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Real dynamic assessment of tear film optical quality for monitoring and early prevention of dry eye

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Abstract

To evaluate real dynamic assessment of tear film optical quality for monitoring and prevention of dry eye.

Right eyes of 62 normal and 39 dry eye subjects were included. Dynamic measurement of objective scatter index (OSI) was performed by using the Optical Quality Analysis System II (OQAS II), correlation coefficient between OSI and time (CCOT) was calculated. According to whether the CCOT was significantly ascending, normal and dry eye groups were further subdivided for comparison. By using Scheimpflug-Placido topographer, non-invasive tear break-up time (NITBUT) was recorded, and a 2-dimensional precorneal tear film map was reconstructed and divided into central, middle, and peripheral corneal zones, distribution of tear break-up spots in the 3 corneal zones were analyzed.

The numbers of tear break-up spots were higher in all the 3 corneal zones of the dry eye subjects ($P < .01$), when compared with the normal subjects. The Dry Eye subjects with ascending CCOT had the shortest NITBUT ($P < .001$–$.034$) and the most tear break-up spots over the whole cornea ($P < .001$–$.044$). Between the dry eye subjects with non-ascending CCOT and those with ascending CCOT, difference of tear break-up spots was found significant only in the peripheral corneal zone ($P < .01$).

Non-ascending and ascending CCOT of dry eye patients reflect different stability of tear film. Real dynamic assessment of tear film optical quality is potential for monitoring and early prevention of dry eye.

Abbreviations: CCOT = coefficient between OSI and time, NITBUT = non-invasive tear break-up time, OQAS II = Optical Quality Analysis System II, OSDI = ocular surface disease index, OSI = objective scatter index, TBUT = tear break-up time.

Keywords: break-up dynamics, dry eye, objective scatter index, optical quality, tear film

1. Introduction

The tear film is the first refractive surface in front of the eye, providing refractive power even greater than the cornea.[1] A stable tear film on the ocular surface has paramount effects on vision.

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M-FW and HG authors have contributed equally.

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Dry eye is a common disease that characterized by dysfunctional, unstable tear film.[2] Dry eye patients often suffer vision problems such as blurred vision, even if their visual acuity is unimpaired, since aberrations are increased by the temporal variation of tear film thickness and regularity after a blink.[3–5]

For dry eye diagnosis and evaluation, some most widely used techniques, like fluorescein tear break-up time (TBUT) test, have been developed 50 years ago. However, instillation of fluorescein on the ocular surface may induce reflex tearing or interfere with the tear film stability, result in the lack of reproducibility of the measurement.[6] The development direction has been towards non-invasive techniques that can assess the dynamic, temporal instability of the tear film. For example, corneal topography systems can measure the non-invasive TBUT (NITBUT) without the use of fluorescein.[7–9] Furthermore, it can digitally record multiple tear break-up spots on cornea, together with the time from the last blink to the appearance of each tear break-up spots, then reconstruct a 2-dimensional precorneal tear film map, to provide information about the tear film break-up dynamics.[10,11]

Tear film break-up has been found to associate with the deterioration in tear film optical quality for decades.[12,13] Recently the Optical Quality Analysis System II (OQAS II, Visiometrics, Tarrasa, Spain) based on double-pass technique has been developed as a non-invasive, dynamic technique to assess the optical quality of tear film. This system is able to quantify the optical quality of the eye by recording the degradation of image projected on the retina and calculating the objective scatter index (OSI). A series of consecutive retinal images can reflect the changes of the tear film optical quality over time.[14] Yu et al[15] reported that many of both dry eye and asymptomatic subjects whom were assessed by OQAS II had an OSI that increased over time. By calculating the correlation coefficient between OSI and time (CCOT), they proposed this to be a sensitive and reproducible method for the dynamic assessment of tear film optical quality. However, they did not study the correlation between CCOT and the other aspects of tear film dysfunction, such as tear film break-up dynamics and tear film volume. It is still unknown how the raise of CCOT is involved in the dry eye progression.

In the present study, we combined the 2 real dynamic techniques for tear film assessment, OQAS II and Scheimpflug-Placido topography, to investigate the correlation between the tear film optical quality dynamics and the tear film break-up dynamics in both dry eye and asymptomatic subjects. The diagnosis of dry eye was according to the diagnostic criteria proposed by the Tear Film and Ocular Surface Society Dry Eye Workshop II in 2017.[9] Subjects whose ocular surface disease index (OSDI) ≥13 and NITBUT <10 seconds were diagnosed with dry eye.

2. Materials and methods

2.1. Subjects

Subjects who are ≥18 years old and visited the Department of Ophthalmology, Union Hospital affiliated to Tongji Medical College of the Huangzhong University of Science and Technology, were recruited into this study between March 2019 and October 2019. The study adhered to the tenets of the Declaration of Helsinki, and was approved by the Tongji Medical College Medical Ethics Committee. Informed consent was obtained from all subjects after they received an explanation of the nature and possible consequences of the study.

Right eyes of the subjects underwent a battery of examinations in the following sequence, OSDI questionnaire, Auto Ref/Keratometer (ARK-510A, NIDEK, Gamagori, Japan), best corrected visual acuity, slit-lamp examination (SL-2G, Topcon, Oakland, CA), ophthalmoscope examination (YZ6H, 66 Vision Tech, Suzhou, China).

The best-corrected visual acuity for all subjects was 20/20 or better. Subjects with spherical errors ranged from –8.00 to + 5.00 diopters, and astigmatism ≤2.00 diopters, were included. Subjects were excluded if they had eye disorders that could impair the objective optical quality other than tear film abnormality, such as significant eye discharge, ocular surface staining, corneal opacity, cataract, significant vitreous opacities. Subjects with history of recent contact lens wearing or any ocular surgery were also excluded.

2.2. Measurement of tear film optical quality dynamics

The tear film optical quality dynamics was measured in a dark room by using OQAS II. Before the measurement, subjects waited in the dark room for a period of dark adaptation to achieve the largest possible natural pupil size. Astigmatism ≥0.50 diopters was corrected by wearing trial lenses, while spherical errors were corrected internally by an optometer (ranged from –8.00 to +5.00 diopters) in the OQAS II instrument. When the measurement started, subjects were advised to naturally blink twice and then keep their eyes open for at least 10 seconds. Serial double-pass retinal images of a point source and their corresponding OSIs were recorded, in the interval of 0.5 second. CCOT was calculated from the OSI fluctuation in these 10 seconds right after the blinking (Fig. 1). For each eye, the measurement was repeated 3 times. Subjects waited at least 1 minute between each measurement and were advised to blink freely.

2.3. Non-invasive measurement of tear film break-up dynamics

The tear film break-up dynamics was measured in a dark room. Subjects were advised to naturally blink twice and then keep their eyes open for at least 10 seconds. Right after the blinking, the tear film break-up video was recorded for 10 seconds by using Scheimpflug-Placido topographer (Sirius, CSO, Firenze, Italy). Meanwhile a Placido disc pattern composed of 22 white and black rings was projected onto the cornea by the instrument. The locations and times of tear break-up spots were reconstructed into a two-dimensional precorneal tear film map. To further investigate the distribution of the tear break-up spots, the tear film map was divided arbitrarily into central (the central ring 1 to ring 7), middle (ring 8 to ring 15), and peripheral (ring 16 to ring 22) zones according to the concentric rings of the Placido disc projection (Fig. 2). The measurement was repeated 3 times for each eye. Subjects waited at least 1 minute between each measurement and were advised to blink freely.

2.4. Invasive tests for tear film

To avoid the disturbance of the invasive tests, the fluorescein TBUT test and Schirmer test without anesthesia were carried out after the non-invasive measurements. For TBUT test, 1 μL 2% fluorescein sodium solution (Alcon, Fort Worth, TX) was pipetted in the inferior cul de sac, and the subject was asked to blink several times, then keep eyes open when TBUT was recorded under the cobalt blue light. The measurement was repeated 3 times for each eye.

For Schirmer test, test strips (Jingming, Tianjin, China) were placed on the lateral one-third of the lower lid margin without topical anesthesia for 5 minutes.

2.5. Statistical analysis

The continuous variables were presented as the means ± standard deviation. One-way analysis of variance followed by independent samples t test was used to compare the means. The Pearson bivariate correlation was used to calculate CCOT. The chi-square test was used to compare the frequency with ascending CCOT in 2 different groups. $P < .05$ was accepted to be statistical significant.

3. Results

One hundred and one eyes were included in this study. The mean age of 62 subjects in the normal group was 25.3 ± 3.4 years, the mean age of 39 subjects in the dry eye group was 24.9 ± 4.6 years.

Table 1 shows the comparison between the normal and the dry eye subjects. CCOT in the dry eye subjects were not significantly higher than the normal subjects ($P = .063$). The numbers of tear break-up spots were higher in all the 3 corneal zones of the dry eye subjects ($P < .01$), when compared with the normal subjects.

Figure 3 shows that the frequencies with ascending CCOT in the normal (66.13%) and the dry eye (66.67%) groups were not different ($P = .956$).

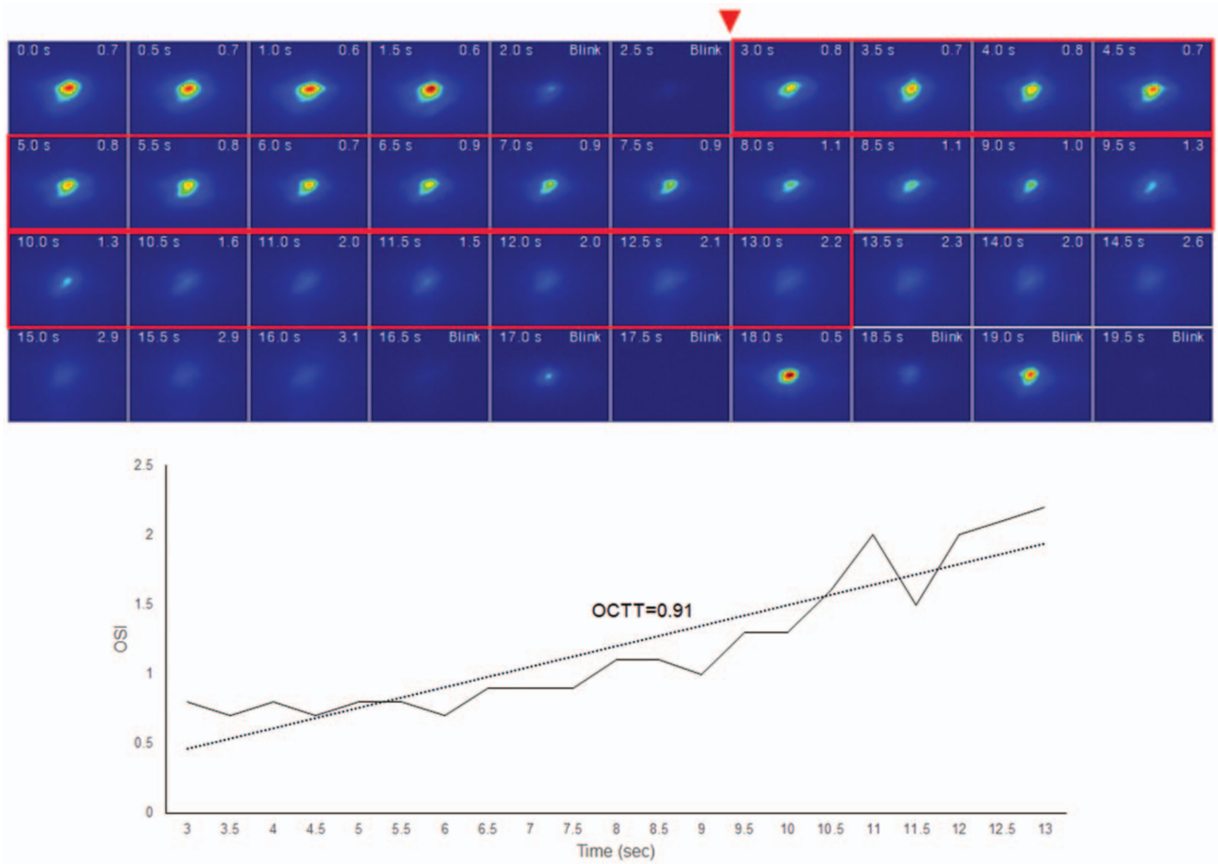

Figure 1. An example for the measurement of tear film optical quality dynamics. As the measurement started, subjects were advised to naturally blink twice and then keep their eyes open for at least 10 seconds. Serial double-pass retinal images of a point source and their corresponding OSIs were recorded automatically, in the interval of 0.5 second. CCOT was calculated from the OSI fluctuation in these 10 seconds right after the blinking. CCOT=coefficient between OSI and time, OSI=objective scatter index.

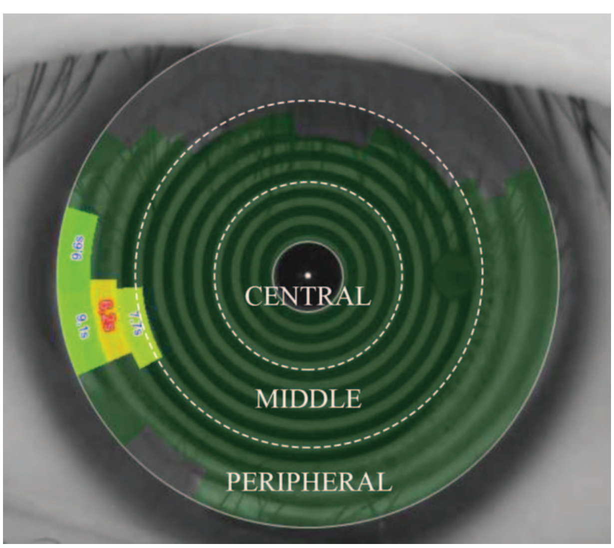

Figure 2. A Placido disc pattern composed of 22 white and black rings was projected onto the cornea. The locations and times of tear break-up spots were reconstructed into a 2-dimensional precorneal tear film map, which was divided into central (the central ring 1 to ring 7), middle (ring 8 to ring 15), and peripheral (ring 16 to ring 22) zones.

According to whether the subjects were with ascending CCOT, we subdivided the normal and the dry eye groups into 2 subgroups, respectively. Normal/NA (n=21) or Dry Eye/NA (n=13) was subgroup of normal or dry eye subjects with non-

Table 1

Comparison between the normal and the dry eye groups.

	Normal	Dry eye	*P* value
CCOT	0.46±0.47	0.61±0.33	.063
Mean OSI	1.17±0.76	1.33±0.68	.296
OSI-SD	0.21±0.43	0.27±0.26	.429
OSDI	6.26±5.78	22.12±10.40	<.001**
NITBUT	8.22±2.04	6.27±2.21	<.001**
F-TBUT	7.65±5.93	5.23±2.70	.007*
Schirmer test	17.22±10.03	16.91±8.15	.872
Distribution of tear break-up spots			
Central	0.44±1.01	1.42±1.81	.006*
Middle	1.48±2.77	4.26±4.76	.003*
Pripheral	1.69±2.81	4.06±3.83	.003*
Total	3.62±5.99	9.75±9.74	.002*

CCOT=correlation coefficient between objective scatter index and time, F-TBUT=fluorescein tear break-up time, NITBUT=non-invasive tear break-up time, OSI=objective scatter index, OSI-SD=OSI standard deviation.

* *P* value <.01.

** *P* value <.001.

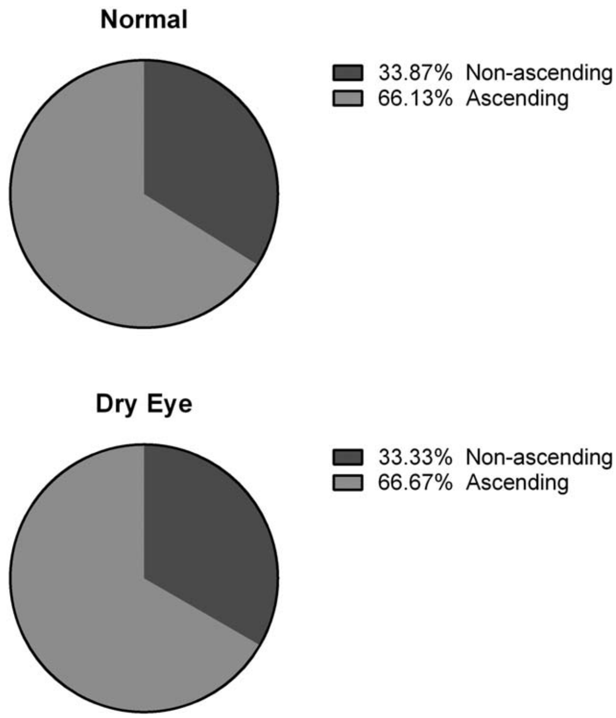

Figure 3. The frequencies with ascending correlation coefficient between OSI and time (CCOT) in the normal and the dry eye groups were very close (P=.956). OSI=objective scatter index.

ascending CCOT, while Normal/A (n=41) or Dry Eye/A (n=26) was subgroup of normal or dry eye subjects with ascending CCOT, respectively. The differences between these 4 subgroups were compared and shown in Figures 4 and 5.

Figure 4 shows CCOT, OSDI, NITBUT, and Schirmer test results. In the Normal/A and Dry Eye/A subgroups, CCOT were both ascending, but not significantly different (P=.08). While CCOT were both non-ascending in the Normal/NA and Dry Eye/NA subgroups, it was lower in the Normal/NA subgroup ($P<.001$). The dry eye subjects were always with higher OSDI compared with the 2 normal subgroups, no matter whether the CCOT was ascending ($P<.001$). The Dry Eye/NA subgroup with non-ascending CCOT had NITBUT that not significantly different from the 2 normal subgroups. While NITBUT in the Dry Eye/A subgroup was significantly shorter than that in the Dry Eye/NA subgroup (P=.034) and the Normal/A subgroup ($P<.001$).

Figure 5 shows the distribution of tear break-up spots in the 3 corneal zones. The Dry Eye/A subgroup with ascending CCOT had the most tear break-up spots on the whole cornea, when compared with the 2 normal subgroups ($P\leq.001$), or to the Dry Eye/NA subgroup (P=.044). Between the Dry Eye/NA and the Dry Eye/A subgroups, difference of tear break-up spots was found significant only in the peripheral corneal zone ($P<.01$), but not in the central or middle corneal zones, although the laser beam that OQAS II used for measurement mainly passed through the central cornea before it projected on the retina.

4. Discussion

Since visual disturbances were brought in the definition of dry eye in 2007,[16] assessment for the tear film optical quality of dry eye has received growing attention.[17,18] Aberrations and scattering are both the dominant factors that lead to the degradation of tear film optical quality. The Hartmann-Shack wavefront sensor can measure the aberrations of tear film,[18] but neglect the contribution of scattering, and overestimate the optical quality.[19]

The double-pass system, like the OQAS II used in this study, was then developed to objectively assess the real dynamic change of tear film optical quality, including both aberrations and scattering.

By using OQAS II, the tear optical quality was found significantly worse in the dry eye patients with severe conditions, such as short TBUT, meibomian gland dysfunction, or aqueous deficiency, when compared with the control groups.[20,21] But in these studies only the dry eye subjects with severe conditions were recruited.

Similarly, the real dynamic change of OSI was found different between the dry eye and the control groups, reported by Yu et al[15] and Tan et al[22] in their previous studies. They both adopted the previous diagnostic criteria proposed in 2007,[16] and recruited the healthy subjects without symptoms to compare with dry eye patients. Although the normal subjects are not completely without symptoms in reality.

Lately, Herbaut et al[23] reported that the tear film optical quality was correlated with most symptoms and signs of dry eye, but did not compare the dry eye patients with any normal subjects.

It is controversial that whether the subjects should blink during the real dynamic measurement of OSI. Subjects kept their eye opened for 20 seconds in Yu's and Herbaut's studies, but blinked freely in Tan's study. We asked the subjects to avoid blinking as proposed by Yu et al,[15] since blinking could be deliberate or unnatural due to the awareness of the measurement, making the blinking frequency unstable, and bringing more confounding factors.

Our current study is the first of its kind that adopted the diagnostic criteria proposed by the Tear Film and Ocular Surface Society Dry Eye Workshop II in 2017, according to which subjects with symptoms but OSDI <13 were also assigned in the normal group.[9] Therefore, the comparison between the dry eye and the normal groups in this study was closer to the real clinical context.

We found that CCOT in the dry eye subjects were not significantly higher than that in the normal subjects, and the frequencies with ascending CCOT in the normal and the dry eye groups were surprisingly close. These finding suggested that the degradation of tear film optical quality is not totally in consistency with dry eye diagnosis, but a relatively independent pathological process.

Evaluation of tear film optical quality is not always considered and available in clinical practice. The current diagnostic criteria of dry eye emphasize more on tear film break-up measurement, although the poor reproducibility of TBUT has been long recognized,[7] and patients with mild to moderate dry eye have broadly distributed TBUT, making them difficult to be differentiated from the normal subjects.[24] All these may lead to the discrepancy between the optical quality measurement and dry eye diagnosis.

However, the commonness of ascending CCOT in the measurement indicated that the deterioration in tear film optical quality may start much earlier than we had thought. The very early optical disturbances could be a few microns of tear film thinning, which may lead to micro-aberrations but not tear film

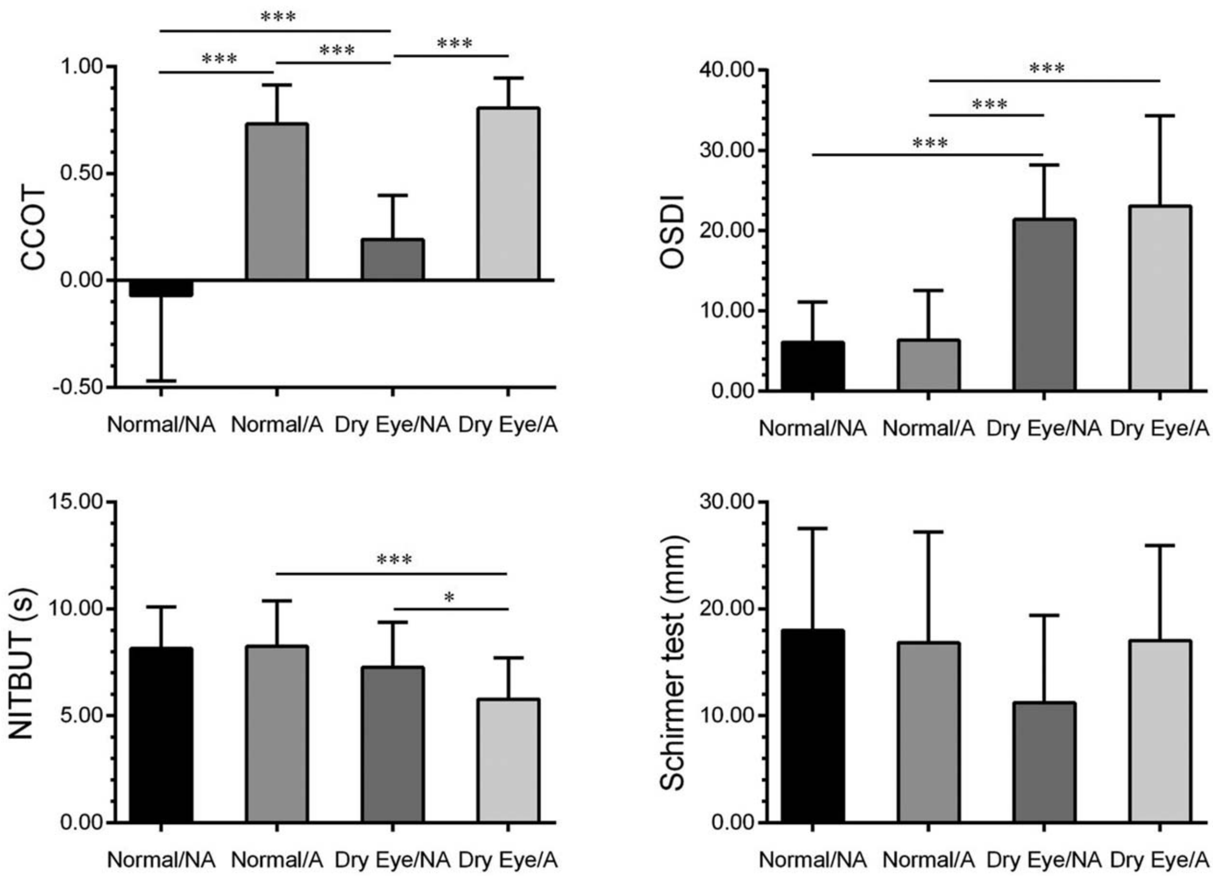

Figure 4. The correlation coefficient between OSI and time (CCOT) (top left), ocular surface disease index (OSDI) (top right), non-invasive tear break-up time (NITBUT) (bottom left), and Schirmer test (bottom right) were compared between Normal/NA versus Normal/A, Dry Eye/NA versus Dry Eye/A, Normal/NA versus Dry Eye/NA, Normal/A versus Dry Eye/A subgroups. /NA, /non-ascending; /A, ascending. $^{*}P$ value < .05; $^{***}P$ value < .001. OSI = objective scatter index.

break-up, therefore undetectable by conventional clinical tests.[25] Symptoms at this stage could also be compensated and covered in the normal subjects. By using the double-pass system, early detection of optical disturbance enables early prevention of dry eye.

When we compared between the entire groups of dry eye and normal subjects, we found the tear break-up spots of dry eye patients overwhelmingly outnumbered that of the normal subjects in all corneal zones. Then we subdivided the groups according to whether the CCOT was ascending. It is surprising that, without ascending CCOT, both tear break-up spots and NITBUT of the dry eye subgroup were no longer different from that in the normal group. While the dry eye subgroup with ascending CCOT has the most tear break-up spots, and the shortest NITBUT. This suggests that CCOT is a sensitive indicator of tear film quality, reflecting more subtle variation than the other conventional tests for dry eye.

However, since we had excluded patients with other significant eye conditions, such as the very common cataract in the aged, the subjects recruited in our study were mostly young. When a patient is with other eye problems, optical quality of the eye can be so bad that it is difficult or even impossible to measure the subtle change of tear film optical quality. The limit of OQAS II for the assessment of tear film is yet to be found.

Recently the tear film was found more likely to break in the inferior quadrant of corneal surface by using non-invasive Keratograph.[26] In this study we once again confirmed the heterogeneity of tear film by dividing the corneal zones in a different way. While ascending CCOT was detected by the OQAS II in the central corneas of dry eye patients, the change of tear-film break-up dynamics was still undetectable in the central and middle corneal zones. This provided an evidence that the peripheral corneal zone was the most susceptible to the change of tear film quality. By monitoring tear film break-up dynamics in the peripheral corneal zone, an early indication of degradation of tear film could be found. This can be especially valuable when measurement of tear film optical quality is unavailable.

To our knowledge, this is the first study that combined the 2 real dynamic techniques for tear film assessment, demonstrate the correlation between tear film optical quality dynamics and tear film break-up dynamics. It is also the first time that dry eye patients were subdivided and compared according to whether the CCOT was ascending. We have demonstrated the potential of real dynamic measurement of tear film optical quality for monitoring and early prevention of dry eye. However, we did not follow up the subjects in the current study. Further prospective study will be meaningful to demonstrate if the normal subjects with ascending CCOT or more tear break-up spots finally develop dry eye.

Author contributions

Conceptualization: Yu-Kan Huang.
Formal analysis: Ming-Feng Wu.

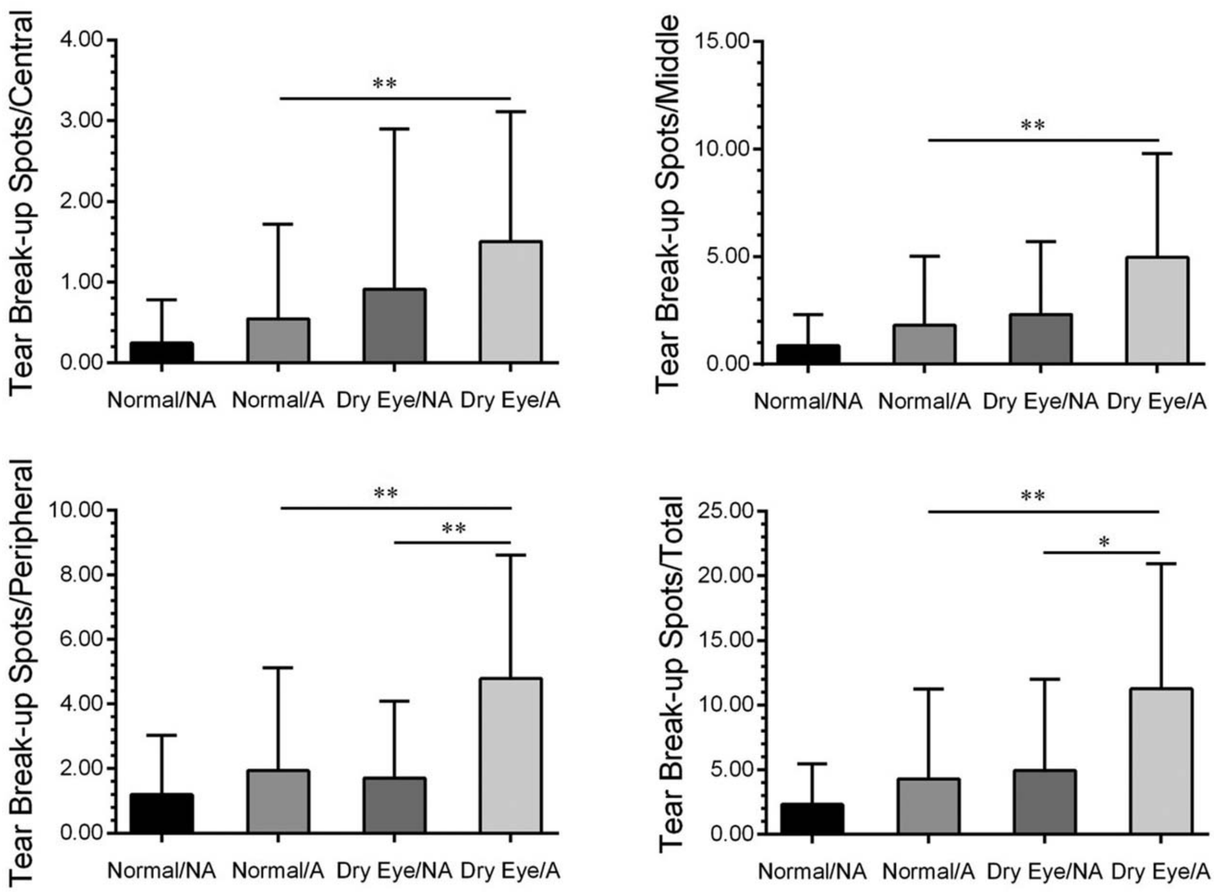

Figure 5. The distribution of tear break-up spots in central (top left), middle (top right), peripheral (bottom left) corneal zones, and the total tear break-up spots on the whole cornea (bottom right) were compared between Normal/NA versus Normal/A, Dry Eye/NA versus Dry Eye/A, Normal/NA versus Dry Eye/NA, Normal/A versus Dry Eye/A subgroups. /NA, /non-ascending; /A, ascending. $^{*}P$ value < .05; $^{**}P$ value < .01.

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Methodology: Yu-Kan Huang & Ming-Feng Wu.
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