

In Vivo 3-Dimensional Corneal Epithelial Thickness Mapping as an Indicator of Dry Eye: Preliminary Clinical Assessment

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- **PURPOSE:** To evaluate in vivo epithelial thickness in dry eye by anterior segment optical coherence tomography.
- **DESIGN:** Observational, retrospective case-control study.
- **METHODS:** Two age-matched groups of female subjects, 70 eyes each, age \approx 55 years, were studied in clinical practice setting: a control (unoperated, no ocular pathology) and a dry eye group (clinically confirmed dry eye, unoperated and no other ocular pathology). Corneal epithelium over the entire cornea was topographically imaged via a novel anterior segment optical coherence tomography (AS-OCT) system. Average, central, and peripheral epithelial thickness as well as topographic epithelial thickness variability were measured.
- **RESULTS:** For the control group, central epithelial thickness was $53.0 \pm 2.7 \mu\text{m}$ (45-59 μm). Average epithelium thickness was $53.3 \pm 2.7 \mu\text{m}$ (46.7-59.6 μm). Topographic thickness variability was $1.9 \pm 1.1 \mu\text{m}$ (0.7-6.1 μm). For the dry eye group, central epithelial thickness was $59.5 \pm 4.2 \mu\text{m}$ (50-72 μm) and average thickness was $59.3 \pm 3.4 \mu\text{m}$ (51.4-70.5 μm). Topographic thickness variability was $2.5 \pm 1.5 \mu\text{m}$ (0.9-6.9 μm). All pair tests of respective epithelium thickness metrics between the control and dry eye group show statistically significant difference ($P < .05$).
- **CONCLUSIONS:** This study, based on very user-friendly, novel AS-OCT imaging, indicates increased epithelial thickness in dry eyes. The ease of use and the improved predictability offered by AS-OCT epithelial imaging may be a significant clinical advantage. Augmented epithelial thickness in the suspect cases may be employed as an objective clinical indicator of dry eye. (Am J Ophthalmol 2014;157:63-68. © 2014 by Elsevier Inc. All rights reserved.)

DRY EYE IS A MULTIFACTORIAL DISEASE OF THE tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film

instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.¹

Dry eye is responsible for significant population morbidity and is a common clinical problem for eye clinicians. Besides the significant symptoms and toll on quality of life, it may present significant challenges in refractive surgery patient assessment.² As reported in the peer-review literature,³⁻⁷ its manifestations may range from episodic and mild condition to chronic and severe disease: the disorder can be presented with any or many symptoms of visual disturbance and blurred vision, eye discomfort, irritation, foreign body sensation, ocular surface damage, redness, excess tearing, and photosensitivity.

Epidemiologic review studies estimate the prevalence of dry eye disease between 4% and 33%, largely depending, among other factors, on the diagnosis mode, the geographic locale,^{8,9} age, and sex, being most prominent in the middle-aged (over age 45 years) female populace.¹⁰⁻¹²

Several clinically available modalities may facilitate in vivo measurement of corneal epithelium, including high-frequency scanning ultrasound biomicroscopy (HF-UBM),¹³ anterior segment optical coherence tomography (AS-OCT),¹⁴ and confocal microscopy through focusing (CMTF).^{15,16} In the clinical practice, epithelial evaluation is limited by the resolution and the variability of the ocular surface tests.¹⁷

In pursuit of an objective, repeatable, and quantitative clinical test that may aid in the differential diagnosis of dry eye, we introduce the concept of corneal epithelial thickness as a possible tool in dry eye assessment. We report herein initial clinical results regarding 3-dimensional corneal epithelial thickness mapping in dry eye corneas with a newly commercially available anterior segment optical coherence tomography system.

MATERIALS AND METHODS

THIS OBSERVATIONAL, RETROSPECTIVE CASE-CONTROL study received approval by the Ethics Committee of our Institution (LaserVision.gr Eye Institute), and was adherent to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject

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for imaging and dry eye assessment at the time of the first clinical visit.

• **GROUP FORMATION, INCLUSION/EXCLUSION CRITERIA:** The “control” group (n = 70 eyes, 35 patients) consisted of female patients with unoperated, normal eyes with no ocular pathology other than refractive error, and no dry eye condition, confirmed by a complete ocular clinical evaluation.

The “dry eye” group (n = 70 eyes, 35 patients) consisted of female patients with clinically confirmed dry eye, otherwise unoperated and with no other ocular pathology, save for possible refractive error. Both groups consisted of female patients because in our practice they compose, in a 10:1 ratio, the dry eye population compared to male subjects that we encounter (unpublished data). Dry eye was diagnosed via tear-film breakup time (TBUT) measurement (dry considered if under 5 seconds) and Schirmer basic lacrimation test (dry considered if under 5 mm). Exclusion criteria were anterior basement membrane and other corneal dystrophies, and/or rheumatic diseases.

No patient with reported previous use of contact lens or with recent dispensing of artificial tear drops was enrolled in this study in either group.

• **IMAGING INSTRUMENTATION:** The Fourier-domain AS-OCT system RTVue-100 (Optovue Inc, Fremont, California, USA), running on software version A6 (9,0,27), was employed in the study. Data output included total corneal and corneal epithelial thickness maps over the 6-mm-diameter corneal area (representative examples from both groups shown in Figure 1). The settings were L-Cam lens, 8 meridional B-scans per acquisition, consisting of 1024 A-scans each, with axial resolution of 5 μm . Following correct fixation and centering, acquisition time was in the order of few seconds per scan. Four individual acquisitions were performed in each case on the same day. All measurements were obtained by the same investigator prior to any tear-film breakup time measurement and Schirmer lacrimation test.

• **DATA ACQUISITION AND ANALYSIS:** For each eye we measured and analyzed statistically within the central 5-mm zone the average, superior, and inferior epithelial thickness, as well as topographic thickness variability, as reported by the standard deviation of the 17 sectors’ (shown in Figure 1) local thickness measurements. Average epithelium thickness was computed for each case within the 5-mm zone as the average of the 17 sectors’ local thickness measurements.

Linear regression analysis was performed to seek possible correlations of epithelial thickness. Descriptive statistics (average, minimum, maximum, standard deviation), comparative statistics and linear regression analysis, and receiver operating characteristic (ROC) curve analysis were performed with statistics tools provided by Minitab

version 16.2.3 (MiniTab Ltd, Coventry, UK) and SPSS version 21.0 (IBM Corporation, New York, New York, USA).

RESULTS

MEAN AGE AT THE TIME OF EXAMINATION FOR THE control group was (average \pm standard deviation) 47.5 ± 15.6 years, ranging from a minimum of 35 to maximum of 70 years of age. Mean age for the dry eye group was 50.8 ± 16.9 years, ranging from 36-69 years. The mean age of the control group was not significantly different from the mean age of the dry eye group ($P = .235$).

Regarding the dry eye group, mean Schirmer test value, expressed in mm wetting of the paper after 5 minutes (following topical anesthesia), was 2.4 ± 1.8 mm (range 0.6-4.2 mm). For the same group, the tear-film breakup time was 3.5 ± 1.5 seconds (range 2-5 seconds).

The AS-OCT system’s software output produced full corneal thickness as well as epithelium thickness maps, extending to a 6×6 -mm corneal area. Examples of such maps from each group are shown in Figure 1. Epithelial thickness comparison between the control and the dry eye groups, specifically central thickness, minimum thickness, maximum thickness, and average, is illustrated in Figure 2.

As shown in Table 1, on average, for the control group, central epithelial thickness was 53.0 ± 2.7 μm , ranging from a minimum of 45 to a maximum of 59 μm . Minimum thickness was on average 48.4 ± 3.9 μm , ranging from 37-55 μm , and maximum thickness was 56.3 ± 3.4 μm , ranging from 49-65 μm . Average epithelial thickness was 53.1 ± 2.7 μm , with a range from 46.70-59.60 μm .

For the dry eye group, central epithelial thickness was 59.5 ± 4.2 μm , ranging from minimum 50 to maximum 72 μm . Minimum thickness was, on average, 52.7 ± 4.6 μm , ranging from 37-61 μm , and maximum thickness was 63.4 ± 4.1 μm , ranging from 54-77 μm . Average epithelial thickness was 59.3 ± 3.4 μm , with range from 51.4-70.5 μm .

All pair tests of the respective epithelium thickness metrics between the control and dry eye groups show statistically significant differences ($P < .05$).

The topographic thickness variability, measured on each eye as the standard deviation of the 17 sectors shown in Figure 1, was 1.9 ± 1.1 μm (range 0.7-6.1 μm) for the control group and 2.5 ± 1.5 μm (range 0.9-6.9 μm) for the dry eye group.

ROC analysis was performed for the average (as well as central) epithelium thickness as a predictor. As shown in Table 2, with the area under the curve of 0.93, true positives and true negatives were 58 and 61, respectively, while false positives and false negatives were 12 and 9, respectively.

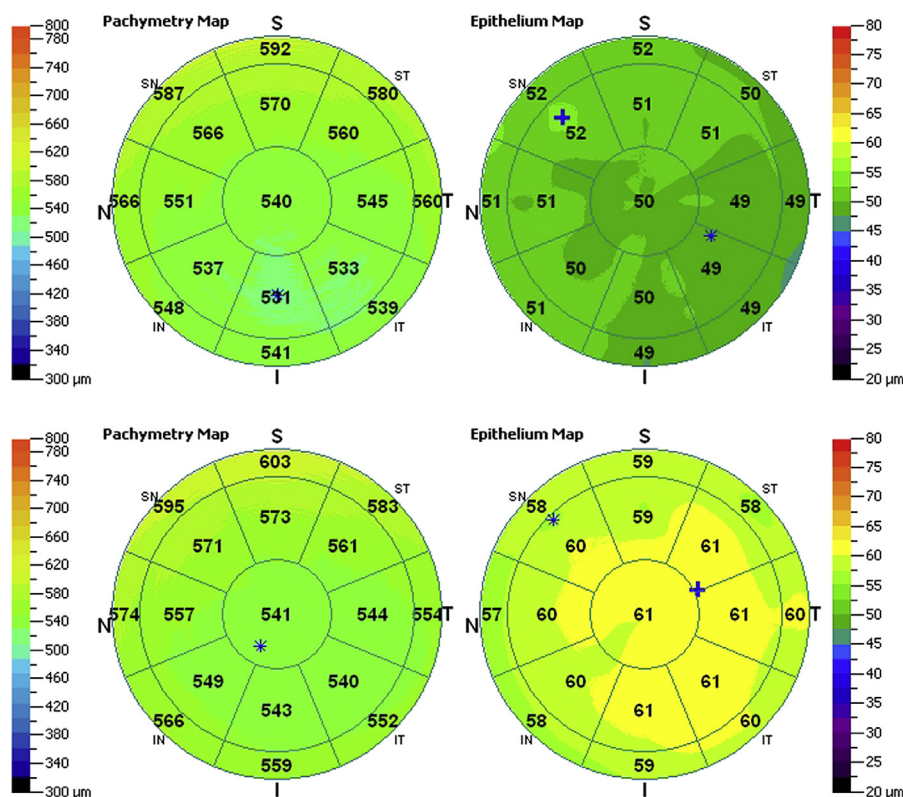


FIGURE 1. Representative corneal total thickness maps (left) and corneal epithelium thickness maps (right) of (Top) a “normal” patient from Group A and (Bottom) a dry eye patient from Group B, as provided by the optical coherence tomography system report.

DISCUSSION

THE CHALLENGE OF OBJECTIVE DRY EYE ASSESSMENT HAS been argued in length. The current options of the clinical investigator includes slit-lamp observations, osmolarity test, tear-film breakup time measurement, Schirmer lacrimation test, corneal and conjunctival staining, meibomian grading, and Ocular Surface Disease Index.¹⁰ Research evidence suggests that clinical dry eye symptoms alone may be insufficient for the diagnosis and management of dry eye, and there is argument for a consensus of newer metrics that may better reflect the differential discrimination of the disease.¹⁸

One such possible element in diagnosis is overall epithelial thickness, as well as the topographic distribution of epithelial thickness. For example, atopic keratoconjunctivitis has been associated with significant alterations of the basal epithelium and subbasal and stromal corneal nerves, related to the changes in tear functions and corneal sensitivity.¹⁹

Very little is reported, however, in the peer-review literature on the subject matter of entire corneal area in vivo measurement of epithelial thickness, particularly in relationship with dry eye. This can be justified by the fact that neither HF-UBM nor AS-OCT nor CMTF techniques have been fully applicable and/or with a commercially available mode for this use, as well as the fact that some

(eg, HF-UBM) employ instrument or fluid interface contact with the epithelium. We have not identified, for example, reported correlation of dry eye and HF-UBM measurements. CMTF has been restricted in this application because of the degraded precision by eye movement during the long acquisition time; in addition, other available clinical evaluation techniques for the corneal epithelium either are invasive or require contact between the probe and the ocular surface, and thus cannot provide precise in vivo measurement of the epithelial thickness.²⁰ In a confocal laser scanning microscopy study in dry eye,²¹ the mean superficial and intermediate epithelial cell densities in the central cornea in the dry eye groups were significantly lower than in normal participants. Dry eye corneas showed significant alterations, presumably attributable to increased desquamation of the superficial cell layer.

Reports on entire corneal epithelium imaging via AS-OCT, a novel entity, have been also few. In most of these studies, investigator-modified software/hardware^{22–24} or caliper software measurement techniques^{25,26} have been employed (for example, by manually placing cursors to measure epithelial thickness in each location).

The recent availability of full-cornea corneal epithelial thickness imaging by AS-OCT potentially presents a practical clinical tool for qualitative (by examination of the

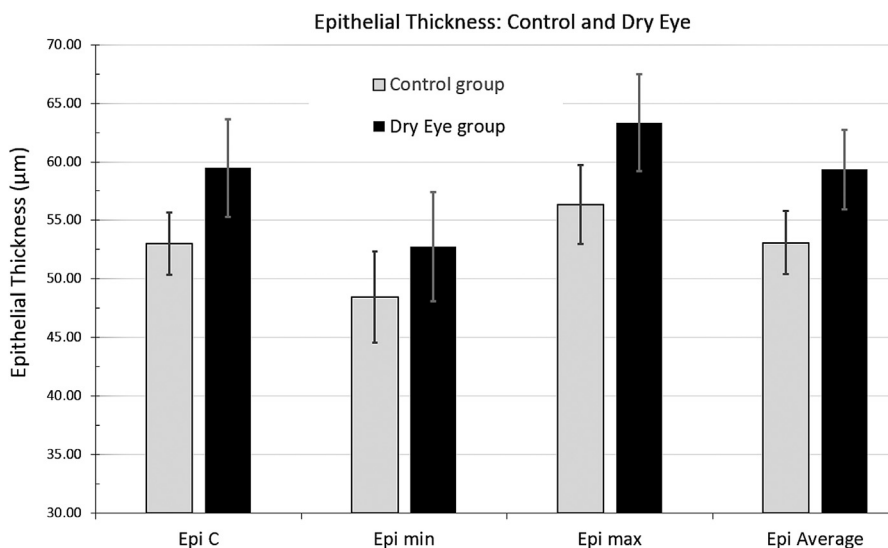


FIGURE 2. Epithelial thickness comparison between the control and the dry eye groups. All units in μm . Epi C: central thickness; Epi min: minimum thickness; Epi max: maximum thickness; Epi average: average epithelium thickness computed within the 5-mm zone.

TABLE 1. Corneal and Epithelial Thickness (in μm) in the Control and Dry Eye Groups, as Measured by the Optical Coherence Tomography System

	CCT	Min CT	Epi C	Epi Min	Epi Max	Epi Stdev	Epi Average
Control							
Average	540.7	532.5	53.0	48.4	56.3	1.8	53.1
Stdev	± 23.4	± 22.9	± 2.7	± 3.9	± 3.4	± 1.1	± 2.7
Max	573	565	59	55	65	6.2	59.6
Min	494	489	45	37	49	0.7	46.7
Dry eye							
Average	551.1	540.0	59.5	52.7	63.4	2.5	59.3
Stdev	± 21.3	± 19.5	± 4.2	± 4.6	± 4.1	± 1.5	± 3.4
Max	578	570	72	61	77	6.9	70.5
Min	513	507	50	37	54	0.9	51.4

CCT = central corneal thickness; Epi Average = average epithelium thickness; Epi C = central epithelium thickness; Epi Max = maximum epithelial thickness; Epi Min = minimum epithelial thickness; Epi Stdev = topographic thickness variability; Min CT = minimum corneal thickness.

3-dimensional epithelial thickness mapping produced by interpolation of successive meridional scans) and quantitative epithelium evaluation (absolute average, central, and peripheral epithelial thickness measurements), with the ease of noncontact application and speed of optical imaging.²⁷

The current study suggests an overall thicker epithelium in the group of dry eye female patients, and specifically a statistically different epithelial thickness between the dry eye group and the control group. The differences

(average in dry – normal eyes) ranged for the central thickness by $+6.5 \mu\text{m}$ and for the average thickness by $+6.2 \mu\text{m}$. Despite the overlap in the thickness between control and dry eye epithelial layer thickness, these differences were statistically significant. Moreover, these differences were larger than the repeatability measurement fluctuations. In a recent study²⁷ regarding a large population of healthy eyes (373 cases), average epithelial thickness repeatability was measured at $0.8 \pm 0.7 \mu\text{m}$. The ROC results (Table 2) are indicative of the clinical screening facility of average epithelial thickness as a dry eye indicator, although one must be cautious, as the false positive rate, as well as the miss rate are in the order of 15%. We thus suggest that overall epithelial thickness may be a clinical indicator for dry eye.

Epithelial thickening may also be an alarming indication for corneal abnormality. In previous investigation of 3-dimensional epithelial thickness in keratoconic eyes,^{13,28} we identified an overall thicker epithelium, which might be a result of a reactive process; the epithelium appears to thicken in less “rigid” corneas possibly owing to being more susceptible to mechanical variations produced by 1 or a combination of factors, including eye rubbing and increased blinking mechanism.²⁹ The differentiating factor among the thicker “dry eye” and the thicker keratoconic epithelium exists in the topographic thickness variability. In normal eyes we measured an average of $1.8 \pm 1.1 \mu\text{m}$ (present study), and $1.8 \pm 0.9 \mu\text{m}$ in a study of a large, healthy population.²⁷ In the dry eye population (present study) the topographic thickness variability was $2.5 \pm 1.5 \mu\text{m}$, slightly larger than in the “healthy eye” population, while in the keratoconic study thickness variability was found to be

TABLE 2. Receiver Operating Characteristic Curve Analysis Results Showing the Performance of the Central and the Average Epithelial Thickness as Binary Classifier System Between Normal and Dry Eye Cases.

Test Result Variables	Area Under the Curve	Standard Error ^a	Asymptotic Significance ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Central epithelial thickness	0.908	±0.025	0.000	0.860	0.957
Average epithelial thickness	0.932	±0.021	0.000	0.891	0.973

^aUnder the nonparametric assumption.
^bNull hypothesis: true area = 0.5.

significantly larger (up to 10.3 μm),²⁸ thus enabling differentiation.

Dry eye epithelial measurements by the AS-OCT device in this study might also be influenced by the specific imaging in the RtVue. In a previous OCT study of epithelial thickness by Francoz and associates²⁵ with different instrumentation, such difference between central epithelial thickness between a middle-aged normal (48.8 ± 3.0 μm) and dry eye population (49.0 ± 4.1 μm) was much smaller. This can be attributed to the investigative differences: in the current study average epithelial thickness was accurately reported on the select meridian scans and interpolated on the space between, while the study by Francoz and associates implemented manual position on select scanned meridians to measure epithelial thickness. The different geographic locale might have also been a factor.

Further cell morphology studies of this increased epithelial thickness associated with dry eye (ie, with confocal microscopy) may be warranted to differentiate the possible causes, which may include epithelial hypertrophy/hyperplasia, swollen cells, and an increase in the number of cellular layers, possibly attributed to insidious injury by a deficient tear film.

One may wonder why one would use this criterion of augmented epithelial thickness when it takes a few seconds

on the slit lamp to perform the TBUT, and Schirmer strips do not take long either, given that both options are established and they continue to be the “gold standard.” We believe that the clinical difference observed may nevertheless play a role in objective routine screening and treatment assessment that may precede the specific dry eye measurements (such as TBUT and Schirmer) that may or may not be part of the screening protocol. In addition, the proposed screening by AS-OCT provides a highly repeatable, quantitative, accurate, and easy-to-document procedure. The findings reported herein may also be very useful in the screening of refractive surgery candidates, and even in the assessment of postoperative iatrogenically induced dry eye.³⁰

The anticipated clinical ramifications of the application are prospectively very positive, since this screening indicator is based on a commercially available instrument that can be easily integrated in the daily clinical practice and with increasing clinical screening potential.

This study suggests that there is a statistically significant thicker corneal epithelium in the mid-40s-aged female population, in comparison to an age-matched control population. Advantages of this measurement are speed, no need for corneal contact, facility, and repeatability. Larger studies may further explain and validate these initial findings.

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Biosketch

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Biosketch

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