Relationship of Corneal Pain Sensitivity With Dry Eye Symptoms in Dry Eye With Short Tear Break-Up Time

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Purpose. The purpose of this prospective comparative study was to investigate corneal sensitivity in subjects with unstable tear film, with and without dry eye (DE) symptoms.

Methods. Forty-one eyes of 41 volunteers (mean age: 45.1 ± 9.4 years; age range, 23–57 years), with normal tear function and ocular surface except for tear stability, were studied. The eyes were divided into two groups depending on the presence or absence of DE symptoms: 21 eyes with DE symptoms (symptomatic group); and 20 eyes without DE symptoms (asymptomatic group). Three types of corneal sensitivity values were measured using a Cochet-Bonnet esthesiometer: the sensitivity for perception of touch (S-touch), the sensitivity for blinking (S-blink), and the sensitivity for pain (S-pain).

Results. Mean S-blink and S-pain were significantly higher in the symptomatic group than in the asymptomatic group ($P < 0.05$), whereas there was no significant difference in mean S-touch between these groups ($P > 0.05$).

Conclusions. Corneal sensitivity for blinking and pain evoked by increased stimuli was higher in the symptomatic group (subjects with short break-up time DE) compared with subjects who have no DE symptoms despite decreased tear stability. The presence of both tear instability and hyperesthesia, rather than tear instability alone, may contribute to DE pathogenesis.

Keywords: corneal sensitivity, dry eye, hyperesthesia, tear break-up time, tear film

The tear film is an interface between the eye and the outside world, maintaining the health and function of the ocular surface. It protects the optical surface against dryness and maintains corneal smoothness under conditions of environmental stress. Blinking plays an important role in the wettability of the ocular surface.[1] Disruption of the tear film between blinks results in reduced wettability and eventually causes dry eye (DE).

Short tear break-up time (BUT) DE is characterized by tear film instability and the presence of DE symptoms.[2,3] Although short-BUT DE leads to severe DE symptoms similar to aqueous tear-deficient DE,[2,4] it is sometimes regarded as a mild or borderline case of DE because there is little or no corneal damage. This type of DE has shown high prevalence among office workers in recent decades, rising in parallel with the diffusion of electronic devices in our highly technological and information-oriented society.[5–7]

On the other hand, we often encounter people who have a decreased BUT value but no DE symptoms, suggesting that a decreased BUT value alone is not sufficient to induce subjective DE symptoms. In fact, several reports show a discrepancy between subjectively reported DE symptoms and objectively measured clinical signs.[8–11] What, in addition to tear stability, causes the provocation of DE symptoms in short-BUT DE?

Rosenthal et al.[12,13] described the concept of the corneal pain system in the context of neuropathic pain associated with DE disease. We hypothesized that DE symptoms might be provoked in cases featuring alteration of corneal sensitivity in addition to tear instability. In this study, we investigated corneal sensitivity in subjects with unstable tear film, with and without DE symptoms.

Methods

Participants

We studied 41 eyes of 41 volunteers seen at Shinanozaka Clinic and Wada Eye Clinic (12 men, 29 women; mean age: 45.1 ± 9.4 years; age range, 23–57 years), with normal tear function and ocular surface except for tear stability (specifically, BUT ≤5 seconds; Schirmer test >5 mm; and keratoconjunctival vital staining score <3 points). Eyes were divided into two groups depending on the presence or absence of DE symptoms: the symptomatic group comprised 21 eyes of 21 subjects with DE symptoms (3 men, 18 women; mean age: 45.7 ± 8.5 years; age range, 28–57 years), and the asymptomatic group comprised 20 eyes of 20 subjects without DE symptoms (9 men, 11 women; mean age: 43.5 ± 9.5 years; age range, 23–57 years). When both eyes were affected, the right eye was studied. To avoid bias caused by age-related decrease in corneal sensitivity, we recruited only subjects younger than 60 years. Subjects were excluded from the study if they had a history of ocular trauma, ophthalmic surgery, ophthalmic diseases other than DE, contact lens use, or daily ophthalmic solution use.

This research followed the Tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after

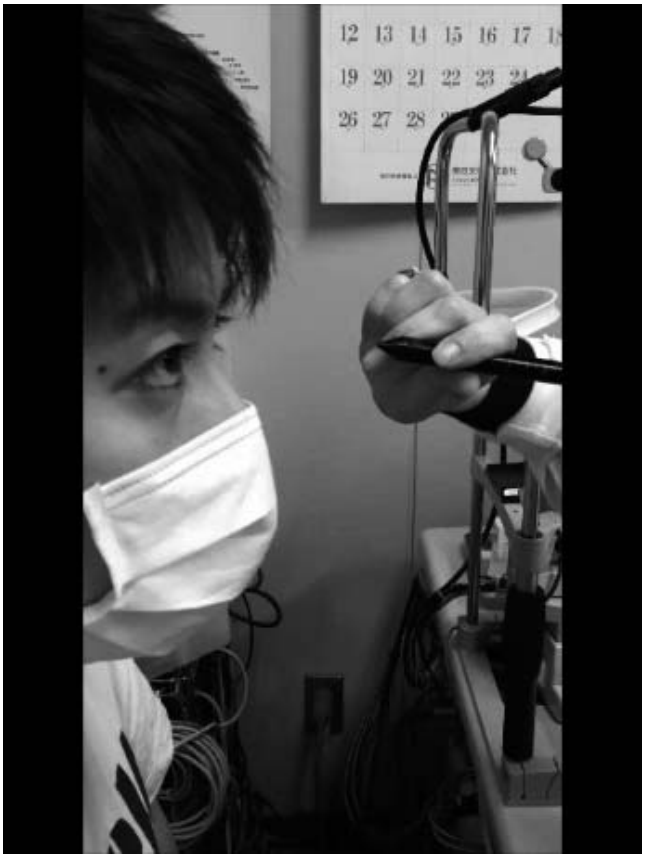

FIGURE 1. Corneal sensitivity measurement using a Cochet-Bonnet esthesiometer. The thread was pressed into the central cornea at a perpendicular angle, with the tester's arm held steady via propping on the slit-lamp instrument to allow good stimulus repeatability.

explanation of the nature and possible consequences of the study. Ethics committee approval for the examination procedures and study protocol was obtained from the institutional review board of Shinanozaka Clinic, Tokyo.

Questionnaire

We administered a DE questionnaire widely used in Japan, including 12 questions pertaining to the diagnostic symptoms of DE disease.[2] Possible answers to questions regarding symptoms included "constantly" (3 points), "often" (2 points), "sometimes" (1 point), and "never" (0 points). Response to more than 1 of the 12 questions with "constantly" or "often" was considered to indicate the presence of subjective DE symptoms. On the other hand, only subjects who responded to all 12 questions with "never" were assigned to the asymptomatic group. Information on age and sex was also obtained.

Dry Eye Examinations

Dry eye examinations included conjunctival and corneal vital staining with lissamine green and fluorescein, BUT measurement, and Schirmer test without topical anesthesia. Tear stability was assessed by standard BUT measurement. Keratoconjunctival epithelial damage was evaluated after BUT measurement. Two microliters of preservative-free 1% lissamine green and 1% sodium fluorescein was separately instilled into the conjunctival sac by micropipette. Overall epithelial damage was scored on a scale of 0 to 9 points.[14] To evaluate tear quantity, the Schirmer test was administered after completion of all other examinations, using a sterilized Schirmer strip (Whatman No. 41; Showa, Tokyo, Japan).

TABLE 1. Tear Function Profile in the Symptomatic and Asymptomatic Groups

	Short BUT Dry Eye Group, 21 Eyes	Control Group, 20 Eyes
BUT, s	3.4 ± 1.0	2.6 ± 1.8
ST value, mm	17.7 ± 11.3	13.5 ± 7.2
VS score, points	0.4 ± 0.6	0.05 ± 0.2

ST, Schirmer test; VS, keratoconjunctival vital staining.

Corneal Sensitivity

Corneal sensitivity was measured with a Cochet-Bonnet esthesiometer. We modified the measurement method of the esthesiometer so as to quantitate three types of corneal sensation by increasing the stimuli. The maximal length at which the subject responded to stimuli represented the sensitivity for touch (S-touch). As we retracted the esthesiometer thread incrementally, the length at which a blink was induced (after counseling the subject to refrain from blinking for as long as possible) represented the sensitivity for blinking (S-blink), and the length at which the subject felt pain represented the sensitivity for pain (S-pain). After receiving an explanation of the testing method, subjects underwent the corneal sensitivity test while in a sitting position and looking straight ahead. The nylon monofilament was first extended to its full length of 6.0 cm, corresponding to maximum corneal sensitivity. The thread was pressed against the central cornea at a perpendicular angle, and the thread length retracted in 1.0-cm increments from a length of 6.0 cm to 1.0 cm, then in 0.5-cm increments from a length of 1.0 cm onward (Fig. 1).

To evaluate stimulus repeatability, corneal sensitivity was measured twice in 10 asymptomatic subjects who consented to undergo an additional corneal sensitivity test on another day.

Statistical Analysis

For subjects undergoing two corneal sensitivity tests, values from the first and second measurements of S-touch, S-blink, and S-pain were compared using a paired *t*-test. A Student's *t*-test was used to compare corneal sensitivity (S-touch, S-blink, and S-pain) between the symptomatic and asymptomatic groups. The relation between corneal sensitivity and DE parameters was analyzed by Pearson's correlation analysis. SPSS software (Version 17.0J for Windows; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. A P value of less than 0.05 was considered statistically significant.

RESULTS

Tear Function Assessment

The tear functions of symptomatic and asymptomatic groups are shown in Table 1. No significant differences in tear function were observed.

Dry Eye Symptoms

Figure 2 shows the frequency score of each DE symptom in the symptomatic group. "Ocular fatigue" and "uncomfortable sensation" were the most prevalent symptoms. None of the DE symptoms was observed in the asymptomatic group, indicating accurate selection of subjects.

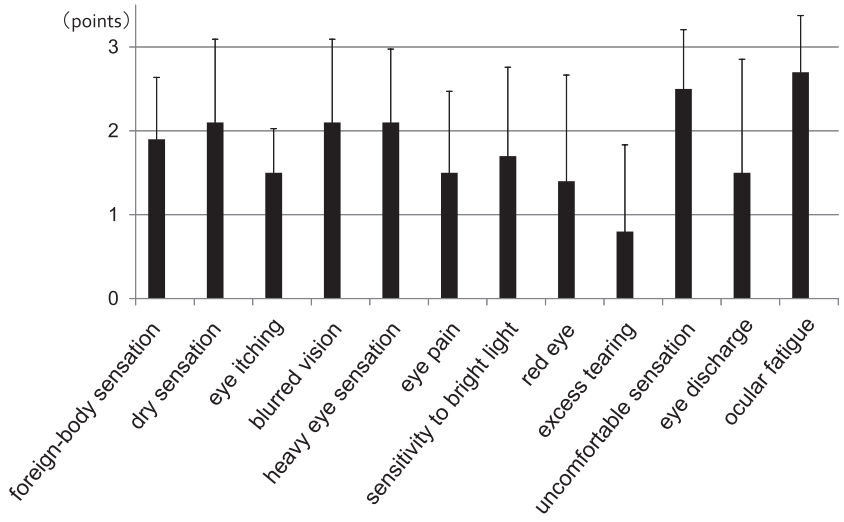

Figure 2. Frequency scores of DE symptoms in the short-BUT DE group. Subjects in the asymptomatic group had frequency scores of 0 points for each DE symptom. sBUTDE, short break-up time dry eye.

Corneal Sensitivity

There were no significant differences between the first and the second measurements of S-touch, S-blink, and S-pain (S-touch: 6.0 ± 0 and 5.8 ± 0.4, respectively; S-blink: 1.4 ± 1.1 and 1.2 ± 0.4, respectively; S-pain: 1.2 ± 0.9 and 1.0 ± 0.2, respectively; $P > 0.05$ for all). Thus, the modified corneal sensitivity test was consistent and repeatable.

The S-blink and S-pain were induced in all subjects. Figures 3a–c show the corneal sensitivity for S-touch, S-blink, and S-pain in each group. Although the difference in mean S-touch was not statistically significant between the symptomatic and asymptomatic groups ($P > 0.05$), S-blink and S-pain were significantly higher in the symptomatic group compared with the asymptomatic group ($P < 0.05$).

Table 2 shows the correlation between corneal sensitivity and DE parameters (total scores of DE symptoms, BUT values, vital staining scores, and Schirmer values).

Discussion

Pain can be categorized into three types based on pathophysiology: nociceptive, neuropathic, and psychogenic.[15] Nociceptive pain results from neural pathway activity in response to actual tissue damage or potentially tissue-damaging stimuli,[16] and may be an essential defense mechanism. On the other hand, neuropathic pain is defined as pain resulting from injury to or dysfunction of the somatosensory system.[17] It is associated with abnormal sensations from normally nonpainful stimuli. Psychogenic pain is a pain disorder attributed to psychological factors such as mental or emotional problems.[18]

The corneal sensory nerve is composed of A-delta fibers and C-fibers, which are axonal fibers that terminate as free nerve endings, forming nociceptors.[19,20] The A-delta fibers, which are myelinated and send impulses faster than unmyelinated C-fibers, are associated with acute pain and therefore contribute to the detection of noxious stimuli. The C-fibers are polymodal

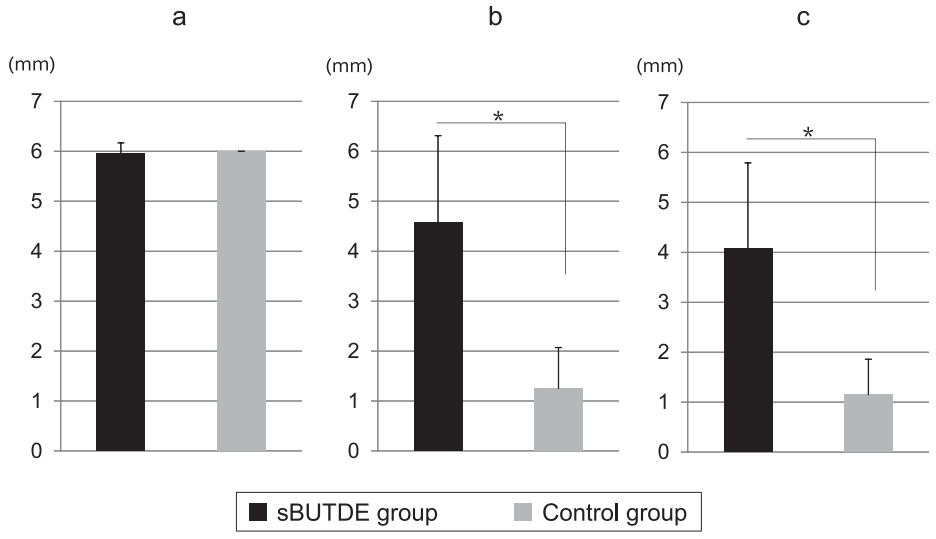

Figure 3. Corneal sensitivity scores in the symptomatic and asymptomatic groups. (**a**) S-touch, the sensitivity at which the subject perceives touch. (**b**) S-blink, the sensitivity at which blinking is induced. (**c**) S-pain, the sensitivity at which the subject feels pain.

Table 2. Correlation Between Corneal Sensitivity and DE Parameters

	Corneal Sensitivity		
	S-Touch	S-Blink	S-Pain
	Pearson's CC		
Total scores of DE symptoms	−0.18	0.70*	0.69*
BUT	−0.17	0.21	0.21
VS score	−0.26	0.13	0.10
ST value	−0.26	0.13	0.10

CC, correlation coefficient.
* $P < 0.05$.

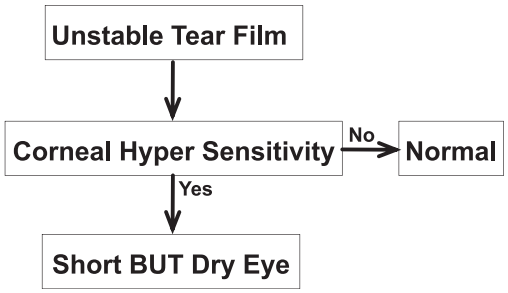

Figure 4. Relationship between DE provocation and corneal sensitivity.

nerves, and respond to more intense stimuli, such as thermal, mechanical, or chemical stimuli; these fibers account for the slow, but deeper pain that is spread out over an unspecific area. The C-fibers constitute approximately 70% of the total nerves in the cornea.[21] Several studies have demonstrated reduction of corneal sensitivity, which may be correlated with a low density of subbasal nerves, in patients with neurotrophic keratopathy,[22] herpes simplex keratitis,[23] and DE with primary and secondary Sjögren's syndrome.[24,25] In this study, there was no difference in the corneal sensitivity to touch between symptomatic and asymptomatic subjects with decreased BUT values, suggesting the absence of loss of corneal sensory nerves.

Corneal sensitivity for blinking and pain was higher in subjects who had both DE symptoms and decreased BUT (subjects with short-BUT–type DE) compared with asymptomatic subjects who had decreased BUT values, suggesting corneal hyperesthesia in short-BUT DE (Fig. 4). Situ et al.[26] assessed corneal sensitivity in subjects with and without DE symptoms, and showed ocular surface hyperesthesia in the symptomatic group. We observed similar results in short-BUT DE. We propose three types of mechanisms for high corneal pain sensitivity. One possible cause for neuropathic pain is the activation of C-fibers by neurotransmitters. The C-fibers interact with the process of inflammation and neurotransmitter release; histochemical studies have revealed the presence of various neurotransmitters, including substance P, calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal peptide, galanin, methionine-enkephalin, catecholamines, and acetylcholine, in the cornea.[27] Hypersensitivity may result when nerve endings morbidly exhibit spontaneous activity in response to inflammatory mediators, or become sensitized even in the absence of morphologic changes. In fact, Liu et al.[28] denoted the relation between hyperosmolarity and tear instability. They demonstrated that tear hyperosmolarity may transiently spike during tear instability, resulting in corneal inflammation and stimulation of sensory neurons.

Neuropathic pain may also be due to abnormal morphologic changes. Dry eye symptoms are known to develop after refractive surgery as a result of damage to corneal nerve fibers, which accordingly alters corneal sensitivity.[29–33] Tear condition after refractive surgery, however, may not be related to the development of DE symptoms.[30] Belmonte et al.[34,35] suggested that DE symptoms after refractive surgery may be attributed to the activation of sensory nerves at the ocular surface. They inferred that the regeneration of injured nerve fibers after refractive surgery gives rise to aberrant firing of nerve impulses, both spontaneous and stimulus-evoked.[36] In other words, denervation-induced regeneration and dysesthesia may be related to DE symptoms, independent of tear deficiency. In DE conditions, excess stimulation of nociceptive pathways due to lack of a protective tear film on the ocular surface may result in aberrant nerve regeneration, causing spontaneous firing and peripheral sensitization, and consequently, inducing DE symptoms (i.e., short-BUT DE). Rosenthal[37] showed the presence of morphologic changes, such as beadings and tortuosity, in the subbasal nerve fiber bundles and increased numbers of dendritic cells in a patient with severe subjective DE symptoms, despite the absence of decreased tear volume and corneal damage. When unstable tear film has little involvement of the corneal sensory nerve fibers, abnormal sensitivity is not evoked, resulting in no DE symptoms (i.e., nondry eye). According to this concept, asymptomatic subjects with unstable tear film may be categorized in the preclinical stage of short-BUT DE. Early prophylactic treatment may be recommended in this stage to reduce damage of sensory nerves.

Psychogenic pain can also play a role in the provocation of short-BUT DE symptoms. Short-BUT DE is often observed in office workers performing large amounts of video display terminal work. Work-related stress, emotional instability, or various mental disorders are potential causes for pain disorders.[38]

Quantitative methods for the measurement of corneal sensitivity include the handheld Cochet-Bonnet esthesiometer and the noncontact corneal esthesiometer. Tagawa et al. (unpublished data, 67th Annual Congress of Japan Clinical Ophthalmology, 2013, Kanagawa, Japan) reported the measurement of corneal sensitivity to pain using the Cochet-Bonnet; the pain sensitivity was decreased in DE patients, and improved after treatment. We modified the measurement method so as to quantitate three types of sensitivity: S-touch, S-blink, and S-pain. Either the specificity theory of pain or the intensity theory[39] can be applied to infer the differences between S-touch and S-blink. According to the specificity theory, different types of corneal sensory nerve fibers may mediate depending on different qualities of touch. The S-touch may be elicited when minimal threshold corneal spots are activated, whereas S-blink may be elicited when different threshold spots, which respond to a little stronger stimuli, are activated. In contrast, the intensity theory explains that each tactile nerve fiber can evoke distinct qualities of sensation of touch depending on the intensity of stimulation, and excessive stimulation may evoke a blink reflex. The blink reflex is elicited by stimulation of the cornea by touch and/or alteration of extracellular osmolality on the ocular surface,[40] so as to protect the cornea from aggravation by foreign bodies. We defined S-blink as the sensitivity at which a blink was induced (after counseling the subject to refrain from blinking for as long as possible). The S-blink as assessed in our study may be ambiguous when the stimulus is minimal. Adjustment of methods to more precisely measure the threshold of the blink reflex may be necessary.

There are a couple of limitations in this study. One is that we used a Cochet-Bonnet esthesiometer, which stimulates only the mechanosensitive nerve fibers; however, the cornea is also

known to possess polymodal nociceptors and cold receptors.[41] The Cooperative Research Centre for Eye Research and Technology (CRCERT)-Belmonte esthesiometer, a noncontact esthesiometer with superior stimulus repeatability, permits the application of controlled mechanical pulses, irritant chemical stimuli, and pulses of cold and hot air to specific areas of the ocular surface.[42,43] Assessment using a Belmonte esthesiometer may therefore have been preferable. Another limitation is that we did not assess the tear composition in terms of the presence of inflammatory products, tear osmolality, nerve morphologic changes, and psychosomatic factors, such as work-related stress, emotional problems, and mental disorders. We would like to conduct further research to investigate the relationship between alteration of corneal nerve fibers and superficial epithelial cells, and corneal sensitivity in short-BUT DE.

In conclusion, we revealed that corneal sensitivity for blinking and pain are increased in subjects with short-BUT DE compared with subjects who have no DE symptoms despite decreased tear stability. The presence of both tear instability and hyperesthesia may contribute to DE symptom provocation. Although the Cochet-Bonnet esthesiometer has some limitations, it can be used to assess several types of corneal sensitivity by modifying the measurement method.

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