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Persistent dry eye syndrome after and late functional outcomes of excimer laser correction for myopia

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Background: *Laser In Situ Keratomileusis (LASIK) is the laser vision correction procedure of choice for refractive surgeons and accounts for 80% to 85% of the procedures. Dry eye syndrome (DES) is the most common complication of LASIK, with 20% of patients having this complication at 6 months after intervention. Chronic DES after LASIK can cause epithelial hyperplasia, which may be associated with myopic regression.*
Purpose: *To assess the impact of DES after ELC for myopia on the late functional outcomes.*
Material and Methods: *Sixty-five myopic patients (130 eyes) were divided into two groups, group 1 (a LASIK group) and group 2 (a FemtoLASIK group). The control group was composed of 40 individuals (80 eyes). An examination was performed before surgery and throughout the study and included manifest and cycloplegic refraction, corneal topography, anterior segment optical coherence tomography (AS-OCT), tear production, tear film stability and ocular surface staining. Follow-up duration was 12 months.*
Results: *A myopic regression of 0.5 ± 0.1 D was observed in eyes with postoperative DES. At 6 months after ELC for myopia, study patients had a 10.7% incidence of myopic regression of 0.5 ± 0.1 D. The epithelial thickness in the central zone increased by 7.9 ± 0.25 μm, and in the peripheral zone, by 2.0 ± 0.3 μm; corneal irregularity measurement (CIM) increased to 3.01 ± 0.12 μm, and ocular surface staining score, from 0.22 ± 0.08 to 2.3 ± 0.08, over the follow-up period in patients with persistent DES. Patients without DES exhibited neither myopic regression nor ocular surface staining at 6 months, with their CIM values being in the range of 0.49–1.68 μm. An increase in the epithelial thickness in the central zone was by no more than 2.5±0.3 μm larger than that in the peripheral zone, and mean manifest refraction was +0.12 ± 0.1 D.*
Conclusion: *First, we found that 10.7% of our study patients had signs of persistent DES and a myopic regression of 0.5 ± 0.1 D after ELC for myopia. Second, the post-ELC increase in central corneal epithelial thickness over the follow-up period was 37.5% smaller in patients without DES than in patients with DES. Third, corneal epithelial thickness values were 6.4% lower in patients with myopia than in individuals without refractive abnormalities. Fourth, corneal topography maps of patients with DES show irregular astigmatism, which causes a decreased quality of vision associated with changes in epithelial thickness and myopic regression after ELC for myopia. Finally, the presence of corneal epithelial fluorescein staining can be considered to be evidence of DES-induced damage to the epithelium after ELC for myopia.*

Keywords:
excimer laser correction, myopia, persistent dry eye syndrome, myopic regression

Introduction

In 2020, an estimated 161 million people worldwide were blind or had moderate to severe vision impairment from uncorrected refractive error, the leading cause of vision impairment.[1] Worldwide, a total of 123 million people are estimated to be visually impaired from uncorrected refractive errors.[2]

Optical methods as well as refractive surgery are used for the correction of ametropia. Laser In Situ Keratomileusis (LASIK) will be the laser vision correction (LVC) procedure of choice for many years to come and accounts for 80% to 85% of the procedures.[3] In the Patient-Reported Outcomes With Laser In Situ Keratomileusis (PROWL) Studies conducted by the Food and Drug Administration (FDA), the rates of dissatisfaction with vision ranged from 1% to 4%, and the rates of dissatisfaction with surgery ranged from 1% to 2%.[4]

LASIK is a safe and effective surgical option for treatment of refractive errors; however, dry eye syndrome (DES) is a frequent consequence of LASIK. Postoperative dry eye affects approximately 60% of patients at 1 month postoperatively and 20% at 6 months [5].

In 2001, Wilson [6] described a phenomenon of LASIK-induced neurotrophic epitheliopathy (LINE), in which corneal fluorescein staining occurs at the flap, whereas the epithelium of the cornea/flap interface remains intact. In femto LASIK, a femto laser is used to create a corneal flap.

Both LASIK and femto LASIK affect the development and progression of dry eye, with the signs and symptoms being usually transient in nature and not depending on the method.[7]

We have reported previously [7, 8, 9] that 10% of the patients showing no signs of DES preoperatively had persistent DES after ELC, whereas others [10] estimated the incidence of persistent post-LASIK dry eye to be as high as 20%.

The corneal surface is characterized by a complex interaction the tear film, epithelium and surface stroma. [11, 12] Corneal topography maps of patients with DES show irregular astigmatism, and these patients frequently have symptoms of a decreased quality of vision. Tear film abnormalities can contribute to surface irregularity, resulting in epithelial cell injury and death.[13] There is clinical evidence that persistent post-LASIK dry eye may cause epithelial hyperplasia and stromal remodeling. [10] When the epithelial thickening of the central regions exceeds the midperipheral regions, it will increase the optical power in the central regions, which is equivalent to adding a convex lens on the anterior corneal surface. The epithelial hyperplasia seen in this case has been associated with post-LASIK myopic regression.[14]

Studies in the field selected are important to reduce the incidence of visual impairment due to uncorrected refractive errors, because LASIK is a common procedure worldwide, post-LASIK dry eye is extremely common, and there is a potential association between the persistent DES and the functional outcome of ELC for myopia.

The purpose of the study was to assess the impact of DES after ELC for myopia on the late functional outcomes.

Material and Methods

Approval for the study was obtained from the Bioethics Committee, the Shupik National Healthcare University of Ukraine. The procedures followed were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association, European Convention on Human Rights and Biomedicine (1977), relevant provisions of WHO's Constitution, Council for International Organizations of Medical Science, International Code of Medical Ethics (1983), and Ministry of Health Order No. 690, dated 23 September, 2009.

This was a prospective, observational, interventional clinical case-control study.

Informed consent was obtained from all participants.

Sixty-five myopic patients (130 eyes) were divided into two groups, group 1 (a LASIK group) and group 2 (a FemtoLASIK group). Patient age ranged from 20 to 44 years, and there were 30 men and 35 women. Of the 130 eyes, 58 (44.6%) were mildly myopic, 44 (33.8%), moderately myopic, and 28 (21.5%), highly myopic. In addition, 40 eyes (30.7%) had compound myopic astigmatism of 2 D or less. Mean preoperative spherical equivalent (SE) manifest refraction was 3.12 ± 0.4D (range, -1.0 to -7.5D).

The control group was included in the study to assess the impact of refractive abnormalities on the morphological changes in the cornea. The group was composed of 40 individuals (17 men and 23 women; 80 eyes) without refractive abnormalities, signs or symptoms of DES, or history of eye surgery.

Patients of group 1 (68 eyes) received thin-flap LASIK using an EX500 Excimer Laser system (Alcon, Fort Worth, Texas), with a 110-μm corneal flap created by a Carriazo-Pendular microkeratome and the optic zone ranging in diameter from 6.0 to6.5 mm. Patients of group 2 (62 eyes) received thin-flap FemtoLASIK using an EX500 Excimer Laser system (Alcon, Fort Worth, Texas), with a 110-μm corneal flap created by an FS200 femto laser (Alcon), and the optic zone ranging in diameter from 6.0 to 6.5 mm. All interventions were performed by one team of surgeons.

An ophthalmological examination was performed before and 1 week, 1, 3 and 6 months after ELC for myopia, and included uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), manifest and cycloplegic refraction, keratometry, optical biometry, corneal topography, biomicroscopy, corneal OCT, tear production. Corneal staining was graded using the Oxford Scheme for grading ocular surface staining in dry eye. Controls underwent the same examination.

Corneal epithelial thickness was measured using an Anterior Segment Spectral Domain® OCT (AS-OCT) device (REVO SOCT Copernicus, OPTOPOL Technology, Zawiercie, Poland). Scans reflected the corneal thickness in the central, parancetral and peripheral zones with diameters of 2 mm, 2-5 mm, and 5-7 mm, respectively. Images with poor scan quality (less than 7/10 signal strength index) were excluded. Epithelial thickness in the central 2-mm zone, mean epithelial thickness in the central 5-mm zone, and mean peripheral epithelial thickness in 8 meridians for all participants of the study, and differences in longitudinal changes in corneal thickness for different zones of the study groups were assessed.

In addition, ocular surface fluorescein staining was assessed. A fluorescein paper strip was moistened with a drop of isotonic saline and placed on the lower lid margin near the external angle of the eye. The corneal surface was examined using a broad-beam of slit lamp with a blue filter. Fluorescein staining of the conjunctiva was observed using a broad-beam of slit lamp with a yellow filter. The Oxford Scheme for grading ocular surface staining in dry eye was employed.[15]

Corneal topography measurements were obtained using the Zeiss Atlas 9000 corneal topographer (Carl Zeiss Meditec, Inc. Jena, Germany). The state of the corneal surface was monitored by the assessment of corneal irregularity measurement (CIM), with CIM values ranging from 0.42 to 5.33 μm and classified as normal (0.49-1.68 μm), borderline (1.69-3.01 μm) and abnormal (0–0.42 μm or 3.02–5.33 μm).[16]

Statistical analyses were performed using SPSS 61 11.0, MedStat and MedCalc v.15.1 (MedCalc Software

bvba). A paired t-test (two-tailed) was used to analyze the difference between baseline and post-intervention measures. A p-value of < 0.05 was considered statistically significant.

Follow-up duration was 6 months.

Results

At baseline, function tests showed mild dry eye in some patients of group 1 and group 2. Ocular surface fluorescein staining showed mild irritation in 10.3% and 11.3% of patients of group 1 and group 2, respectively, but ocular surface irritation was not found in any control. Mean central epithelial thickness and mean peripheral epithelial thickness as assessed by AS-OCT in patients at baseline were 50.1±1.2 μm and 57±1.0 μm, respectively, and in controls, 53.1 ± 1.2 μm and 58.2 ± 1.3 μm, respectively ($p < 0.05$). In addition, mean corneal irregularity measurement (CIM) in groups 1 and 2 (1.43 ± 0.07 μm and 1.45 ± 0.06 μm, respectively) was significantly larger than in controls (0.56 ± 0.05 μm, $p < 0.05$).

At 1 week after ELC for myopia, central corneal epithelial thickness in both study groups increased by 1.4 ± 0.5 μm, whereas peripheral epithelial thickness in groups 1 and 2 increased by 1.0 ± 0.2 μm and 1.1 ± 0.2 μm, respectively.

At 1 month after ELC for myopia, central corneal epithelial thickness in both study groups increased by 3.6 ± 0.4 μm compared to the previous time point, and there was no statistical difference between the results for the 2-mm zone and 5-mm zone.

At 3 months, corneal epithelial thickness of the overall corneal surface in both study groups increased by 2.0 ± 0.2 μm.

At 6 months after ELC for myopia, central corneal epithelial thickness in groups 1 and 2 increased by 0.1 ± 0.03 μm and 0.05 ± 0.01 μm, respectively ($p < 0.05$).

Mean CIM in groups 1 and 2 increased by 14% by month 1 and did not change thereafter.

Ocular surface staining was found at 1 week in 50% of patients of group 1 and 51.6% of patients of group 2, at 1 month, in 39.7% of patients of group 1 and 40.3% of patients of group 2, and at 3 months, in 35.3%% of patients of group 1 and 35.4% of patients of group 2. In addition, at 6 months, ocular surface staining was found in 11% of patients of both study groups, and mean manifest refraction SE was +0.12 ± 0.1D for group 1 and +0.11 ± 0.09D for group 2.

A myopic regression of 0.5 ± 0.1 D was observed in eyes with postoperative DES. At 6 months after ELC for myopia, study patients had a 10.7% incidence of myopic regression of 0.5 ± 0.1 D. At 1 week after surgery, mean SE manifest refraction for total study patients was +0.12 ± 0.05 D.

We conducted statistical analysis of longitudinal data in dry eyes exhibiting post-LASIK myopic regression. Over the postoperative period, the epithelial thickness in the central zone increased by 7.9 ± 0.25 μm, and in the peripheral zone, by 2.0 ± 0.3 μm. By 1 week after ELC for myopia, total epithelial thickness increased by 1.3 ± 0.2 μm. At 1 month, the epithelial thickness in the central zone increased by 3.9 ± 0.2 μm, and in the peripheral zone decreased by 1.0 ± 0.3 μm. At 3 months, the epithelial thickness in the central zone increased by 2.2 ± 0.22 μm, and in the peripheral zone, by 1.7 ± 0.28 μm. At 6 months, the epithelial thickness in the central zone increased by 0.5 ± 0.1 μm, and in the peripheral zone, did not change, compared to the previous time point. In addition, at 6 months after ELC for myopia, mean CIM in patients with persistent DES was 3.01 ± 0.12 μm. Moreover, at 6 months after ELC for myopia, mean Oxford staining score in patients with persistent DES was 2.3 ± 0.09.

In patients without post-LASIK myopic regression, the staining and CIM value were normal at 6 months. In addition, an increase in the epithelial thickness in the central zone was by no more than 2.5±0.3 μm larger than that in the peripheral zone, and mean manifest refraction was +0.12 ± 0.1 D.

Table 1 shows Oxford corneal/conjunctival staining scores for groups 1 (LASIK) and 2 (femtoLASIK) at baseline, 1-week post-intervention, and 1, 3 and 6 month-post intervention, as well as for controls. At baseline, the Oxford corneal/conjunctival staining scores for groups 1 and 2 were higher than the scores for controls (Table 1). At week 1, month 1 and month 3, Oxford corneal/conjunctival staining scores for groups 1 and 2 were significantly increased compared to baseline values.

A regression in the grade of Oxford corneal/conjunctival staining for groups 1 and 2 was noted at 6 months after ELC for myopia. There was no significant difference in the grade of staining between the treatment groups. The presence of corneal epithelial fluorescein staining can be considered to be evidence of DES-induced damage to the epithelium.

Table 2 shows corneal irregularity measurement (CIM) values for groups 1 (LASIK) and 2 (femtoLASIK) at baseline, 1-week post-intervention, and 1, 3 and 6 month-post intervention, as well as for controls. CIM values for groups 1 and 2 were increased at month 1 and month 3 compared to baseline and controls, but remained within the reference range throughout the follow-up period (Table 2).[16]

Table 3 shows corneal epithelial thickness in different zones as assessed by AS-OCT for groups 1 (LASIK) and 2 (femtoLASIK) at baseline, 1-week post-intervention, and 1, 3 and 6 month-post intervention, as well as for controls. There was a difference in corneal epithelial thickness between the treatment groups and controls (Table 3). In myopes, corneal epithelial thickness at baseline was thinner than in controls. Corneal epithelial thickness values after surgery for groups 1 and 2 were increased compared to baseline and controls, the largest increase noted 1 month after surgery for both groups. There was no significant change in corneal epithelial thickness in the treatment groups from month 3 till the end of the follow-up period. The central corneal epithelial thickness increased greater

than the peripheral corneal epithelial thickness. There was no significant difference in longitudinal changes in epithelial thickness between 2-mm and 5-mm zones for both treatment groups.

Table 4 shows manifest refraction values for groups 1 (LASIK) and 2 (femtoLASIK) at baseline, 1-week post-intervention, and 1, 3 and 6 month-post intervention, as well as for controls.

There was no significant difference in the manifest refraction between the time points and between treatment groups (Table 4).

Discussion

The study findings included the following. A relationship was noted between the persistent post-LASIK DES, myopic regression and increased central corneal epithelial thickness. Corneal irregularity measurement (CIM) provided by corneal topography was higher in patients with DED who exhibited changes in corneal epithelial thickness. In addition, these patients exhibited corneal fluorescein staining, which can be considered to be evidence of DES-induced damage to the epithelium. The CIM had a relationship with the refractive regression in both treatment groups.

The clinical symptoms of DES such as ocular irritation, photosensibilization, and vision fluctuation may be signs of damage to the corneal epithelium.[17] In the current study, there was OCT and corneal topographic evidence of the morphological changes confirming corneal surface damage in persistent DES. Bearing this in mind, we believe that patients exhibiting clinical signs of DES before and after ELC should have epithelial thickness measurements and corneal topography throughout at least 6 months.

Of note that, in patients with DES, corneal topography may reveal mild epithelial abnormalities which are not always revealed by biomicroscopy. CIM is a statistical measurement which uses topographic data from the central area of the cornea and compares it to the best fit surface found. It determines the regularity or irregularity of the corneal surface used for vision. The CIM measurement determines how much the actual corneal surface varies from a smooth fitted ellipsoidal toric surface as Root Mean Square (RMS) error in micrometers (μm). The fitted surface includes any regular astigmatism which may be present. The higher the irregularity index, the more uncorrectable or uneven the surface is optically, thereby highlighting irregular astigmatism that often results in visual distortions. CIM uses the thousands of data points within the first fourteen rings of the corneal topography data to determine the difference in "height" or elevation between the patient's cornea and the best matching, perfect model ellipsoidal toric cornea.[16]

OCT, a noncontact method, accurately shows the corneal epithelial thickness (CET) pattern thanks to its high axial resolution.[17] The OCT produced excellent repeatability for both corneal epithelial thickness and corneal thickness measurements.[18, 19]

In the current study, mean central epithelial thickness and mean peripheral epithelial thickness in controls were 53.1 ± 1.2 μm and 58.2 ± 1.3 μm, respectively. Our findings are in agreement with those of others. Three-dimensional thickness mapping of the corneal epithelium demonstrated that the epithelial thickness is not evenly distributed across the cornea. Central corneal epithelial thickness has been previously measured with the reported values varying between 48±5 μm and 59.9±5.9 μm. The

Table 1. Oxford staining scores for the LASIK (group 1) and FemtoLASIK (group 2) at baseline and at 1 week, 1 month, 3, 6 and 12 months after excimer laser correction (ELC) for myopia and for the control group

	Baseline		1 week after ELC		1 month after ELC		3 months after ELC		6 months after ELC		Control group
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Oxford ocular surface staining score	0.22 ±0.08	0.22 ±0.08	2.18 ±0.08*	2.19 ±0.08*	2.2 ±0.08*	2.3 ±0.08*	1.67 ±0.1	1.7± 0.1	0.22 ±0.07	0.23 ±0.07	0.15±0.05
	t=0 p=1.0		t=0.09 p=0.93		t=0.88 p=0.38		t=0.21 p=0.83		t=0.1 p=0.92		$^1t_{baseline}$=0.74; p=0.46; $^1t_{1week}$=21.52; p=0.0000; $^1t_{1mnth}$=21.73; p=0.0000; $^1t_{3mnth=}$13.60; p=0.0000; $^1t_{6mnth=}$0.81; p=0.42; $^2t_{baseline}$=0.74; p=0.46; $^2t_{1week=}$21.62; p=0.0000; $^2t_{1mnth}$=22.79; p=0.0000; $^2t_{3mnth=}$13.86; p=0.0000; $^1t_{6mnth=}$0.93; p=0.35.
	$^1t_{baseline\ -1week}$=17.32, p=0.0000; $^1t_{baseline\ -1mnth}$=17.5, p=0.0000; $^1t_{baseline\ -3mnth}$=11.32, p= 0.0000; $^1t_{baseline\ -6mnth}$=0, p=1.0; $^2t_{baseline\ -1week}$=17.41, p=0.0000; $^1t_{baseline\ -1mnth}$=18.38, p=0.0000; $^1t_{baseline-3mnth}$=11.56, p= 0.0000[1]; $t_{baseline\ -6mnth}$=0.09, p=0.93.										

Note: 1t, Student's t test for patients undergoing thin-flap LASIK; 2t, Student's t test for patients undergoing thin-flap FemtoLASIK; *, significant difference compared to controls and baseline for the same treatment group (paired t-test)

Table 2. Topography corneal irregularity (CIM) values for the LASIK (group 1) and FemtoLASIK (group 2) at baseline and at 1 week, 1 month, 3, 6 and 12 months after excimer laser correction (ELC) for myopia and for the control group

	Baseline		1 week after ELC		1 month after ELC		3 months after ELC		6 months after ELC		Control group
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
CIM (Corneal Irregularity Measurement)	1.43±0.07	1.45±0.06	1.61±0.08	1.62±0.09	1.63±0.1	1.65±0.1	1.64±0.15	1.65±0.13	1.638±0.13	1.649±0.14	0.56±0.05
	t=0.22 p=0.83		t=0.08 p=0.93		t=0.14 p=0.89		t=0.05 p=0.96		t=0.05 p=0.96		$^1t_{baseline}$=10.11; p=0.0000; $^1t_{1week}$=11.13; p=0.0000; $^1t_{1mnth}$=9.57; p=0.0000; $^1t_{3mnth=}$6.83; p=0.0000; $^1t_{6\ mnth\ =}$7.75; p=0.0000; $^2t_{baseline}$=11.4; p=0.0000; $^2t_{1week=}$10.3; p=0.0000; $^2t_{1mnth}$=9.75; p=0.0000; $^2t_{3mnth=}$7.83; p=0.0000; $^2t_{6\ mnth\ =}$7.33; p=0.0000.
	$^1t_{baseline\ -1week}$=1.69, p=0.09; $^1t_{baseline\ -1mnth}$=1.64, p=0.1; $^1t_{baseline\ -3mnth}$=1.27, p= 0.2; $^1t_{baseline\ -6\ mnth}$=1.42, p=0.16; $^2t_{baseline\ -1week}$=1.57, p=0.12; $^2t_{baseline\ -1mnth}$=1.71, p=0.09; $^2t_{baseline\ -3mnth}$=1.4, p= 0.17; $^2t_{baseline\ -6\ mnth}$=1.31, p=0.19.										

Note: 1t, Student's t test for patients undergoing thin-flap LASIK; 2t, Student's t test for patients undergoing thin-flap FemtoLASIK; *, significant difference compared to controls and baseline for the same treatment group (paired t-test)

Table 3. Corneal epithelial thickness in different zones as assessed by AS-OCT for the LASIK (group 1) and FemtoLASIK (group 2) at baseline and at 1 week, 1 month, 3, 6 and 12 months after excimer laser correction (ELC) for myopia and for the control group

	Baseline		1 week after ELC		1 month after ELC		3 months after ELC		6 months after ELC		Control group
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Epithelial thickness in the 2-mm zone	50.1±.2	50.3±1.3	51.5±1.3	51.7±1.2	55.1±1.4	55.3±1.6	57.1±2.3	57.3±2.1	57.2+2.2	57.35+2.2	53.1±1.2
	t=0.11 p=0.91		t=0.11 p=0.91		t=0.09 p=0.93		t=0.06 p=0.95		t=0.05 p=0.96		
	$^1t_{baseline\ -1week}$=0.79, p=0.43; $^1t_{baseline\ -1mnth}$=2.71, p=0.008; $^1t_{baseline\ -3mnth}$=2.7, p= 0.08; $^1t_{baseline\ -6\ mnth}$=2.83, p=0.005; $^2t_{baseline\ -1week}$=0.79, p=0.43; $^2t_{baseline\ -1mnth}$=2.43, p=0.02; $^2t_{baseline\ -3mnth}$=2.83, p= 0.005; $^2t_{baseline\ -6\ mnth}$=2.78, p=0.006.						*$^1t_{baseline}$=1.77, p=0.08; $^1t_{1week}$=0.9, p=0.37; $^1t_{1mnth}$=1.08, p=0.28; $^1t_{3mnth}$=1.54, p= 0.13; $^1t_{6\ mnth}$=1.64, p=0.1; $^2t_{baseline}$=1.58, p=0.12; $^2t_{1week}$=0.82, p=0.41; $^2t_{1mnth}$=1.1, p=0.27; $^2t_{3mnth}$=1.74, p= 0.08; $^2t_{6\ mnth}$=1.7, p=0.09.				
Epithelial thickness in the 5-mm zone	51±1.1	51.2 ±1.15	52.5 ±1.2	52.8 ±1.2	56.1 ±1.5	56.4±1.4	58.2±2.1	58.5±2.0	58.3±2.2	58.52±2.15	54.1 ±1.3
	t=0.13 p=0.9		t=0.18 p=0.86		t=0.15 p=0.88		t=0.1 p=0.92		t=0.03 p=0.97		
	$^1t_{baseline\ -1week}$=0.92, p=0.36; $^1t_{baseline\ -1mnth}$=2.74, p=0.007; $^1t_{baseline\ -3mnth}$=3.04, p= 0.003; $^1t_{baseline\ -6\ mnth}$=2.97,p=0.004; $^2t_{baseline\ -1week}$=0.96, p=0.34; $^1t_{baseline\ -1mnth}$=2.87, p=0.005; $^1t_{baseline\ -3mnth}$=3.16, p= 0.002; $^1t_{baseline\ -6\ mnth}$=3.0, p=0.003						*$^1t_{baseline}$=1.82, p=0.07; $^1t_{1week}$=0.9, p=0.37; $^1t_{1mnth}$=1.01, p=0.31; $^1t_{3mnth}$=1.66, p= 0.09; $^1t_{6\ mnth}$=1.64, p=0.1; $^2t_{baseline}$=1.67, p=0.1; $^2t_{1week}$=0.73, p=0.46; $^2t_{1mnth}$=1.2, p=0.23; $^2t_{3mnth}$=1.84, p= 0.07; $^2t_{6\ mnth}$=1.76, p=0.08.				
Epithelial thickness in the 5-7-mm zone	57±1.0	57.1 ±1.2	58 ±1.3	58.2 ±1.2	58 ±1.7	58.2±1.6	60 ±1.9	60.2±2.0	60.1±2.3	60.25±2.2	58.2±1.3
	t=0.06 p=0.95		t=0.11 p=0.91		t=0.09 p=0.93		t=0.07 p=0.94		t=0.05 p=0.96		
	$^1t_{baseline\ -1week}$=0.61, p=0.54; $^1t_{baseline\ -1mnth}$=0.51, p=0.61; $^1t_{дbaseline\ -3mnth}$=1.4, p= 0.16; $^1t_{baseline\ -6\ mnth}$=1.24, p=0.22. $^2t_{дbaseline\ -1week}$=0.65, p=0.52; $^1t_{baseline\ -1mnth}$=0.55, p=0.58; $^1t_{baseline\ -3mnth}$=1.33, p= 0.19; $^1t_{baseline\ -6\ mnth}$=1.26, p=0.21						*$^1t_{baseline}$=0.73, p=0.47; $^1t_{1week}$=0.11, p=0.9; $^1t_{1mnth}$=0.09, p=0.93; $^1t_{3mnth}$=0.78, p= 0.44; $^1t_{6\ mnth}$=0.72, p=0.47; $^2t_{baseline}$=0.62, p=0.54; $^2t_{1week}$=0, p=1.0; $^2t_{1mnth}$=0, p=1.0; $^2t_{3mnth}$=0.84, p= 0.4; $^2t_{6\ mnth}$=0.8, p=0.42.				

Note: 1t, Student's t test for patients undergoing thin-flap LASIK; 2t, Student's t test for patients undergoing thin-flap FemtoLASIK; *, significant difference compared to controls and baseline for the same treatment group (paired t-test)

Table 4. Manifest refraction values for the LASIK (group 1) and FemtoLASIK (group 2) at baseline and at 1 week, 1 month, 3, 6 and 12 months after excimer laser correction (ELC) for myopia and for the control group

	1 week after ELC		1 month after ELC		3 months after ELC		6 months after ELC	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Manifest refraction values	0.12±0.05	0.11±0.05	0.1±0.05	0.12±0.05	0.11±0.08	0.12±0.08	0.12±0.1	0.11±0.09
	t=0.14 p=0.89		t=0.28 p=0.78		t=0.09 p=0.93		t=0.07 p=0.94	

Note: t, Student's t test for patients undergoing thin-flap LASIK or thin-flap FemtoLASIK; *, significant difference compared to controls and baseline for the same treatment group (paired t-test)

corneal epithelium accounts for an average of +1.03 D of the power of the eye at the central 2-millimeter diameter zone and +0.85 D at the 3.6-millimeter diameter zone. [17, 20, 21] Theoretical calculation of induced refractive errors can range from -1.32 to +1.27 D, in accordance with different epithelial profiles.[22]

In a study by Reinstein and colleagues [23], an epithelial thickness profile was measured by Artemis 1 very high frequency digital ultrasound scanning across the central 10-mm diameter of the cornea of 110 eyes of 56 patients who presented for refractive surgery assessment. The mean epithelial thickness at the corneal vertex was 53.4 ± 4.6 μm (the tear-film was not incorporated in the corneal or epithelial thickness measurement).

The AS-OCT is a valuable method for assessing corneal epithelial thickness after LASIK. CET mapping can also convey information on whether myopic regression after excimer laser treatment is due to epithelial hyperplasia or corneal biomechanical changes.[24, 25] We found that the mean epithelial thickness after LASIK increased by an average value of about 5 μm. In patients with persistent DES, the epithelial thickness in the central zone increased by 7.9 ± 0.25 μm. Others [26] have also reported previously that the epithelial thickness changes after refractive surgery may affect treatment outcomes. It is a common phenomenon for the anterior surface areas flattened by laser ablation to be compensated by epithelial remodeling and thickening to maintain good optical quality of the cornea, after corneal reflective surgery.[27] Reinstein et al [28] found that the epithelium thickened at all points within the 7-mm zone by up to 5 μm between 1 day and 1 month after LASIK for myopia, with the maximum change in SE refraction being -0.39 D. However, epithelial thickening after LASIK does not always result in myopic regression; it is the central epithelial thickening that is of importance. Kanellopoulos and Asimellis [29] showed that the epithelium thickened by 6 μm in the central regions but by approximately 10 μm in the midperipheral regions one year after LASIK for high myopia. The risk for epithelial hyperplasia-induced refractive regression after LASIK was reportedly increased in patients with chronic dry eye. [30]

Manifest refraction value is an important measure for assessing the outcome of ELC for myopia. The manifest refraction is measured without cycloplegia of the eyes, with the measurement carried out using a manual or automatic phoropter. At 6 months after ELC for myopia, 10.7% of our study patients had a myopic regression of 0.5 ± 0.1 D, signs of DES and morphological epithelial changes revealed by AS-OCT and corneal topography.

Studies are underway on the mechanisms of refractive changes due to epithelial damage in ELC-induced chronic dry eye.[31] We believe that further research of the biochemical and immunological composition of the tear film is warranted to identify the key factors of DES after ELC for myopia.

Therefore, our study (1) demonstrated the impact of persistent DES on the refractive outcome of LASIK and femtoLASIK for myopia, and (2) provided AS-OCT, corneal topography and corneal fluorescein staining evidence of the details of typical structural changes in the corneal epithelium.

Conclusion

First, a relationship was found between the persistent DES and the myopic regression after ELC for myopia. We found that 10.7% of our study patients had a myopic regression and signs of persistent DES.

Second, there was AS-OCT evidence that the post-ELC increase in central corneal epithelial thickness over the follow-up period was 37.5% smaller in patients without DES than in patients with DES.

Third, mean AS-OCT-based corneal epithelial thickness values were 6.4% lower in patients with myopia than in individuals without refractive abnormalities.

Fourth, corneal topography maps of patients with DES show irregular astigmatism, which causes a decreased quality of vision associated with changes in epithelial thickness and myopic regression after ELC for myopia.

Finally, the presence of corneal epithelial fluorescein staining can be considered to be evidence of DES-induced damage to the epithelium after ELC for myopia.

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Disclosures

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Abbreviations: *AS-OCT, Anterior Segment Spectral Domain-OCT; CET, corneal epithelial thickness; CIM, corneal irregularity measurement; DES, dry eye syndrome; ELC, excimer laser correction; FDA, Food and Drug Administration; LASIK, Laser-Assisted in Situ Keratomileusis; SE, sphere equivalent; LINE, LASIK-induced neurotrophic epitheliopathy.*