Irregular Astigmatism and Higher-Order Aberrations in Eyes With Dry Eye Disease

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The tear film greatly influences ocular optics because it is the first refracting surface that light comes into contact with. This may seem obvious, but the influence of the tear film on optical quality and visual function has not been discussed in great detail in eyes with dry eye. This is likely because most dry eye patients have a good best-corrected visual acuity, with the exception of advanced or severe cases (e.g., Sjögren’s syndrome and Steven-Johnson syndrome). Visual acuity measurements have become the hallmark of visual function. Unfortunately, these conventional assessments do not detect all aspects of degraded visual function. In the early 1990s, Rieger first demonstrated the importance of the tear film in vision by comparing vision and static perimeter results in patients with dry eye. Thereafter, the effect of the tear film on contrast sensitivity has been the focus of investigations, as this subjective measurement more accurately reflects visual performance.

The development of refractive surgery marked a major turning point in ophthalmology. Successful refractive outcomes relied on understanding quantitative quality of vision (QoV) evaluations and not just conventional visual acuity testing results. As a result, remarkable advances in objective QoV assessments have been made, including the development of corneal topography systems and wavefront sensors. Notably, QoV assessments are also applicable to ophthalmology fields other than refractive surgery. Corneal topography systems and wavefront sensors are now widely used in clinical practice to objectively and quantitatively assess optical quality. These measurements revealed an increase in irregular astigmatism and have facilitated further study on how tear film behavior relates to QoV in dry eyes. Dry eye is a multifactorial disorder of the tear film and ocular surface that results in discomfort, visual disturbance, tear film instability, and, potentially, ocular surface damage. Therefore, advances in objectively assessing optical quality are of particular importance for better understanding and treating dry eye disease.

Recent Progress Around the World

Corneal Topographic Analyses

Corneal topographic analyses are used to detect corneal irregular astigmatism. Conventional Placido ring-based corneal topographers measure anterior corneal surface contours by analyzing reflected images of a ring projected onto the air-tear film interface. Therefore, this system is capable of detecting tear film-related changes in corneal topography. Several studies have indicated that fluctuations and irregularities in the tear film increase irregular astigmatism. Previous studies on eyes with dry eye have measured surface regularity index (SRI) and surface asymmetry index (SAI) to better understand local corneal variations. These studies showed that both SAI and SRI were higher in dry eyes than in healthy eyes. High-speed videokeratoscopy was also recently developed to document and assess dynamic corneal topography changes associated with precorneal tear film behavior.

Wavefront Sensing

Wavefront sensing measures the refractive status, including irregular astigmatism, of the eye’s whole optical system. The wavefront sensor detects and quantifies irregular astigmatism as higher-order aberrations (HOAs). Exploding interest in QoV and how it relates to wavefront analyses indicates the new trend of focusing on the tear film. Wavefront sensors are sensitive enough to objectively quantify increases in HOAs that occur with tear film fluctuations.

Wavefront analyses have utilized the same technologies and analysis methods as corneal topographic analyses. Sequential
corneal wavefront aberration measurements (not whole-eye HOAs) were made in and compared between normal and dry eyes.\textsuperscript{25,26} Additionally, several Japanese studies (fully described below) have examined how HOAs of the whole eye change in connection with postblink changes to tear film dynamics. These sequential wavefront measurements revealed that dynamic tear film changes affect postblink optical quality.\textsuperscript{27–31} Additionally, French researchers found that the progression index for corneal HOAs was correlated with subjective, patient-reported visual outcomes in subjects with dry eye.\textsuperscript{29} They also found that optical quality degradation in dry eyes is associated with visual impairment during driving.\textsuperscript{30} Furthermore, simultaneous evaluation of ocular HOAs and tear meniscus dimensions makes it possible to investigate the influence of real-time tear film changes, including tear volume, on optical quality.\textsuperscript{31}

**RECENT PROGRESS IN JAPAN**

**Corneal Topographic Analyses**

Attention to assessing corneal irregular astigmatism induced by tear film changes has increased around the world, including in Japan. Goto et al.\textsuperscript{32} reported an increase in SRI after sustained eye opening in dry eyes, but not in normal eyes. After this study was done, tear film stability analysis system (TSAS) software was developed for the TMS-2N corneal topography instrument (Tomey Technology, Nagoya, Japan). This new software gave the system the ability to capture serial corneal surface images once a second for 10 seconds. Using reverse-engineered Placido ring–based corneal topographic map calculations, the system was able to detect subtle tear film changes from mire ring distortions. This software program also allows tear breakup time (TMS-BUT), and the ratio of breakup area to the entire color-coded area (TMS-BUA), to be calculated from corneal topographic data. According to Goto et al.,\textsuperscript{35} TMS-BUT and TMS-BUA sensitivity were both significantly higher than conventional BUT sensitivity (measured with fluorescein tear film staining) in normal eyes. In a subsequent study, Goto et al.\textsuperscript{36} reported that laser in situ keratomileusis (LASIK) significantly decreased tear film stability in the early postoperative period. Furthermore, Kojima et al.\textsuperscript{35} used TSAS to measure tear film stability, regularity, and asymmetry indices (i.e., TSRI and TSAl, which were derived from SRI and SAI, respectively). They found that both TSRI and TSAl were significantly greater in dry eyes than in normal eyes (Fig. 1). Additionally, the insertion of punctal plugs to treat dry eye was associated with a significant decrease in both SRI and SAI.\textsuperscript{35}

**Wavefront Sensing**

Interest in wavefront analysis has been growing worldwide. Koh et al.\textsuperscript{37} quantified the optical impact of tear film breakup for the first time using a wavefront sensor from Japan. This study confirmed that physicians need to perform careful preoperative wavefront measurements before refractive surgery to avoid the effects of tear film breakup.

The introduction of sequential measurements of corneal wavefront aberration allowed the postblink changes in HOA to be quantified over time.\textsuperscript{25,26} This, in turn, led to a better understanding of how the tear film influences QoV. Koh and colleagues (Koh et al.,\textsuperscript{37–40} Mihashi et al.,\textsuperscript{41} and Hirohara et al.\textsuperscript{42}) specifically examined sequential ocular wavefront aberrations and the optical effect of tear film dynamics after blinking. They introduced the following quantitative indices that describe sequential HOA change over time: the total HOA fluctuation index (FI) and stability index (SI). Both FI and SI are useful in describing time-dependent HOA changes that cannot be detected with a single measurement.\textsuperscript{37} FI and SI measurements can now be performed in the clinical setting, because the Hartmann-Shack wavefront aberrometer developed in their study was used as the prototype for the commercially available KR-1W (Topcon Corp., Tokyo, Japan).

Wavefront analysis studies in Japan have played a significant role in understanding the mechanisms underlying visual disturbances associated with dry eye.\textsuperscript{4} Total ocular HOAs are believed to be stable between blinks in normal eyes (Fig. 2A), but evidence shows that, even in clinically normal subjects, HOAs can change dynamically after blinking.\textsuperscript{25,26} Subjects with a decreased tear film BUT and dry eye symptoms, but without ocular surface damage or tear deficiency, are designated as having “short BUT dry eye.” In these eyes, HOAs increase over time after blinking, and continue to increase during the 10-second measurement period, during which the subject does not blink (Fig. 2B).\textsuperscript{25} In contrast, subjects with “aqueous tear-deficient” dry eye showed high initial total ocular HOAs, and dry eyes with superficial punctate keratopathy (SPK) of the central...
cornea had even higher initial HOAs (Fig. 2C). Interestingly, dry eyes without SPK in the central corneal region had consistently lower total HOAs, which exhibited similar changes over time relative to those seen in normal eyes (Fig. 2 in Ref. 4). These findings were confirmed by Kaido et al., who reported that optical disturbances in the central optical zone of corneas with dry eye may affect visual performance. This is particularly true in short BUT dry eye, which often has an underestimated impact. In short BUT dry eye, patients often complain of severe dry eye symptoms, particularly ocular fatigue. Functional visual acuity and sequential wavefront measurements have helped physicians better understand the importance of treating short BUT dry eye.

Two unique topical pharmacologic agents for treating dry eye are commercially available in Japan. Diquafosol ophthalmic solution 3% (Diquas, ophthalmic solution 3%; Santen Pharmaceutical Co. Ltd, Osaka, Japan) stimulates aqueous and mucous secretions directly on the ocular surface. Rebamipide ophthalmic suspension 2% (Mucosta ophthalmic suspension UD2%; Otsuka Pharmaceutical, Co., Ltd, Tokyo, Japan) stimulates mucus secretion. The long-term use of diquafosol in eyes with aqueous-deficient dry eye has been shown to reduce HOAs, improve tear film stability, and decrease corneal epithelial damage. Diquafosol treatment also significantly improved ocular HOAs in eyes with short BUT dry eye. Rebamipide improved optical quality in the short BUT type; after treatment, a decrease was observed in the “progressive increase pattern” of the dynamic HOAs. Eyes with short BUT dry eye showed improvement in both optical quality and tear film BUT (measured with fluorescein).

**FUTURE DIRECTIONS**

Quantifying optical quality with corneal topographic and wavefront analyses has demonstrated that both tear film instability and ocular surface damage degrade QoV in dry eye patients. Moreover, continuous corneal topographic and wavefront measurements provide detailed information about how optical quality changes with precorneal tear film changes over time. Trends in the study of optical quality have largely

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**FIGURE 2.** Representative serial ocular higher-order aberration (HOA) color maps following a blink. The simulated retinal images of the 20/20 Landolt ring are shown for clinical reference. Wavefront data were obtained at a rate of one image per second. Maps from a normal eye (A) show that optical quality is stable throughout the measurement period. However, maps from an eye with short breakup time (BUT) dry eye (B) indicate an eye with initially normal optical quality that progressively deteriorates over time as tear film stability declines. This finding explains the complaint of fluctuating vision associated with blinking in patients with short TBUT dry eye. Maps from a dry eye with superficial punctate keratopathy (SPK) in the central corneal region (C) show that simulated retinal image quality is impaired immediately after blinking and during the entire measurement period. This explains the complaint of blurred vision by dry eye patients with SPK in the central corneal region. Reprinted with permission from Koh S. Mechanisms of visual disturbance in dry eye. Cornea. 2016;35:S83–S88. Copyright © 2016 Wolters Kluwer Health, Inc.
been similar between Japan and other countries. However, similar studies that have been performed outside of Japan are limited in that the vast majority were performed in the basic science setting, whereas studies performed in the clinical setting are essential for understanding disease pathophysiology, as well as for introducing novel diagnostic methods for clinical use.

Interestingly, optical quality has not been shown by objective assessment to be correlated with subjective visual dry eye symptoms. Further investigation of this relationship is required. Blinking plays an important role in providing the smooth optical surface of the tear film; however, there are variations in blinking that arise from intrinsic and environmental factors. The effects of variations in blinking (e.g., left-eye-right eye variations, longitudinal variations between examinations, and variations throughout the course of the day) on the measurement of optical quality should be investigated in further studies. The evolution of corneal topographers and wavefront sensors may enable the assessment of optical quality in a simple and accurate fashion in situations that simulate the activities of daily life.

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