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Dry Eye Disease and Refractive Corrections

Lead Guest Editor: David Madrid-Costa
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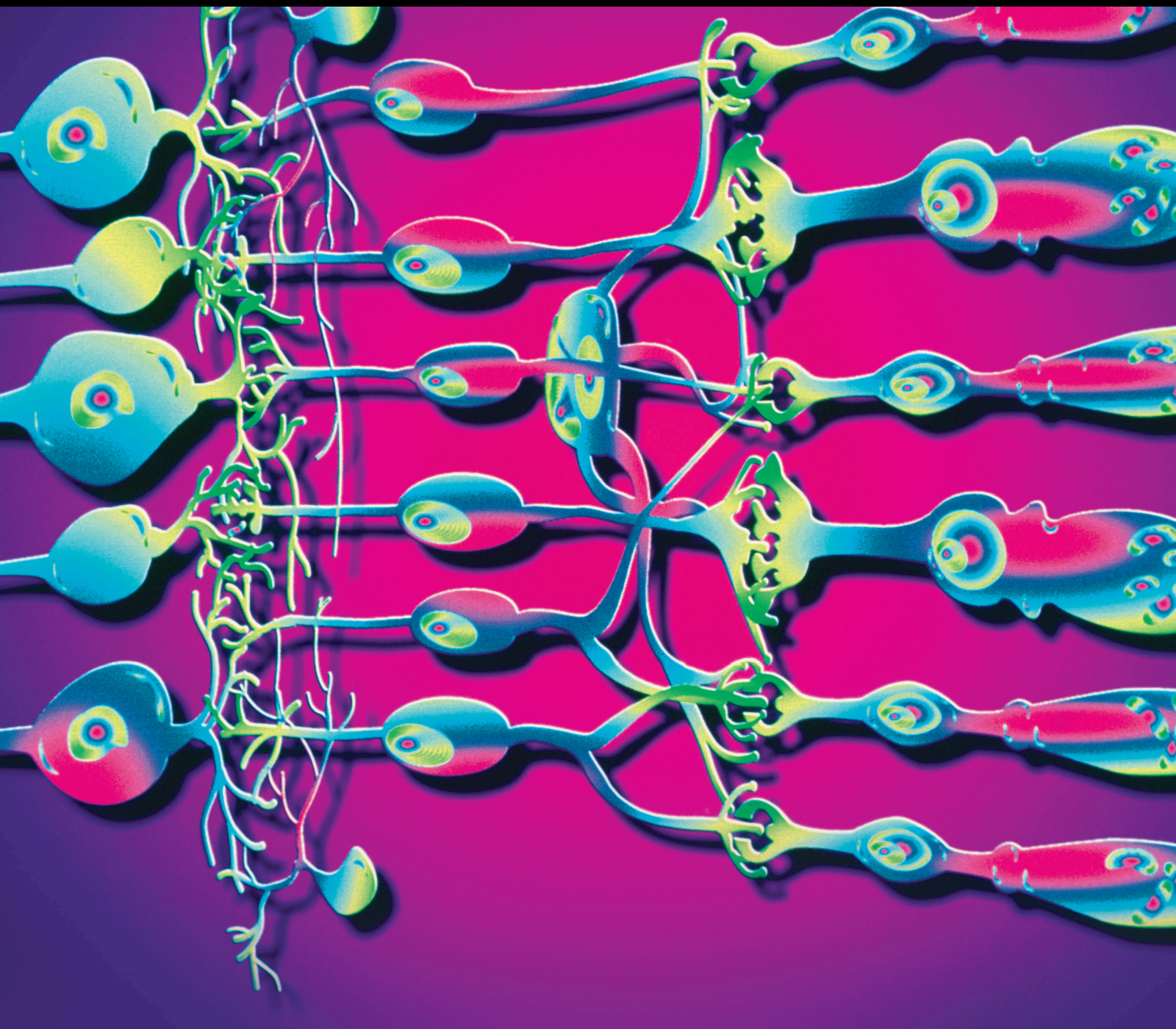

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Editorial

Dry Eye Disease and Refractive Corrections

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Between the early 90s and 2004, more than 17 million patients received LASIK surgery worldwide. Nowadays, almost one million patients undergo corneal refractive surgery in the United States of America every year [1]. In addition, cataract surgery has become the most common surgical procedure [2, 3]. At the same time, the number of contact lens wearers is on the rise with a worldwide estimated number of around 120–140 million. Furthermore, the growing popularity of corneal refractive surgery, intraocular lens implantation, and contact lens use provokes that the number of patients that undergo several of these treatment modalities has also risen. This creates scenarios where tear film physiology is dramatically affected by one or several of the abovementioned procedures. In turn, this increases the risk of developing dry eye disease (DED). The prevalence of DED naturally increases with age, and the abovementioned treatments are often used to alleviate conditions in elderly patients such as cataracts or presbyopia.

Different types of refractive treatments can induce changes in tear film stability, an intensification of the ocular signs related to dry eye and symptoms, and an exacerbation of DED. The reverse pathway also occurs; an alteration on the ocular surface and tear film compromises the success of the abovementioned techniques for vision correction by altering the final visual quality and comfort of patients. The two-way interactions between several vision restoration techniques and DED have a worldwide impact that is on the rise.

DED and vision correction are hot topics on the field of vision science research and are key to public health organizations. This special issue aimed at focusing on novel approaches to treat and manage DED, advances in refractive corrections, and in the interrelations between both of these factors. Accordingly, this special issue gathered seven articles that addressed different aspects related to this hot topic.

In order to contextualize the current research efforts in the DED field and to know which are the most relevant topics, Sanchez-Tena et al. performed a citation network study and concluded that the definition and classification of DED followed by its treatment are the most researched area in this field. Regarding DED treatment approaches, Sakane et al. have presented the effects of a commercially available ophthalmic suspension (mucin secretagogue) on the quality of life of Japanese patients with DED.

It is very well known that DED is a multifactorial condition that can be exacerbated by systemic conditions. Wang et al. investigated the incidence, severity, and influencing factors of DED in systemic lupus erythematosus patients without secondary Sjögren's syndrome. Their conclusions stress the importance of monitoring the ocular surface of systemic lupus erythematosus patients and the early diagnosis of DED for improving the quality of life of these patients.

DED coexists sometimes with other ocular diseases aggravating its symptomatology and evolution. One clear example of these two-way interactions is found when keratoconus patients suffer greater symptoms of DED. Meibomian gland dysfunction (MGD), with a higher prevalence in keratoconus patients, plays a central role in DED and keratoconus. Meibomian glands heavily contribute to a healthy tear film, so when they are dysfunctional, the tear

film is affected and eye rubbing normally increases. Very interestingly, eye rubbing is one of the mechanical etiological factors in keratoconic disease. Moreover, DED or tear film instability influences the success of the refractive correction of patients with keratoconus. Exploring these interactions, Mostafa et al. used noncontact meibography to examine the morphological changes in the meibomian glands of patients with keratoconus and its relationship with tear film parameters.

Blink rate affects tear film stability, and it can affect both DED symptomatology and the success of the refractive correction. This topic was addressed in two studies. García-Montero et al. reported the influence of different blink rate patterns on the tear film and on optical quality dynamics with different contact lens materials. Additionally, Itokawa et al. investigated the association between ocular surface temperature, tear film stability, and blink rate in patients after cataract surgery and concluded that blink rate may be a useful parameter for evaluating tear film stability in post-cataract surgery patients.

In summary, this special issue identifies the research hot topics and reports information on novel treatments for DED, explores the association between DED and other ocular and systemic diseases, and explores the interactions between blink rate, ocular surface temperature, contact lens materials, tear film stability, cataract surgeries, and optical quality dynamics. Hence, we believe this special issue provides extremely useful knowledge intimately related to *Dry Eye Disease and Refractive Corrections*.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

David Madrid-Costa
James S. Wolffsohn
Javier Ruiz-Alcocer
Pablo De Gracia

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Research Article

Dry Eye Indexes Estimated by Keratograph 5M of Systemic Lupus Erythematosus Patients without Secondary Sjögren's Syndrome Correlate with Lupus Activity

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Purpose. To investigate the incidence, severity, and influencing factors of dry eye in systemic lupus erythematosus (SLE) patients without secondary Sjögren's syndrome (sSS). *Methods*. A total of 78 patients who were diagnosed with systemic lupus erythematosus and met inclusion criteria were selected as the study subjects in this cross-sectional study. Tear meniscus height (TMH) and noninvasive Keratograph tear breakup time (NIKBUT) including NIKBUT-first and NIKBUT-average of the subjects were measured using a noninvasive ocular analyzer, the Keratograph 5M (Oculus, Wetzlar, Germany). Symptoms related to dry eye were assessed using the Ocular Surface Disease Index (OSDI). The severity of SLE was evaluated by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). Results of the levels of 4 serum antibodies were collected from the patients' medical records. Correlations between SLEDAI and various ocular surface parameters were analyzed, and multiple-factor binary logistic regression analysis was conducted. *Results*. In the study subjects, mean TMH was 0.22 mm, mean NIKBUT-first was 9.12 s, and mean OSDI was 13.14. The subjects (19 eyes) whose NIKBUT-average was < 10 s and OSDI was ≥ 13 accounted for 24.36% of all the included patients. SLEDAI showed a statistically significant correlation with TMH ($r = -0.233$, $p = 0.040$), NIKBUT-first ($r = -0.254$, $p = 0.025$), NIKBUT-average ($r = -0.343$, $p = 0.002$), and OSDI ($r = 0.256$, $p = 0.024$). According to multiple-factor binary logistic regression analysis, SLEDAI could be considered as a risk factor of the incidence of dry eye in SLE patients without sSS. *Conclusions*. One-fourth of the SLE patients without sSS suffered from dry eye, and the severity of dry eye correlated with the activity of SLE.

1. Introduction

According to Definition and Classification Report of 2017 Tear film & ocular surface society and dry eye workshop II (TFOS DEWS II) [1], dry eye is a multifactorial disease of the ocular surface. It happens when the dynamic balance of tear film is disrupted and is accompanied by ocular surface symptoms. Dry eye disease was classified into two subtypes: aqueous deficient dry eye and evaporative dry eye, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities may play etiological roles. However, a recent pathophysiological study [2] supports a new scheme that aqueous deficient and evaporative dry eye may exist as a continuum. Tear deficiency is the predominant cause of immune-related dry eye, and partial or total impairment of autoimmune system could lead to reduction or even absence of tear [3].

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs in the human body [4]. The disease is characterized by erythema of cheeks, and young women are more likely to be affected. SLE patients usually experience persistent headaches, fever, swelling of joints, limited mobility, and swelling of muscle in the whole body. Meanwhile, abnormal results of laboratory tests, such as hematuria, proteinuria, low complement, low leukocyte, and low platelet, are observed in SLE patients. Accordingly, serological tests of anti-double-stranded DNA antibody (anti-dsDNA) level and the titer of antinuclear antibody

(ANA) are commonly used to assess disease activity and predict lupus flare. Moreover, SLEDAI-2K questionnaire [5] is an internationally acknowledged tool to evaluate the activity of SLE. It was reported that incidence of dry eye in systemic lupus erythematosus (SLE) patients is relatively high, and thus, the pathogenesis has been explored [6–9]. It is worthy to point out that some studies [6] regarding dry eye in SLE patients ruled out the impact of secondary Sjögren's syndrome (sSS), but some [7–9] did not. Previously, a cohort study [10] has shown that 1/5 SLE patients suffered from sSS, and sSS was observed in the early course of SLE disease. Since sSS itself has nonnegligible impact on SLE patients, it is difficult to distinguish whether the damage of ocular surface is due to SLE or sSS.

To further evaluate the ocular surface condition of included SLE patients, a newly developed noninvasive technique Keratograph 5M was used in the present study. Lan et al. [11] stated that ocular surface microenvironment was very sensitive and susceptible to many factors including temperature, humidity, and sodium fluorescein. In comparison with invasive methods such as sodium fluorescein, Keratograph 5M allows assessment of ocular surface noninvasively without interfering with its balance or altering its condition [12–14]. In addition, keratograph 5M detects very early changes of tear film, displaying more sensitive detection abilities than other conventional assessment methods [15]. To the best of our knowledge, there are no studies which have investigated the ocular surface condition of SLE patients without sSS through Keratograph 5M.

The present study focused on the incidence, severity, and influencing factors of dry eye in SLE patients without sSS. The correlation between dry eye indexes and SLE severity was assessed, and multiple-factor binary logistic regression analysis was adopted to identify the risk factors of dry eye in SLE patients without sSS.

2. Materials and Methods

2.1. Participants. During February 2017 to January 2018, ophthalmic assessments such as visual acuity, slit lamp, and ophthalmoscope examination were conducted in 97 eyes of 97 participants at the First Affiliated Hospital of Anhui Medical University. For each participant, right eye was selected for measurement and statistical analysis. These subjects were diagnosed as SLE through Derivation and Validation of the Systemic Lupus International Collaborating Clinics Classification Criteria [16]. At the moment of exclusion, patients were denied of having a history of eye surgical procedures during the past year, using eye drops and contact lens in the past week. In addition, patients who suffered from cataract, retinal detachment, vitreous hemorrhage, especially pterygium, corneal scarring, and epithelium irregularity were ruled out from the research. To eliminate the impact caused by sSS, patients with positive anti-Sjögren's syndrome antigen A/Ro antibody (anti-SSA/Ro antibody) and anti-Sjögren's syndrome antigen B/La antibody (anti-SSB/La antibody) were ruled out, and the remaining 78 patients (78 eyes) denied having dry mouth symptoms. Since SLE is more common in females, 76 females and 2 male patients were enrolled in this study. The present study followed the tenets of the Declaration of Helsinki, and all patients informed consent. Moreover, the research was supported by the Clinical Ethics Committee of the First Affiliated Hospital of Anhui Medical University.

2.2. Dry Eye Examination. Tear meniscus height (TMH) and noninvasive Keratograph tear breakup time (NIKBUT) including NIKBUT-first and NIKBUT-average of the subjects were measured using a noninvasive ocular analyzer, the Keratograph 5M (Oculus, Wetzlar, Germany). Keratograph 5M was adjusted to fit the patient's position with the patient looking ahead; a photo was taken and particular attention was paid to the area below the pupil to record the TMH. For NIKBUT, Keratograph 5M was focused on the center of the pupil with the patient staring at the point in front of her/him. The subject was required to blink twice. Then, eyes were kept open until the subject could not tolerate. Keratograph 5M could calculate the NIKBUT-first and NIKBUT-average automatically. The average of three consecutive examination values was calculated, and the interval time was at least 60 s. Subjects were tested between 14:30 and 17:30 in a small office centrally heated to a temperature of 21°C–25°C with diffuse lighting. There were no ventilation ducts over the equipment.

2.3. Symptomatology Assessment. Patient symptoms were evaluated by the Ocular Surface Disease Index (OSDI) [17], a subjective questionnaire. The question asked whether the eyes had photophobia, foreign body sensation, pain, soreness, blurred vision, ghosting, and visual loss in the past week and whether eye discomfort made to suspend activities such as reading, driving at night, operating computer or bank machines, and watching TV during the past week. The scale also asked if eye discomfort occurred under the following conditions: windy weather, dry weather, and air condition. In order to quantify the symptomatology, each question had 5 levels, corresponding to different scores. The total OSDI score was then calculated on the basis of the following formula: $\text{OSDI} = [(\text{sum of scores for all questions answered}) \times 100]/[(\text{total number of questions answered}) \times 4]$ [18]. Thus, the OSDI is scored on a scale of 0 to 100, with higher scores representing greater disability.

2.4. SLEDAI-2K. The activity of SLE was assessed by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [5], a modification of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) which emphasized recent skin rash and proteinuria. However, SLEDAI-2K eliminated those newly developed manifestations to focus on the continuous state of the disease. SLEDAI-2K contained 24 components, 16 of which were clinical results and 8 were laboratory results. The total score of SLEDAI-2K was the sum of all 24 descriptor scores and fell between 0 and 105. The score represented manifestations which were present at the time of the visit or in the preceding

10 days. To have a valid degree of lupus activity, a 4-level scale was used for this purpose. 0–4 points were rated as basically no activity [19], 5–9 points were defined as mild activities, 10–14 points mean moderate activities, and more than 15 points were defined as severe activities.

2.5. Antibody Determinations. ANA, anti-dsDNA, and anti-SSB/La antibody, anti-SSA/Ro antibody were determined from their medical records. ANA is always tested in a patient who is suspected of having SLE. Anti-dsDNA is identified to be highly specific for SLE and has strong correlation with lupus activity. It has been widely acknowledged that anti-SSA/Ro and anti-SSB/La antibody have critical roles in sSS diagnosis [20–22]. To monitor the level of all the autoantibodies, the indirect immunofluorescence method was conducted, which is based on the principle of the binding of autoantibody/antigen complexes to the immune-fluorescent secondary antibody. Afterwards, fluorescence microscope was used to observe the fluorescence representing the existence of autoantibodies.

2.6. Statistical Analysis. Data were expressed as mean ± standard deviation. Kolmogorov–Smirnov test was used to validate whether the data were normally distributed. Pearson linear correlation analysis was used for data that were normally distributed, and Spearman's rank correlation was applied if variables did not meet the normal distribution. The correlations were considered strong if r was > 0.80, moderately strong if r was between 0.5 and 0.8, fair within if r was the range of 0.3 and 0.5, and poor if r was < 0.30 [23]. T-test was introduced for normally distributed data between groups, and the Mann–Whitney test was used to assess the differences between groups if the data were not normally distributed. Chi-square test was recommended for qualitative data. The relevant parameters were taken into multiple-factor binary logistic regression model to identify the risk factors of dry eye. The significance level was set at $p < 0.05$ (both sides). Dataset and statistical analysis were performed using SPSS software 19.0 (SPSS Inc., Chicago, USA) and MATLAB software 2017b (MathWorks Inc., Natick, USA).

3. Results

In Table 1, the general characteristics, including age, disease duration, dry eye indexes, and serological test results, were listed. The mean value of NIKBUT-first of 78 SLE patients was 9.12 s, which was less than 10 s the normal population. Moreover, the NIKBUT-first < 5 s (25 eyes) accounted for 32.05%, 5–10 s (28 eyes) accounted for 35.90%, and >10 s (25 eyes) accounted for 32.05% of SLE patients. The NIKBUT-average < 5 s (10 eyes) accounted for 12.82%, 5–10 s (27 eyes) accounted for 34.62%, and >10 s (41 eyes) accounted for 52.56% of patients with SLE, indicating that at least 50% of the patients included in this study had abnormal NIKBUT. Although the mean value of TMH was 0.22 mm, it should be taken into consideration that the TMH of 39.74% patients (31 eyes) was less than 0.20 mm. SLE subjects had moderate ocular discomfort OSDI scores, and the mean value was 13.14.

Table 1: Patient demographics.

Parameter	
Age (years)	37 ± 11
Female/male	76/2
Disease duration (years)	5.60 ± 4.32
Oral hydroxychloroquine (yes/no)	78/0
Eyedrop during the last week (yes/no)	0/78
TMH (mm)	0.22 ± 0.05
NIKBUT-first (s)	9.12 ± 5.97
NIKBUT-average (s)	11.71 ± 6.01
OSDI (score)	13.14 ± 12.92
SLEDAI (score)	6.55 ± 6.99
ANA titer	1544.36 ± 1423.68
Anti-dsDNA (positive/negative)	27/51
Anti-SSA/SSB antibody (positive/negative)	0/78

Values are expressed as average ± standard deviation. TMH = tear meniscus height. NIKBUT = noninvasive Keratograph tear breakup time. OSDI = Ocular Surface Disease Index. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index. ANA = antinuclear antibody. Anti-dsDNA = anti-double-stranded DNA antibody. Anti-SSA/SSB antibody = anti-Sjögren's syndrome antigen A/B antibody.

Subsequently, the data of TMH, NIKBUT-first, NIKBUT-average, and OSDI were ranked according to the scores of SLEDAI, and the results are shown in Table 2. As the SLEDAI score increases, that is, the disease activity of SLE increases, dry eye indexes gradually change accordingly, indicating a possible correlation between the symptoms and signs of dry eye and the disease activity of SLE.

Pearson linear correlation analysis and Spearman's rank correlation coefficient analysis were performed to analyze the correlations between variables indicating lupus activity and dry eye indexes, including TMH, NIKBUT-first, NIKBUT-average, and OSDI, respectively (Table 3). The results indicated that SLEDAI were correlated with TMH ($r = -0.233$, $p = 0.040$) (Figure 1(a)), NIKBUT-first ($r = -0.254$, $p = 0.025$) (Figure 1(b)), NIKBUT-average ($r = -0.343$, $p = 0.002$) (Figure 1(c)), and OSDI ($r = 0.256$, $p = 0.024$) (Figure 1(d)). NIKBUT-first showed strong correlation with NIKBUT-average ($r = 0.870$, $p < 0.01$). No correlations were observed between ANA and dry eye parameters except the OSDI.

Based on the criteria obtained from TFOS DEWS II Diagnostic Methodology report [24], patients with OSDI ≥ 13 and NIKBUT < 10 s were enrolled into dry eye group, and the rest were defined as control group. NIKBUT-average was chosen to diagnose dry eye since its repeatability and reproducibility are better than NIKBUT-first [25]. Additionally, some other parameters were used to further explore the differences between two groups. Table 4 showed that two groups were not significantly different in terms of age, disease duration, ANA titers, anti-dsDNA levels, and TMH ($p > 0.05$). In contrast, the scores of SLEDAI, NIKBUT-first, NIKBUT-average, and OSDI were significantly different between dry eye group and control group ($p < 0.05$), indicating incidence of dry eye was related to the severity of SLE.

Finally, multiple-factor binary logistic regression analysis was performed to examine the correlations between the incidence of dry eye with clinical characteristics and

Table 2: Data of TMH, NIKBUT-first, NIKBUT-average, OSDI, and ANA titer according to the severity of SLEDAI.

SLEDAI (score)	0–4 ($n = 40$)	5–9 ($n = 16$)	10–14 ($n = 11$)	≥15 ($n = 11$)
Age (years)	35 ± 10	36 ± 8	39 ± 13	42 ± 11
Duration (years)	5.07 ± 3.42	6.23 ± 5.53	7.36 ± 5.46	4.86 ± 4.04
TMH (mm)	0.23 ± 0.06	0.22 ± 0.06	0.21 ± 0.03	0.19 ± 0.04
NIKBUT-first (s)	10.43 ± 5.99	8.49 ± 5.94	8.81 ± 7.29	5.56 ± 2.52
NIKBUT-average (s)	13.76 ± 5.45	10.30 ± 6.15	10.23 ± 6.77	7.80 ± 4.53
OSDI (score)	9.04 ± 8.40	18.06 ± 16.86	14.65 ± 10.99	19.38 ± 17.68
ANA titer	1217.50 ± 1360.33	1597.50 ± 1487.17	2476.36 ± 1251.74	1723.64 ± 1443.16

Values are expressed as average ± standard deviation. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index. TMH = tear meniscus height. NIKBUT = noninvasive Keratograph tear breakup time. OSDI = Ocular Surface Disease Index. ANA = antinuclear antibody.

Table 3: Correlation analysis between each group of data.

	Age (years)	Duration (years)	TMH (mm)	NIKBUT-first (s)	NIKBUT-average (s)	OSDI (score)	SLEDAI (score)	ANA titer
Age (years)		$r = 0.256$ **$p = 0.024$**	$r = -0.196$ $p = 0.085$	$r = -0.263$ **$p = 0.020$**	$r = -0.368$ **$p < 0.001$**	$r = 0.176$ $p = 0.124$	$r = 0.251$ **$p = 0.027$**	$r = -0.017$ $p = 0.880$
Duration (years)	$r = 0.256$ $p = 0.024$		$r = 0.086$ $p = 0.452$	$r = 0.169$ $p = 0.138$	$r = 0.125$ $p = 0.275$	$r = -0.145$ $p = 0.206$	$r = 0.006$ $p = 0.955$	$r = -0.126$ $p = 0.272$
TMH (mm)	$r = -0.196$ $p = 0.085$	$r = 0.086$ $p = 0.452$		$r = 0.033$ $p = 0.771$	$r = 0.174$ $p = 0.128$	$r = -0.003$ $p = 0.980$	$r = -0.233$ **$p = 0.040$**	$r = 0.052$ $p = 0.650$
NIKBUT-first (s)	$r = -0.263$ $p = 0.020$	$r = 0.169$ $p = 0.138$	$r = 0.033$ $p = 0.771$		$r = 0.870$ **$p < 0.001$**	$r = -0.241$ **$p = 0.033$**	$r = -0.254$ **$p = 0.025$**	$r = -0.051$ $p = 0.660$
NIKBUT-average (s)	$r = -0.368$ $p < 0.01$	$r = 0.125$ $p = 0.275$	$r = 0.174$ $p = 0.128$	$r = 0.870$ $p < 0.01$		$r = -0.341$ **$p = 0.002$**	$r = -0.343$ **$p = 0.002$**	$r = -0.103$ $p = 0.370$
OSDI (score)	$r = 0.176$ $p = 0.124$	$r = -0.145$ $p = 0.206$	$r = -0.003$ $p = 0.980$	$r = -0.241$ $p = 0.033$	$r = -0.341$ $p = 0.002$		$r = 0.256$ **$p = 0.024$**	$r = 0.288$ **$p = 0.011$**
SLEDAI (score)	$r = 0.251$ $p = 0.027$	$r = 0.006$ $p = 0.955$	$r = -0.233$ $p = 0.040$	$r = -0.254$ $p = 0.025$	$r = -0.343$ $p = 0.002$	$r = 0.256$ $p = 0.024$		$r = 0.290$ **$p = 0.010$**
ANA titer	$r = -0.017$ $p = 0.880$	$r = -0.126$ $p = 0.272$	$r = -0.052$ $p = 0.650$	$r = -0.051$ $p = 0.660$	$r = -0.103$ $p = 0.370$	$r = 0.288$ $p = 0.011$	$r = 0.290$ $p = 0.010$	

TMH = tear meniscus height. NIKBUT = noninvasive Keratograph tear breakup time. OSDI = Ocular Surface Disease Index. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index. ANA = antinuclear antibody.

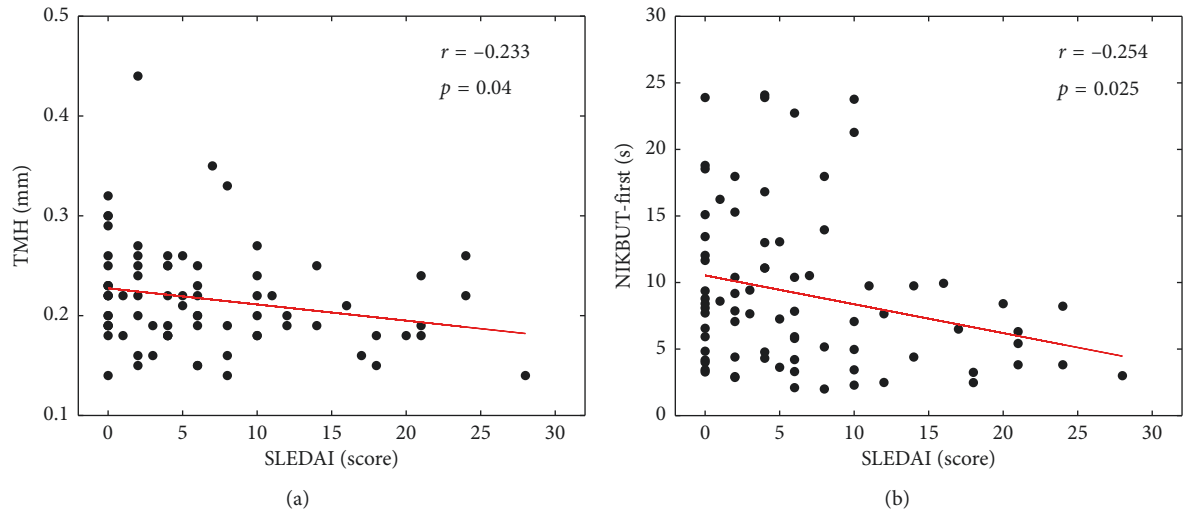

Figure 1: Continued.

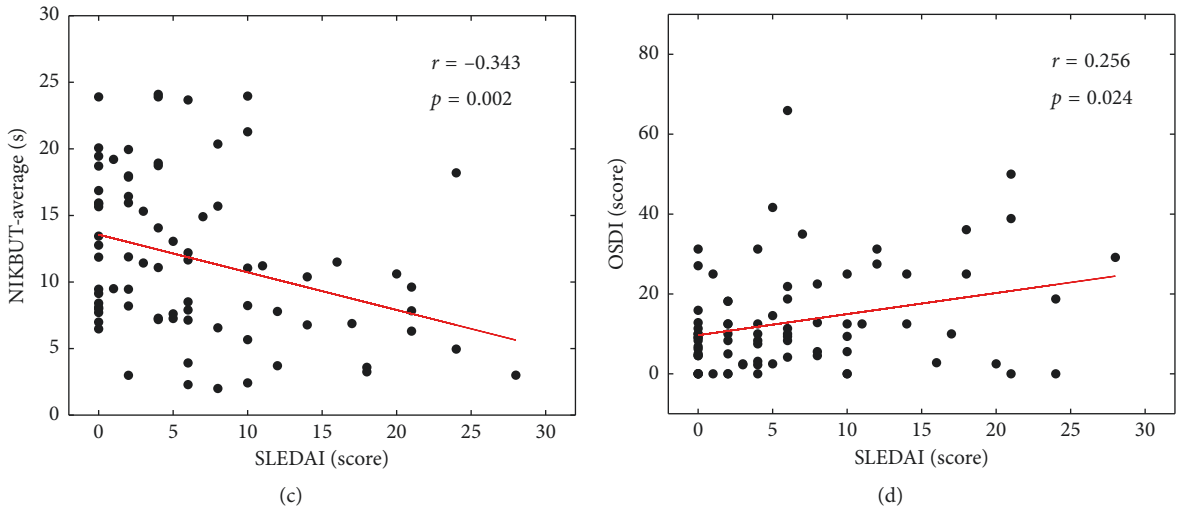

Figure 1: Correlations between (a) TMH and SLEDAI ($r = -0.233$, $p = 0.040$), (b) NIKBUT-first and SLEDAI ($r = -0.254$, $p = 0.025$), (c) NIKBUT-average and SLEDAI ($r = -0.343$, $p = 0.002$), (d) OSDI and SLEDAI ($r = 0.256$, $p = 0.024$) in SLE patients without sSS.

Table 4: Demographic information of dry eye and control group.

	Dry eye group ($n = 19$)	Control group ($n = 59$)	Statistics	p value
Age (years)	41 ± 11	35 ± 10	1.903	0.061
Duration (years)	4.92 ± 4.51	5.82 ± 4.27	−0.788	0.433
SLEDAI (score)	11.37 ± 8.31	5.00 ± 5.77	−3.232	**0.001**
ANA titer	1986.32 ± 1346.83	1402.03 ± 1429.43	−1.829	0.067
Anti-dsDNA*	6	21	0.727	0.394
TMH (mm)	0.21 ± 0.05	0.22 ± 0.05	−0.914	0.364
NIKBUT-first (s)	4.78 ± 2.21	10.51 ± 6.13	−6.065	**<0.01**
NIKBUT-average (s)	5.77 ± 2.38	13.62 ± 5.56	−8.667	**<0.01**
OSDI (score)	28.66 ± 13.50	8.14 ± 7.80	6.295	**<0.01**

*Positive ratio of anti-dsDNA in dry eye group and control group. Values are expressed as average ± standard deviation. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index. ANA = antinuclear antibody. Anti-dsDNA = anti-double-stranded DNA antibody. TMH = tear meniscus height. NIKBUT = noninvasive Keratograph tear breakup time. OSDI = Ocular Surface Disease Index.

Table 5: Multiple-factor binary logistic regression analysis for dry eye incidence.

Parameter	B value	SE value	OR value	95% CI	p value
Age (years)	0.046	0.029	1.047	0.989–1.109	0.115
Duration (years)	−0.090	0.074	0.914	0.790–1.058	0.227
SLEDAI (score)	0.113	0.042	1.119	1.031–1.215	**0.007**
Anti-dsDNA	−0.269	0.644	0.764	0.216–2.699	0.676
ANA titer	1.231	1.195	3.425	0.329–35.642	0.303

ANA = antinuclear antibody. Anti-dsDNA = anti-double-stranded DNA antibody. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

biochemical parameters, such as age, disease duration, anti-dsDNA levels, ANA titers, and SLEDAI scores in the subjects. As shown in Table 5, only SLEDAI score significantly affected the incidence of dry eye ($p = 0.007$). OR value of SLEDAI score was 1.119, suggesting that SLEDAI score could be considered as a risk factor for the incidence of dry eye in SLE patients without sSS.

4. Discussion

Patients whose anti-SSA antibody and anti-SSB antibody were positive without any oral symptoms were ruled out in this study. Despite the fact the mean value of NIKBUT-first was 9.12 s and TMH was 0.22 mm for the SLE patients enrolled in this study, which has not met the diagnosis criteria of dry eye, it should be emphasized that NIKBUT-first of 2/3 patients and NIKBUT-average of 1/2 patients was abnormal. Moreover, almost 1/4 of the study subjects can be diagnosed as dry eye according to TFOS DEWS II Diagnostic Methodology report [24].

Statistically significant correlations were observed between the OSDI score and NIKBUT-first, NIKBUT-average, but not TMH. However, Sullivan et al. [26] suggested that no relationship could be found between any of the common signs and symptoms of dry eye disease. One explanation may be that the different clinical signs reflect different subtypes of dry eye, and each clinical sign provides distinct information regarding ocular surface conditions. Besides, the intervals between the collection of questionnaires and the examinations of signs, which were conducted a few weeks later, could

also introduce errors in their study. Similarly, Kyei et al. [27] reported statistically significant associations between the OSDI scores and blink rate, contrast sensitivity scores, but not corneal staining, Schirmer test, tear breakup time, meibomian gland expressibility, and meibomian gland quality. One cause contributing to the discrepancy may be that their study subjects are first-year students who are relatively younger. Moreover, a system review [28] revealed that the correlations between dry eye signs and symptoms were between −0.4 and 0.4, indicating low-to-moderate correlation. The r values between dry eye signs and symptoms in this study fall into the same range.

The patients enrolled in this study were classified into dry eye group and control group according to the criteria mentioned before (Table 4). There were no differences in terms of age, disease duration, ANA titers, and anti-dsDNA levels between the two groups, indicating that the two groups were comparable. A statistically significant difference in SLEDAI scores was observed between two groups, suggesting that SLEDAI score may be related with occurrence of dry eye, and thus, the activity of SLE correlates with the incidence of dry eye.

The incidence of dry eye in SLE patients has been extensively studied. A case-control study [7] showed that tear film osmolarity in SLE group was much higher when compared with the control group. Resch et al. [8] revealed that the density of Langerhans cells in the cornea of SLE patients was greater than that in the control healthy group, supporting the idea that the increase of Langerhans cells and the change of morphology in cornea contributed to the pathophysiology of dry eye in SLE patients. Moreover, the dry eye symptoms and signs and ocular surface inflammation of SLE patients were significantly more severe than those of dry eye patients without systemic immune disease [3].

The studies about the correlation between dry eye and SLE activity in SLE patients without sSS are rare. Chen et al. [6] showed that the dry eye parameters such as corneal sensation, superficial punctuate keratopathy, and Schirmer I test exhibited moderately strong correlations ($r > 0.8$, $p < 0.01$) with anti-dsDNA level in SLE patients without sSS. Moreover, anti-dsDNA level showed high efficacy in monitoring lupus activity and that its rise predicted the relapse of SLE. The present study showed that dry eye indexes such as NIKBUT, TMH, and OSDI had correlations with SLEDAI yet at relatively low levels. One cause leading to the differences of correlations may be that this study evaluated ocular surface with noninvasive method in comparison with Chen's study. Tone et al. [29] found no correlations between the symptoms of dry eye and other objective parameters measured in children with SLE. Moreover, no differences were observed regarding Canadian Dry Eye Assessment questionnaire, tear film osmolarity, slit lamp examination, tear film breakup time, corneal fluorescein staining, Schirmer I test, and conjunctival lissamine green staining between SLE children with and without sSS group. However, the present study obtained results distinct from their studies. One possible reason may be that children have fewer symptoms compared with adults despite similar dry eye signs [30]. The other reason may be the relatively poor cooperation of children which results in measurement errors, not to mention that their study sample size is relatively small.

The present study revealed that the incidence and severity of dry eye were closely related to SLEDAI scores, suggesting the relationship between dry eye and the activity of SLE disease. However, one question remaining elusive is whether cytokine or chemokine induces dry eye in SLE patients without sSS. Lee et al. [31] elucidated that cytokines, such as IL-2, IL-4, IL-5, IL-6, IL-17, and TNF-α in tears, were associated with the progression of dry eye. They also found that IL-1 and IL-6 induced the proliferation of Th17 cells, which played a pivotal role in adaptive and innate immunity by releasing IL-17. Stern et al. [32] detected the relative protein level of Klk13 in serum of SS rabbit compared with control wild rabbit. They found that Klk13 appeared in SS group while absent in control group and the mRNA level of Klk13 was also upregulated in the SS group. Furthermore, they confirmed that complement played an essential role in inflammation of ocular surface. Xiao et al. [33] stated that cytokines-MMPs/MAPKs vicious cycle played pivotal roles in the development of dry eye disease. Blockage or reversal of the cytokines-MMPs/MAPKs vicious cycle relieved inflammatory responses in ocular surface tissues and alleviated damage to goblet cells, lacrimal gland, cornea, conjunctiva, etc.

ANA is deemed relevant to the severity of dry eye. Lim et al. [34] reported that SS patients with positive ANA levels ($\geq 1:320$) showed significantly higher conjunctival staining scores than those with negative ANA titers. Liew et al. [35] demonstrated that ANA positivity was associated with an approximately 14-fold increase in the likelihood of primary Sjögren's syndrome (pSS) versus healthy control, and the ocular surface assessed by Schirmer test, corneal fluorescein staining, conjunctival lissamine green staining, and tear breakup time was worse in patients positive in ANA. Contradictorily, the present study showed that ANA was not a risk factor influencing the occurrence of dry eye in SLE patients without sSS. One possible reason may be due to the difference of research subjects: SLE patients without sSS were enrolled in this study while their study subjects were pSS patients with relatively more severe dry eye. Another reason to explain the discrepancy might be the low specificity of ANA to reflect the disease state of SLE since the expression of ANA was relatively high in healthy individuals and ones with other autoimmune diseases [36, 37].

Based on present study, clinicians should pay attention to the ocular surface condition of patients with active SLE, and even more importantly, appropriate measures should be taken to prevent the irreversible deterioration of ocular surface. Also, if a patient with SLE history is found to have severely damaged ocular surface in his/her visits to ophthalmology department, this could be considered as an accessional indicator of SLE activity for diagnosis.

There were still some shortcomings in this study. The patients were enrolled from outpatient department of the First Affiliated Hospital of Anhui Medical University; as a result, limitations could be generated due to the area

restriction and disease severity. Secondly, the subjects selected in this study were patients with SLE, a systemic disease, which requires long-term use of hormones and immune-modifiers, especially hydroxychloroquine. Yavuz et al. [38] reported that hydroxychloroquine caused damage to the ocular surface of patients with pSS. Thus, the side-effect of systemic drugs on the incidence of dry eye could not be ignored.

In conclusion, a noninvasive, newly developed technique, Keratograph 5M, was used in this study to investigate the ocular surface condition of patients with SLE yet without sSS. The results showed that SLE patients without sSS had a relatively higher risk for the incidence of dry eye, and the severity of dry eye was closely related to the disease activity of SLE. Due to the fact severe damage of ocular surface is irreversible, it is important to monitor the ocular surface of SLE patients and diagnose the disease at the early stage. Furthermore, molecular links between SLE and dry eye occurrence should be deciphered in the future.

Data Availability

The primary data used to support the findings of this study can be obtained by contacting the first author through e-mail (wangan930115@163.com).

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Clinical Study

Association among Blink Rate, Changes in Ocular Surface Temperature, Tear Film Stability, and Functional Visual Acuity in Patients after Cataract Surgery

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Purpose. To investigate the association among the ocular surface temperature (OST), tear film stability, functional visual acuity (FVA), and blink rate in patients after cataract surgery. *Methods*. We recruited 98 eyes of 69 patients (mean age, 73.7 ± 5.2 years) 1 month after phacoemulsification with implantation of acrylic intraocular lenses and assessed slit-lamp microscopy, corrected distance VA, FVA, noninvasive tear breakup time (NIBUT), and OST. We defined the changes in the OST from 0 to 10 seconds after eye opening as the ΔOST. We measured the FVA and blink rate using the FVA measurement system. We divided the patients into two groups based on tear film stability: stable tear film (NIBUT, >5.0 seconds) and unstable tear film (NIBUT, ≤5.0 seconds). We evaluated the differences between the two groups and the association between the blink rate and other clinical parameters. *Results*. The unstable tear film group (56 eyes) had significantly ($p < 0.0001$, unpaired t-test) shorter NIBUTs than the stable tear film group (42 eyes). The ΔOSTs and blink rates were significantly ($p < 0.0001$) higher in the unstable tear film group than in the stable group. Linear single regression analysis showed that the ΔOST ($r = -0.430$, $p < 0.0001$), NIBUT ($r = -0.392$, $p < 0.0001$), and gender ($r = -0.370$, $p = 0.0002$) were correlated significantly with the blink rate. Multiple regression analysis showed that the ΔOST independently contributed to the blink rate. *Conclusions*. The frequency of blinks is associated with tear film stability in patients after cataract surgery. The blink rate may be useful for evaluating the tear film stability in clinical practice. The ΔOST should be an important contributing factor to the blink rate. [This trial is registered with UMIN000026970].

1. Introduction

With improvements in the techniques of cataract surgery, the invasiveness of the surgery has been minimized greatly [1–4]. However, some patients are unsatisfied with the visual quality even though they have good visual acuities (VAs) [5]. Tear film instability on the ocular surface is a possible cause of the problem [6–11]. *After cataract surgery, problems with the ocular surface and tear film stability contribute to reduced corneal sensitivity, number of goblet cells, and mucin expression, resulting in decreased tear film breakup time* (*BUT*) [6–10]. These phenomena are believed to impair tear film stability and reduce visual quality. Koh et al. reported that tear film instability degraded the optical quality and increased the higher order aberrations [11].

The ocular surface temperature (OST) represents the physiological function and pathological diagnosis of the ocular surface, and OST has been used to investigate ocular diseases such as dry eye, contact lens discomfort, allergic conjunctivitis, and glaucoma [12–15]. When the tear film is disrupted and becomes unstable, the OST decreases due to evaporation of the tear fluid, convective heat transfer, emission of infrared radiation, and heat conduction [16–21]. Several studies have reported that changes in the OST during

eye opening are correlated consecutively with the tear film stability on the cornea [12, 13]. We also reported that changes in the OST are associated with tear film stability not only on the cornea but also over soft contact lenses [13]. Giannaccare et al. reported that 1 month after cataract surgery, the tear film stability decreased and the changes in OST increased compared with preoperative findings. The investigators concluded that the tear film stability and subjective symptoms were correlated with the changes in the OST [22].

Blinking plays an important role in maintaining the normality of the ocular surface. The blink rates of patients with dry eye have been reported to be higher than in normal eyes [23, 24]. Fibers that are sensitive to cold perceive the changes in the OST on the cornea and facilitate the ability to feel dryness and/or coolness on the ocular surface [25–28]. The changes in OST were thought to affect the ocular protective reflex, such as basal tearing and blinking [23–28]. Several researchers have reported that the number of blinks increases with wind stimulation; in contrast, the number of blinks decreases with instillation of artificial tears and topical anesthesia and with wearing of moisture glasses [23, 29]. It should be noted that the number of blinks decreases when the tear film is stable and increases when the tear film is unstable due to the ocular environment and/or external factors. Li and Lin reported that the maximal interblink period was related to the cooling rate of the ocular surface (°C/second) [30].

Functional visual acuity (FVA) measurement has been developed to evaluate the daily visual function [31–33]. The FVA that measures the changes in the VA over time enables detection of impaired visual function that was not detectable based on conventional VA assessment. *Kaido et al. reported that the FVA parameters such as the FVA and visual maintenance ratio were correlated significantly with the blink rate, which tended to increase with increasing severity of the ocular surface staining scores in patients with dry eye* [34]. Yamaguchi et al. found that the FVA improved significantly after surgery to remove a mildly cataractous lens even though the conventional VA did not change significantly [35]. However, it is unclear if the FVA is associated with the tear film stability after cataract surgery. The aim of the current study was to investigate the relationships among the OST, tear film stability, blink rate, and FVA in patients after cataract surgery.

2. Methods

2.1. Subjects. We conducted a prospective study at Toho University Omori Medical Center from April 2017 to December 2018. Ninety-eight eyes of 69 patients (44 women, 25 men; average age, 73.7 ± 5.2 years) who underwent cataract surgery were enrolled in this study (Table 1). The inclusion criteria were 60 years of age or older and a corrected distance visual acuity (CDVA) of at least 20/25 or better in patients who had undergone an uneventful phacoemulsification surgery. To avoid variations in the OST, patients who had a history of infection; refractive surgery; corneal diseases such as dry eye, keratoconus, and edema; glaucoma; diabetic retinopathy; allergic conjunctivitis; or a systemic disease such as cancer were excluded.

The FVA, noninvasive tear breakup time (NIBUT), and OST were measured 1 month (average, 31.5 ± 6.0 days) after cataract surgery. The cornea also was assessed for corneal epithelial damage, which was identified by the fluorescein staining scores of the area (*A*) and density (*D*) over the damaged corneal lesions [36]. The degrees of staining of the area and density were scored on a scale from 0 to 3, with A0 indicating none, *A*1 less than one third of the area, *A*2 one third to two thirds, *A*3 more than two thirds, and *D*0 none, *D*1 sparse density, *D*2 moderate density, and *D*3 high density [36]. To investigate the difference in the clinical parameters, i.e., FVA, OST, and corneal staining, based on the effect of tear film stability, the patients were classified into two groups: those with stable tear film (BUT, >5.0 seconds) and unstable tear film (BUT, ≤5.0 seconds). *Although we believe that fluorescein BUT and NIBUT are different, no previous reports have statistically investigated the differences between DR-1 interferometry and fluorescein BUT.* In the current study, we set the cutoff line at NIBUT 5.0 seconds according to the 2016 Asia Dry Eye Society criteria, which establish a diagnosis of dry eye with positive subjective symptoms and decreased fluorescein BUT (≤5 seconds). We also measured the blink rate and investigated the association between the blink rate and the other clinical parameters.

The Ethics Committee of Toho University Omori Medical Center approved the study (study protocol, M16246). All patients provided informed consent after they received an explanation of the possible consequences of the study, which adhered to the tenets of the Declaration of Helsinki.

2.2. Measurements of Blink Rate and FVA. The temperature (25.2 ± 1.6°C) and humidity (39.2 ± 11.2%) in the examination room were maintained at constant levels. We used the FVA measurement system (Kowa, Aichi, Japan) to measure the FVA and the blink rate. Kaido et al. [31–33] previously described the use of the measurement system. In brief, the FVA was measured monocularly with the best spectacle correction under photopic conditions and natural blinking during a 60-second period. The major outcome parameters were the baseline VA, FVA, visual maintenance ratio (VMR), and blink frequency. The baseline VA was defined as the conventional Landolt CDVA. The FVA was the average value of all VA measurement for 60 seconds. The VMR was defined as the ratio of the FVA value divided by the baseline VA. On the basis of the recorded data for 60 seconds, we defined the total number of blinks as the blink rate (frequency/minute) [31–33].

2.3. Measurement of Tear Film Stability. To evaluate the tear film stability, we measured the NIBUT only once to avoid reflex tearing using a tear film interferometer (DR-1α, Kowa Co. Ltd., Tokyo, Japan) with low magnification (7.2 × 8.0 mm) [13, 37, 38]. After natural blinking, the patients were asked to keep their eyes open for 10 seconds [13, 38, 39]. The NIBUT was recorded at the first appearance

Table 1: Demographic data.

	Stable tear film (56 eyes)		Unstable tear film (42 eyes)	
Mean patient age (years)	74.7 ± 5.3 (range, 74.2–76.0)		72.5 ± 4.7 (range, 70.9–74.0)	
	Women (29 eyes)	Men (27 eyes)	Women (36 eyes)	Men (6 eyes)
Age by gender (years)	75.0 ± 5.0 (range, 73.0–76.9)	74.3 ± 5.7 (range, 72.1–76.6)	72.3 ± 4.9 (range, 70.6–73.9)	73.8 ± 3.7 (range, 70.0–77.7)

The data are expressed as the average ± deviation (95% confidence interval).

of the breakup of the tear film. When no noninvasive breakup was observed during the 10-second observation period, the NIBUT was recorded as 10 seconds.

2.4. Measurement of OST. To measure the OST, we used a noninvasive ocular surface thermographer (TG1000, Tomey, Nagoya, Japan) [12, 13]. The instrument was equipped with a modified optical head of an autorefractor/keratometer (RC-50000, Tomey, Nagoya, Japan) and enabled determination of the central cornea along the optical axis. The method of measuring the OST was the same as described by Mori et al. [40]; i.e, the patients were instructed to close their eyes for 5 seconds and then to keep their eyes open for 10 seconds. The OST was measured in the central cornea (4.0 mm diameter) every second for 10 seconds without blinking. The difference in the OST from 0 to 10 seconds was defined as the ΔOST [12, 13].

2.5. Surgical Technique and Postoperative Treatment. Two surgeons (HY and OY) performed all surgeries with the same procedure technique. In all cases, the same methods of lens extraction and intraocular lens implantation were performed with creation of superior corneoscleral incisions (2.4 mm). Postoperatively, 0.1% betamethasone phosphate and 1.5% levofloxacin eye drops (Levaquin, Johnson & Johnson, New Brunswick, NJ, USA) (4 times daily) were used for 1 week, and 0.1% nepafenac ophthalmic solution (Nevanac, Alcon, Ft. Worth, TX, USA) (3 times daily) was used for 4 weeks. Patients were asked to not instill eye drops within 2 hours before the measurements.

2.6. Statistical Analysis. The unpaired t-test was used to compare the clinical parameters between the stable and unstable tear film groups. Pearson's correlation coefficients and multiple regression analysis were used to identify the independent factors associated with the blink rate. $p \leqq 0.05$ was considered statistically significant. All analyses were conducted using JMP version 11 statistical analysis software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Comparison of Clinical Parameters between the Stable Tear Film and Unstable Tear Film Groups. Of the 98 eyes, 56 eyes were in the stable tear film group, and 42 eyes were in the unstable tear film group. Representative cases of patients with unstable tear film and stable tear film are shown in Figure 1. There was no difference in the FVA, but the blink rate increased in patients with unstable tear film more than in those with stable tear film. Table 2 shows the comparisons of the clinical parameters between the groups. The NIBUTs in the stable and unstable tear film groups were, respectively, 9.1 ± 1.6 and 3.0 ± 1.1 seconds, a difference that reached significance ($p < 0.0001$, unpaired t-test). The respective blink rates in the stable and unstable groups were 4.9 ± 5.8 and 9.3 ± 7.5, a difference that reached significance ($p = 0.0013$). The ΔOSTs in the stable and unstable tear film groups were −0.27 ± 0.23°C and −0.56 ± 0.23, respectively, a difference that reached significance ($p < 0.0001$). The NIBUT was correlated significantly with the ΔOST ($r = 0.607$; $p < 0.0001$, Pearson's correlation coefficients). The grading of the corneal epithelial damage, CDVA, FVA, VMR, and OST did not differ significantly between the two groups.

3.2. Associations between Blinks and Other Parameters. Table 3 shows the correlation coefficients identified by single regression analysis between the blink rate and other parameters. The blink rate was correlated significantly with the difference in gender (male = 1, female = 0; $r = -0.370$, $p = 0.0002$), ΔOST ($r = 0.430$, $p < 0.0001$; Figure 2(a)), and NIBUT ($r = -0.392$, $p < 0.0001$; Figure 2(b)). Age tended to be correlated with the blink rate but did not reach significance ($p = 0.094$). From this result, it was found that the blink rate increased when the ΔOST enlarged and the tear film stability became unstable. Regarding gender, the blink rate was higher in women compared to men.

3.3. Factors Independently Contributed to the Blink Rate. Table 4 shows the results of multiple regression analysis for factors that independently contributed to the blink rate in the study population. The factor that contributed independently to the blink rate was the ΔOST ($\beta = -0.2514$; t-value = −2.12; $p = 0.0369$). When multiple regression analysis was performed with gender, ΔOST, and NIBUT as independent variables, the ΔOST contributed independently to the blink rate. In other words, blinking was triggered by the decrease of the OST following tear film instability.

4. Discussion

Some researchers have reported that tear film stability in patients after cataract surgery may change due to decreased corneal sensitivity, reduced number of goblet cells, and mucin expression [6–10]. *Similar to the results of the current study, several other studies have proved that the changes in the*

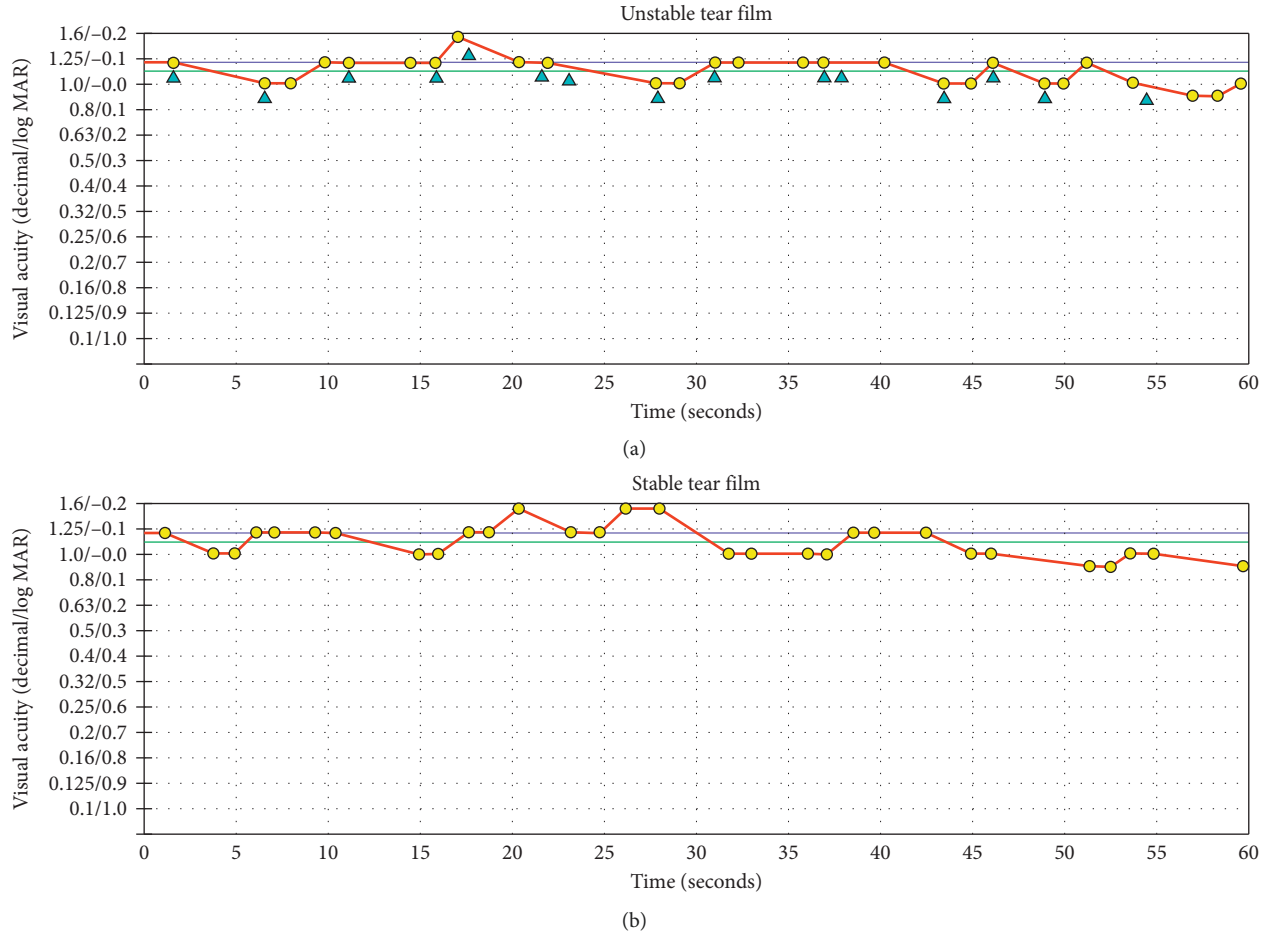

Figure 1: Representative results of functional visual acuity (FVA) in patients after cataract surgery. (a) A 69-year-old woman with unstable tear film (noninvasive tear breakup time (NIBUT), 2.1 seconds; functional visual acuity (FVA) logarithm of minimum angle of resolution (log MAR), −0.05; visual maintenance ratio (VMR), 0.99%; and blink rate (frequency/minute), 15). (b) A 79-year-old man with stable tear film (NIBUT, 10.0 seconds; FVA (log MAR), −0.04; VMR, 0.99%; and blink rate (frequency/minute), 0). The red line indicates the time-wise changes in the visual acuity (VA) for 60 seconds. The blue line indicates the starting VA, and the green line indicates the mean FVA for 60 seconds. The yellow dots indicate the number of correct responses, and the blue triangles indicate the spontaneous blinks.

Table 2: Comparison of clinical parameters between the groups.

	Stable tear film (56 eyes)	Unstable tear film (42 eyes)	p value
Area	0.2 ± 0.5 (0.0–0.4)	0.3 ± 0.6 (0.1–0.5)	0.3529
Density	0.3 ± 0.7 (0.1–0.4)	0.3 ± 0.7 (0.1–0.6)	0.5560
NIBUT (seconds)	9.1 ± 1.6 (8.7–9.4)	3.0 ± 1.1 (2.6–3.5)	<0.0001
CDVA (log MAR)	−0.04 ± 0.06 (−0.06 to−0.03)	−0.02 ± 0.07 (−0.04 to−0.01)	0.1052
FVA (log MAR)	0.10 ± 0.12 (0.07 to 0.13)	0.11 ± 0.13 (0.07 to 0.14)	0.8179
VMR (%)	0.95 ± 0.04 (0.94 to 0.96)	0.95 ± 0.03 (0.94 to 0.96)	0.7175
Blink rate (frequency/minute)	4.9 ± 5.8 (3.1 to 6.6)	9.3 ± 7.5 (7.3 to 11.3)	0.0013
OST (°C)	34.41 ± 0.57 (34.26 to 34.56)	34.43 ± 0.57 (34.25 to 34.56)	0.8310
ΔOST (°C)	−0.27 ± 0.23 (−0.32 to−0.20)	−0.56 ± 0.23 (−0.63 to−0.49)	<0.0001

The data are expressed as the average ± deviation (95% confidence interval). Compared with the unstable tear film group, the NIBUT, ΔOST and blink rate differ significantly in the stable tear film group. log MAR: logarithm of the minimum angle of resolution; NIBUT: noninvasive tear breakup time; CDVA: corrected distance visual acuity; FVA: functional visual acuity; OST: ocular surface temperature; VMR: visual maintenance ratio; ΔOST: difference in OST from 0 to 10 seconds without blinking.

OST and blink rate increase when the tear film is unstable [12, 13, 23, 24]. *In addition, it was found that the evaluation of the daily visual function, measured via the FVA, also was related to tear film stability* [34]. However, few studies have attempted to investigate the relationships among the OST, tear film stability, blink rate, and FVA in patients who underwent cataract surgery. In the current study, we found that the blink rate was correlated negatively with the ΔOST and NIBUT. Multiple regression analysis showed that the ΔOST contributed independently to the blink rate.

Table 3: Correlations between the blink rate and other parameters.

Explanatory variables	r value	p value
Men = 1; women = 0	−0.370	0.0002
Age	−0.170	0.0940
NIBUT	−0.392	<0.0001
ΔOST	−0.430	<0.0001
OST	0.004	0.9680
FVA	−0.001	0.9938
VMR	0.067	0.5126

NIBUT: noninvasive tear breakup time; FVA: functional visual acuity; VMR: visual maintenance ratio; OST: ocular surface temperature; ΔOST: difference in OST from 0 to 10 seconds without blinking.

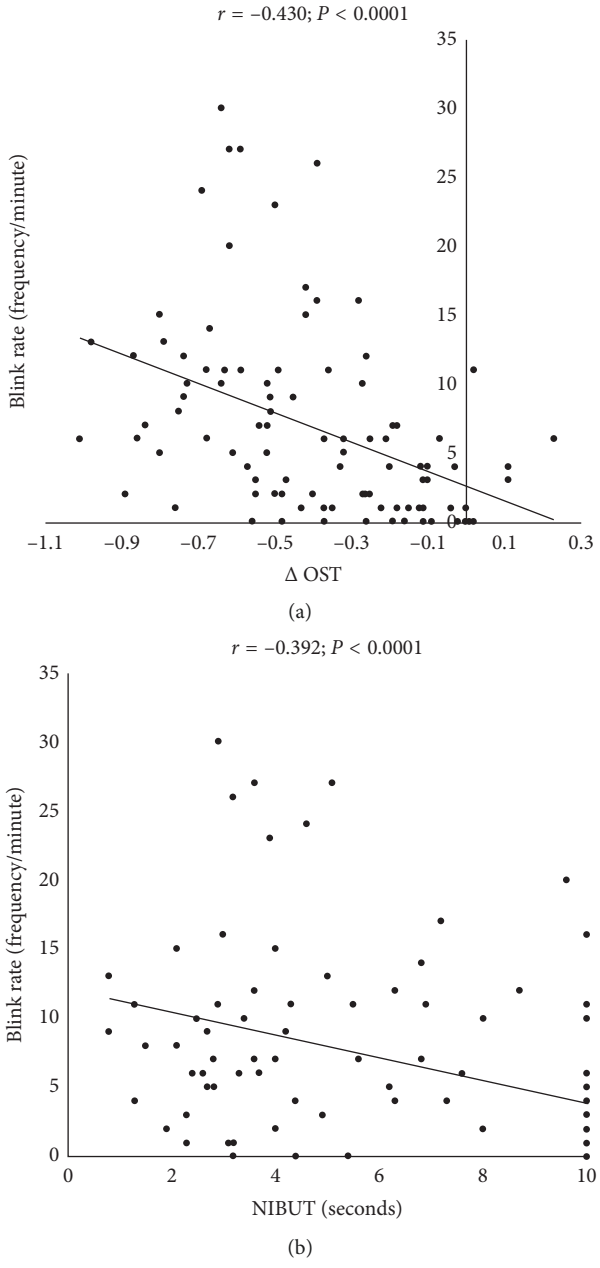

Figure 2: Correlation between the blink rate and the changes in the ocular surface temperature (ΔOST) (a) and noninvasive tear breakup time (NIBUT) (b). ΔOST = difference in the OST from 0 to 10 seconds without blinking.

Table 4: Results of multiple regression analysis for factors independently contributing to the blink rate.

Dependent	Variable Independent	β	p value
Blink rate	Men = 1; women = 0	−0.1693	0.1211
	NIBUT	−0.1564	0.1888
	ΔOST	−0.2514	0.0369

NIBUT: noninvasive tear breakup time; ΔOST: difference in OST from 0 to 10 seconds without blinking.

The OST varied in accordance with the tear film stability. The tear film BUT has been reported to be correlated with the ΔOST [12, 13, 41]. It is well known that tear film evaporation is the major cause of the decreasing OST [16–21]. The current study found that the NIBUT also was correlated with the ΔOST in patients after cataract surgery. This result agreed with a previous study performed by Giannaccare et al. in which both the tear BUT and subjective score were correlated with the ΔOST in patients before and after cataract surgery [22].

Fibers that are sensitive to cold, which perceive the OST, comprise 10% to 15% of the corneal afferents [42]. Cold sensitivity is activated primarily by transient receptor potential M8 (TRPM8), *which responds to temperature reduction and osmotic stimulation*. There are two types of cold thermoreceptors in the cornea: one is activated by a small change in the OST (within 2°C) through which dryness is perceived, and the other is by a large change in the OST through which pain is perceived. Cold thermoreceptors over the cornea play an important role in these sensations [25, 26]. Some researchers have reported that osmotic stimulation and menthol, which are agonists of TRPM8 stimulation, excite the nerves and increase the number of blinks as an ocular protective reflex [43, 44]. In the current study, the ΔOST and blink rate were correlated significantly, i.e., the more the change in the OST increased, the higher the blink rate became.

Blinking plays an important role in maintaining the tear film stability and a healthy ocular surface. Inomata et al. reported that the maximal blink interval was correlated significantly with tear film stability [45]. Rahman et al. found that the blink rate was associated with the degree of ocular surface disease and tear stability [24]. The current results agreed with those previous studies; i.e., the blink rate was correlated with tear film stability in patients after cataract surgery.

Nosch et al. reported that the blink rate and ΔOST were not correlated significantly in young normal subjects [46]. In the current study, however, we recruited elderly people who had undergone cataract surgery. Moreover, their tear film stability distributed to various degree from collected data. We theorized that in cases of tear film instability after cataract surgery, blinking plays a more important protective role in protecting the ocular surface, and the blink rate was correlated significantly with the tear film stability and changes in the OST.

The current results showed that the blink rate was significantly higher in the group with unstable tear film; however, no significant changes were found in the CDVA, corneal staining such as area and density grade, FVA, or

VMR between the stable and unstable groups. Kaido et al. reported that the blink rate increased significantly in patients with dry eye even though the FVA and VMR did not change [47]. However, those investigators also reported that the FVA and VMR changed significantly in patients with moderate and severe dry eye with corneal staining but did not change significantly in patients with mild dry eye without corneal staining [34]. Koh et al. also reported that higher order aberrations were higher in patients with dry eye with superficial punctate keratopathy (SPK) on the central cornea than in patients without SPK [11]. In the current study, there were no significant differences in corneal staining grade, FVA, and VMR because we excluded patients with dry eye with severe corneal staining. These data indicate that the FVA could remain at a normal level by increasing the blink rate in cases of abnormal tear film stability; however, in cases in which the corneal epithelial cells are damaged, the FVA may be affected even if the blink rate increases. From the collected data and analysis, we hypothesized that visual abnormalities due to transient tear dysfunction after cataract surgery may be compensated for by increasing the blinking frequency. *Further clinical research is needed to investigate the association among these parameters, including higher order aberration in patients with dry eye before and after cataract surgery*.

The current study had several limitations. First, because we enrolled patients who were 60 years of age or older, we could not exclude all systemic diseases such as high blood pressure and diabetes. These systemic diseases might have affected the value of the OST [48]. Second, subjective symptoms were not examined using a questionnaire in this study; the blink rate might have changed depending on the subjective symptoms. *Furthermore, we did not evaluate measurements of higher order aberration to investigate visual quality and anterior segment cells and/or flares to evaluate inflammation; these data may explain the degraded visual quality and relationship between OST and inflammation*. Finally, in this study, the number of blinks was counted during measurement of the FVA, which means that the blink rate could not be measured under natural conditions.

5. Conclusions

Although FVA, VMR, and corneal epithelial damage grade did not show significant differences between the groups with stable and unstable tear film, the blink rate and ΔOST showed significant differences. The blink rate was correlated significantly with the ΔOST and tear film stability in patients after cataract surgery, and the ΔOST contributed independently to the blink rate. The FVA in patients with unstable tear film after cataract surgery might remain in the normal range by increasing the blink rate.

Data Availability

The data used to support the findings of this study are available from the first author, Tadashi Itokawa (takashi.itokawa@med.toho-u.ac.jp).

Disclosure

This study was presented in part at the 57th Annual Meeting of the Japan Society for Cataract Research and entitled "Correlation between Changes in Ocular Surface Temperature and Blink Rate after Cataract Surgery" by Takashi Itokawa in July 2018. Takashi Itokawa was honored to receive a young researchers travel grant from the meeting for this work.

Conflicts of Interest

The authors have no financial conflicts of interest to disclose.

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Research Article

Dry Eye Analysis: A Citation Network Study

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Introduction. Dry eye is one of the most frequent eye problems with prevalence and incidence from 5% to 50%. Citation network analysis allows us to simplify information in a visual way and provides a better understanding of the research done in a specific field. The objective of this paper is to quantify and analyse the relationships among the scientific literature in this field using citation network analysis. *Materials and Methods*. The program used to analyse the citations was CitNetExplorer®. Previously, papers published in the research field during a predefined period were found using the keywords defined in Web of ScienceTM (WOS). *Results*. Using the keyword "dry eye," during the period 2007 to 2018, the most cited paper is by Lemp, MA (2007), with a citation index score of 913 in our citation network containing 6,500 most relevant papers. Analysing clustering, we found 5 relevant groups that match the main areas of research in this field: definition and classification, treatment, retina, refractive surgery, and quality of vision. Core Publication is composed of 64% of the papers in the network, which is a high percentage. It indicates a clear focus on the research carried out in this field. *Conclusions*. This citation network analysis shows definition and classification of dry eye to be the most researched area in this field, followed by treatment.

1. Introduction

Dry eye is one of the most frequent eye problems reported by adults in eye care practitioner consultations. The prevalence and incidence vary from 5% to 50%, depending on the diagnosis criteria or on the type of dry eye. Women and older people are the most affected. Dry eye prevalence is rising, due to the gradual increase of the population age and to a higher incidence of some risk factors [1].

Dry eye was defined as a disease just 30 years ago. Since then, there have been many advances in the knowledge and definition of this pathology. In 1995, it was defined as a "disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort". In 2017, a new definition was published in the DEWS II report [2].

Nowadays, according to the abovementioned report, dry eye is defined as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [3]. This new definition admits the multifactorial origin of dry eye and points out the etiological factors implied in this disease.

Regarding dry eye classification, traditionally, dry eye was classified into aqueous tear-deficient and evaporative. Now, we know that both exist as a continuum and, as dry eye progresses, it is used to find characteristics of both subtypes [2]. The aqueous tear-deficient dry eye implies a failure of lacrimal tear secretion, while the evaporative dry eye is related to eyelids and ocular surface.

The great number of patients suffering from dry eye and the impact of this disease on patients both financially and in terms of quality of life justify the analysis of all the research studies published about this public health problem.

Citation network analysis allows us to simplify information in a visual way and provides a better understanding of the research done in a specific field. It also lets

us quantify the most cited papers and create groups based on connections between papers and citation frequencies [4]. Citation network analysis has been a very useful tool since the citation index concept appeared.

These citation networks appear as different fields related through connections. Authors, journals, and papers are an essential part of these networks [5].

Because research on dry eye pathology is so extensive, use of this citation analysis methodology will allow us to identify the most relevant authors, publications, and journals, as far as their citation is concerned, the most important years in terms of their publications, and the different clusters of study within dry eye pathology.

The aim is to identify not only the most relevant research but also the different areas of study and thus focus future research on dry eye.

The objective of this paper is to quantify and analyse the relationships among the scientific literature in this field using citation network analysis.

2. Materials and Methods

CitNetExplorer® was used to analyse the citation networks of individual publications. This software is a tool for visualizing the most important publications in a field and showing the citation relations between these publications [6].

First, the researchers define the keywords and look for the publications according to these words in Web of ScienceTM (WOS). The file from WOS shows papers in the research field published during the predefined period.

The final file is the selection of 6,500 publications of the WOS list sorted by relevance, because the citation network program does not allow more publications to be introduced.

Then, once the file is imported to CitNetExplorer®, the software produces the first graph about the most cited publications, with a maximum of 40 papers for a clearer understanding.

Quantitative analysis shows values of publications, citation links (total number of citations in the network), and time period. This analysis shows the most cited papers in order from the highest to the lowest, according to their citation index score.

The clustering function allows us to identify groups according to the level of association among papers. In this way, subnetworks are obtained depending on the citations among them [7].

Finally, central publications are analysed through the Core Publication function, revealing the main papers of the field. For this analysis, only those that have 4 citations or more are selected.

3. Results

The keywords used for the search were "dry eye". The period chosen was from 2007 to 2018. The year 2007 was chosen as the starting point because of the change that the Dry Eye Workshop (DEWS) report represented in the definition and treatment of dry eye. 9,359 papers were found using the previous criteria.

We made a citation network with 6,500 most relevant papers, obtaining 44,942 citations across the network.

Table 1 shows the 20 most cited papers in this network.

The paper by Lemp et al., published in 2007, is the most cited, with a citation index score of 913.

Figure 1 shows the graph of this network.

With the clustering function, we obtained 13 groups or clusters, 5 of them having a relevant number of papers, while the other 8 did not reach 1%.

Figures 2–6 show the citation network of each group, and Figure 7 shows that there are no citations among different groups.

In group 1, we had 4,014 papers, almost 61% of the network. Lemp's paper, published in 2007 in Ocular Surface Journal [2], was the most cited in this group.

In group 2, we found 360 publications. Yoon's paper, published in 2007 in American Journal of Ophthalmology [26], was the most cited.

In group 3, we found 198 publications. Lim's paper, published in 2012 in The Lancet [27], was the most cited.

In group 4, we found 179 publications. Ambrosio's paper, published in 2008 in Journal of Refractive Surgery [28], was the most cited.

Finally, in group 5, we found 143 publications. Kaido's paper, published in 2007 in Cornea [29], was the most cited.

When we analysed relationships among clusters, we could not find any connections.

When we analysed the Core Publication, we found a total of 4,161 papers that cited, or were cited by, at least 4 papers. This 4,161 represented 64% of the papers, and the citation network across this group is 42,791. Figure 8 shows the graph of this network.

4. Discussion

This analysis has proved how publications about dry eye have been increasing in recent years, 2007 being a key year.

There is no doubt about the relevance of the publication of the DEWS report since Lemp et al. in 2007 [2].

The network analysed papers published from 2007 to 2018, but the most cited papers are in the period from 2007 to 2012. This suggests that 2012 could be another key year in dry eye research because of the number and content of papers, analysing the different publications.

Regarding clustering, we found 5 relevant groups that match the main areas of research in this field: definition and classification, treatment, retina, refractive surgery, and quality of vision.

This clustering also shows a difference among the journals that published each of the clusters. It clearly indicates the editorial lines of each scientific journal, no matter how cross the subject was, as in the case of dry eye.

The biggest cluster is the one related to definition and classification of dry eye, with more than 60% of the papers of this network. DEWS report heads this cluster due to the broad consensus on the new definition and classification of

Table 1: 20 most cited papers from 2007 to 2018 in the dry eye citation network.

Authors	Paper title	Journal	Year	Citation index
Lemp et al. [2]	The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007)	The Ocular Surface. 2007 Apr; 5(2): 75–92.	2007	913
Smith et al. [1]	The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007)	The Ocular Surface. 2007 Apr; 5(2): 93–107	2007	380
Miljanović et al. [8]	Impact of dry eye syndrome on vision-related quality of life	American Journal of Ophthalmology. 2007 Mar; 143(3): 409–15.	2007	271
Bron [9]	Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye Workshop (2007)	The Ocular Surface. 2007 Apr; 5(2): 108–52.	2007	253
Sullivan et al. [10]	An objective approach to dry eye disease severity	Investigative Opthalmology & Visual Science. 2010 Dec; 51(12): 6125–30.	2010	213
Lemp et al. [11]	Tear osmolarity in the diagnosis and management of dry eye disease	American Journal of Ophthalmology. 2011 May; 151(5): 792–798.e1.	2011	211
Schaumberg et al. [12]	Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies.	Archives of Ophthalmology. 2009 Jun; 127(6): 763–8.	2009	207
Lam et al. [13]	Tear cytokine profiles in dysfunctional tear syndrome.	American Journal of Ophthalmology. 2009 Feb; 147(2): 198–205.	2009	192
Pflugfelder et al. [14]	Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye Workshop (2007)	The Ocular Surface. 2007 Apr; 5(2): 163–78.	2007	182
Knop et al. [15]	The international workshop on meibomian gland dysfunction: report of the Subcommittee on Anatomy, Physiology, and Pathophysiology of the Meibomian Gland.	Investigative Opthalmology & Visual Science. 2011 Mar 30; 52(4): 1938–78.	2011	171
Stevenson et al. [16]	Dry eye disease: an immune-mediated ocular surface disorder.	Archives of Ophthalmology. 2012 Jan; 130(1): 90–100.	2012	156
Massingale et al. [17]	Analysis of inflammatory cytokines in the tears of dry eye patients.	Cornea. 2009 Oct; 28(9): 1023–7.	2009	147
De Paiva et al. [18]	IL-17 disrupts corneal barrier following desiccating stress.	Mucosal Immunology. 2009 May; 2(3): 243–53.	2009	146
Nelson et al. [19]	The international workshop on meibomian gland dysfunction: report of the Definition and Classification Subcommittee	Investigative Opthalmology & Visual Science. 2011 Mar 30; 52(4): 1930–7.	2011	141
Tomlinson et al. [20]	The international workshop on meibomian gland dysfunction: report of the Diagnosis Subcommittee.	Investigative Opthalmology & Visual Science. 2011 Mar 30; 52(4): 2006–49.	2011	133
Liu et al. [21]	A link between tear instability and hyperosmolarity in dry eye.	Investigative Opthalmology & Visual Science. 2009 Aug; 50(8): 3671–9.	2009	129
Arita et al. [22]	Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population.	Ophthalmology. 2008 May; 115(5): 911–5.	2008	128
De Paiva et al. [23]	Dry eye-induced conjunctival epithelial squamous metaplasia is modulated by interferon-gamma.	Investigative Opthalmology & Visual Science. 2007 Jun; 48(6): 2553–60.	2007	122
Enríquez de Salamanca et al. [24]	Tear cytokine and chemokine analysis and clinical correlations in evaporative-type dry eye disease.	Molecular Vision. 2010 May 19; 16: 862–73.	2010	122
Chotikavanich et al. [25]	Production and activity of matrix metalloproteinase-9 on the ocular surface increase in dysfunctional tear syndrome.	Investigative Opthalmology & Visual Science. 2009 Jul; 50(7): 3203–9.	2009	120

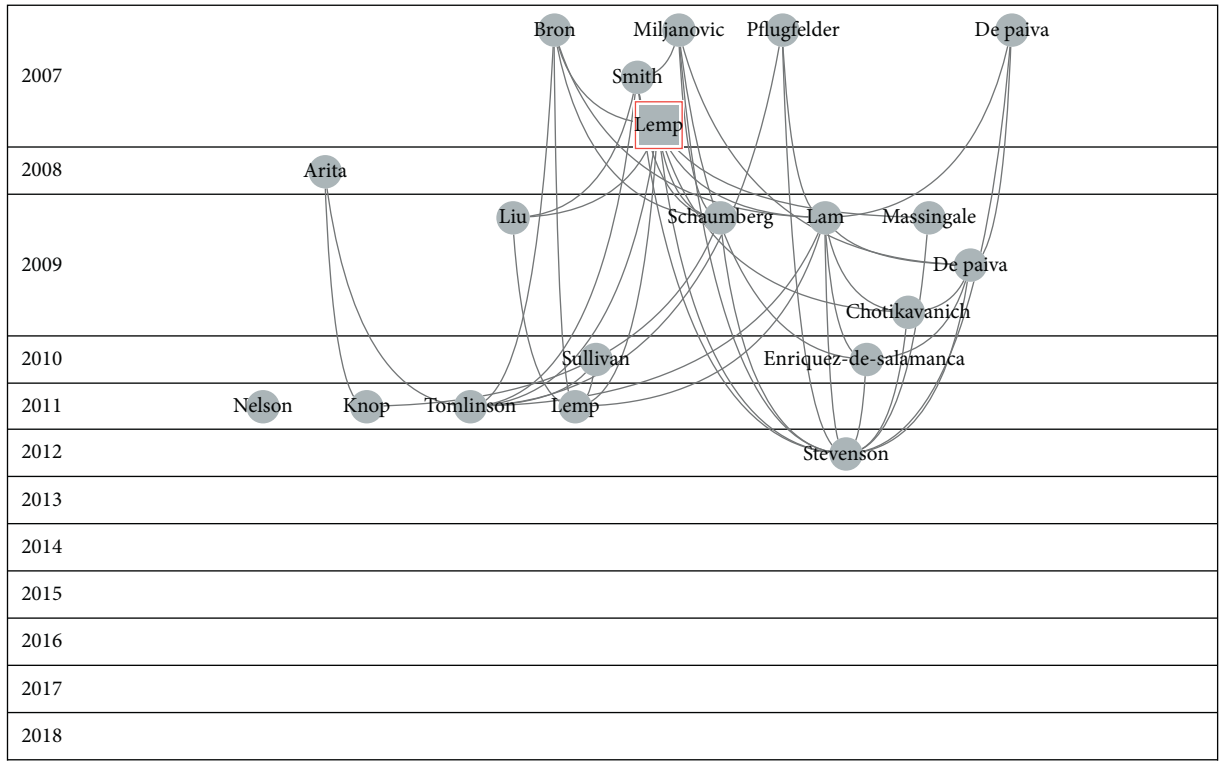

Figure 1: Dry eye citation network graph from CitNetExplorer.

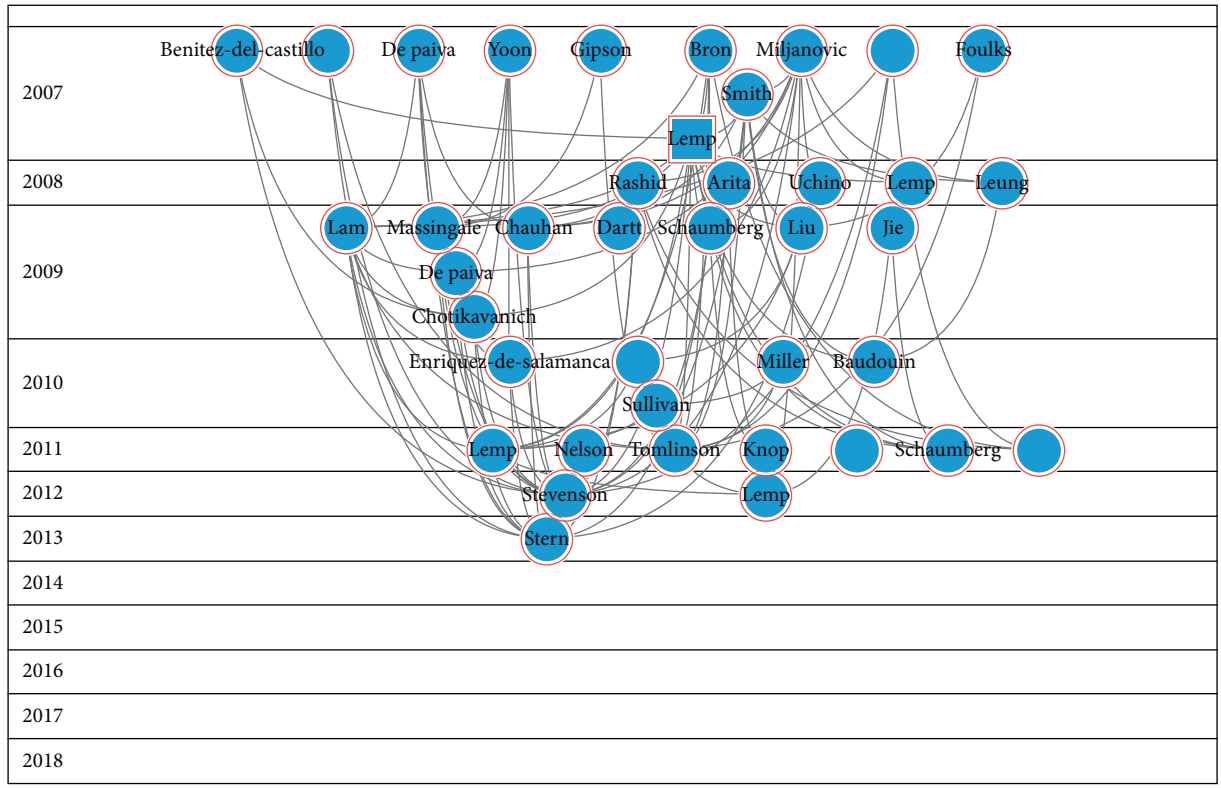

Figure 2: Citation network of cluster 1.

dry eye established in this report. This was used until DEWS II was published in July 2017, which included a redefinition of dry eye.

The second cluster we found is related to the treatment. It shows that dry eye is a chronic pathology and how treatment is one of the main challenges for vision

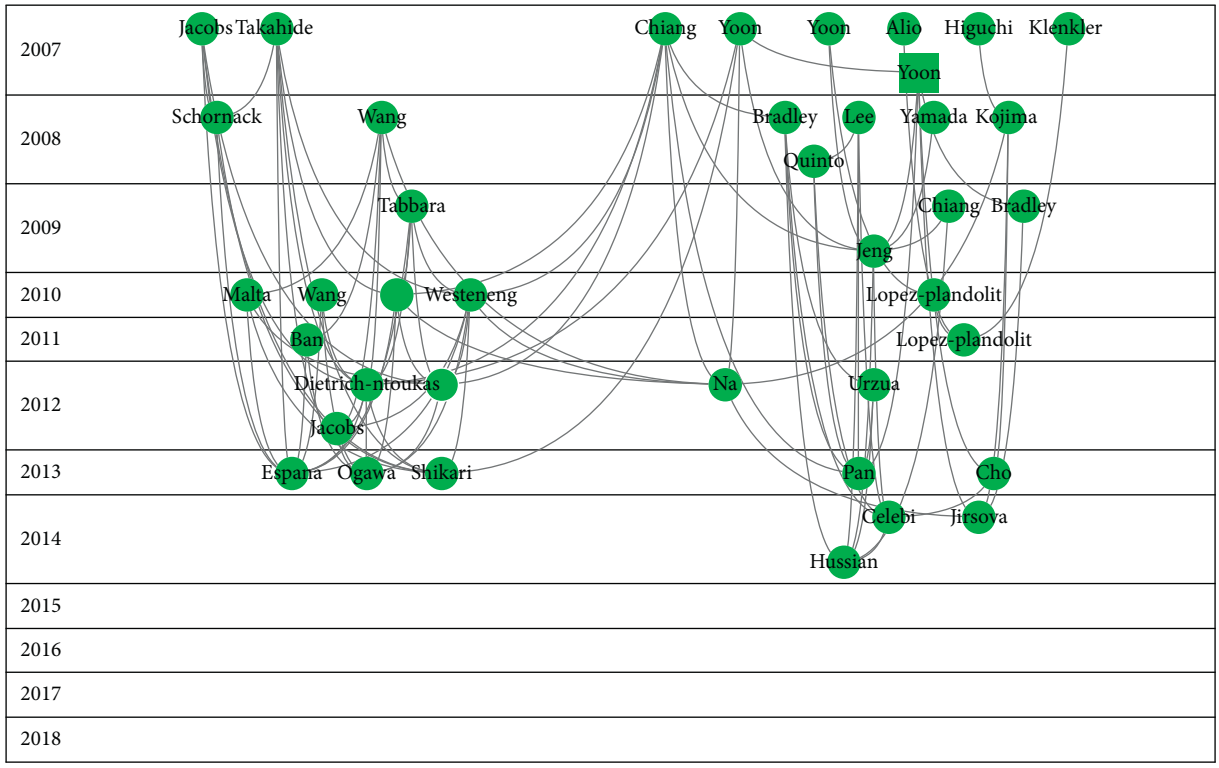

Figure 3: Citation network of cluster 2.

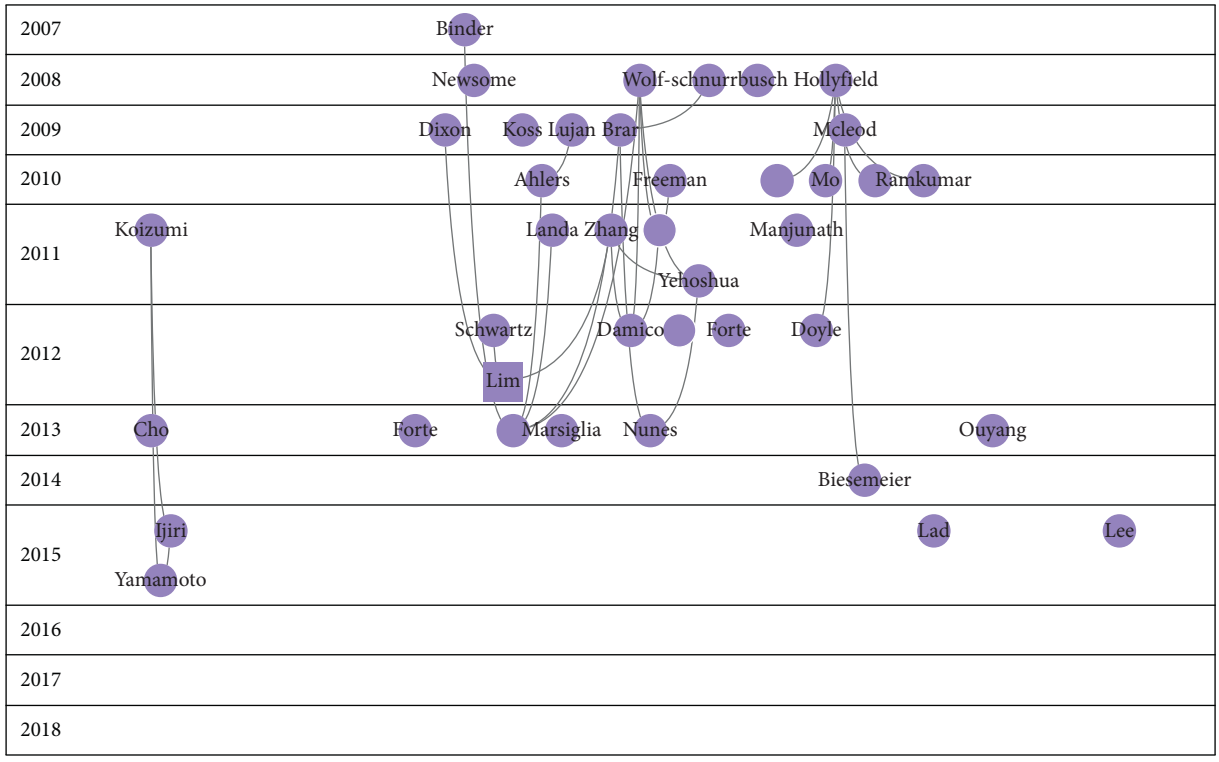

Figure 4: Citation network of cluster 3.

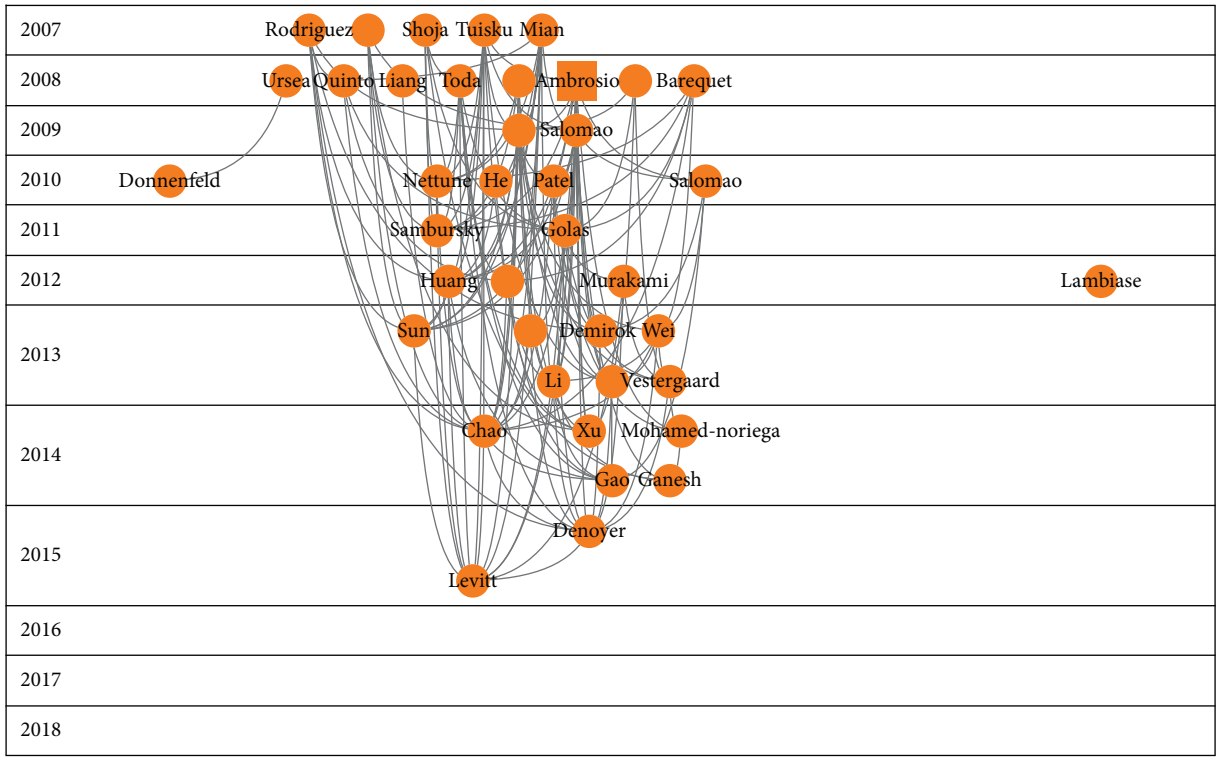

Figure 5: Citation network of cluster 4.

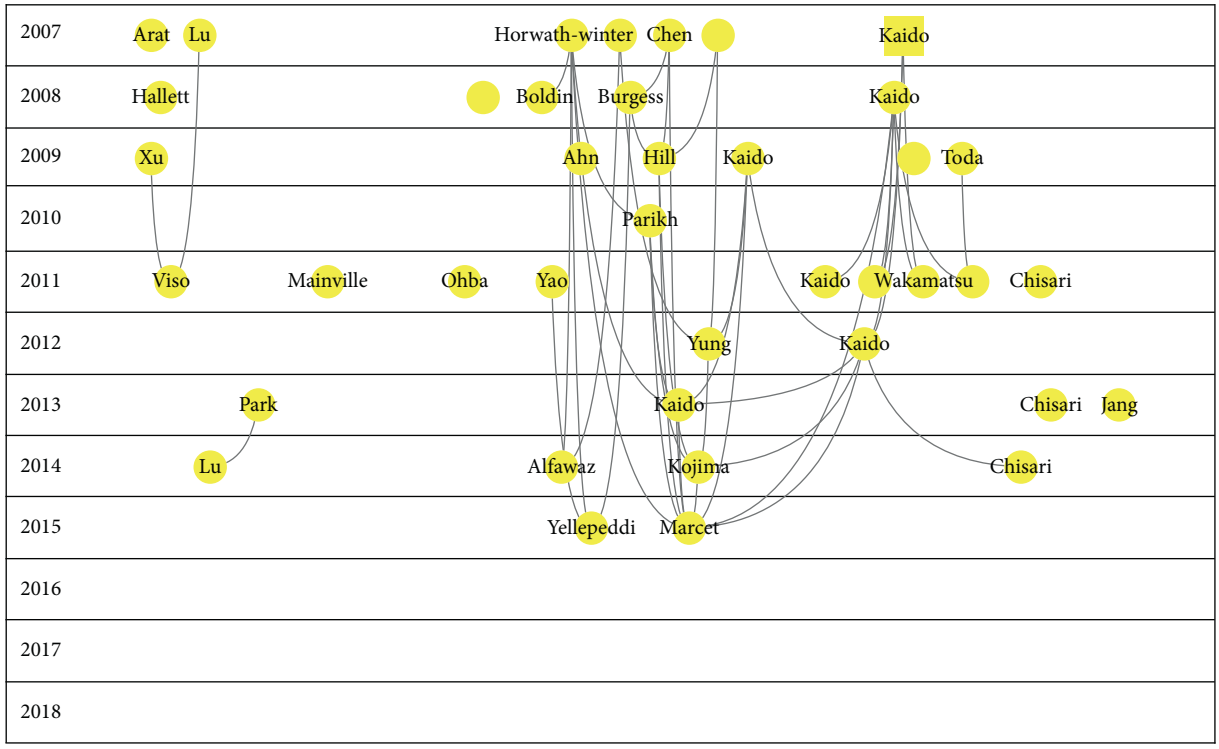

Figure 6: Citation network of cluster 5.

professionals. The cluster is led by the prospective case-control study of Yoon et al., published in 2007 in American Journal of Ophthalmology, where autologous serum was compared with umbilical cord serum eye drops in 48 patients with severe dry eye syndrome.

Finding retina as a third cluster could seem surprising because retina has no bearing on the relationship between ocular surface and dry eye. However, it could be explained by the relationship between age and dry eye and between age and pathology of the retina. In other words, studies with

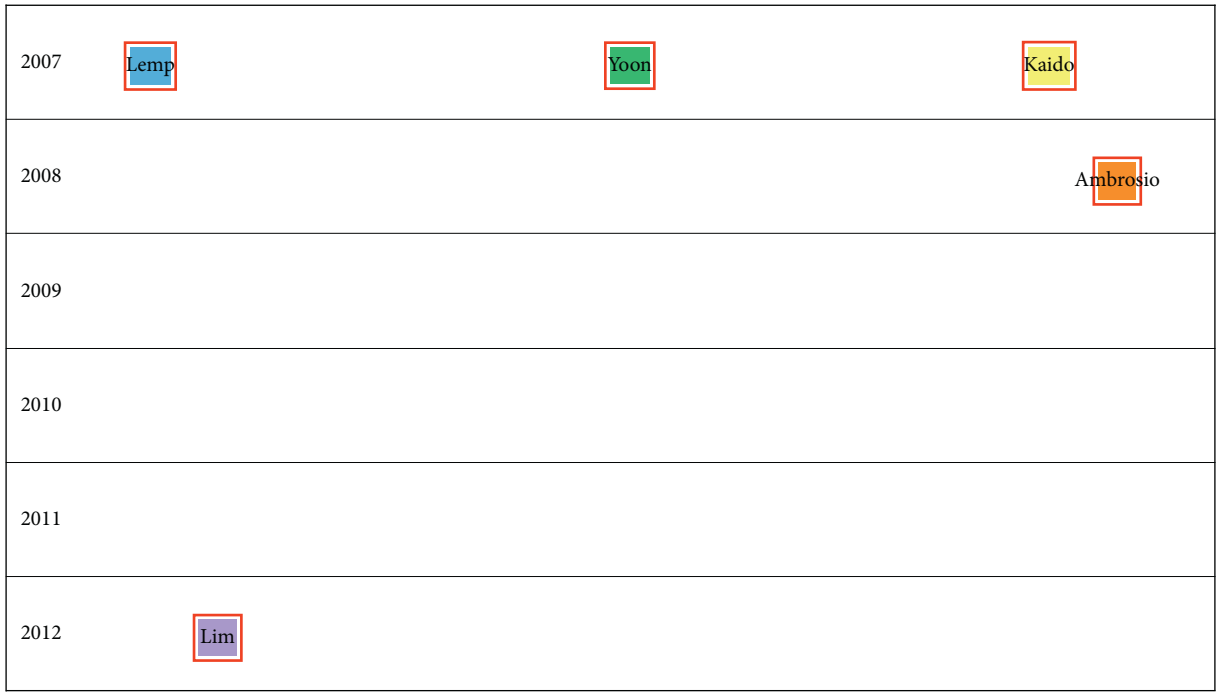

Figure 7: Relationships among different clusters.

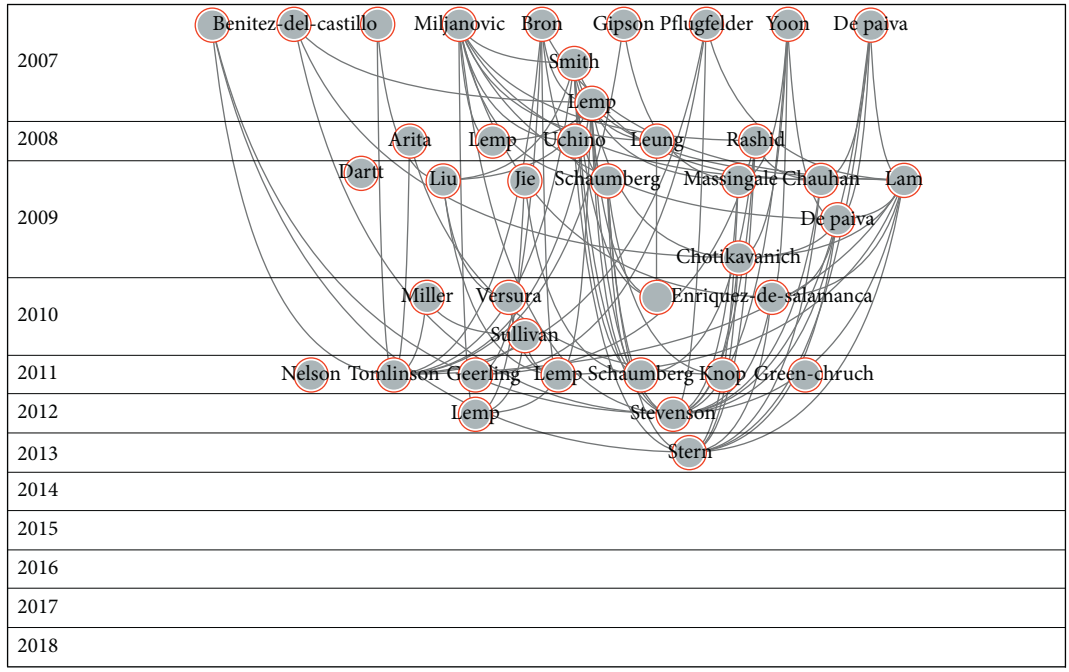

Figure 8: Core Publication of the dry eye citation network analysis.

older people could shed light on different pathologies such as dry eye and retina problems. It would be worth carrying out further research in the future.

The fourth cluster is about refractive surgery. This is due to the fact that one of the most common complications of LASIK is dry eye. The most cited article in this cluster is a review from Ambrosio et al., published in 2008 in Journal of Refractive Surgery. They reviewed the scientific literature and summarized the experience of the authors to propose methods for decreasing dry eye after surgery.

Finally, the fifth cluster relates to quality of vision. This is one of the concerns for patients suffering from dry eye.

The absence of relationships among the clusters' most cited articles is striking. We assumed we would find some

connections between clusters, but in fact, none of the five articles cites any of the others. Therefore, we see five clearly different topics in five differentiated clusters.

Core Publication accounts for 64% of the papers in the network, which is a high percentage. This means there is a clear focus on the research carried out in this field. Definition and classification made up most of this Core Publication. Treatment and refractive surgery are also represented in this core, albeit in less quantity.

5. Conclusions

Dry eye is a very important field for researchers, with a very high number of publications and many connections among articles.

This citation network analysis shows that definition and classification of dry eye is still very important, most of the articles being related to this cluster. It is followed in relevance by treatment.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Effects of Blink Rate on Tear Film Optical Quality Dynamics with Different Soft Contact Lenses

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Objective. The aim of this study was to investigate tear film optical quality dynamics for four types of silicone hydrogel contact lenses (SHCLs) for daily wear over a 15-day period and for different blink rate (BR) patterns. *Methods*. A prospective randomized, double-blind, cross-over pilot study including four SHCLs (A: lotrafilcon B (Air Optix plus HydraGlyde, Alcon Laboratories); B: samfilcon A (Ultra, Bausch & Lomb); C: comfilcon A (Biofinity, CooperVision); and D: filcom V3 (Blu:gen, Mark'Ennovy)). Serial measurements of Objective Scatter Index (OSI) using the HD Analyzer (Visiometrics S.L., Terrassa, Spain) were taken at different blinking patterns: blinking every 2.5 seconds (high BRs) and every 9 seconds (low BRs). They were performed during the first visit before CL insertion (baseline), after 20 minutes of CL wear (Day 1), and during the last visit after 8 hours of CL wear on day 15 of use (Day 15). *Results*. Normal young healthy subjects were recruited and fitted with the four lenses. For low BRs, the mean OSI value increased over time for all CLs and the slope of the curve also increased for all CLs, except for CL D. However, for high BRs, the mean OSI value increased only for CLs B and C and the slope of the curve did not change over time for any of them. *Conclusions*. These results suggest that the tear film optical quality dynamics after wearing SCHLs for 15 days seems to undergo a slight deterioration only for lowest BR.

1. Introduction

The tear film plays an important role in the optical quality of the human eye [1–4]. Several authors have studied changes in tear film quality over time in contact lens wearers [5–10], using dynamic-area high-speed videokeratoscopy [5, 6, 9, 10] and a double-pass method [7]. The results show that there is a significant decrease in prelens tear film quality with respect to the baseline precorneal tear film quality with monthly hydrogel and silicone hydrogel contact lenses (CLs) over one week of use [5]; daily CLs (delefilcon A silicone hydrogel and omafilcon A hydrogel) over 4 hours of use [6]; daily hydrogel CLs over one day of use [9]; hard CLs (PMMA), rigid gas permeable (RGP) CLs (Boston XO), and soft silicone hydrogel CLs over one day of use [8]; and HEMA multifocal CLs over one day of use [7].

New CL materials currently focus on improving tear film stability in order to provide optimal vision quality. At the same time, the use of desktop, laptop, and tablet computers, smartphones, and electronic reading devices has become ubiquitous with today's society [11]. Under these conditions, the blink rate (BR) decreases, creating a risk factor for ocular exposure [12]. Additionally, CL wearers tend to increase their BRs, presumably because of surface irritation from the lens or unstable tear film [13]. All these above-mentioned conditions can affect the optical quality of the tear film and consequently the success of CL adaptation.

The High Definition Analyzer (HD Analyzer™) (Visiometrics S.L., Terrassa, Spain) is an instrument that uses a double-pass method that was developed to perform an objective evaluation of optical quality. It determines the Objective Scatter Index (OSI) using the point spread function (PSF), which determines how a point source of light is imaged on the retina. The OSI is an objective index of intraocular scattered light. It is a parameter that has been used for assessment of the dynamics of the human tear film

in dry eyes or normal eyes [14–17]. Thus, an indirect approach can be used to quantify tear film quality based on dynamic analysis of OSI values [18]. However, there are not studies that reported OSI dynamic changes in silicone hydrogel CL wearers. Applying the dynamic analysis of OSI values is a novel approach in the study of the behavior of different contact lenses with low and high blinking patterns.

The aim of the current study was to evaluate the tear film optical quality dynamics for four types of silicone hydrogel contact lenses (SHCLs) over 15 days of wear for different BR patterns.

2. Materials and Methods

2.1. Subjects. A total of 15 subjects (12 men and 3 women; mean age 24.1 ± 2.2 years; age range 29 to 21 years) took part in this study. The study was carried out at the Faculty of Optics and Optometry of the Complutense University of Madrid. It was reviewed and approved by the Institutional Review Board of the San Carlos University Hospital in Madrid. It was conducted in accordance with the Declaration of Helsinki. All the subjects gave informed consent and agreed to all the procedures after being informed in detail about the nature of the study. Inclusion criteria were age range of 20 to 30 years, current CL wearers, cylinder refractive error <0.50 D, and spherical refractive error range of +4.00 to −4.00 D. Exclusion criteria included active ocular allergy and refractive surgery or systemic medication known to affect tear film production.

2.2. Optical Quality Analysis System: High Definition Analyzer. Optical quality was evaluated using the HD Analyzer™ (Visiometrics S.L., Terrassa, Spain). This instrument, based on the double-pass method, provides an objective clinical evaluation of the eye's optical quality. It was designed for use in clinical practice to objectively determine the optical quality of the human eye, including intraocular scattering, using a double-pass method.

The OSI is a parameter that allows intraocular scattered light to be evaluated objectively. It is computed by evaluating the amount of light on the periphery of the double-pass image in relation to the amount of light at its centre. The central area selected was a circle with a radius of 1 minute of an arc, while the peripheral zone was a ring set between 12 and 20 minutes of an arc. As the OSI value increases, the level of intraocular scattering also increases [17].

The "Tear Film Analysis" program included in the commercially available software was used to record dynamic changes in OSI values. This program consists of a 20-second examination with an OSI measurement every 0.5 seconds that gives a quantitative and objective evaluation of the loss of optical quality due to tear film degradation. The HD Analyzer™ (Visiometrics S.L., Terrassa, Spain) system allows to monitor the dynamic changes in optical quality. The result screen shows all images recorded during the process, with one OSI value for each image. When the subject blinked, the OSI value was replaced by a blink mark and no value was recorded at this point.

2.3. Measurement of Dynamic Optical Quality. The subject's spherical refractive error was automatically corrected by the HD Analyzer™ (Visiometrics S.L., Terrassa, Spain).

The OSI dynamic measurements were taken in two different situations after a 5-minute period of dark adaptation. Two blink patterns had been defined based on how often the subject was allowed to blink. They were asked to blink every 2.5 seconds (high BRs) during the whole recording process (20 seconds), and finally, they were asked not to blink for 9 seconds (low BRs). Blink rates were controlled by an audible signal that the instrument emits. Before starting, the registration subjects were instructed to blink twice naturally and then keep their eyes open. There was a wash-out period of 10 minutes between both measurements (high and low BRs).

2.4. Study Protocol and CL Types. This is a prospective, randomized, double-blind, cross-over pilot study (see Figure 1 for a detailed explanation of the protocol). It was conducted over five consecutive weeks, using 4 types of monthly CLs made of silicone hydrogel (SH) material for daily wear. The lens parameters are shown in Table 1.

Previously, one week of wash out without any CL was given to participants. During the first two weeks, each subject used one CL in the right eye and another different CL in the left eye. After a week of wash out, another two CLs were assigned to the right and the left eye for two more weeks. CLs were assigned randomly, and subjects were instructed to wear the CLs for 8 hours a day. Slit lamp assessment was performed after one week of wash out without any CL and after 15 days of use of the two pairs of CLs assigned.

The OSI dynamic measurements (high and low BRs) were taken for each pair of CL on the first visit and last day of wear (15 days). On the first day of wear, measurements were taken before CL insertion (baseline) and at 20 minutes of wear (Day 1). On the last day of wear (after 15 days of use), measurements were taken at 8 hours of wear (Day 15). All subjects used the same solutions to care for the lenses (OptiFree Express MDS; Alcon Laboratories, Inc., Fort Worth, TX, USA). Subjects were exposed to the controlled environmental conditions, temperature 24 ± 2°C and humidity 38 ± 2%, before being examined for 10 minutes.

2.5. Statistical Analysis. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). The data exported from the HDA contained 40 OSI values with the "Tear Film Analysis" program. The software registered an OSI value every 0.5 seconds for 20 seconds. For high-BR situations, all values were analyzed, but for low-BR situations, only the first 9 seconds were analyzed. Statistical analysis was performed by descriptive analysis to obtain the mean results and standard deviations. In order to assess tear film stability, the relationship between OSI values and time was analyzed by regression models and the slope of the curve was calculated. Therefore, the mean and standard deviation were analyzed for the OSI dynamic values and slope of the curve for each BR situation registered. The Shapiro–Wilk test for normality was applied followed by the appropriate parametric ANOVA test with

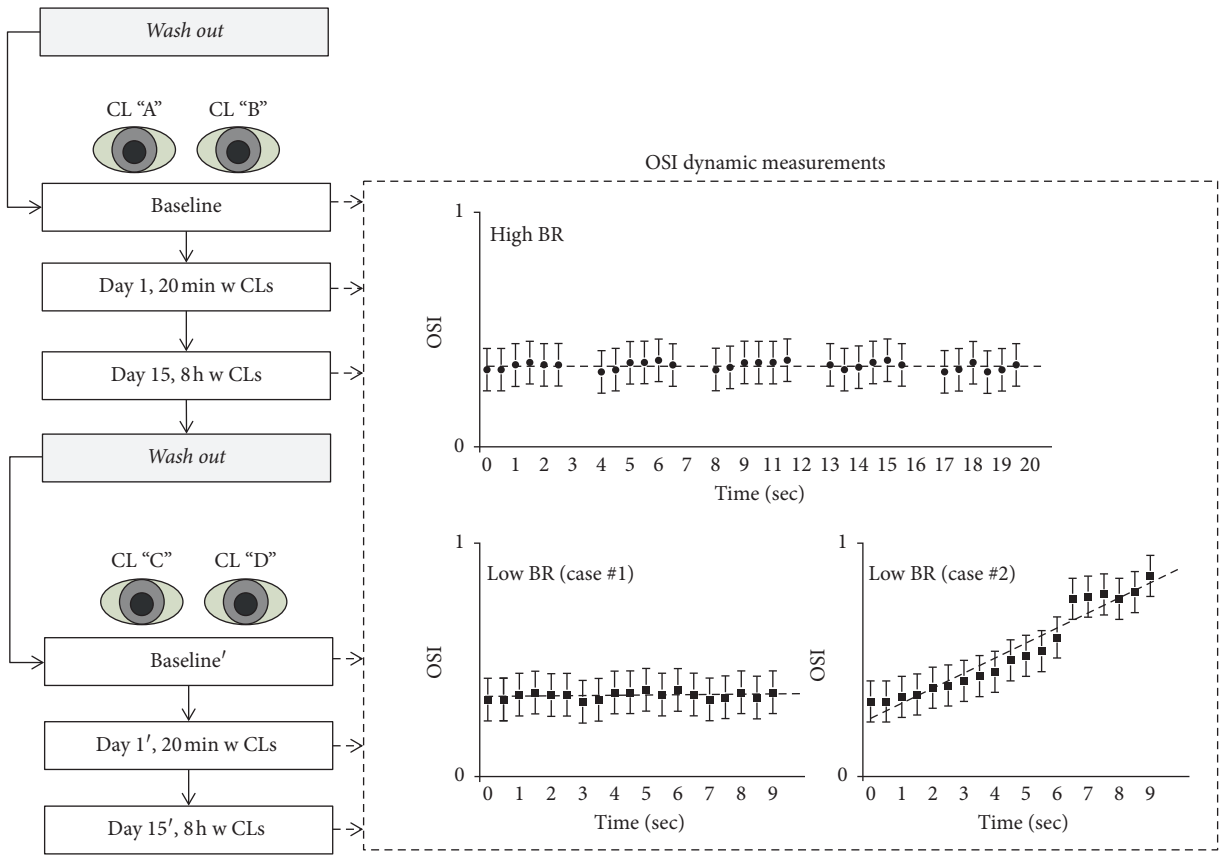


Figure 1: Clinical protocol. Repeated-measures ANOVA of the Objective Scatter Index (OSI) was performed for two different blinking patterns: blinking every 2.5 seconds (high BRs) and not blinking for 9 seconds (low BRs). The graphic representation of OSI values for high BRs was recorded over 20 seconds. Successive intervals were registered separated by blinks, and the graph represents a stability model of the OSI value with a flat curve. The graphic representation of OSI values for low BRs was recorded over 9 seconds, and only one interval was registered and analyzed. The distribution of OSI values over time has different behaviors: case #1 represents a stable model with a flat curve, while case #2 represents a model of instability with an increase in the slope of the curve. Measurements were performed for each visit (baseline, Day 1, and Day 15) using randomly assigned contact lenses. OSI: Objective Scatter Index; dyn.: dynamic; BR: blink rate; CL: contact lens; w CLs: wearing contact lenses; sc: seconds.

Table 1: Marketed silicone hydrogel contact lenses used in the study.

	CL A	CL B	CL C	CL D
Material	Lotrafilcon B	Samfilcon A	Comfilcon A	Filcom V3
Laboratory	Alcon	Bausch & Lomb	CooperVision	Mark'Ennovy
Commercial name	Air Optix plus HydraGlyde	Ultra	Biofinity	Blu:gen
Base curve (mm)	8.60	8.50	8.60	6.50–9.80 (step 0.30)
Diameter (mm)	14.20	14.20	14.00	11.50–16.50 (step 0.50)
Oxygen transmissibility (Dk/t)	138	163	160	50
Water content (%)	33	46	48	75
Modulus (MPa)	1.0	0.70	0.75	0.25

the Greenhouse–Geisser correction or nonparametric Friedman test to compare the effects of time (comparison between visits). The significance level used was $p < 0.05$.

3. Results

The baseline OSI values were 0.31 ± 0.16, 0.46 ± 0.13, 0.34 ± 0.08, and 0.40 ± 0.13 for CLs A, B, C, and D, respectively. There were not differences between them ($p = 0.10$). No adverse events on the ocular surface occurred during the study.

3.1. OSI Dynamic Analysis for Low-BR Situations. A summary of the results is shown in Table 2. Repeated-measures ANOVA on the effect of the visits (baseline, Day 1, and Day 15) showed the effect of CL wear over time on OSI dynamics. The mean OSI dynamic value increased for all CLs. The baseline slope of the curve showed values between 0.03 ± 0.05 (CL A) and 0.04 ± 0.07 (CL C). The slope of the curve also increased for CLs A and B and for CLs C and D, and there was no statistical significance (Figure 2).

Table 2: Analysis statistics for dynamic Objective Scatter Index (dyn. OSI) for low blink rates.

		Low blink rate (mean ± SD)			
		Baseline	Day 1	Day 15	p value
Dyn. OSI	CL A	0.83 ± 0.46	1.07 ± 0.61	1.84 ± 1.64	0.04*
	CL B	0.79 ± 0.26	2.02 ± 2.28	1.88 ± 1.98	0.02*, 0.03†
	CL C	1.02 ± 0.60	2.16 ± 2.04	2.23 ± 2.44	0.05*†
	CL D	0.66 ± 0.16	1.24 ± 0.63	1.10 ± 0.43	0.03†
Slope	CL A	0.03 ± 0.05	0.07 ± 0.08	0.22 ± 0.32	0.05*
	CL B	0.03 ± 0.04	0.26 ± 0.58	0.15 ± 0.36	0.05*†
	CL C	0.04 ± 0.07	0.25 ± 0.60	0.11 ± 0.13	0.06
	CL D	0.03 ± 0.05	0.09 ± 0.17	0.07 ± 0.10	0.629

*Significant difference noted between baseline and Day 15; †significant difference noted between baseline and Day 1; Day 1: after 20 minutes of CL wear; Day 15: after 8 hours of CL wear on day 15 of use; significant p value <0.05.

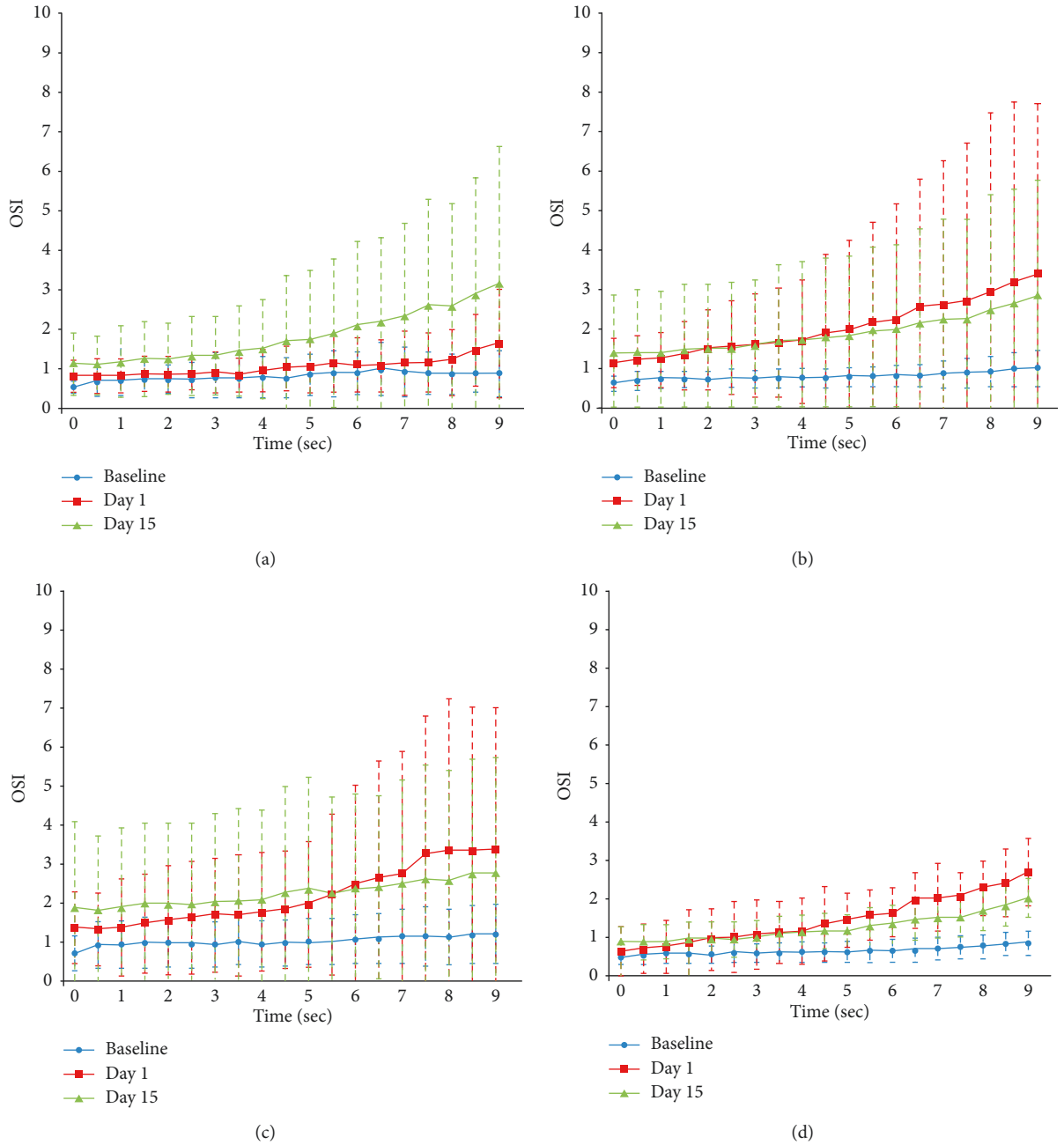


Figure 2: Graphic representation of OSI dynamics for low BRs. OSI: Objective Scatter Index; dyn.: dynamic; BR: blink rate; CL: contact lens. (a) CL A. (b) CL B. (c) CL C. (d) CL D.

3.2. OSI Dynamic Analysis for High-BR Situations. Analysis statistics for OSI dynamics are summarized in Table 3. The OSI dynamic score increased (optical quality decreased) over time for all CLs, although the changes were statistically significant only in CLs B and C ($p < 0.05$). Nevertheless, the stability of the curve for different interval measurements during the 20 seconds recorded showed a flat slope for all CLs (Figure 3).

Table 3: Analysis statistics for dynamic Objective Scatter Index (dyn. OSI) for high blink rates.

	Dyn. OSI (mean ± SD)			
	Baseline	Day 1	Day 15	p value
CL A	0.66 ± 0.26	0.70 ± 0.20	0.93 ± 0.61	0.06
CL B	0.79 ± 0.22	1.12 ± 0.79	1.15 ± 0.58	0.02*
CL C	0.70 ± 0.34	1.07 ± 0.77	1.15 ± 0.76	0.01*
CL D	0.64 ± 0.16	0.82 ± 0.45	1.01 ± 0.67	0.08

*Significant difference noted between baseline and Day 1; Day 1: after 20 minutes of CL wear; Day 15: after 8 hours of CL wear on day 15 of use; significant p value <0.05.

4. Discussion

A CL compartmentalizes the tear film, isolating the mucin layer behind the lens, thinning the prelens tear film, and disrupting the lipid layer [19–22]. Various studies have shown that CLs induce tear film changes and play an important role in the maintenance of optical quality [23]. This could potentially influence CL tolerance and lead to blurriness or fluctuations in vision. New designs for CLs focus on improving some of their properties, such as wettability [24] and lubricity, in order to provide the best quality vision and keep it stable over time, even under the more stressful conditions associated with the use of desktop, laptop, and tablet computers, smartphones, and electronic reading devices.

The aim of this cross-over pilot study was to assess the dynamic changes of optical quality during CL wear in a normal sample of participants. All of them wore 4 different types of SHCLs for 15 days.

The evidence suggests that the average OSI value in a healthy population is 0.7 ± 0.3 [17], 0.47 ± 0.11 [25], 0.41 ± 0.18 [15], and 0.32 ± 0.13 [26]. These results are in agreement with the average OSI value obtained in the current study. This observation reinforces the healthy characteristics of the eyes of the participants in the present study. Furthermore, it is important to assess the repeatability of the OSI. A sample classified by an ordinal scale depending on the increment of the OSI dynamic after each blink with the high-BR pattern revealed a quadratic kappa agreement k of 0.59 (95% CI 0.44 to 0.74) [27]. Regarding the OSI static value, the limit of repeatability was 0.26 (56.1%) [25] and 0.11 (34.4%) [26]. The tear film is generally evaluated in terms of quality and quantity, which are essential factors when characterizing tear film dynamics [28]. Regardless of the tear film quality, the tear film stability parameters in the present study were defined based on the OSI dynamic value and the slope of the curve. The ability of the prelens tear film to retain a smooth refractive surface on the CL surface was altered for some different types of CLs and even more so for low BRs. In fact, the variability of the OSI measurement increased for materials B and C, although it was more dramatic for low-BR patterns compared to high-BR patterns in the current pilot study.

A previous study shows that the best optical quality studied objectively by measuring the modulation transfer function (MTF) of the anterior surface of the film in the baseline situation was reached between 6 and 7 seconds after blinking, after which there was a progressive decrease [29]. However, the current study did not show a decrease in baseline optical quality. All participants had stable optical quality in the baseline situation under both BRs studied; OSI dynamic values were <1.00, and the slope of the curves was flat (the maximum value was 0.04 ± 0.07).

This situation changed when a CL was fitted. Both the types of CLs and the blink rate affect these results, which have been confirmed by other authors [5–10]. These results are also similar for non-contact lens wearers who suffer from dry eye disease (DED) [14].

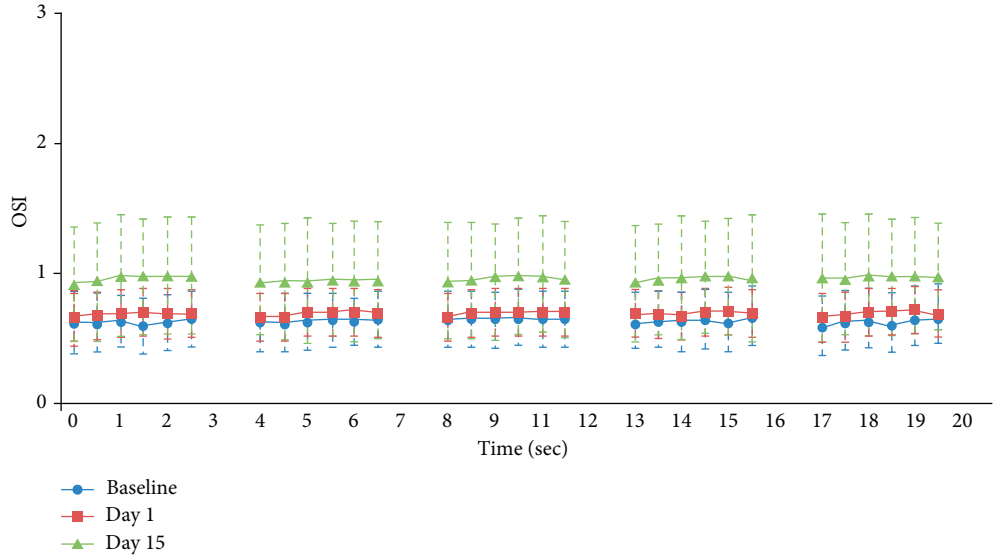
In addition, it has been reported that CL wearers tend to increase their BRs, presumably because of surface irritation from the lens or unstable tear film [13]. Therefore, in order to determine optical quality during CL wear, it is interesting to analyze it for different BRs.

It is widely known that one of the functions of blinking is to reestablish a stable tear film, so it seems reasonable to assume that thinning tear film may induce poor quality of vision. A high blink rate has been evidenced in conversation situations (21.5 ± 5.6 blinks per minute), while a low blink rate in attention tasks and digital device situations [30].

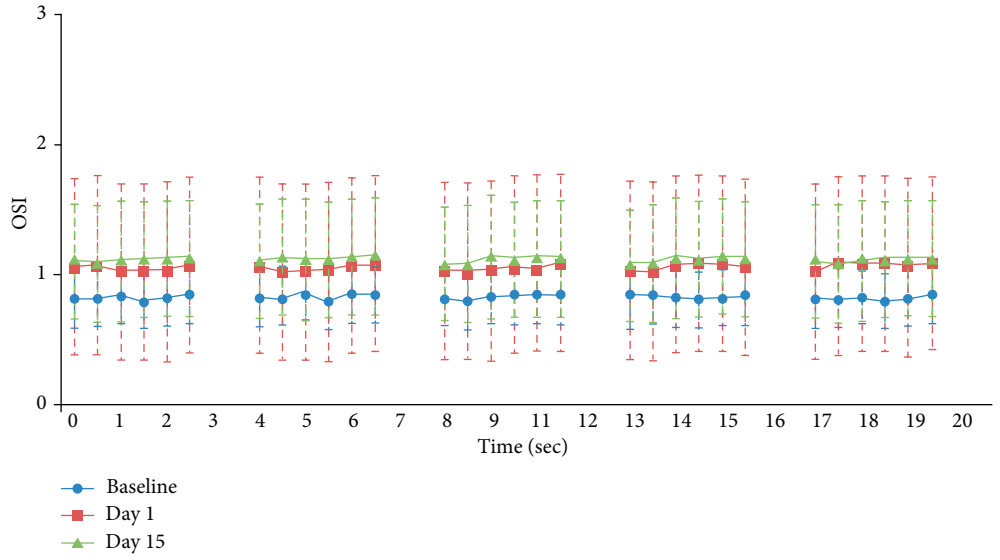
Furthermore, spontaneous eye blinking has been found to be significantly reduced during activities such as reading, computer work, or other visual tasks requiring concentration [31, 32]. Many types of computers are currently used in everyday life. In most parts of the world, it is impossible to use a product or service that does not involve the use of a computer. In this way, the current results obtained by reducing the blink rate in CL users showed a worsening behavior in the stability of tear film optical quality compared to those obtained with high BRs. Table 2 shows that, for low BRs, there was an increase in the OSI dynamic value on day 15 of use for all CLs with respect to the baseline precorneal condition, except for CL D. There was a significant decrease in prelens tear film optical quality dynamics that was reflected in the slope of the curve.

However, for high-BR situations, the slope of the curve for all CLs remained constant. Despite the fact that, for higher BRs, the stability of the OSI value was maintained, there were observed changes in the OSI value. That is, after 15 days of use of CLs B and C, the OSI value worsened with respect to the baseline condition but stability was maintained. It is more than likely, however, that this finding has no negative impact on the participants' visual quality. The mean OSI values on Day 15 for high BRs were 0.93 to 1.15, in the limit of normal values of OSI. These findings suggest that all CLs studied provided optimal optical quality stability for high-BR situations over 15 days of use.

A CL is defined as a nonpathological factor impacting the tear film [33], and it is interesting to compare the effect of



(a)



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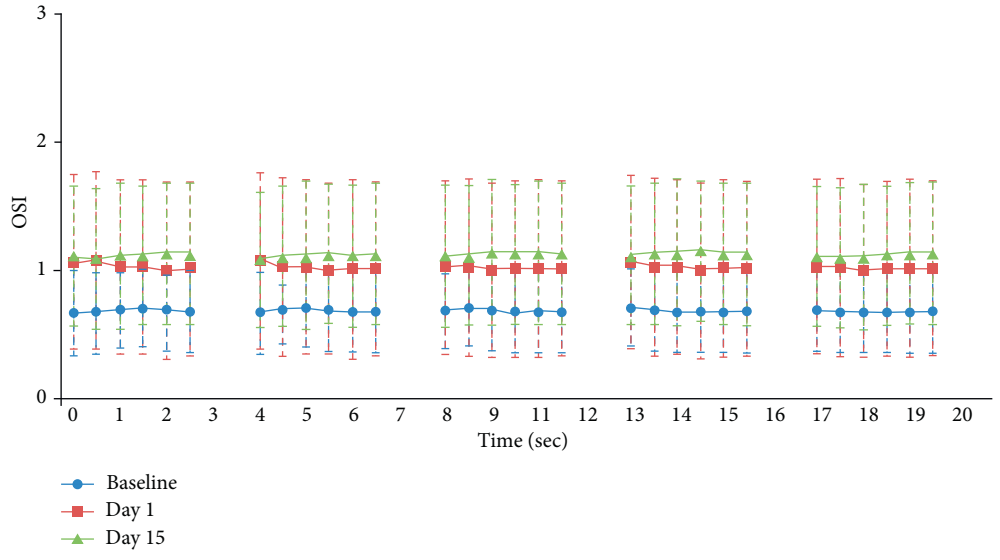
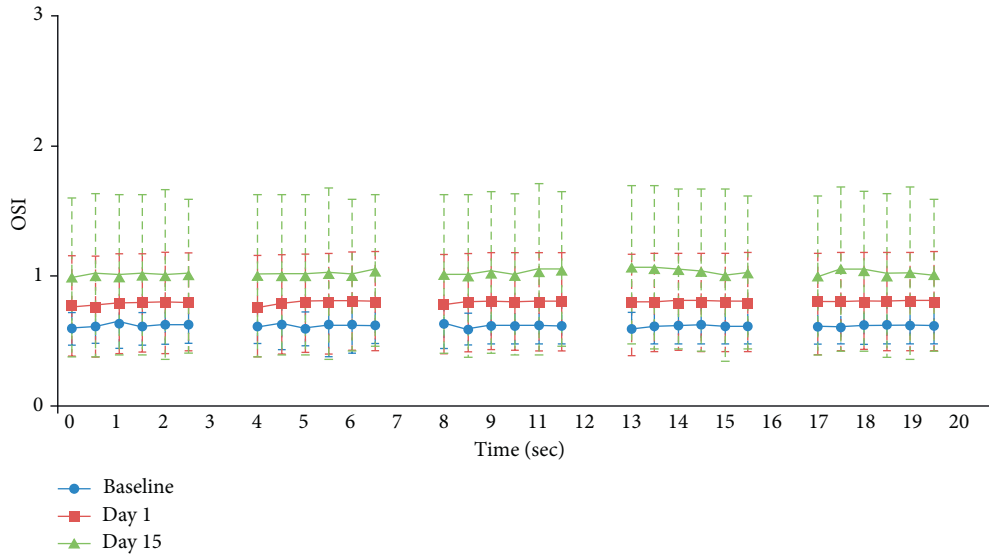


(c)

Figure 3: Continued.



(d)

Figure 3: Graphic representation of OSI dynamics for high BRs. OSI: Objective Scatter Index; dyn.: dynamic; BR: blink rate; CL: contact lens. (a) CL A. (b) CL B. (c) CL C. (d) CL D.

different blink rates over time. We have observed that, with a high BR, CL wear time does not cause a decrease in optical stability. In contrast, in conditions where the BR decreases, optical stability decreases as CL wear time increases.

Primarily, the CLs which provide worse optical quality stability could provide visual disturbance (fluctuation of vision). Depending on the lens, this could be more important after 15 days of using and/or for low BRs. Secondarily, visual disturbance could affect the subjective outcomes [34]. The results of the current study have 71% power to detect a difference in mean OSI values of 0.350, assuming a standard deviation in difference of 0.500, using a paired t-test with a 0.050 two-sided significance level. So, this result should be taken with caution even more considering that it is a pilot study.

It is difficult to assess the stability of tear film optical quality during CL wear with standard clinical examinations. With the results of the present study, the aim is to work on CL materials to provide better optical quality over the lifetime of the CL or reconsider CL replacement times in order to assess tear film stability and efficiency over time. Contact lens manufacturers improve wettability by increasing the surface energy and polarity of the lenses by coating, surface pretreatment, or incorporation of hydrophilic groups [24]. These conditions can improve the tear film surface quality and in consequence report a higher optical quality.

Dynamic models of optical changes in the human eye based on OSI values explain changes in vision due to tear film changes in normal eyes [14] and dry eyes [16, 35, 36]. It would be relevant to study this in the presbyopic population, which has poorer tear film stability when compared to the younger population [37] and needs more complex multifocal CL designs.

5. Conclusions

The parameters developed in this study show the difference in the dynamic behavior of OSI values between baseline and SHCL wear conditions and the influence of the BR on the shape of the curve. The final results show that CLs disrupt the tear film and increase OSI scores. Research is now focused on the properties of CLs, such as wettability, dehydration, lubricity, and modulus, and antimicrobial surface treatment, with the aim of providing the best vision quality, defined as optical quality stability between blinks over time.

Data Availability

The data that support the findings of this study are not publicly available because they contain information that could compromise research participants' privacy/consent.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Noncontact Meibography in Patients with Keratoconus

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Purpose. To examine the morphological changes in the meibomian glands of patients with keratoconus as well as to study the relationship between these changes in the morphology and several tear film parameters. *Methods*. Examination of the meibomian gland (MG) of 300 keratoconus patients presenting to the center using infrared noncontact meibography system (Sirius, CSO, Italy) between January 2017—January 2019. 100 eyes of healthy individuals were also enrolled as a control group. Tear breakup time (TBUT) test and Schirmer test II were evaluated. Subjective symptoms were also assessed using Ocular Surface Disease Index (OSDI). *Results*. Mean age of keratoconus patients was 19 ± 12 years and 21 ± 14 years in control group. Average TBUT was 4.9 ± 2.1 sec. and average Schirmer test was 5.3 ± 2.2 mm which was significantly lower than control group ($p = 0.05$). Meibomian gland dropout in the lower eyelid of the keratoconus group was as follows: grade 0 (no loss of meibomian glands): 100 eyes; grade 1 (gland dropout area <1/3 of the total meibomian glands): 85 eyes; grade 2 (gland dropout area 1/3 to 2/3): 68 eyes; and grade 3 (gland dropout >2/3): 47 eyes. *Conclusion*. Keratoconus shows significant meibomian gland dropout and distortion that can be recorded by noncontact meibography. Sirius meibography is a simple, cost-effective method of evaluating meibomian gland dropout as a part of the routine refractive examination.

1. Introduction

Meibomian gland dysfunction (MGD) is considered the main cause of dry eye disease, leading to evaporative dry eye. The lipid layer in the tear film is derived mainly from the meibomian glands which are of utmost importance for preserving the ocular surface [1]. Meibomian glands (MG) are sebaceous glands located in the eyelids with increasing number in the upper eyelid [2]. MGD-related dry eye can be diagnosed by indirect tests, such as tear breakup time (TBUT) [3] or by direct methods such as meibography, which is using transillumination or infrared (IR) light to image the MGs [4, 5]. Indirect tests are liable for a certain degree of interobserver or intraobserver error. On the contrary, the direct method gives detailed anatomic data of the meibomian glands [6]. MGD has some slit lamp characteristics as clogging of orifices with failure of expressibility of meibum, telangiectasia and hyperemia around the orifices, and thickening of the inner border of the lid margin [7].

Tapie [8] was the first to describe meibography using transillumination of the everted eyelid followed by many other researchers who used confocal microscopy [9], noncontact infrared meibography, [1] or video meibography [10]. Normal meibomian glands appear as hypoilluminant grape-like clusters. However, the orifices and ducts transmit light and appear hyperillunimant [11].

Carracedo et al. [12] reported that keratoconus (KC) patients suffer greater symptoms of dry eye and greater tear instability. Moreover blepharitis was found to occur more often in keratoconus patients than in healthy individuals. Blepharitis is associated with eye rubbing which is considered one of the mechanical etiological factors in keratoconus [13]. Eye rubbing results in sheer strength reduction and cone deformation which may contribute to disease progression [14].

Our aim was to detect structural damage in meibomian glands via meibography in cases of KC and correlating them with indirect tests as TBUT and Schirmer test along with the Ocular Surface Disease Index (OSDI).

2. Materials and Methods

2.1. Participants. This study examined the meibomian gland of 300 keratoconus patients presenting to the Sohag Cornea and Refractive Center, Sohag, Egypt, using infrared noncontact meibography software in the Scheimpflug topographer (Sirius, CSO, Italy) between January 2017 and January 2019. Hundred eyes of healthy individuals were also enrolled as a control group. The study was approved by the ethical committee of Sohag University and conducted in compliance with the Helsinki declaration. Informed consent was obtained from all of the patients and normal control participants before clinical assessment.

The KC patients enrolled in this study are as follows: Stage 1 included 157 patients, stage 2 had 100, and stage 3 included 43 patients. Only one eye was tested for each patient, and the more diseased eye was the one included in this study. The control participants were randomly selected from patients attending the outpatient clinic and had no signs or symptoms of dry eye or other ocular inflammation.

Exclusion criteria included any other ophthalmic disorder especially blepharitis or chronic use of eye drops for at least 3 months prior to examination, contact lens wearers, eyes with keratoconus grade 4, and chronic systemic disease. The diagnosis of keratoconus was based on classic corneal biomicroscopic and topographic findings in accordance with the criteria of Rabinowitz and McDonnell [15]. Neither the control nor the KC patients reported wearing contact lenses.

2.2. Assessment

2.2.1. Ocular Surface Disease Index (OSDI). The Questionnaire was administered by the examining physician who translated to the patient the 12-item scoring survey, in which the patient rates his or her own ocular symptoms induced by environmental factors over the past 2–4 weeks. Answers were scored on a scale from 0 to 4, with the total score ranging from 0 to 100 and with higher scores denoting greater disability [16].

2.2.2. Tear Breakup Time (TBUT). TBUT was measured after fluorescein instillation and was represented by the time elapsed from the last complete eyelid blink until appearance of the first dry spot on the cornea. It was measured 3 times consecutively, and the mean value was taken for analysis.

2.2.3. Schirmer II Test. The test (with anesthesia) was performed to evaluate aqueous production. Dryness was considered if wetting of the filter paper was 10 mm or less 2 min after applying topical anesthetic eye drops [17].

2.2.4. Noncontact Meibography. Noncontact meibography was performed by using the Sirius (CSO, Florence, Italy) corneal topographic device with the Phoenix-Meibography Imaging software module. Patients were positioned in front of the scanner, and their forehead was touching the headrest. Only the upper eyelid was evaluated as Dogan et al. reported that it showed better interexaminer agreement as regards grading [18]. Also, upper eyelid MGs outnumber the lower eyelid MGs and are longer in length [19].

The MGs that did not transvere the total tarsal plate were indicated as a "dropout." The Phoenix software gave the measurements of the dropout by percentage, as well as grouped the dropout by a scale within the area, which was highlighted by the users' free-hand tool: grade 0, no loss at all; grade 1, ≤25%; grade 2, 26%–50%; grade 3, 51%–75%; and grade 4, greater than 75% [6].

2.2.5. Meibograde System. The meibograde system was developed and validated by Call et al. [20]. This system involves gland distortion which is an abnormal gland to tarsus ratio, tortuous glands, and/or discordant patterning depending on previously studied histopathological changes [21–23]. Gland shortening refers to glands not extending from the eyelid margin to the opposite edge of the tarsal plate. Each category was graded from 0 to 3 based on the extent of eyelid involvement: grade 0, no significant eyelid involvement; grade 1, less than 33% involved; grade 2, 33% to 66% involved; and grade 3, more than 66% involved. Then, a maximal score of 9 represented complete gland dropout in the lid [20].

3. Statistical Analysis

It was performed by the Statistical Package for the Social Sciences version 17.0 (SPSS Inc, Chicago, Illinois, USA). Normality of the data distribution was tested using the Kolmogorov–Smirnov test. The student test was used to compare gender differences between KC patients and control patients. The Mann–Whitney test was used to determine age and the examination (OSDI, TBUT, and Schirmer test meiboscore) differences among KC patients in different groups and control subjects. ANOVA test was used to compare multiple findings in multiple stages of KC. Spearman correlation was used for detecting correlation between the meiboscore and the other continuous variables. These correlations were considered strong if they were >0.80, moderately strong if they were between 0.5 and 0.8, fair if they were within the range of 0.3 and 0.5, and poor if they were <0.30 [24]. A value less than 0.05 was considered to be statistically significant.

4. Results

Table 1 shows the difference between the KC and control group in demographic data as well as in clinical tests. KC group and the control group were age and sex matched with no statistical difference. The TBUT and Schirmer test indicated statistically significant differences between both groups with the lower values belonging to the KC group. The OSDI was significantly higher in the KC group than that in

Table 1: Clinical findings of both groups.

Mean ± SD	Keratoconus group ($n = 300$)	Control group ($n = 100$)	p value
Sex (M/F)	133/167	42/58	0.23
Age	19 ± 12	21 ± 14	0.25
OSDI score	32.12 ± 14.2	12.2 ± 6.5	0.032
TBUT (sec.)	4.9 ± 2.1	8.3 ± 3.3	0.02
Schirmer test (mm)	5.3 ± 2.2	9.4 ± 3.4	0.05
Total meiboscore	1.36 ± 1.2	1.02 ± 1.1	0.06

OSDI: Ocular Surface Disease Index; TBUT: tear breakup time.

the control group. On the contrary, there was no statistical difference in meibography between the KC group and the controls. On stratifying the KC groups according to their stage, there was only significant difference in the OSDI (Table 2).

Meibomian gland dropout in the upper eyelid of the whole KC group according to the Phoenix software was grade 0 (no loss of meibomian glands): 100 eyes; grade 1: 142 eyes; and grade 2: 58 eyes; grades 3 and 4: 0 eyes (Figure 1). Table 3 shows the number of patients showing each type of characteristic gland abnormality as well as its divided scores. There was statistical difference between the different groups of KC and the control group in the gland dropout with a total score approaching significance. While on comparing the whole KC groups against the control group, there was significance in all characteristics. KC stage 3 showed significant difference from KC stage 1 in gland distortion and shortening as well as the total score. There was no difference between all stages in gland dropout.

Meiboscore correlated significantly with age, sex, KC stage, Schirmer test, and TBUT (ranging between fair and moderate correlation) (Table 4). Yet, it did not have any significant correlation with the OSDI. Table 5 shows correlation between the shortening, distortion, and dropout of MG with other parameters: there was fair correlation with clinical significance between all gland characteristics and KC staging as well as TBUT and Schirmer test.

Table 2: Clinical findings in different keratoconus stages.

	KC 1	KC 2	KC 3	p value
OSDI	30.1	32.5	33.8	0.027
TBUT (sec.)	5.2	5.1	4.6	0.79
Schirmer II test (mm)	5.9	5.3	4.8	0.07
Meiboscore	2.1	2.4	2.6	0.32

OSDI: Ocular Surface Disease Index; TBUT: tear breakup time.

5. Discussion

Our results of meibography imaging showed no difference between the keratoconus group and the control group. There was only significant difference in gland distortion between different stages of KC. Yet the meiboscore correlated well with the KC staging, TBUT, and Schirmer test. And as expected, all clinical testing of dry eye showed clinical difference between the KC patients and the controls. There have always been indirect methods of evaluating MGD such as TBUT and tear osmolarity. Despite the fact that they are objective, results can vary due to interobserver and intraobserver differences [25]. The direct imaging of meibomian gland can offer an anatomical analysis that can contribute to the scope of diagnosis and treatment as well [25].

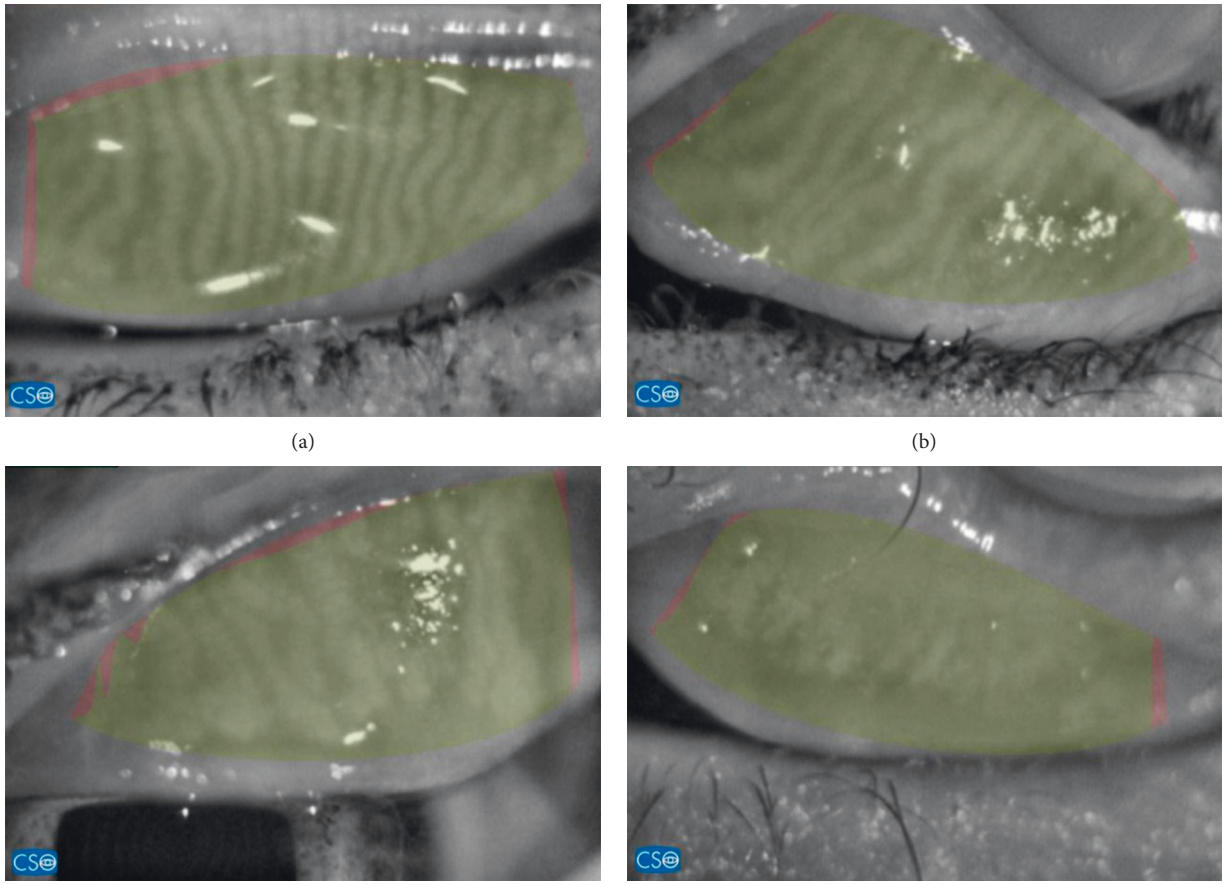
Keratoconus shows higher dropout in MG when compared to the control group despite the fact that there was no significant difference in the meiboscore. This might be attributed to the young age group of the KC patients. In further studies, evaluation of an older group of KC patients would help elucidate the progress of the MG dysfunction. There was no correlation between the OSDI sand the meibography grading. Ngo et al. [26] reported that dropout scores based on the IR images for MGs did not correlate with clinical signs as well. Blackie et al. mentioned that nonchronic blepharitis with no visible inflammation can cause evaporative dry eye which might interpret the lack of correlation between meibograding and OSDI [27].

Our results show that OSDI scores were much higher in the KC group compared to those in control which relates to the results by Dienes et al. [28].

The importance of detecting MGD in cases of KC patients lies in the presence of different lines of treatments that should be chosen depending on the diagnosis to guarantee an optimum response. The appropriate treatment would work on reducing the burning sensation, irritation, tearing, photophobia, blurred vision, and red eyes related to blepharitis thus decreasing patients' tendency to rub their eyes which would eventually improve the quality of vision. On one hand, obstructive MGD with the dropout of acini would benefit from lipid-containing eye drops to improve the stability of the tear film [29–31]. On the other hand, in advanced cases of obstructive MGD that show progressive loss of acini, treatment may involve eyelid hygiene [32] and warm compresses to improve the secretion function [33].

Different technologies were used for meibography [34] such as infrared meibography, [1] confocal meibography, [9] and optical coherence meibography [35]. For comparing the technology, we used the confocal technique: the latter has the disadvantage of being a contact method that can result in patient discomfort, [9] while the optical coherence method shows a relatively difficult interpretation as it requires testing at the same area for consequent measurement [35]. Arita et al. [36] demonstrated diagnostic cutoff values for the meiboscore in combination with symptoms and lid margin abnormalities with a sensitivity of 84.9% and specificity of 96.7% for the diagnosis of MGD.

We are aware that this study focuses on the anatomic details of the MG rather the function of the meibum or its



(a) (b) (c) (d)

Figure 1: (a) Normal meibomian glands with no distortion nor dropout. (b) Grade 1 with dilatation and tortuosity of the MG. (c) Grade 2: dropout of MG along with gland distortion. (d) Grade 3: MG does not traverse the total tarsal with mottling of details.

Table 3: Meibomian gland characteristics in all groups.

Mean ± SD (n)	KC 1 ($n = 157$)	KC 2 ($n = 100$)	KC 3 ($n = 43$)	Control ($n = 100$)	P_0	P_1	P_2	P_3
Gland distortion	0.22 ± 0.11 (30)	0.21 ± 0.12 (21)	0.18 ± 0.11 (8)	0.21 ± 0.14 (18)	0.423	0.09	0.21	0.04
Gland shortening	0.31 ± 0.12 (44)	0.35 ± 0.18 (18)	0.36 ± 0.15 (8)	0.33 ± 0.13 (19)	0.751	0.087	0.088	0.023
Gland dropout	0.71 ± 0.25 (26)	0.73 ± 0.28 (12)	0.79 ± 0.33 (17)	0.51 ± 0.23 (11)	0.002	0.75	0.44	0.56
Total score	2.1	2.4	2.6	1.5	0.06	0.05	0.21	0.025

KC: keratoconus. n: number of patients; SD: standard deviation. P_0 value between the four groups by ANOVA test. P_1 value: KC 1 vs KC 2. P_2 value: KC 2 vs KC 3. P_3 value: KC 1 vs KC 3.

Table 4: Correlation between the meiboscore and other factors in KC patients.

	Meiboscore	
	r	p
Age	0.421	0.006
Sex	0.509	0.03
KC stage	0.621	0.05
OSDI	0.162	0.72
TBUT	0.320	0.02
Schirmer II test	0.499	0.032

KC: keratoconus; OSDI: Ocular Surface Disease Index; TBUT: tear breakup time.

Table 5: Correlation between the meibomian gland characteristics in meibography and other factors in KC patients.

	Gland distortion		Gland shortening		Gland dropout	
	r	p	r	p	r	p
Age	0.12	0.92	0.16	0.87	0.22	0.82
KC stage	0.21	0.45	0.42	0.64	0.22	0.45
OSDI	0.23	0.34	0.33	0.43	0.31	0.53
TBUT	0.22	0.05	0.18	0.04	0.24	0.05
Schirmer test	0.21	0.03	0.19	0.032	0.22	0.05

KC: keratoconus; OSDI: Ocular Surface Disease Index; TBUT: tear breakup time.

chemical composition which warrants further studies. Yet the indirect tests and the questionnaire were an attempt to correlate the dropout of MG and its effect on the function of the tear film.

In general, meibography provides a feasible method of recording and documenting the MGs for better diagnosis of its dysfunction in various diseases and its severity. It should be taken into account that meibography should be used in context of clinical findings and symptoms. Sirius meibography is a simple, noncontact, cost-effective method of evaluating meibomian gland dropout as a part of the routine refractive examination. Accessible screening of MGs dropout and distortion in KC patients allows for better management of dry eye diseases in these patients. Effective management of dry eye disease makes it possible to decrease eye rubbing and thus reduce the mechanical stress on the already vulnerable corneas.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

This submission was presented as free paper in the ESCRS Vienna 2018 yet it has not been published anywhere previously and that it is not simultaneously being considered for any other publication.

Conflicts of Interest

The authors have no proprietary interests or conflicts of interest related to this submission.

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Clinical Study

Retrospective Observational Study on Rebamipide Ophthalmic Suspension on Quality of Life of Dry Eye Disease Patients

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Purpose. The Dry Eye-Related Quality-of-Life Score (DEQS) is a Japanese dry eye-specific questionnaire that has been used to assess the symptoms of dry eye and their effects on the quality of life (QOL) in Japanese individuals. The purpose of this study was to determine the effect of rebamipide (RBM) on the QOL of Japanese patients with dry eye disease (DED). *Method*. The medical records of 43 patients (3 men and 40 women; mean age: 64 ± 14 years; range: 32 to 83 years), who were diagnosed with DED and treated with RBM at the Ehime University Hospital between November 2012 and June 2016, were reviewed. The effects of 2% rebamipide (RBM) ophthalmic suspension on the symptoms of DED was determined by the answers to the DEQS questionnaire and clinical findings. The clinical findings before and 1, 3, 6, 12, and 24 months after initiating the RBM treatment were reviewed. The following data were collected from the DEQS: the Summary score and two subscale scores, the Bothersome ocular symptoms score, and the Impact on daily life score. In addition, the standard fluorescein staining score, the Schirmer I test score, and the tear breakup time (TBUT) score were analyzed. *Result*. The Summary score and Impact of daily life score of the DEQS were improved significantly after 1, 3, 6, and 12 months of RBM, and the Bothersome ocular symptoms scores of the DEQS were also improved after 1, 3, and 6 months. The fluorescein staining scores were significantly decreased after 1, 3, 6, and 12 months, and the TBUT score was significantly increased after 1 month. *Conclusion*. RBM treatment improves the QOL by alleviating the corneal and conjunctival epithelial damages. The DEQS is a useful questionnaire that can assess the severity of the DED symptoms and their impact on the QOL. This trial is registered with UMIN000024405.

1. Introduction

Dry eye disease (DED) is a multifactorial ocular surface disorder that is characterized by a breakdown of the homeostasis of the tear film causing various symptoms and visual disturbances. The report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes in 1995 emphasized the requirement of the presence of symptoms in the definition of DED [1], and this requirement was included in the Japanese definition of DED in 2006 [2]. The Bothersome symptoms and visual disturbances of DED have a negative impact on the daily activities such as reading, computer use, driving, and watching television [3]. The goals of treating DED are to improve the patient's ocular comfort and restoring the ocular surface and tear film to the normal homeostatic state [4]. Therefore, a comprehensive questionnaire that assesses the symptoms and the impact of DED on the quality of life (QOL) is as important as the clinical findings.

The Dry Eye-Related Quality-of-Life Score (DEQS) is a Japanese dry eye-specific questionnaire that can be used to assess the symptoms of dry eye and their effects on the QOL [5]. The DEQS has good reliability, validity, specificity, and responsiveness, and it has been shown to be helpful in assessing the QOL in several clinical studies [6–9]. Because the DEQS is the only dry eye-specific questionnaire that has been validated in Japanese individuals, its use is expected to increase in future clinical studies on DED in Japan. The DEQS is appropriate for evaluating the changes in the DED conditions and the therapeutic effects. Utsunomiya et al. [7]

reported the cutoff score for DED diagnosis by the DEQS may be set at 15.

Rebamipide (RBM) ophthalmic suspension (Mucosta Ophthalmic Suspension UD2%; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) has recently become commercially available as a mucin secretagogue in Japan. RBM ophthalmic suspension has been shown to increase the production of mucins from the cornea and conjunctiva, and it has improved the objective findings of the ocular surface and subjective symptoms in patients with DED [10]. In addition, RBM has been shown to have anti-inflammatory effects [11, 12]. Kinoshita et al. reported the long-term effect of RBM on the objective signs and subjective symptoms [13]. They reported that the scores of the subjective symptoms were significantly improved at week 2 compared with those at the baseline, and further improvements of the scores were observed at every visit up to week 52. However, there have not been any studies that reported the long-term effect of RBM on the QOL of patients with DED obtained by a validated questionnaire.

Thus, the purpose of this study was to determine the long-term effects of RBM on the symptoms of DED and the QOL. To accomplish this, patients with DED were requested to answer the DEQS questionnaire before and during the treatment with RBM.

2. Methods

This was a retrospective case series study. The procedures used conformed to the tenets of the Declaration of Helsinki and were approved by the Internal Review Board of the Ehime University Hospital. The study was registered with the University Hospital Medical Information Network in Japan (number UMIN000024405). Informed consent was obtained in the form of opt-out on the website.

The diagnostic criteria used conformed to those defined by the Japanese Dry Eye Society in 2006 [2] and were used to diagnose DED based on the presence of 2 or more of the following 3 items: the presence of symptoms associated with dry eye including ocular discomfort such as dry sensation, irritation, foreign body sensation, pain, and other symptoms; an abnormality of the tear film breakup time (TBUT) of ≤5 seconds or a Schirmer I test value ≤ 5 mm; and the presence of keratoconjunctival epithelial disorders with a fluorescein staining score ≥3 and a maximum score of 9.

2.1. Subjects. Outpatients who were diagnosed with DED and treated with RBM in the Ehime University Hospital between April 2013 and June 2016 were initially screened for this study. The eligible subjects were ≥20 years and had been followed up for at least one month. The subjects were excluded if any of the following was found: active ocular infection, ocular inflammation, abnormal eyelids or blinking, or history of ocular surgery that could have an influence on the cornea and tears during the investigation period.

2.2. Assessments. We reviewed the clinical findings obtained before and 1, 3, 6, 12, and 24 months after initiating the RBM treatment. The following data were collected: the demographic characteristics, the DEQS results, fluorescein staining score, Schirmer I test, and tear breakup time (TBUT).

The DEQS consists of 15 items and 2 subscales including the "Bothersome effects of the ocular symptoms (6 items)" and the "Impact of dry eye on daily life (9 items)" scores. We evaluated three scores of the DEQS: the Summary score, the Bothersome ocular symptoms score, and the Impact on daily life score. All of the scores ranged from 0 to 100, with a higher score representing a greater disability.

The fluorescein ocular surface staining test was performed with observations through a blue-free barrier filter. It was used to determine whether the corneal and conjunctival epithelium was damaged. According to the van Bijsterveld system [14], the ocular surface was divided into three zones: the nasal bulbar conjunctiva, the cornea, and the temporal bulbar conjunctiva. The maximum staining score for each area was 3 points, and the maximum staining score for the overall surface was 9 points. The Schirmer I test was performed for 5 minutes without topical anesthesia. In most cases, the Schirmer I test was not measured after beginning the RBM treatment; therefore, only the results before the initial administration were recorded. The TBUT score was measured with observations of the cornea and conjunctiva through a slit lamp after an instillation of fluorescein into the conjunctival sac. The time from normal blinking to the first appearance of a dry spot in the tear film was measured three times and the average was used for the statistical analyses.

2.3. Statistical Analyses. Parametric or nonparametric tests were used for all analyses with descriptive statistics and statistical testing according to the results of the Kolmogorov–Smirnov tests. The values of the different parameters are presented as the means ± standard deviations. The eye with the higher fluorescein staining score was used for the statistical analyses, or if the scores were the same in the two eyes, the scores of the right eye were used. One sample paired t tests or Wilcoxon's signed-rank tests were used to determine the significance of the differences between two groups at the baseline and at each visit. Pearson's product-moment correlations or Spearman's rank-order correlation analyses were performed to determine the significance of the correlations between different parameters. All tests were 2-tailed, and $p < 0.05$ was taken to be statistically significant. The statistical analyses were performed using the SAS software, ver.9.3.

3. Results

Forty-three patients with DED were studied. There were 3 men and 40 women with a mean age of 64 ± 14 years. The characteristics of participants before initiating the RBM treatment are shown in Table 1.

The number of subjects who completed the DEQS questionnaire was 25 at 1 month, 17 at 3 months, 19 at 6 months, 9 at 12 months, and 8 at 24 months. The number of subjects at each analysis period was different because the

Table 1: Characteristics of participants before initiating the RBM treatment.

Parameters	
Age, mean ± SD (range), years	64 ± 14 (32–83)
Sex (male : female)	3 : 40
DEQS questionnaire	
Summary score, mean (SD), point	41.7 (22.7)
Bothersome ocular symptoms score, mean (SD), point	48.1 (23.1)
Impact on daily life score, mean (SD), point	37.7 (25.0)
Fluorescein staining score, mean (SD), point	2.3 (2.1)
Tear film breakup time score, mean (SD), s	1.9 (0.5)
Schirmer's testing, mean (SD), mm	8.9 (10.6)

reexamination times differed; e.g., some patients visited at 1 month and 6 months and other patients visited at 3, 6, and 12 months after initiating the RBM treatment. Thus, patients who were not included in the 1-month period may be included in the 3-month period. Only 4 subjects completed all the visits, and it was too few for statistical analysis.

The Summary score and Impact on daily life score of the DEQS questionnaire indicated a significant improvement over the corresponding scores at the baseline and at 1, 3, 6, and 12 months. The Bothersome ocular symptoms score was significantly improved at 1, 3, and 6 months (Table 2).

The fluorescein staining score was obtained from 22 patients at 1 month, 14 at 3 months, 17 at 6 months, 9 at 12 months, and 7 at 24 months. The fluorescein staining score was significantly lower than the baseline scores at 1, 3, 6, and 12 months (Table 3). The TBUT score was also improved significantly at 1 month, but the sample size after 3 months were too few for statistical analyses (Table 3).

The correlations between the scores of DEQS and the clinical findings were analyzed in subjects where both sets of data were available. There were no significant correlations between the Summary score of DEQS, the fluorescein staining score, and the TBUT score at all time points (Table 4).

The most frequently observed adverse event during the RBM treatment was eye pain which was reported by 6 patients (14.0%). Foreign body sensations and eye discharge were observed in three patients (7.0%), dryness and redness were observed in two patients (4.7%), and an itching sensation and a bitter taste were observed in one patient (2.3%). However, no serious treatment-related adverse events occurred in any subject. Three patients were discontinued because of the development of adverse events (2 patients at 3 months and 1 patient at 6 months).

4. Discussion

Our results showed that the DEQSs were significantly improved as soon as one month after initiating the RBM treatment, and the improvements were reported throughout the treatment period. Similar improvements were found in the fluorescein staining scores and TBUT score after initiating the RBM treatment.

RBM was launched in the Japanese market in 2012 for the treatment of DED. Rebamipide is a mucoprotective drug, and it has been widely used for the treatment of gastric and duodenal ulcers. RBM has been shown to increase the production of mucins from corneal and conjunctival tissues [15, 16], increase the number of goblet cells [16], and increase the anti-inflammatory properties of the tissues [11, 12]. Because of these properties, RBM is considered to be an effective agent to improve the signs and symptoms of DED.

Kinoshita et al. performed a 52-week study of RBM in patients with DED and reported that all the objective signs, viz., fluorescein corneal staining, lissamine green conjunctival staining, and TBUT, and the subjective symptoms scores were significantly improved at week 2 compared with that at the baseline [13]. They also reported that further improvements were observed at almost every visit up to 52 weeks. Another 12-week study that evaluated the effect of RBM treatment also reported that the dry eye symptoms scores and fluorescein ocular surface staining score were significantly improved at 2 weeks and maintained until 12 weeks [10]. In our study, the DEQS and the fluorescein staining score were improved at 1 month which indicated that the RBM treatment was effective from an early time. But, we could not compare among the later treatment periods. Unfortunately, we could only compare baseline values for each visit due to differences in the constitution of the subjects at each follow-up visit.

The strength of our study is the use of the DEQS to assess the subjective symptoms of DED and its impact on the QOL. Previous studies neither used validated questionnaire to assess the subjective symptoms nor evaluated the impact on the QOL. In this study, the Summary score and one of the subscale score of the DEQS which are associated with the activities of daily living were significantly improved at 1, 3, 6, and 12 months after the RBM treatment. The Bothersome ocular symptoms score was significantly improved at 1, 3, and 6 months after beginning the RBM treatment. These results indicated that RBM is effective in improving the symptoms of DED during the treatment periods, especially their impact on the QOL. On the contrary, the Summary score and both subscale scores showed no significant difference at 24 months after the RBM treatment compared to that before the RBM treatment. This may be caused by the decrease in the sample size due to the improvement of the DED and a discontinuation of the treatment or transfer to neighboring clinic. However, the scores were not significantly different between 12 and 24 months.

Utsunomiya et al. [7] reported that the cutoff score for DED diagnosis by the DEQS can be set at 15. In a validation study of DEQS [5], the average Summary score of DEQS was 33.7 in patients with DED and 6.0 in normal subjects. In this study, the average Summary scores of DEQS before the RBM treatment were high (Table 2). After initiating the RBM treatment, the average Summary scores were improved significantly, but it still remained higher than normal. The higher scores of the DEQS might be related to neuropathic pain which has received increasing recognition as a factor in DED [17, 18]. Neuropathic pain is defined as pain caused by

Table 2: DEQS questionnaire score at each visit.

DEQS questionnaire score	1 month (n = 25)			3 months (n = 17)			6 months (n = 19)			12 months (n = 9)			24 months (n = 8)		
	Before	1 month	p value	Before	3 months	p value	Before	6 months	p value	Before	12 months	p value	Before	24 months	p value
Summary score	51.4 (24.4)	37.7 (23.2)	**0.008**	53.9 (23.9)	42.9 (28.3)	**0.018**	57.5 (25.9)	41.5 (21.7)	**0.001**	49.5 (19.4)	39.4 (23.8)	**0.049**	41.1 (24.7)	42.2 (16.0)	0.58
Bothersome ocular symptoms score	38.2 (26.9)	31.9 (27.1)	**0.019**	42.0 (26.6)	37.7 (24.8)	**0.016**	43.3 (20.5)	29.8 (21.7)	**0.02**	46.0 (17.2)	29.3 (19.1)	0.180	39.7 (19.2)	29.2 (13.8)	0.82
Impact on daily life score	43.0 (23.6)	34.2 (24.6)	**0.014**	44.5 (24.1)	39.8 (24.8)	**0.004**	53.2 (20.0)	34.4 (20.8)	**0.001**	47.4 (16.3)	33.3 (17.1)	**0.034**	41.0 (20.3)	34.4 (12.1)	0.40

Values are the means (±SDs). One sample paired t test was used for statistical comparisons.

Table 3: Clinical findings at each visit.

	1 month			3 months			6 months			12 months			24 months		
	Before	1 month	p value	Before	3 months	p value	Before	6 months	p value	Before	12 months	p value	Before	24 months	p value
		$n = 22$			$n = 14$			$n = 17$			$n = 9$			$n = 7$	
Fluorescein staining score	1.8 (2.1)	1.2 (1.6)	**0.008**	2.4 (2.5)	1.4 (1.3)	**0.003**	2.8 (2.5)	1.7 (1.7)	**0.011**	2.3 (2.1)	0.9 (1.1)	**0.049**	1.9 (1.7)	0.9 (1.4)	0.17
		$n = 6$			$n = 3$			$n = 4$			$n = 2$			$n = 1$	
Tear breakup time (TBUT, s) score	2.1 (0.5)	4.1 (1.3)	**0.042**	2.3 (0.3)	3.3 (0.3)	0.25	2.3 (0.3)	3.3 (2.0)	0.50	1.8 (0.3)	1.5 (0.7)	1.0	1.0	2.0	

Values are the means (±SD). Wilcoxon's signed-rank test was used for statistical comparisons.

Table 4: The correlations between the DEQS and the clinical findings.

	Summary score of DEQS											
	Before		1 month		3 months		6 months		12 months		24 months	
	r	p value	r	p value	R	p value	r	p value	r	p value	r	p value
	$n = 43$		$n = 22$		$n = 14$		$n = 17$		$n = 9$		$n = 7$	
Fluorescein staining score	−0.01	0.97	0.29	0.19	0.08	0.78	−0.31	0.23	−0.12	0.76	0.26	0.58
	$n = 17$		$n = 6$		$n = 3$		$n = 4$		$n = 2$		$n = 1$	
Tear breakup time (TBUT, s) score	0.1	0.7	0.37	0.47	−1.0	0.44	0.6	0.4	−1		N/A	

r = correlation coefficient. N/A = not available. Spearman's rank-order correlation analyses were used for statistical comparisons.

a lesion or disease of the somatosensory nervous system. DED patients with neuropathic pain have more severe and chronic DED symptoms such as a spontaneous burning pain and pain evoked by wind and light. Nonresponses to therapies that target the ocular surface and tears and discordance between symptoms and clinical signs are also features suggestive of a neuropathic component to dry eye symptoms. In addition, the fluorescein staining scores were <3 points at all visit, and discrepancy between subjective symptoms and clinical findings was found. The inclusion of patients with neuropathic pain might have limited the improvement of the DEQS after the RBM treatment.

The fluorescein staining score was significantly improved at 1, 3, 6, and 12 months which is similar to the results of the DEQS. The TBUT score was significantly improved at 1 month; however, the number of patients after 3 months was too few for statistical analyses. Although the TBUT score was not found to be significantly improved, RBM improved the corneal and conjunctival epithelial damage as well as the symptoms of DED. The effect of these changes led to improvements of the QOL during the treatment period. Similarly, RBM has been shown to be effective for other ocular surface diseases such as allergic conjunctivitis, lid wiper epitheliopathy, and superior limbic keratoconjunctivitis [19–22].

Although the DEQSs and the fluorescein staining scores improved during the treatment periods, the correlations between the changes of the fluorescein staining scores and the DEQS scores were not significant at all time points. Similar disagreements between clinical findings and subjective symptoms of DED have been reported [23–25]. This discrepancy can be explained by the natural variations of the disease processes, the "subjective" nature of the symptoms, and the variability in pain thresholds, and cognitive responses to questions about physical sensations of the eyes [26]. On the contrary, DED patients generally seek medical treatment to alleviate the irritating ocular symptoms that affect their QOL, and they want an improvement of their QOL rather than an improvement of the clinical findings. Therefore, a validated questionnaire that assesses the symptoms, vision-related functions, and the impact of the DED on their QOL is needed for assessing the therapeutic effects of anti-DED agents. To evaluate the therapeutic effect properly, a simple, reproducible, reliable, and quantitative questionnaire is necessary.

Many of the instruments used for assessing the DED symptoms and their impact on the QOL are time consuming, and their ability to quantify changes is limited. In 2017, the Tear Film and Ocular Surface (TFOS) and Dry Eye Workshop II (DEWS II) reports summarized the twelve validated questionnaires for DED [27]. Among them, 5 questionnaires, viz., the National Eye Institute Visual Function Questionnaire-25 (VFQ-25), the Ocular Surface Disease Index (OSDI), the Impact of Dry Eye on Everyday Life (IDEEL), the North Carolina Dry Eye Management Scale (UNC DEMS), and the DEQS, included items related to the QOL. The VFQ-25 is probably the most widely used questionnaire that is used to assess the visual function and vision-related QOL [28–30]. However, the VFQ-25 is not disease specific; thus, it may not be suitable for evaluating more subtle changes of the symptoms. The OSDI and the IDEEL are frequently used to assess the severity of DED. The OSDI is very useful for diagnosing and evaluating the severity of the symptoms [31], but it has some limitations in that it does not fully cover the impact of DED on the QOL such as the psychological and social aspects. The IDEEL is a 57-item questionnaire that was developed to evaluate the QOL, dry eye symptoms, and treatment satisfaction [32]. The IDEEL includes all relevant domains of DED; however, it is not easy to use in routine clinical practice because of its long testing time of approximately 30 min. The UNC DEMS is a single-item questionnaire that asks DED patients to rate their symptoms and the effects of those symptoms on their daily life [33]. Because the UNC DEMS was created as a quick and reliable measure, it is not suitable for evaluating the DED symptoms in detail.

The DEQS questionnaire was developed to evaluate the symptoms of DED and the effects of DED on the activities of daily living. Our experience with its use on DED patients showed that it can be used easily in routine clinical practice. It is easy for patients to answer the DEQS questionnaire while waiting for their examination because the DEQS requires approximately 5 min for completion. The DEQS questionnaire was recently used to assess the QOL in dry eye patients and also to determine the effectiveness of different kinds of dry eye treatments [7–9, 34, 35]. Thus, we conclude that DEQS is an appropriate method to evaluate the therapeutic effects of different types of treatments for DED.

This retrospective study had limitations. Although the objective and subjective data were collected from each

subject during the treatment period, the number of collected data decreased due to an improvement of the DED and a discontinuation of the treatment or transfer to a neighborhood clinic by the patients. Therefore, statistical comparisons became difficult. In particular, the TBUT score was not routinely recorded after beginning the RBM treatment. However, the DEQS questionnaire score and the fluorescein staining score were significantly improved. This suggests that RBM is effective for treating DED and can improve the clinical signs and the QOL. The answers to the DEQS questionnaire showed that there was a significant improvement up to 12 months indicating that the DEQS is appropriate for evaluating changes in the DED conditions and in determining the therapeutic effects of RBM [6–9].

In conclusion, the DEQS questionnaire is a useful tool that can be used in routine clinical practice to assess the symptoms of DED and their impact on the QOL. Topical RMB can improve the corneal and conjunctival epithelial damage, the symptoms of DED, and the QOL during the treatment period. The DEQS questionnaire can be used to evaluate the therapeutic effects of a treatment regimen and to follow the symptoms of DED patients.

Data Availability

The data used to support the findings of this study are restricted by the Certified Review Board of Ehime University in order to protect patient privacy. The data are however available from the authors upon reasonable request and with permission of the Certified Review Board of Ehime University (rinri@m.ehime-u.ac.jp).

Conflicts of Interest

All authors declare that there are no conflicts of interest regarding the publication of this paper.

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