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Originals

Increased Corneal Thickness and Associated Factors After Laser in situ Keratomileusis

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SUMMARY

The aim of this study is to investigate changes in central corneal thickness (CCT) and to detect any associated factors after laser in situ keratomileusis (LASIK). The charts of 46 patients who had undergone bilateral LASIK were retrospectively reviewed. The postoperative changes in CCT were measured until 6 months postoperatively and the relation between CCT increases and other clinical factors was investigated. The factors analyzed were age, gender, preoperative CCT, ablation depth, ablation ratio, refractive regression, and development of diffuse lamellar keratitis (DLK). The CCT significantly increased from 1 week to 6 months postoperatively. Age, preoperative CCT, refractive regression, and development of DLK were not correlated with increased CCT. The CCT increase was greater in women than in men. The ablation depth and the ablation ratio were significantly positively correlated with increased CCT ($r = 0.544$, $P < 0.0001$ and $r = 0.539$, $P < 0.0001$, respectively). The increase in CCT was greater in corneas that underwent more tissue ablation. Accurate CCT evaluation is important for LASIK enhancement to avoid the postoperative keratectasia by overestimating the corneal pachymetry.

Key Words : central corneal thickness, keratectasia, laser ablation, LASIK, wound healing

INTRODUCTION

Measurement of the corneal thickness is necessary to determine who are candidates for laser in situ keratomileusis (LASIK). At present, the prevailing belief is that a residual stromal bed less than 250 μm thick after laser ablation may result in development of postoperative keratectasia[1～3]. Although LASIK has become a standard refractive procedure since the 1990s because of the high predictability of the surgical results, some patients require enhancement due to the refractive regression[4,5]. In eyes that undergo a retreatment procedure, accurate evaluation of the corneal thickness is especially important to avoid postoperative keratectasia. Overestimating the corneal pachymetry can induce inadvertent thinning of the residual stromal bed and consequently increase the risk of keratectasia. Underestimating the corneal pachymetry may unnecessarily exclude appropriate candidates for LASIK.

Recently, investigators have suggested that there are changes in corneal thickness after LASIK and have documented increases in central corneal thickness (CCT)[6～8]. However, LASIK enhancement is usually performed without considering this increase. Therefore, when the increase in CCT is substantial, the risk of the development of postoperative keratectasia may increase. With this in mind, we measured increases in

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CCT after LASIK to detect the clinical factors associated with the increase. These results will be important not only to predict the increases in CCT after LASIK but also to estimate the actual corneal thickness immediately after the primary LASIK procedure, which can be helpful to ensure safe LASIK enhancement.

PATIENTS AND METHODS

The charts of patients who underwent simultaneous bilateral LASIK for myopia or myopic astigmatism at Shin-koshigaya Eye Clinic, Koshigaya, Saitama, Japan, were retrospectively reviewed. One surgeon (M.N.) performed all the procedures. Ninety-two eyes of 46 patients who had undergone uneventful LASIK between April 1, 2004 and September 30, 2004 were enrolled in this study. All the preoperative and postoperative examinations were performed by the same experienced technician.

The mean patient age of the 25 women and 21 men was 32.0 years ± 6.5 standard deviation (SD) (range, 20 to 45 years). The manifest spherical equivalent (SE) and CCT were evaluated before surgery and 1 week and 1, 3, and 6 months postoperatively. CTT was measured using ultrasound pachymetry (DGH Technologies, Exton, PA, USA) . Ultrasound pachymetry and slit scanning pachymetry in the Orbscan system (Bausch & Lomb, Rochester, NY, USA) are currently available to measure the corneal pachymetry. Ultrasound pachymetry is the most commonly used technique[9~11], and the Orbscan system has recently become more widely accepted among refractive surgeons. However, the Orbscan system underestimates the corneal pachymetry after refractive surgery, and ultrasound pachymetry has been reported to be more accurate[12~15]. For this reason, we used ultrasound pachymetry to obtain accurate pachymetry measurements. The postoperative changes in CCT were measured and the relation between the increases in CCT postoperatively and other clinical factors was investigated. The factors analyzed were age, gender, preoperative CCT, ablation depth, ablation ratio, refractive regression, and the development of diffuse lamellar keratitis (DLK). All cases of DLK, which was detected in 14 eyes of nine patients within 4 days postoperatively, were mild to moderate and resolved within 1 week after onset. The postoperative changes in CCT and refractive regression were defined as the difference between 1 week and 6 months postoperatively. The ablation depth was defined as the difference between the preoperative CCT and the postoperative CCT at 1 week, and the ablation ratio was defined as the ratio of the ablation depth to the preoperative CCT.

All patients underwent simultaneous binocular LASIK with the goal of emmetropia. The VISX Star S3 excimer laser (VISX USA, Inc., Santa Clara, CA, USA) (wavelength, 193 nm ; fluence, 160 mJ/cm^2 ; pulse rate, 10 Hz) and the Moria LASIK M2 (Antony, France) microkeratome with the 130-μm head were used. The eye tracking system of the excimer laser was operative during the procedure. A corneal flap was created using the microkeratome and then lifted. The planned laser ablation (6-mm diameter ablation zone) was performed on the corneal stroma. After ablation, the corneal flap and stromal bed were washed using 0.3 mM oxiglutatione solution (BSS Plus, Santen, Osaka, Japan). The corneal flap was returned to the original position and reattached spontaneously. After the procedure, 0.5 % levofloxacin (Cravit, Santen) and 0.1 % betamethasone sodium phosphate (Rinderon, Shionogi & Co., Ltd., Osaka, Japan) were applied to the patients' eyes. The patients then applied 0.5 % levofloxacin, 0.1 % fluorometholone (Flumetholon 0.1, Santen), and 0.3 % sodium hyaluronate (Hyalein Mini 0.3, Santen) four times daily for 1 week after surgery. One week later, 0.5 % levofloxacin and 0.1 % fluorometholone were tapered to twice daily and 0.3 % hyaluronate sodium was used as needed ; 0.5 % levofloxacin and 0.1 % fluorometholone were discontinued 1 month postoperatively.

Statistical Analysis

All results were analyzed with the JMP IN for Windows (version 5.1.2, SAS Institute Inc., Cary, NC, USA). Changes in CCT and SE were analyzed using the paired *t* test. Differences in CCT increases between women and men and the presence or absence of DLK were analyzed using the unpaired t test. Pearson's correlation coefficients were determined in the relations between increases in CCT and clinical factors (age, preoperative CCT, ablation depth, ablation ratio, and refractive regression). P values less than 0.05

Table 1 Central corneal thickness and spherical equivalent after laser in situ keratomileusis.

Time After LASIK	Mean CCT ± SD (μm)	*P* Value*	Mean SE ± SD (D)	*P* Value*
Pre-op	543.1 ± 28.4	]< 0.0001	− 5.25 ± 2.40	]< 0.0001
1 week	485.4 ± 40.5	]< 0.0001	+ 0.05 ± 0.36	] = 0.112
1 month	493.1 ± 38.6	]< 0.0001	+ 0.01 ± 0.32	] = 0.011
3 months	500.2 ± 39.8	] = 0.104	− 0.08 ± 0.36	] = 0.960
6 months	501.2 ± 37.7		− 0.10 ± 0.34	

LASIK = laser in situ keratomileusis ; CCT = central corneal thickness ; SE = spherical equivalent ; D = diopter ; SD = standard deviation

*By the paired *t* test comparison of sequential time points.

Table 2 Comparison of the increase in central corneal thickness between women and men and the presence and absence of DLK 6 months postoperatively.

Gender And DLK	Mean CCT Increase ± SD (μm)	*P* Value*
Women	17.0 ± 12.1	] = 0.041
Men	12.0 ± 9.6	
DLK (+)	15.0 ± 13.9	] = 0.974
DLK (−)	14.9 ± 10.9	

DLK (+) = presence of diffuse lamellar keratitis ; DLK (−) = absence of diffuse lamellar keratitis ; CCT = central corneal thickness ; SD = standard deviation

*By the unpaired *t* test comparison of women and men and the presence and absence of diffuse lamellar keratitis.

Table 3 Correlation between the increase in central corneal thickness and clinical factors.

Factor	Mean ± SD	Correlation Coefficient*	*P* Value*
Age	32.0 ± 6.5 (yrs)	0.101	0.353
Preoperative CCT	543.1 ± 28.4 (μm)	0.073	0.512
Ablation depth	57.7 ± 29.2 (μm)	0.544	< 0.0001
Ablation ratio	10.6 ± 5.3 (%)	0.539	< 0.0001
Refractive regression	− 0.14 ± 0.36 (D)	− 0.090	0.409

CCT = central corneal thickness ; D = diopter ; SD = stndard deviation

*Using Pearson's correlation test analysis of the CCT increase from 1 week to 6 months postoperatively.

were considered statistically significant.

RESULTS

The mean CCT was 543.1 ± 28.4 μm (range, 486 to 614 μm) and the mean SE was −5.25 ± 2.40 diopters (D) (range, −1.37 to −10.88 D) preoperatively. Table 1 shows the mean CCT and SE at the various follow-up examinations. The pachymetry data show a significant increase from 1 week to 1 month and from 1 month to 3 months, but no significant increase occurred from 3 to 6 months. The mean increase in CCT from 1 week to 6 months postoperatively was 15.8 μm (range, −15 to 46 μm) ($P < 0.0001$). The spherical equivalent data showed a significant refractive regression from 1 to 3 months, but no significant regression occurred from 1 week to 1 month and from 3 to 6 months after LASIK. The mean refractive regression from 1 week to 6 months postoperatively was −0.15 D

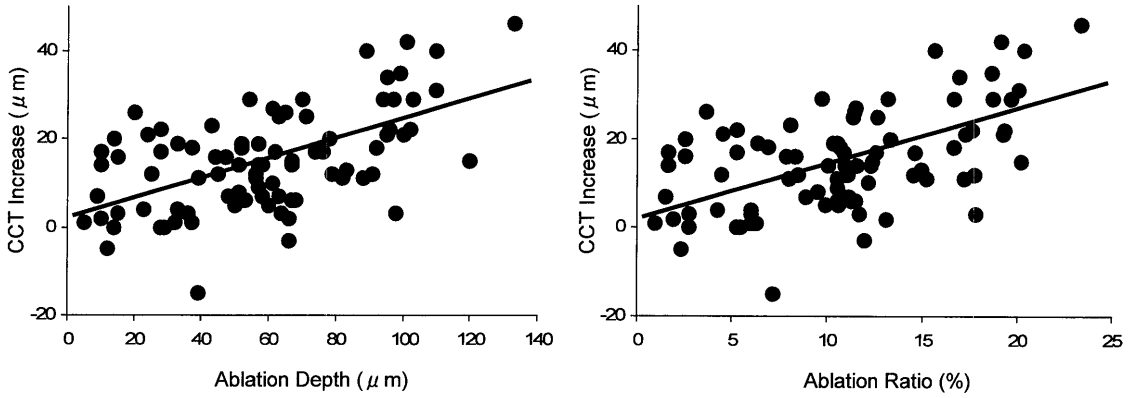

Fig. 1 Correlation between the increase in central corneal thickness and the ablation depth and the ablation ratio ($r = 0.544$, $P < 0.0001$; $r = 0.539$, $P < 0.0001$, respectively). CCT = central corneal thickness.

(range, −1.25 to + 0.88 D) ($P = 0.0004$).

Table 2 shows a comparison of CCT increases between women and men and the presence and absence of DLK. There was a significant difference between women and men, while no significant difference was detected between the presence and absence of DLK.

Table 3 shows the correlations between the increase in CCT and the other clinical factors. The ablation depth and the ablation ratio were significantly positively correlated with the increase in CCT ($r = 0.544$, $P < 0.0001$; $r = 0.539$, $P < 0.0001$, respectively), but no other variables were significantly correlated with increases in CCT. Figure 1 shows the correlation of the CCT increase and the ablation depth and the ablation ratio.

DISCUSSION

Measuring pachymetry is essential to determine the patients who are appropriate candidates for LASIK. This study demonstrated that the CCT after LASIK increased from 1 week to 6 months postoperatively. The potential mechanisms of this CCT increase after LASIK include corneal hydration, epithelial thickening and corneal stromal synthesis. Corneal hydration is usually a temporary result of LASIK, but the others result in a long-lasting effect increase in the CCT. There is a lot of evidence that supports the hypothesis that postoperative epithelial thickening is the cause of the increased CCT after laser refractive surgery. An increase in the epithelial thickness has been demonstrated after myopic photorefractive keratectomy (PRK)[16~18]. Lohmann and Guell found that the epithelial thickness varied between 35 and 111 μm after LASIK, and no increase or only a slight increase of less than 5 μm was observed in 11 eyes, while in seven eyes, a significant increase in epithelial thickness was found compared to the preoperative thickness[19]. Spadea et al. reported that the epithelium was thicker postoperatively compared to preoperative measurements and that the epithelial thickness peaked 3 months after LASIK and remained stable through 12 months[20]. Erie et al. also reported that the epithelial thickness increased significantly by 22 % 1 month after LASIK[21]. Reinstein et al. described the epithelial thickening after LASIK using 3D very high-frequency digital ultrasound scanning system[22,23]. Flanagan and Binder found that flap thickness at enhancement was 10 to 17 μm thicker than at primary surgery[24]. Although histopathologic studies of human corneas after successful LASIK did not reveal epithelial hyperplasia except at the corneal flap margins, vertical elongation of basal epithelial cells over the entire cornea which certainly can result in the increase of epithelial thickness was detected[25,26].

Corneal stromal synthesis along with the wound-healing process is also a possible cause of increased corneal thickness after LASIK. The wound-healing process, i.e., the activation of keratocytes in the corneal stroma, occurs behind the flap interface after LASIK. This wound-healing process results in the accumulation of extracellular matrix in the stroma. Kato et al. reported that electron microscopy 9 months after

LASIK showed that about a 5-μm thick disorganized extracellular matrix was deposited along the flap interface in rabbits[27]. Studies of human corneal specimen several years after successful LASIK also documented accumulated extracellular matrix along the flap interface[25,26]. The accumulation of the extracellular matrix, which may be permanently observed in the stroma, may induce increased corneal pachymetry after LASIK. Actually, Avunduk et al. reported that the posterior stromal thickness was significantly increased 1 month after LASIK compared with the 1-week postoperative thickness in their prospective confocal study[28]. Reinstein et al. also reported the part of corneal stroma thickening after LASIK[23]. We found that the CCT increase was greater in corneas that underwent greater tissue ablation, which may mean that the degree of wound healing was greater in those corneas, and consequently, the degree of extracellular matrix accumulation also was greater in those corneas compared with eyes with less tissue ablation. Therefore, we speculate that stromal thickening where the tissue was ablated would coincide with the epithelial thickening after LASIK. Refractive surgeons should estimate the flap and stromal thickening after LASIK, or the residual stromal bed after LASIK will be overestimated, which increases the risk of keratectasia following enhancement procedure especially when performed with the lift of corneal flap created at primary LASIK.

There was a significant difference in the increase in CCT between women and men. In this study, the preoperative spherical equivalent was significantly more myopic in women than in men, consequently, both the ablation depth and the ablation ratio were significantly greater in women (Table 4). This fact would affect the significant difference in the CCT increase between women and men.

The relationship between the increased CCT and refractive regression is controversial. We did not detect a significant relation between these two factors in this study. Feltham and Stapleton reported that the change in the total CCT was inversely proportional to the residual refractive error 2 months after LASIK ($r = -0.364$, $P < 0.01$)[29]. Although Chayet et al. did not report a significant relation between refractive regression and increased pachymetric values, they reported that the mean refractive regression was −1.07 D from 1 week to 3 months after LASIK and that the mean regression of the manifest SE and the increased corneal thickness were parallel in magnitude and time course[6]. To the contrary, Pan et al. denied this relationship[8]. Postoperative compensatory epithelial hyperplasia or the change in anterior and/or posterior corneal curvature, i.e., corneal ectasia, are also considered causes of refractive regression after refractive surgery. Further investigation is needed to detect the cause of refractive regression after LASIK.

Table 4 Comparison of preoperative spherical equivalent, ablation depth, and ablation ratio between women and men.

Factor	Gender	Mean ± SD	*P* Value*
Preoperative SE (D)	Women	− 6.04 ± 2.02	] = 0.0002
	Men	− 4.34 ± 2.49	
Ablation depth (μm)	Women	68.1 ± 25.5	] < 0.0001
	Men	45.6 ± 28.7	
Ablation ratio (%)	Women	12.6 ± 4.6	] < 0.0001
	Men	8.4 ± 5.2	

SE = spherical equivalent ; SD = standard deviation
*By the unpaired *t* test comparison of women and men.

In summary, the corneal thickness increased from 1 week to 6 months after LASIK, and the increase was correlated with the ablation depth and the ablation ratio. It is necessary to consider this CCT increase in order to avoid the development of keratectasia after LASIK enhancement by overestimating the corneal pachymetry.

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