European Review for Medical and Pharmacological Sciences 2020; 24: 1593-1601

Analysis of factors leading to lid wiper epitheliopathy

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Abstract. – OBJECTIVE: Lid wiper epitheliopathy (LWE) has received more attention during the diagnosis and treatment of the dry eye. However, its causes and pathogenesis remain unclear. We aimed to explore the etiology of LWE by analyzing the association between the severity of LWE and different anatomical and tissue morphological examination characteristics using confocal microscopy on eyes with dry eye syndrome.

PATIENTS AND METHODS: We recruited 350 patients with LWE and dry eye syndrome (350 eyes). We examined the eyes with lid-wiper staining, conjunctival staining, a comprehensive ocular surface exam using the OCULUS keratography 5M, conjunctival impression cytology, and confocal microscopy observations. We analyzed the associations between each indicator and the LWE staining score.

RESULTS: According to the Spearman's analysis, the LWE staining score was weakly associated with thickness of the lipid layer (r=0.1737, *p*=0.0005) and severity of Meibomian gland dysfunction (r=0.2026, *p*<0.0001); and strongly associated with staging of conjunctival impression cytology (r= -0.7694, *p*<0.0001). Pearson's correlation analysis indicated that, LWE staining score was moderately associated with age (r=0.4165, *p*<0.0001), tear meniscus height (r=0 -0.4019, *p*<0.0001), and NIKBUT-first (noninvasive keratography tear film breakup time) (r= -0.5108, *p*<0.0001); and strongly associated with NIKBUT-average (r= -0.7820, *p*<0.0001) and ocular staining score (r=0.6113, *p*<0.00001). Some patients presented abnormal blinking. We observed deeper lesion depths and more holes and fissures in the lid wipers of patients with more severe LWE than in patients with milder LWE.

CONCLUSIONS: Abnormal friction factors caused by insufficient lubrication between the lid wiper area and the ocular surface seem to influence the development and/or the severity of LWE. Aggravation of LWE further increases the frictional damage between the lid wiper and the ocular surface.

Key Words:
Lid wiper, Lid wiper epitheliopathy, Dry eye.

Introduction

The incidence of dry eye has been increasing yearly, showing a trend of development among younger patients. Dry eye can cause eye discomfort and seriously affect people's work and quality of life[1]. Severe dry eye can cause keratoconjunctival lesions that affect vision[2]. Dry eye requires long-term treatment and there is no particularly effective treatment[3]. Therefore, early diagnosis and early treatment are particularly important. In 2002, Korb et al[4,5] first proposed the concept of "lid wiper epitheliopathy (LWE)" and suggested that this lesion might represent an early change in dry eye. Yan et al[6] found that the LWE detection might help diagnose dry eye earlier than other routine examinations in the clinic providing an objective examination index. However, the study of LWE is still preliminary; its causes and pathogenesis are unclear, and its treatment is also in the exploratory stages[7]. In this research, we stained, observed, and graded the lid wiper region of patients with dry eye symptoms and examined patients with positive staining using the OCULUS keratography 5M, impression cytology, and confocal microscopy. We determined tear volumes, tear film quality, lipid layer condition, Meibomian gland function, grading of impression cytology, and examined the conjunctival staining and anatomical and histo-morphological changes of the lid wiper region to explore the etiology of LWE.

Patients and Methods

Ethical Approval

We conducted this study in accordance with the Declaration of Helsinki and the Medical Ethics Committee of Beijing Jishuitan Hospital approved it. We obtained informed written consents from the patients before their enrollment.

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Subjects

We randomly recruited 350 patients with LWE (350 eyes) and dry eye symptoms treated at the ophthalmology department of Beijing Jishuitan Hospital between January 2015 and January 2019. The inclusion criteria included (1) ages between 20 and 75 years, (2) absence of scars or neovascularization at the cornea by slit lamp examination, (3) absence of anatomical abnormalities by external eye examination (including eyelid inflammation, spasm, and eversion, or embolism at the punctum), and (4) willingness to cooperate with the examination and ability to have their upper eyelid turned up. We excluded patients (1) with conjunctival abnormality or inflammation, (2) those using local or systemic antibiotics due to eye infection, (3) those using eye drops other than artificial tears, (4) those who had used artificial tears within 2 h prior to examination, (5) and those with a history of eye trauma or surgery.

Examination and Grading of the Lid Wiper Region by Staining

We adopted the optimized staining method proposed by Varikooty et al[8]: briefly, the lissamine green B & fluorescein sodium ophthalmic strip (Tianjin Jingming Electron Material, China) was soaked in normal saline and dropped into the inferior fornix conjunctiva; this step was repeated after 1 min. After 3 min, the upper eyelid was turned over, and the wiper region was observed under the 5-mm ×100-mm slit light band under 16X magnification and cobalt blue filtration. We recorded and graded the sodium fluorescein staining level and sagittal width of the upper lid wiper region. We observed the upper lid wiper region with the white light of the slit lamp and recorded and graded the level of lissamine green staining and the sagittal width of the region. We analyzed data from the right eye in each patient.

We applied the grading method of Korb et al[4,5], where the horizontal staining width affords 0 points if <2 mm,1 point if between 2 and 4 mm, 2 points if between 5 and 9 mm, and 3 points if ≥10 mm; and the ratio of sagittal staining height over the lid wiper area affords 0 points if <25%, 1 point if between 25 and 50%, 2 points if 50 to <75%, and 3 points if ≥75%. The average score of the horizontal width and sagittal height is the score of the particular staining. The average score of the sodium fluorescein and lissamine green staining methods gave the final LWE score of the patient. We graded LWE lesions according to the LWE score of the patients, with 0.25 to 1 point being level 1 (mild), 1.25 to 2 points being level 2 (moderate), and 2.25 to 3 points being level 3 (severe).

Examination and Grading of Conjunctiva by Staining

We graded the conjunctiva according to the ocular staining score (OSS) grading method. We divided the eye surface into three parts: nasal, corneal, and temporal conjunctivas. We graded the nasal and temporal conjunctivas individually according to the number of conjunctival lissamine green staining points of the lid wiper region (the highest score for the bilateral bulbar conjunctiva of each eye was 6 points). We graded the corneal staining according to the number, morphology and distribution of sodium fluorescein staining points. The highest score for the cornea of a single eye was 6 points, and the highest OSS score for a single eye was 12 points[9].

Examination By an Ocular Surface Analyzer

We examined patients with LWE using an ocular surface analyzer OCULUS keratography 5M apparatus (K5M, OCULUS, Germany) between 9:00 and 11:00 in the morning after the initial examination. The examination room was a quiet, closed set-up with no light stimulation and thermal light source interference. The temperature was controlled at 25°C, and the relative humidity at 30%- 40%.

We measured and recorded the noninvasive keratography tear meniscus height (NIKTMH), noninvasive keratograph tear film breakup time (NIKBUT), lipid layer distribution (TF-lipid), and the number and morphology of Meibomian glands. Each patient was also observed for 30 s to determine whether they exhibited abnormal blinking frequencies or incomplete blinking, and we recorded the frequencies as increased if the number of blinks was greater than 8 times and as decreased if less than 4 times.

Confocal Microscopy Examination

We performed laser confocal microscopic examinations (using a Heidelberg Retina Tomograph III and a Rostock corneal module) on the eyes of patients with LWE to see the lid wiper region and its adjacent area. The laser wavelength was 670 nm, the viewing field was 380 μm×380 μm, the magnification was 800X, and the resolution was 1 μm.

Impression Cytology Examination

We selected 90 patients with mild, moderate, and severe LWE (30 eyes from each group for a total of 90 eyes) and performed conjunctival impression cytology examinations in the upper conjunctivas. We observed conjunctival cell morphological and goblet cell distributions following periodic acid-Schiff staining (PAS) and classified them according to the Nelson grading criteria[10].

Statistical Analysis

We analyzed the data using the SPSS 19.0 statistical software (IBM, Armonk, NY, USA). We determined the correlation between the LWE staining score and continuous variables of age, TMH, NIKBUT-first, NIKBUT average, and OSS by Pearson's correlation analysis. Spearman's correlation coefficient was used to assess correlation between LWE staining scores and ordinal variables of thickness of lipid layer, severity of Meibomian gland dysfunction, and impression cytology grading scores. We also compared LWE staining scores amongst sub-groups of TMH by *t*-test and amongst sub-groups of lipid layer thickness and severity of Meibomian gland dysfunction by means of One way Analysis of Variance (ANOVA) with Tukey honestly significant difference (HSD) post-hoc test. We considered *p*-values <0.05 as statistically significant.

Results

Clinical Characteristics of Patients With LWE

From January 2015 to January 2019, we randomly selected 350 symptomatic patients with LWE, 128 patients (128 eyes) were men and 222 patients (222 eyes) were women, and their ages ranged between 23 and 72 years. The clinical characteristics found are shown in Table I.

Correlation Between LWE Staining Score and Other Examination Results Relevant to Dry Eye Syndrome

According to the Spearman's analysis, the LWE staining score was weakly, but significantly associated with the thickness of the lipid layer

Table I. Clinical characteristics of patients with LWE.

Variables	Values
LWE staining score (points)	1.58 ± 0.49
Mild	44 (12.57%)
Moderate	270 (77.14%)
Severe	36 (10.28%)
Age (years)	46.19 ± 11.70
TMH (mm)	0.21 ± 0.07
< 0.2 mm (n=190)	1.81 ± 0.41
≥ 0.2 mm (n=160)	1.39 ± 0.47
NIKBUT	
First (s)	4.43 ± 1.730
Average (s)	7.29 ± 2.49
Lipid layer thickness	
Normal	180 (51.42%)
Thick	114 (32.57%)
Thin	56/350 (16%)
Meibomian gland deficiency (points)	1.88 ± 1.51
Mild	221 (73.43%)
Moderate	47 (15.61%)
Severe	33 (10.96%)
OSS of conjunctival staining (points)	3.22 ± 2.47
Impression cytological classification	
Level 0	18/90
Level 1	39/90
Level 2	24/90
Level 3	9/90

Data expressed as number of patients (percentage) or Mean ± Standard Deviation. *Legends*: LWE, lid wiper epitheliopathy; TMH, non-invasive keratography tear meniscus height; mm, millimeter; NIKBUT, non-invasive keratography tear film breakup time; OSS, ocular staining score; n=number of patients.

(r=0.1737, p=0.0005; Figure 1A) and the severity of Meibomian gland dysfunction (r=0.2026, p<0.0001; Figure 1B); and strongly and significantly associated with the staging of conjunctival impression cytology (r= -0.7694, p<0.0001; Figure 1C). According to Pearson's correlation analysis, LWE staining score was moderately and significantly associated with age (r=0.4165, p<0.0001; Figure 2A), TMH (r=0 –0.4019, p<0.0001; Figure 2B), and NIKBUT-first (r= –0.5108, p<0.0001; Figure 2C); and strongly and significantly associated with NIKBUT-average (r= –0.7820, p<0.0001; Figure 2D) and OSS (r=0.6113, p<0.00001; Figure 2E).

We also found statistically significant difference in LWE staining scores amongst patients with TMH <0.2 mm and those with ≥0.2 mm (p<0.0001; Table II). Similarly, the LWE staining scores of patients with thick, thin, and normal lipid layers differed significantly from each other (p<0.00001). The LWE staining scores of patients with mild, moderate, and severe Meibomian gland deficiency differed significantly from each other (p<0.00001).

Examination of Blinking Frequency and Incomplete Blinking

Among the 350 patients, 4 (1.15%) had increased blinking frequencies, 55 (15.71%) had decreased blinking frequencies, and 18 (5.14%) had incomplete blinking. In all, patients with abnormal blinking accounted for 22% of all subjects.

Examination of the Lid Wiper Region by Confocal Microscopy

Confocal microscopy showed that the cells of the epithelial tissue at the palpebral margin were arranged regularly and had an even size. The boundary of the tissues had high reflection and the center had low reflection, showing bright and neat high-reflection networks. At the transition zone of the skin mucosa, the keratinized and stratified squamous epithelial cells terminated at the center of the Meibomian gland opening, forming a clear

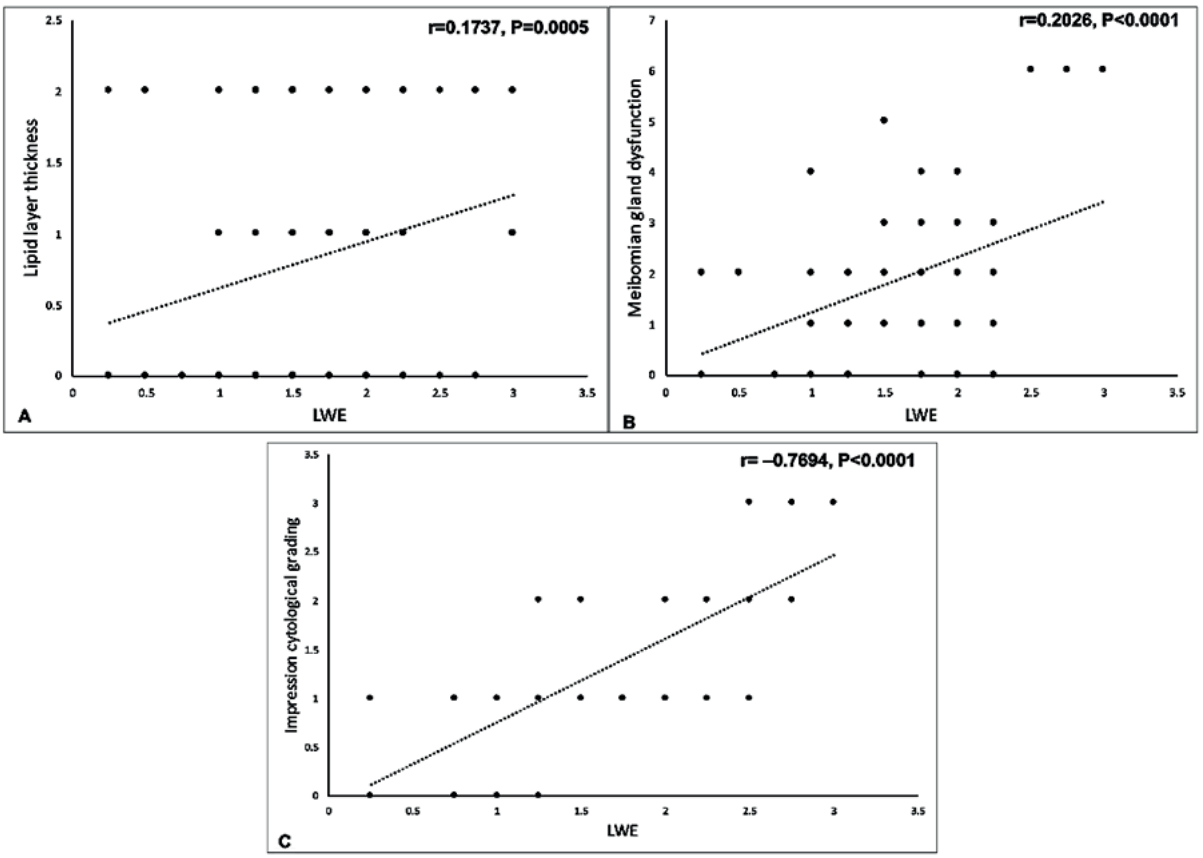

Figure 1. Scatter chart of Spearman's correlation analysis between lid wiper epitheliopathy (LWE) staining scores. **A,** Thickness of the lipid layer. **B,** Meibomian gland dysfunction. **C,** Staging of conjunctival impression cytology.

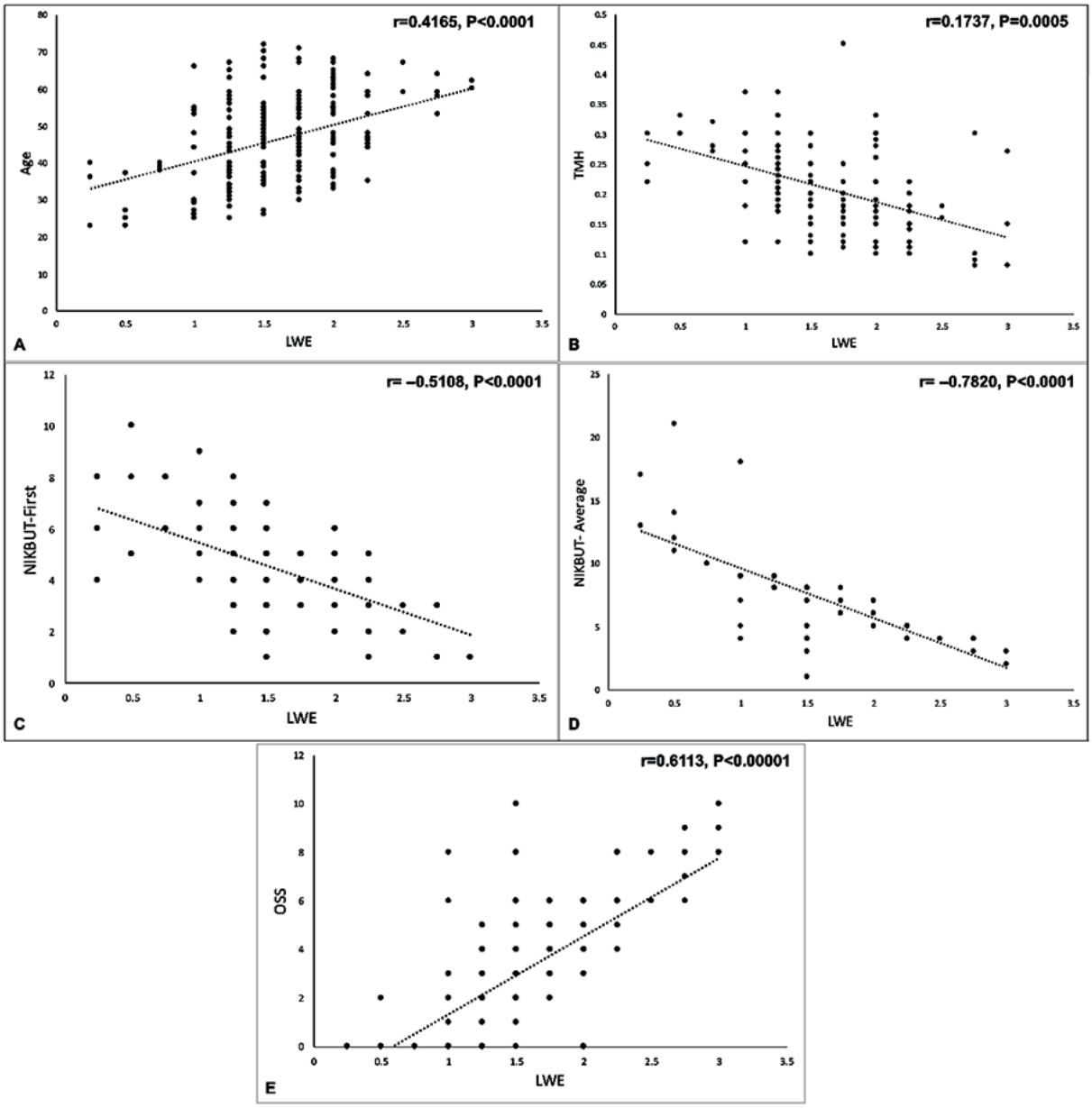

Figure 2. Scatter chart of Pearson's correlation analysis between lid wiper epitheliopathy (LWE) staining scores. **A,** Age. **B,** Tear meniscus height (TMH). **C,** Non-invasive keratography tear film breakup time (NIKBUT)-first. **D,** NIKBUT-average. **E,** Ocular staining score (OSS).

dividing line. Patients with different severities of LWE had no significant differences in the cell and tissue structures of the palpebral margin or at the transition zone of the skin mucosa.

The cell reflection at the lid wiper regions was weak, with no clear boundaries or obvious high reflection boundaries. The cell densities were reduced, and cells were loosely arranged. We detected large numbers of elliptical and highly reflective white blood cells, as well as some highly reflective spots (possibly cell debris). Some goblet-shaped cells had large volumes with low reflection at the edge and high reflection at the center; these cells had a double wall structure and may have been goblet cells. We detected substantial amounts of a highly reflective substance on the surface of these goblet-shaped cells, which may have been highly reflective mucus secreted by them. The depth of lid wiper lesions in patients with moderate and severe LWE were

Table II. Analysis of LWE staining scores based on different clinical characteristics.

Characteristic	No. of patients	LWE staining scores	*p*-value
TMH (mm)			$p < 0.0001$*
< 0.2 mm	160	1.81 ± 0.41	
≥ 0.2 mm	190	1.38 ± 0.47	
Lipid layer thickness			$p < 0.00001^{\#}$
Normal	180	1.48 ± 0.44	$p < 0.000011$
Thick	114	1.66 ± 0.53	$p = 0.0362$
Thin	56	1.73 ± 0.5	$p = 0.633$
Meibomian gland deficiency (points)			$p < 0.00001^{\#}$
Mild	221	1.47 ± 0.4	$p < 0.00001^{a}$
Moderate	47	1.87 ± 0.17	$p < 0.00001^{b}$
Severe	33	2.09 ± 0.67	$p = 0.05^{c}$

LWE, lid wiper epitheliopathy; TMH Tear meniscus height; mm, millimeter. **t*-test, #One way Analysis of Variance (ANOVA) with Tukey honestly significant difference (HSD) post-hoc test.[1]Normal *vs*. Thin, [2]Normal vs. Thick, [3]Thick *vs*. Thin. aMild vs. Moderate, [b]Mild vs. Severe, [c]Moderate *vs*. Severe.

significantly deeper than those in patients with mild LWE. Compared to patients with mild LWE, the lid wiper region of patients with moderate to severe LWE had more fissures and holes (Figure 3). However, eyes with different LWE severities did not differ significantly in their amounts of white blood cells, highly reflective substances, or goblet cells.

Discussion

Korb et al[4] found a stainable region in the upper conjunctiva that is in contact with eyeball surface during blinking, and they named it "lid wiper". Shaw et al[11] confirmed the presence of the lid wiper region by adhering pressure-sensitive test paper to the surface of right contact lens and showing that this region is the only tissue of the upper eyelid in contact with the ocular surface. Both Knop et al[12,13] (through staining of eyelid tissue sections) and authors in this study (through confocal microscopy) found that the morphology of the lid wiper region was more similar to the cubic epithelium of conjunctival tissue than the stratified squamous epithelium (the epithelial tissue structure of this region was loose and contained more water). As a result, these tissues cause little friction injury to the cornea and conjunctiva during blinking and conform to the cornea and produce a thin and uniform tear film. Humans blink 10-12 times per min. The nonsleeping time in each day is approximately 16 h, so normal individuals blink almost 10,000 times each day, and the lid wiper is

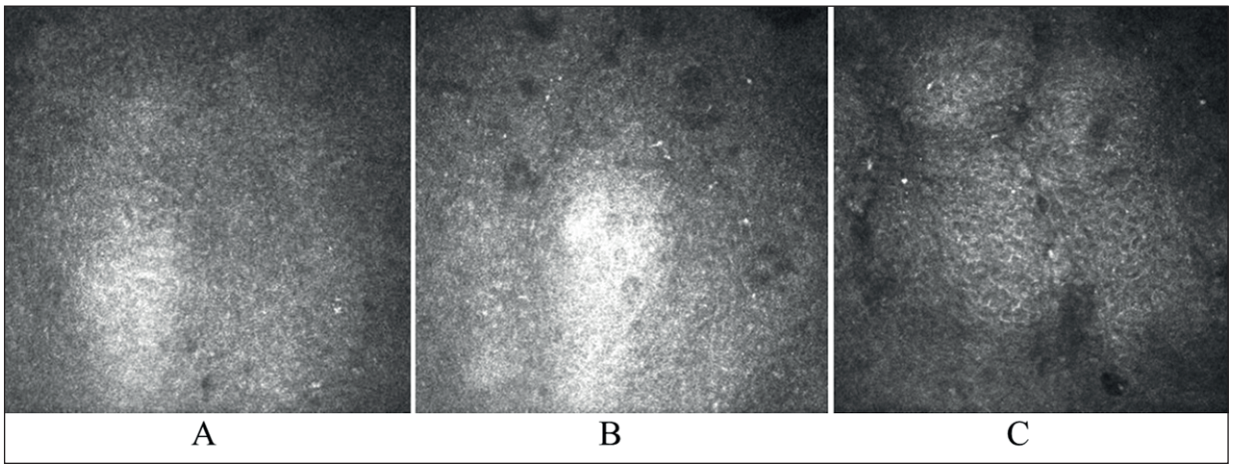

Figure 3. Examination of the lid wiper region under confocal microscopy (magnification ×800). **A**, Patients with mild LWE had few holes and fissures in the lid wiper region. **B**, Patients with moderate LWE had many holes in the lid wiper region. **C**, Patients with severe LWE had many fissures in the lid wiper region.

exposed to the friction of the ocular surface every day. Therefore, the pathogenesis of LWE has been related to abnormal friction[14]. The lid wiper region and abnormal ocular surface frictions derive from the following main aspect: insufficient lubrication of the interface leads to increased friction. A thin layer of tear film between the lid wiper region and the ocular surface that lubricates the interface. If the tear film is abnormal and lubrication is reduced, the friction increases. During blinking, the constant friction between the lid wiper and the ocular surface causes mechanical injury of the epithelial cells, which leads to lesions in the lid wiper region[15]. The tear film includes three main layers: the lipid, aqueous, and mucin layers. In this study, we found the NIKTMH to be moderately and significantly correlated with the LWE score, and the LWE scores in patients with NIKTMH >0.2 mm differed significantly from those in patients with NIKTMH <0.2 mm, suggesting that the degree of LWE staining is associated with the tear amount. However, our data suggest insufficient water in the tear film is not the main cause of LWE. The LWE staining score was moderately and significantly correlated with the NIKBUT-first and was strongly and significantly correlated with the NIKBUT-average. NIKBUT represents the stability of the tear film, and the NIKBUT-average can better reflect the overall status of tear film stability than the NIKBUT-first. Therefore, our data indicate the severity of LWE is closely related to the stability of tear film. The thickness of the lipid layer and the severity of Meibomian gland deficiency were significantly different among groups, suggesting that the function of the Meibomian gland is also associated with LWE. The Meibomian gland function affects the quality of the lipid layer and thereby the lubrication of the interface, which eases the friction. Our results also demonstrated moderate significant correlation between age and LWE score. Moss et al[16] have shown that age is one of the risk factors of dry eye. Perhaps the decrease of tear secretion and Meibomian gland dysfunction caused by the increased age leads to the increase of interface friction, and increased incidence of LWE.

The conjunctival impression cytology classification was strongly and significantly correlated with the LWE staining score, suggesting that the two are closely related. The impression cytology classification can indirectly reflect the distribution and number of goblet cells, which reflects the status of the tear mucin layer. Therefore, abnormal mucin also promotes LWE. Studies[17,18] have suggested that topical rebamipide application increases the number of goblet cells and improves LWE, suggesting an effect of abnormal mucin on LWE. In all, these and our observations show that the factors affecting the quality of the tear film, such as insufficient tear volume, reduced tear film stability, abnormal Meibomian gland function, and lipid layer, and abnormal mucin, are all related to LWE, and that the LWE associations are stronger with the tear film stability and the abnormal mucin.

If the surface of the conjunctiva is not smooth, the friction of the interface increases. In this study, we found that the conjunctival staining score was strongly and significantly correlated with the LWE staining score. This is consistent with the findings of Wang et al[19]. Injury of the conjunctival epithelia leads to roughness of the ocular surface and increased friction, which in turn aggravates LWE.

At the same time, LWE aggravation increases the friction damage between the lid wiper and the ocular surface. In this study, through confocal microscopy, we found that patients with different severities of LWE had similar epithelial tissues at the palpebral margin or at the transition zone of the skin mucosa. However, compared to patients with mild LWE, the lesion depths in the lid wiper areas were deeper and had more holes and fissures in patients with moderate to severe LWE than in those with only mild LWE. The increased friction due to insufficient interface lubrication may be the cause of these fissures and holes. The positive corneal fluorescein and lissamine green staining may be related to these fissures and holes. These fissures and holes may further disturb the function of the lid wiper, leading to an incomplete ocular surface tear film and to increased friction damage between the lid wiper and ocular surface, inducing dry eye syndrome and corneal injury. We also noticed that the epithelial morphology of the lid wiper region was similar to that in the cubic epithelia of the conjunctival tissue which is loose. As a result, the lid wiper region is more susceptible to lesions than other regions, and this may also explain why LWE occurs before other dry eye indicators.

Blinking Abnormalities and Changes in Friction Frequency

Abnormal blinking involves either increased or decreased frequencies or incomplete blinding. An increased blinking frequency augments the number of frictions between interfaces, promot-

ing injury. A decreased blinking frequency or an incomplete blinking lead to thinning of the lipid layer of the tear film, resulting in reduced tear film stability[20]. By applying the clear magnification of the ocular surface analyzer, in the absence of illumination stimuli, we found that among the 350 patients, 4 had increased blinking frequency, 55 had decreased blinking frequency, and 18 had incomplete blinking. It may be argued that the results of OCULUS keratography 5M apparatus may be affected by temperature, humidity, air mobility, and other factors. However, the data acquisition for this study was conducted in the same examination room at the same time period. We also controlled other environmental factors by managing light, temperature, and humidity in a closed quite examination room. However, due to the large variability in the records, LIPIVIEW needs to be applied in a future study to further examine this indicator. There are some limitations, we did not consider other characteristics like abnormal eyelid anatomy, abnormal contact between the upper and lower palpebral margins, and inflammation of the lid wiper region[21]. Additionally, Yamamoto et al[22] showed that increased pressure on the eyeball by the eyelids could also lead to increased friction, which aggravated LWE. We will further examine and confirm these factors in our future studies.

Conclusions

In summary, the etiology of LWE is complicated, but it is associated with abnormal friction factors caused by insufficient lubrication between the lid wiper region and the ocular surface. At the same time, the aggravation of LWE increases the interface friction, which induces or aggravates dry eye syndrome and cornea damage.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This study was supported by Beijing Talents Fund (No: 2015000021467G176) from the Organization Department of the Beijing Municipal Party Committee of China.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

LS conceived and designed the study; LS, DH, and HX collected and analyzed the data of this study; LS wrote the paper; and TS reviewed and edited the manuscript. All authors read and approved the manuscript.

Ethics Approval and Consent to Participate

The Ethics Committee of the Beijing Jishuitan Hospital approved this research (approval number: 201907-10).

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