

Ocular Forward Light Scattering and Corneal Backward Light Scattering in Patients With Dry Eye

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PURPOSE. To evaluate ocular forward light scattering and corneal backward light scattering in patients with dry eye.

METHODS. Thirty-five eyes in 35 patients with dry eye and 20 eyes of 20 healthy control subjects were enrolled. The 35 dry eyes were classified into two groups according to whether superficial punctate keratopathy in the central 6-mm corneal zone (cSPK) was present or not. Ocular forward light scattering was quantified with a straylight meter. Corneal backward light scattering from the anterior, middle, and posterior corneal parts was assessed with a corneal densitometry program using the Scheimpflug imaging system.

RESULTS. Both dry eye groups had significantly higher intraocular forward light scattering than the control group (both $P < 0.05$). The dry eye group with cSPK had significantly higher values in anterior and total corneal backward light scattering than the other two groups. Moderate positive correlations were observed between the cSPK score and corneal backward light scattering from the anterior cornea ($R = 0.60$, $P < 0.001$) and corneal backward light scattering from the total cornea ($R = 0.54$, $P < 0.001$); however, no correlation was found between cSPK score and ocular forward light scattering ($R = 0.01$, $P = 0.932$).

CONCLUSIONS. Ocular forward light scattering and corneal backward light scattering from the anterior cornea were greater in dry eyes than in normal eyes. Increased corneal backward light scattering in dry eye at least partially results from cSPK overlying the optical zone.

Keywords: dry eye, light scattering, superficial punctate keratopathy

The tear film and cornea are important optical elements of the eye, as the cornea is the first transparent tissue of the eye and the tear film ensures a smooth refracting surface. Dry eye, a multifactorial disease of the tears and ocular surface,¹ is characterized by impairment of the integrity of the tear film and cornea and generally thought as a chronic, symptomatic ocular surface disease that affects visual function in a limited manner (e.g., in advanced or severe cases).²⁻⁵ With regard to optical function, the instability of a disrupted tear film over the irregular ocular surface of dry eye is thought to be associated with optical disturbances.⁶ Recent emerging techniques have enabled us to quantify and show degraded optical quality or visual disturbance in dry eye.

In human eyes, aberrations and light scattering are the main factors in the degradation of optical quality. Irregular astigmatism or higher-order aberrations (HOAs) of the entire eye can be determined quantitatively with wavefront sensor.⁷ In eyes with diseases of the ocular surface or anterior segment, the irregularity of the refractive surfaces, such as anterior/posterior corneal surfaces or the precorneal tear film, can cause increased HOAs. A number of studies have shown that in dry eyes, the increase in HOAs is caused by an irregular ocular surface with an unstable tear film.⁸⁻¹⁴

Light scattering can be subdivided into light scattered toward the retina (forward light scattering) and light scattered backward (backward light scattering).¹⁵ Forward light scattering produces a veiling luminance on the retina, which reduces

contrast of the retinal image. This phenomenon may particularly lead to glare. In clinical practice, forward light scattering is measured using a double-pass imaging technique or with a straylight meter. Optical clarity is a fundamental property of the cornea,¹⁶ and corneal haze with decreased corneal transparency is associated with increased ocular scattering. Clinically, corneal haze is typically estimated as corneal backward light scattering as observed by slit-lamp examination or use of a Scheimpflug camera.¹⁷

The sequence of events leading to dry eye is mainly exacerbated by an unstable tear film. The phenomenon of local disruption of the tear film is known as tear film break-up. Previous studies have reported increased scatter due to tear film break-up and simultaneous exposure of the rough surface of the corneal epithelium.^{6,14} Recently, Himebaugh et al.¹⁴ reported the formation of scatter-producing microaberrations associated with tear film break-up, which are too fine to be resolved with a clinical Hartmann-Shack wavefront sensor.¹⁸ A recent study using a double-pass imaging technique reported an increase in ocular forward light scattering in dry eye.¹⁹ Although glare and associated light sensitivity, which might partly be attributed to forward light scattering, are part of the symptomatology of dry eye, little is known about backward light scattering in dry eye.

In this study, we quantified ocular forward light scattering and corneal backward light scattering in patients with dry eye

and explored the relationship between ocular surface regularity and light scattering in dry eyes.

METHODS

The study was designed as a prospective case-control study. The institutional review board of Osaka University Hospital approved this study, which adhered to the tenets of the Declaration of Helsinki. All patients provided informed consent after receiving an explanation of the nature and possible consequences of the study.

Patient Population

Thirty-five eyes in 35 female patients (mean age 49.6 ± 9.5 years; 23 eyes in 23 patients with Sjögren's syndrome and 12 eyes in 12 patients with keratoconjunctivitis sicca) with dry eye were enrolled. The diagnosis of dry eye was made using the following criteria²⁰: presence of dry eye symptoms, abnormal tear production as determined by Schirmer's test (≤ 5 mm after 5 minutes), abnormal tear film instability as determined by tear break-up time (BUT) (≤ 5 seconds), and the presence of conjunctival and corneal epithelial damage as evidenced by a fluorescein staining score of 3 or higher (out of 9) according to the van Bijsterveld method.²¹ The exclusion criteria were the following: any corneal scarring pathology, such as infections or dystrophies, any history of corneal or intraocular surgery, ocular trauma, permanent occlusion of the lacrimal puncta or a temporary occlusion caused by a punctal plug, meibomian gland dysfunction, and contact lens wear. Twenty eyes of 20 age-matched healthy female subjects (mean age 51.9 ± 7.2 years) with no ocular pathological features except refractive errors served as controls. All eyes in both groups had best-corrected distance visual acuity better than 20/20 and were deemed clear by slit-lamp examination.

Ocular Surface Examinations

Tear break-up time was measured using fluorescein and a metronome; the average of three consecutive BUT durations was calculated. Corneal fluorescein staining was evaluated using the National Eye Institute (NEI) scale of five corneal regions (central, superior, temporal, nasal, and inferior).²² The degree of staining in each region was graded from 0 to 3, according to the NEI/Industry Workshop method: no staining (0), mild staining (1), moderate staining (2), and severe staining (3). The scores of all five areas were summed to obtain a total score for each eye. Fluorescein staining of the nasal and temporal conjunctiva was scored from 0 to 3 in each eye using a blue-free barrier filter.²³ The sums of the fluorescein scores of the nasal and temporal conjunctivae were calculated for each eye. The 5-minute Schirmer's test was performed using sterile strips without anesthesia.

According to the presence of superficial punctate keratopathy (SPK) in the central corneal region, patients with dry eye were divided into two groups: one with dry eye and SPK in the central corneal region (cSPK) and the other with dry eye but without cSPK.

Measurements

Ocular forward light scattering was measured quantitatively using the C-Quant straylight meter (Oculus GmbH, Wetzlar, Germany), which uses the compensation comparison method to measure the level of intraocular straylight. The principles, technique, and reproducibility of this device have been described previously.²⁴⁻²⁷ Briefly, the tested eye was posi-

tioned at a minimal distance from the eyepiece, and the subjects performed a forced-choice comparison of two half-fields in the center of the visual field to determine which one flickered more strongly. A psychometric response curve was computed from the subject's responses. The amount of straylight was expressed as the logarithm of the straylight parameters ($\log[s]$); greater values indicate more straylight and more glare sensitivity. A reliability parameter in the straylight meter, specified as the expected standard deviation (ESD), can be designated that predicts the accuracy of an individual measurement. The quality (Q) of each measurement also can be evaluated. The measurement is considered reliable when ESD is less than 0.08 and Q is greater than 1.0.²⁶

Corneal backward light scattering was measured using the corneal densitometry analysis program of a Scheimpflug camera (Pentacam HR; Oculus GmbH). The principles, technique, and reproducibility of the device have been described previously.²⁸ Briefly, 25 images were obtained during a single scan to reconstruct a three-dimensional model of the entire cornea. The program automatically locates the corneal apex and analyzes the area around the apex, with a diameter of 12 mm. Output is expressed in grayscale units. Densitometry output is provided according to corneal depth into the anterior, middle, and posterior parts of the cornea. The anterior part corresponds to the anterior 120 μm , whereas the posterior part corresponds to the most posterior 60 μm of the cornea. The middle part is defined by subtracting the anterior and posterior parts from the total corneal thickness. The device also provides a densitometry output from the total cornea. Because we were specifically interested in exploring the relationship between corneal backward light scattering and cSPK, which corresponds to the central 6-mm diameter zone, anterior, middle, posterior, and total densitometry output from the central 2-mm diameter zone, and the annulus extension zone (i.e., the circle with 2-6-mm diameter) were analyzed.

Statistical Analysis

Data were analyzed using JMP version 9 statistical analysis software (SAS Institute, Cary, NC, USA). The Wilcoxon rank-sum test was used to analyze the clinical parameters between the two dry eye groups. Kruskal-Wallis one-way ANOVA for ranks was performed to compare ocular forward light scattering and corneal densitometry data among the three groups. The appropriate post hoc Dunnett's correction for multiple comparisons was used for these comparisons. Correlations were assessed with Spearman's rank-correlation coefficient. *P* values less than 0.05 were considered significant for all analyses.

RESULTS

The demographic and clinical data of the two dry eye groups and the normal eye group are presented in Table 1.

The ESD (a reliability parameter) and Q values (a quality parameter) of straylight measurements were 0.06 ± 0.01 and 1.54 ± 0.23 in the dry eye group and 0.06 ± 0.01 and 1.46 ± 0.25 in the normal group, respectively. Thus, the measurements were considered reliable.

Compared with normal eyes, ocular forward light scattering was significantly increased in both dry eye groups with and without cSPK, although no significant difference was detected between the two dry eye groups (Table 2).

Compared with dry eyes without cSPK and normal eyes, corneal backward light scattering of the central 2-mm zone and the surrounding 2- to 6-mm zone in the anterior part increased significantly in dry eyes with cSPK. Corneal backward light scattering of the central 2-mm zone and surrounding 2- to 6-

TABLE 1. Demographic and Clinical Data of the Three Groups

Parameter	Normal, <i>n</i> = 20	Dry Eye Without cSPK, <i>n</i> = 13	Dry Eye With cSPK, <i>n</i> = 22	<i>P</i> Value
Age, y	51.9 ± 7.2	50.7 ± 11.4	49.0 ± 8.4	0.282
Schirmer's test, mm	21.6 ± 7.2	2.5 ± 3.0	2.7 ± 5.3	0.285
BUT, s	7.9 ± 1.2	2.2 ± 1.0	1.6 ± 0.8	0.144
Corneal staining score	0.0 ± 0.0	3.2 ± 2.5	6.7 ± 3.4	0.003
Conjunctival staining score	0.2 ± 0.4	3.5 ± 2.3	4.1 ± 1.7	0.539

P values for comparisons between dry eye with and without cSPK. Data are expressed as the mean ± SD.

mm zone in the middle part were significantly increased in dry eyes with cSPK compared with normal eyes. No significant difference in corneal backward light scattering from the posterior part was observed among the groups. Compared with dry eyes without cSPK and normal eyes, corneal backward light scattering of the central 2-mm zone of the total cornea were significantly increased in dry eye with cSPK. A significant difference surrounding the 2- to 6-mm zone was found between dry eyes with cSPK and normal eyes (Table 2).

The correlations between cSPK score and ocular forward light scattering/corneal backward light scattering values are presented in Figures 1 and 2. Significant positive correlations were found between the cSPK score and corneal backward light scattering from the anterior part ($R = 0.600$, $P < 0.001$ for the central 2-mm zone; $R = 0.590$, $P < 0.001$ for the 2-6-mm zone). Significant positive correlations also were found between the cSPK score and corneal backward light scattering from the total cornea ($R = 0.546$, $P < 0.001$ for the central 2-mm zone; $R = 0.549$, $P < 0.001$ for the 2-6-mm zone). Less significant correlations also were found between the cSPK score and corneal backward light scattering from the middle part ($R = 0.422$, $P = 0.011$ for the central 2-mm zone; $R = 0.391$, $P = 0.020$ for 2-6-mm zone); however, no significant correlation was observed between the cSPK score and ocular forward light scattering (Fig. 2) or corneal backward light scattering from the posterior part (Fig. 1).

DISCUSSION

Our findings reveal a significant increase in ocular forward light scattering in both dry eyes with and without cSPK and increased corneal backward light scattering from the anterior corneal part in dry eyes with cSPK, compared with those in normal eyes. The severity of corneal epithelial damage in the central cornea of dry eyes correlated with corneal backward light scattering from the anterior or middle parts, as well as the

total cornea. We are unaware of any other studies that reported corneal backward light scattering in patients with dry eye.

Ní Dhubhghaill et al.²⁸ reported normal corneal densitometry values in a large number of healthy subjects using the same Scheimpflug device used in the current study. According to that study, corneal densitometry values in the anterior part were significantly greater than those in the middle or posterior parts. Our results from both normal eyes and dry eyes were consistent with the results of Ní Dhubhghaill et al.²⁸ Interestingly, mean corneal densitometry values in all parts measured in the current study were smaller than those reported in their study. Differences in populations (possibly due to racial differences) between the studies may have contributed to the difference in the corneal densitometry values. A future investigation of normal corneal densitometry values in a large number of healthy Asian subjects would be helpful to clarify this issue.

Our results showed a significant correlation between cSPK score and corneal backward light scattering from the anterior corneal part. Recent studies have investigated the morphological changes in dry eyes using confocal microscopy,²⁹⁻³⁶ and have shown a decreased density of corneal epithelial cells and irregular, patchy, opaque, and superficial epithelial cells. An increase in the density of inflammatory cells in the corneal epithelium of dry eyes also has been shown using confocal microscopy imaging.³⁴ Chen et al.³⁶ quantified the area of opaque superficial epithelial cells using confocal microscopy and found that the area of opaque cells in the corneal endothelium of dry eyes correlates with the corneal fluorescein score, blurred vision, and the videokeratographic surface regularity index. Although the cause of opaque cells remains unclear, it is speculated to occur because of increased production of cornified envelope precursor proteins³⁷ or because opaque cells represent dead or detaching epithelial cells. We assume that such changes as the consequences from ocular surface damage caused by mechanical and inflammatory phenomena could have contributed to the increased corneal

TABLE 2. Corneal Light Scattering Data

	Normal Eyes, <i>n</i> = 20	Dry Eye Without cSPK, <i>n</i> = 13	Dry Eye With cSPK, <i>n</i> = 22
Straylight values log(s)	1.09 (0.95-1.19)	1.24 (1.16, 1.38)*	1.33 (1.04, 1.47)*
Corneal densitometry			
Anterior, 0-2 mm	16.0 (15.4-16.6)	16.3 (15.9-17.5)	18.1 (17.4-20.5)* †
Anterior, 2-6 mm	15.1 (14.6-15.6)	15.8 (14.9-16.3)	17.2 (16.0-18.8)* †
Middle, 0-2 mm	11.1 (10.7-11.8)	11.5 (11.0-11.8)	12.1 (11.4-12.8)*
Middle, 2-6 mm	10.7 (10.3-11.0)	10.8 (10.5-11.2)	11.1 (10.8-12.2)*
Posterior, 0-2 mm	9.6 (9.0-9.9)	9.7 (9.4-10.1)	9.8 (9.6-10.7)
Posterior, 2-6 mm	9.1 (8.8-9.4)	9.3 (8.9, 9.6)	9.4 (9.0-10.2)
Total, 0-2 mm	12.4 (11.7-12.6)	12.6 (12.1-12.9)	12.8 (12.8-14.8)* †
Total, 2-6 mm	11.7 (11.3-11.9)	11.9 (11.6-12.3)	12.5 (12.0-13.8)*

Data are expressed as median ± interquartile range.

* $P < 0.05$ versus normal eyes.

† $P < 0.05$ versus dry eyes without cSPK.

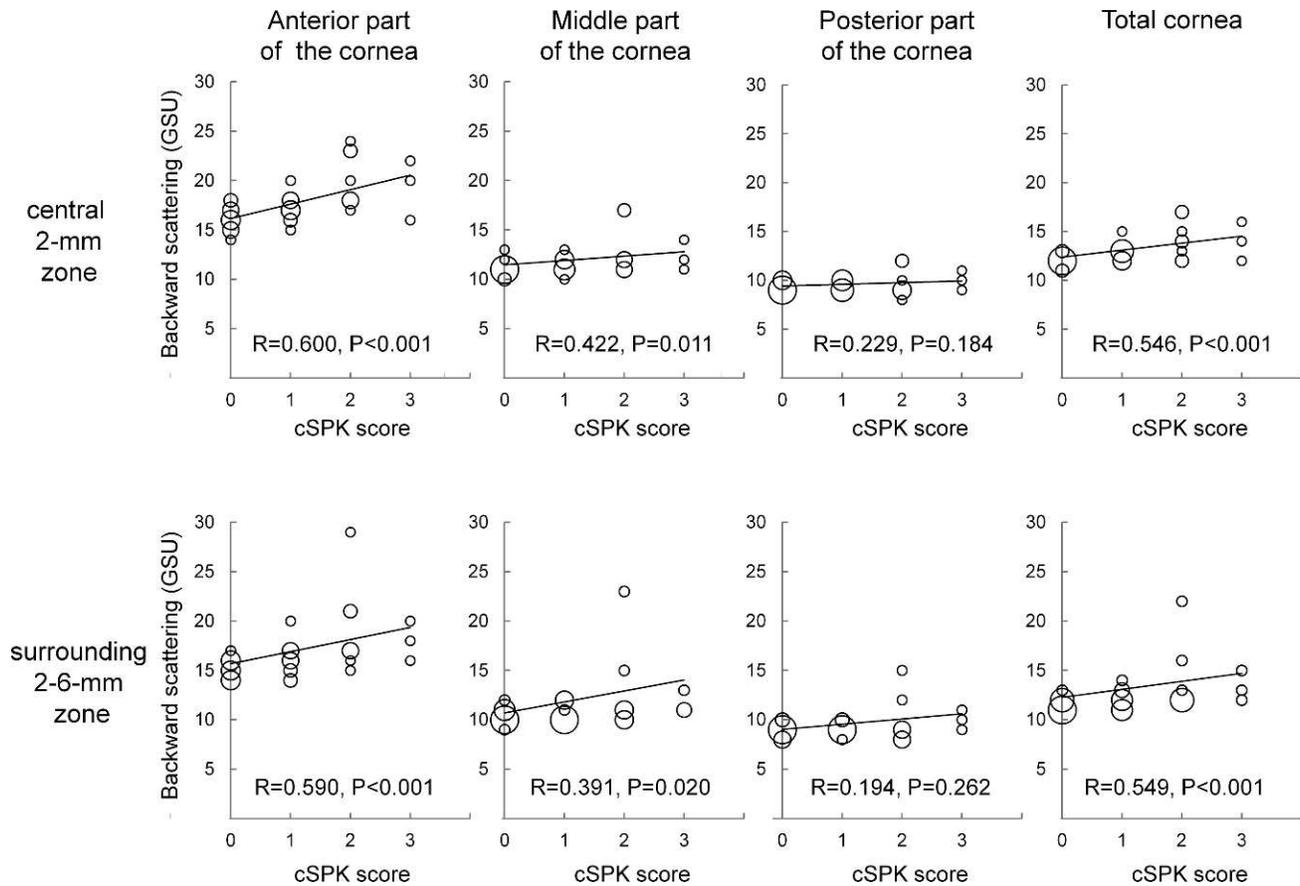


FIGURE 1. Correlation between cSPK score and corneal backward light scattering values. (First column, top and bottom) Corneal backward light scattering from the anterior part significantly correlated with cSPK ($R = 0.600$, $P < 0.001$ for the central 2-mm zone, $R = 0.590$, $P < 0.001$ for the 2-6-mm zone). (Second column, top and bottom) Less significant correlations were found between cSPK score and corneal backward light scattering from the middle part ($R = 0.422$, $P = 0.011$ for the central 2-mm zone, $R = 0.391$, $P = 0.020$ for the 2-6-mm zone). (Third column, top and bottom) No significant correlation was observed between cSPK score and corneal backward light scattering from the posterior part. (Fourth column, top and bottom) Corneal backward light scattering from the total cornea correlated significantly with cSPK ($R = 0.546$, $P < 0.001$ for the central 2-mm zone, $R = 0.549$, $P < 0.001$ for the 2-6-mm zone). GSU, scatter units. Backward scattering, corneal backward light scattering

backward light scattering from the anterior part in dry eyes of the present study.

Increased corneal backward light scattering from the middle part was found in dry eyes with cSPK, but no difference was observed between dry eyes without cSPK and normal eyes. A previous study on the characteristics of corneal backward light scattering in eyes that underwent post-Descemet's stripping automated endothelial keratoplasty reported that the reason for increased corneal backward light scattering from the host stroma might be ultrastructural changes in response to chronic endothelial dysfunction.³⁸ Considering that dry eye is a chronic disease of the tears and ocular surface, it may be caused by ultrastructural changes in response to chronic epithelial dysfunction. The presence of abnormal hyperreflective keratocytes in dry eye presumably induced by inflammatory mediators has been reported in confocal microscopy imaging studies.^{29,39} In the present study, the anterior corneal part was defined as the anterior 120 μm , and this part corresponds to both the epithelium and anterior stroma. The middle part corresponded to the middle to posterior stroma. Future study using both corneal densitometry and confocal microscopy would be helpful to clarify the relationship between morphological changes in each corneal layer and light scattering, and localize light scattering in dry eye.

Although the results obtained in this study showed statistically significant differences between groups, these

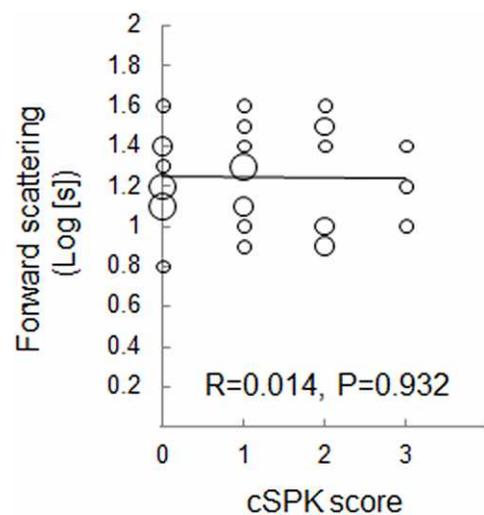


FIGURE 2. Correlation between cSPK score and ocular forward light scattering. No significant correlation was found between cSPK score and ocular forward light scattering.

differences were relatively small. Previous studies⁴⁰⁻⁴⁴ reported greater densitometry values in eyes with corneal clouding and corneal haze after corneal surgery, as well as during infection or various healing stages. In mild to moderate dry eyes, which accounted for most of the enrolled patients in the current study, corneal staining generally reveals punctate distribution, whereas eyes with corneal haze or scarring exhibit an expanse of pathological lesions, not punctate lesions. This may partly explain the small differences observed in this study. Also, in the current study, cSPK was graded on a scale from 0 to 3; however, quantitative SPK grading by area and density also is an option.⁴⁵

Greater backward light scattering from the anterior cornea in dry eye with cSPK may suggest the potential influence of disorders in the corneal epithelium on backward light scattering. So far, we are unaware of any other study that investigated backward light scattering in unoperated eyes with pathological abnormalities mainly related to the corneal epithelium (anterior part of the cornea). As the next step, the correlation of corneal backward light scattering with corneal epithelial disorders, such as corneal erosion or filamentary keratitis, needs to be clarified. Although a study addressing this issue is under way, it would help to clarify the relationship of corneal backward light scattering with its potential for degradation of the quality of the retinal image in dry eye and to validate corneal backward light scattering as a possible factor.

Because the tear film may disrupt quickly over areas of SPK in dry eye, we expected to find increased forward light scattering in dry eyes with cSPK. However, no significant difference was observed between the two dry eye groups, although ocular forward light scattering was significantly greater in these groups than in the control group. Diaz-Valle et al.¹⁹ investigated intraocular forward light scattering in patients with dry eye using a double-pass imaging technique and found a significant increase in intraocular forward light scattering after 20 seconds without blinking versus controls. According to that study, poor visual quality in dry eyes could be related to tear film instability reflected by increased light scattering, and the objective scatter index did not correlate with corneal staining score. We also found no correlation between cSPK score and ocular forward light scattering. From the point of tear film stability, one possible reason for the difference between ocular forward light scattering and corneal backward light scattering may be because of the difference in measurement techniques. Although corneal densitometry values can be obtained with a single scan using a Scheimpflug camera in a few seconds, measurements with a straylight meter require more time. Although subjects could blink freely during the straylight measurements, the subjects may have gazed to concentrate. As reported by Himebaugh et al.,¹⁴ this blink-suppressed condition in dry eye may induce tear film break-up and exposure of the rough corneal surface, thereby causing light-scattering aberrations in regions of tear film break-up. In contrast, we reported previously that the sequential pattern of total ocular HOAs has higher initial values and consistently higher values in dry eyes with cSPK, whereas that of dry eyes without cSPK show consistently lower total HOAs, similar to the pattern in normal eyes.¹¹ Sequential increases in ocular HOAs were not observed in either dry eye group. As discussed above, with regard to corneal backward light scattering, the difference in ocular forward light scattering between dry eyes and normal eyes appeared to be small. As variations in the noncataractous eyes have been reported,⁴⁶ the clinical relevance of potential relationships between ocular forward light scattering and tear film or other dry eye parameters remains to be examined. The relationships between ocular

forward light scattering and corneal backward light scattering are complex.^{38,47,48}

Because of the small sample size and the nonhomogeneous nature of the enrolled patients in the current study, the results of dry eyes with grade 3 cSPK were widely scattered, despite a small number of these patients. Therefore, further investigations regarding the correlation between light scattering and cSPK or SPK severity in a large number of patients with dry eye are warranted. Although we were specifically interested in exploring both ocular forward light scattering and corneal backward light scattering in dry eye, the relationship between subjective dry eye symptoms and light scattering would be a topic for a future study.

In conclusion, ocular forward light scattering and corneal backward light scattering from the anterior cornea were greater in dry eyes than in normal eyes. Superficial punctate keratopathy in the central corneal zone above the optical zone in dry eye is likely to contribute to increased corneal backward light scattering in the anterior part of the cornea.

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