Serial Measurements of Higher-Order Aberrations after Blinking in Patients with Dry Eye

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Purpose. To study the sequential postblink changes in ocular higher-order aberrations (HOAs) in patients with dry eye.

Methods. A wavefront sensor was used to measure HOAs sequentially for 30 seconds in 20 eyes of 20 patients with dry eye. The 20 eyes were classified into two groups, with or without superficial punctate keratopathy (SPK) in the central cornea. During the measurement, subjects were required to blink every 10 seconds. The aberration data were analyzed in the central 4-mm diameter for coma-like, spherical-like, and total HOAs up to sixth-order Zernike polynomials. Total HOAs, as well as fluctuation index (FI) and stability index (SI) of the total HOAs over time were compared between the two groups. The sequential changes in coma-like aberration, spherical-like aberration, and total HOAs were also investigated.

Results. The total ocular HOAs were significantly ($P = 0.001$) greater in dry eyes with central SPK than in dry eyes without central SPK. The sequential pattern of the total ocular HOAs had higher initial and consistently higher values in dry eyes with central SPK, whereas that of dry eyes without central SPK showed consistently lower total HOAs that were similar to the pattern of normal eyes.

Conclusions. Increased HOAs in dry eye at least partially result from SPK above the optical zone. The low tear volume in dry eye may not cause sequential increases in HOAs after blinking. Sequential measurement of HOAs may be useful for evaluating the sequential changes in optical quality in patients with dry eye. (*Invest Ophthalmol Vis Sci.* 2008;49:133–138) DOI: 10.1167/iovs.07-0762

Dry eye has been thought of as a disease that rarely affects visual function except in advanced cases.[1] Recent studies, however, have shown impaired optical quality in dry eye compared with normal eyes.[1–6] It is not difficult to imagine that the unstable and irregular tear film is disrupted over the irregular ocular surface in dry eyes, particularly in some situations that require the patients to inhibit blinking. Studies using functional visual acuity measurements have shown impaired functional visual acuity in patients with dry eye during gazing.[1,5] Moreover, investigators in several studies who measured continuous corneal topographic data or corneal and ocular wavefront aberrations in normal eyes and dry eyes have reported that the dynamic changes in tear film affect the optical quality after blinking,[7–15] and decreased optical quality in dry eyes has been confirmed.[7–9]

Recent studies have shown that corneal higher-order aberrations (HOAs) after blinking tend to increase in dry eyes,[9] and both ocular and corneal HOAs are significantly greater than those in normal eyes.[6,9] However, little is known about the continuously varying postblink changes in HOAs of the entire eye. It is of interest how the irregular corneal surface with unstable thin tear film affects the postblink changes in ocular HOAs in dry eyes. We, therefore, conducted the current prospective study to investigate the sequential postblink changes in the ocular HOAs in patients with dry eye.

Methods

This study was approved by the institutional review board of Osaka University Hospital. The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study.

Subjects

Twenty eyes of 20 patients (20 women; average age, 59.2 ± 12.5 years) with dry eye (13 patients with Sjögren's syndrome and 7 with keratoconjunctivitis sicca) were enrolled in this study at the Department of Ophthalmology, Osaka University Medical School Hospital. They had no ocular disease except dry eye and had not undergone ocular surgery or punctal plug insertion.

Dry eye was diagnosed by both positive tear tests and the presence of damaged corneal and conjunctival epithelium, based on the Japanese diagnostic criteria of dry eyes.[16] Tear abnormalities were diagnosed by either the Schirmer I test (measurement of tear secretion during 5 minutes of natural blinking without anesthesia) results of less than 5 mm or tear break-up time (BUT) shorter than 5 seconds. Ocular surface abnormalities were diagnosed by positive results on either corneal fluorescein staining or corneal and conjunctival rose bengal staining scores of 3 or more, according to the method of van Bijsterveld.[17]

Based on the examination, patients were divided into two groups. Group A included patients without superficial punctate keratopathy (SPK) in the central cornea. It included three women with Sjögren's syndrome and four with keratoconjunctivitis sicca (average age, 45.8 ± 10.3 years). The SPK was mainly in the inferior paracentral cornea and not over the pupil on the cornea. Group B included 10 patients with Sjögren's syndrome and three patients with keratoconjunctivitis sicca (average age, 51.3 ± 3.4 years). These patients had SPK over the pupil on the cornea as well as over the inferior paracentral cornea. The measurements were conducted in a room in which the temperature

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and humidity were maintained at 22 ± 2°C and 40% ± 5%. All measurements were obtained in the afternoon from 1:00 to 3:00 PM.

Sequential Measurement of Wavefront Aberrations

Serial measurements of ocular HOAs were performed by using the newly developed Hartmann-Shack wavefront aberrometer (Topcon Corp., Tokyo, Japan), in accordance with the procedure used in earlier studies.[12,15,18] Briefly, each subject was instructed to blink every 10 seconds during the measurement (total measurement time, 30 seconds). This blinking interval has been reported to be close to that of patients with dry eye during activities in which patients gaze, such as while working on a video display terminal (VDT) or while reading.[1,19] A series of 30 consecutive measurements consisting of three postblink intervals was taken. Obtaining appropriate wavefront measurements was difficult through a natural pupil without use of dilating drugs for typical patients with dry eye aged 50 years and older. Therefore, pupils were dilated with a mixture of 0.5% phenylephrine and 0.5% tropicamide (Mydrin P; Santen Pharmaceutical Co., Osaka, Japan). Measurements were taken at least 1 hour after pupil dilation when the dilated pupil was greater than 6 mm. In addition, based on previous studies that measured continuous functional visual acuity or corneal topographic data in patients with dry eye,[1,5,8] preservation-free topical anesthesia (benoxinate hydrochloride 0.4% ophthalmic solution, Minims; Senju Pharmaceutical Co., Osaka, Japan) was applied at least 5 minutes before the measurement to prevent blinking or reflex tearing and to minimize patient discomfort.

The ocular HOA data were analyzed quantitatively in the central 4-mm diameter up to the sixth order by expanding the set of Zernike polynomials. From the Zernike coefficients, the root mean square (RMS) was calculated to represent the wavefront aberrations. S3, S4, S5, and S6 are the RMS of the third-, fourth-, fifth-, and sixth-order Zernike coefficients, respectively. Coma-like aberrations (S3+S5), spherical-like aberrations (S4+S6), and total HOAs (S3+S4+S5+S6) were also calculated.[20]

Fluctuation and Stability Indexes

Two quantitative indices were used to indicate the sequential change in HOAs over time: the fluctuation index (FI) and the stability index (SI) of the total HOAs.[12,18] The FI was defined as the average of the SD of the ocular total HOAs obtained that showed the fluctuations in the total HOAs measured between blinks. SI was defined as the slope of the linear regression line of the total ocular HOAs between blinks. The data from three postblinks were calculated and averaged for each eye.

Statistical Analysis

The total HOAs, FI and SI of the total HOAs, coma-like aberrations, and spherical-like aberrations were compared between the two groups. The data were analyzed with Student's *t*-test. In addition, the sequential changes in coma-like aberration, spherical-like aberration, total HOAs, and the C_4^0 value (spherical aberration) among the Zernike coefficients also were investigated in both groups. A repeated-measures one-way ANOVA was used to analyze the sequential changes in both groups. The appropriate post hoc Tukey correction for multiple comparisons was used. $P < 0.05$ was considered significant for all analyses.

Results

The profile of each group and the results of the tear BUT and the Schirmer I test are shown in Table 1.

Table 1. Profiles of the Study Groups

Group*	Tear BUT (sec)	Schirmer I Test (mm)
Group A (n = 7)	2.2 ± 0.7	5.0 ± 4.1
Group B (n = 13)	1.7 ± 0.7	2.6 ± 1.6
P†	0.114	0.110

Data are expressed as the mean ± SD.

* Patients in group A had dry eye without SPK in the central cornea; patients in group B had dry eye with SPK in the central cornea.

† By Student's *t*-test.

Total HOAs, FI, SI, Coma-like Aberrations, and Spherical-like Aberrations

Figure 1 shows the mean total HOAs, FIs, and SIs calculated from the data obtained from groups A and B, and those from normal subjects (11 women, 9 men; average age, 30.0 ± 4.4 years) were shown as reference values.[12] The mean total HOAs of group A and B were 0.139 and 0.241, respectively. The total HOAs of group B were significantly (P = 0.001) higher than those of group A. The mean FIs in groups A and B were 0.0144 and 0.0171, respectively, and the mean SIs in each group 0.0015 and 0.0012, respectively. There were no significant differences in the FIs (P = 0.250) and SIs (P = 0.792) between two groups (Fig 1). The mean coma-like aberrations in groups A and B were 0.114 and 0.197, respectively. The mean spherical-like aberrations were 0.077 and 0.141, respectively. Both coma-like and spherical-like aberrations in group B were significantly higher than those in group A (P = 0.001).

Serial Changes in HOAs

Shown in Figure 2 are the averages of the sequential changes in HOAs during the measurements in each group.

In group A, the sequential total HOAs remained constant at each blink (Fig. 2A). There were significant differences during nine measurements of the sequential postblink changes in the spherical-like aberrations over 10 seconds (P = 0.001). At 7 and 9 seconds, spherical-like aberrations were significantly higher than those 2 seconds after the blink ($P < 0.05$). There were no significant changes in coma-like aberrations and total HOAs among the nine measurements (P = 0.665 and P = 0.089, respectively).

In group B, the sequential total HOAs tended to be stable, with small fluctuations (Fig. 2B). There were significant changes during nine measurements of the sequential postblink changes in the spherical-like aberrations over 10 seconds (P = 0.001). At 9 seconds, spherical-like aberrations were significantly higher than those 2 and 4 seconds after the blink ($P <$ 0.05). There were no significant changes in coma-like aberrations and total HOAs among the nine measurements (P = 0.999 and P = 0.247, respectively).

In both groups, the C_4^0 values (spherical aberration) among the Zernike coefficients did not show a significant negative shift during 10 seconds (P = 0.734 and P = 0.805, respectively).

Case Presentations

The color-coded maps of ocular HOAs obtained between blinks in representative cases from both groups are shown with the changes in the simulated retinal images of a Landolt ring (optotype with logMAR value of 0; Fig. 3). In a dry eye without SPK in the central cornea (Fig. 3A), no marked deterioration was found in consecutive wavefront maps and simulated retinal images (Fig. 3B). In contrast, more noteworthy are the severely blurred retinal images from the beginning (Fig. 3D) in dry eye with SPK in the central cornea (Fig. 3C) than in a dry eye without SPK in the central cornea.

Discussion

In the present study, we measured the sequential ocular HOAs after blinking in dry eyes under the suppression of blinking.

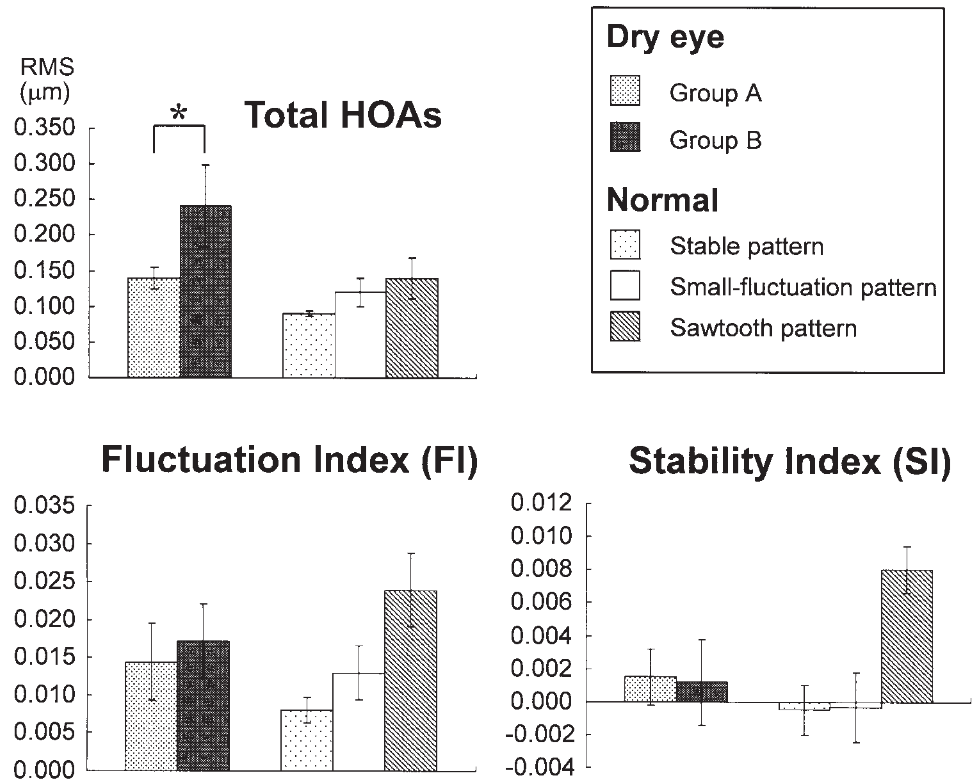

FIGURE 1. Comparison of the total HOAs, the FI, and the SI of the total HOAs. The total HOAs in group B were significantly higher than those in group A ($P = 0.001$). Data from normal eyes are from Koh et al.[12]

Our findings suggested that HOAs in dry eye with SPK in the central cornea were higher than those in dry eye without SPK in the central cornea and that sequential increases of ocular wavefront aberrations were not observed, at least during the 10-second blink intervals, regardless of SPK in the central cornea.

Regarding the pattern of the time-wise change in HOAs, previous studies have reported that dry eyes had greater ocular HOAs than normal eyes[6] and continuous measurements of corneal HOAs tended to show an upward curve in patients with dry eye.[9] Our results in dry eye with SPK in the central cornea agree with the results that dry eyes had greater HOAs.[6] However, in the present study, no upward tendency in ocular HOAs was found in both groups with dry eye. The disagreement in the results between the previous finding[9] and the present study could be explained partly by the difference in the diagnostic criteria for dry eye or by the differences in the measurements of HOAs. The diagnostic criteria for dry eye were different (i.e., the cutoff value for the Schirmer test was 5 mm in our study, whereas it was 10 mm in the previous study), and the severity of corneal damage was not described.[9] The differences in gender and age, the measurement device,

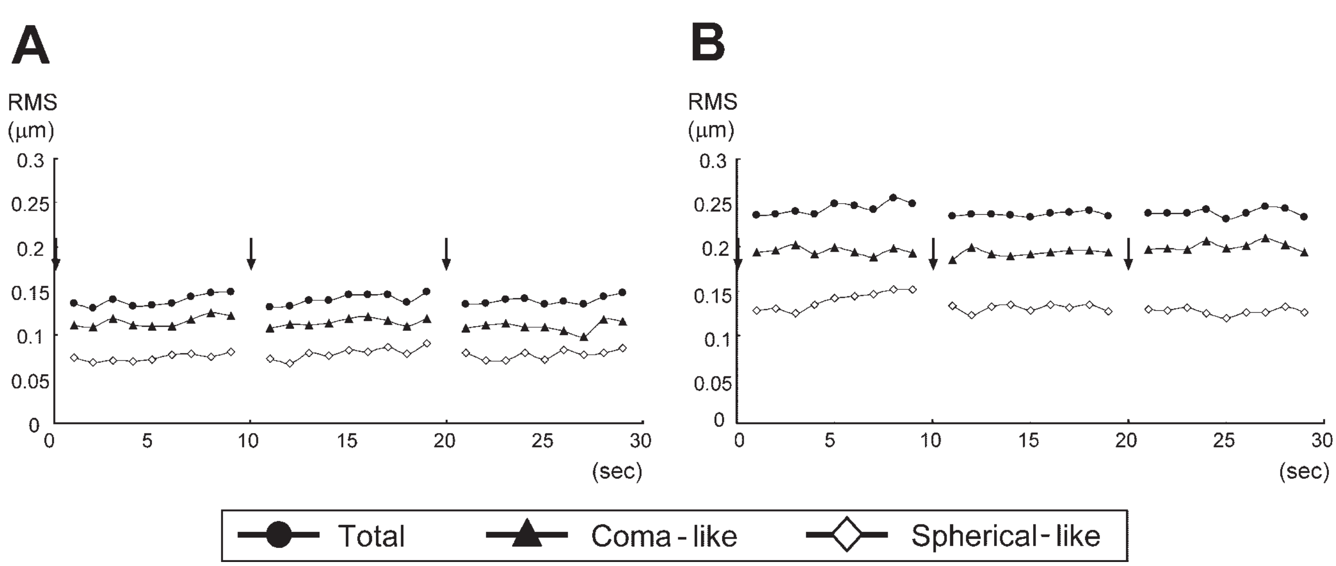

FIGURE 2. The sequential changes in higher-order aberrations over 30 seconds consisting of three postblink intervals are presented for both groups of patients with dry eye. (**A**) Group A ($n = 7$ patients). (**B**) Group B ($n = 13$ patients). Error bars have been omitted for clarity. *Vertical arrows*: blinks.

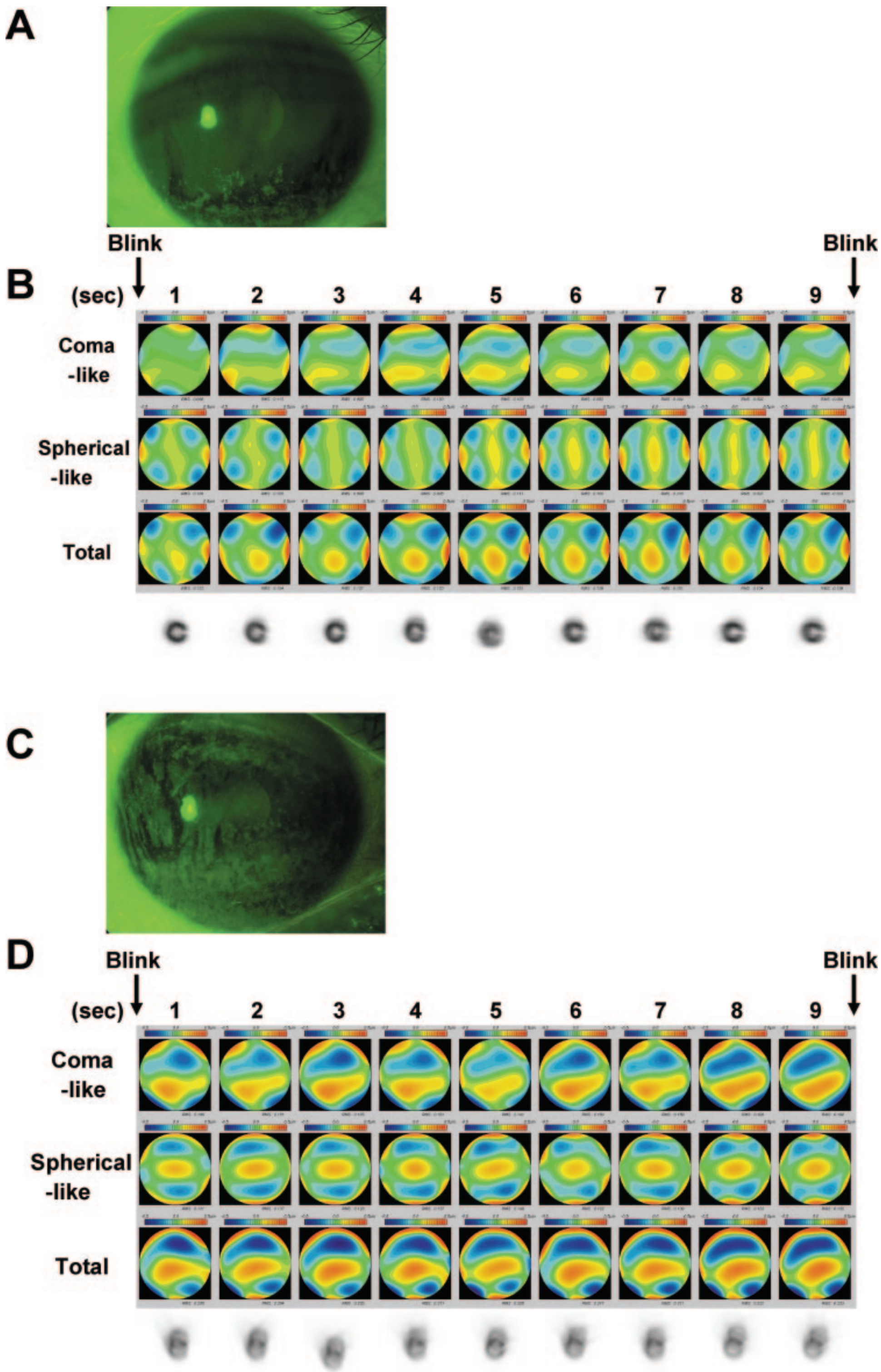

FIGURE 3. Representative cases and sequential wavefront color-coded maps of ocular higher-order aberrations in each group. (**A**, **B**) A 40-year-old woman with dry eye without SPK in the central cornea who had a Schirmer test result of 5 mm and tear BUT of 2 seconds. (**C**, **D**) A 45-year-old woman with dry eye with SPK in the central cornea who had Sjögren's syndrome with a Schirmer test result of 2 mm and tear BUT of 1 second. Total, total HOAs.

the blinking conditions (repeated or not), the duration of the measurements, the use of topical anesthesia and environmental conditions may also contribute to the difference.

Previous reports have suggested that the postblink behavior of both the ocular and corneal HOAs of normal or dry eyes may develop mainly because of the asymmetric changes in tear film thickness between the superior and inferior cornea.[9,11,12,21] We reported that the normal eyes with the sawtooth pattern in which an upward curve of sequential HOAs was found at each postblink interval with a higher SI had the potential to develop dry eye.[12] Based on these findings,[9,12] changes such as the sawtooth pattern with a higher SI were expected to be found in dry eye before we conducted the present study. However, there was no such pattern in the patients with dry eye in this study. In the normal eyes with sawtooth pattern, the tear film may be unstable; however, the tear volume is not deficient. Therefore, the alteration in aqueous tear layer may develop the upward tendency in HOAs. In contrast, although the tear film stability is considerably impaired and tear evaporation rate is increased in dry eye,[22–24] the decreased volume of tear film

(<5 mm by Schirmer test) may be insufficient to cause the dynamic upward curve in HOAs, or the dynamic upward curve may be observed before the tear film break-up. Our results suggest that a certain amount of tear film thickness may be a main factor in the development of the dynamic change in HOAs. The absence of a marked upward curve in dry eye may result from the thin aqueous tear film layer, because tear film breaks up rapidly in dry eye and the decrease in tear film thickness may persist. In cases with milder dry eyes, which may cause reflex tearing, a sequential upward curve in HOAs may be observed when measurements are performed without topical anesthesia.

In both groups of dry eye, there was significant change over time between the blinks only in the spherical-like aberrations. This phenomenon also was observed in normal eyes with a small-fluctuation pattern in our previous study.[12] The C_4^0 value (spherical aberration) among the Zernike coefficients did not change substantially during 10 seconds in both groups. In each pattern, the RMS value of the spherical-like aberration at 9 seconds after the blink when the tear film break-up occurred was significantly higher than 2 seconds after the blink at the exact moment of tear break-up. Despite reduced tear film thickness, the rapid tear evaporation at the central cornea compared with the periphery[9] may be associated with changes over time in the symmetrical components of the HOAs. Further study of the relationship between the wavefront aberrations and physiologic effects of tear film may clarify this question.

We theorized that the irregular optical surface due to epithelial damage in the optical zone may be responsible for the consistently higher HOAs without particular dynamic changes in dry eye with SPK in the central cornea. In mild dry eye without SPK in the central cornea, the sequential total HOAs did not have higher values, and no dynamic upward trend in HOAs was found, perhaps as a result of the smooth optical surface on the entrance pupil and the thin aqueous layer that developed after the tear film deteriorated approximately 2 seconds after the blink. In contrast, in a dry eye with SPK in the central cornea, we believe that the poor aqueous tear volume and an irregular optical surface due to the corneal epithelial damage may be responsible for the consistently higher HOAs without particular dynamic changes in pattern. When the pattern of the sequential changes in ocular total HOAs is stable or has small fluctuations within the normal range of total HOAs, it is difficult to differentiate between normal eyes and eyes with mild dry eye without SPK in the central cornea. Because the importance of spatial location and wavefront aberrations has been reported,[25–28] further studies would be helpful in evaluating the relationship between the spatial location and HOAs.

Huang et al.[4] reported that, whereas the surface regularity index (SRI) and the surface asymmetry index (SAI) obtained by corneal topography were significantly higher in dry eyes with SPK than in dry eyes without SPK, there were no differences in the two parameters between dry eyes without SPK and normal eyes. Although the location of SPK was not described in their study,[4] it is interesting to note that similar effects of SPK were found by wavefront aberrometry. According to previous reports, the cornea is thinner in dry eyes than in normal eyes.[29,30] It also would be of interest in future studies to evaluate the effect of the differences in corneal thickness or corneal surface regularity[2,31] on the serial changes in HOAs between normal eyes and dry eyes.

The present study had some limitations. The blink rate used in the present study was set at six times/minute for several reasons. Using a uniform blink interval enabled us to average multiple measurement data and to analyze the data quantitatively. The 10-second blink interval overlapped with the blink rate during daily activities that patients with dry eye may experience in daily life and are associated with optical quality.[1,19] However, forced repeated blinking differs from spontaneous blinking, in that repeated forced blinking may distort the tear film stability or distribution in dry eye with abnormal tear dynamics. Spontaneous blinking seems to be desirable; however, it is doubtful whether patients can blink spontaneously during measurements when they are too conscious of the need to blink.

We cannot rule out the possibility that topical anesthesia and the mydriatic agent used in the present study may have influenced the results. According to previous reports, mydriasis could affect the measurement of HOAs.[32,33] Also, the eyes with epitheliopathy are more susceptible to these effects due to the altered barrier function. However, in the continuous measurements of functional visual acuity or corneal topographic data with blink suppression, previous studies in this field used topical anesthesia for patients with dry eye[1,5,8] and, as reported in the previous study,[8] our preliminary attempts to perform sequential wavefront measurements without topical anesthesia resulted in induced blinking or reflex tearing in some patients with dry eye who could not keep their eyes open for 10 seconds without blinking. Therefore, sequential wavefront measurements with topical anesthesia in patients with dry eye are considered to be acceptable. Ideally, the wavefront measurements should be performed without anesthesia through a natural pupil without dilating drugs, and this methodology especially in patients with dry eye, should be considered in future studies.

Another limitation of the present study is that the wavefront measurements were performed at 1-second intervals. Considering that tear BUT in patients with dry eye in this study ranged from approximately 1 to 3 seconds, if the wavefront measurements were performed more frequently between just after the blink and the tear BUT, the HOAs might cause a trend or fluctuate more during the measurement. Measurement of a shorter interval might be a better approach in a future study; however, the effect of blink suppression should be considered during the evaluation of quality of vision.[34,35]

In conclusion, serial measurements of wavefront aberrations showed that the optical quality in dry eye may be affected partially by SPK above the entrance pupil; a small tear volume in dry eye may not affect the sequential increase in HOAs measured with a 4-mm pupil diameter at least 10 seconds after blinking. Wavefront sensing has a potential to be a useful quantitative method to evaluate the quality of visual performance and the effects of treatment in patients with dry eye.

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