Original Article

Postoperative changes in corneal epithelial and stromal thickness profiles after SMILE in high myopic eyes

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Background: To observe changes in the epithelial and stromal thickness after small incision refractive lenticule extraction (SMILE) and investigate their relationship with the different refractive error.

Methods: One hundred and eighty eyes of 90 patients with a manifest refraction spherical equivalent (MRSE) of –6.36±1.53 diopters (D) were included. The eyes were assigned to the moderate myopic group (MRSE –3.00 to –6.00 D), high myopic group (MRSE –6.00 to –8.00 D) and super-high myopic group (MRSE above –8.00 D). The spectral-domain optical coherence tomography (SD-OCT) measured corneal and epithelial thickness in 17 zones preoperatively and 1, 3, and 6 months postoperatively. Stromal thickness was calculated by subtracting the epithelial thickness from the total corneal thickness. The observed changes were correlated with the degree of myopia corrected.

Results: MRSE showed significant differences between 3 and 6 months in the super-high myopic group (P=0.024). At 6 months, a statistically significant epithelial thickness increase was observed in the central zone (7.18% for moderate, 10.23% for high, and 13.76% for super-high myopia, P<0.05 for all groups). The peripheral thickness decreased between 3 and 6 months in the high myopia and super-high myopia groups (P<0.05, respectively). A positive correlation between MRSE corrected and the postoperative epithelial thickening was observed in the central (r^2=0.551, P<0.05). Compared to 1 month values, the central stromal thickness showed a decrease (3.2±4.5 μm) at 3 months and an increase (4.4±4.9 μm) at 6 months. The stroma thickened in moderate and high myopic groups but the thickness reduction were in super-high myopia group at 6 months paracentrally and peripherally.

Conclusions: Significant thickness changes in the epithelium and stroma were detected during the 6 months after SMILE. Preliminary results suggest that epithelial and stromal thickness profile changes after SMILE may have an impact on the refractive outcome in the long-term postoperative period, especially in super-higher degrees of myopia.

Keywords: Epithelium; stroma; high myopia; small incision refractive lenticule extraction (SMILE)

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Introduction

In the small incision refractive lenticule extraction (SMILE) procedure, a stromal lenticule is created and removed through a small peripheral incision. Previous studies (1-5) have reported an increase in epithelial thickness after SMILE but studies (1,6) examining stromal thickness changes were few. Luft *et al.* has observed that the stromal thickness decreased significantly during the first 6 weeks and amounted to a mean of 10.4±6.3 μm at the apex. The central stroma thickened by a mean of 8.8±5.9 μm up until the 1-year follow-up (6). Refractive regression impacts the predictability of SMILE surgery. It is supposed that the epithelial and/or stromal remodeling induced partly to refractive regression after PRK and LASIK (7-9). Changes in epithelial thickness after SMILE have shown to be related with the regression (2).

In the present work, we used spectral-domain optical coherence tomography (SD-OCT) to study epithelial and stromal remodeling of eyes with different refractive diopter throughout 6 months after SMILE. A better understanding of these might help surgeons in accurate treatment planning and further improving the predictability of outcomes.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/aes-20-105).

Methods

One hundred and eighty eyes (90 patients) with a manifest refraction spherical equivalent (MRSE) of –6.36± 1.53 diopters (D) (range, –3.00 to –10.00 D) were divided into three groups. The moderate myopic group (MRSE –3.00 to –6.00 D) includes 74 eyes (37 right, 37 left) of 37 patients; the high myopic group (MRSE –6.00 to –8.00 D) includes 60 eyes (30 right, 30 left) of 30 patients; the super-high myopic group (MRSE above –8.00 D) includes 46 eyes (23 right, 23 left) of 23 patients.

This study was approved by the Institutional Review Board of Tongren Hospital and adhered to the tenets of the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants.

Preoperatively, all patients received a thorough clinical examination, including MRSE, uncorrected distance visual acuity (UDVA), history of refractive stability, slit-lamp evaluation, dilated fundoscopy and corneal topography (Tomey Inc., Japan), SD-OCT (RTVue OCT, Optovue, USA). The SD-OCT was used for the corneal epithelial and total thickness data. Stromal thickness was calculated by subtracting the epithelial thickness from the total corneal thickness. Scanning was performed by a single trained investigator at all visits. The mean values were calculated in the central zone, paracentral and peripheral zones.

Patients were reexamined at 1 day, 1 week, 1 month, 3 months and 6 months postoperatively (10).

Refraction procedure

All procedures were performed by the same experienced ophthalmologist (FZ) using a VisuMax 500-kHz femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany). The intended cap thickness was 120 μm and the diameter of the optical zone was 6.0–6.5 mm. A 2-mm incision was made at the 12 o'clock position. The upper interface was separated and the lower layer was dissected. Once both layers had been separated, the lenticule was removed from the cornea. All patients received one drop of topical ofloxacin 0.3% (Tarivid; Santen Inc., Osaka, Japan) at the end of the procedure, and postoperatively four times a day for 10–14 days. Fluorometholone 0.1% (flumetholon; Santen Inc., Osaka, Japan) was also applied four times a day for 1 week and then tapered over 9 days. Artificial tears were used four times a day for 4 weeks or more (10).

Statistical analysis

SPSS (version 23.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The normality of all data samples was checked using the Kolmogorov-Smirnov test. A repeated measures ANOVA with Bonferroni correction was used to compare the thickness changes between different times. The difference in the thickness between the two groups was compared using the Student's *t*-test. Linear regression analysis was performed. A P value of less than 0.05 was considered significant.

Results

There was no data missing at every stage. No significant MRSE changes occurred at the 1, 3 and 6 months in the moderate and high myopic groups. MRSE only showed significant differences between 3 and 6 months in the super-high myopic group (P=0.024).

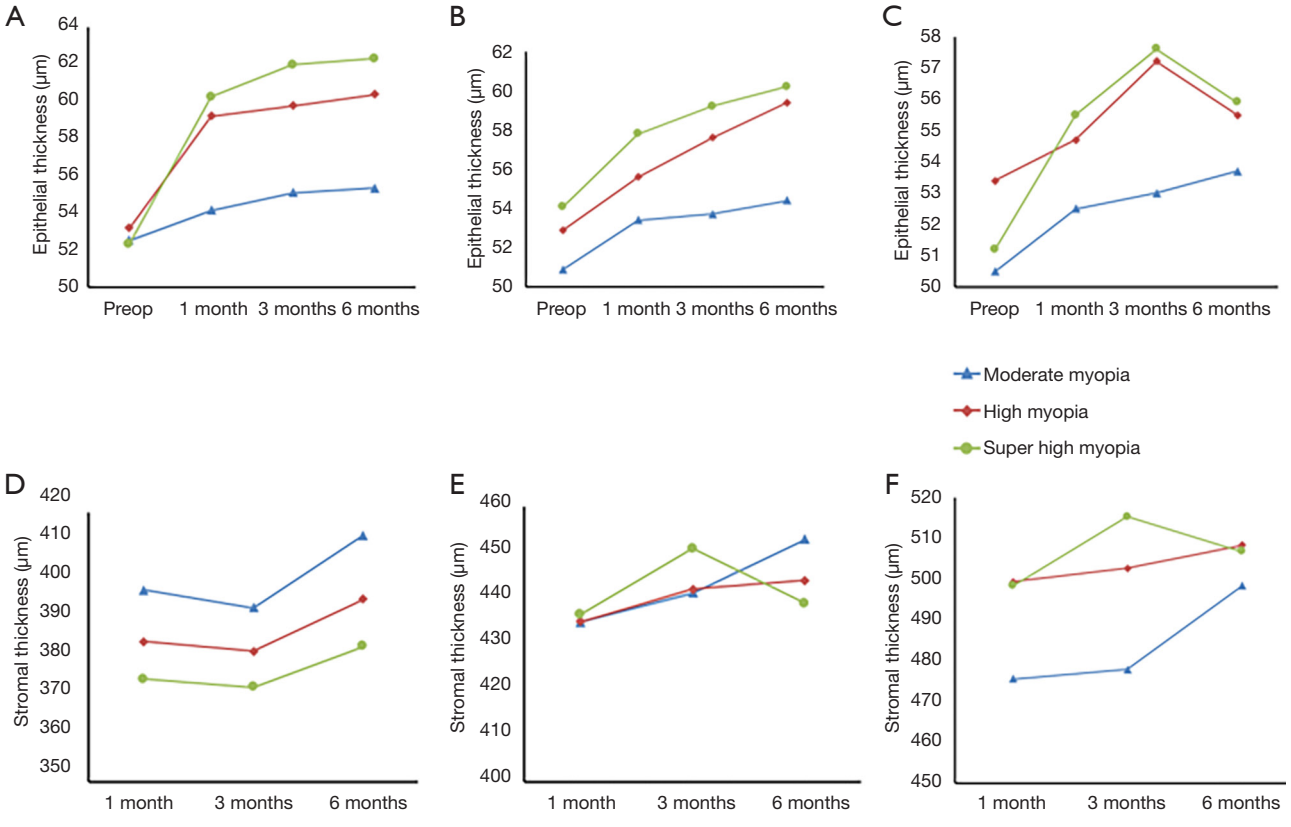

Figure 1 Epithelial thickness profile changes over time after SMILE in the (A) central zone (B) paracentral zone (C) peripheral zone; stromal thickness profile changes in the (D) central zone (E) paracentral zone (F) peripheral zone. SMILE, small incision refractive lenticule extraction.

Epithelial thickness changes

Average preoperative central epithelial thickness was 55.2±2.7 (range, 50 to 57) μm. There was a 7.18%, 10.23%, and 13.76% increase in epithelial thickness compared to preoperative values in the respective groups at the end of 6 months. *Figure 1* and *Table 1* illustrate the changes of epithelial over time. The epithelium were thicker at 1 month after the surgery compared to preoperative measurements in three myopia groups in all the zones (P<0.05). In the central zone, epithelial thickness increased more in super-high myopia group than in moderate and high myopic groups both 1 and 3 months postoperatively. There were statistically significant differences between 3 and 6 months centrally in moderate and high myopic groups, respectively (P<0.05). Overall, progressive epithelial thickening were observed in the central and paracentral zones until 6 months but not in the peripheral zone. The peripheral thickness decreased between 3 and 6 months in the high myopia and super-high myopia groups (P<0.05, respectively). Hence, the bulk of epithelial thickening occurred in 1 month and the epithelial profile stabilized after 3 months. A positive correlation between MRSE corrected and the postoperative epithelial thickening was observed in the central (r^2=0.581, P<0.05).

Stromal thickness changes

One month postoperatively, the mean measured ablation depth was 95.4±15.8 (range, 61–127) μm. The mean residual stromal bed thickness was 332.6±23.5 (range, 280–361) μm.

In central stromal zone, stromal thickness decreased by a mean of 3.2±4.5 μm at 3 months compared to 1 month values (P<0.05). Thereafter, an increase (4.4±4.9 μm) was observed at 6 months (P<0.05). The stromal thickness decreased paracentrally and peripherally at 3 months in three groups (*Table 2* and *Figure 1*). Subsequently, increased changes in paracentral and peripheral zones were detected

Table 1 Changes in epithelial thickness over time

Group	Central zone		Paracentral zone		Peripheral zone	
	Mean ± SD (μm)	P	Mean ± SD (μm)	P	Mean ± SD (μm)	P
Moderate myopia						
Preop	52.2±2.8	–	50.9±2.9	–	50.5±2.9	–
1 month postop	54.1±2.4	0.006	53.4±2.6	0.011	52.5±3.0	0.020
3 months postop	55.2±2.3	0.017	53.9±3.3	0.026	53.0±3.2	0.047
6 months postop	56.8±2.6	0.013	54.4±2.7	0.037	53.7±2.7	0.085
High myopia						
Preop	54.1±2.8	–	52.9±3.1	–	52.4±3.4	–
1 month postop	59.2±3.3	0.021	55.6±3.1	0.026	54.7±2.8	0.035
3 months postop	60.7±3.2	0.032	57.6±3.4	0.027	57.2±3.5	0.017
6 months postop	61.4±3.0	0.044	59.4±3.3	0.025	55.5±3.4	0.014
Super high myopia						
Preop	52.2±3.2	–	54.1±3.1	–	51.2±2.9	–
1 month postop	58.3±3.3	0.028	57.8±3.6	0.033	55.0±3.0	0.035
3 months postop	62.3±2.6	0.017	59.2±2.7	0.025	57.6±2.8	0.024
6 months postop	63.4±3.4	0.064	60.2±3.1	0.061	55.9±3.5	0.038
Entirety						
Preop	52.7±3.1	–	52.4±3.5	–	51.4±3.3	–
1 month postop	56.2±3.6	0.012	55.7±2.7	0.017	54.9±2.8	0.035
3 months postop	57.9±2.8	0.033	57.0±3.5	0.047	55.7±3.2	0.041
6 months postop	58.1±3.3	0.082	57.5±3.1	0.058	55.2±3.1	0.023

Preop, preoperative; postop, postoperative.

Table 2 Comparison of the change in postoperative corneal stromal thickness over time

Group	Central zone		Paracentral zone		Peripheral zone	
	Mean ± SD (μm)	P	Mean ± SD (μm)	P	Mean ± SD (μm)	P
Moderate myopia						
3 months postop	–4.6±7.8	0.016	–7.3±7.6	<0.001	–2.35±7.0	0.025
6 months postop	9.8±6.9	0.021	11.2±8.3	0.026	21.5±8.8	0.047
High myopia						
3 months postop	–3.5±7.2	<0.001	–7.0±8.1	<0.001	–7.8±6.8	0.033
6 months postop	7.5±8.7	0.031	1.9±7.4	0.023	0.7±8.5	0.019
Super high myopia						
3 months postop	–1.8±8.0	<0.001	–4.4±7.6	<0.001	–7.3±8.0	<0.001
6 months postop	17.7±8.1	<0.001	–12.0±7.7	0.026	–9.1±8.2	0.032

Comparison between 1 and 3 months, 3 and 6 months. Postop, postoperative.

in moderate and high myopic groups at 6 months. In contrast, stromal thickness decreased paracentrally and peripherally significantly in super-high myopia group at 6 months.

Discussion

Previous studies have reported the corneal epithelial changes using SD-OCT after SMILE. Ryu *et al.* suggested that epithelial thickness showed a statistically significant increase in the center, paracentral and peripheral regions at both 1 and 3 months postoperatively (1). Ganesh *et al.* demonstrated that the significant epithelial thickness increased until 3 months in low [spherical equivalent (SE) <–4.00 D], moderate (SE –4.00 to –6.00 D), and high (SE >–6.00 to –10.00 D) myopia groups at central and superior zone (2).

Our study reconfirmed that epithelial thickness showed a statistically significant increase in three zones in three groups at 1 month. The increase in epithelial thickness was greatest in central zone. Epithelial thickness increase was continuously decreased toward the periphery zone, in agreement with the result (3) which described a lenticular shape change in epithelial thickness following SMILE. On the contrary, Ryu *et al.* described a different pattern of epithelial thickening, which epithelial thickness changes were less marked centrally but increased radially (centrifugally) toward the mid-periphery (1). We observed epithelial thickness increased most in super-high myopia group, less in high myopic group, least in moderate group in central and paracentral zones. The peripheral thickness decreased statistically between 3 and 6 months in the high myopia and super-high myopia groups.

The present study found significant central stromal thickness increased between 1 and 6 months in three groups postoperatively. The finding may agree with Reinstein *et al.* (4) and Luft *et al.* (6) studies. Reinstein *et al.* (4) suggested that the central stroma might expand as a result of tension release of the stromal collagen lamellae disrupted during the creation of the lenticule. We observed continuous thickening in paracentral and peripheral zones until 6 months in moderate and high myopic groups. The stromal thickness decreased significantly in super-high myopia group in paracentral and peripheral zones between 3 and 6 months. The results were inconsistences with the report (6) in which stromal thickness remained stable after 6 weeks in the 1.25 mm and 2.5 mm corneal zone. The keratocyte-mediated wound healing in the laser-cut interface, glycosaminoglycans (GAG's), fibrin and other extracellular matrix components induced stromal thickening response (11-13). Dong *et al.* (11) showed keratocytes were transformed into fibroblasts or myofibroblasts and migrated to repopulate the depleted stroma. Subsequently, the remodeling of the extracellular matrix and the stroma was achieved by myofibroblasts. Luft *et al.* (6) reported central stromal thickness was highest on the first postoperative day (mean 407.2±29.8 μm) and decreased by a mean of 10.4±6.3 μm until the minimum at 6 weeks. The potentially influential factor may be early transient stromal edema which elevated the thickness then normalized.

We analyzed the epithelial and stromal thickness postoperative changes in central zone were different. The epithelial thickness increased continuously until 6 months. The range of thickness change was 0.5±2.8 to 4.2±3.2 μm. The stromal thickness decreased at 3 months and increased at 6 months compared to 1 month. The range of thickness change was –1.7±7.9 to 18.9±7.6 μm. The central stromal thickness changes were more obviously. A positive correlation between MRSE corrected and the postoperative epithelial thickening was similar to the observations by Ganesh *et al.* (2).

However, MRSE was not associated with the postoperative central stromal thickening in the present study.

In the current study, observed increases in epithelial and stromal thickness did not lead to any significant refractive change in the moderate and high groups at 6 months. It proved the refractive stability of SMILE for most myopic patients. MRSE only showed significant differences between 3 and 6 months in the super-high myopic group, as observed in both eyes of two patients in previous study (2).

The epithelial thickening was positively correlated with MRSE of myopia, which may indicate that eyes with super-high myopia may have an increased tendency toward epithelial hypertrophy. Our study found significant central stromal thickness increased between 1 and 6 months in three groups postoperatively. Luft *et al.* (6) have demonstrated the central stromal expansion observed between 6 weeks and 1 year coincided with a mild (nonsignificant) myopic regression. So, the hypothesis in this study put forward that epithelial hypertrophy and stromal remodeling might lead to potential chances of refractive regression of super-high myopic group after SMILE. These results suggested that properly prolonged steroid eyedrops management may decrease the epithelial and stromal thickening resulting in super-high myopic regression.

The limitations need to be considered. The epithelial thickness changes within the 6.0–6.5 mm corneal zone should be evaluated. Moreover, some deviation may have been caused by incorporating the tear film thickness into the epithelial thickness measurement. Furthermore, a relatively short follow-up period of 6 months was not long enough to conclude that cornea stopped remodeling completely. Additional studies are required to confirm our findings.

Conclusions

To conclude, this study demonstrated a wide epithelial and stromal remodeling profile after SMILE, which is correlated to different refraction. The corneal epithelial and stromal thickness increases that did not affect the refractive stability were observed during the 6-month follow-up period. A further research in super-high myopia is advocated to elucidate potential effects of corneal remodeling on refractive outcomes.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of Tongren Hospital (IRB: R/17.05.119) and adhered to the tenets of the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants.

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