that in wearers of soft contact lenses, but this difference was not statistically significant.[37] A general consensus that contact lens wear affects meibomian glands or induces MGD has not been achieved, however, despite the many studies that have examined the relation between the wearing of contact lenses and meibomian gland changes.[38] We therefore included disposable contact lens users with a wearing history of less than 1 year as normal subjects. Given the large number of contact lens wearers, the inclusion of such individuals as normal subjects in studies like the present one seems reasonable.

We have also now shown that repeated warming with Azuki no Chikara improved clinical parameters such as TFBUT, meibum grade, tarsal conjunctival temperature, meibomian gland area, and SPK score in patients with MGD, indicating that such warming might be effective for the treatment of this condition. Eyelid warming is recommended as primary care for MGD patients.[7] Our data now provide practical information regarding the application of eyelid warming for such patients, suggesting that it should be performed repeatedly, with a non-wet warming device, and for at least 1 month. LipiFlow (Tear Science, Morrisville, NC) was introduced as an ideal theoretical device for the treatment of MGD.[39,40] The effects of a single LipiFlow treatment including an increase in eyelid temperature were found to persist for more than 9 months.[41,42] A more recent study showed that repeated eyelid warming with massage improved objective signs such as the lid margin condition in patients with MGD to an extent similar to that observed with a single LipiFlow treatment.[43] Lipiflow treatment is performed in hospital clinics, whereas warming procedures can be performed daily by patients themselves at home.

Meibomian gland area detected by meibography was recently shown to correlate with the thickness of the oily layer of the tear film as evaluated with LipiView (Tear Science).[44] Although current settings for meibomian gland imaging in vivo do not allow evaluation of the volume of meibum inside meibomian glands, they are sufficient to provide an indirect index of meibomian gland function. We have also developed methodology for quantitative evaluation of meibography images[27] and have applied such quantitation in the present study, revealing it to be sufficient for statistical analysis. Indeed, the difference in meibomian gland area between baseline and after repeated warming with Azuki no Chikara was 7.1% and 9.6% in normal subjects and patients with MGD, respectively. We previously found that the variance of repeated examinations in the same subjects ranged from 0.40% to 0.59%,[27] an order of magnitude less than the differences between before and after treatment in the present study.

Given the relatively small number of patients with MGD enrolled in the present study, it was not possible to classify them according to the severity of disease or age. Nevertheless, our results have shown that repeated warming was effective for the amelioration of MGD. Future clinical investigations with larger numbers of subjects should provide more detailed information on the treatment of MGD by repeated eyelid warming.

Clinical examinations related to the condition of the tear film, such as measurement of TFBUT, are subjective to a certain degree and therefore susceptible to bias. In the single-application protocol, examiners were completely masked regarding the applied devices. However, we were not able to mask the examinations as to whether the devices were warmed or not warmed because the application of non-warmed devices was introduced as a control late in the study. The comparison between the application with warmed devices and that with non-warmed devices demonstrated varied significance immediately and 10 minutes after application; however, the significance was decreased 30 minutes after application, indicating that the single warming effect was possibly regressive. Although this lack of masking may potentially have affected the TFBUT results, it is unlikely to have influenced the objective measurement of ocular temperatures. In addition, we did not set a non-warmed control for the repeated warming protocols in normal subjects and MGD patients. Instead, we examined the effects of the two representative devices by comparing baseline and post-warming values of the measured parameters. Although such comparisons are potentially subject to regression-to-the-mean effects, the improvement in objective parameters such as tarsal conjunctival temperature and meibomian gland area suggest that repeated eyelid warming with Azuki no Chikara was effective for the treatment of MGD.

V. CONCLUSION

A single application of commercially available eyelid warming devices provides a temporary improvement in tear film condition. Repeated non-wet warming for 2 weeks or 1 month was required to achieve a stable improvement in the tear film associated with an increase in meibomian gland area in normal subjects and patients with MGD, respectively. Further masked and well-controlled studies are warranted to confirm our provisional results in larger numbers of subjects.

REFERENCES

1. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. *Invest Ophthalmol Vis Sci* 2011;52:1922-9
2. Lekhanont K, Rojanaporn D, Chuck RS, Vongthongsri A. Prevalence of dry eye in Bangkok, Thailand. *Cornea* 2006;25:1162-7
3. Lin PY, Tsai SY, Cheng CY, et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology* 2003;110:1096-101
4. Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. *Arch Ophthalmol* 1995;113:1266-70
5. Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. *Eye* 2009;23:688-93
6. Lemp MA, Crews LA, Bron AJ, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea* 2012;31:472-8
7. Geerling G, Tauber J, Baudouin C, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci* 2011;52:2050-64
8. Borchman D, Foulks GN, Yappert MC, et al. Human meibum lipid conformation and thermodynamic changes with meibomian-gland dysfunction. *Invest Ophthalmol Vis Sci* 2011;52:3805-17
9. Terada O, Chiba K, Senoo T, Obara Y. Ocular surface temperature of meibomian gland dysfunction patients and the melting point of meibomian gland secretions. *Nippon Ganka Gakkai zasshi* 2004;108:690-3
10. Foulks GN. The correlation between the tear film lipid layer and dry eye disease. *Surv Ophthalmol* 2007;52:369-74
11. Morgan PB, Tullo AB, Efron N. Infrared thermography of the tear film in dry eye. *Eye* 1995;9(Pt 5):615-8
12. McCulley JP, Shine WE. Meibomian secretions in chronic blepharitis. *Adv Exp Med Biol* 1998;438:319-26
13. Borchman D, Foulks GN, Yappert MC, et al. Spectroscopic evaluation of human tear lipids. *Chem Phys Lipids* 2007;147:87-102
14. Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. *Ocul Surf* 2004;2:149-65
15. Miyashita K. Smear cytology of meibomian secretion. *Jpn J Clin Ophthalmolol* 1991;45:1017-9
16. Nagymihalyi A, Dikstein S, Tiffany JM. The influence of eyelid temperature on the delivery of meibomian oil. *Exp Eye Res* 2004;78:367-70
17. Goto E, Monden Y, Takano Y, et al. Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device. *Br J Ophthalmol* 2002;86:1403-7
18. Mori A, Oguchi Y, Goto E, et al. Efficacy and safety of infrared warming of the eyelids. *Cornea* 1999;18:188-93
19. Mori A, Shimazaki J, Shimmura S, et al. Disposable eyelid-warming device for the treatment of meibomian gland dysfunction. *Jpn J Ophthalmol* 2003;47:578-86
20. Matsumoto Y, Dogru M, Goto E, et al. Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction. *Cornea* 2006;25:644-50
21. Pult H, Riede-Pult BH, Purslow C. A comparison of an eyelid-warming device to traditional compress therapy. *Optom Vis Sci* 2012;89:E1035-41
22. Mitra M, Menon GJ, Casini A, et al. Tear film lipid layer thickness and ocular comfort after meibomian therapy via latent heat with a novel device in normal subjects. *Eye* 2005;19:657-60
23. Ishida R, Matsumoto Y, Onguchi T, et al. Tear film with "Orgahexa EyeMasks" in patients with meibomian gland dysfunction. *Optom Vis Sci* 2008;85:684-91
24. Arita R, Itoh K, Maeda S, et al. Proposed diagnostic criteria for obstructive meibomian gland dysfunction. *Ophthalmology* 2009;116: 2058-63. e1
25. Goto E, Endo K, Suzuki A, et al. Improvement of tear stability following warm compression in patients with meibomian gland dysfunction. *Adv Exp Med Biol* 2002;506:1149-52
26. Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. *Ophthalmology* 2008;115:911-5
27. Arita R, Suehiro J, Haraguchi T, et al. Objective image analysis of the meibomian gland area. *Br J Ophthalmol* 2014;98:746-55
28. Solomon JD, Case CL, Greiner JV, et al. Warm compress induced visual degradation and Fischer-Schweitzer polygonal reflex. *Optom Vis Sci* 2007;84:580-7
29. Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye Contact Lens* 2003;29:96-9
30. Blackie CA, Solomon JD, Greiner JV, et al. Inner eyelid surface temperature as a function of warm compress methodology. *Optom Vis Sci* 2008;85:675-83
31. Bron AJ. Anterior corneal mosaic. *Br J Ophthalmol* 1968;52:659-69
32. Bron AJ. Photography of corneal pattern. *Arch Ophthalmol* 1968;79: 119-20
33. Bron AJ, Tripathi RC. Anterior corneal mosaic. Further observations. *Br J Ophthalmol* 1969;53:760-4
34. Blackie CA, McMonnies CW, Korb DR. Warm compresses and the risks of elevated corneal temperature with massage. *Cornea* 2013;32: e146-9
35. Arita R, Shirakawa R, Maeda S, et al. Decreased surface temperature of tarsal conjunctiva in patients with meibomian gland dysfunction. *JAMA Ophthalmol* 2013;131:818-9
36. Record NB, Onion DK, Prior RE, et al. Community-wide cardiovascular disease prevention programs and health outcomes in a rural county, 1970-2010. *JAMA* 2015;313:147-55
37. Arita R, Itoh K, Inoue K, et al. Contact lens wear is associated with decrease of meibomian glands. *Ophthalmology* 2009;116:379-84
38. Efron N, Jones L, Bron AJ, et al. The TFOS International Workshop on Contact Lens Discomfort: report of the contact lens interactions with the ocular surface and adnexa subcommittee. *Invest Ophthalmol Vis Sci* 2013;54:TFOS98-122
39. Friedland BR, Fleming CP, Blackie CA, Korb DR. A novel thermodynamic treatment for meibomian gland dysfunction. *Curr Eye Res* 2011;36:79-87
40. Lane SS, DuBiner HB, Epstein RJ, et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. *Cornea* 2012;31: 396-404
41. Greiner JV. A single LipiFlow(R) Thermal Pulsation System treatment improves meibomian gland function and reduces dry eye symptoms for 9 months. *Curr Eye Res* 2012;37:272-8
42. Korb DR, Blackie CA. Case report: a successful LipiFlow treatment of a single case of meibomian gland dysfunction and dropout. *Eye Contact Lens* 2013;39:e1-3
43. Finis D, Hayajneh J, Konig C, et al. Evaluation of an automated thermodynamic treatment (LipiFlow(R)) system for meibomian gland dysfunction: a prospective, randomized, observer-masked trial. *Ocul Surf* 2014;12:146-54
44. Eom Y, Lee JS, Kang SY, et al. Correlation between quantitative measurements of tear film lipid layer thickness and meibomian gland loss in patients with obstructive meibomian gland dysfunction and normal controls. *Am J Ophthalmol* 2013;155:1104-10. e2