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ORIGINAL ARTICLE

Infrared thermography in the evaluation of meibomian gland dysfunction

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meibomian gland dysfunction;
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Background/Purpose: To evaluate meibomian gland dysfunction (MGD) by infrared thermography.
Methods: An observational study was conducted at the Department of Ophthalmology, Far Eastern Memorial Hospital, New Taipei City, Taiwan. Participants included 89 MGD patients (30 in Grade 1, 49 in Grade 2, and 10 in Grade 3) and 65 controls. The close-eye thermographic images of the eyelid were obtained noninvasively by infrared thermography. Temperatures at 8 regions of interest (ROIs) of the eyelid margin and a reference temperature at the center of the upper eyelid were measured. The temperature ratio was defined as the temperature of ROI divided by the reference temperature.
Results: Eyelid margin temperature measured by infrared thermography increased from temporal side (ROI 1) to the nasal side (ROI 8) of the eye in both MGD patients and control groups. The temperature ratios were significantly higher in MGD participants than in controls, especially at ROI 8.
Conclusion: The eyelid margin temperature measured by infrared thermography was higher in MGD participants. Further development of this infrared thermography system may become a rapid and non-invasive tool for MGD screening.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Introduction

Meibomian gland dysfunction (MGD) is a leading cause of dry eye disease, characterized by abnormality of the meibomian glands, including terminal duct obstruction and changes in glandular secretion.[1] Changes in the quantity or quality of secreted meibum can cause reduced quality of tear film, leading to tear film instability and a higher rate of evaporation.[2–4] Symptoms such as sandy-gritty irritation, dryness, and blurred vision can develop thereafter.[5] Furthermore, the obstruction of meibomian glands can cause local inflammation, and the level of inflammation is often proportionate to disease severity.[6]

Diagnosis of MGD includes questionnaires regarding symptoms, examining the meibomian function as well as evaluating tear film quality and stability.[7] Traditionally, the meibomian function is evaluated by applying digital pressure over the eyelids to determine the expressibility and quality of secreted meibum under slit lamp microscopy.[6] The invasive nature of the examination may cause patient's discomfort, which may further increase the variability of the result. Therefore, recently-developed noninvasive devices, such as meibography, are necessary for consistent and reliable screening for MGD.[8,9]

In addition to the aforementioned devices, infrared thermography has emerged as an important diagnostic tool in dry eye disease. Originally designed to detect changes in the skin temperature, infrared thermography has now been used to detect changes in the ocular surface temperature caused by tear film evaporation.[10–18] However, few studies used thermography to detect changes in the eyelid margin temperature in patients with MGD. In this study, we used infrared thermography and a customized measurement program to measure the eyelid margin temperature and analyze the relationship between the eyelid margin temperature and MGD. We also evaluated the potential of this tool in MGD screening.

Methods

All procedures in this study were adhered to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board of Far Eastern Memorial Hospital, Banciao District, New Taipei City, Taiwan. We obtained informed consent from each participant after providing a full explanation of the study. A total of 154 participants were enrolled in the study, including 97 women and 57 men with a mean age of 46.7 $\pm$ 14.0 years (age range, 20–65 years). Exclusion criteria included signs of ocular surface abnormalities, previous ocular surface surgery, superficial punctate keratopathy, and allergy to fluorescein. All the study participants underwent thermographic examination first, followed by the fluorescein tear break-up time (FTBUT) test, meibomian gland function test, and Schirmer's test. No participants received eye drop instillations within 6 hours prior to measurement. All examinations were performed between 10:00 AM and 3:00 PM. The temperature and humidity conditions were maintained constant during examination.

Thermography measurement procedure

We used an ocular surface thermography device (IT-85, United Integrated Services Co., Hsin-Tien District, New Taipei City, Taiwan) and a customized computer program in MATLAB (MATLAB Software, The MathWorks, Inc., Natick, Massachusetts, USA) to measure thermal radiation. Participants were instructed to close their eyes, and the thermal detector was aligned and focused on the eyelids. Thermographic images were constructed by converting the digital value to the temperature value by a third-order polynomial. The transfer function in this study was $T = aI^3+bI^2+cI+d$,[17] where T was the temperature, I was the digital level recorded by the thermographic camera, and a, b, c, and d were the response coefficients ($a = 7.93181 \times 10^{-10}$, $b = -4.57262 \times 10^{-6}$, $c = 0.02987$, and $d = 9.97763$) in the temperature range of 10–40°C.

Temperature ratio

After capturing the thermographic images, we measured the temperature at eight regions of interest (ROI) on the eyelid margin (Figure 1). Each ROI was a circular area, 3 mm in diameter, aligned along the upper eyelid margin. To correct the body temperature among different participants, we designated a circular area, 12 mm in diameter, as the reference temperature, which was located at the center of the upper eyelid and 10 mm from the eyelid margin. The reference temperature was the mean of all pixel values in this area. After calculating the reference temperature and the temperature of each ROI, we calculated the temperature ratio of each ROI by dividing the ROI temperature by the reference temperature.

Meibomian gland functional test

We examined the expressibility, inflammation, and the quality of meibum by a functional test adopted from the international workshop to assess the severity of MGD.[6] We briefly pressed the lower tarsus and scored the quality of expressed meibum in each of the eight glands of the central third of the lower lid as follows: 0 = clear, 1 = cloudy, 2 = cloudy with debris, and 3 = thick. The total score of the eight glands was used to assign MGD grade (Grade 1, from $\geq$ 2 to $<$ 4; Grade 2, from $\geq$ 4 to $<$ 8; Grade 3, from $\geq$ 8 to $<$ 13; and Grade 4, $\geq$ 13). Plugging and increased vascularity of lid margin was graded as MGD grade 3, whereas gland dropout was graded as MGD Grade 4. Participants with zero meibum quality score and no lid margin abnormalities were defined as controls.

FTBUT test

To measure FTBUT, the participants were instilled with 2 μL of 2% fluorescein onto the bulbar conjunctiva using a micropipette. Participants were asked to blink three to five times, and the time for the appearance of the first dark spot was recorded. Each eye was measured four times. The

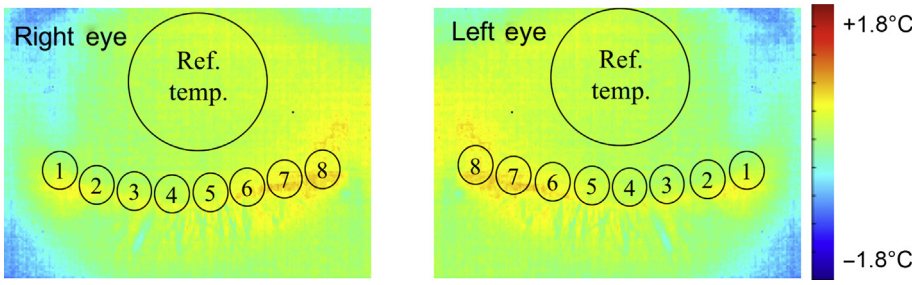

Figure 1 Region of interest (ROI) selection for close-eye thermograms from both eyelids. Eight ROIs (1—8) were selected from the upper eyelid margin. The reference temperature was measured in a circular area, 12 mm in diameter, located at the center of the upper eyelid. The dynamic temperature range of the thermogram was ± 1.8°C. Ref. temp. = reference temperature.

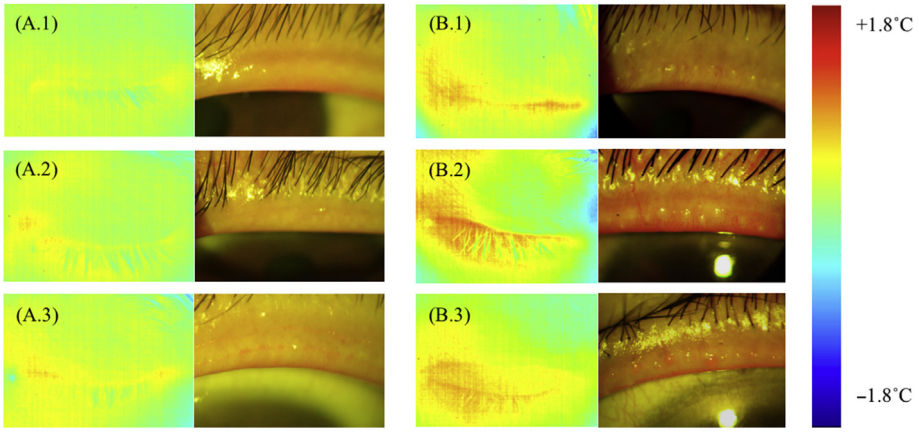

Figure 2 Representative thermographic and external eye images from three controls (A.1—3) and three MGD participants (B.1—3). Participants with MGD generally exhibited higher eyelid margin temperatures than controls.

mean of the four measurements was calculated for further analysis.

Schirmer's test

The standard basal secretion Schirmer's test was performed in this study. A 0.5% proparacaine hydrochloride ophthalmic solution (Alcaine, Alcon Laboratories, Inc., Fort Worth, TX, USA) was instilled twice at 5-minute intervals, and filter paper strips (5 mm × 35 mm Whatman Grade 41 filter paper) were placed at the lower conjunctival fornix near the lateral canthus for 5 minutes with the eyes closed. The paper strips were then removed, and the wetting of the paper strips was measured in millimeters.

Statistical analysis

Data analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation. We applied the analysis of variance test to compare temperature ratios among different MGD grades and control. The level of statistical significance was set at $p < 0.05$. Receiver operating characteristic (ROC) curves were used to analyze the screening potential for MGD, and the areas under the ROC curves (AUC) were calculated.

Results

In this study, 89 participants were diagnosed with MGD (30 participants, 49 participants, and 10 participants with Grade 1, Grade 2, and Grade 3, respectively). Their mean

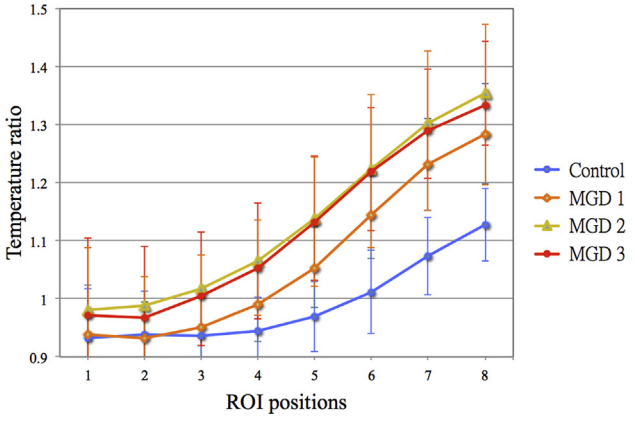

Figure 3 The temperature ratios from ROI positions 1—8 in controls and MGD participants. The temperature ratios were significantly higher in MGD patients than in controls ($n = 65$). MGD Grade 1 ($n = 30$), MGD Grade 2 ($n = 49$), and MGD Grade 3 ($n = 10$). MGD = meibomian gland dysfunction, ROI = region of interest.

age, FTBUT, and Schirmer's test value were 50.0 ± 11.9 years, 3.4 ± 3.3 seconds, and 6.5 ± 4.1 mm, respectively. The mean age, FTBUT, and Schirmer's test value of the 65 control participants were 41.3 ± 15 years, 5.0 ± 4.3 seconds, and 6.4 ± 4.6 mm, respectively. The participants with MGD exhibited significantly shorter FTBUT ($p < 0.01$) and were significantly older in age ($p < 0.01$) than the controls; however, the difference in Schirmer's test value was not significant.

For thermography examination, there was a steady increase in temperature from ROIs 1—8, indicating that the temperature was higher in the medial canthal region (Figure 2). We then measured the temperature of eight ROIs and the reference temperature and calculated the temperature ratio. Figure 3 shows that there was an increase in the temperature ratio from ROIs 1—8. Furthermore, the temperature ratios at ROIs 4—8 were significantly higher in participants with MGD, especially at ROI 8 ($p < 0.001$ for ROIs 4—8), than in controls. However, there was no significant difference between controls and MGD participants in ROI 1—3 ($p = 0.14$, $p = 0.181$, and $p = 0.08$ for ROI 1, ROI 2, and ROI 3, respectively), and there was no significant difference in the temperature ratios among the three MGD grades (Figure 3). The measurement results from both the eyes were highly correlated in both the groups of participants (for MGD participants, $p < 0.001$, r = 0.78; for controls, $p < 0.001$, r = 0.84).

As aforementioned, the mean age of MGD participants was significantly higher than that of controls. To avoid age-related confounding effect, we stratified the participants into different age groups. The result showed that the eyelid margin temperature was still significantly higher in MGD participants after matching for age. To further verify the screening value of the temperature ratio in ROIs 6—8, we constructed the ROC curve. AUC of the ROC curve gradually increased from ROI 6 to ROI 8, and the temperature ratio of ROI 8 had the highest AUC (0.92) (Figure 4). When we used the temperature ratio in ROI 8 to differentiate MGD participants from controls, the sensitivity and the specificity were 0.90 and 0.88, respectively.

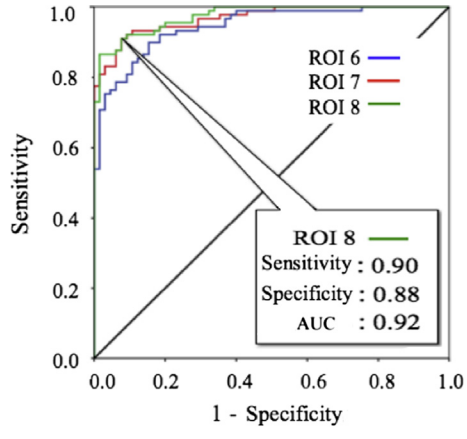

Figure 4 ROC curves of ROIs 6, 7, and 8. Area under curve of ROI 8 was the highest (AUC = 0.92). The sensitivity was 0.90, and the specificity was 0.88. AUC = area under curve; ROC = receiver operating characteristic.

Discussion

In this study, we used infrared thermography to measure the eyelid margin temperature and demonstrated for the first time that the temperature of the eyelid margin was significantly higher in MGD participants than in controls. We also showed that infrared thermography can be used to obtain thermographic images and to measure eyelid margin temperature in a quick and noninvasive manner, which can avoid patient discomfort and reflex tearing caused by the traditional diagnostic method.

MGD is characterized by obstruction of the meibomian gland orifices, lid margin hyperemia and telangiectasia, and subsequent glandular atrophy, which compromises tear film quality and results in evaporative dry eye.[6] In our study, we found that the eyelid temperature was higher in MGD participants than in controls. This approach is an addition to previous studies, in which researchers have used thermography to evaluate MGD, focusing on the temperature change on the ocular surface after eye opening. They concluded that patients with MGD had lower ocular surface temperature caused by excessive tear film evaporation.[19—21] Moreover, Arita et al[19] used thermography and meibography simultaneously to capture the images of tarsal conjunctiva and found that areas with lower temperature corresponded to dropout of meibomian gland. The discrepancy of the study results may be caused by different study methods and participants enrolled. In our study, we measured the temperature of the eyelid margin with the eye closed, focusing on the eyelid margin temperature instead of that of the ocular surface. Furthermore, different stages of MGD will exhibit different degrees of eyelid inflammation. In earlier stages of MGD, obstruction of meibomian gland orifices can cause local inflammation, which may lead to increased blood flow and higher eyelid margin temperature, as shown in this study. However, in the terminal stage, the whole meibomian ductal epithelium can become cornified and the meibocytes will be replaced by a stratified squamous epithelium.[1] Decreased blood flow resulted from meibomian gland dropout will have lower temperature detected, as demonstrated in the previous study.[19]

Our results showed that eyelid margin temperature increased steadily from the temporal side to the nasal side (from ROI 1 to ROI 8) of the normal eye. Our predefinition and verification are as follows: we assume that the eyelid temperature per se will be the same from temporal to the nasal area if there is no pre-existing disease or anatomical abnormalities. However, the nasal cavity is full of mucosa that might contribute to a higher temperature at nasal canthal area. Previous studies have demonstrated that levels of tear cytokines and chemokines were higher on the ocular surface of patients with MGD than on that of participants without MGD,[22,23] and these inflammatory molecules may flow through the puncta to the lacrimal drainage system. Therefore, these inflammatory molecules may accumulate on the nasal side of the eye, contributing to increased inflammation and, thus, higher eyelid margin temperature in patients with MGD. Further studies are needed to verify the contribution of these inflammatory molecules to the elevated eyelid margin temperature as

well as the impact of different inflammatory cytokines levels to the temperature change.

In our study, MGD participants were significantly older than the controls. This is compatible with previous findings that changes in meibomian glands increase with age.[24] To avoid age-related confounding effect on our temperature ratio analysis, we performed age covariate adjustments and confirmed that the temperature ratios of participants with MGD were significantly higher than those of controls. We also demonstrated a trend of higher temperature ratio in participants with more severe MGD. However, the differences in eyelid margin temperature among MGD grades were not statistically significant. This could result from the relatively small number of severe MGD participants and the variability in the MGD grading system.[25] Furthermore, in the end stage of MGD, withered glands without vascularity and inflammation may instead cause decreased temperature.

The procedure of the experiment can potentially influence the results of the measurement, especially in the invasive test. Therefore, we first performed thermography examination (non-contact), followed by the invasive tests, including the FTBUT test, meibomian gland function test, and Schirmer's test. The experiment procedure we designed for this study was to minimize the carry-over effect.

Several other limitations are noted in this study. First, we grouped the participants by meibomian gland functional test of eight glands of the central third of the lower lid, adopted from the international workshop to assess the severity of MGD.[6] This might result in including some participants with aqueous-deficient dry eye into the control group. However, this confounding issue in grouping wound does not debilitate our conclusion that thermography may be regarded as a fast and noninvasive MGD screening tool. Second, the ROIs in our study were manually defined. Third, our results exhibited a good prediction (sensitivity = 0.9, specificity = 0.88, and AUC = 0.9) of MGD screening. However, future studies with larger scale clinical trials will be most rewarding, considering the relatively small sample size in this study. In addition, participants with MGD were pre-screened based on the clinical meibomian gland functional test. Some of them may have been excluded from this study because of the unreliable nature of the test. Therefore, in order to demonstrate the true diagnostic value of thermography, a spectrum of patients ranging from early dry eye symptom should be enrolled.

The eyelid configuration is different between individuals in terms of size and shapes. Consequently, developing a fully automatic system is challenging in the identification of eyelid margin. However, a fully automated method may be possible if the size and shapes of the eyelid margin can be pre-categorized before the test. In this study, we used operator-friendly method to accrue a maximum accuracy and found significantly higher eyelid margin temperature in MGD participants. Although there might be a disadvantage of hardware cost in adopting thermography device, its objectiveness of measurement would not only standardize the diagnosis but also facilitate the communication between ophthalmologist and their patients. At the current stage, the time for ROI definition might seem a disadvantage; nevertheless, our results provide a good reference for a future development of a fully automated system.

Clinicians may use thermographic devices for the evaluation of meibomian gland inflammation. A higher eyelid temperature indicates active inflammation and potential meibomian gland orifice obstruction. This could further lead to meibomian atrophy and subsequent lipid deficiency dry eye disease. In addition, monitoring temperature change of the eyelid margin could represent disease progression and/or treatment response. The examination is noncontact, quick, and operator friendly. We believe that these advantages are clinically helpful for both patients and ophthalmologists. By contrast, the traditional MGD functional test requires applying finger pressure to the lid margin to evaluate meibomian gland expressibility. This method is limited by its invasiveness and subjectiveness and is highly uncomfortable for patients. Clinicians may potentially use MGD screening by using thermographic devices to evaluate dry eye disease in the near future.

Conclusion

This paper proposed a fast and noncontact thermography eyelid temperature measurement method. We conclude that participants with MGD have a higher eyelid margin temperature than the controls because of eyelid inflammation. Therefore, further development of this infrared thermography system may lead to the implementation of a noncontact MGD screening system.

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