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ORIGINAL RESEARCH

Measurement of the Lid Margin Thickness in Meibomian Gland Dysfunction with Vernier Micrometer

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ABSTRACT

Introduction: To investigate the lid margin thickness (LMT) from the posterior lash line to the mucocutaneous junction at the middle position in adults with and without meibomian gland dysfunction (MGD) by vernier micrometer (VM).

Methods: This is a cross-sectional, observational study. A hundred eyes from 100 volunteers aged 20 to 79, including 56 normal participants and 44 participants with MGD, were recruited. Measurements of the LMT by VM were performed by the same person.

Results: The mean age of 56 normal subjects (24 males and 32 females) and 44 MGD subjects (16 males and 28 females) was 40.0 ± 13.2 years and 42.7 ± 17.1 years, respectively. There was a significant difference in the upper LMT between normal and MGD subjects (1.36 ± 0.25 vs. 1.60 ± 0.27 mm, $P < 0.001$), but not in the lower LMT (1.0 ± 0.23 vs. 1.10 ± 0.28 mm, $P = 0.07$). In both normal and MGD subjects, the upper or lower LMT was significantly positively correlated with age ($P < 0.05$), and the upper LMT was greater than the lower LMT ($P < 0.001$). In addition, the lower LMT in MGD subjects was significantly positively correlated with meibum expressibility ($r_s = 0.35$, $P = 0.02$).

Conclusions: The LMT was closely related to age and could be an important indicator for detecting MGD. Furthermore, we found that the upper LMT was greater than the lower LMT, and the lower LMT in MGD subjects seemed to be related to meibum expressibility.

Keywords: Lid margin thickness; Meibomian gland dysfunction; Meibum expressibility; Vernier micrometer

Key Summary Points

Vernier micrometer is a reliable method for measuring the lid margin thickness (LMT).

The LMT could be an important indicator for detecting meibomian gland dysfunction (MGD).

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The LMT was closely related to age with the upper LMT value being greater than the lower LMT value.

The lower LMT in MGD subjects seemed to be related to meibum expressibility.

INTRODUCTION

Meibomian gland dysfunction (MGD) is a common disease in clinical practice, which is closely associated with evaporative dry eye [1]. Previous literature indicated that the prevalence of MGD increases with age [2–7]. Thickening of the lid margin is a common feature of MGD [8–10], which has been used as one of the diagnostic indicators of MGD [9], but it was inconvenient and difficult to measure. At present, it is mainly determined by the ophthalmologists/eyecare providers based on their own subjective experiences [8, 10].

The lid margin changes may also be observed in other ocular diseases, such as blepharitis, lid-wiper epitheliopathy (LWE) and conjunctivochalasis (CCh) [9, 11, 12]. In addition, the eyelid pressure may also be associated with some eyelid-related diseases, such as dry eye, CCh and LWE [11–13], but taking eyelid pressure measurements is still not easy. Through a different dimension, if the eyelid pressure can be measured indirectly by the measurement of LMT, even for a specific ocular disease, it will greatly help clinical practice.

Through the previous studies [15–17], we found that the LMT from the posterior lash line to the mucocutaneous junction (MCJ) was a relatively constant feature of the lid margin in normal adults and could be quantitatively measured by anterior segment optical coherence tomography (AS-OCT), oculus keratograph and vernier micrometer (VM). However, we only reported the data of the lower LMT, not the data of the upper LMT. In addition, due to the optical properties of AS-OCT and oculus keratograph devices, and the slope of the upper lid margin and the presence of upper eyelashes, only the lower LMT can be measured to obtain noninvasive and accurate measurements [15, 17]. In other words, the VM is superior to AS-OCT and oculus keratograph devices in the measurement of the upper LMT.

It should be emphasized that there are some downstream effects of the disease in later stage MGD, such as abnormal lid margin, orifices and meibum, which may offer easier assessment for diagnosis than the measurement of LMT. However, in early-stage MGD or nonobvious obstructive MGD [14], its clinical signs may not be obvious to the observers. That the meibomian glands can produce lipid secretions is well known, and some studies have reported that MGD may be related to dyslipidemia or body mass index (BMI) [18–21]; however, whether the LMT in MGD subjects is related to BMI is worthy of further investigation.

Therefore, the purpose of this study was to compare the upper and lower LMT measured by VM in adults with and without MGD to provide new insights into the study of early-stage MGD.

METHODS

Participants

This was a single-center, prospective, cross-sectional, observational study, which was an extension of our previous works [15–17]. In this study, 100 volunteers (40 males and 60 females) aged 20 to 79 years were recruited from the ophthalmic clinic of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, including 56 participants with healthy eyes and 44 participants with MGD. Only the right eye data were analyzed. The research followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (no. 2019LCSY031). All subjects signed the informed consent after explaining the purpose of the study.

The diagnostic criteria of MGD are as follows [9, 22]: (1) ocular symptoms—dryness, foreign body sensation, ocular fatigue, burning sensation, stimulation, sticky sensation, heavy sensation, pain, itching, redness, photophobia, epiphora, blurred vision, excessive blinking,

etc.; (2) lid margin and gland orifices abnormalities—thickening, rounding, hyperemia, cicatrices, dimpling/notching and serration of lid margin with or without telangiectasia; pouting or plugging, capping and reduction in number of the meibomian gland orifices and loss of definition of the orifice cuffs; dilation and/or exposure of the terminal ducts; anterior or posterior replacement of the MCJ, etc.; (3) meibum quality and expressibility abnormalities—cloudy or milk-yellowish or toothpaste-like secretions, meibum not easily expressed with mild to moderate pressure; (4) meibomian gland loss; (5) tear film lipid layer thickness. If items (2) and/or (3) and item (1) are met, patients will be diagnosed with MGD. In addition, items (4) and/or (5) are used to strengthen the diagnosis of MGD, but are not mandatory.

Study Exclusion Criteria [15–17]: irregular lid margin structures—cicatrices, dimpling or notching, serration; meibomian gland loss area $> 33\%$ of the total area in each eyelid [4]; history of chalazion or hordeolum within the past 3 months; eyelid tattoos; ocular surface disease index (OSDI) score < 12 points in MGD subjects; active ocular allergies; ocular infection/inflammation; entropion and trichiasis; eyelid tumor; no eyelashes or central eyelashes loss; conjunctivochalasis; nystagmus; paralytic strabismus; have worn contact lens within the past 3 months; had a history of intraocular surgery or ocular surgery; used isotretinoin (accutane) within the past 6 months; autoimmune disease requiring systemic treatment; was pregnant or lactating.

Clinical Assessments

Referring to our previous article [22], all participants were asked to fill out the Ocular Surface Disease Index (OSDI) questionnaire and undergo the slit-lamp biomicroscopy examinations as well as clinical tests including the fluorescein tear break-up time (FBUT), corneal fluorescein staining (CFS), Schirmer test without anesthesia (SIT), meibum expressibility and meibum quality [8, 9]. It should be noted that all clinical assessments were performed by a single specialist in the field of ocular surfaces (X.-Q. L.) for consistency.

Body Mass Index

The height (meters, m) and weight (kilograms, kg) were measured while the subjects were barefoot and wore light daily clothes. The BMI was calculated by using the formula of weight in kilograms divided by height in meters squared. Normal weight is defined as a BMI between 18.5 and 23.9 kg/m^2, underweight is defined as a BMI $< 18.5\ kg/m^2$, overweight is defined as a BMI between 24.0 and 27.9 kg/m^2, and obesity is defined as a BMI $\geq 28.0\ kg/m^2$ [23].

Reliability of Vernier Micrometer

In this study, the LMT was defined as the distance from the posterior lash line to the MCJ at the center eyelid, directly above or below the center of the subject's pupil. While using a VM (Shanghai Tool Works Co., Ltd., China) to measure the LMT, we needed to slightly evert the eyelid under the slit-lamp microscope. During this process, the distance between the posterior eyelash line and the MCJ could be artificially increased because of stretching of the eyelid tissues during eversion and the lid margin might become thicker without eyeball support [16]. To reduce the measurement error, the lower LMT in 30 healthy volunteers was measured by the same operator (D.-H. W.) before and after 3 months to determine the reliability of the VM. Two measurements were taken and averaged at each measurement session. Furthermore, to avoid subjectively converging the results of two measurements, the first measurement data were masked during the process of the second measurement.

Measurements of Lid Margin Thickness

The lid margin thicknesses corresponding to the pupil center of 100 subjects were measured by a VM. The protocol process of VM was the same as in our previous research [16]. During the process, subjects were seated in front of the slit-lamp microscope, their heads were comfortably

placed on the chin and forehead rested, and then they were asked to look straight ahead and blink normally. When observations on the lower or upper eyelids were made by pulling the lid margin away from the globe with fingers, a VM was used to directly measure the LMT from the posterior lash line to the MCJ (specular reflection) at the central eyelid without ocular surface staining (Fig. 1). The average value of two measurements was recorded as the LMT.

It should be noted that compared to the AS-OCT or Keratograph, the VM is steel-based and invasive. Therefore, to reduce the measurement errors and avoid ocular injuries, using VM to measure the LMT was performed by a skilled and experienced doctor (D.-H. W.) in this study.

Statistical Analysis

All data were presented as the mean ± standard deviations (SD). Statistical analyses were performed with Student's *t*-test, nonparametric test, intraclass correlation coefficient (ICC), Bland-Altman plots and Spearman's rank correlation coefficient analysis. $P < 0.05$ was considered significant. All analyses were performed with PASW Statistics, version 25.0 (SPSS Inc., Chicago, IL, USA).

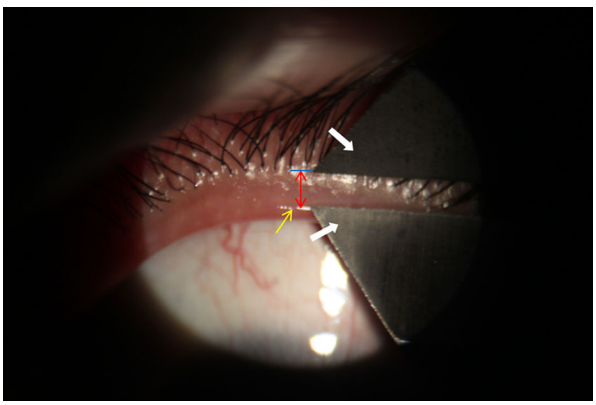

Fig. 1 Measurement of the upper LMT by a vernier micrometer under the slit-lamp microscope. The yellow arrow stands for the MCJ (specular reflection); the blue line stands for the posterior eyelash line; the red double arrows stand for the LMT; the two white thick arrows stand for a vernier micrometer

RESULTS

Reliability of Vernier Micrometer

The mean age was 37.3 ± 10.2 years in 30 subjects (10 males and 20 females) aged 20 to 59 years. ICC and Bland-Altman plots demonstrated good agreement between the first and second measurement of the lower LMT (0.95 ± 0.19 vs. 0.93 ± 0.18 mm, ICC = 0.87, $P = 0.25$, Fig. 2). Therefore, the measurement of LMT with VM was judged to be reproducible.

Measurements of Lid Margin Thickness

A total of 100 subjects were enrolled in this study, with an average age of 41.2 ± 15.0 years. The average age of 56 normal subjects (24 males and 32 females) and 44 MGD subjects (16 males and 28 females) was 40.0 ± 13.2 years and 42.7 ± 17.1 years, respectively. The demographic characteristics and clinical parameters of the study are presented in Tables 1 and 2, respectively. There were no significant differences in age, sex and BMI between normal and MGD subjects ($P = 0.67$, 0.51 and 0.58, respectively).

As shown in Table 3, there was a significant difference in the upper LMT between normal and MGD subjects (1.36 ± 0.25 vs. 1.60 ± 0.27 mm, $P < 0.001$), but not in the lower LMT (1.0 ± 0.23 vs. 1.10 ± 0.28 mm, $P = 0.07$). Additionally, in both normal and MGD subjects, the upper LMT was greater than the lower LMT ($P < 0.001$), and the scatter plot and Spearman's rank correlation coefficient showed that the upper or lower LMT was significantly positively correlated with age ($_{normal}r_s = 0.50$ and 0.77, $P = < 0.001$ and < 0.001; $_{MGD}r_s = 0.42$ and 0.68, $P = 0.005$ and < 0.001, respectively), as shown in Fig. 3.

In normal subjects, the average age between sexes was not significantly different (43.5 ± 14.9 vs. 37.3 ± 11.2 years, $P = 0.09$), and the LMT in males was thicker than that in

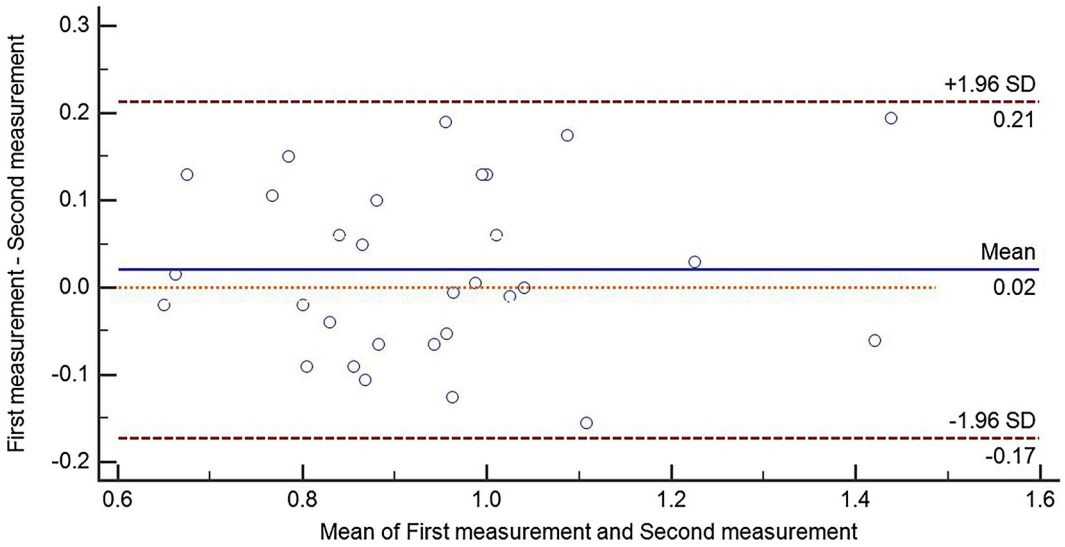

Fig. 2 Agreement between the first and second measurement of the lower LMT. Bland-Altman plots demonstrated that 30 of 30 spots were within 95% limits of agreement (95% LoA); the maximum difference was 0.21 mm, and the arithmetic mean was 0.02 mm

Table 1 Demographic data for all participants

	Normal	MGD	Total
Number of subjects	56	44	100
Age, years			
Mean ± SD	40.0 ± 13.2	42.7 ± 17.1	41.2 ± 15.0
Median	36.0	38.0	37.0
Minimum, maximum	22, 72	21, 79	21, 79
Gender, *n* (%)			
Male	24 (42.9)	16 (36.4)	40 (40)
Female	32 (57.1)	28 (63.6)	60 (60)
Height, m	1.67 ± 0.08	1.67 ± 0.07	1.67 ± 0.08
Weight, kg	61.9 ± 12.9	62.9 ± 11.5	62.3 ± 12.2
BMI, kg/m^2	22.0 ± 3.3	22.6 ± 3.5	22.3 ± 3.4

MGD meibomian gland dysfunction, *SD* standard deviations, *BMI* body mass index

Table 2 Clinical parameter values for subjects

Parameters	Normal	MGD
OSDI	5.11 ± 3.31	30.02 ± 13.28
FBUT (s)	8.31 ± 2.44	3.20 ± 1.77
CFS	–	1.57 ± 2.41
SIT (mm)	12.70 ± 5.07	11.80 ± 7.04
Meibum expressibility	–	1.27 ± 0.69
Meibum quality	–	6.02 ± 3.22

MGD meibomian gland dysfunction, *OSDI* ocular surface disease index, *FBUT* fluorescein tear break-up time, *CFS* corneal fluorescein staining, *SIT* Schirmer test without anesthesia

females, but the upper and lower LMT between sexes seemed to be not significantly different (1.37 ± 0.25 vs. 1.34 ± 0.25 mm, $P = 0.64$; 1.06 ± 0.22 vs. 0.95 ± 0.22 mm, $P = 0.07$). In addition, there seemed to be no significant difference in the upper or lower LMT between overweight or obese subjects and those with a BMI < 25 kg/m^2 (1.32 ± 0.24 vs. 1.36 ± 0.25 mm, $P = 0.66$; 1.01 ± 0.21 vs. 1.0 ± 0.23 mm, $P = 0.78$, respectively). In MGD subjects, Spearman's rank correlation coefficient demonstrated that the lower LMT was

Table 3 Lid margin thickness (LMT) for both normal and MGD subjects

LMT	Normal	MGD	*P* value
Upper LMT, mm			
Mean ± SD	1.36 ± 0.25	1.60 ± 0.27	< 0.001
Minimum, maximum	0.82, 1.96	1.15, 2.23	
Lower LMT, mm			
Mean ± SD	1.0 ± 0.23	1.10 ± 0.28	0.07
Minimum, maximum	0.66, 1.49	0.70, 1.84	

SD standard deviations

significantly positively correlated with meibum expressibility (r_s = 0.35, P = 0.02) and marginally positively correlated with meibum quality (r_s = 0.27, P = 0.075). No adverse events from the measurements were observed in all subjects.

DISCUSSION

In a clinic-based patient cohort study conducted in the European Union and US, 86% of dry eye patients demonstrated signs of MGD [24]. In Asia, the incidence of MGD in dry eye subjects is also high, with a range of 46.2 to 69.3% [2, 25–27]. Therefore, it has been suggested that MGD-related evaporative dry eye is the most common form of DED [1]. In addition, rounding and thickening of the lid margin is a common feature of advanced MGD [8–10], but as to whether there are changes of the LMT in early-stage MGD or nonobvious obstructive MGD, there are no relevant published studies at present.

Although the LMT is difficult to measure, people are still trying to measure it with several different methods [15–17, 28–30]. Hykin et al.

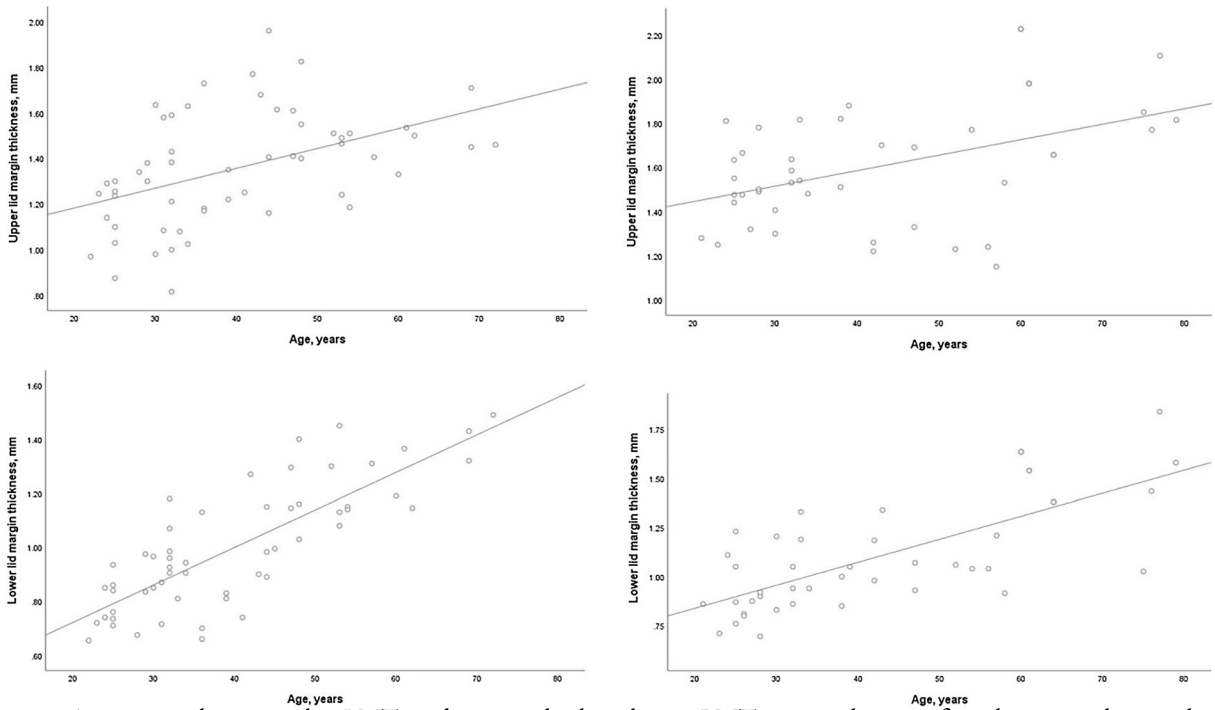

Fig. 3 Association between the LMT and age in both normal and MGD subjects. **A** Upper and lower LMTs were significantly positively correlated with age (r_s = 0.50 and 0.77, P = < 0.001 and < 0.001, respectively). **B** Upper and lower LMTs were also significantly positively correlated with age (r_s = 0.42 and 0.68, P = 0.005 and < 0.001, respectively)

[28] measured the LMT including marginal mucous membrane with VM in different age groups and found that the upper and lower LMT in children was 1.53 ± 0.10 mm and 1.51 ± 0.10 mm and in adults was 1.95 ± 0.07 mm and 1.87 ± 0.06 mm, respectively, with no significant difference between genders. Meanwhile, Bron et al. [8] suggested that the lid margin width in normal adults including wet mucosa was approximately 2.5 mm. He [29] reported that the upper and lower LMT in Chinese aged 15 to 80 years measured with a ruler was about 2.0 mm and 1.5 mm, respectively. Pult et al. [30] measured the LMT (distance between eyelash line and cornea) of 15 adults with a Scheimpflug camera and found that the upper and lower LMT in the opened eye was 1.7 ± 0.22 mm and 1.7 ± 0.24 mm, respectively. In addition, our previous investigation [15, 17] suggested that the lower LMT of 60 subjects measured by VM and AS-OCT was about 1.03 ± 0.25 mm and 0.8 ± 0.21 mm, respectively, and the lower LMT of 90 subjects measured with an oculus keratograph was 0.95 ± 0.17 mm.

In this study, the LMT in normal and MGD adults was about 1.36 ± 0.25 mm and 1.60 ± 0.27 mm for the upper eyelid and 1.0 ± 0.23 mm and 1.10 ± 0.28 mm for the lower eyelid, respectively, which were all lower than that reported in the earlier literature [8, 28–30]. One possible reason for this discrepancy was that the LMT we measured only included the width of the keratinized lid margin surface, excluding the wet part of the lid margin (mucosa). Another possible reason was that compared to AS-OCT, oculus keratograph or Scheimpflug camera, the VM was invasive. Additionally, the upper LMT in both normal and MGD subjects was greater than the lower LMT, consistent with the previously published articles [28–30]. The anatomical structures might contribute to this difference. Meanwhile, our study showed that the upper or lower LMT in MGD subjects was separately greater than that in normal subjects, which demonstrated that the LMT could be used as an important indicator to differentiate MGD from healthy eyes. Although there was a marginal difference in the lower LMT ($P = 0.07$), it was obvious that the difference was in the right direction with the increase of sample size.

Previous studies [8, 28] had shown that the lid margin thickened with age because of enlargement of the orbicularis and meibomian glands in the first 20 years of life, but the LMT in adults did not change with age. Contrary to the above conclusions, our present and previous studies [15, 17] suggested that the LMT, especially the lower LMT, also seemed to be related to age. This further supported the literature reports on age-related changes in the lid margin anatomy [3, 8, 28] and the theory that the incidence of MGD increased with age [2–7]. Meanwhile, our findings can be indirectly supported by multi-dimensional evidence [31–33]. Sakai et al. [31] found that the eyelid pressure of the upper and lower eyelids decreased significantly with age, which meant that the keratinized lid margin might become thicker from the perspective of compression force. Yamaguchi et al. [32] demonstrated a forward movement of the MCJ with age, and the location change of the MCJ was strongly correlated with MGD, which indirectly indicated that the location change of the MCJ might be accompanied by changes of the LMT [8–10]. Furthermore, the lower lid margin may be directly exposed to more ultraviolet radiation (UVR) in sunlight [33], which may have a pathological impact on the lower lid margin with or without eyelid disease with age.

In normal subjects, although the upper or lower LMT in men was thicker than that of women, there were no significant differences ($P = 0.64$ and 0.07). This result was consistent with the observations of Hykin [28] and our previous research [17]. In MGD subjects, we found that the lower LMT had an approximately linear relationship with meibum expressibility ($r_s = 0.35$, $P = 0.02$) and was marginally positively correlated with meibum quality ($r_s = 0.27$, $P = 0.075$). Compared with advanced MGD, the clinical features of early-stage MGD may not be obvious to the observers. At present, the early diagnosis of MGD is mainly through the meibomian gland expression or meibography [9]. Moreover, the LMT of MGD subjects in this study was thicker than that of normal subjects. Therefore, we believed that

with the development of disease and the obstruction of the meibomian gland terminal ducts and orifices may lead to thickening of the lid margin [32].

In addition, we found that there was no significant difference in BMI between normal and MGD subjects ($P = 0.58$), and there seemed to be no significant difference in the LMT in normal or MGD subjects between overweight or obese subjects and those with a BMI < 24 kg/m^2. Currently, the information available on BMI affecting the LMT was limited because most prevalence studies on MGD failed to provide BMI-specific data. Pinna et al. [18] revealed that MGD in patients aged 18–54 years was significantly associated with higher blood levels of total cholesterol. Kuriakose et al. [19] suggested that there was a relation between MGD and dyslipidemia. Baser et al. [20] indicated that a high BMI played an important role in the presence of MGD with tear film instability. Furthermore, a recent article also suggested that BMI may be related to the pathogenesis of MGD [21]. As a summary of the above literature, MGD might be related to BMI, which indirectly indicated that the changes of the lid margin in MGD, including LMT, might be associated with BMI. Further studies are warranted to provide more information.

In this pilot study, good agreement between the first and the second measurement showed the measurements of LMT with VM were reproducible. Then, we used VM to measure the upper and lower LMT and successfully obtained the LMT data. It should be emphasized that although VM is invasive compared with AS-OCT and oculus keratograph devices, it has some advantages in the measurement of upper LMT, regardless of the slope of the upper lid margin and the influence of upper eyelashes. Meanwhile, we found that the LMT in normal subjects was less than that in MGD patients, suggesting that the measurement of LMT may be helpful for discriminating patients with early-stage MGD from normal subjects in the future. Finally, in theory, after the treatment of MGD with physical therapy [22, 34, 35], the LMT will become thinner correspondingly with the discharge of meibomian gland secretions. Concerning the changes of LMT after MGD treatment, it is worth further study. In addition, exploring the relationship of LMT to the prognosis or severity of MGD will be the focus of our future work.

However, several limitations of our study should be noted. (1) This study only measured the keratinized lid margin surface width from posterior lash line to MCJ, not the full length of the LMT. (2) We did not measure the LMT in people < 20 years old or > 80 years old, nor did we report the LMT in other races/ethnicities and regions. (3) To facilitate the measurement of LMT, we excluded MGD patients with irregular lid margin structures, which might diminish the relevance of this article. (4) In addition, we did not compare the difference of LMT in early-stage MGD and advanced MGD, so future studies will be needed. (5) Finally, to better investigate the LMT in MGD, a larger sample size will be needed in the future.

CONCLUSIONS

The LMT was closely related to age and could be an important indicator for detecting early-stage MGD or nonobvious obstructive MGD, which could provide new insight into the study of MGD. Furthermore, we found that the upper LMT was greater than the lower LMT in both normal and MGD subjects, and the lower LMT in MGD subjects seemed to be related to meibum expressibility.

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Editors (ICMJE) criteria for authorship of this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. H-Y Zhu: Conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review & editing. X-Q Liu: Conceptualization, investigation, data curation, funding acquisition, methodology, formal analysis, writing—original draft, writing—review & editing. Y-Z Yuan: Methodology, data curation, writing—review & editing. D-H Wang, Conceptualization, investigation, methodology, funding acquisition, resources, project administration, writing—review & editing.

Disclosures. Hua-Ying Zhu, Xin-Quan Liu, Yuan-Zhi Yuan and Da-Hu Wang all confirm that they have no conflicts of interest to declare.

Compliance with Ethics Guidelines. The study was conducted in strict accordance with the principles of the Helsinki Declaration under the guidance of the Ethics Committee of the Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. Each subject signed informed consent for the study.

Data Availability. The datasets analyzed for the present study are available from the corresponding author.

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