Excimer laser refractive surgery for myopia involves flattening of the central corneal surface by ablation of the corneal stroma. Refractive regression is a major factor limiting the predictability of myopic excimer laser refractive surgery.\cite{1-3} The etiology remains to be fully elucidated; it is generally suspected that the epithelial and/or stromal remodeling play an important role in refractive regression.\cite{4-7}

Knowledge of the preoperative corneal epithelial and stromal thickness profiles and their respective changes after corneal refractive surgery may contribute to a better understanding of the outcomes. Apart from studies applying Artemis very high-frequency digital ultrasound (ArcScan, Inc., Morrison, CO),\cite{8} the majority of studies are based solely on central corneal thickness measurements. One of the recent applications of spectral-domain optical coherence tomography (SD-OCT) allows non-contact, in vivo three-dimensional mapping of the corneal epithelial thickness.\cite{9-11} Kanellopoulos and Asimellis applied this technique to acquire epithelial thickness profiles in normal eyes\cite{9} and their changes after LASIK.\cite{10} The responses of the epithelium and the stroma after LASIK and PRK have been reported to be different.\cite{4,12} To the best of our knowledge, our study is the first to use SD-OCT three-dimensional mapping in evaluating epithelial and stromal thickness profile changes after PRK. The study also aims to investigate the possible association of these thickness changes with preoperative parameters, surgical parameters, and their effect on postoperative refractive stability.

**ABSTRACT**

**PURPOSE:** To study the corneal epithelial and stromal thickness profile changes after photorefractive keratectomy (PRK) for myopia.

**METHODS:** Retrospective analysis of the postoperative corneal epithelial and stromal thickness profile changes in 46 left eyes of 46 patients treated with PRK for myopia. Corneal and epithelial thickness maps within the central 6 mm were obtained by anterior segment spectral-domain optical coherence tomography preoperatively and at 1, 3, and 6 months postoperatively. Stromal thickness was calculated by subtracting the epithelial thickness from the total corneal thickness. Correlations between postoperative thickness changes and the amount of correction, treatment zone, and preoperative epithelial thickness were analyzed.

**RESULTS:** Compared to preoperative values, the central 2 mm and the paracentral 2- to 5-mm zone epithelium was 5.20 ± 3.43 and 5.72 ± 3.30 µm thicker, respectively, at 3 months postoperatively (P < .05). No significant difference was detected between 3 and 6 months postoperatively. The stromal thickness did not change between 1 and 6 months postoperatively. The spherical equivalent (SE) changed from -2.82 ± 1.54 diopters (D) preoperatively to -0.06 ± 0.42 D at 1 month postoperatively, and remained stable thereafter. There was a trend toward greater epithelial thickening with a larger amount of programmed SE correction, smaller treatment zone, and thinner preoperative epithelium. No correlation between epithelial thickness change and postoperative change in refraction was detected.

**CONCLUSIONS:** The corneal epithelial thickness increased after PRK up to 3 months postoperatively. It was affected by the amount of myopia treated, treatment zone, and preoperative epithelial thickness. The postoperative epithelial thickening did not affect the refractive outcomes.

PATIENTS AND METHODS

This retrospective study comprises 46 left eyes of 46 patients (17 female and 29 male) who completed at least 3 months of postoperative follow-up after treatment for myopic astigmatism at SynsLaser Clinic, Oslo, Norway, using transepithelial topography-guided surface ablation. Among those, 40 eyes completed 6 months of postoperative follow-up at the time the data were collected. Inclusion criteria were: no ocular pathology other than myopia with or without astigmatism, no epithelial defects, no previous surgery, refractive stability for at least 2 years, and astigmatism of 1.0 diopter (D) or less. Informed study consent for anonymous use of data for analysis and publication was obtained from all patients.

All patients underwent complete ophthalmologic evaluation preoperatively and postoperatively, including slit-lamp biomicroscopy, Scheimpflug-based corneal topography/tomography (Precisio; iVIS Technology, Taranto, Italy), Placido-based corneal topography and wavefront aberrometry (Nidek OPD II; Nidek Co. Ltd, Aichi, Japan), eye tonometry (Icare tonometer; Revenio Group Corporation, Helsinki, Finland), uncorrected (UDVA) and corrected (CDVA) distance visual acuity testing, subjective spectacle refraction, and SD-OCT (RTVue-100; Optovue, Inc., Fremont, CA) corneal scanning. The OCT imaging preceded other examinations to avoid potential artifacts.

THE RTVUE-100 SD-OCT

We employed the RTVue-100 SD-OCT system with a corneal adaptor module, running on software version A6 (9.0.27). It features a 26,000-Hz scanning with 5-µm axial resolution and 15-µm transverse resolution.13 The cornea was imaged by use of Pachymetry pattern (6-mm scan diameter, 8 meridians, 1,024 axial-scans each) centered on the pupil. The eight radial meridional scans are employed by the system software to produce three-dimensional thickness maps by interpolation. Data output includes thickness maps of the total cornea and the epithelium, across a diameter of 6 mm. Each map is divided into 17 sectors: 1 central circle, centered around the pupil, of 2-mm in diameter (center), 8 octants within an annulus between 2- and 5-mm circles (paracentral), and 8 octants within an annulus between 5- and 6-mm circles (mid-periphery) (Figure 1). For each of these sectors, average thickness is displayed over the corresponding area. Three measurements were obtained at a single visit, of which the two with best image quality were chosen and the average value was used for further analysis. The data acquired within the central 5 mm were analyzed in the current study.

SURGICAL TECHNIQUE

All of the surgeries were performed by one surgeon using transepithelial topography-guided surface ablation using 1-KHz flying spot laser (iRES; iVIS Technology) as previously described.14 The ablation consists of a refractive part, which reshapes the corneal surface within the treatment zone into an aspheric regular shape of desired curvature and a lamellar part of 52 µm in depth (adjustable default value) for the removal of the epithelium. These two parts are summed and executed in a single uninterrupted ablation. Mitomycin C 0.02% was applied to the cornea for 15 seconds after the treatment in two eyes, in which maximum stromal...
ablation depth exceeded 100 µm. At the end of the surgery, one to two drops of dexamethasone with chloramphenicol mixture (Spermsadex med kloramfenikol; Laboratoires Thea, Clermont-Ferrand, France) and one drop of bromfenac 0.9% (Yellox; Croma-Pharma GmbH, Leobendorf, Austria) eye drops were applied, followed by a bandage contact lens (Acuvue Oasys; Johnson & Johnson Vision Care, Inc., Jacksonville, FL). Bromfenac 0.9% twice a day was used 2 days before and 3 days after the surgery. Dexamethasone with chloramphenicol four times a day was used the first 2 weeks, and then replaced by a low potency steroid rimexolone 1% (Vexol; Alcon Laboratories, Surrey, United Kingdom) eye drops in tapering doses for another 3 weeks. The bandage contact lens was removed from the cornea between postoperative days 5 and 7.

**DATA ANALYSIS**

Preoperative and postoperative maximum ($\text{SimK}_{\text{max}}$), minimum ($\text{SimK}_{\text{min}}$), and mean ($\text{SimK}_{\text{mean}}$) simulated keratometric values were obtained from the OPD Scan II. Stromal thickness was calculated by subtracting the epithelial thickness from the total corneal thickness in the pachymetry map generated by the SD-OCT. The average value of the 8 octants within the annulus between the 2- and 5-mm circles was calculated as the paracentral thickness.

Statistical analyses were performed using IBM SPSS Statistics, version 21 (IBM Corp., Armonk, NY). The Shapiro–Wilk test was used to test the normality of the data. Linear mixed model was employed to compare the central and paracentral epithelial and stromal thickness, as well as the spherical equivalent (SE) refraction and $K_{\text{mean}}$ measured at different times. Preoperative paracentral differences in epithelial thickness superiorly versus inferiorly and nasally versus temporally were calculated using the paired $t$ test. The independent samples $t$ test was used to test the difference between male and female eyes. Repeated measurements were used to compare the differences between different measurement zones. Pearson or Spearman correlation coefficient was applied to seek possible correlations between different parameters. In all analyses, a $P$ value less than .05 was considered statistically significant.

**RESULTS**

**PREOPERATIVE**

The mean age of all patients at the time of surgery was 32.40 ± 7.52 years (range: 19 to 55 years). The mean SE was -2.82 ± 1.54 D (range: -0.88 to -7.25 D). The mean preoperative central corneal thickness measured by SD-OCT was 547.03 ± 32.74 µm (range: 473 to 608 µm). The mean optical zone and total ablation zone were 6.15 ± 0.42 mm (range: 5.2 to 7.2 mm) and 8.13 ± 0.56 mm (range: 6.5 to 9.0 mm), respectively. The programmed maximum stromal ablation depth was 53.50 ± 21.79 µm (range: 20.0 to 108.0 µm).

**Figure 2A** demonstrates the mean value of preoperative epithelial thickness profile. After annular averaging, no significant difference was detected between central (54.79 ± 3.71 µm) and paracentral (54.55 ± 3.79 µm) epithelial thickness ($P > .05$). However, compared to the paracentral epithelium, the central epithelium was thinner than the inferior epithelium and thicker than the superior epithelium ($P < .05$). Paracentrally, the epithelium was 1.67 ± 2.07 µm thinner superiorly. 

![Figure 2](image-url)
than inferiorly \((P < .001)\) and 1.00 ± 1.00 µm thinner temporally than nasally \((P < .001)\).

Preoperative epithelial thickness was not significantly correlated with Sim\(K_{\text{max}}\), Sim\(K_{\text{min}}\), age, or SE \((P > .05)\). However, male patients demonstrated significantly thicker epithelium than females \((55.71 ± 4.01 \text{ vs } 53.24 ± 2.57 \mu m \text{ centrally}, P < .005; 55.56 ± 4.01 \text{ vs } 52.84 ± 2.68 \mu m \text{ paracentrally}, P < .005)\).

**POSTOPERATIVE**

At 6 months postoperatively, 85% of eyes (34 of 40 eyes) were within ±0.50 D of emmetropia. At the last follow-up, trace of haze was seen in 5 eyes. **Figures 2-3** and **Table 1** illustrate the changes of epithelial and stromal thickness and SE over time. The epithelium was thicker at 1 month after the surgery compared to preoperative measurements \((1.33 ± 3.76 \mu m \text{ centrally}, P = .08; 1.42 ± 3.83 \mu m \text{ paracentrally}, P < .05)\). The most pronounced epithelial thickness change was observed between 1 and 3 months postoperatively \((3.87 ± 2.94\text{ and }4.31 ± 2.73 \mu m \text{ thickening centrally and paracentrally, respectively, both } P < .001\)\). There was no statistically significant difference in epithelial thickness between 3 and 6 months postoperatively \((P > .05)\). The stromal thickness demonstrated thinning of \(57.46 ± 25.46\) and \(45.37 ± 21.00 \mu m \text{ centrally and paracentrally, respectively, at 1 month postoperatively (both } P < .001)\). No statistically significant change in stromal thickness was detected between different postoperative follow-up time points \((P > .05)\).

Manifest refraction spherical equivalent changed from \(-2.82 ± 1.54\) D preoperatively to \(-0.06 ± 0.42\) D at 1 month postoperatively, and remained stable thereafter \((P > .05 \text{ for all postoperative measurements comparison})\). No statistically significant change in Sim\(K_{\text{mean}}\) was detected between different postoperative follow-up points \((P > .05)\).

The epithelial thickening at 3 and 6 months, in reference to the baseline preoperative level, did not correlate with age, maximum ablation depth, preoperative keratometric values, or postoperative refraction change. The epithelial thickening correlated centrally and paracentrally with the preoperative epithelial thickness \((r = -0.493 \text{ and } -0.583 \text{ at } 3 \text{ months, } P < .05; \text{ and } r = -0.486 \text{ and } -0.623 \text{ at } 6 \text{ months, } P < .05)\), with optical zone diameter \((r = -0.382 \text{ and } -0.454 \text{ at } 3 \text{ months, } P < .05; \text{ and } r = -0.327 \text{ and } -0.416 \text{ at } 6 \text{ months, } P < .05)\), and with the total ablation zone diameter \((r = -0.334 \text{ and } -0.391 \text{ at } 3 \text{ months, both } P < .05; \text{ and } r = -0.287 \text{ and } -0.291 \text{ at } 6 \text{ months, both } P = .07)\) \((\text{Figure 4})\). The paracentral epithelial thickening correlated with the SE of the programmed correction \((r = -0.326 \text{ and } -0.392 \text{ at } 3 \text{ and } 6 \text{ months, respectively, } P < .05)\).

At 3 and 6 months, there was \(0.53 ± 1.63 \text{ and } 0.62 ± 1.79 \mu m\), respectively, more thickening of the epithelium paracentrally compared to centrally \((P < .05)\). The paracentral thickening was more pronounced in female eyes \((17 \text{ eyes, } 7.01 ± 2.62 \mu m)\) compared to male eyes \((29 \text{ eyes, } 4.97 ± 3.45 \mu m)\) at 3 months \((P < .05)\).
This trend remained at 6 months \( (7.75 \pm 2.08 \, \mu m) \) thickening in 13 female eyes vs \( 5.86 \pm 2.76 \, \mu m \) thickening in 27 male eyes, \( P < .05 \).

**DISCUSSION**

The corneal epithelium protects the eye and plays an important role in maintaining corneal transparency and optical quality.\(^1\) It has a rapid cell turnover and is highly reactive to irregularities of the underlying stromal surface.\(^{16-18}\) Studies using Artemis very high-frequency digital ultrasound,\(^8\) confocal microscopy,\(^19\) OCT,\(^20\) ultrasound,\(^21\) and optical pachymetry\(^22\) have demonstrated corneal epithelial thickness change after excimer laser refractive surgery. In this study, we investigated previously unreported changes in corneal epithelial and stromal thickness profiles after PRK, using SD-OCT technology. Kanellopoulos and Asimellis\(^9,10,23\) used the same measurement instrument as the one used in the current study, and reported intra-individual repeatability for the epithelial thickness centrally, superiorly, and inferiorly to be \( 0.88 \pm 0.71 \), \( 1.01 \pm 0.87 \), and \( 0.83 \pm 0.77 \, \mu m \), respectively.\(^9\)

The preoperative average central epithelial thickness of \( 54.79 \pm 3.71 \, \mu m \), measured in the current study, is within the range of previously reported values (from \( 48.3 \) to \( 58.4 \, \mu m \)).\(^{16,23-27}\) Similar to the finding by Kanellopoulos and Asimellis,\(^9\) we found the preoperative epithelium in male eyes to be thicker than in female eyes. The non-uniform preoperative epithelial thickness profile characterized by thinner epithelium superiorly than inferiorly and temporally than nasally is also in accordance with other studies.\(^8,9,16,24,28\)

**TABLE 1**

<table>
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<tr>
<th>Parameter</th>
<th>1 Month</th>
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<td>Paracentral</td>
<td>Central</td>
<td>Paracentral</td>
<td>Central</td>
<td>Paracentral</td>
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<td>Mean ± SD</td>
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<td>1.42 ± 3.83</td>
<td>5.20 ± 3.43</td>
<td>5.72 ± 3.30</td>
<td>5.85 ± 2.86</td>
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<tr>
<td></td>
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<td>(-5.6 to 9.5)</td>
<td>(-2.0 to 16.0)</td>
<td>(-1.4 to 15.6)</td>
<td>(0.0 to 13.0)</td>
</tr>
<tr>
<td>Stroma</td>
<td>Mean ± SD</td>
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<td>–</td>
<td>3.29 ± 5.61</td>
<td>3.09 ± 5.87</td>
<td>1.80 ± 6.35</td>
</tr>
<tr>
<td></td>
<td>Range</td>
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<td>–</td>
<td>(-13.5 to 15.0)</td>
<td>(-11.9 to 14.1)</td>
<td>(-11.0 to 16.0)</td>
</tr>
</tbody>
</table>

SD = standard deviation

Epithelial thickening referred to preoperative value, whereas the stromal thickness changes were compared to the values measured at 1 month postoperatively.
with Artemis demonstrated 2.3 µm thinner epithelium centrally (within 1.5 mm) than paracentrally (annulus between 3 and 3.4 mm). In addition, the difference of 1.7 ± 2.1 µm between superior and inferior paracentral epithelium in the current study is considerably smaller than 5.3 to 5.9 µm, as reported by Reinstein et al.8,24 The variations may be caused by differences in instrumentation and the measurement technique (non-contact SD-OCT vs saline immersion ultrasound). The SD-OCT measurements’ inability to discriminate the tear film and the central specular hyperrefractive reflex may affect the layer boundaries detection in the center due to reduced signal-to-noise ratio. The patients’ demographics may also contribute to the discrepancies. For example, Yang et al.29 reported that except for the central 2-mm sector and the inferotemporal sector in the paracentral area, corneal epithelial thickness was negatively correlated with age.

There are some inconsistencies in reported postoperative corneal epithelial and stromal thickness changes and their relation to refractive regression after PRK. One study did not observe changes in central epithelial thickness 1 year after PRK,7 whereas others reported an increase.4,12,22,30,31 It has been suggested that epithelial hyperplasia after refractive surgery may contribute to loss of postoperative effect22,30; however, other studies7,12,32 demonstrated that the postoperative refractive changes did not correlate with the changes in central epithelial thickness. Erie31 found no change in stromal thickness between 1 and 6 months after the surgery, whereas some studies7,12 reported stromal regrowth from 1 to 12 months after PRK, which was strongly correlated with the concurrent loss of effect of photorefractive surgery. Patel et al.4 described thickening of the central stroma between 1 month and 1 year after PRK; however, no correlation was noted between changes in stromal thickness and refractive regression.

In the current study, the epithelial thickness in all of the measured areas continued to increase between 1 and 3 months after the surgery, whereas the refractive stability was achieved by 1 month. No correlation was found between the epithelial thickening and postoperative refraction change. The stromal thickness in the current study did not change from 1 month postoperatively.

The variations between the studies may be due to the differences in the measurement techniques, the magnitude of refractive error treated,32 instrumentation, treatment zone,33 and epithelial debridement method (eg, mechanical or alcohol assisted vs integrated into excimer laser ablation). Furthermore, the epithelium may affect refraction due to its shape at the air–tear film interface and because of its different refractive index compared to stroma,34 so that a uniform epithelial thickening would not appreciably change the curvature of the corneal surface and refraction. The difference between central and paracentral epithelial thickening in the current study was within 1 µm; therefore, it did not affect the postoperative SimK mean or the manifest refraction. More pronounced postoperative epithelial thickening22,30 and larger difference in postoperative central and paracentral epithelial thickness changes seems to occur in eyes with significant refractive regression.

Unlike the post-LASIK lenticular shape epithelial thickening detected by Artemis,8 with more thickening centrally and progressively less thickening centrifugally, our data revealed slightly more thickening of the epithelium paracentrally compared to centrally. This pattern is in line with the post-LASIK epithelial thickness profile changes noted by Kanellopoulos and Asimellis,10 using the same measurement technology. Nevertheless, the current study agrees with the Artemis result in that the maximum amount of epithelial thickening is located temporally. When compared to the post-LASIK study using the same instrument setting,10 the central and paracentral epithelial thickening at 6 months after PRK in the current study (5.85 ± 2.86 and 6.47 ± 2.68 µm) was more profound compared to that of 12 months after LASIK treatment (1.42 ± 2.62 and 3.19 ± 2.82 µm), despite a lower refractive treatment (refractive sphere -2.82 ± 1.54 vs -4.86 ± 1.75 D). This difference may be attributed to the different surgical approaches and different time points.

In agreement with previous findings,8,10,21,33,35 the postoperative epithelial thickening in the current study correlated with the programmed SE correction and the treatment zone. Our findings concur with those of Gauthier et al.33,35 who demonstrated that epithelial hyperplasia was greater with smaller zone sizes. Interestingly, we found a significant negative correlation between the postoperative epithelial thickening and the preoperative epithelial thickness. Our data demonstrated that the preoperatively thinnest epithelium in the temporal superior region had the most profound postoperative thickening. The preoperative superior-inferior epithelial thickness asymmetry has been explained by eyelid dynamics24 and the effect of gravity on tear film when measured with SD-OCT.9 However, the mechanism behind the negative correlation between epithelial thickening and the preoperative epithelial thickness is unclear. One may speculate that the corneal flattening due to myopic treatment results in a mismatch of anatomy between the eyelid and the cornea, allowing the epithelium to fill the gap.

One limitation of the current study is the inability of the RTVue 100 to measure corneal and epithelial
thickness outside the central 6-mm diameter of the cornea. The validity of our analysis should also be viewed by taking the limitations of the current SD-OCT technology (limited axial resolution and tear film discrimination) into consideration. Still, the values presented in our results are in accordance with the earlier findings obtained by very high-frequency ultrasound technology, which features higher resolution, as well as with the findings of the related research with similar instrumentation. Higher axial resolution equipment with better ability for discrimination of the tear film would be beneficial.

Future studies with longer follow-up time, particularly pertaining to changes in epithelial thickness profile extending beyond the 6-mm diameter, are warranted. Likewise, there is a need to explore the corneal changes after hyperopic and high astigmatism treatments. Transepithelial topography-guided custom ablation, as used in the current study, may lead to different epithelial remodeling/healing compared to ordinary PRK or other surface ablation techniques. Studying the differences in different surface ablation techniques would be a third avenue for further research.

Exploring the three-dimensional epithelial morphology following PRK is critical to broaden our understanding of corneal wound healing. Because PRK is increasingly used for re-treatments after femtosecond laser-assisted LASIK or small incision lenticule extraction (SMILE), knowledge about the epithelial contribution to the refraction may improve the programming of the re-treatments. Estimation of the epithelial refractive contribution to the refractive status in any particular case would represent a great improvement compared to the current use of empirical nomograms for adjusting refractive retreatments that involve epithelial removal. Moreover, a precise epithelial mapping is essential in planning corneal regularization using topography-guided surface ablation in the treatment of irregular astigmatism and keratoconus.

**AUTHOR CONTRIBUTIONS**

Study concept and design (XC, AS, YC); data collection (XC, YL, YZ); analysis and interpretation of data (XC, TPU); writing the manuscript (XC, AS, YC, YZ); critical revision of the manuscript (XC, AS, YC, TPU); statistical expertise (XC, YL, YC, YZ); obtaining funding (AS); supervision (AS, TPU).

**REFERENCES**


