Regional changes in corneal shape over a 6 month follow-up period post FS-LASIK

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Conflict of Interest

The authors indicate no financial conflict of interest.

Running title

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Synopsis:

Corneal shape changes after LASIK followed different trends in different regions (from central to peripheral area). Over the follow-up period, the shape changes were small and followed a reverse trend.

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Abstract

PURPOSE: To assess the regional changes in corneal shape following FS-LASIK in patients with different myopia extents.

SETTING: Eye Hospital, WenZhou Medical University, WenZhou, China.

DESIGN: Retrospective case series.

METHODS: A retrospective study of 608 myopic eyes treated with FS-LASIK was conducted to assess the shape changes within different corneal regions following surgery. Corneal curvature was measured in the central region (0-3mm diameter), pericentral region (3-6mm diameter) and peripheral region (6-9 mm diameter) before (pre) and after surgery (1 week: pos1w to 6 months: pos6m).

RESULTS: During the 6 month follow-up, the anterior cornea became steeper in central and pericentral regions, but flatter in the peripheral region ($p< 0.01$), representing a partial, gradual, yet significant reversal of the immediate change in corneal shape after laser ablation. In contrast, the posterior surface experienced much less change than the anterior surface, with the cornea becoming slightly flatter ($p< 0.01$) in the central region at pos1w, and steeper elsewhere ($p< 0.05$), and remaining stable in the rest of follow-up. On the other hand, anterior astigmatism experienced significant decreases in the central region (pos1w, $p< 0.01$) and slight increases in the peripheral region (pos1w, $p< 0.01$), and that remained stable over the follow-up period. In contrast, posterior astigmatism experienced little and non-significant changes throughout follow-up ($p> 0.05$).

CONCLUSIONS: Post-surgery shape changes that were different in different regions, the follow-up period saw shape changes in individual corneal regions that represented reverse trends but were much smaller than the short-term changes observed 1 week after surgery.

Keywords: FS-LASIK, Corneal topography

Introduction

Most Refractive surgeries (RS), which reshape the anterior corneal surface to adjust the refractive power of the eye, are becoming increasingly popular worldwide. Laser in situ keratomileusis (LASIK) is currently the most common refractive surgery procedure, known to be relatively safe and effective [1-4]. The refractive outcome of LASIK, which depends on the post-operative corneal shape, is affected by several factors including the surgery parameters (flap thickness and diameter, and ablation depth and profile), the value of intraocular pressure (IOP), wound healing (causing alteration in corneal tissue ultrastructure and hence mechanical stiffness) [5], and possible post-operative inflammation.

The introduction of new technologies has enabled better control of the ablation profile, improved energy delivery to corneal tissue and development of more effective ablation algorithms. With these developments, 93% of eyes undergoing LASIK achieve a ±1.00 D refractive outcome [6], and reach an acceptable visual acuity with few debilitating visual complaints [7]. Further, while current surgery planning is largely based on a population-based normative response, corneal reaction to surgical ablation is individualized, possibly causing residual refractive error, refractive regression, and even corneal ectasia [8]. The current increasing emphasis on customization of treatment make it important to characterize corneal shape changes caused by the surgery.

Several earlier studies sought to evaluate the topographical changes after LASIK and predict corneal response to surgical tissue subtraction [9-12]. These studies relied on interpretation of corneal topography to analyze the changes in curvature, asphericity, aberrations, whole corneal thickness, epithelium thickness and elevation of posterior cornea [12-17]. In these studies, the cornea was covered as one region without considering that different sub-regions could be affected differently. This study attempts to address this shortfall through a retrospective analysis of topography data with emphasis on the regional variation in response to surgery, and with attention given to the shape changes in a 6 months follow up period. The analysis covers separately the central, pericentral and peripheral regions of both the anterior and posterior surfaces, and considers the induced, and sometimes unexpected, modifications of corneal shape caused by LASIK.

Materials and Methods

Study participants

Patients who had undergone femtosecond assisted LASIK for myopia between -0.75 and -10.75 D and/or astigmatism between 0.00 and -3.00 D were evaluated retrospectively, and records were included if the patients had completed a 6 month-long post-operative follow-up including ophthalmologic examinations before surgery (pre), and 1 week (pos1w), 1 month (pos1m), 3 months (pos3m) and 6 months (pos6m) post-LASIK. 608 patients (303 male and 305 female, age: 22.8±5.5 years) who had undergone LASIK were included in the study. Since bilateral corneas are correlated with each other and behave with mirror symmetry as reported in our earlier study [18], only the right eyes were selected for analysis to avoid this confounding effect.

The protocol for the retrospective analysis was reviewed and approved by the ethic Committee of the Eye Hospital, WenZhou Medical University. The LASIK procedure, and pre-operative and post-operative ophthalmologic examinations were performed at the Refractive Surgery Center of the Eye Hospital. In the LASIK procedure, 90-110 μm thick, 8.0-9.0 mm diameter flap with a superior hinge was created using two femtosecond laser machines (FEMTO LDV, Ziemer Ophthalmic Systems AG, Port, Switzerland) or (IntraLase iFS150, Abbott Medical Optics, CA, USA). A 0.4-mm-thick flap hinge was chosen in the former, and a 45° hinge with a 70° side-cut angle was set up in the latter. This step was followed by tissue ablation using the Schwind Amaris 750 excimer laser (Schwind eye-tech-solutions, Kleinostheim, Germany).

Data Acquisition

The following clinical observations were recorded before surgery and after by 1 week, 1 month, 3 months and 6 months: refractive error (RE), corneal thickness data, and elevation data of corneal anterior and posterior surfaces. Surgical parameters including refractive error correction (REC), which consists of spherical (S) and cylindrical (C) corrections, spherical equivalent (SE), astigmatism axis, and optical/transition zones (OZ/TZ) were excerpted from medical records. Manifest RE before and 1 week and 6 months after surgery was measured with a phoroptor (Nidek RT-2100; Nidek Inc, Gamagori, Japan) and converted to SE. According to SE measured pre-surgery, participants were divided into three groups with low myopia (-0.50D>SE≥-3.00D, 59 eyes), moderate myopia (-3.00D>SE≥-6.00D, 323 eyes) and high myopia group (-6.00D>SE, 226 eyes). Corneal thickness and elevation were provided by a Pentacam HR (OCULUS Optikgerate GmbH, Wetzlar, Germany; Software Version 6.02r23). The best Pentacam measurement in each follow-up stage, with an instrument-generated quality factor of at least 95% and 90% for the anterior and posterior surfaces, respectively, was selected for analysis.

Elevation data with reference to a plane that is tangential to the corneal surface at the apex and perpendicular to the ocular longitudinal axis was exported from Pentacam. As some of the peripheral data were missing because of the eyelids and eyelashes, only elevation data within the 9mm diameter central region were used in analysis. This region included approximately 6400 data points with 0.1mm spacing in the horizontal (temporal-nasal) and vertical (inferior-superior) directions. The elevation data $z(x, y)$ at each point (x, y) on either the anterior or posterior corneal surface with Cartesian coordinates was defined as the Z distance from corneal surface to an XOY plane passing through the origin point, at which the instrument axis intercepts the cornea, which was described in a previous study [18] (Figure 1).

Computation of corneal curvature

The elevation data of corneal topography within an aperture of 9 mm diameter was imported into a bespoke Matlab code for surface fitting with a set of Zernike polynomials up to order 10. The first and second derivatives of this Zernike expression were then derived to calculate the principal curvatures and their corresponding principal directions at each point on corneal surface, based on the differential geometry theory [19]. The local power of corneal surface was obtained as

$$P_i(x,y) = (n'-n)\cdot\kappa_i(x,y),\quad i=1,2$$

where $\kappa_i(x, y)$ is the principal curvature at the location (x, y), κ_1 and κ_2 are the min and max principal curvatures, respectively, n and n' are the refractive indexes of the medium separated by corneal surface. Then, the local corneal surface astigmatism $A(x, y)$ was given by

$$A(x,y) = P_2(x,y) - P_1(x,y)$$

we converted the local corneal surface power to local power vector form [20] by using the following equations:

$$\begin{aligned} M(x,y) &= \frac{P_2(x,y)+P_1(x,y)}{2} \\ J_0(x,y) &= -\frac{A(x,y)}{2}\cos 2\alpha_1(x,y) \\ J_{45}(x,y) &= -\frac{A(x,y)}{2}\sin 2\alpha_1(x,y) \end{aligned}$$

where $\alpha_1(x, y)$ is the principal direction of the min principal curvature, $M(x, y)$ is the local spherical equivalent, and $J_0(x, y)$ and $J_{45}(x, y)$ are the local astigmatism at 0-degree and 45-degree meridians, respectively. Numerical integration was used to determine the mean values of the power components M, J_0 and J_{45} over three corneal sub-regions; central 0-3mm, pericentral 3-6 mm and peripheral 6-9 mm.

Keratometry, normally calculated based on topography data obtained in the central 3 mm diameter zone, is used to describe the central corneal shape [21]. Further, most refractive surgery procedures (such as LASIK and SMILE) consider the optical zone to be around the 6 mm diameter area. In addition, there is high likelihood of peripheral data beyond the 9 mm diameter region being missed due to interference by eyelids and eyelashes [18, 22]. For these reasons, the cornea's topography data was divided in this study into three regions with diameters 0-3, 3-6 and 6-9 mm, respectively.

Statistical analysis

Commercial software SPSS Statistics (version 20.0, IBM, Inc.) was utilized for all statistical analyses. Analysis of variance (ANOVA) was carried out to compare the shape parameters among the three groups with different myopia severity, while MANOVA of repeated measurements was employed in the analysis of data obtained at different follow-up periods for the same participant. Correlation analyses were assessed using the Pearson's or Spearman linear correlation factor according to a normal distribution test.

Results

Before surgery, SE was -2.38±0.55D, -4.62±0.86 D and -7.73±1.23 D in low, moderate and high myopia groups, respectively. After the surgery procedure, RE showed some limited hyperopia (pos1w: 0.09±0.40 D, 0.23±0.41 D and 0.32±0.54 D for the three myopia groups), and this hyperopia decreased during the follow-up period in moderate and high myopia groups (pos6m: 0.12±0.30 D, 0.19±0.38 D and 0.13±0.58 D). The change in RE at pos6m compared with pos1w was statistically significant in high myopia group (-0.19±0.53 D, $p< 0.01$), while not significant in low and moderate myopia groups (0.02±0.39 D, $p= 0.806$; -0.04±0.41 D, $p=0.078$).

Changes in spherical refractive power

Within the 0-3mm diameter anterior central region, the cornea became flatter with surgery (42.67±2.29 D vs 48.18±1.58 D; $p< 0.01$), then gradually steeper post-surgery in all three myopic groups (43.03±2.13 D for pos6m; $p< 0.01$, Table 1), Figure 2A,C,E (black lines). The steepening at pos6m compared with pos1w was statistically significant: 0.14±0.24 D (45.37±1.54 D vs 45.22±1.61 D; $p< 0.01$), 0.21±0.31 D (43.54±1.86 D vs 43.33±1.89 D; $p< 0.01$) and 0.63±0.45 D (41.68±1.75 D vs 41.07±1.86 D; $p< 0.01$) in low, moderate and high myopia groups, respectively, and these curvature changes showed significant increases with myopic correction ($r= -0.537$, p< 0.01).

In contrast, the anterior peripheral annulus region (6-9mm diameter) showed the opposite trends as curvature became steeper after surgery (48.54±2.12 D vs 44.94±1.65 D for pos6m and pos1w, respectively; $p < 0.01$), then flatter gradually from pos1w to pos6m in all myopic groups (47.90±2.04 D; $p < 0.01$, Table 1), Figure 2A,C,E (blue lines). Corneal curvature became flatter at pos6m compared with pos1w by -0.45±0.73 D (46.15±1.79 D vs 46.59±1.71 D; $p < 0.01$), -0.62±0.92 D (47.56±1.86 D vs 48.19±1.89 D; $p < 0.01$) and -0.71±1.12 D (48.85±1.88 D vs 49.54±2.02 D; $p < 0.01$) in low, moderate and high myopia groups, respectively, while no correlation was found with REC (Total: $r = 0.078$, $p = 0.058$).

The red lines in Figure 2A,C,E show that the anterior surface shape changes within the pericentral annulus region (with diameter between 3 and 6 mm) were similar to the central regions (Table 1). The steepening at pos6m compared with pos1w was statistically significant; 0.31 ± 0.25 D (45.47±1.46 D vs 45.15±1.49 D; $p < 0.01$), 0.38 ± 0.41 D (44.69±1.72 D vs 44.33±1.73 D; $p < 0.01$) and 0.35 ± 0.35 D (44.74±1.64 D vs 44.40±1.66 D; $p < 0.01$) from low to high myopia groups, respectively. However, these curvature changes were not correlated with REC ($r = 0.016$, $p = 0.690$).

Compared with anterior corneal surface, the curvature of posterior surface in all three regions experienced much less change (Table 2). In all groups, posterior corneal curvature became slightly flatter (-6.26±0.24 D vs -6.29±0.23 D; $p < 0.01$) in the central region (0-3mm diameter), and slightly steeper in both the pericentral (-6.25±0.23 D vs -6.24±0.22 D; $p < 0.05$) and peripheral regions (-5.70±0.28 D vs -5.65±0.25 D; $p < 0.05$) after surgery (pos1w) compared with pre-operation period (pre), then remained almost unchanged in the remainder of the follow-up period (Figure 2B,D,F). The difference in posterior curvature between pre-surgery and pos1w increased with REC in the central region ($r = -0.12$, $p < 0.01$) but not the pericentral and peripheral regions ($p > 0.05$).

Changes in astigmatic refractive power

The anterior central region with 0-3mm diameter experienced significant changes ($p < 0.01$) in corneal astigmatism, from J_0: -0.60±0.39 D and J_{45}: -0.04±0.23 D pre-surgery to J_0: -0.26±0.27 D and J_{45}: 0.04±0.19 D at pos1w, then remained stable in the follow-up period compared to pos1w ($p > 0.05$), Figures 3A,C,E; 4A,C,E (black lines), Table 3, 5. The small differences in astigmatic curvature between pos1w and pos6m were not correlated with REC (J_0: r= -0.039, p= 0.338; J_{45}: r= -0.071, p= 0.084).

On the other hand, the anterior peripheral annulus region (6-9mm diameter) exhibited slight increases in corneal astigmatism at pos1w (J_0: -0.85±0.82 D, $p < 0.01$; J_{45}: -0.22±0.46 D, $p < 0.01$) compared with pre surgery (J_0: -0.58±0.54 D and J_{45}: -0.13±0.26 D), then remained stable in the rest of the follow up period ($p > 0.05$), Figures 3A,C,E; 4A,C,E (blue lines), Table 3, 5. In contrast, the anterior pericentral region (with 3-6 mm diameter) had stable J_0 at all stages ($p > 0.05$), while J_{45} changed slightly ($p < 0.01$) until pos1m (-0.10±0.23 D) vs pre stage (-0.13±0.21 D), then remained stable afterwards ($p > 0.05$), Figures 3A,C,E; 4A,C,E (red lines), Table 3, 5. As for the posterior surface, corneal astigmatism J_0 and J_{45} experienced little and non-significant changes ($p > 0.05$) between groups with different myopia extents, over the follow up period and in all three surface regions considered, Figures 3B,D,F; 4B,D,F (black lines) , Table 4, 6.

Changes in corneal thickness

Corneal thickness at 0.7mm radial distance from apex (taken to represent the cornea's central 0-3mm region) experienced large reductions following surgery of -52.8±14.9 µm, -85.4±18.9 µm and -117.1±16.8 µm in the low, moderate and high myopia groups, respectively. These values reduced significantly to -36.6±13.4 µm, -54.2±15.1 µm and -69.3±14.1 µm at 2.2mm radial distance (representing the pericentral 3-6mm region) and then -10.6±17.4 µm, -8.4±11.4 µm and -11.8±12.3 µm at 3.7mm distance (representing the peripheral 6-9mm region).

Over the rest of the follow-up period, the thickness experienced gradual small recovery in the central and pericentral regions ($p< 0.01$). The increase in thickness at 0.7mm radial distance was less in low (3.7±7.3 μm, $p< 0.01$) and moderate (5.2±7.6 μm, $p< 0.01$) myopia groups than that in high myopia group (9.3±8.6 μm). These values reduced significantly to 2.1±8.1 μm, 3.0±8.0 μm and 4.6±9.1 μm ($p< 0.05$) at 2.2mm radial distance. Further, the differences in thickness between pos1w and pos6m were significantly correlated with REC (0.7mm: $r= -0.244$, $p< 0.01$, Figure 5A; 2.2mm: $r= -0.089$, $p< 0.05$, Figure 5B). On the other hand, the peripheral region experienced small and insignificant decreases in thickness at pos6m compared with pos1w of -0.7±11.4 μm, -1.7±12.0 μm and -1.5±12.8 μm ($p>0.05$), which were not significantly correlated with REC (3.7 mm: $r= -0.001$, $p> 0.05$, Figure 5C).

Discussion

Despite the significant corneal tissue loss in laser refractive surgeries, the planning of the procedures still ignores the resulting effect on corneal biomechanics, and hence on surgical outcome [8, 23]. This effect is made complex by the microstructure of the cornea, in which the cornea has mainly horizontal and vertical collagen fibrils at the centre, circumferential fibres at the limbus and intermediate fibrils in between [24]. Since collagen fibrils are the main load carrying components of the stroma, this variation in microstructure is expected to lead to variations in the cornea's response to refractive surgery from one region to another. This paper aims to quantify these variations, with particular emphasis on the topography change over a long, 6 month follow-up period.

In the central corneal region (0-3mm diameter), the central corneal surface undergoes significant changes following surgery, becoming flatter and less astigmatic while the posterior surface undergoes a smaller change in both spherical curvature and astigmatism. This trend became more evident with deeper ablation, in groups with moderate and high myopia, where the flattening trend was stronger in both anterior and posterior surfaces than in the low myopia group. Compared with the anterior surface, the posterior surface continued to undergo lower but still significant changes. A similar but less clear trend was observed in the anterior pericentral annulus region (3-6mm diameter), where ablation made the anterior cornea flatter while astigmatism remained stable, and this trend was stronger with moderate and high myopia, it was weaker than in the central region. Meanwhile, the posterior cornea continued to undergo little but still significant steepening regardless of the extent of myopia, similar to what has been reported in a previous study [25]. This trend was partly reversed in the peripheral region (6-9mm diameter) where both the anterior and posterior surfaces became steeper and more astigmatic following surgery. Such trend became stronger from low to high myopia in the anterior surface, as well as the posterior surface but with smaller changes, which were not correlated with the degree of refractive error correction.

The extended follow-up (up to 6 months) in this study enabled analysis of the long-term shape changes following LASIK and the subsequent wound healing process. The results point clearly at the reversal of the short-term trends discussed above, with the anterior cornea becoming steeper in the central region and flatter in the peripheral region, albeit with much less change compared with that observed immediately after surgery. The same observation was repeated with thickness measurements, where the immediate reductions, caused by ablation, was followed by slight increases over the 6 month follow up period. The increase in corneal thickness was correlated with refractive error correction in both central and pericentral regions. Meanwhile, the astigmatic corneal refractive power in anterior surface, and both spherical and astigmatic refractive power in posterior surface remained stable during the follow-up period.

The reshaping of the cornea is undoubtedly influenced by a combination of flap separation, tissue ablation, associated biomechanical weakening and later wound healing. In the short term, immediately after surgery, tissue ablation should lead to flattening of the anterior central surface. However, the associated mechanical weakening, due to tissue ablation and flap separation, will cause shape changes that can follow one of the two options depicted in Figures 6A and C, or the intermediate behavior illustrated in Figure 6B. In option A, weakening of the central cornea leads to easier pushing out of the peripheral region under intraocular pressure (IOP), and flattening of anterior central region. In contrast, in option C, the weaker central region is further curved under IOP, pulling the peripheral region towards the center. The result is that the central cornea becomes steeper while the periphery becomes flatter. Considering the hyperopia outcome at one week after surgery (0.25±0.46D), it is expected that Option A was more plausible. Then over the rest of the follow up period, up to 6 months after surgery, it is expected that the wound healing would take effect in anterior stroma, and this possibly was responsible for most if not all the reverse changes in corneal shape to account for the decrease in hyperopia according to the mechanism depicted in Figure 6C (0.16±0.46D).

Therefore, the immediate changes in corneal topography observed after surgery are caused by both the geometric effects and biomechanical weakening of corneal structure associated with tissue ablation and flap separation. On the other hand, the long-term changes, observed in this study between pos1w and pos6m stages, are expected to be related to the biomechanical effect of wound healing. Since wound healing is expected to lead to tissue stiffening [26], it is logic to cause some reversal of the immediate effects of surgery, which leads to mechanical softening and weakening of the cornea. These progressive changes will continue according to a previous study [27], which indicated that manifest refraction continued to regress up to 5 years after surgery, but the variation amplitude would become significantly small beyond 6 months.

Epithelial and stromal remodeling may play a further role in post-surgery changes in corneal shape, but this role remains controversial [28]. While epithelial response to myopic ablation was found greater in the central sub-region than in pericentral in some studies with very high-frequency (VKH) digital ultrasound [29, 30], others reported the opposite trend [16]. Erie reported no change in stromal thickness between pos1m and pos12m after LASIK [31], while it was found to be significantly higher at pos1m [32] in Avunduk's study. The change in manifest refractive error was much lower than the steepening effect of anterior central cornea for the three levels of correction at pos6m compared with pos1w. The calculation of post-operative corneal refraction assumed the shape change only took place in the stroma. However, the shape change in anterior central corneal surface during the follow up after LASIK is mainly due to regrowth of both the epithelium and stroma [33], which meant that the actual change in corneal refraction was lower than that calculated for the corneal anterior surface.

The apex in Pentacam topography maps, which coincides with corneal vertex where the instrument axis intersects the cornea, was close to the corneal purkinjie reflex [34] used as the ablation center in this study. Therefore, the changes in angle kappa would not be expected to lead to any notable change in analysis results. However, as laser ablation instruments vary in their cutting algorithms, these variations may have an effect on the topography results obtained for different corneal regions. Further, the thickness information on epithelium and stroma could not be assessed in our study due to limitations in the instrument used (Pentacam). All above indicated were considered as the shortcomings of the study.

While there is agreement among most studies on the significant trends of anterior topography changes following refractive surgery, there is still disagreement on the posterior changes – apart from the fact that they are much smaller than those observed in the anterior surface. A number of earlier studies reported increased posterior corneal elevation after surgery [9, 35-37] that grew with smaller corneal thickness, lower residual thickness, higher myopic correction and higher IOP [9, 35]. However, these findings, which are not compatible with the results of the present study, were derived from Orbscan measurements (Bausch & Lomb, Rochester, NY), whose accuracy post corneal refractive surgery, especially for posterior corneal surface assessment, has been largely contested [38].

Other studies, based on scheimpflug or OCT technology, reported insignificant changes in posterior corneal elevation and curvature [14, 22, 39-42], including slight central flattening and peripheral steepening [17] (in agreement with the present study), followed by further longer-term overall flattening [25, 43-46] or small fluctuations [11, 12]. Similar inconsistent findings were reported following other forms of corneal refractive surgery; PRK, SMILE and LASEK [39, 46-49]. The posterior surface showed a slight backward shift during the post SMILE period [50].

In order to evaluate the changes in corneal elevation caused by surgery, it would be ideal to use a reference surface that remains stable throughout all pre and post-surgery stages, possibly located on the limbus (with 11-12mm diameter). However, since the accuracy of topography maps reduced progressively towards corneal periphery, only data located within the 8-9 mm diameter region were included in analysis [11, 18, 22]. For this data, the reference surface, such as the best-fit sphere (BFS), varied between pre and post-surgery, even if the same data region and surface setting were chosen [11, 49], since the change in corneal apex location post-surgery introduced changes in the coordinate system used. These possible alterations in the reference surface may make the elevation changes at specific points, caused by refractive surgery, appear to undergo fluctuations as described in earlier studies [14, 42, 11, 12, 25, 43]. For this reason, tangential curvature, which depends on the relative position of adjacent points and is not influenced by the change in reference plane, was used in this study instead of elevation data. This was considered more reliable than the BFS, which could not be used accurately to characterize corneal astigmatism especially in the peripheral sub-region.

To conclude, the study used a large, gender-balanced database of topography maps obtained before and up to 6 months after LASIK refractive procedure. The database was analyzed to determine the shape changes in both anterior and posterior topography at central, pericentral and peripheral regions, and in groups with low (-0.50D>SE≥-3.00D), moderate (-3.00D>SE≥-6.00D) and high myopia (-6.00D>SE). The analysis showed immediate steepening and increased astigmatism in the anterior peripheral regions, opposite trends in the central and pericentral anterior region, and smaller yet significant similar changes in the posterior surface. Over a 6 month follow-up period, shape changes in most anterior regions followed a reverse trend with amplitudes that were much smaller than the short-term changes observed 1 week post-surgery, yet significantly correlated with refractive error correction in the central anterior region. Meanwhile corneal astigmatism and posterior surface curvature in the three sub-regions remained stable during the follow up period. The results observed in this study are expected to lead to better understanding of the shape changes – both short and long term – following refractive surgery, and to assist in efforts to improve the prediction and planning of the procedures.

WHAT WAS KNOWN

- Most earlier studies, sought to evaluate the topographical changes after LASIK, in which the cornea was covered as one region without considering that different sub-regions may respond differently to surgery.
- Central anterior cornea becomes flatter after myopic refractive surgery.
- Change in posterior corneal surface remain controversial.

WHAT THIS PAPER ADDS

- Evidence has been presented that different corneal regions and different corneal surfaces respond differently to LASIK surgery.
- Analysis results based on a large, gender-balanced database of topography maps obtained before and up to 6 months after FS-LASIK showed immediate steepening and increased astigmatism in the anterior peripheral regions, opposite trends in the central and pericentral anterior region, and smaller yet significant similar changes in the posterior surface.
- Over a 6 month follow-up period, shape changes in most regions followed a reverse trend with amplitudes that were much smaller than the short-term changes observed 1 week post-surgery, these curvature changes showed significant increases with myopic correction in central anterior region.
- Corneal astigmatism and posterior surface curvature in the three sub-regions remained stable during the follow up region.

References

1. Reinstein DZ, Threlfall WB, Cook R, et al. Short term LASIK outcomes using the Technolas 217C excimer laser and Hansatome microkeratome in 46,708 eyes treated between 1998 and 2001. Br J Ophthalmol 2012;96(9):1173-9.
2. Tomita M, Waring GOt, Magnago T, Watabe M. Clinical results of using a high-repetition-rate excimer laser with an optimized ablation profile for myopic correction in 10 235 eyes. J Cataract Refract Surg 2013;39(10):1543-9.
3. Tomita M, Watabe M, Mita M, Waring GOt. Long-term observation and evaluation of femtosecond laser-assisted thin-flap laser in situ keratomileusis in eyes with thin corneas but normal topography. J Cataract Refract Surg 2014;40(2):239-50.
4. Solomon KD, Fernandez de Castro LE, Sandoval HP, et al. LASIK world literature review: quality of life and patient satisfaction. Ophthalmology 2009;116(4):691-701.
5. Comaish IF, Lawless MA. Progressive post-LASIK keratectasia: biomechanical instability or chronic disease process? J Cataract Refract Surg 2002;28(12):2206-13.
6. Yuen LH, Chan WK, Koh J, et al. A 10-year prospective audit of LASIK outcomes for myopia in 37,932 eyes at a single institution in Asia. Ophthalmology 2010;117(6):1236-44 e1.
7. Bailey MD, Mitchell GL, Dhaliwal DK, et al. Patient satisfaction and visual symptoms after laser in situ keratomileusis. Ophthalmology 2003;110(7):1371-8.
8. Seven I, Vahdati A, De Stefano VS, et al. Comparison of Patient-Specific Computational Modeling Predictions and Clinical Outcomes of LASIK for Myopia. Invest Ophthalmol Vis Sci 2016;57(14):6287-97.
9. Wang Z, Chen J, Yang B. Posterior corneal surface topographic changes after laser in situ keratomileusis are related to residual corneal bed thickness. Ophthalmology 1999;106(2):406-9; discussion 9-10.
10. Yoshida T, Miyata K, Tokunaga T, et al. Difference map or single elevation map in the evaluation of corneal forward shift after LASIK. Ophthalmology 2003;110(10):1926-30.
11. Wang B, Zhang Z, Naidu RK, et al. Comparison of the change in posterior corneal elevation and corneal biomechanical parameters after small incision lenticule extraction and femtosecond laser-assisted LASIK for high myopia correction. Cont Lens Anterior Eye 2016;39(3):191-6.
12. Chan TC, Liu D, Yu M, Jhanji V. Longitudinal evaluation of posterior corneal elevation after laser refractive surgery using swept-source optical coherence tomography. Ophthalmology 2015;122(4):687-92.
13. Liu Y, Wang Y, Wang Z, Zuo T. Effects of error in radius of curvature on the corneal power measurement before and after laser refractive surgery for myopia. Ophthalmic Physiol Opt 2012;32(4):355-61.
14. Gyldenkerne A, Ivarsen A, Hjortdal JO. Comparison of corneal shape changes and aberrations induced By FS-LASIK and SMILE for myopia. J Refract Surg 2015;31(4):223-9.
15. Rocha KM, Krueger RR. Spectral-domain optical coherence tomography epithelial and flap thickness mapping in femtosecond laser-assisted in situ keratomileusis. Am J Ophthalmol 2014;158(2):293-301 e1.
16. Kanellopoulos AJ, Asimellis G. Longitudinal postoperative lasik epithelial thickness profile changes in correlation with degree of myopia correction. J Refract Surg 2014;30(3):166-71.
17. Dai ML, Wang QM, Lin ZS, et al. Posterior corneal surface differences between non-laser in situ keratomileusis (LASIK) and 10-year post-LASIK myopic eyes. Acta Ophthalmol 2018;96(2):e127-e33.
18. Bao F, Chen H, Yu Y, et al. Evaluation of the shape symmetry of bilateral normal corneas in a Chinese population. PLoS One 2013;8(8):e73412.

19. Pressley A. Elementary Differential Geometry. London: Springer Undergraduate Mathematics Series, 2010.
20. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. Optom Vis Sci 1997;74(6):367-75.
21. Savini G, Hoffer KJ, Barboni P, et al. Accuracy of optical biometry combined with Placido disc corneal topography for intraocular lens power calculation. PLoS One 2017;12(2):e0172634.
22. Ciolino JB, Khachikian SS, Cortese MJ, Belin MW. Long-term stability of the posterior cornea after laser in situ keratomileusis. J Cataract Refract Surg 2007;33(8):1366-70.
23. Roberts C. Biomechanical customization: the next generation of laser refractive surgery. J Cataract Refract Surg 2005;31(1):2-5.
24. Meek KM, Boote C. The use of X-ray scattering techniques to quantify the orientation and distribution of collagen in the corneal stroma. Prog Retin Eye Res 2009;28(5):369-92.
25. Martin R, Rachidi H. Stability of posterior corneal elevation one year after myopic laser in situ keratomileusis. Clin Exp Optom 2012;95(2):177-86.
26. Raghunathan VK, Thomasy SM, Strom P, et al. Tissue and cellular biomechanics during corneal wound injury and repair. Acta Biomater 2017;58:291-301.
27. Kato N, Toda I, Hori-Komai Y, et al. Five-year outcome of LASIK for myopia. Ophthalmology 2008;115(5):839-44 e2.
28. Moshirfar M, J DD, B DW, et al. Mechanisms of Optical Regression Following Corneal Laser Refractive Surgery: Epithelial and Stromal Responses. Med Hypothesis Discov Innov Ophthalmol 2018;7(1):1-9.
29. Reinstein DZ, Srivannaboon S, Gobbe M, et al. Epithelial thickness profile changes induced by myopic LASIK as measured by Artemis very high-frequency digital ultrasound. J Refract Surg 2009;25(5):444-50.
30. Reinstein DZ, Archer TJ, Gobbe M. Change in epithelial thickness profile 24 hours and longitudinally for 1 year after myopic LASIK: three-dimensional display with Artemis very high-frequency digital ultrasound. J Refract Surg 2012;28(3):195-201.
31. Erie JC, Patel SV, McLaren JW, et al. Effect of myopic laser in situ keratomileusis on epithelial and stromal thickness: a confocal microscopy study. Ophthalmology 2002;109(8):1447-52.
32. Avunduk AM, Senft CJ, Emerah S, et al. Corneal healing after uncomplicated LASIK and its relationship to refractive changes: a six-month prospective confocal study. Invest Ophthalmol Vis Sci 2004;45(5):1334-9.
33. Ivarsen A, Fledelius W, Hjortdal JO. Three-year changes in epithelial and stromal thickness after PRK or LASIK for high myopia. Invest Ophthalmol Vis Sci 2009;50(5):2061-6.
34. Xu J, Bao J, Lu F, He JC. An indirect method to compare the reference centres for corneal measurements. Ophthalmic Physiol Opt 2012;32(2):125-32.
35. Baek T, Lee K, Kagaya F, et al. Factors affecting the forward shift of posterior corneal surface after laser in situ keratomileusis. Ophthalmology 2001;108(2):317-20.
36. Seitz B, Torres F, Langenbucher A, et al. Posterior corneal curvature changes after myopic laser in situ keratomileusis. Ophthalmology 2001;108(4):666-72; discussion 73.
37. Grzybowski DM, Roberts CJ, Mahmoud AM, Chang JS, Jr. Model for nonectatic increase in posterior corneal elevation after ablative procedures. J Cataract Refract Surg 2005;31(1):72-81.
38. Cairns G, McGhee CN. Orbscan computerized topography: attributes, applications, and limitations. J Cataract Refract Surg 2005;31(1):205-20.

39. Ciolino JB, Belin MW. Changes in the posterior cornea after laser in situ keratomileusis and photorefractive keratectomy. J Cataract Refract Surg 2006;32(9):1426-31.
40. Nishimura R, Negishi K, Saiki M, et al. No forward shifting of posterior corneal surface in eyes undergoing LASIK. Ophthalmology 2007;114(6):1104-10.
41. Ha BJ, Kim SW, Kim SW, et al. Pentacam and Orbscan II Measurements of Posterior Corneal Elevation Before and After Photorefractive Keratectomy. Journal of Refractive Surgery 2009;25(3):290-5.
42. Grewal DS, Brar GS, Grewal SP. Posterior corneal elevation after LASIK with three flap techniques as measured by Pentacam. J Refract Surg 2011;27(4):261-8.
43. Smadja D, Santhiago MR, Mello GR, et al. Response of the posterior corneal surface to myopic laser in situ keratomileusis with different ablation depths. J Cataract Refract Surg 2012;38(7):1222-31.
44. Zhang L, Wang Y. The shape of posterior corneal surface in normal, post-LASIK, and post-epi-LASIK eyes. Invest Ophthalmol Vis Sci 2010;51(7):3468-75.
45. Perez-Escudero A, Dorronsoro C, Sawides L, et al. Minor influence of myopic laser in situ keratomileusis on the posterior corneal surface. Invest Ophthalmol Vis Sci 2009;50(9):4146-54.
46. Kim H, Kim HJ, Joo CK. Comparison of forward shift of posterior corneal surface after operation between LASIK and LASEK. Ophthalmologica 2006;220(1):37-42.
47. de Jong T, Wijdh RH, Koopmans SA, Jansonius NM. Describing the corneal shape after wavefront-optimized photorefractive keratectomy. Optom Vis Sci 2014;91(10):1231-7.
48. Miyata K, Kamiya K, Takahashi T, et al. Time course of changes in corneal forward shift after excimer laser photorefractive keratectomy. Arch Ophthalmol 2002;120(7):896-900.
49. Zhao Y, Jian W, Chen Y, et al. Three-Year Stability of Posterior Corneal Elevation After Small Incision Lenticule Extraction (SMILE) for Moderate and High Myopia. J Refract Surg 2017;33(2):84-8.
50. Zhang L, Wang Y, Zhao W, et al. Corneal remodeling and spatial profiles following small incision lenticule extraction. Int Ophthalmol 2018.

Figure Captions:

Figure 1 Corneal regions including, central 0-3mm, pericentral 3-6 mm and peripheral 6-9 mm regions

Figure 2 Changes in mean corneal curvature in different corneal regions and in eyes with low, moderate and high myopia

Figure 3 Change in astigmatic corneal curvature at 0-degree (J_0) in different corneal regions and in eyes with low, moderate and high myopia

Figure 4 Change in astigmatic corneal curvature at 45-degree (J_{45}) in different corneal regions and in eyes with low, moderate and high myopia

Figure 5 Correlation between the changes in corneal thickness between pos1w and pos6m among different corneal regions with refractive error correction

Figure 6 Conceptual models that depict possible corneal shape changes in response to the LASIK procedure

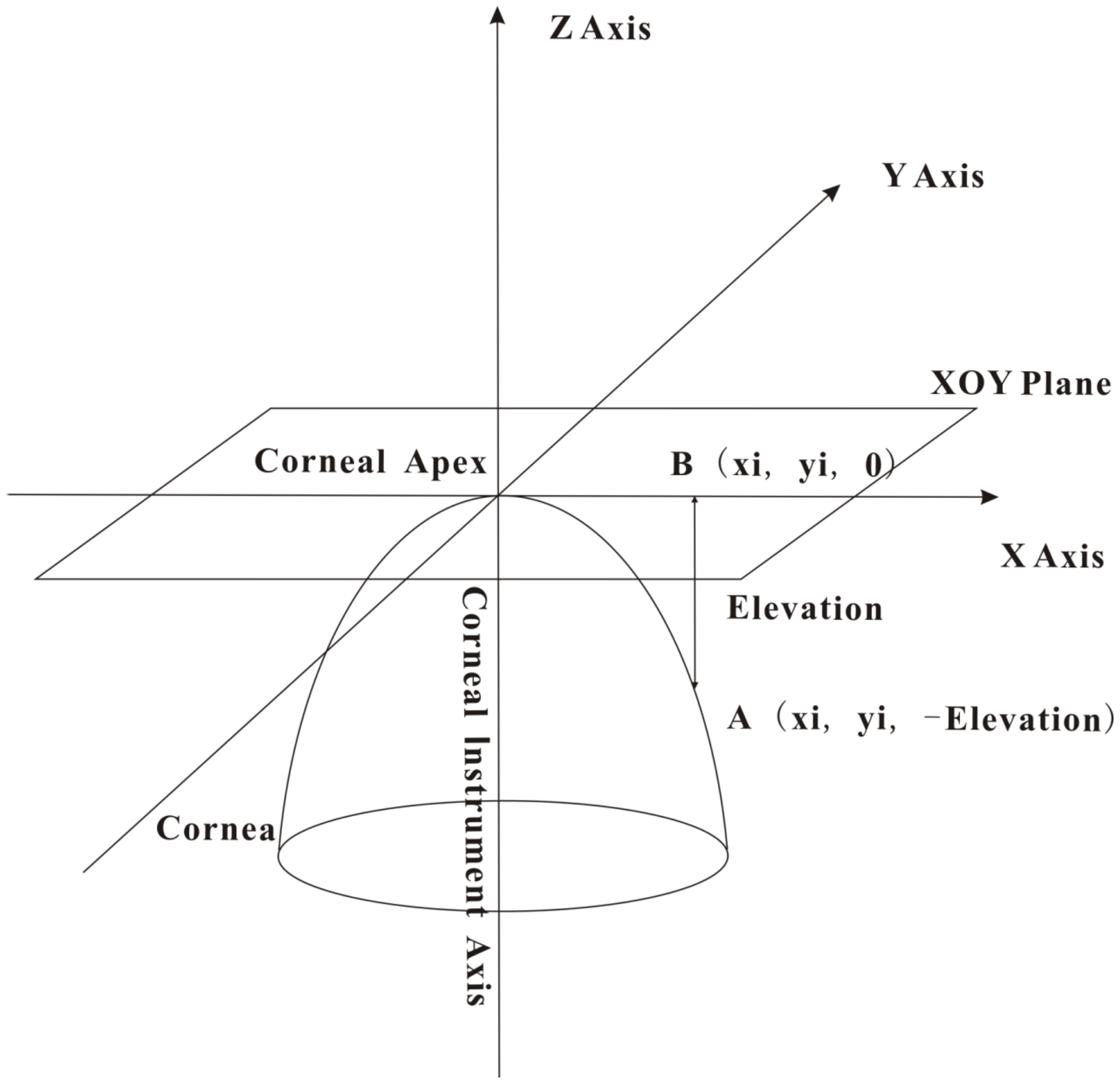

Figure 1 Elevation data obtained from the Pentacam. Elevation zi is defined as the z axis distance between Point i and the XOY plane

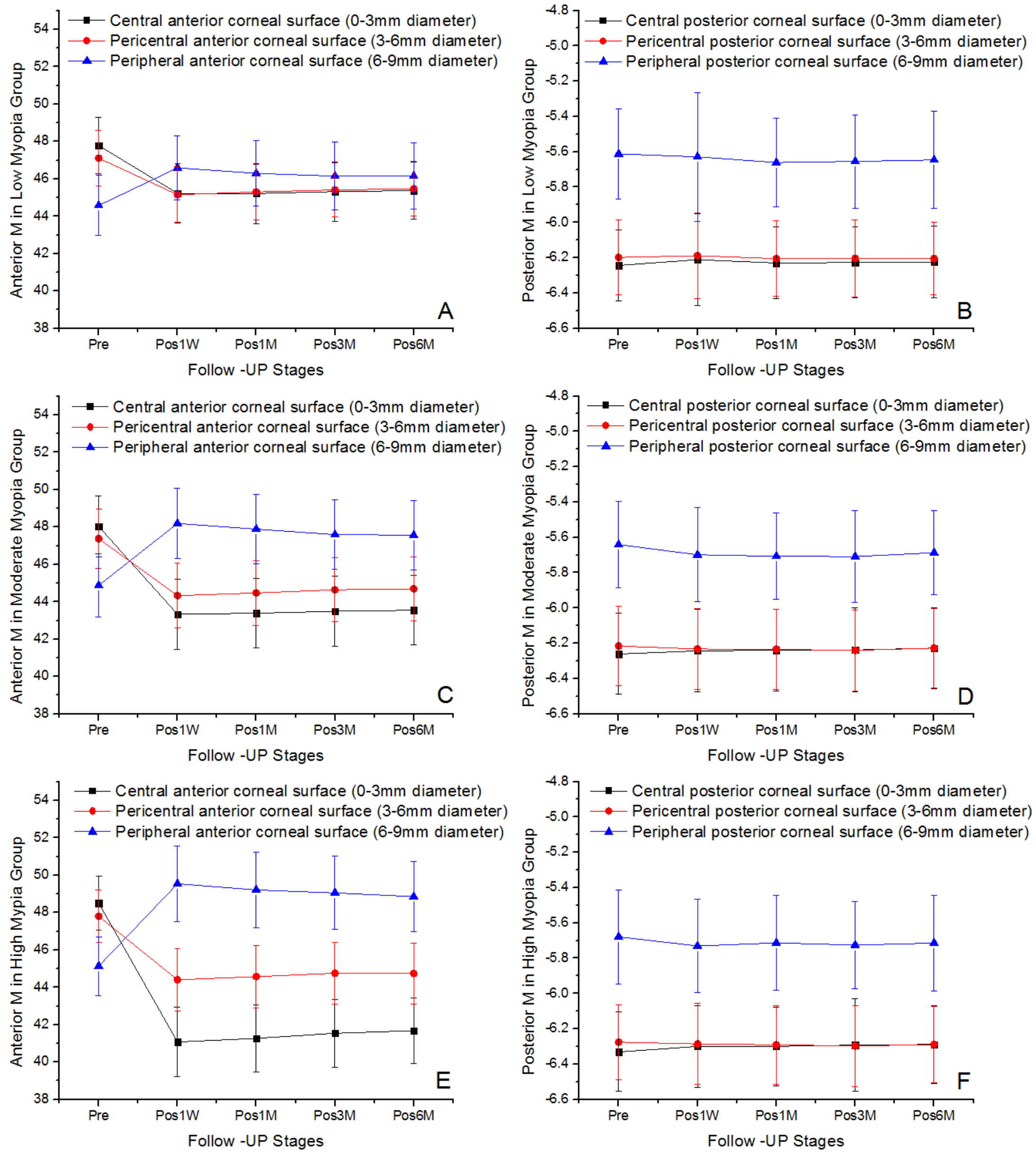

Figure 2 Changes in mean corneal curvature (M) in different corneal regions and in eyes with low, moderate and high myopia

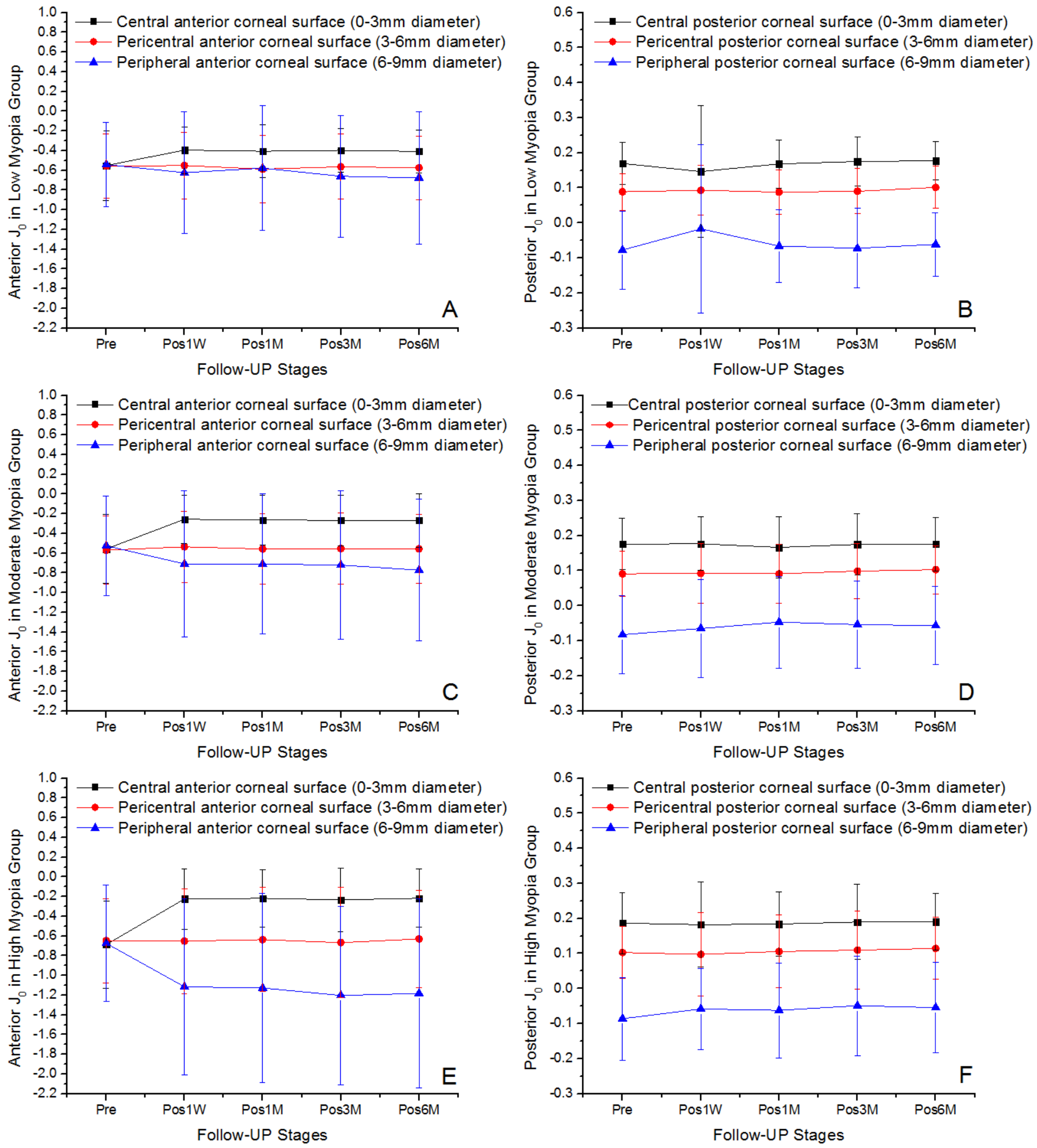

Figure 3 Change in astigmatic corneal curvature at 0-degree (J_0) in different corneal regions and in eyes with low, moderate and high myopia

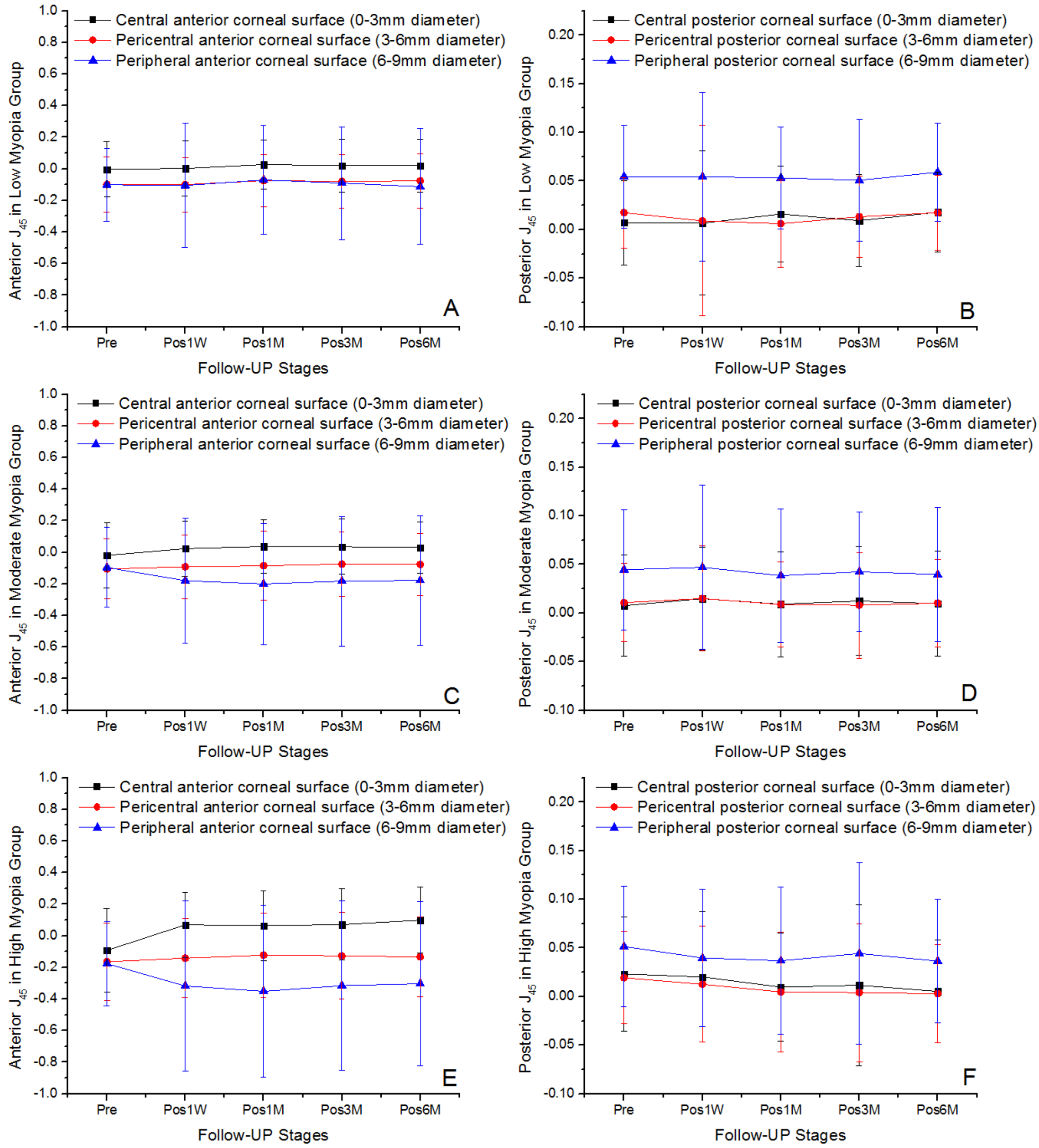

Figure 4 Change in astigmatic corneal curvature at 45-degree (J_{45}) in different corneal regions and in eyes with low, moderate and high myopia

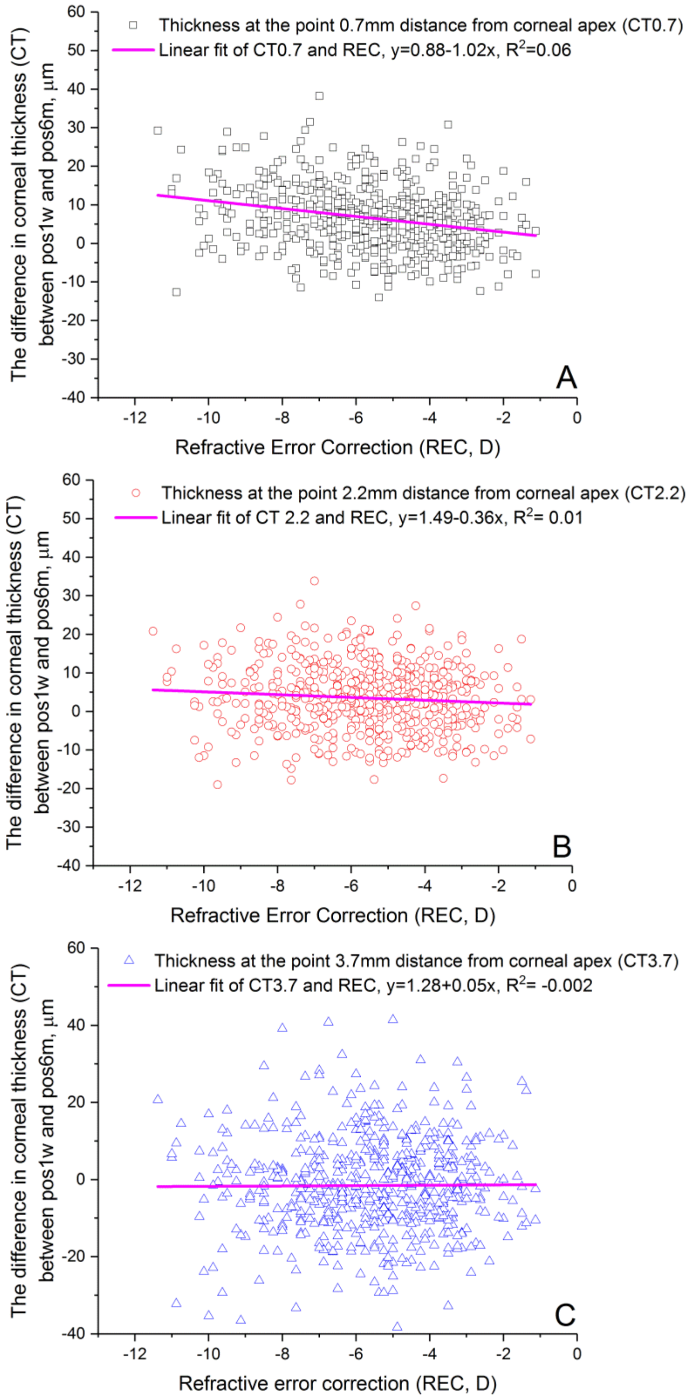

Figure 5 Correlation between the changes in corneal thickness between pos1w and pos6m among different corneal regions with refractive error correction

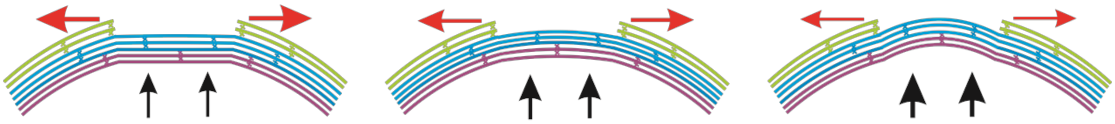

Figure 6 Conceptual models that depict possible corneal shape changes in response to the LASIK procedure

Table Captions:

Table 1: Changes in mean local spherical equivalent curvature (M) of anterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Table 2: Changes in mean local spherical equivalent curvature (M) of posterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Table 3: Changes in local astigmatism at 0-degree (J_0) of anterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Table 4: Changes in local astigmatism at 0-degree (J_0) of posterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Table 5: Changes in local astigmatism at 45-degree (J_{45}) of anterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Table 6: Changes in local astigmatism at 45-degree (J_{45}) of posterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Table 1: Changes in mean local spherical equivalent curvature (M) of anterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Changes between pre and post surgery stages	Central Area (0-3 mm)			Pericentral Area (3-6 mm)			Peripheral Area (6-9 mm)		
	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia
Pos1W - Pre	-2.55±0.59	-4.69±0.96	-7.43±1.21	-1.95±0.61	-3.05±0.79	-3.39±0.79	2.01±0.72	3.32±0.9	4.41±1.04
Pos1M - Pre	-2.57±0.56	-4.64±0.92	-7.24±1.08	-1.81±0.59	-2.90±0.75	-3.22±0.77	1.72±0.76	3.01±0.84	4.07±1.07
Pos3M - Pre	-2.46±0.59	-4.54±0.91	-6.97±1.13	-1.70±0.63	-2.74±0.7	-3.04±0.76	1.57±0.89	2.72±0.87	3.91±1.08
Pos6M - Pre	-2.41±0.58	-4.48±0.89	-6.83±1.01	-1.64±0.62	-2.68±0.74	-3.06±0.66	1.57±0.85	2.68±1.02	3.72±1.08

Table 2: Changes in mean local spherical equivalent curvature (M) of posterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Changes between pre and post surgery stages	Central Area (0-3 mm)			Pericentral Area (3-6 mm)			Peripheral Area (6-9 mm)		
	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia
Pos1W - Pre	0.03±0.15	0.02±0.05	0.03±0.06	0.01±0.09	-0.02±0.07	-0.01±0.07	-0.02±0.28	-0.06±0.16	-0.05±0.14
Pos1M - Pre	0.01±0.04	0.02±0.05	0.03±0.06	-0.01±0.05	-0.02±0.05	-0.02±0.08	-0.04±0.15	-0.07±0.12	-0.03±0.14
Pos3M - Pre	0.02±0.05	0.02±0.08	0.04±0.14	-0.01±0.06	-0.02±0.06	-0.02±0.10	-0.04±0.15	-0.07±0.14	-0.05±0.16
Pos6M - Pre	0.02±0.05	0.03±0.05	0.04±0.06	-0.01±0.06	-0.01±0.06	-0.01±0.07	-0.03±0.16	-0.05±0.14	-0.04±0.16

Table 3: Changes in local astigmatism at 0-degree (J_0) of anterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Changes between pre and post surgery stages	Central Area (0-3 mm)			Pericentral Area (3-6 mm)			Peripheral Area (6-9 mm)		
	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia
Pos1W - Pre	0.16±0.29	0.30±0.33	0.46±0.45	0.01±0.14	0.03±0.21	0.00±0.25	-0.08±0.5	-0.19±0.55	-0.44±0.68
Pos1M - Pre	0.15±0.29	0.29±0.35	0.47±0.44	-0.03±0.14	0.01±0.21	0.01±0.27	-0.04±0.49	-0.19±0.54	-0.45±0.73
Pos3M - Pre	0.15±0.30	0.29±0.33	0.45±0.43	-0.01±0.14	0.02±0.20	-0.02±0.32	-0.12±0.55	-0.20±0.56	-0.53±0.66
Pos6M - Pre	0.14±0.28	0.29±0.31	0.47±0.41	-0.02±0.16	0.01±0.20	0.02±0.24	-0.13±0.48	-0.25±0.53	-0.51±0.67

Table 4: Changes in local astigmatism at 0-degree (J_0) of posterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Changes between pre and post surgery stages	Central Area (0-3 mm)			Pericentral Area (3-6 mm)			Peripheral Area (6-9 mm)		
	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia
Pos1W - Pre	-0.02±0.18	0.00±0.05	0.00±0.1	0.00±0.05	0.00±0.07	-0.01±0.1	0.06±0.23	0.02±0.14	0.03±0.11
Pos1M - Pre	0.00±0.04	-0.01±0.07	0.00±0.07	0.00±0.03	0.00±0.07	0.00±0.09	0.01±0.10	0.04±0.11	0.02±0.14
Pos3M - Pre	0.01±0.05	0.00±0.07	0.00±0.09	0.00±0.04	0.01±0.06	0.01±0.10	0.00±0.11	0.03±0.12	0.04±0.14
Pos6M - Pre	0.01±0.05	0.00±0.05	0.00±0.05	0.01±0.04	0.01±0.05	0.01±0.06	0.02±0.1	0.03±0.11	0.03±0.12

Table 5: Changes in local astigmatism at 45-degree (J_{45}) of anterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Changes between pre and post surgery stages	Central Area (0-3 mm)			Pericentral Area (3-6 mm)			Peripheral Area (6-9 mm)		
	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia
Pos1W - Pre	0.01±0.18	0.04±0.21	0.16±0.31	0.00±0.11	0.01±0.12	0.02±0.15	0.00±0.28	-0.08±0.29	-0.14±0.42
Pos1M - Pre	0.03±0.18	0.06±0.21	0.16±0.29	0.02±0.09	0.02±0.14	0.04±0.14	0.03±0.26	-0.11±0.29	-0.18±0.41
Pos3M - Pre	0.02±0.18	0.05±0.21	0.16±0.28	0.02±0.11	0.03±0.14	0.04±0.17	0.01±0.26	-0.09±0.32	-0.14±0.41
Pos6M - Pre	0.02±0.19	0.05±0.19	0.19±0.25	0.02±0.12	0.03±0.12	0.03±0.14	-0.01±0.28	-0.08±0.31	-0.13±0.40

Table 6: Changes in local astigmatism at 45-degree (J_{45}) of posterior corneal surface between pre and post-surgery stages (1 week: pos1w, 1 month: pos1m, 3 months: pos3m and 6 months: pos6m) in different corneal regions and in eyes with low, moderate and high myopia

Changes between pre and post surgery stages	Central Area (0-3 mm)			Pericentral Area (3-6 mm)			Peripheral Area (6-9 mm)		
	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia	Low Myopia	Moderate Myopia	High Myopia
Pos1W - Pre	0.00±0.07	0.01±0.04	0.00±0.06	-0.01±0.1	0.00±0.04	-0.01±0.05	0.00±0.09	0.00±0.08	-0.01±0.07
Pos1M - Pre	0.01±0.05	0.00±0.05	-0.01±0.05	-0.01±0.04	0.00±0.04	-0.01±0.05	0.00±0.06	-0.01±0.07	-0.01±0.08
Pos3M - Pre	0.00±0.05	0.00±0.05	-0.01±0.08	0.00±0.03	0.00±0.05	-0.02±0.06	0.00±0.07	0.00±0.06	-0.01±0.09
Pos6M - Pre	0.01±0.04	0.00±0.04	-0.02±0.05	0.00±0.03	0.00±0.03	-0.02±0.04	0.00±0.05	0.00±0.07	-0.01±0.07