Corneal epithelial remodeling refers to the potential of the corneal epithelium to compensate for irregularities or changes of the underlying stromal surface shape by altering its thickness profile. These compensatory changes of the epithelium so as to uphold the integrity of the optical surface of the cornea have been reported to occur in keratoconus,\textsuperscript{1,2} postoperative corneal ectasia,\textsuperscript{3} after stromal injuries,\textsuperscript{4} and corneal crosslinking.\textsuperscript{5,7} In addition, corneal epithelial remodeling also has been reported to occur after corneal refractive surgery. For example, various studies previously demonstrated changes in epithelial thickness (ET) following photorefractive keratectomy (PRK),\textsuperscript{8,14} which represents a surface ablation technique, and laser in situ keratomileusis (LASIK),\textsuperscript{15-22} a method that requires the creation of a corneal flap.

Small incision lenticule extraction (SMILE) represents the latest femtosecond laser-based corneal refractive procedure, which bears multiple advantages over techniques that involve excimer laser surface ablation with or without flap creation. In SMILE, the femtosecond laser cuts a refractive lenticule by creating two interfaces entirely in the corneal stroma.\textsuperscript{23} This involves the creation of a lamellar cut parallel to the anterior corneal surface at a depth of 120 to 140 μm. Subsequently, the lenticule is extracted in one piece through a single, small peripheral incision. Small incision lenticule extraction thereby leaves intact the strongest anterior-most lamellae of the corneal stroma by eliminating the need to create a flap or to ablate the corneal surface.\textsuperscript{24} Hence, this procedure may result in a biomechanically more stable cornea compared with PRK or LASIK, which has been substantiated by mathematical modeling.\textsuperscript{25} In addition, the disruption of the subepithelial stromal nerve plexus is less profound in SMILE compared with other corneal refractive techniques. This entails less impact on the innervation of the corneal surface and, subsequently, less pronounced dry eye symptoms postoperatively.\textsuperscript{26,27}

To date, the knowledge on corneal epithelial remodeling following SMILE is limited. Two previous studies using spectral-domain optical coherence tomography (SD-OCT)\textsuperscript{28} and very high-frequency ultrasound (VHFUS),\textsuperscript{29} respectively, showed that ET at the corneal vertex is increased after SMILE. These findings suggest that, similarly to PRK and LASIK, a postoperative corneal epithelial remodeling response might be induced by SMILE. However, ET changes in the corneal periphery as well as the temporal dynamics of the remodeling process are yet to be investigated.

Keywords: small incision lenticule extraction, SMILE, corneal epithelial remodeling, refractive surgery, optical coherence tomography


This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.
The purpose of our study was to prospectively assess the corneal epithelial remodeling during the first 6 months after SMILE using high-resolution SD-OCT. Furthermore, we aimed to elucidate the potential impact on the refractive outcome of the procedure. To our knowledge, this was the first study to comprehensively evaluate the changes of the corneal ET profile subsequent to SMILE.

**Patients and Methods**

This prospective observational study included patients who were scheduled for SMILE for treatment of myopia or myopic astigmatism. Patients with prior corneal injury or surgery or any present contraindication for corneal refractive surgery (e.g., corneal ectatic disorders) were excluded. The research adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee (Ethikkommission des Landes Oberösterreich, Linz, Austria). After explanation of the nature and possible consequences of the study, informed consent was obtained from all subjects.

**Surgical Procedure and Postoperative Care**

All SMILE procedures were performed under topical anaesthesia by the same surgeon (SGP) using the VisuMax 500 kHz femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany). The principles of the SMILE procedure have been outlined elsewhere. In all cases, a 4.5-μm laser spot spacing and a laser cut energy of level 32 (corresponding to 160 nanojoules) was applied. The optical zone was 6.5 mm and cap thickness was programmed to 1.40 μm at all times. A superior-temporal (at 45° or 135°) 4.0-mm incision was created by the femtosecond laser.

Postoperative treatment regimen consisted of dexamethasone 0.1% and tobramycin 0.3% eye drops (Tobradex; Alcon Ophthalmika, Vienna, Austria) six times daily during the first week. Thereafter, rimexolone 1% eye drops (Vexol; Alcon Ophthalmika, Vienna, Austria) four times daily were tapered over the course of 4 weeks. In addition, patients were encouraged to use preservative-free lacrimal substitutes as needed.

**Preoperative and Postoperative Assessment**

Preoperatively, all patients received a thorough clinical examination, including medical, ocular, and family history, anterior segment slit-lamp biomicroscopy, Goldmann aplana
tometry, dilated fundus examination, as well as dry eye screening using the Schirmer I test and tear film break up time assessment. In addition, manifest and cycloplegic refraction was determined using the Jackson cross-cylinder method. Best spectacle-corrected distance visual acuity (CDVA) was measured using Early Treatment Diabetic Retinopathy Study charts at 4 meters. Endothelial cell density was assessed with specular microscopy (CEM-530; Nidek Co., Ltd., Gamagori, Japan). Further preoperative examinations included corneal Scheimpflug tomography (Pentacam HR; Oculus, Wetzlar, Germany), placido disc topography (Atlas Topographer; Carl Zeiss Meditec, Jena, Germany), as well as pupillometry in scotopic and mesopic conditions (Colvard; Oasis Medical Inc., Glendora, CA, USA). Patients were reexamined on the first postoperative day, and 1 week, 6 weeks, 3 months, and 6 months postoperatively. On the first postoperative day, only slit-lamp examination was performed. All subsequent follow-up visits additionally included manifest refraction, uncorrected distance visual acuity (UDVA) and CDVA readings.

**Epithelial Thickness Measurements**

Preoperatively and at all follow-up time points, corneal ET profiles of the central 5 mm zone were acquired with high-resolution SD-OCT. All participants’ OCT scans were scheduled after 12:00 PM to reduce the influence of diurnal variations in ET. Measurements of ET in this study included the precorneal tear film layer, which can be thickened after instilling lubricant eye drops. Therefore, the use of lacrimal substitutes or other topical eye medications was prohibited during a period of 2 hours before scanning in an effort to minimize their effect on tear film thickness.

An SD-OCT system with an anterior segment adaptor lens (RS 3000 Advance; Nidek Co., Ltd., Gamagori, Japan) was used for B-scan acquisition. The system had an axial resolution of 4 μm, a transversal resolution of 7.8 μm, and a scanning speed of 53,000 A-scans per second. Four meridional OCT scans with a length of 8.0 mm were acquired along the horizontal, vertical, and the two oblique corneal meridians. On each meridian, 10 B-scans were automatically averaged to one image by the manufacturer’s software. Three consecutive scans were taken and the best quality scan was selected for further analysis. It was ensured that all scans were centered on the hyper-reflective corneal vertex reflex with the patient focusing on the central fixation target. In SMILE, patient-controlled fixation ensures alignment of the treatment zone with the patient’s visual axis, which closely approximates the corneal vertex.

Hence, it can be assumed that the central hyperreflective corneal reflex in the OCT scan corresponded to the center of the treatment zone of the SMILE procedure.

All OCT images were exported, and a customized image segmentation software was applied to measure ET at 17 regions of interest: at the corneal vertex as well as paracentral (1.25 mm) and mid- peripheral (2.5 mm) on either side of the four meridional scans. This semiautomated algorithm has been described in detail elsewhere and it has been shown by our group to provide highly repeatable and reproducible measurements of ET both in healthy and in post-SMILE eyes. Finally, epithelial profile maps were created and left eye maps were mirrored vertically so as to make them comparable with right eyes.

**Statistical Analysis**

All statistical analysis was performed using R Statistical Software (Version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria) and the add-on software packages “GEE” and “GEEPACK.” Descriptive data are always presented as mean, SD, and range. A P value less than 0.05 was considered as statistically significant.

The generalized estimating equation (GEE) model is an extension of the general linear regression model and provides a statistical method to account for the situation of “correlated observations” (e.g., paired-eye data). Generalized estimating equation was used to test for differences in ET between corresponding corneal sectors (e.g., superior versus inferior). Moreover, a linear GEE model with adjustment for multiple comparisons (Bonferroni correction) was applied to determine differences in manifest refraction spherical equivalent (MRSE), absolute deviation from target refraction, and ET between time points. Nonlinear least-squares estimation for one randomly selected eye of each patient as well as for the mean value of both eyes of each patient was used to model ET changes over time. Multiple GEE regression modeling was performed to identify independent predictors of postoperative ET change by including gender, patient age at the time of surgery, preoperative ET, and surgical refractive correction. In addition, GEE modeling was used to evaluate relationships between mor-
phological (e.g., ET increment) and/or functional parameters (e.g., MRSE).

**RESULTS**

**Study Population and Characteristics**

A total of 46 myopic eyes of 23 patients were included. Male-to-female ratio was 9:14 and mean age was 33 ± 6 years (range 25–45). Mean spherical equivalent of surgical refractive correction was −4.78 ± 1.75 (range −8.5 to −2.0) diopters (D) corresponding to a mean thickness of 94.3 ± 24.3 (range 55–143) μm of the extracted refractive lenticule. No intraoperative or postoperative complications were encountered during the 6-month follow-up.

Preoperative clinical features and postoperative outcome values including visual acuity readings, MRSE, and absolute deviation from target refraction are summarized in the Table. Uncorrected distance visual acuity and CDVA improved continuously after surgery and the latter exceeded preoperative levels 6 weeks postoperatively (Table). All 37 (80.4%) eyes with plano target refraction achieved UDVA of 20/25 or better at 6 months postoperatively. Nine patients had opted for a “mini-monovision” concept with a target refraction of −0.25 or −0.50 D in their nondominant eye. Hence, overall mean target refraction was slightly myopic (−0.13 ± 0.26 D).

**Epithelial Thickness Profile**

Epithelial thickness profile maps for the examined time points are presented in Figure 1. Preoperatively, ET was significantly higher at the inferior (53.5 ± 2.8 μm) corneal aspect compared with the corresponding superior corneal sector (52.2 ± 2.5 μm; P < 0.001). Moreover, ET was higher nasally (55.0 ± 3.0 μm) than temporally (52.3 ± 2.5 μm) with P = 0.013. Six months postoperatively, the ET profile exhibited similar vertical asymmetry with mean ET of 57.2 ± 4.6 μm at the superior sector versus 58.2 ± 4.1 μm at the corresponding inferior sector (P < 0.01) as well as minor (reversed) horizontal asymmetry between the nasal (57.3 ± 4.3 μm) and temporal (57.8 ± 4.6 μm) sector (P = 0.04).

**Extent and Temporal Dynamics of Corneal Epithelial Remodeling**

Significant postoperative epithelial thickening was observed at all examined regions of interest (ROIs) as depicted in Figures 1 and 2. Average ET (= mean ET averaged over the entire central 5-mm zone) increased by 10.3% (5.4 ± 3.4 μm) from 52.3 ± 3.6 μm preoperatively to 57.7 ± 5.1 μm 6 months postoperatively (P < 0.001). Significant epithelial thickening was detected at the vertex on the first postoperative day (P = 0.01) and at all other ROIs during the first postoperative week (P < 0.001). Average ET was 101.9% of the preoperative thickness at 24 hours postoperatively, 103.2% at 1 week, 106.7% at 6 weeks, 109.3% at 3 months, and 110.4% of the baseline value at 6 months postoperatively. Epithelial thickness increment rate was highest during the first 24 hours after surgery and, subsequently, showed an exponential decrease with time (Fig. 3). No statistically significant change in ET was observed between the 3- and 6-month time point (P = 0.99). Hence, the bulk of epithelial thickening occurred in the first 6 postoperative weeks and the epithelial profile stabilized after 5 months.

Nonlinear least-squares estimation for one randomly selected eye of each patient as well as for the mean value of both eyes of each patient revealed that postoperative epithelial thickening closely followed an exponential recovery curve (defined as y = 1.066ln(x)+52.48 and y = 1.026ln(x)+52.39, respectively). Exponential fitting was highly statistically significant (P < 0.001) for both curves with R² = 0.996 and R² = 0.983, respectively. For both functions, the calculated half-time of recovery amounted to the theoretical number of approximately 13 days (13.3 and 12.5, respectively).

**Determinants and Predictability**

Moreover, as apparent from Figure 2, high SDs for ET increment data were observed, indicating high interindividual variability in the compensatory epithelial response after SMILE. This observation can be explained by the fact that the extent of ET increment was significantly correlated with the magnitude of the surgical refractive correction as revealed by GEE regression modeling (P = 0.002, Fig. 4). In contrast, preoperative ET (P = 0.24) and sex (P = 0.92) did not add significantly to the prediction of postoperative epithelial thickening. In addition, the predictive value of patient age at the time of surgery was not significant by itself (P = 0.85). However, multiple GEE regression modeling revealed that the interaction term “patient age at time of surgery × spherical equivalent of extracted lenticule” was a statistically significant independent predictor of postoperative epithelial response (P < 0.001). This finding indicates that patient age affected the epithelial thickening response to a given corneal curvature change. A highly statistically significant regression equation (P < 0.001) was found to predict postoperative central epithelial thickening (Formula 1).

**Formula 1:** Regression equation for the prediction of postoperative epithelial thickening: \( \text{SE}_{\text{Lenticule}} = 0.707 + 2.408 \times \text{SE}_{\text{Lenticule}} - 0.038 \times \text{SE}_{\text{Lenticule}} \times \text{Age} \)

Refraction Accuracy and Stability

Finally, we evaluated the significance of the herein demonstrated postoperative epithelial hyperplasia with regard to potential effects on the refractive outcome of the procedure. There was no significant correlation between the magnitude of ET increment and the absolute deviation from target refraction after 6 months (P = 0.68). Furthermore, we did not observe a statistically significant refractive regression or postoperative change in MRSE during the 6-month follow-up (P = 0.052; Table).

**DISCUSSION**

This is the first study to assess the temporal dynamics of corneal ET (ET) changes following SMILE. We used high-resolution SD-OCT and a semiautomated image analysis algorithm to prospectively assess the 5-mm corneal ET profile over the course of 6 months after surgery. Excellent reliability of this method has been demonstrated by our group in previous work.\(^3\) In the present study, mean corneal ET averaged over the central 5-mm zone increased by 5.4 μm or 10.3% from baseline during the course of 6 months after SMILE. The ET increment rate was highest during the first 24 postoperative hours and thereafter decreased exponentially with time until a stabilization of the ET profile was observed after 5 months. The epithelial response could be modeled by an exponential recovery function with high statistical signifi-
TABLE. Summary of Preoperative Clinical Features and Postoperative Outcome Values

<table>
<thead>
<tr>
<th>Time Point</th>
<th>UCVA, logMAR (range)</th>
<th>BCVA, logMAR (range)</th>
<th>MRSE, D (range)</th>
<th>Absolute Deviation From Target Refraction, D (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>NA</td>
<td>−0.02 ± 0.05 (−0.10 to 0.20)</td>
<td>−4.92 ± 1.80 (−1.00 to +0.63)</td>
<td>NA</td>
</tr>
<tr>
<td>1 wk postoperative</td>
<td>0.02 ± 0.07 (−0.10 to 0.16)</td>
<td>0.00 ± 0.10 (−0.10 to 0.16)</td>
<td>−0.26 ± 0.36 (−1.13 to +0.38)</td>
<td>0.27 ± 0.25 (0.00–0.88)</td>
</tr>
<tr>
<td>6 wk postoperative</td>
<td>−0.04 ± 0.08 (−0.18 to 0.10)</td>
<td>−0.03 ± 0.10 (−0.18 to 0.20)</td>
<td>−0.17 ± 0.28 (−1.00 to +0.25)</td>
<td>0.17 ± 0.16 (0.00–0.50)</td>
</tr>
<tr>
<td>3 mo postoperative</td>
<td>−0.06 ± 0.08 (−0.18 to 0.05)</td>
<td>−0.06 ± 0.09 (−0.10 to 0.16)</td>
<td>−0.19 ± 0.28 (−1.00 to +0.25)</td>
<td>0.18 ± 0.16 (0.00–0.63)</td>
</tr>
<tr>
<td>6 mo postoperative</td>
<td>−0.07 ± 0.08 (−0.18 to 0.10)</td>
<td>−0.11 ± 0.07 (−0.10 to 0.16)</td>
<td>−0.25 ± 0.29 (−1.15 to +0.25)</td>
<td>0.25 ± 0.18 (0.00–0.63)</td>
</tr>
</tbody>
</table>

* Eyes with plano target refraction.

FIGURE 1. Epithelial thickness profile maps at various time points. Epithelial thickness was measured in micrometers and mean values ± SDs are presented. Left eye maps were mirrored in the vertical axis and merged with right eye maps. Color-coding represents the relative change from baseline (in %).
cance and the half-time of recovery was calculated to be approximately 13 days. Furthermore, we demonstrated that the extent of epithelial hyperplasia subsequent to SMILE strongly correlated with greater surgical refractive correction. Interestingly, our data also showed that increasing patient age at the time of surgery diminished the effect of surgical refractive correction on epithelial remodeling. This important finding suggests that the compensatory potential of the corneal epithelium diminishes with increasing age. The epithelial thickening could be accurately predicted by a GEE regression model.

To our knowledge, only two studies have previously investigated on the ET changes after SMILE. In our SD-OCT-based study, we observed central epithelial thickening of 6.3 ± 3.4 μm six months postoperatively. Our findings are in good agreement with Vestergaard et al., who were first to report central epithelial thickening of 6 ± 5 μm 6 months after SMILE. In their trial, however, a purely manual SD-OCT image analysis method was used, which was not validated for reliability. In the second study, Reinstein et al. detected an increase in central ET of 15 ± 5 μm 3 months postoperatively using VHFUS. However, the results of these studies are not comparable, as different imaging modalities were used and SD-OCT- and VHFUS-based measurements of corneal ET cannot be considered interchangeable.35

For the first time, we assessed the noncentral changes of corneal ET subsequent to SMILE. Preoperatively, we found the epithelium to be thinner superiorly than inferiorly, which is in accordance with previous work investigating the ET profile in a healthy population.36–38 This finding supports the validity of the methods used in the present study. Six months after SMILE,
we observed similar vertical asymmetry of the epithelial profile suggesting that the natural superoinferior disparity of the corneal ET profile is preserved after SMILE.

It is a well-established fact that the corneal epithelium changes induced by other corneal refractive procedures are of permanent nature.8,9,13–17,20,22 For instance, after PRK and LASIK, persistent epithelial thickening has been demonstrated for up to 7 years.14 To date, it is unknown whether the changes in ET induced by SMILE are permanent or transient. This question might not be addressed in all certainty by the present study design due to its limited follow-up period. Nevertheless, we found a high increment rate of ET immediately after surgery, which thereupon decreased exponentially until an apparent stabilization of the epithelial profile was observed at the third postoperative month. This type of exponential (recovery) response to an external stimulus (in this case the stromal surface curvature change) is in fact a common characteristic of biological systems, which always endeavor to establish a steady-state status. Hence, we hypothesize that the postoperative remodeling process after corneal refractive surgery corresponds to the reestablishment of a new steady-state equilibrium, which is actively preserved. In support of this “steady-state hypothesis,” previous reports have shown a stabilization of the postoperative ET changes between 3 months and 1 year after PRK8,13 and between 1 week and 3 months after LASIK.15-18,20,21 In conclusion, our findings indicate that SMILE induces permanent changes to the corneal epithelial profile.

To date, the knowledge on the underlying mechanisms of epithelial remodeling after corneal refractive surgery is limited. It has been hypothesized that the epithelial response to corneal refractive surgery might be partly due to the mechanical influence of the upper eyelid tarsus during blinking.59 In addition, the “rate of change of curvature” hypothesis40 states that postoperative epithelial remodeling is mainly driven by the extent of induced change to the stromal surface curvature. This rationale was supported by previous observations that showed a clear association of the amount of refractive correction with the magnitude of ET changes after PRK8,9 and LASIK.16-18,20,22 Moreover, Huang et al.41 proposed a mathematical model that quantitatively links changes of corneal curvature induced by laser refractive surgery to postoperative ET modulation. The authors hypothesized that the underlying mechanism of postoperative epithelial smoothing may be found in epithelial cell (EC) migration toward areas of the cornea that are located lower relatively to the line perpendicular to the local corneal surface. As the key driver of reactive EC migration, the authors quoted the so-called cell contact inhibition phenomenon.41 To conclude, our data further endorse “the rate of change of curvature” hypothesis, as we found a close correlation between apical epithelial thickening and the extent of surgical refractive correction (i.e., the rate of stromal curvature change).

In the end, the question arises as to whether postoperative epithelial remodeling affects the refractive outcome of SMILE. With respect to refractive precision, in the present work, no association of ET increment with the absolute deviation from target refraction was detected. Furthermore, no relevant refractive regression was observed during the first 6 postoperative months. Nevertheless, a (statistically nonsignificant) hyperopic change from −0.26 to −0.19 D was seen between 1 week and 6 weeks postoperatively: the period in which almost two-thirds of the observed epithelial thickening occurred. Interestingly, we observed a mild myopic regression from −0.19 to −0.23 D between 3 and 6 months postoperatively, well after the epithelial remodeling had come to a halt. This “relative delay in refractive regression,” which was also found after LASIK,20 implies that corneal epithelial remodeling may not be primarily responsible for refractive regression after SMILE. Instead, we believe that other anatomical (e.g., stromal remodeling), optical (e.g., alterations to the corneal refractive index), or confounding factors (e.g., ocular surface irregular-
Corneal Epithelial Remodeling After SMILE

ITIES due to dry eye) may be accountable for these subtle refractive variations during the earlier postoperative period of SMILE. Hence, future studies are warranted to augment the body of evidence on stromal thickness changes subsequent to SMILE so as to establish a better understanding of the postoperative corneal behavior.

Limitation to this study may be found. First and foremost, ET changes were evaluated only over the central 5 mm corneal zone despite an optical zone of 6.5 mm created by the SMILE procedure. Even though the SD-OCT device used in the present study is capable of capturing a maximum B-scan width of 8.0 mm when used for imaging the anterior segment, nevertheless, measurements of corneal ET become increasingly challenging and less repeatable toward the corneal periphery.33–38 This may be attributable to the specular reflective properties of the cornea itself as well as the planar OCT scanning pattern used in contemporary OCT systems.35 Therefore, the present study was unable to assess ET modulations over the entire optical zone of the SMILE procedure as well as the more peripheral cornea. In future studies, the implementation of an arcuate-type OCT scanning pattern might resolve these shortcomings and may render possible the characterization of epithelial profile alterations over the entire cornea. As further limitations to this work, no control group was included in the study protocol and no objective means of measuring refraction were applied.

In conclusion, we present the first study to characterize the changes of the corneal ET profile subsequent to SMILE. Epithelial thickening of approximately 10% was observed during the first 6 postoperative months with the highest increment rate immediately after surgery. The epithelial remodeling reaction stabilized after 3 months and its extent was strongly determined by the amount of surgically induced refractive correction. Moreover, our findings indicated that the compensatory potential of the corneal epithelium decreases with increasing age. In our hands, the refractive predictability of SMILE did not appear to be affected by epithelial remodeling, nor was there an association with refractive regression.

Acknowledgments

Disclosure: N. Luft, None; M.H. Ring, None; M. Dirisamer, None; A.S. Mursch-Edlmayr, None; T.C. Kreutzer, None; J. Pretzl, None; M. Bolz, None; S.G. Priglinger, None

References


23. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic...


