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Assessment of Tear Film Optical Quality Dynamics

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Purpose. To investigate tear film optical quality dynamics by analyzing the postblink temporal changes of objective scatter index (OSI).

Methods. A total of 109 myopic subjects without symptoms of dry eye and 32 myopic subjects diagnosed with dry eye disease were recruited in this cross-sectional study. The right eye for each subject was analyzed. Serial measurements of OSI were performed for 20 seconds in the interval of 0.5 second using a double-pass instrument, and 10 successive seconds of nonblinking immediately after a blink was selected to analyze the tear film optical quality dynamics. The tear breakup time (TBUT) was also measured. The mean OSI in 10 successive seconds and the correlation coefficient between OSI and time were analyzed.

Results. For subjects without symptoms of dry eye, 109 eyes were divided into two categories based on the correlation coefficient between OSI and time: category A (without positive correlation) and category B (with positive correlation). Categories A and B were further divided into four categories based on the mean OSI for 10 seconds: category A1 (36.7%, lower than 1.00); category A2 (33.0%, equal to or greater than 1.00); category B1 (13.8%, lower than 1.00), and category B2 (16.5%, equal to or greater than 1.00). Dry eye subjects were set as category C for comparison. There was no significant difference in the TBUT among the five categories (A1, A2, B1, B2, C) except between category C and category A1 ($P < 0.01$) and category C and category A2 ($P < 0.05$).

Conclusions. Dynamic changes of OSI after blinking showed variations even in clinically asymptomatic subjects, and four categories of tear film were proposed based on the optical quality dynamics. The procedure using serial measurements of OSI as a noninvasive and objective method may have potential applications for detecting preclinical phase of dry eye disease in asymptomatic subjects.

Keywords: tear film, optical quality, dynamics

The tear film that coats and protects the ocular surface is the major refractive surface of the visual system.[1,2] It impacts the quality of the retinal image by changing its homogeneity; therefore the optical quality of the tear film is a vital component of clear vision. The behavior of the tear film is dynamic between each blink: It is replenished immediately after a blink, then followed by several phases and eventually deteriorated if the eye is nonblinking for a sufficiently long period of time.[3] Tear film deterioration will increase the ocular aberrations and scatter as a consequence of the nonuniform tear film surface and exposure of the underlying irregular corneal surface.[4–7]

Currently, several methods are available to evaluate the tear film quality from different aspects. Tear breakup time (TBUT) remains the most frequently used diagnostic test to determine tear film instability.[8] However, it is a simple examiner-subjective endpoint that is unable to evaluate the successively temporal changes of the tear film in an interblink interval. High-speed videokeratoscopy and lateral shearing interferometry, both noninvasive techniques, can be used to measure the time-dependent changes of tear film stability.[3,9] However, high-speed videokeratoscopy and lateral shearing interferometry fail to directly evaluate the optical performance of tear film because they assess only the morphology or spatial variability of the tear film. Since the most significant aspect of the tear film is its optical quality, an objective technique that evaluates the temporal changes of optical quality of the tear film, rather than focusing on the physical property, would be ideal. Optical Quality Analysis System II (Visiometrics S.L., Tarrasa, Spain) is a noninvasive instrument based on double-pass technique to objectively assess optical quality of eyes and has been demonstrated to have excellent repeatability of measurements.[10] It can be used to assess the tear film quality dynamics.[11,12] A previous study showed that Optical Quality Analysis System II can detect mild symptoms of dry eye by evaluating the tear film optical quality based on the dynamic analysis of retinal images.[11] Because retinal image quality is significantly affected by the optical quality of the tear film, serial measurements of the retinal image quality such as the objective scatter index can indirectly reflect temporal changes in optical quality of the tear film.

The present study aimed to investigate tear film optical quality dynamics in a group of myopic subjects who presented without symptoms of dry eye by using Optical Quality Analysis System II, and four categories of tear film were proposed based on the optical quality dynamics observed in these subjects. Meanwhile, the clinical value of the tear film optical quality dynamics was further investigated by comparing the parameters of the four categories with a group of dry eye subjects.

FIGURE 1. A photo of Optical Quality Analysis System II (Visiometrics S.L., Tarrasa, Spain) used in this study.

SUBJECTS AND METHODS

Myopic subjects without symptoms of dry eye who attended the Refractive Surgery Center of the Eye Hospital of Wenzhou Medical University for refractive surgery consultation were recruited into this cross-sectional study between December 2012 and May 2013. A group of dry eye subjects were also recruited. The diagnosis of dry eye disease was based on the association of ocular symptoms and tear film abnormalities (TBUT shorter than 5 seconds) according to the International Dry Eye Workshop 2007.[13] However, eyes with ocular surface lesions (corneal and conjunctival staining) were excluded since corneal abnormalities will affect the ocular scatter significantly. All subjects underwent a comprehensive eye examination, which included slit-lamp examination (SL 115; Zeiss, Oberkochen, Germany), fundus examination under dilation (Volk SuperField NC; Volk Optical, Inc., Mentor, OH, USA), automated refraction and keratometry (RC-5000; Tomey, Nagoya, Aichi, Japan), subjective refraction (RT-5100; Nidex, Gamagori, Aichi, Japan), anterior segment analysis (Pentacam HR; Oculus, Wetzlar, Germany), and noncontact tonometry (TX-F; Canon, Tokyo, Japan). Tear breakup time was measured with a slit-lamp by instilling fluorescein into the inferior palpebral conjunctiva, and the average of three measurements was used for analysis.

Subjects were excluded if they had impaired nasolacrimal drainage, a recent history of contact lens wearing, or history of any ocular surgery. All subjects were free of any other ocular conditions that could increase ocular scatter such as superficial punctuate keratitis, corneal opacities, or significant cataract. The best-corrected visual acuity for all subjects was 20/20 or better. Ethics approval was obtained from the institutional review board of the Eye Hospital of Wenzhou Medical University, and the study was carried out in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after they received an explanation of the nature and possible consequences of the research.

Measurement of Tear Film With Double-Pass System

The double-pass system used in this study was Optical Quality Analysis System II (Fig. 1), which recorded and analyzed double-pass retinal images of a point source. For all subjects, the double-pass images were acquired at best focus by performing the objective refraction (Fig. 2) to correct the subject's refractive error internally by an optometer (ranged from −8.00 to +5.00 diopters [D] in the instrument). Astigmatism $\geq$ 0.75 D was corrected by using external ophthalmic cylindrical lenses. After a period of dark adaptation to achieve the largest possible natural pupil size, subjects were instructed to naturally blink twice and then keep their eyes open as long as possible. Optical Quality Analysis System II was used to take serial measurements of objective scatter index in the interval of 0.5 second for 20 seconds (Fig. 3). The serial measurements were performed just after the blink. For each subject, serial measurements were recorded three times. The objective scatter index is defined as the ratio of the intensity at an eccentric location in the double-pass image and the central area,[14] and its temporal changes can represent the ocular scatter fluctuation in the real-time base. In this study, the main source of the objective scatter index fluctuation resulted from change of the tear film optical quality since other sources (e.g., cornea, crystalline lens, vitreous) were relatively steady. For each subject, only well-recorded images taken between blinks were analyzed. Because some subjects blinked during the 20 seconds, a successive 10 seconds of nonblinking immediately after a blink was selected to analyze the tear film optical quality dynamics for each eye (Fig. 3).[15]

Statistical Analysis

All statistical analyses were performed using SPSS 20.0 (SPSS, Inc., Chicago, IL, USA). Only the data of the right eye were analyzed for each subject. All continuous variables were expressed as the means ± standard deviation. One-way analysis of variance was used to compare the means of each parameter among the five categories of tear dynamics. Correlational analysis was used to calculate the correlation coefficient between objective scatter index and time. The level of significance was $P < 0.05$.

RESULTS

One hundred nine right eyes from 109 asymptomatic subjects and 32 right eyes from 32 dry eye patients were enrolled in this study. For the 109 asymptomatic subjects, the mean value of age was 24.6 ± 4.2 years (range, 18–38 years), spherical equivalent −4.4 ± 1.9 D, objective scatter index, 1.05 ± 0.63. For the 32 dry eye patients, the mean value of age was 24.8 ± 5.3 years (range, 18–48 years), spherical equivalent −3.4 ± 2.5 D, objective scatter index 1.41 ± 0.88.

Figure 4 shows the four categories of tear film dynamics in asymptomatic subjects. Based on the correlation coefficient between the objective scatter index and time, 109 eyes were divided into two categories: Category A refers to eyes without positive correlation between objective scatter index and time;

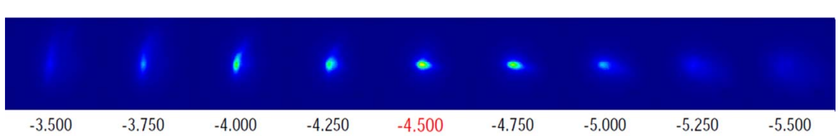

FIGURE 2. Example of objective refraction performed by Optical Quality Analysis System II. The double-pass images were acquired with nine different refractions, and the best focus objective refraction image was selected automatically (−4.50 D in this case) for subsequent analysis.

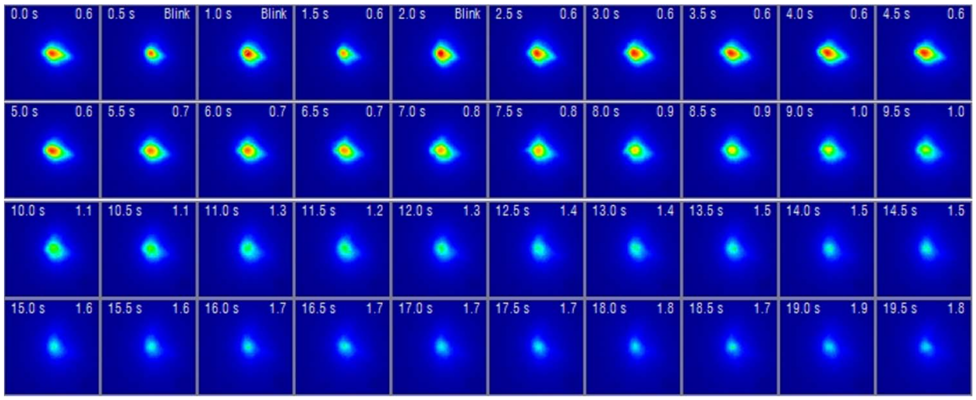

Figure 3. Example of tear film analysis with Optical Quality Analysis System II. For each double-pass image, the *upper left number* is the time (seconds) for recording, and the *upper right number* is the objective scatter index value. When the subject blinked, the objective scatter index value was replaced by a blink mark (*fifth image* at 2.0 seconds in this case). A successive 10 seconds of nonblinking double-pass images (from 2.5 to 12.0 seconds in this case) immediately after a blink (2.0 seconds) were selected to analyze the tear film optical quality dynamics.

category B refers to eyes with positive correlation between objective scatter index and time. Categories A and B were further divided into four categories based on the mean objective scatter index for 10 seconds: Category A1 (steady-low value) refers to eyes with mean objective scatter index lower than 1.00; category A2 (steady-high value) refers to eyes with mean objective scatter index equal to or greater than 1.00; similarly for category B1 (ascending-low value) and category B2 (ascending-high value).

Subjects diagnosed with dry eye disease were placed into category C for comparison. Table 1 shows the characteristics of eyes in the five categories. Comparing sex distribution among categories, the difference was significant between A1 and A2, A1 and B2, and A1 and C; female sex was dominant in categories B1 and C. The percentage of eyes in each category of asymptomatic subjects is shown in Figure 5. In category C, 93.8% (30/32) of the eyes demonstrated an ascending pattern of tear film dynamics (positive correlation between objective scatter index and time), and only two eyes demonstrated a steady pattern of tear film dynamics. The temporal changes of mean objective scatter index of 32 eyes in category C are shown in Figure 6.

Table 2 shows the mean value, correlation coefficient, and coefficient of variation of objective scatter index (in 10 seconds) in each category. There was no significant difference in the TBUT among the four categories of asymptomatic subjects, and a significant difference was found only between category A1 and category C ($P < 0.01$) and category A2 and category C ($P < 0.05$). Note that in the total 109 asymptomatic eyes, 9 eyes showed a negative correlation between objective

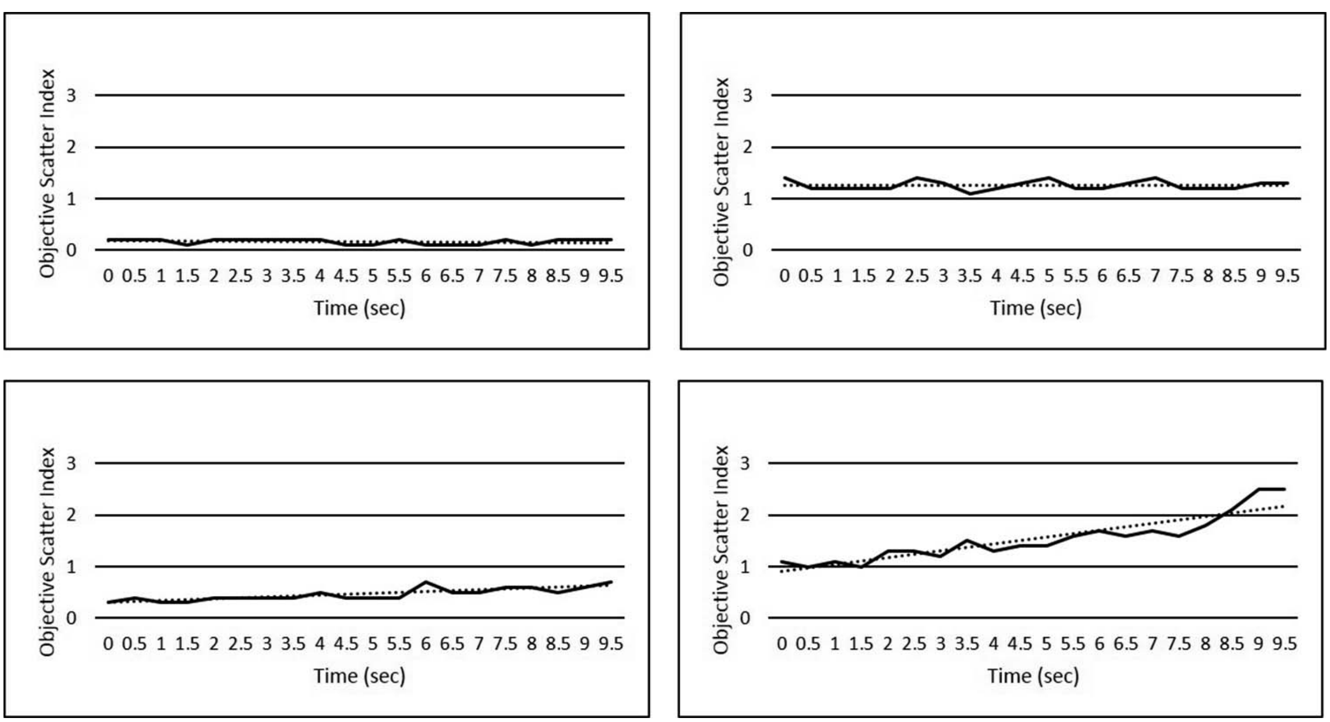

Figure 4. Temporal changes of objective scatter index of a representative case in each category. *Top left*: Category A1 showed a steady-low value pattern; *top right*: category A2 showed a steady-high value pattern; *bottom left*: category B1 showed ascending-low value pattern; *bottom right*: category B2 showed ascending-high value pattern.

Table 1. Comparison of Age, Sex, and Spherical Equivalent Among Five Categories

	Category A1	Category A2	Category B1	Category B2	Total for A1–B2	Category C	*P* Value
Number of eyes (%)	40 (36.7)	36 (33.0)	15 (13.8)	18 (16.5)	109 (100)	32	
Age, y	24.6 ± 3.6	24.6 ± 4.9	25.3 ± 3.9	24.3 ± 4.4	24.6 ± 4.2	24.8 ± 5.3	0.971
Sex							
Male (%)	25 (62.5)	14 (38.9)	6 (40.0)	5 (27.8)	50 (45.9)	11 (34.4)	0.057*
Female (%)	15 (37.5)	22 (61.1)	9 (60.0)	13 (72.2)	59 (54.1)	21 (65.6)	
Spherical equivalent, D	−4.0 ± 1.8	−5.3 ± 1.7	−3.3 ± 2.1	−4.5 ± 1.4	−4.4 ± 1.9	−3.4 ± 2.5	<0.01†

A1, steady-low value; A2, steady-high value; B1, ascending-low value; B2, ascending-high value; C, dry eye.
* Significant difference noted between A1 versus A2, A1 versus B2, A1 versus C, $P < 0.05$.
† Significant difference noted between A1 versus A2, A2 versus B1, A2 versus C, $P < 0.01$.

scatter index and time; since the correlation coefficients were relatively low, these 9 eyes were incorporated into category A1.

Discussion

Previous studies have reported increased scatter due to tear film instability in dry eye disease[5,12,16]; light scattering was analyzed by Hartmann-Shack wavefront sensor, double-pass system, C-Quant straylight meter, and Scheimpflug imaging system in those studies. Koh et al.[16] reported that significantly higher intraocular forward light scattering was noted in a dry eye group, and significantly higher corneal backward light scattering was also found in dry eye subjects who had central superficial punctate keratopathy. In that study, the subjects blinked freely during the measurement, and the measurement was taken at a single time point versus measurement of the temporal changes in our study. Himebaugh et al.[5] reported that the degradation of the tear film increased wavefront aberrations, and instable tear film and possible exposed rough epithelial surface with no blinking will cause light-scattering aberrations in regions of tear film breakup. However, the wavefront sensor used in Himebaugh's study may overestimate optical quality.[17]

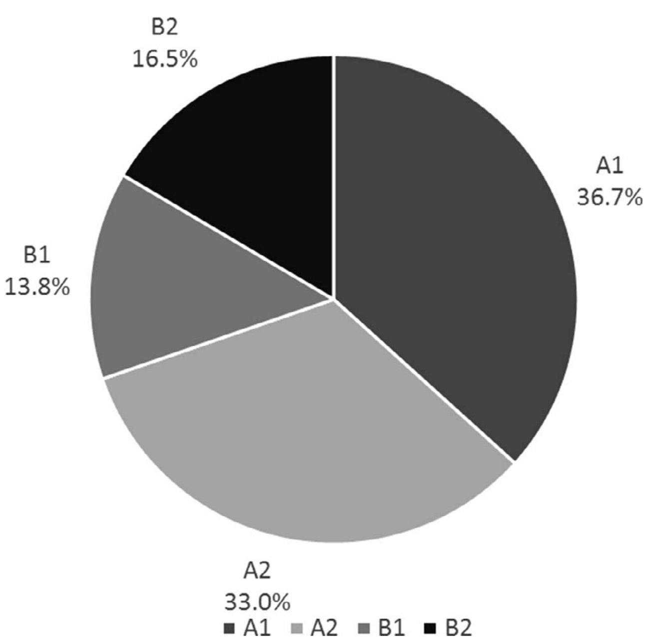

Figure 5. Percentage of eyes in each category. A1, steady-low value; A2, steady-high value; B1, ascending-low value; B2, ascending-high value.

In the present study, we analyzed serial measurements of objective scatter index for a successive 10 seconds of nonblinking in a cohort of subjects without clinically diagnosed dry eye, and a group of dry eye patients was also investigated for comparison. Eyes with dry eye disease (category C) demonstrated an ascending pattern of tear film dynamics without blinking (Fig. 6). The tear film is the first refractive surface of the visual system, and the only source of ocular scatter changes during the short time period (10 seconds) was tear film alterations; therefore, the ascending pattern of tear film dynamics indicated that the tear film was unstable and gradually deteriorated in dry eye disease. This result agreed with those reported by Benito et al.[11] and Diaz-Valle et al.[12] As compared to categories A1 and A2, category C demonstrated a shorter TBUT (A1 versus C, $P < 0.01$; A2 versus C, $P < 0.05$) and a higher correlation coefficient ($P < 0.05$) as expected. In contrast, there was no statistical difference between category B1 and category C or category B2 and category C regarding the TBUT and correlation coefficient. This indicated that categories B1 and B2 shared similar features with symptomatic dry eye.

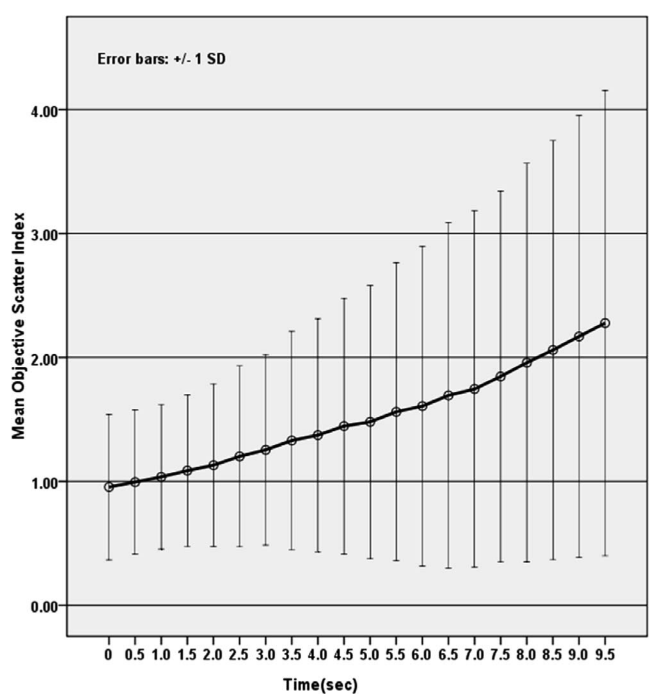

Figure 6. Temporal changes of mean objective scatter index of 32 eyes in the dry eye group. The mean objective scatter index increased with time and demonstrated an ascending pattern of tear film dynamics.

TABLE 2. Comparative Analysis of Objective Scatter Index, Correlation Coefficient, Coefficient of Variation, and Tear Breakup Time Among the Five Categories

	Category A1	Category A2	Category B1	Category B2	Total for A1–B2	Category C	*P* Value
OSI	0.53 ± 0.17	1.42 ± 0.43	0.63 ± 0.24	1.82 ± 0.56	1.05 ± 0.63	1.41 ± 0.88	<0.01*
CC	−0.1 ± 0.33	−0.03 ± 0.31	0.71 ± 0.13	0.77 ± 0.14	0.18 ± 0.10	0.84 ± 0.21	<0.01†
CV	0.16 ± 0.07	0.16 ± 0.07	0.16 ± 0.10	0.28 ± 0.14	0.18 ± 0.46	0.24 ± 0.12	<0.01‡
TBUT	4.8 ± 2.68	4.00 ± 1.87	3.93 ± 1.53	3.6 ± 3.09	4.22 ± 2.40	2.9 ± 1.12	<0.05§

A1, steady-low value; A2, steady-high value; B1, ascending-low value; B2, ascending-high value; C, dry eye; OSI, objective scatter index; CC, correlation coefficient; CV, coefficient of variation.

* Significant difference noted between A1 versus A2, A1 versus B2, A1 versus C, A2 versus B1, A2 versus B2, B1 versus B2, B1 versus C, B2 versus C, $P < 0.01$.

† Significant difference noted between A1 versus B1, A1 versus B2, A1 versus C, A2 versus B1, A2 versus B2, A2 versus C, $P < 0.01$.

‡ Significant difference noted between A1 versus B2, A1 versus C, A2 versus B2, A2 versus C, B1 versus B2, B2 versus C, $P < 0.01$.

§ Significant difference noted between A1 versus C, $P < 0.01$; A2 versus C, $P < 0.05$.

For the 109 asymptomatic subjects, four categories of tear film optical quality dynamics were proposed based on the mean objective scatter index (for 10 seconds) and correlation coefficient, and the differences among categories were investigated. Most (69.7%) of the eyes fit into category A1 (36.7%) and category A2 (33.0%); these subjects had relative steady tear film optical quality dynamics. This is mainly because the subjects recruited into this group were asymptomatic and all without clinically diagnosed dry eye.

However, a significant number of these eyes still fell under the ascending categories B1 (13.8%) and B2 (16.5%). This again indicates that these eyes shared the feature of increased objective scatter index over time with the symptomatic dry eyes included in this study and described by Benito et al.[11] One potential reason why the eyes in category B1 and B2 were asymptomatic may be that these subjects have higher blink rates and another blink is carried out before subsequent deterioration of tear film occurs in daily life. It would be of interest in future studies to evaluate the blink rate along with the dry eye disease symptoms (such as Ocular Surface Disease Index[18]) in category B1 and category B2 subjects.

Clinically, it was of great importance to identify category B1 and category B2 subjects in the asymptomatic population because these subjects were at the preclinical phase and may present with dry eye symptoms when affected by certain factors: aging, contact lens wearing, environmental stimuli, and, more importantly, ocular surgery. Numerous studies have focused on the impact of different ocular surgeries on the ocular surface and tear film dynamics,[19–21] and corneal surgeries are well known to cause loss of corneal sensory nerves.[13] Presurgical evaluation of the tear film may predict patient satisfaction and visual outcomes. Moreover, from a clinical standpoint, identification of preclinical-phase dry eye disease patients (such as category B1 and category B2 subjects), who are often neglected by established tests, prior to surgery and then treating them appropriately both before and after surgery may improve visual outcomes. Future studies investigating postsurgical tear film changes, visual outcomes, and patient satisfaction in subjects from the four categories using serial measurements of objective scatter index can provide further information regarding the significance of evaluation of the tear film optical quality dynamics in asymptomatic subjects.

The TBUT remains the most frequently used diagnostic test for dry eye assessment. The TBUT cutoff for dry eye diagnosis has changed over years from 10 seconds initially[22] to 5 seconds recently with reduced volume of fluorescein.[23] In this study, the mean TBUT for each category in the asymptomatic group was less than 5 seconds; this may due to the fact that the young subjects recruited are frequently exposed to visual display terminals, which may affect the signs associated with dry eye,[24,25] such as reduced TBUT. Clinically, a TBUT less than 5 seconds has been regarded as one of the diagnostic criteria for dry eye. However, a TBUT less than 5 seconds alone is insufficient, and the presence of dry eye symptoms is necessary for diagnosis of dry eye.[13] In the present study, all the subjects in categories A1, A2, B1, and B2 were asymptomatic and thus were not diagnosed with dry eye; the slightly reduced TBUT may indicate the subclinical instability of tear film rather than definite dry eye. In a retrospective study,[26] only 57% of the subjects reported symptoms consistent with a diagnosis of dry eye even though they had measured clinical signs. These results, consistent with our study, suggested that in asymptomatic subjects, a significant number of subjects had tear film instability. Clinically, it is important to distinguish and classify these preclinical-phase subjects with reference to normal subjects in order to start early intervention or avoid exacerbating factors to prevent the onset of dry eye symptoms. In this study, there was no significant difference observed regarding TBUT among categories A1, A2, B1, and B2. This suggests that for the purpose of differentiation or even early detection, tear film optical quality dynamics assessed by objective scatter index are more sensitive for evaluating tear film compared to TBUT, since this takes into account the different temporal changing patterns of the tear film optical quality in eyes that may have a similar TBUT.

Female sex has been reported to be more susceptible to dry eye disease,[27,28] and this was also shown to be true for the population in China.[29] However, most of the studies[28,30,31] focused on older women and indicated that both menopausal and postmenopausal women were more frequently affected by instable tear film compared to men of the same age. In this study, female sex dominated all categories except A1, particularly categories B2 and category C (72.2% and 65.6% of the subjects were female, $P < 0.05$). This suggests that not only in the older population, but also in the young population, especially asymptomatic subjects, more women compared to men had unstable tear film optical quality dynamics. The significant implication of this finding is to take the sex of the subject into consideration when dealing with dry eye–related problems in a young population.

Category A1 and category A2 both had steady tear film optical quality dynamics, with category A2 possessing higher objective scatter index values ($P < 0.01$) and more myopic values ($P < 0.05$). This may indicate, in agreement with the findings of Miao et al.,[32] that high myopia has more intraocular scatter, although the exactly mechanism is still unclear. In contrast, category B2 had higher objective scatter index values ($P < 0.01$) compared to category B1 without a significant difference in myopic values between B1 and B2. This suggests that the higher objective scatter index values in category B2 may result from unsteady tear film optical quality, such as tear film breakage,[11] rather than high refractive error.

The limitation of this study is that all the measurements were conducted under the exit aperture of 7.0 mm set by Optical Quality Analysis System II. In fact, not all eyes reached a natural pupil size of 7.0 mm or larger. However, this is not relevant to this study because we mainly focused on the dynamic variations of tear film optical quality, and the pupil size was relative constant during the measurement for each eye. In addition, this study was conducted in subjects in the Refractive Surgery Center of the Eye Hospital of Wenzhou Medical University as a hospital-based population. Thus, the prevalence of each category and sex distribution might not reflect the tendency in the general population.

To our knowledge, this is the first study to divide subjects without any dry eye symptoms into four different categories based on tear film optical quality dynamics. Our procedure using serial measurements of objective scatter index as a noninvasive and objective method may be more sensitive compared to TBUT and have potential applications with regard to detecting the preclinical phase of dry eye disease in asymptomatic subjects.

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