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Original Research

Corneal hyperalgesia in patients with short tear film break-up time dry eye

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ABSTRACT

Purpose: To evaluate corneal tactile and pain sensations in patients with short tear film break-up time dry eye (sBUT DE).

Methods: This study enrolled 60 patients with sBUT DE and 46 healthy volunteers from Japan. We evaluated corneal tactile and pain sensations using a modified method with the Cochet-Bonnet corneal esthesiometer.

Results: Patients with sBUT DE had higher corneal pain sensitivity (26.3 ± 23.1 mm) than healthy subjects (6.9 ± 16.4 mm), but similar corneal tactile sensation (52.0 ± 15.5 mm and 52.9 ± 14.9 mm, respectively). In patients with sBUT DE and corneal hyperalgesia (n = 22, 36.7%), defined as a pain sensitivity ≥40 mm (i.e., the cutoff value at the 95th percentile of corneal pain sensitivity in healthy subjects), a strong significant correlation was found between the subjective pain score and objective corneal pain sensation (R = 0.79). However, for the entire cohort, we found a weak positive correlation between the subjective pain score and objective corneal pain sensation.

Conclusions: Patients with sBUT DE were hypersensitive to corneal pain, which suggested that corneal hyperalgesia partly accounted for subjective symptoms in patients with sBUT DE.

1. Introduction

Dry eye disease (DED) is a multifactorial disease classified into two clinical categories: aqueous tear-deficient and evaporative types [1]. Short tear film break-up time dry eye (sBUT DE), a subcategory of evaporative DED, is defined by a short tear break-up time (BUT < 5 s), a normal Schirmer test (> 5 mm), and few epithelial lesions [2,3]. To date, tear film instability on the ocular surface is thought to be one of the core pathological mechanisms of DED [1]. It has also been reported that subjective symptoms were dissociated from objective findings in DED, particularly in sBUT DE [2,3].

Corneal tactile sensitivity was reported to be reduced in patients with either aqueous tear-deficient DE [4] or non-Sjogren DE [5]. On the other hand, corneal tactile sensitivity is not necessarily reduced in all types of DE [6]. To our knowledge, few studies have described corneal sensation in sBUT DE, and only a few studies have reported an increase in corneal pain sensitivity in patients with DE [7,8].

The corneal nervous system comprises somatosensory nerves that arise from the first branch of the trigeminal nerve. These nerves are responsible for corneal tactile and pain sensations [9], and dysfunction of these nerves causes corneal diseases. Alterations in the corneal nerves are reportedly associated with the pathogenesis of ocular surface diseases [10,11,12]. Therefore, it is possible that the dissociation between subjective symptoms and objective findings might be related to alterations in trigeminal nerve function in patients with sBUT DE.

In the current study, we investigated the correlation between pain sensation and subjective symptoms in patients with sBUT DE by evaluating corneal pain sensation with a Cochet-Bonnet corneal esthesiometer.

2. Methods

2.1. Participants

This study included 60 Japanese patients with sBUT DE (18 men and 42 women; mean age, 63.8 ± 15.8, range: 20–93 years) and 46 healthy volunteers (11 men and 35 women; mean age, 61.1 ± 17.7, range: 22–94 years). All participants were followed at the Health Sciences University of Hokkaido General Hospital and Hokkaido University Hospital from September 2012 to March 2017 (Table 1). The study was approved by the Ethics Committee of the Health Sciences University of Hokkaido and Hokkaido University Hospital (IRB

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Table 1
Demographics of patients with sBUT DE (n = 60) and healthy subjects (n = 46).

Demographics	sBUT DE	Controls	P value
Gender (Male: Female)	18:42	11:35	
Age, mean ± SD	63.8 ± 15.8	61.1 ± 17.7	0.43

sBUT DE: short tear film break-up time dry eye.

Table 2
Objective findings and subjective symptoms at baseline for patients with sBUT DE (n = 60) and healthy subjects (n = 46).

Dry eye clinical findings	sBUT DE	Controls	P value
SPK score	0.8 ± 1.1	0.5 ± 1.0 (n = 46)	0.12
BUT (s)	3.1 ± 1.9	6.3 ± 2.5** (n = 24)	< 0.01
Schirmer (mm)	11.1 ± 8.9	13.0 ± 7.8 (n = 24)	0.49
Subjective symptom scores			
Foreign body sensation			1.8 ± 1.3
Fatigue			2.5 ± 1.3
Dryness			2.4 ± 1.3
Pain			1.9 ± 1.3
Difficulty in opening eyelids			1.1 ± 1.2
Uncomfortable feelings in the morning			1.1 ± 1.3
Blurred vision			1.7 ± 1.4
Total			12.5 ± 5.8

Values represent the mean ± SD; sBUT DE: short tear film break-up time dry eye; SPK: superficial punctate keratitis; Schirmer: Schirmer test; **p < 0.01.

#2012–007 and #014–0146). The tenets of the Declaration of Helsinki were followed, and informed consent was obtained from all subjects after they received an explanation of the nature and possible consequences of the study. All patients with sBUT DE had dry eye symptoms, BUT ≤5 s, Schirmer test > 5 mm, with or without faint corneal–conjunctival staining with fluorescein (defined as 3 or less with the van Bijsterveld system) [3,13].

Patients were recruited from both the Health Sciences University of Hokkaido General Hospital and Hokkaido University Hospital. All patients made regular visits. Healthy subjects without dry eye symptoms and with scores of zero on the questionnaire were enrolled as controls. We excluded individuals that used ocular medications, except for DE eye drops; wore contact lenses; had undergone refractive surgery; had had cataract surgery within the last 12 months; had undergone any past glaucoma or retinal surgery; or had a systemic disease, such as human immunodeficiency virus infection, rheumatoid arthritis, and other autoimmune diseases.

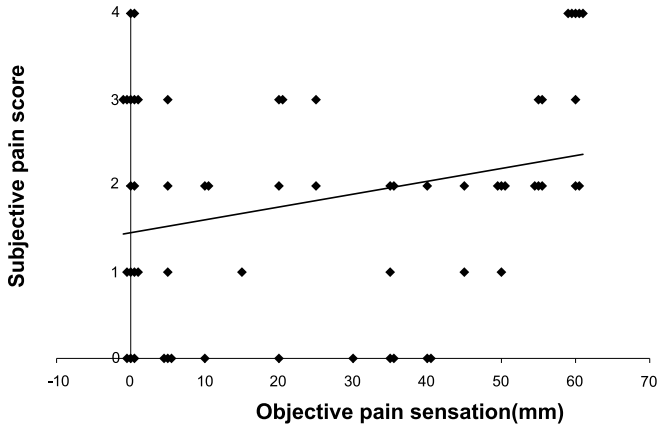

Fig. 2. Correlation between subjective pain score and objective pain sensation in patients with sBUT DE.
The correlation analysis shows a significant association between the subjective symptom of pain and the objective corneal pain sensation measurement (R = 0.24, *p < 0.05, n = 60).

2.2. Questionnaire

Subjective symptoms were assessed with 7 questions that asked about the frequency of foreign body sensations, eye fatigue, dryness, pain, difficulty in opening the eyelids, uncomfortable feelings in the morning, and blurred vision. This questionnaire was a modified version of standardized Dry Eye-related Quality of life Score (DEQS) [14]. Participants responded to questions on a scale of 0–4 points (never: 0, seldom: 1, often: 2, usually: 3, always: 4). The total subjective symptom score was defined as the sum of the responses to all 7 questions. Subjective symptoms, including eye fatigue, dryness, pain, foreign body sensation, and blurred vision, were severe in the sBUT DE patients (Table 2).

2.3. Dry eye examinations

After obtaining informed consent, we assessed objective findings in patients with sBUT DE and healthy subjects with the superficial punctate keratitis (SPK) score, the BUT score, and the Schirmer I test. First, tear stability was assessed with the standard BUT measurement. After the BUT measurement, keratoconjunctival epithelial damage was evaluated with fluorescein dye (SPK). Epithelial damage in the cornea and conjunctiva was scored on a scale of 0–9 points, as described previously (van Bijsterveld system) [13]. For all subjects, 10 min after the BUT and SPK examinations, we tested corneal tactile and pain sensation. Then, after another 10 min, the Schirmer I test was performed.

All patients received DE examinations. All healthy controls received

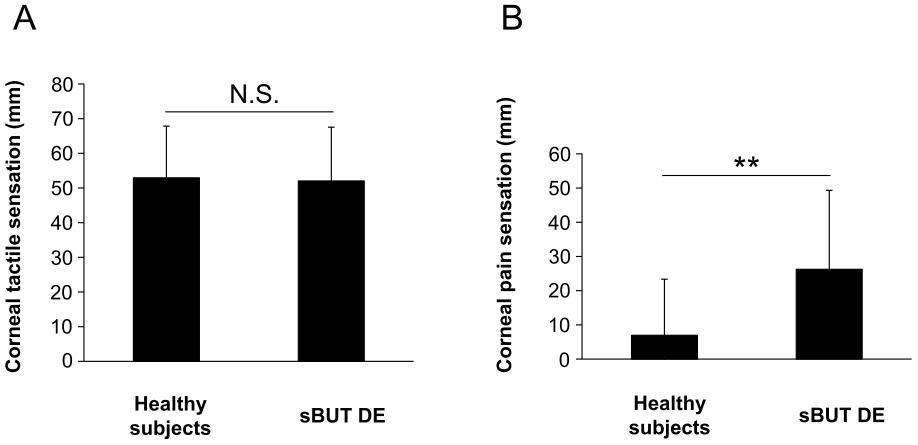

Fig. 1. Corneal tactile and pain sensations.
(A)Corneal tactile and (B) pain sensations in healthy subjects and patients with sBUT DE. Corneal tactile sensation in patients with sBUT DE (n = 60) was almost identical to that in healthy subjects (n = 46, p = 0.60). However, corneal pain sensation was significantly more sensitive in patients with sBUT DE than in healthy subjects (**p < 0.01).

Table 3A
Correlations between corneal sensation and DE metrics for all patients with sBUT DE (n = 60).

	Subjective DE symptoms							
	Foreign body sensation	Fatigue	Dryness	Pain	Difficulty in opening eyelids	Uncomfortable feelings in the morning	Blurred vision	Total
Tactile	0.07	−0.08	0.17	0.01	−0.08	−0.01	0.14	0.05
Pain	0.07	0.02	0.07	0.24*	0.08	0.20	0.19	0.15

	SPK	BUT	Schirmer
Tactile	0.13	0.00	−0.08
Pain	0.09	−0.10	0.16

sBUT DE: short tear film break-up time dry eye; SPK: superficial punctate keratitis; Schirmer: Schirmer test; *p < 0.05.

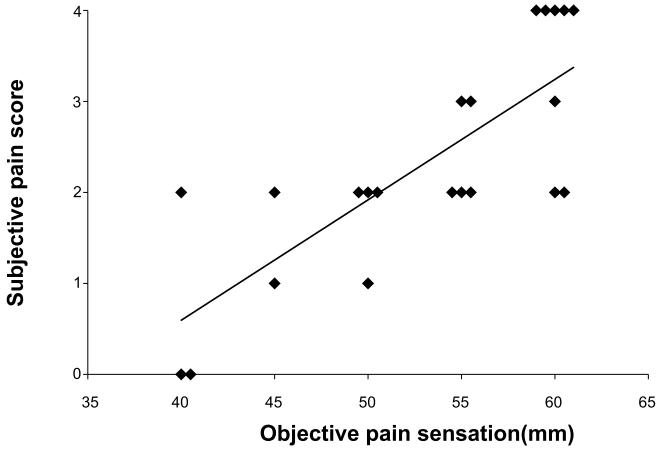

Fig. 3. Correlation between subjective pain score and objective pain sensation in patients with sBUT DE and corneal hyperalgesia.
The correlation analysis shows a strong, significant correlation between the subjective symptom of pain and the objective corneal pain sensation measurement in 22 patients with sBUT DE that exhibited corneal hyperalgesia (R = 0.79, **p < 0.01).

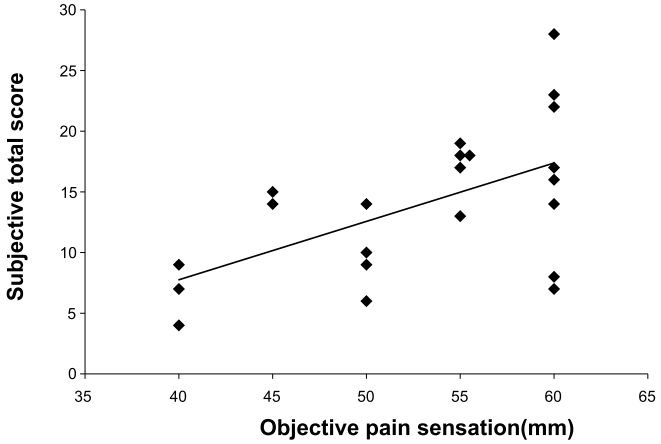

Fig. 4. Correlation between the total subjective score and objective pain sensation in patients with sBUT DE and corneal hyperalgesia.
The total subjective symptoms score was positively correlated with the objective corneal pain sensation measurement in 22 patients with sBUT DE that exhibited corneal hyperalgesia (R = 0.52, *p < 0.05)

SPK scores, and 24 of 46 healthy subjects received the BUT measurement and the Schirmer I test. Among the patients with sBUT DE (n = 60), the mean (± SD) BUT measurement was 3.1 ± 1.9 s, the mean SPK score was 0.8 ± 1.1, and the mean Schirmer I test value was 11.1 ± 8.9 mm. The latter two scores were within the normal range, based on the criterion of DE [1,15,16]. Consequently, all patients in the current study met the criteria for the sBUT DE diagnosis (Table 2).

2.4. Corneal tactile and pain sensation

Corneal sensation was measured in all subjects in the central area of the cornea with the Cochet-Bonnet esthesiometer (Luneau Ophthalmologie, Chartres, France) using a slit-lamp microscope [17]. Mechanical stimulation was performed by touching the corneal surface with the tip of a retractable, flexible monofilament nylon thread, 60 mm long and 0.12 mm in diameter. As the flexible monofilament was retracted (shortened), the stiffness increased. Briefly, the filament was retracted in steps of 10 mm, until a response was elicited; then, it was advanced by 5 mm to determine the measurement. Corneal tactile sensation was expressed as the maximum length of filament that elicited a tactile sensation. Corneal pain sensation was defined as the maximum length of filament that elicited a pain sensation. Corneal hyperalgesia was defined as a pain sensitivity ≥ 40 mm, which was the cutoff value at the 95th percentile of corneal pain sensation in the healthy subjects.

2.5. Statistical analysis

For subjects examined for corneal tactile and pain sensations, we tested the data distributions for normality with the Shapiro-Wilk test. A parametric test (*t*-test) and non-parametric test (Mann-Whitney test) were performed for normally distributed and non-normally distributed data, respectively. We performed the Mann-Whitney test to compare corneal tactile and pain sensations between healthy subjects and patients with sBUT DE. Correlations between corneal tactile or pain sensation and DE symptom parameters were calculated with Spearman's correlation coefficient. We considered p-values less than 0.05 as statistically significant.

3. Results

3.1. Objective corneal tactile and pain sensations

To examine corneal sensitivity in patients with sBUT DE, we quantified corneal tactile and pain sensations. We found that the corneal tactile sensation was similar between patients with sBUT DE (52.0 ± 15.5 mm, n = 60) and healthy subjects (52.9 ± 14.9 mm, n = 46, p = 0.60). In contrast, the corneal pain sensation was significantly higher in patients with sBUT DE (26.3 ± 23.1 mm, n = 60) than in healthy subjects (6.9 ± 16.4 mm, n = 46, p < 0.01, Fig. 1). This finding indicated that pain sensation was elevated, but not tactile sensation, in patients with sBUT DE.

Table 3B
Correlation between corneal sensation and DE metrics for patients with sBUT DE and corneal hyperalgesia (n = 22) (*p < 0.05,**p < 0.01).

Subjective DE symptoms								
	Foreign body sensation	Fatigue	Dryness	Pain	Difficulty in opening eyelids	Uncomfortable feelings in the morning	Blurred vision	Total
Tactile	−0.15	−0.14	0.08	−0.24	−0.10	−0.13	−0.39	−0.30
Pain	0.23	0.29	0.39	0.79**	0.17	0.37	0.39	0.52*

Objective DE parameters			
	SPK	BUT	Schirmer
Tactile	0.32	−0.12	0.11
Pain	0.08	0.30	0.20

sBUT DE: short tear film break-up time dry eye; SPK: superficial punctate keratitis; Schirmer: Schirmer test; *p < 0.05, **p < 0.01.

3.2. Pain sensation and subjective symptoms

To investigate further the association between corneal pain sensation and the pathogenesis of sBUT DE, we evaluated whether corneal pain sensation was correlated with subjective symptoms in patients with sBUT DE. We found a positive correlation between the subjective pain symptom (Table 2) and the objective corneal pain sensation measurement (R = 0.24, p < 0.05, Fig. 2). In contrast, we did not find any significant correlations between the subjective pain symptom and the other objective measurements (the SPK, BUT, Schirmer, or corneal tactile sensation) in patients with sBUT DE. Furthermore, we found no significant correlations between the other six subjective symptoms and the objective pain score measured with the Cochet-Bonnet esthesiometer (Table 3a). Accordingly, the total subjective symptom score did not correlate with the objective pain score (Table 3a).

The mean value of corneal pain sensation in healthy subjects was 6.9 ± 16.4 mm in the present study (Fig. 1). Twenty-two patients with sBUT DE (36.7%) exhibited corneal hyperalgesia (i.e., they were at the 95th percentile of corneal pain sensation in healthy subjects). In this group, there was a strong, significant correlation between the subjective pain symptom and the objective corneal pain sensation (R = 0.79, p < 0.01, n = 22, Fig. 3). In addition, for the corneal hyperalgesia group, the total subjective symptom score showed a significant correlation with the objective corneal pain sensation measurement (R = 0.52, P < 0.05, n = 22, Fig. 4, Table 3b).

4. Discussion

In the present study, we showed that patients with sBUT DE were significantly more sensitive to corneal pain than healthy subjects, but the corneal tactile sensation was similar in patients with sBUT DE and healthy subjects. Our study also demonstrated a weak correlation between subjective pain and objective corneal pain sensation in patients with sBUT DE. Moreover, in patients with sBUT DE and corneal hyperalgesia, subjective pain was strongly correlated with objective corneal pain sensation. Thus, clinically, patients with sBUT DE were hypersensitive to pain in the cornea. Our data suggested that corneal hyperalgesia, increased response to a stimulus that is normally painful [18], was correlated with the subjective symptoms of sBUT DE.

Since its development in the 1960's, the Cochet-Bonnet esthesiometer has been widely used as a clinical method for evaluating corneal tactile sensation [17]. Studies that used the esthesiometer have demonstrated that corneal tactile sensation was reduced in patients with aqueous tear-deficient DEDs [4]; however, it was not reduced in patients with evaporative type DE [6]. On the other hand, only a few reports have described corneal pain sensation in patients with DE [7,8]. Our modified method for using the Cochet-Bonnet esthesiometer was confirmed as a useful method for measuring corneal pain sensation [7].

In the present study, we demonstrated that corneal tactile sensation was similar, but corneal pain sensation was elevated in patients with sBUT DE compared to healthy subjects. Hyperalgesia is a neurological abnormality that increases response to a painful stimulus [18]. Therefore, it is likely that our study shows the presence of corneal hyperalgesia in patients with sBUT DE. In the present study, patients with sBUT DE that exhibited an objective pain sensation of 40 mm or more (measured with the esthesiometer) showed a strong correlation between objective and subjective symptoms of pain. These results suggested that corneal hyperalgesia could account for part of the subjective symptoms in patients with sBUT DE. Hyperalgesia is a known symptom of neuropathic pain, which is caused by a lesion or disease of the somatosensory nervous system [18]. Some studies suggested that patients with DE experience neuropathic pain arising from the corneal nerves [19,20,21]. Our present results in the patients with sBUT DE appeared to be consistent with that concept of “neuropathic pain”.

Our study had some limitations, which must be considered when interpreting the study results. First, we measured only mechanical hyperalgesia, but other stimulations, such as thermal and chemical hyperalgesia, might also have contributed to the development of DE symptoms. Second, we did not assess morphological abnormalities of the corneal nerve fibers although corneal neuropathic pain is considered to occur in some patients with sBUT DE. Third, the Cochet-Bonnet esthesiometer cannot quantify pain thresholds less than 5 mm or tactile thresholds more than 60 mm. Therefore, we may need more sensitive equipment or methods to perform more precise measurements of corneal tactile and pain sensations. Further studies are required to address these points.

In conclusion, we demonstrated that corneal hyperalgesia was correlated with the severity of DE symptoms, based on measurements of corneal pain sensation with the Cochet-Bonnet corneal esthesiometer. Recently, Hamrah et al. and Galor et al. have described approaches for diagnosing and managing neurological abnormalities in patients with DE [22,23]. In addition, a new treatment for relieving pain related to DE was reported to improve DE symptoms without changing the objective findings [24]. We believe that the findings in the present study have provided a rationale for that new analgesic treatment.

Disclosure

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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