Measurement of the Lower Lid Margin Thickness by Anterior Segment Optical Coherence Tomography

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Keywords

Meibomian gland dysfunction · Lower lid margin thickness · Anterior segment optical coherence tomography

Abstract

Purpose: To verify the feasibility of using anterior segment optical coherence tomography (AS-OCT) to measure the lower lid margin thickness (LLMT) from posterior lash line to the mucocutaneous junction. **Methods:** This was a prospective, single-center, observational study. Fifty-six volunteers between 20 and 79 years old with normal healthy eyes were included in this study. Using AS-OCT to measure the LLMT at the middle position was separately performed by two operators under the same conditions. **Results:** The mean age of 56 subjects (24 males and 32 females) was 45.4 ± 15.7 years. The LLMT measured by AS-OCT between two operators was 0.86 ± 0.23 mm and 0.85 ± 0.22 mm, respectively. The reliability and repeatability between two operators were evaluated by intraclass correlation coefficient ($ICC = 0.97$). Based on one operator's measurements, the LLMT was 0.70 ± 0.10 mm at ages 20–29, 0.68 ± 0.09 mm at ages 30–39, 0.94 ± 0.12 mm at ages 40–49, 0.93 ± 0.20 mm at ages 50–59, 1.03 ± 0.15

mm at ages 60–69, and 1.24 ± 0.19 mm at ages 70–79, which indicated a significant positive correlation with age ($r_s = 0.74$, $p < 0.001$). In addition, there was a significant difference in the LLMT between genders (0.94 ± 0.26 vs. 0.80 ± 0.19 mm, $p = 0.03$). **Conclusions:** A good agreement between two operators indicated that it seemed to be feasible to use AS-OCT to measure the LLMT. Additionally, we found that the LLMT appeared to be closely related to age and gender.

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Introduction

The free edge of the eyelid is called the lid margin, which is divided into anterior lid margin and posterior lid margin according to the gray line [1, 2]. Thickening of the lid margin is a common feature of advanced meibomian gland dysfunction (MGD) [3–5], which is closely associated with evaporative dry eye [2, 6–8], but it is difficult to measure because of rounding of the posterior lid margin.

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Fig. 1. A representative AS-OCT image of measuring the lower lid margin thickness. The long green arrow stands for the optimal position of OCT scanning, the two white arrows stand for the lower lid, the two blue arrows stand for the lower tear meniscus, the two red arrows stand for the cornea, and the two yellow double arrows stand for the lower lid margin thickness (posterior lash line to anterior edge of the tear meniscus or mucocutaneous junction).

However, in later-stage MGD, there were other downstream effects of the disease (e.g., telangiectasia, abnormal orifices, irregular lid margin), which offered easier assessment for diagnosis than measurement of the lid margin thickness. But in early-stage MGD or asymptomatic MGD (preclinical stage), its clinical features may not be obvious to the observers. At this stage, it may be diagnosed by the meibomian gland expression or meibography [3]. As to whether there are early changes in the lid margin thickness, there is no relevant published literature at present.

In addition, changes in the lid margin thickness may also be seen in some diseased eyes, such as blepharitis, lid-wiper epitheliopathy, and conjunctivochalasis. Therefore, the measurement of the lid margin thickness could be helpful to evaluate several different eye disorders. Up to date, several measurements such as ruler, vernier micrometer, and Scheimpflug camera [9–11] have been used to measure the lid margin thickness from the posterior lash line to the posterior margin, which is a relatively constant feature of the lid margin [5], but these measurements have some limitations in clinical practice due to the inconvenience and/or complexity of the instruments.

Optical coherence tomography (OCT) has been clinically used for nearly 30 years since it was introduced for medical purpose in 1991 [12]. At present, anterior segment optical coherence tomography (AS-OCT) plays an

important role in ophthalmology, which includes cornea, the anterior chamber and angle, the aqueous outflow system, ocular surface, and dry eye disease [13]. Compared with the traditional methods such as ruler and vernier micrometer [9, 10], the main advantages of AS-OCT include the rapid, simple, convenient, and noninvasive in vivo imaging of the eye structures, while providing accurate quantitative measurements and imaging data. Therefore, in this study, we try to introduce AS-OCT to measure the lid margin thickness at the middle position of the lower lid (Fig. 1) and evaluate its reliability.

Materials and Methods

Subjects

This was a prospective, single-center, observational study. Fifty-six volunteers (24 males and 32 females) between 20 and 79 years with normal healthy eyes were included in this study. The study was conducted in strict accordance with the principles of the Helsinki Declaration under the guidance of Ethics committee of the Longhua Hospital Shanghai University of Traditional Chinese Medicine (No. 2019LCSY031). Each subject signed informed consent for the study.

Study exclusion criteria were Ocular Surface Disease Index scores higher than 12 points [3]; lid structural abnormalities; irregular lid margins; acne rosacea; eyelid entropion and trichiasis; eyelid tumor; no eyelashes or central eyelashes loss in lower lid; conjunctivo chalasis; nystagmus; paralytic strabismus; ocular allergies; topical antiglaucoma therapy; ocular infection and/or in-

Table 1. Demographic characteristics for subjects

	Age group						Total
	20–29	30–39	40–49	50–59	60–69	70–79	
Subjects	10	16	8	8	9	5	56
Age, years							
Mean $\pm$ SD	26.5 $\pm$ 1.6	33.9 $\pm$ 3.3	45.2 $\pm$ 2.4	54.3 $\pm$ 2.2	63.6 $\pm$ 3.4	73.2 $\pm$ 2.5	45.4 $\pm$ 15.7
Median	27	32.5	45.5	54.0	63.0	73.0	43.0
Min., max.	24, 28	30, 39	42, 48	52, 58	60, 69	70, 77	24, 77
Gender, <i>n</i> (%)							
Male	3 (30.0)	6 (37.5)	4 (50)	2 (25.0)	5 (55.5)	4 (80.0)	24 (42.9)
Female	7 (70.0)	10 (62.5)	4 (50)	6 (75.0)	4 (44.5)	1 (20.0)	32 (57.1)

Fig. 2. Agreement analysis between two operators. Bland-Altman plots demonstrated that 53 of 56 spots were within 95% limits of agreement (95% LoA). The maximum difference was 0.11 mm within 95% LoA and the arithmetic mean was 0.01 mm.

flammation; had worn contact lens; had penetrating intraocular surgery or ocular surgery; used intense pulsed light or isotretinoin (accutane); was pregnant or lactating.

Measurements of Lid Margin Thickness

The thicknesses of the lower lid margin were measured by AS-OCT (Spectralis OCT, Heidelberg Engineering, Germany) for each subject, and the protocol process was basically the same as the measurement of tear meniscus height [14]. The specific steps were as follows. During the process, subjects were seated in front of AS-OCT, their heads were comfortably placed on the chin and forehead rested, and they were asked to look straight ahead, then AS-OCT was used to measure the lower lid margin thickness (LLMT) at the middle position (see online suppl. video at www.karger.com/doi/10.1159/000507221, which demonstrates the measurement of LLMT with AS-OCT). Measurements were respectively performed by two operators under the same conditions.

Because the optical properties of AS-OCT technique determines its poor tissue penetration, we cannot measure the full thickness of lid margin. Then, in order to get an accurate measurement, we only measured the LLMT from posterior lash line to anterior edge or outer edge of the tear meniscus, i.e., the keratinized skin width. We all knew that the palpebral border of lid margin in healthy people corresponded with the mucocutaneous junction (MCJ), i.e., the position of anterior edge of tear meniscus. When measuring the LLMT with AS-OCT, the boundary of MCJ was not very clear in the image, so we regarded the anterior edge of tear meniscus to replace the MCJ as the posterior boundary of the lid margin skin. In this study, without specific explanation, the LLMT we measured referred to the keratinized lid margin surface width, rather than the full thickness of lid margin.

Statistical Analysis

Only the right eye data were analyzed, as there was no statistically significant difference between the results of the right and left eyes. All data were presented as the mean $\pm$ standard deviations. Statistical analyses were performed with Student's *t* tests, intraclass correlation coefficient (ICC), Spearman's rank correlation coefficient, and Bland-Altman plots. $p < 0.05$ was considered significant. Data analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Fifty-six subjects (24 males and 32 females) were enrolled in the study. The mean age was 45.4 ± 15.7 years, with a range from 24 to 77 years. The detailed results of the demographic characteristics are presented in Table 1. The LLMT measured by AS-OCT between two operators was 0.86 ± 0.23 mm and 0.85 ± 0.22 mm, respectively. The test of inter-operator variation showed that there was a good reliability and repeatability between two operators (ICC = 0.97, $p = 0.22$) and Bland-Altman plots also demonstrated a good agreement between two operators (Fig. 2). Based on one operator's measurements, the

Fig. 3. Correlation between the lower lid margin thickness and age. The lower lid margin thickness was significantly positively correlated with age ($r_s = 0.74$, $p < 0.001$).

LLMT at the middle position was 0.70 ± 0.10 mm at ages 20–29, 0.68 ± 0.09 mm at ages 30–39, 0.94 ± 0.12 mm at ages 40–49, 0.93 ± 0.20 mm at ages 50–59, 1.03 ± 0.15 mm at ages 60–69, and 1.24 ± 0.19 mm at ages 70–79. In addition, the scatterplots and Spearman's rank correlation coefficient demonstrated that the LLMT was positively correlated with age ($r_s = 0.74$, $p < 0.001$; Fig. 3). The average age between sexes was not significantly different (49.3 ± 16.5 vs. 42.5 ± 14.6 years, $p = 0.11$), but there was a significant difference in the LLMT between genders (0.94 ± 0.26 vs. 0.80 ± 0.19 mm, $p = 0.03$). No adverse events were detected in all subjects after the measurements.

Discussion

MGD is a common disease in clinical practice. Population-based studies suggested that the incidence of MGD was higher in Asia, with a reported prevalence of 46.2% to 69.3% [6, 15–17]. In a study conducted in the United States and Europe, more than 80% of dry eye patients were found to have MGD [18]. The existing literature showed that the prevalence of MGD increased with age [15, 19, 20], and MGD also occurred in young people [21–23]. As a summary of the above literature, high prevalence and younger trend of MGD suggest that it will be important to identify which preclinical features of early-stage MGD or asymptomatic MGD

might be a predictor of progressive disease, and early intervention may thwart MGD. In addition to the meibomian gland expression or meibography [3], we also attempted to measure the LLMT with AS-OCT to detect the presence of MGD, so as to provide a certain clinical guidance for identifying and treating MGD earlier in the disease process.

Although it was difficult to measure the lid margin thickness, people were still working on it in several different ways. Hykin and Bron [9] measured the lid margin thickness at the free edge including the wet part of the eyelid (mucosa) with a vernier micrometer. The lid margin thickness in adults was 1.95 ± 0.07 mm in the upper lid and 1.87 ± 0.06 mm in the lower lid, with no significant difference between sexes. Meanwhile, Bron et al. [5] reported that the normal lid margin from its posterior border to the posterior lash line was approximately 2.5 mm wide in the adults. He [10] suggested that the lid margin thickness in Chinese (15–80 years) measured by a small ruler was approximately 2.0 mm in the upper lid and 1.5 mm in the lower lid. In addition, Pult et al. [11] used a Scheimpflug camera to measure the lid margin thickness in 15 adults, with no significant difference between the upper lid (1.8 mm) and the lower lid (1.7 mm). In this study, the LLMT measured by AS-OCT was less than that reported in the foregoing literature [5, 9–11]. One major reason for this discrepancy was that the LLMT we measured only included the width of the keratinized lid margin surface, excluding the marginal mucous membrane and MCJ. It should be emphasized that for the MCJ, its width varied due to different measurements, ranging from 0.09 to 0.3 mm [24–28].

According to reports in the literature [2, 9], the lid margin thickened with age over the first 20 years of life due to enlargement of the orbicularis and meibomian glands, but Hykin and Bron [9] suggested that the lid margin thickness in adults did not change with age. This conclusion may not be very well understood, because age-related changes in the lid margin anatomy had been described in the previous studies [5, 9, 19]. Contrary to the conclusions drawn by Hykin and Bron [9], our present study showed that the LLMT in adults also seemed to be linked with age, which further supported the theory that the prevalence of MGD, including asymptomatic MGD, increased with age [15, 19, 20, 29–31]. Specifically, in this study, the LLMT in young adults aged 20 to 39 was relatively stable, then increased with age (over 40 years).

The average thickness of the lower lid margin in men was greater than that in women ($p = 0.03$), which was inconsistent with the observations of Hykin and Bron [9].

At present, the relation between the LLMT and sex is not clear, but there were some notable studies regarding the association between changes in the meibomian glands and sex [15, 19, 30–41]. Siak et al. [32] showed that a higher proportion of men had MGD compared with women across all age groups ($p < 0.001$). Den et al. [19] also suggested that a high prevalence of abnormal lid margin and meibomian gland dropout was observed more frequently in men compared with women (≥ 70 years). However, Lin et al. [15] revealed that women with dry eye symptoms showed a higher prevalence of anatomically abnormal meibomian glands than men ($p = 0.078$). Some laboratory studies [34–41] have found that abnormal lid margin and/or meibomian glands may be related to sex hormones. All the above-mentioned studies indicated a controversial association between MGD and sex, which still needs further study. Additionally, the lower lid margin in outdoor workers may be directly exposed to more ultraviolet radiation in sunlight [42–44], which may have a pathological impact on the lower eyelid disease, so labor distribution may have been hypothesized to explain sex differences [44].

In this pilot study, we innovatively used AS-OCT with the advantages of being easier, rapid, and noninvasive to measure the LLMT – the keratinized skin width. A good agreement between two operators showed the measurements of LLMT with AS-OCT were reproducible, which might provide a new insight for some eyelid disorders in the future. For instance, establishing a normal range of the LLMT for different age groups may be helpful for a quantitative analysis for early-stage MGD. In addition, we found that age and gender were significant factors affecting the LLMT in this study, despite the small sample size. Finally, it will be the focus of our future research to explore the relation between the LLMT and eyelid pressure, MGD.

However, there were some limitations in using AS-OCT to measure the LLMT in our study including the following. (1) This study only measured the keratinized lid margin surface width from posterior lash line to the MCJ, not the full thickness of lid margin. (2) This study only measured the lid margin thickness in the lower lid, not the upper lid. (3) Once the images were not well centralized, then the measurement of LLMT would encounter difficulties. (4) We did not investigate associations between the lid margin thickness and clinical signs, systemic diseases. (5) A larger sample size and multicenter study would be helpful for better verifying the feasibility of AS-OCT. Further studies are warranted to provide more information.

In conclusion, a good agreement between two operators indicated that noninvasive AS-OCT seemed to be a reliable method and might be useful for investigating the LLMT in normal and some eyelid-related diseases in the future, especially in early-stage MGD. In addition, we found that the LLMT appeared to be closely related to age and gender.

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Statement of Ethics

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

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

D.-H. Wang conceived and designed the study, with input from X.-Q. Liu. D.-H. Wang and Z.-Y. Li analyzed the data, and wrote the initial manuscript draft. X.-Q. Liu actively reviewed and revised the manuscript, and all authors approved the final submitted manuscript.

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