OCT and dry eye syndrome

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Dry eye syndrome is a multifactorial pathology involving tears and the ocular surface, which can cause lesions of the conjunctival and corneal epithelium. Previous studies have indicated several factors responsible for the proliferation and the differentiation of the conjunctival epithelium. However, little is known about the proliferation and other changes that may occur in the corneal epithelium. This study describes the correlation between morphological changes of the corneal epithelium and the different degrees of dry eye syndrome and effectiveness of optical coherence tomography (OCT) in ocular surface evaluation.

Continuous regeneration of the ocular epithelial cells is necessary to ensure their normal cellular function. Several factors are involved in the safeguarding of epithelial function, including tear film production, neuronal innervation and reflex blinking which mediate the maintenance of a favorable environment.

Recent advances in spectral domain OCT imaging allow a high axial resolution of the anterior segment, and a rapid, precise, non-invasive imaging of the cornea. Pachymetric epithelial mapping thus enables the display of all of the different interfaces, in particular those of the corneal epithelium. Evaluation of the corneal epithelium including the tear film using OCT allows accurate representation of the status of the ocular surface.

The mechanistic pathways involved in the remodeling of the corneal epithelium and those responsible for the compensatory ability of the cornea necessary for the maintenance of a biomechanical balance are well characterized and play important roles in ensuring high optical quality.

Normal epithelial thickness using OCT

Reinstein et al. first reported the analysis of the corneal epithelium using corneal epithelial mapping over the entire corneal surface using the very-high frequency ultrasound equipment known as Artemis [1]. Their study reported that the average corneal epithelial thickness, excluding tear-film thickness (approximately 4.79 ±0.88 µm), was 53.4±4.6 µm in normal subjects, with greater thickness of the corneal epithelium in the lower part versus the upper part in normal corneas, possibly because of the friction generated by the blinking motion of the eyelids (Figure 1). A more pronounced movement of the upper eyelid causes greater friction on the ocular surface and results in mechanical stress on the epithelial cells, thus causing thinning of the epithelium. Recent advances in OCT, particularly in terms of axial resolution, have enabled the isolation of the corneal epithelial layer using segmentation tools capable of automatically detecting the tear film and the interface between the epithelium and Bowman's layer.

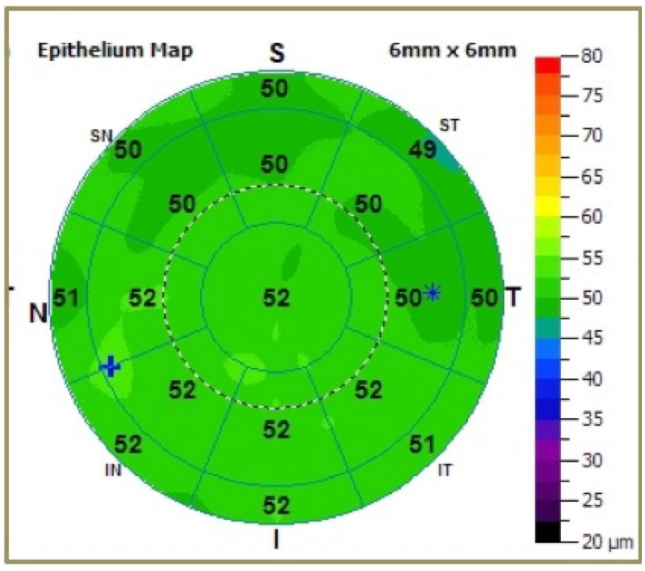

Figure 1. Epithelial mapping in a patient with a normal ocular surface. The corneal epithelium is slightly thinner in the upper regions than in the lower regions, and thicker in the nasal region than in the temporal region.

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The software then generates a map with a diameter of 6mm or 9mm of the corneal epithelium. This study used the XR Avanti OCT platform (Optovue, Fremont, CA, USA), one of the most advanced devices currently used in the field.

In OCT, the non-invasive measurement of the corneal epithelium includes the tear film. Li and Huang [2] have reported that the mean thickness of the corneal epithelium in a normal subject is 52.3 ± 3.6 µm in the center, 49.6 ±3.5 µm in the upper part, and 51.2 ±3.4 µm in the lower part, which corroborates the measurements obtained using the Artemis device.

Kanellopoulos et al. [3] have reported the accuracy of the OCT measurements of the corneal epithelium: repeatability for measurements of 1 µm, and variability of the topographic thickness of around 0.25 µm. Considering the small variations in the corneal epithelium of a few microns, this level of precision is important for evaluating the thickness of the corneal epithelium.

Epithelial thickness in the initial stage of dry eye syndrome

Meibomian gland dysfunction (MGD), irrespective of whether it is associated with blepharitis or not, is the first cause of dry eye syndrome involving hyperevaporation of lachrymal secretions.

Instability of the tear film caused by excessive evaporation is typically confirmed by findings of shorter break-up time (BUT) that characterize tear-film rupture and a sensation of visual fluctuation reported by patients.

In such incipient or mild lesions, epithelial thickness maps reveal the presence of hyperplasia of the corneal epithelium predominantly in the lower part of the corneal apex, the zone generally affected by rupture of the tear film (Figure 2) [4]; hyperplasia may be observed in other areas depending on the location of the rupture of the tear-film .

A software update will soon be available from Optovue to standardize epithelial mapping by modifying the scale from a 5- to 2-µ step-wise gradient, which simulates the AutoScale mode used in corneal topography. This new scale allows highlighting of the corneal epithelium changes and thus enables easier visualization.

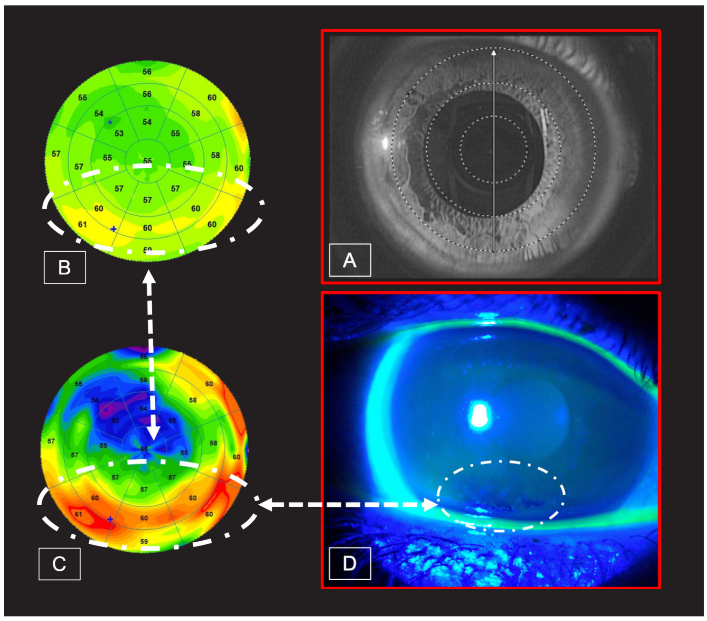

Figure 2. A. Image of a patient's cornea acquired by OCT imaging using infrared camera. **B.** Epithelial thickness map highlighting the crescent-shaped region of hyperplasia below the apex. **C.** Epithelial thickness map using a standardized scale showing the presence of hyperplasia more clearly. **D.** BUT examination showing the presence of rupture of the tear film caused by a few superficial punctate keratitis lesions at the site corresponding to that of corneal epithelial hyperplasia.

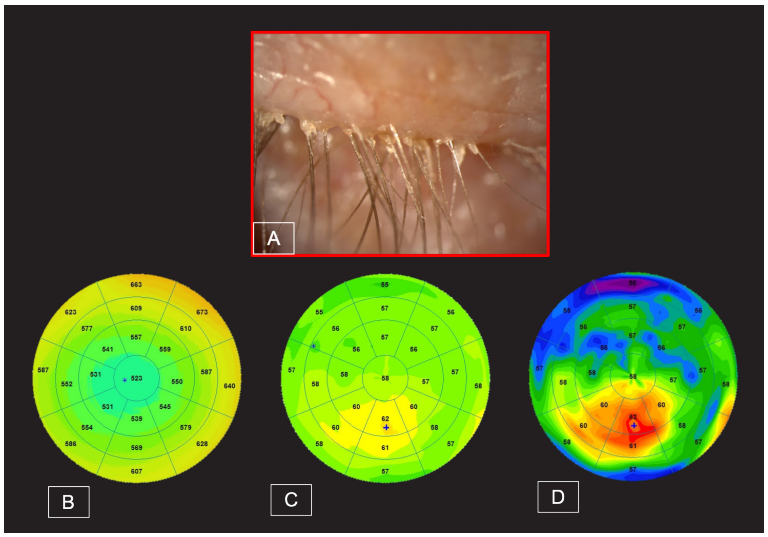

Figure 3. A 23-year old patient with uncompensated ametropia associated with blepharitis. **A**. Biomicroscopic examination of debris at the base of the eyelashes. **B**. Total corneal thickness map shows normal thickness and distribution. **C.** Epithelial thickness map showing the presence of localized hyperplasia of the corneal epithelium below the apex. **D.** Epithelial thickness map using a standardized scale highlighting the presence of epithelial hyperplasia more prominently.

After treatment involving eyelid cleaning and application of a heating mask, improvement of the blepharitis along with nearly-complete resorption of the epithelial hyperplasia and normalization of the ocular surface were observed. (Figure 4).

The finding of regression of epithelial hyperplasia indicates that these changes are related to ocular surface disorders and that OCT is a potentially useful tool during follow-up.

Immunofluorescence studies in mice with induced dry eye in a controlled environmental chamber revealed hyperplasia of corneal epithelial cells based on the expression levels of the cell proliferation marker Ki-67 [5].

Epithelial hyperplasia may reflect a reaction to the microlesions caused by hyperosmolar stress or a micro-abrasive effect induced by blinking on the ocular surface under conditions of moderate dryness.

The mechanisms at play are not yet fully understood. However, the most likely hypothesis is that dry eye syndrome causes neurogenic or non-neurogenic inflammation and that an increase in pro-inflammatory cytokines is involved in cell proliferation and keratinization [6, 7]. Corneal epithelial hyperplasia is a compensatory response to changes in the corneal curvature such as in the case of keratoconus or radial keratotomy. Variability of the distribution of epithelial topography and total pachymetry are factors used to differentiate between epithelial hyperplasia induced by dry eye and ectatic corneas (Figure 5).

In our patients, dry eye syndrome was believed to cause variations in keratometry, refraction, and ultimately visual instability.

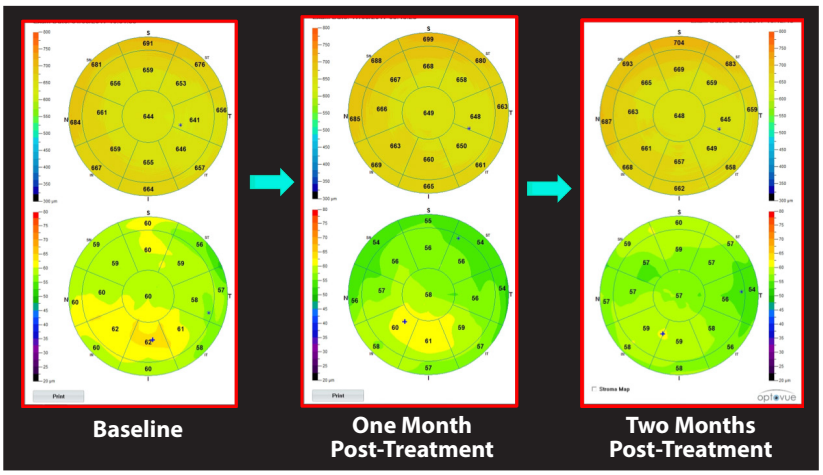

Figure 4. Follow-up of a patient with corneal epithelial hyperplasia with blepharitis associated with MGD. After performing eyelid massage per the clinician's recommendation, progressive disappearance of the hyperplasia and normalization of the ocular surface after resolution of the blepharitis was observed at the 2-month follow-up. Clear improvement in visual stability based on the patient's subjective opinion was noted.

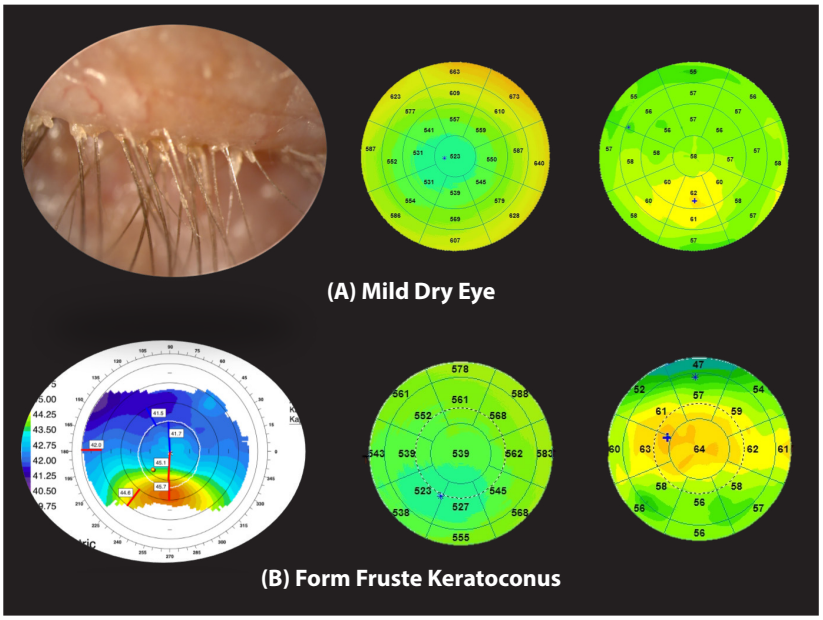

Figure 5. Comparison between two stages of localized epithelial hyperplasia in dry eye syndrome in the same patient described in the case study, and in a patient with forme fruste keratoconus. Variability of distribution of epithelial pachymetry is much greater in dry eye syndrome, whereas that of total pachymetry is greater in subclinical keratoconus.

Epithelial thickness in moderate and severe dry eye syndrome

Severe dry eye syndrome caused by either lacrimal hyposecretion or hyperevaporation, can impair the patient's quality of life considerably. It is often associated with short tear-film rupture time of <3 seconds and may be associated with keratitis.

Many previous studies have reported decreases in the total corneal thickness in patients with severe dry eye syndrome.

In those with moderate dry eye syndrome, lack of tears may induce an increase in blink frequency; as a result, the increased mechanical friction causes greater epithelial damage, leading to thinning of the upper corneal epithelium (Figure 6).

In general, epithelial mapping shows an overall thinning of the corneal epithelium with lower variability of the thickness, as in the case of our patient with keratoconjunctivitis sicca (Figure 7).

In agreement with our interpretation of the results obtained, previous reports have indicated that abnormal proliferation of conjunctival and corneal epithelial cells is correlated with the aberrant synthesis of pro-apoptosis proteins that may play an important role in the pathogenesis of keratoconjunctivitis sicca. In the absence of a compensatory epithelial cycle, excessive apoptosis or mechanical destruction of the corneal epithelium may lead to general thinning of the corneal epithelium in patients with severe dry eye syndrome.

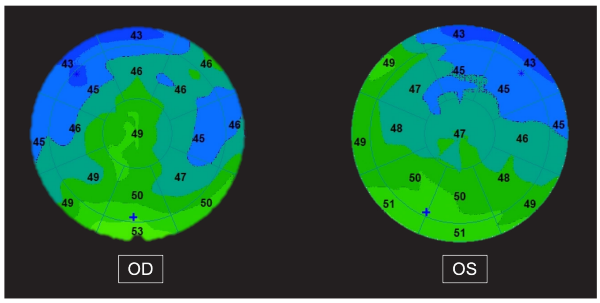

Figure 6. Epithelial thickness map in a patient with moderate dry eye syndrome with BUT of 8 seconds. Significant thinning of the corneal epithelium in the upper part and irregular control distribution of pathological ocular surface is observed.

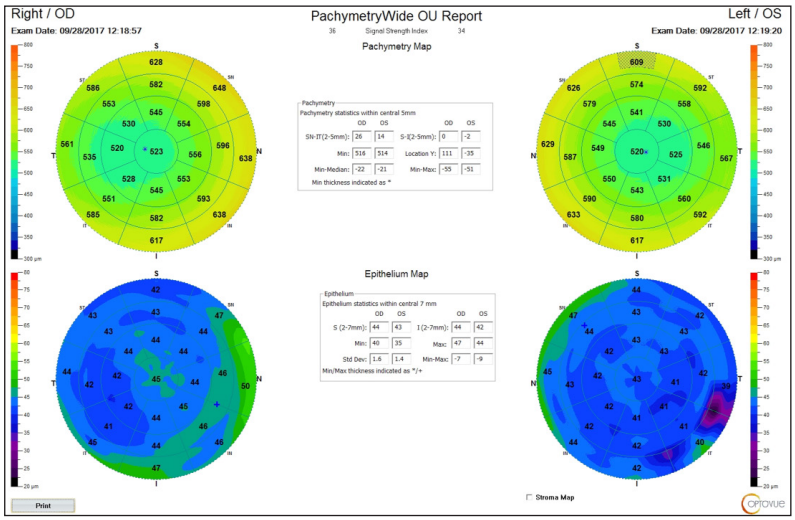

Figure 7. Epithelial thickness map in a patient with dry keratoconjunctivitis with lagophthalmia with BUT of 4 seconds in the bilateral eyes. Diffuse thinning of the corneal epithelium over the entire cornea in relation to the severity of the dry eye syndrome is observed.

Clinical diagnosis perspectives

Hyperplasia of the corneal epithelium observed through epithelial thickness mapping using OCT may be a compensatory phenomenon at the initial stages of the disease; subsequently, trophic degradation manifested as epithelial thinning may be observed during the chronic phase of the disease.

King-Smith et al. [8] have reported that the thickness of the tear film is greater in the upper part than in the lower part, which contrasts with our findings related to the thickness of the corneal epithelium determined through OCT. The thickness of the tear film and that of the epithelium are closely related, in agreement with their respective roles in mediating the optical quality of the eye. The finding that epithelial hyperplasia at the rupture zone of the tear film coinciding with the area of greatest tear-film thinness suggests the presence of active mechanisms regulating the thickness of the epithelium.

Epithelial thickness mapping enables classification of the stages of dry eye syndrome according to four differentiable entities, based on the degree of severity (Figure 8):

- normal ocular surface,
- mild dryness,
- moderate dryness, and
- severe dryness.

Studies including larger patient cohorts are needed to validate the proposed model; however, epithelial thickness mapping has the potential to contribute to multimodal dry eye analysis as an objective tool that is examiner-independent. These elements can be compared with the various subjective questionnaires (such as SPEED or OSDI) presented to patients as part of the follow-up process.

Nevertheless, these variations of the epithelium in dry eye syndrome should be considered by clinicians especially in the differential diagnosis of forme fruste keratoconus or from compensatory changes of the corneal epithelium in relation to stromal changes.

The biometric information obtained should be corroborated by clinical examination. Studies focused on developing additional biometric precision in surgeries for multifocal or toric implants and comparisons between epithelial thickness mapping and keratometry, will allow for a decrease in the need for approximations during keratometry assessments.

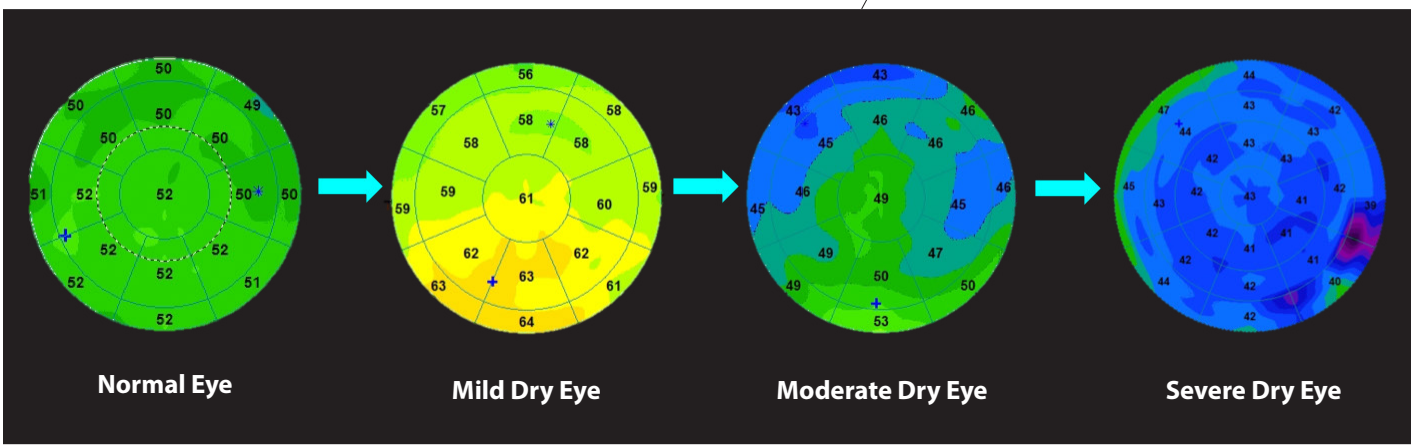

Figure 8. Proposed classification of the severity of dry eye syndrome according to four epithelial thickness map types representing the distribution of the corneal epithelium according to the degree of severity.

Conclusion

Epithelial thickness mapping is a potentially useful tool for objective assessment of the quality of the ocular surface as measured by changes in the corneal epithelial cells in dry eye syndrome. This new approach may become a standard tool in the analysis of dry eye syndrome, for both screening and follow-up, as well as in the pre- and postoperative assessment of refractive surgery and primary cataract surgery.

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