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CORNEAL SENSITIVITY IN A PREVIOUSLY DIAGNOSED MILD DRY EYE DISEASE POPULATION COMPARED TO NON-DRY EYE CONTROLS

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ABSTRACT

Background and Objective

To identify whether a measurable difference in corneal sensitivity exists between patients previously diagnosed with mild dry eye disease and non-dry eye controls using a novel in-office esthesiometry kit.

Material and Methods

This was a consecutive, single-visit, single-center, comparative observational study. Forty patients (20 dry eye patients and 20 non-dry eye controls) were screened for study inclusion. Thirty-six were included in the analysis set (17 dry eye, 19 non-dry eye). Patients completed a dry eye symptom questionnaire (OSDI), tear film break-up time (TBUT) evaluation, Schirmer's I test, and vital dye staining for corneal and conjunctival integrity, and corneal sensitivity measurements in the central and inferior cornea.

Results

Comparison between the two groups revealed statistically significant differences in age, TBUT, conjunctival and corneal staining scores, and central corneal and inferior corneal sensitivity. There were no differences in OSDI score and Schirmer's I score between the two groups. Corneal staining score was inversely correlated with a decrease in central (−0.78) and inferior (−0.77) corneal sensitivity. Corneal sensitivity measurements were more strongly correlated to corneal staining score than age (−0.58; $z = -2.20$).

Conclusion

Patients with a previous diagnosis of mild dry eye disease exhibited higher corneal and conjunctival staining scores, which correlated with reduced corneal sensitivity in both central and inferior regions compared to non-dry eye controls. A stronger correlation existed between reduced sensitivity to corneal staining and age in this study. This demonstrates a decrease in the neurosensory function in the presence of reduced

epithelial integrity. Corneal sensitivity testing may be a useful diagnostic tool in the assessment of dry eye disease.

Keywords: dry eye; esthesiometry; hypoesthesia; neurotrophic keratitis

INTRODUCTION

Dry eye disease (DED) is a common condition affecting between 1.5 and 30 million persons in the United States.[1] It is one of the most common reasons patients present to an eye care provider.[2] Neurotrophic keratitis (NK) is considered a rare disease by the National Institute of Health and has traditionally been thought to occur in fewer than five cases per 10,000 persons. However, epidemiological data are poor and are generally derived from the extrapolation of other common conditions associated with NK.[3] The hallmark sign of neurotrophic keratitis is decreased corneal sensation, accompanied by physical changes to the cornea, which vary according to the severity of neurotrophia.[4] This may include punctate epithelial changes, persistent corneal epithelial defects, or ulceration with stromal volumetric loss and perforation in the most severe cases.

Common objective clinical signs of DED include corneal and conjunctival staining, decreased tear film break-up time (TBUT), and decreased reduced basal and reflex tear secretion as measured by Schirmer's strips. Subjective symptoms are commonly present in dry eye disease and encompass a large variety of descriptive measures, including burning, foreign body sensation, and ocular fatigue, along with a continuum of severity or intensity. A longstanding frustration encountered in the clinical management of patients with dry eye is that subjective symptoms often do not correlate with objective clinical signs. For example, patients who present with minimal symptoms of discomfort may exhibit more pronounced corneal and conjunctival staining or reduced TBUT. The reverse may also be true, in which patients complaining of moderate to severe discomfort exhibit little to no objective clinical signs consistent with dry eye.

Recently, it has become increasingly accepted that the neurosensory system provides sensory feedback from the ocular surface, and the cornea may be affected by dry eye disease. Several studies have demonstrated a decrease in corneal subbasal nerve plexus density in patients suffering from dry eye.[5] This codependency of the health of the corneal epithelium and corneal nerve structure results in both entities potentially experiencing damage, causing a decrease in trophic support for the corneal epithelium by the compromised nervous system, and the degradation of the epithelium also results in decreased neurotrophic factors that support corneal innervation.

The result of this cellular interaction between the corneal nerves and the corneal epithelium leads to potential hypoesthesia in patients with dry eye, which may manifest in mild-stage disease. This hypothesis is supported through literature highlighting chronic ocular surface disease as a potential causative agent in the development of neurotrophic keratitis. Corneal sensitivity testing then may be used as a clinical diagnostic tool to detect a decrease in corneal neurosensory function in patients with dry eye disease. Several studies have attempted to illustrate this over the past two decades with varying results,[5] with many studies showing decreased sensitivity in individuals with dry eye[6–8] and a few showing a seemingly paradoxical increase in corneal sensation between patients with dry eye and non-dry eye controls.[9,10]

Corneal sensitivity testing may be performed via varying methods in a clinical setting. Qualitative means are frequently utilized, such as a cotton wisp or dental floss, versus more quantitative methods such as Cochet–Bonnet, Belmonte, or Brill esthesiometers. Regardless of the method used, it is

imperative to remember that before corneal nerve sensitivity testing, there should be no instillation of topical anesthetic drops.

The Cochet–Bonnet esthesiometer was introduced in the 1950s as a means of quantifying corneal sensitivity measurements. The device utilizes a nylon fiber of either 0.08 or 0.12 mm diameter and a maximum length of 6 cm. With the filament fully extended, less force is applied to the cornea, and conversely, as the length of the filament is reduced, a stronger force is applied to the cornea. The length of the filament indicates the relative corneal sensitivity.

Dompé Farmaceutici S.p.A. (Milan, Italy) developed an esthesiometry kit based on the principles of the Cochet–Bonnet esthesiometer for the clinical testing of corneal sensitivity. The kit includes three handpieces, each with a fixed-length fiber attached to stimulate the cornea. The lengths represented are of 55, 35, and 15 mm. Similar to the Cochet–Bonnet, a shorter fiber length corresponds to a mechanical force applied to the cornea.

This study aimed to determine whether a newly developed esthesiometer kit, complete with predefined lengths, was able to elucidate a reduction in corneal sensation in an established mild dry eye population versus non-dry eye controls.

METHODS

This was a single-centered, observational study with consecutive enrollment. This research was reviewed and approved by an independent institutional review board (IRB) and conformed to the tenets of the Declaration of Helsinki.

Forty patients (20 dry eye patients, 20 non-dry eye controls) aged >22 years were screened. Patients were grouped based on a previous ocular history of mild dry eye or prior reported use of artificial tears versus no ocular history of dry eye.

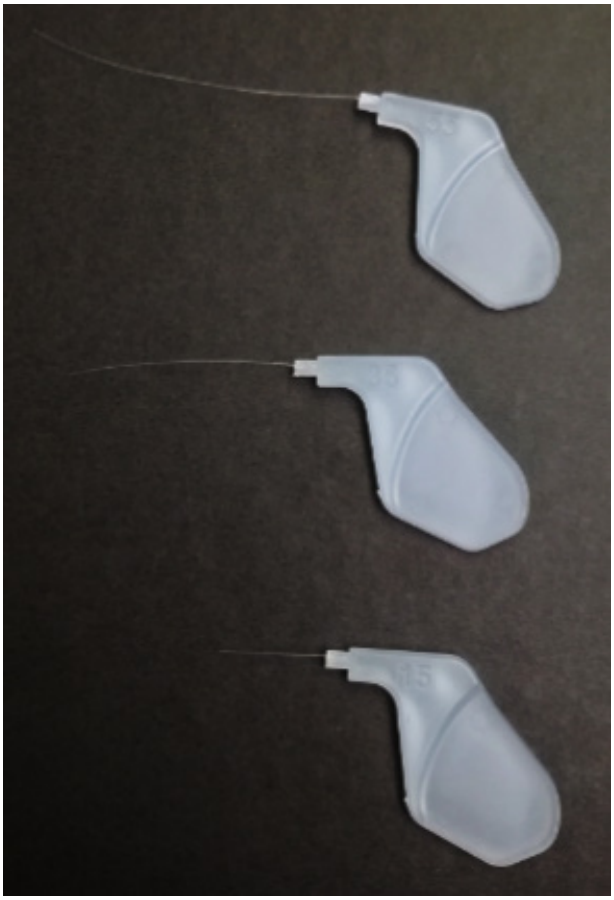
Each cohort of patients completed an Ocular Surface Disease Index (OSDI) questionnaire, which quantified the severity of dry eye symptoms. Exclusion criteria included a best-corrected distance visual acuity (BCDVA) > 20/40 (Snellen), OSDI scores > 22 (moderate to severe dry eye symptoms), concomitant utilization of topical ophthalmic medications with known corneal toxicity, current topical ophthalmic management of glaucoma, a history of corneal surgery within 3 months of enrollment, or prior penetrating keratoplasty. Of the 40 screened patients, 3 from the dry eye cohort and 1 patient from the non-dry eye cohort were excluded. One patient in the dry eye group with an OSDI score of 27 was included in this series; the patient self-reported their symptoms as mild and had previously completed dry eye questionnaires, which had also scored as mild.

Patients were excluded if they were using topical ophthalmic medications that could induce corneal toxicity, if they were on topical ophthalmic medications to treat glaucoma, or if they had a history of corneal surgery within the previous 3 months. Any history of penetrating keratoplasty was also excluded. Patients were also excluded if they had a BCDVA worse than 20/40 Snellen. Of the 40 screened patients, 3 patients from the dry eye cohort and 1 from the healthy control group were excluded.

Corneal sensitivity testing was performed using the esthesiometer kit (Dompé Farmaceutici S.p.A., Milan, Italy). The kit consists of three testing apparatuses with filaments of lengths 55, 35, and 15 mm, which represent mild, moderate, and severe reduction in corneal sensitivity, respectively (Figure 1). Sensitivity testing was performed by holding the filament perpendicular to the corneal surface and touching the central and inferior zones. Testing began with the 55 mm filament and proceeded to the 35 and 15 mm, or until the patient demonstrated a response. The length of the filament used to elicit the first response was recorded in each zone.

Corneal and conjunctival integrity were assessed via instillation of vital dyes onto the ocular surface. This assessment was performed by wetting one paper strip impregnated with sodium fluorescein and another strip impregnated with lissamine green, and then applying the dye into the inferior

FIG. 1. Dompé esthesiometer kit, showing different filament lengths of (top-bottom) 55mm, 35mm, and 15mm.



conjunctival fornix. Sodium fluorescein remained in the tear film and was used to assess the stability of the tear film, which was measured in seconds between the last blink and the appearance of the first break in the integrity of the tear film. Sodium fluorescein is absorbed between corneal epithelial cells that are reduced in size by desiccating stress and appears as a hyperfluorescent area (or spot) on the cornea. The number of spots present indicates the degree of staining. The standardized NEI Workshop Scale for the assessment of corneal staining was used to calculate the total sum score for corneal staining. Conjunctival staining assessment was performed using lissamine green, which absorbs into devitalized epithelial cells that have compromised cell membranes. The NEI Workshop Scale for the assessment of conjunctival staining was used to create a total sum score for the degree of conjunctival staining.

Statistical analysis between the groups was performed by calculating the means for each category and the standard deviations and errors. Comparison between the groups was performed using the Student's t-test, and correlation testing was performed using Pearson's correlation coefficient. Comparative analysis between correlation coefficients was performed by Fisher r-to-z transformation and subsequent analysis with alpha of 0.05.

RESULTS

In the dry eye cohort, 17 patients (16 females, 1 male; average age: 66.71 ± 15.3 years) were enrolled. The enrolled patients had an average OSDI score of 8.24 (range 0–27, SD 7.38, SE 1.79), TBUT of 4.88 s (range 3–8 s, SD 1.62, SE 0.39), and Schirmer's score of 8.82 mm (range 0–20 mm, SD 4.59, SE 1.11). Corneal staining averaged 6.18 (range 1–11, SD 2.74, SE 0.67), and conjunctival staining averaged 1.88 (range 0–6, SD 1.62, SE 0.39). The mean central corneal sensitivity score in this group was 24.41 mm (range 15–35 mm, SD 10.29, SE 2.50), and the mean inferior corneal sensitivity was 22.35 mm (range 0–55 mm, SD 13.48, SE 3.27). See Table 1.

The non-dry eye control cohort consisted of 19 patients (15 females, 4 males; average age 48.91 ± 15.8 years). The mean OSDI score in this cohort was 4.95 (range 0–10, SD 3.36, SE 0.77). TBUT averaged 9.00 s (range 2–12 s, SD 2.16, SE 0.50), and Schirmer's I score averaged 11.21 mm (range 1–30 mm, SD 8.42, SE 1.93). The mean corneal staining score was 0.50 (SD 0.23, SE 0.05), and the conjunctival stain score averaged 0.21 (range 0–2, SD 0.63, SE 0.14). The central corneal sensitivity averaged 52.90 mm (SD 6.31, SE 1.45) and inferior corneal sensitivity averaged 53.95 mm (SD 4.59, SE 1.05).

TABLE 1. Comparison of Mean Data - Dry Eye vs. Healthy Controls.

	Dry Eye	Control	t-Test
n (eyes)	17	19	
Age	66.71 years	48.91 years	< 0.001
OSDI	8.24	4.95	0.106
TBUT	4.88 sec	9.00 sec	< 0.001
Schirmer's I	8.82 mm	11.21 mm	0.285
Conjunctival Stain	1.88	0.21	< 0.001
Corneal Stain	6.18	0.05	< 0.001
Central Sensitivity	24.41	52.90	< 0.001
Inferior Sensitivity	22.35	53.95	< 0.001

None of the patients in the dry eye group showed a response to the 55 mm filament in the central cornea.

In the non-dry eye group, two patients were unable to detect the 55 mm filament in the central cornea, while one patient was unable to detect the 55 mm filament in the inferior cornea.

This study examined the differences between patients with mild dry eye and those with no history of dry eye. Symptom scores using the OSDI were not significantly different between the two groups (P = 0.11). This contributed to a match between the two groups for comparison, which was not based on the symptoms associated with dry eye.

Statistical differences were noted between the two groups with respect to age (P < 0.001), TBUT (P < 0.001), conjunctival stain (P < 0.001), corneal stain, central corneal sensitivity, and inferior corneal sensitivity (P < 0.001). Patients in the dry eye group were significantly older, exhibited significantly reduced TBUT intervals, had significantly more corneal and conjunctival staining, and revealed a significant reduction in both central and inferior corneal sensitivity measurements.

No statistical differences were noted between the two groups for the Schirmer's I score (P = 0.29).

A relatively strong negative correlation was noted between the corneal stain score and central corneal sensitivity (−0.78, Pearson's), as well as between the corneal stain score and inferior corneal sensitivity (−0.77, Pearson's; Figure 2).

While there was some correlation between age and corneal sensitivity, this relationship was not strong (−0.58, Pearson's; Figure 3). The comparison of correlation coefficients via Fisher r-to-z transformation showed a statistically significant difference between central corneal sensitivity and staining versus age, with alpha of 0.05 (Z = −2.20), indicating a stronger relationship between corneal staining and corneal sensitivity versus age.

DISCUSSION

The results identified a difference in both central and inferior corneal sensitivity between subjects with mild dry eye and those with no history of dry eye, despite controlling for symptom severity. Central and inferior corneal sensitivity measurements were inversely correlated with corneal staining, illustrating a relationship between epithelial integrity and corneal nerve function.

In a consensus paper by Dana et al., a panel of 11 experts weighed in on 646 clinical scenarios to determine whether corneal sensitivity testing was warranted.[11] The experts ultimately reached agreement on 93% of these scenarios, with the highest disagreement (14%) occurring in whether to test newly observed epithelial changes without a gross epithelial defect or not. Based on the author's

FIG. 2. Best-fit curve depicting the relationshipbetween central corneal sensitivity and corneal staining score.

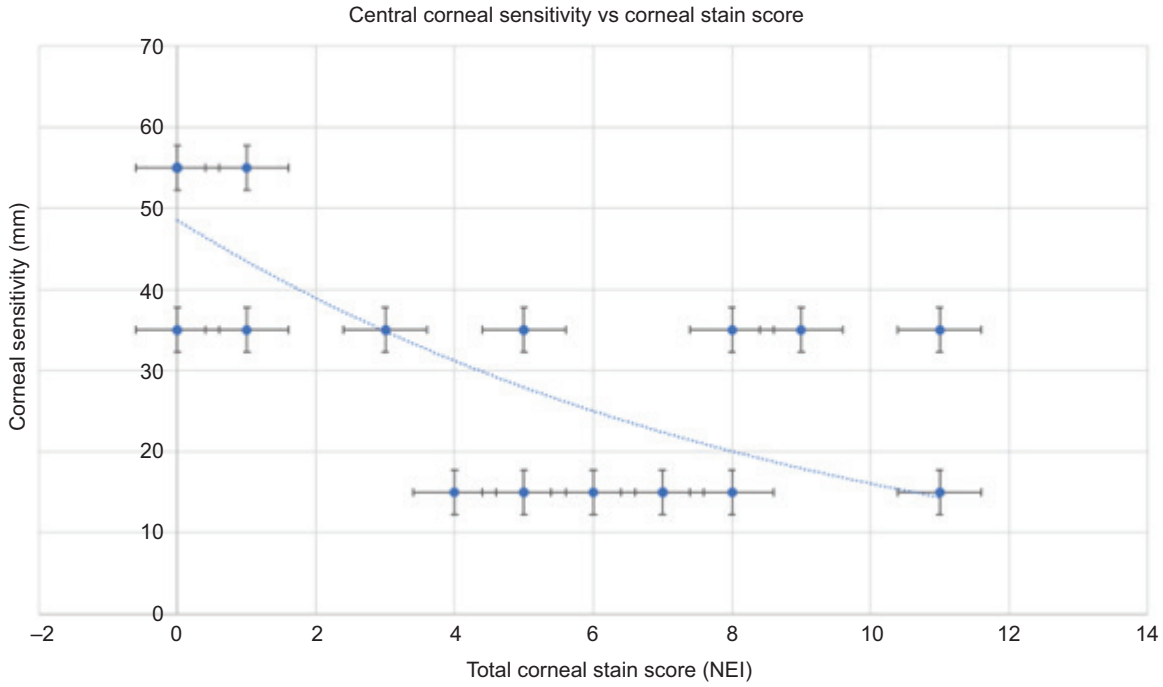
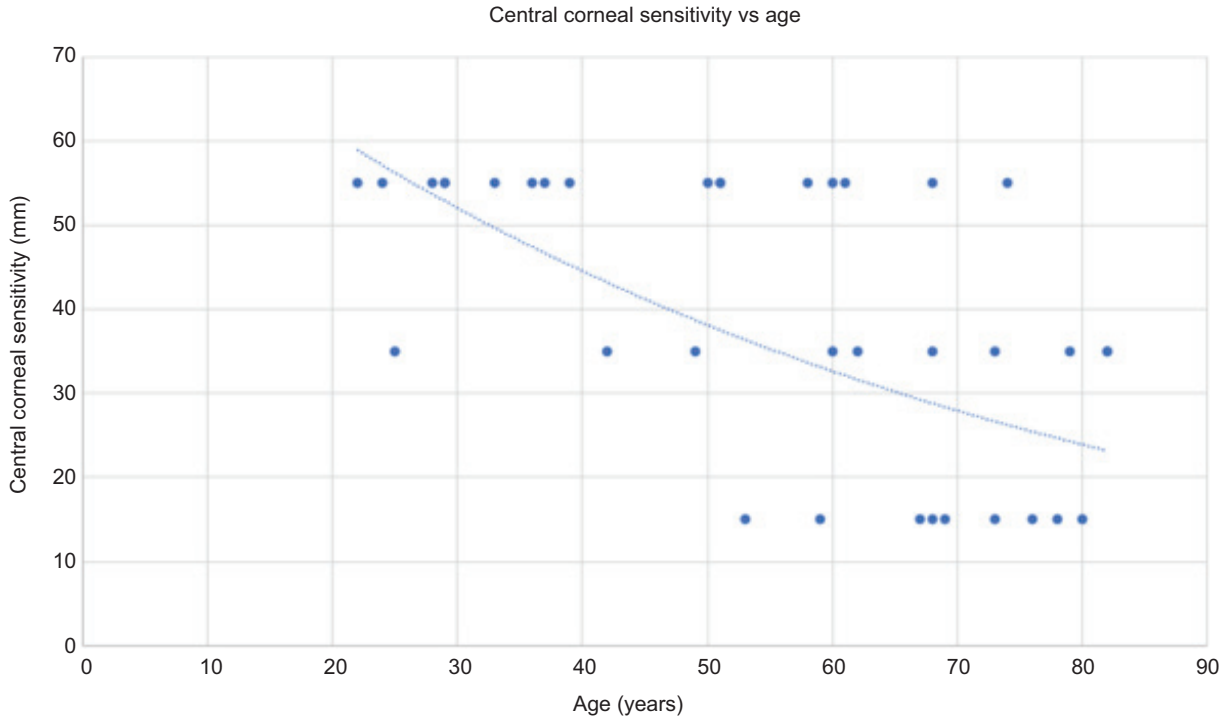


FIG. 3. Best-fit curve depicting the relationship between central corneal sensitivity and age.



experience, coupled with the information from this study, it is suggested that corneal sensitivity testing is justified in patients with minimal symptoms and observable corneal staining, especially in cases where epitheliopathy is persistent or recalcitrant to dry eye therapy.

The major limitation of this study was the small number of patients and the lack of age-matching for each group. It is well documented that corneal sensitivity decreases with increasing age,[12] and this was also observed in our study. An age-matched cohort would have contributed to a stronger data set. However, it is interesting to note that in this small data set, the corneal staining score was more strongly correlated with decreased corneal sensitivity than with age. This outcome reached statistical significance, indicating that the relationship between these two variables deserved further exploration in a larger population.

Corneal sensitivity may also fluctuate over time, owing to neuroadaptation. The overwhelming majority of the studies involving corneal sensitivity measurements have been cross-sectional, making it difficult to address this aspect. At the time of this writing, only one longitudinal study examining sensitivity in dry eye had been published,[13] which demonstrated moderate variability over 3 months. Interestingly, increased severity of dry eye was also correlated with decreased corneal sensitivity and more pronounced clinical signs; however, the study observed a negative correlation between the subjective severity of symptoms and corneal sensitivity. This may indicate that hypersensitivity may be occurring in a portion of the dry eye population, perhaps before the onset of increased corneal epithelial damage. Neither the longitudinal variation nor the length of time patients had been diagnosed with dry eye was explored within this study.

The extrapolation of this information would prove useful in a clinical setting, as dry eye disease may be contributory to the development of neurotrophic keratopathy. Illustrating the factors involved that potentially increase the risk of a patient developing and progressing to more advanced stages of neurotrophic keratitis is a knowledge gap worth exploring, and additional efforts in this area are warranted.

Since this is a population derived from a single primary care practice with some subjects having a history of contact lens wear, it would also make sense to exclude those patients who are currently contact lens wearers, or control for other variables such as duration of contact lens wear and type of contact lenses worn. The effect of contact lens wear seems to point to a reduction in corneal sensitivity over time, with the highest effect in PMMA, rigid gas permeable, and orthokeratology lenses.[14–17] This variable was not explored in this study and should be considered as an exclusion criterion in another iteration. In addition, it would be feasible to study the length of time in contact lenses and the effect on corneal sensitivity to gauge a deeper understanding of that relationship.

Finally, while the esthesiometer kit provided to measure corneal sensitivity is convenient and provides practitioners an uncomplicated means to obtain a numerical measurement of corneal sensitivity, it is still currently not a validated diagnostic method. However, there was a notable difference in the use of the 55 mm filament between the two groups, with nearly all non-dry eye subjects detecting the 55 mm filament, whereas none of the dry eye patients were able to detect it. This finding may represent an important difference between these groups and may prove useful at detecting changes in threshold sensitivity. Further work in this area, including measurement validation, is warranted.

CONCLUSION

This study indicated a negative correlation between corneal staining scores and central and inferior corneal sensitivity measurements when comparing patients with a history of dry eye disease and non-dry eye controls. This underscores the relationship between corneal epithelial health and the neurological mechanisms that supports the ocular surface. Corneal sensitivity testing should be considered

in patients with concurrent corneal staining and mild symptomatology, with additional studies examining the longitudinal impacts of this relationship.

AUTHORS CONTRIBUTION

Dr. Schachter contributed to the design and implementation of the research including collection of data. Dr. Homann contributed to revisions of the manuscript. Dr. Hauser contributed to the design of the study and to revisions of the manuscript. Dr. Hauswirth contributed to the analysis of the results and to the writing of the manuscript.

CONFLICTS OF INTEREST

Dr. Hauswirth and Dr. Schachter reported receiving income from Dompé throughout this study. Dr. Hauswirth is an employee of Dompé farmaceutici, S.p.A., and Drs. Hauser and Homann are employees of Dompé USA.

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