Original Article

Evolution of corneal epithelial remodeling after myopic laser *in situ* keratomileusis surgery measured by anterior segment optical coherence tomography combined with Placido disk

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Purpose: To investigate patterns of short- and long-term variations in corneal epithelial thickness (CET) after myopic laser *in situ* keratomileusis (LASIK) using anterior segment optical coherence tomography (AS-OCT) combined with Placido disk-based topography. **Methods**: In this retrospective study, 36 subjects (72 eyes) who underwent LASIK myopic surgery and 53 healthy subjects (106 eyes) who served as controls were enrolled. AS-OCT (MS-39) was performed in all patients before, 1 day, 1 month, and 6 months after surgery. Statistical analysis was performed to analyze CET changes over time after LASIK and to detect patterns of definitive CET remodeling compared to healthy subjects. Multivariate analysis was performed to look for possible predictors of final CET. **Results**: There was no statistically significant difference between groups in terms of demographic and anterior segment parameters (all $P > 0.05$). After LASIK, all sectors and rings got thicker over time (1.62–8.32 μm; $P < 0.01$). Except for the central sector, all areas achieved the thickest CET value one day after surgery with a progressive epithelial thinning between 1 and 6 months of follow-up. Changes on CET occurred independently of the grade of myopia before LASIK or final refraction ($P > 0.05$). None of the clinical variables studied, including diopters corrected, were found to be correlated with final CET ($P > 0.05$). **Conclusion**: Independent of anterior segment parameters and diopters corrected, CET becomes thicker after LASIK surgery. Central and inner ring sectors thicken more than those more peripheral. CET remodeling after myopic LASIK should be taken into consideration when planning refractive surgery.

Key words: Corneal epithelium, keratomileusis, laser *in situ*, myopia, optical coherence tomography, refractive surgeries procedures

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Corneal epithelium plays a key role as a natural barrier and optical interface that conditions the refractive power of the eye. Recent advances in imaging, such as anterior segment optical coherence tomography (AS-OCT), have allowed noninvasive and *in vivo* mapping of corneal epithelial thickness (CET) with excellent reproducibility and repeatability.[1-3] Besides, the development of new software and devices that include topographic analysis in OCT images has made the CET measurement easy, accurate, and accessible for every ophthalmologist. Clinicians must distinguish healthy from abnormal corneal epithelium as structural and functional changes may result from different corneal conditions such as dry eye, keratoconus, contact lens use or corneal refractive surgery.[4]

Corneal refractive surgeries have undergone an explosive expansion throughout the last decades.[5] The goal of these procedures is to achieve emmetropia or the desired target refraction; thus, it is essential to know all the factors that may influence the accuracy of this surgery. The influence of epithelial profile in refraction has been documented, and variations in CET after corneal refractive procedures have been described.[6-10] Recent studies have also reported undercorrections after myopic LASIK due to higher thickening in central CET than in outer areas.[11] Therefore, changes in epithelial profile after refractive surgery need to be considered because these may result in unplanned refractive outcomes.

The purpose of this article is to investigate patterns of corneal epithelial remodeling after myopic LASIK surgery using AS-OCT combined with Placido disk-based topography. For that purpose, central and peripheral measurements of CET were studied before surgery and over 6 months of follow-up.

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CET values before and after surgery were also compared with healthy subjects to demonstrate significant and definitive epithelial changes. Other clinical and ocular parameters were also analyzed to search for possible predictors of epithelial remodeling.

Methods

This retrospective and observational study included 53 healthy subjects (106 eyes) without prior refractive surgery and 36 subjects (72 eyes) who underwent myopic LASIK surgery at [redacted for review] Clinic between July and October 2018. This work was performed according to the tenets of the Declaration of Helsinki (Fortaeza, 2013) and with the permission of The Provincial Ethics Committee of Málaga. All the patients were contacted and asked for their approval to participate in the study. Written informed consent was then obtained for all the participants.

The inclusion criteria were subjects ≥18 years of age with stable refractive errors (not more than ± 6.5 diopters (D) and astigmatism ±4.5 D, or spherical equivalent less than ± 8.75). Subjects with corneal pathologies (corneal opacity, corneal dystrophies, keratoconus, inflammatory, and allergic or infectious diseases), dry eye disorder, any topical medication, prior ocular surgery, and contact lens wear within 2 weeks before the visit were excluded. Subjects who used topical steroids, antibiotics, or artificial tears with benzalkonium chloride more than 7 days after surgery were also excluded.

All the patients were evaluated at one day, one month, and six months postoperatively. The ophthalmologic examination included best spectacle-corrected visual acuity (BCVA), manifest and cycloplegic refraction (Autokeratorefractometer KR1-Topcon), intraocular pressure, slit-lamp examination, corneal hysteresis measured by Ocular Response Analyzer (Reichert, Depew, NY), corneal tomography and topography (MS-39 device, CSO, Italy), and dilated fundus examination. The control group was formed by healthy subjects who attended our Eye Clinic for preoperative refractive surgical evaluation but did not proceed with surgery.

Instruments

Anterior Segment Spectral Domain-OCT and Placido-disk corneal topography (MS-39, CSO, Firenze, Italy) with a standard scan protocol were performed in all eyes. The device acquires one Placido corneal image and 25 SD-OCT radial scans composed of 1024 A-scans. The MS-39 uses a wavelength of 840 nm, with an axial and transverse resolution of 3.5 μm and 35 μm, and a maximum depth of 7.5 mm. Automatic segmentation provided measurements of nine sectors: one central 3-mm diameter, four inner sectors (inferior, superior, nasal, and temporal) within a ring (3–6 mm in diameter), and four outer areas (inferior, superior, nasal, and temporal) within a ring (6–8 mm diameter). Scans with acquisition quality indices (sections coverage, keratoscopy centration, and keratoscopy coverage) of <80% were excluded.

Technique

LASIK procedure with active compensation of eye movements and a 7D eye-tracker were performed by two experienced surgeons (AMG and JMC) using the Amaris 1050 RS excimer laser system (SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany). Topical eye drops of tetracaine/oxybuprocaine (Double Anesthetic Colircusi®) were instilled as an anesthetic. LASIK flaps were cut using Nidek MK-2000 microkeratome system. The medium flap thickness was 120 μm, and the optical zone values were between 6.5 and 6.7 mm. Tobramicin 0.3% and dexamethasone 0.1% (Tobradex, Novartis, Switzerland) and topical lubrication with artificial tears were prescribed after surgery four times daily for 7 days.

Statistics

SPSS Statistics (IBM-SPSS, version 25.0, Chicago, USA) was used for statistical analysis. All data were presented as average ± standard deviation. Based on an average central CET of 52.24 ± 3.2 μm,[12,13] a variance of 10.72 and a power of 0.90 at a significance level of 0.05, the minimum sample size to detect changes in CET after LASIK of ≥2 μm was 56 cases. Chi-Square and Student's t-tests were performed to detect differences between groups. Within the LASIK group, repeated-measures general linear model was used to detect CET changes over time and Student's *t*-test for paired samples to compare 1- and 6-month mean values with the preoperative visit. Bonferroni's post-test corrections were used for multiple comparisons. Multivariate analysis was used to detect possible correlations between final CET and clinical parameters. The correlation between eyes from the same subject was analyzed and adjusted. Eye variable was also included in the multivariate analysis to control this possible confounding effect. A P value of < 0.05 was considered statistically significant.

Results

In total, 178 eyes from 89 patients were enrolled: 106 eyes from 53 healthy subjects (25 males and 28 females) and 72 eyes from 36 subjects who underwent myopic LASIK (19 males and 17 females). The control group had a mean age of 32.4 ± 10.3 years with a range of 18–54 years and an average spherical equivalent (SE) of − 3.63 ± 3.11 D. The myopic LASIK group had an average of 30.0 ± 5.9 years (range of 21–43 years) and a mean SE of 3.33 ± 1.66 D. No significant differences were achieved between groups in both parameters ($P = 0.076$ and 0.381 for age and SE, respectively). Table 1 shows the comparison of baseline parameters between both groups.

CET

The baseline means and standard deviations of CET at different sectors are shown in Table 2. No statistically significant differences between groups were detected in sectorial CET (all $P > 0.05$). The CET was found to be thinnest in the outer superior location with mean values of 50.66 ± 4.96 μm and 50.86 ± 4.09 μm in the control and LASIK group, respectively. The thickest region in controls and LASIK groups was the outer nasal with average values of 55.02 ± 3.60 μm and 55.21 ± 2.94 μm, respectively. The CET inner ring mean values in controls and LASIK groups were 52.99 ± 3.36 μm and 53.23 ± 3.12 μm, respectively, and the CET outer ring values were 53.48 ± 3.67 μm and 53.73 ± 3.05 μm, respectively. In both groups, the CET outer ring was thicker than the inner ring and the central CET (all $P < 0.01$). The univariate model that included the eye as a fixed factor showed significant differences between the epithelial thicknesses in both groups regardless of the eye studied (group factor: $P < 0.05$; eye factor: $P > 0.05$). In both controls and healthy subjects, no significant differences were found between eyes from the same subject in any of the ocular variables studied (all $P > 0.05$).

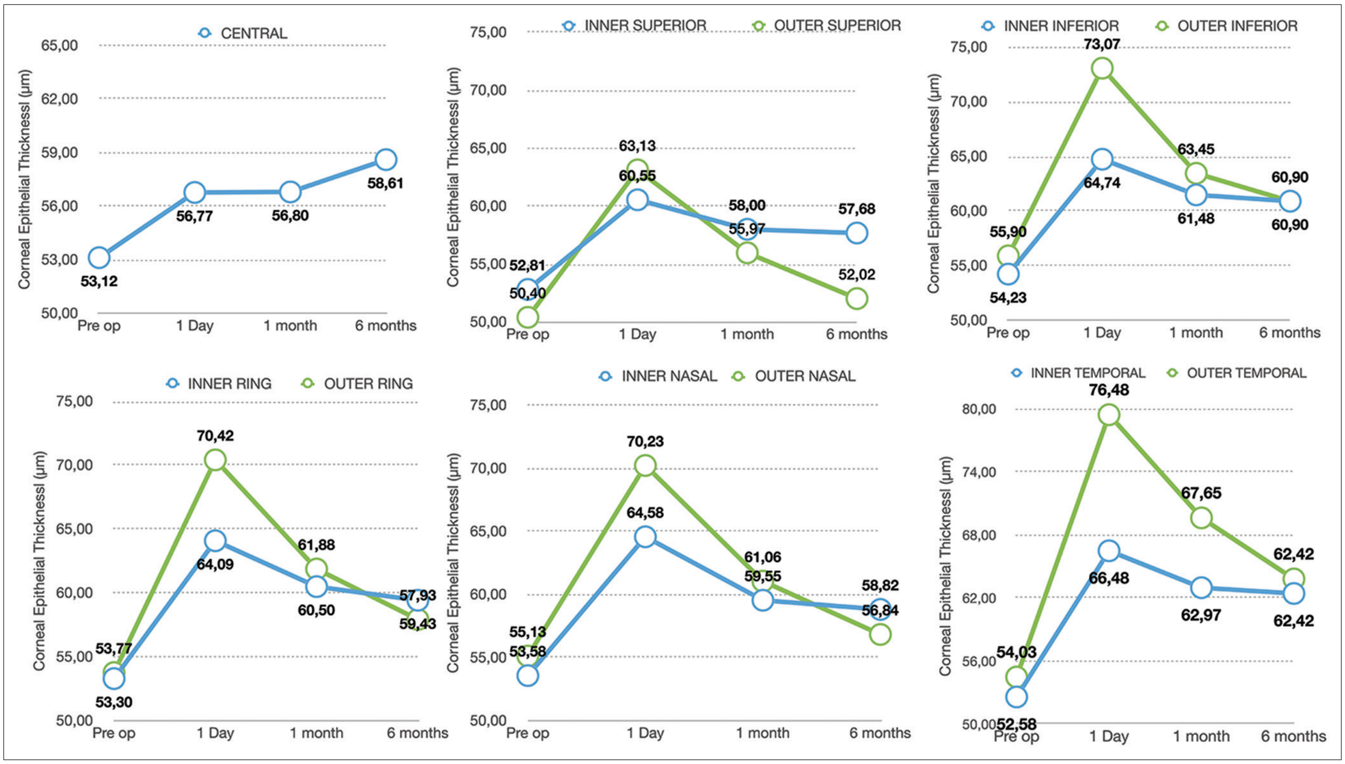

Figure 1: Mean values of sectorial corneal epithelial thickness at baseline and 1 day, 1 month, and 6 months after LASIK surgery

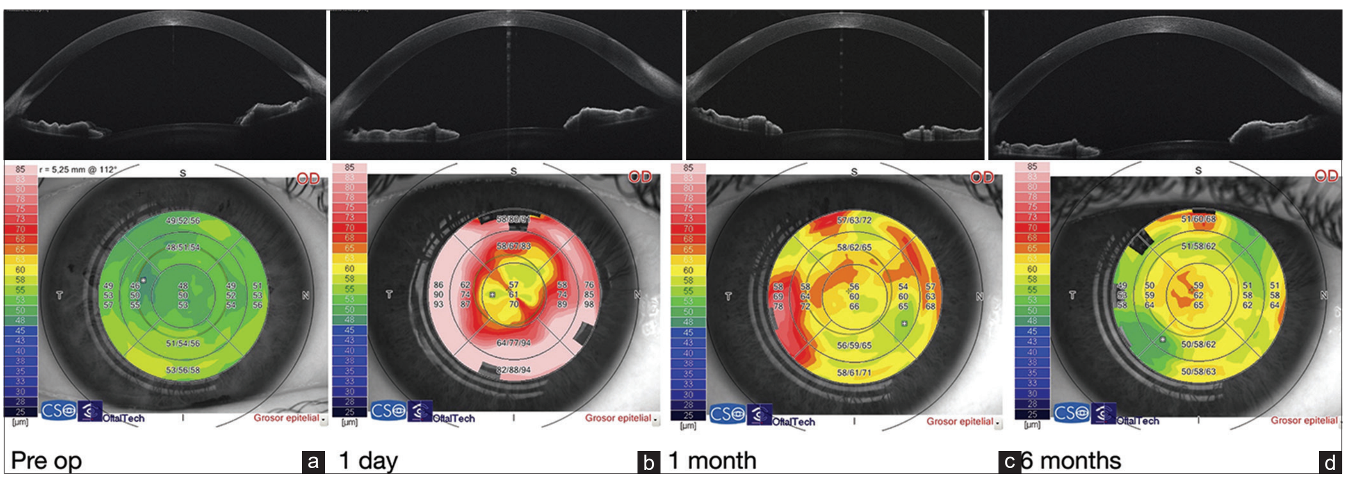

Figure 2: Pre and post-LASIK cross-sectional corneal OCT images and epithelial thickness maps at baseline (a), 1 day (b), 1 month (c), and 6 months (d) after LASIK surgery

Changes in CET after LASIK

Statistically significant changes of CET after LASIK were studied using a repeated-measures general linear model. Central, inner and outer rings, and each sector got thicker over time (Greenhouse-Geisser: Central F = 14.50, Inner ring F = 44.68 and Outer ring F = 59.58; all $P < 0.01$). In all sectors and rings except central value, the thickest values of CET were at one day after surgery with a decrease in their values at 1 and 6 months of follow-up. Central CET got thicker over the 6 months of follow-up [Fig. 1]. When CET at 6-month visit was compared to CET at presentation, all values were thicker after LASIK (all $P < 0.01$ except for outer nasal $P = 0.01$ and Outer temporal $P = 0.02$) [Fig. 2]. The thickest value of CET at 6-month after LASIK was the outer temporal (62.44 ± 9.10 µm); meanwhile, the thinnest was the outer superior sector (52.53 ± 5.37 µm). The sectors that changed the most were the outer and inner temporal CET (8.31 and 8.32 µm, respectively) and the region that changed the least was the outer nasal one (1.62 µm). The central sector and inner ring changed more (5.70 µm and 6.06 µm, respectively) than the outer ring (4.25 µm; $P < 0.01$).

SE after LASIK compared with changes in CET

We divided patients into two groups using the median and mean SE. The median and mean preoperative SE of the LASIK group were −2.81 D and −3.33 ± 1.66 D (range: −7.87 to − 0.62 D). There were no differences in CET changes (central sector and inner and outer rings) over time between patients with more

Table 1: Demographic and clinical characteristics of control and myopic LASIK groups

Variable	Controls (*n*=106)	LASIK (*n*=72)	*P*
Age (years)	32.4	30.0	0.08
Gender (male/female)	25/28	19/17	0.28
BCVA (decimal)	0.98	0.99	0.31
IOP (mmHg)	13.52	13.37	0.69
Spherical equivalent (diopters)	−3.63	−3.38	0.38
Pachymetry (µm)	559.96	548.73	0.08
Minimum pachymetry (µm)	542.25	540.12	0.64
Histeresis	10.44	10.54	0.54
Corneal diameter (mm)	11.91	11.99	0.21
Total corneal power (diopters)	43.19	43.61	0.06
Anterior Asfericity (Q)	−0.24	−0.23	0.40

Table 2: Epithelial thickness measurements of control and myopic LASIK Groups

Variable (µm)	Controls (*n*=106)	LASIK (*n*=72)	*P*
Central	52.24	52.69	0.36
Inner Superior	52.17	52.67	0.38
Inner Inferior	53.83	54.13	0.61
Inner Nasal	53.34	53.54	0.68
Inner Temporal	52.62	52.60	0.96
Inner Ring	52.99	53.23	0.63
Outer Superior	50.66	50.86	0.78
Outer Inferior	54.78	55.08	0.65
Outer Nasal	55.02	55.21	0.71
Outer Temporal	53.46	53.78	0.57
Outer Ring	53.48	53.73	0.63

or less than −2.81 D and between patients with more or less than −3.33 preoperative (all $P > 0.05$). The average SE at 1 and 6 months of follow-up after LASIK surgery were 0.26 ± 0.61 D and 0.01 ± 0.45 D, respectively. There were significant changes of SE between 1- and 6-month visits (Greenhouse-Geisser and pairwise comparison: P =0.00; paired sample T-Student: P = 0.00).

Predictors of CET after LASIK

Multivariate analysis was used to detect possible correlations between final CET and clinical parameters. None of the variables studied, including age, sex, eye, pachymetry, SE, average keratometry, anterior asphericity, and diopters corrected, were correlated with final CET (all $P > 0.05$).

Discussion

In the present study, we have reported changes in CET after myopic LASIK surgery using AS-OCT combined with Placido-disk-based topography. CET got thicker after LASIK surgery, independently of anterior segment variables and demographic parameters. All CET sectors thickened the most at 1 day after surgery except for central CET value, which tended to get thicker over the first month of follow-up. Values toward the center of the cornea thickened slightly more than those more peripherally. The amount and profile of CET changes were also independent of the grade of myopia treated.

To our knowledge, no previous study has demonstrated changes of CET over time after myopic LASIK surgery using an AS-OCT combined with Placido disk. Both corneal curvature and CET are modified after LASIK procedures. Compared with other OCT instruments, this device evaluates simultaneously both anterior corneal curvature and epithelial thickness at a single point. Measurements of CET have been previously reported using confocal microscopy,[12] very-high-frequency ultrasound (VHF-US)[13], and AS-OCT.[14-19] Unlike VHF-US and confocal microscopy, AS-OCT is a noninvasive technique that does not require eye contact and can automatically generate CET maps. High repeatability of automated measurements of CET in healthy, post-excimer, and keratoconus eyes has recently been shown using MS-39 device.[1-3] Central CET measurements described in this work are similar to those of earlier studies using AS-OCT. Although the number of sectors measured differs between AS-OCT machines, precluding appropriate comparisons, the present work finds thicker epithelium superiorly than inferiorly in normal corneas using AS-OCT combined with Placido disk. Our observation agrees with previous reports by Kanellopoulos *et al.*,[14] Hashmani *et al.*[18], and Yan Li *et al.*[20] using AS-OCT and by Vega-Estrada *et al.*[2] with MS-39 device supporting the findings of the current study.

Despite there being no surgical manipulation of corneal epithelium, changes after LASIK are well documented.[8,9,15,21,22] Using VHF-US, Reinstein *et al.* described epithelial thickening after myopic LASIK, which tended to be greater centrally and thinner centrifugally.[23] During myopic LASIK surgery, a volume of the corneal stroma is removed with a maximum ablation depth centrally. It is assumed that epithelial remodeling occurs to compensate for variations in stromal curvature and to restore a smooth and uniform optical surface.[23,24] Despite being a lower contributor to the total corneal thickness compared to stroma, CET plays a key role in defining total corneal power[25] and manifests dynamic changes after refractive surgery.[6,8,9,15,21] Reinstein *et al.* found that change in epithelial thickness profile induced a myopic refractive shift in both low and high myopia.[6] In this regard, these changes should be considered when using corneal wavefront treatment, where very small amounts of ablation are used to correct higher-order aberrations.[26]

In the present study, the average CET was significantly thicker 24 hours after LASIK (16.66 and 10.79-µm thicker than baseline in outer and inner rings, respectively). One month after LASIK, CET remains thicker than baseline measurements (8.12 and 7.21-µm thicker in the outer and inner rings, respectively, compared to baseline values). Later, at 6 months of follow-up, final thickening was found to be higher in the inner ring, which correlates with previous reports (4.17 µm and 6.13 µm thickening in the outer and inner rings, respectively, compared to baseline).[8] On the contrary, we observed a progressive increase in thickness over time in the 3-mm central sector (3.65, 3.58, and 5.49 µm thickening compared to baseline at one day, one month, and six months postoperatively, respectively) with no regression, which has been previously described as well.[9] The epithelial layer is a self-renewing layer, which can achieve a full turnover in 5–7 days.[27] Thus, the one-day thickening after LASIK cannot be due to epithelial hyperplasia and may be as a result of the inflammatory process secondary to surgery, as has been suggested by Molainen *et al*.[28]

Myopic shift following myopic LASIK procedures is also well described in the literature.[29-31] In the present study, there is a considerable range of residual refractive error at 1 month after LASIK. Besides, a myopic shift over time was observed. These changes in refraction over time were statistically significant with initial overcorrection (mean + 0.26 D at 1 month postoperatively) that returned later to the target (mean + 0.01 D at 6 months postoperatively). Although, epithelial remodeling may explain part of these changes based on the greater thickening of central CET sectors, additional biomechanical cofactors within the stroma may also affect the refractive changes reported.[29-31] In this regard, we did not observe significant differences between the degree of myopia and epithelial thickening, as has been described by Reinstein[6] and Kanellopoulous *et al*.[32] OCT devices include lacrimal film within epithelial thickness value; thus, it may generate imaging artifacts that may preclude an accurate measurement. In addition, corneal epithelial changes in our study are less than 6 microns in all sectors (except temporal); thus, the power of the study may not be enough to clarify this point. Larger and prospective studies are needed to establish whether the epithelial response depends on the amount of myopia treated and may quantify the influence on the myopic refractive shift. These changes must be taken into account to determine when epithelial thickness change is responsible for the myopic shift; therefore, LASIK enhancement may not be performed prematurely when epithelial hyperplasia could still be the reason for apparent undercorrection post LASIK.

There are some limitations of this research that should be addressed. First, as this study included measurements only up to 6 months, longer-term variations could not be assessed. Although main changes of CET have been reported to happen during the first 1 month after LASIK[9,15,21,33], possible variations may occur 6 months after surgery, as has been shown by confocal microscopy.[28] Second, this work only includes myopic LASIK cases, which limits the possibility of finding different patterns of corneal epithelial growth depending on the ablated area. Third, although low-quality measurements have been excluded from the analysis, the possibility exists that tear, eyelid, or flap artifacts may have distorted sectoral values. In particular, this fact may be true for peripheral values that have been described as more prone to measurement errors and decreased reproducibility.[2,34] However, recent studies have reported high repeatability of epithelial measurements in peripheral sectors with the MS-39 instrument.[2]

Conclusion

In conclusion, this study demonstrates CET remodeling over time after myopic LASIK surgery, measured by AS-OCT combined with Placido disk. CET becomes thicker as early as 1 day after LASIK and remains thickened at 6-months of follow-up. These changes should be considered before planning this surgery.

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Conflicts of interest

There are no conflicts of interest.

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