· Clinical Research ·

Early changes in corneal densitometry after FS-LASIK combined with accelerated corneal cross-linking for correction of high myopia

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Abstract
● **AIM:** To observe the effects of femtosecond laser-assisted excimer laser *in situ* keratomileusis combined with accelerated corneal cross-linking (FS-LASIK Xtra) on corneal densitometry after correcting for high myopia.
● **METHODS:** In this prospectively study, 130 patients underwent FS-LASIK or FS-LASIK Xtra for high myopia. Their right eyes were selected for inclusion in the study, of which 65 cases of 65 eyes in the FS-LASIK group, 65 patients with 65 eyes in the FS-LASIK Xtra group. Patients were evaluated for corneal densitometry at 1, 3, and 6mo postoperatively using Pentacam Scheimpflug imaging.
● **RESULTS:** Preoperative differences in corneal densitometry between the FS-LASIK and FS-LASIK Xtra groups in different ranges were not statistically significant (P>0.05). Layer-by-layer analysis revealed statistically significant differences in the anterior (120 μm), central, and total layer corneal densitometry between the FS-LASIK and FS-LASIK Xtra groups at 1 and 3mo postoperatively (all P<0.05), the FS-LASIK Xtra group is higher than that of the FS-LASIK group. Analysis of different diameter ranges showed statistically significant differences between the FS-LASIK group and the FS-LASIK Xtra group at 1mo postoperatively in the ranges of 0–2, 2–6, and 6–10 mm (both P<0.05); At 3mo postoperatively, the FS-LASIK Xtra group is higher than that of the FS-LASIK group in the ranges of 0–2 and 2–6 mm (P<0.05). At 6mo postoperatively, there were no statistically significant differences in corneal densitometry between the FS-LASIK group and the FS-LASIK Xtra group in different diameter ranges (all P>0.05).
● **CONCLUSION:** There is an increase in internal corneal densitometry during the early postoperative period after FS-LASIK Xtra for correction of high myopia. However, the densitometry values decreased to the level of conventional FS-LASIK at 6mo after surgery, with the most significant changes observed in the superficial central zone.
● **KEYWORDS:** femtosecond laser; accelerated corneal cross-linking; corneal densitometry; high myopia; femtosecond laser *in situ* keratomileusis
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INTRODUCTION
Myopia is a common ophthalmic disease worldwide, and some studies have speculated that the myopic population in Asia is expected to reach 65% by 2050[1]. Femtosecond laser *in situ* keratomileusis (FS-LASIK) has gradually replaced the corneal laminar knife by virtue of the ultra-high precision of femtosecond laser, and has been widely performed worldwide; however, there are still reports of refractive regression or medical corneal dilatation in the postoperative period. Corneal collagen cross-linking (CXL) enhances corneal stiffness by increasing the connections between collagen fibers. In recent years, FS-LASIK combined with accelerated corneal cross-linking (FS-LASIK Xtra) has been developed during FS-LASIK, and achieved good curative effect[2-4]. However, a decrease in corneal transparency was seen on slit-lamp examination in some patients in the early postoperative period of this combined regimen, and there is no standardized measure of this.

This study sought to evaluate the change in corneal densitometry following FS-LASIK Xtra procedures by Pentacam.

SUBJECTS AND METHODS

Ethical Approval The study was designed in accordance with the expectations of the hospital's Ethical Committee (No.HEC-KS-201900KY). All study procedures followed the tenets of the Declaration of Helsinki. The trial is registered at Chinese Clinical Trial Registry (ChiCTR), registration number: ChiCTR2300073933. The informed consent was obtained from the subjects.

Subjects This prospective nonrandomized study consecutively included 130 eyes of 130 patients with myopia and myopic astigmatism who underwent refractive surgery at the Eye Hospital of Shandong University of Traditional Chinese Medicine from October 2021 to July 2022. All patients had their right eyes selected for inclusion in the study, and were divided all patients into two groups: FS-LASIK Xtra group 65 cases (33 males and 32 females, aged 23.5±4.7y) and FS-LASIK group 65 cases (31 males and 34 females, aged 22.9±4.3y).

After obtaining informed consent, we included all patients with a refractive error between -10.00 and -6.00 diopters (D) who underwent FS-LASIK or FS-LASIK Xtra. For inclusion into the study, patients were more than 18 years of age with at least 24mo of stable visual acuity, able to be with a clear cornea without cloud or spot; soft contact lenses discontinued for at least 2wk before surgery; residual stromal bed under the flap ≥400 μm. Exclusion criteria were previous ocular surgery, ocular diseases other than refractive error and systemic disorders could influence wound healing, such as connective tissue disorders and diabetes. Patients with mental illnesses were also excluded.

According to years of clinical experience of our center, FS-LASIK Xtra group should meet one of the following conditions in addition to the above conditions: 1) Preoperative corneal astigmatism based on Pentacam measurement is greater than 1.5d or the Belin shows yellow or red; 2) The tomographic biomechanical index (TBI) measured by visual corneal biomechanical analyzer (Corvis ST, Oculus, Germany) is between 0.3 and 0.5.

Preoperative examinations included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), slit-lamp biomicroscopy, manifest refraction, corneal topography (Pentacam HR, Oculus, Germany) and corneal biomechanics (Corvis ST, Oculus, Germany). Follow-up examinations were conducted at 1wk and 1, 3, and 6mo postoperatively.

Corneal Densitometry Inspections Corneal densitometry of different diameters and levels of the cornea were measured and analyzed using software analysis within the Pentacam system and expressed as gray values, with 0 indicating complete transparency and 100 indicating complete turbidity and opacity. The densitometry of two measurements were selected for this study: the average value of corneal densitometry measured in the range of 0–2, 2–6, and 6–10 mm diameters centered on the corneal apex; the cornea was stratified according to the corneal thickness, with 120 μm close to the anterior surface of the corneal epithelium as the first layer, 60 μm close to the endothelial surface as the third layer, and the central as the second layer of the cornea (Figure 1).

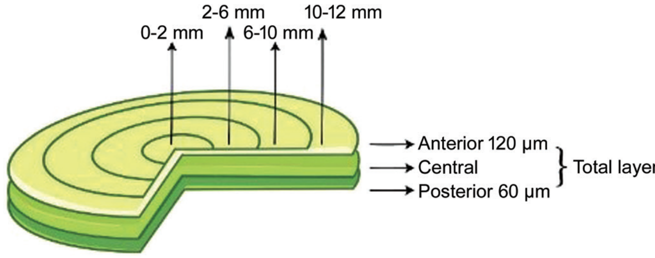

Figure 1 Different diameters and different layers of densitometry.

Surgical Methods

Femtosecond laser-assisted LASIK After preoperative ocular disinfection and corneal surface anesthesia, a corneal flap with a thickness of 100 μm, a flap diameter of 8.1 mm, and a side-cutting angle of 60° was fabricated using a VisuMax femtosecond laser system (Carl Zeiss Meditec, Germany). The flap was lifted by a flap lifter, and ablation of the corneal stroma was performed with the SCHWIND AMARIS 1050RS (SCHWIND, Germany) excimer laser. Following laser ablation of the stromal tissue, the flap was replaced and the stromal bed was washed with balanced salt solution.

Corneal cross-linking For the FS-LASIK Xtra group, the corneal stromal bed was saturated with 0.22% riboflavin diluted with saline (VibeX Xtra; Avedro Inc, Waltham, Massachusetts, USA) for 70s and protected the flap not to contact the riboflavin carefully. After residual riboflavin was rinsed thoroughly with balanced saline solution, and the flap was repositioned properly. Irradiation was then accomplished using a KXL system (Avedro Inc, Waltham, Massachusetts, USA) with ultraviolet radiation A (UVA) fluence of 30 mW/cm^2 for 70s (total energy 2.71 J/cm^2).

Statistical Analysis The data was statistically analyzed using SPSS 25.0 statistical software. Measurement data were subjected to the Kolmogorov-Smirnov normality test, and data satisfying normal distribution were described by means±SD. Data between groups were compared using the independent samples *t*-test, and data that did not satisfy normal distribution were tested using the Mann-Whitney *U* test. Intragroup difference analysis during the follow-up period was performed using repeated ANOVA or the Friedman test. $P<0.05$ was considered a statistically significant difference.

Table 1 Comparison of preoperative baseline data between the two groups mean±SD

Groups	No. of eyes	SE, D	CCT, µm	AD, µm	OZ, mm
FS-LASIK	65	-7.84±1.45	531.62±16.95	109.07±17.83	6.00±0.18
FS-LASIK Xtra	65	-8.18±1.53	529.62±15.15	110.05±18.13	5.94±0.23
t		1.37	0.74	-0.32	-1.82
P		0.172	0.464	0.747	0.069

FS-LASIK: Femtosecond assisted laser *in situ* keratomileusis; FS-LASIK Xtra: FS-LASIK combined with accelerated corneal cross-linking; SE: Spherical equivalent; CCT: Central corneal thickness; AD: Ablation depth; OZ: Optical zone.

RESULTS

Preoperative Baseline Information There were no statistically significant differences in preoperative age, spherical equivalent, central corneal thickness, ablation depth, and optical zones between the FS-LASIK and FS-LASIK Xtra groups (all *P*>0.05; Table 1).

Variation of Corneal Densitometry Within Different Stratifications Preoperative corneal densitometry in the anterior, central, posterior layers and total layer were not statistically significant between two groups (all *P*>0.05). Corneal densitometry within the anterior 120 µm, central and total layer regions difference between the FS-LASIK and FS-LASIK Xtra groups were statistically significant at 1 and 3mo postoperatively (*P*<0.05). Changes in corneal densitometry were shown in Table 2.

Changes in Corneal Densitometry Over a Range of Diameters The difference in corneal densitometry in different diameter ranges between the two groups preoperatively was not statistically significant (all *P*>0.05). At 1mo postoperatively, the differences in corneal densitometry within 0–2, 2–6, and 6–10 mm were statistically significant between the FS-LASIK and FS-LASIK Xtra group (all *P*<0.05); at 3mo postoperatively, the differences were statistically significant between the two groups only in the ranges of 0–2 and 2–6 mm (*P*<0.05; Table 3).

DISCUSSION

Corneal transparency serves as a vital indicator for evaluating corneal health. Traditionally, slit lamp examination of the anterior segment of the eye has been employed to assess corneal transparency. However, this method lacks consistent and objective assessment criteria. In contrast, Pentacam, utilizing Scheimpflug imaging technology, enables the quantification of light scattering within the cornea, providing an objective assessment of corneal transparency through densitometry values. Furthermore, Pentacam facilitates the optical characterization of corneal nerves in keratoconus patients and the evaluation of stromal tissue recovery following corneal surgery[5]. Corneal densitometry has gained widespread recognition for its diagnostic utility in corneal diseases[6-7], as well as its application in post-keratoconus assessments[8], CXL procedures[9-10], and combined CXL treatments for refractive surgery[11-12].

Table 2 Corneal densitometry within different stratifications in FS-LASIK and FS-LASIK Xtra groups

Different layers (GSU)	FS-LASIK	FS-LASIK Xtra	*t*	*P*
Anterior 120 µm				
Preop.	19.33±1.93	19.35±1.60	0.03	0.871
Postop. 1mo	18.57±1.84	19.74±1.83	12.81	<0.001
Postop. 3mo	18.43±1.84	19.45±2.30	7.62	0.007
Postop. 6mo	18.52±1.86	18.55±1.71	0.43	0.512
Central				
Preop.	13.14±1.17	13.27±1.04	0.29	0.592
Postop. 1mo	12.84±1.05	13.77±0.96	33.35	<0.001
Postop. 3mo	12.76±1.10	13.31±1.03	9.99	0.002
Postop. 6mo	12.78±0.96	13.05±0.97	2.72	0.102
Posterior 60 µm				
Preop.	8.82±0.81	8.88±0.96	0.03	0.854
Postop. 1mo	8.82±0.72	8.78±0.64	0.25	0.619
Postop. 3mo	8.70±0.88	8.73±0.81	0.09	0.771
Postop. 6mo	8.81±0.75	8.79±0.64	0.04	0.851
Total layer				
Preop.	13.75±1.19	13.69±1.24	0.23	0.632
Postop. 1mo	13.38±1.10	14.15±1.01	16.07	<0.001
Postop. 3mo	13.34±1.18	13.87±1.04	7.02	0.009
Postop. 6mo	13.42±1.08	13.40±0.98	0.01	0.937

FS-LASIK: Femtosecond assisted laser *in situ* keratomileusis; FS-LASIK Xtra: FS-LASIK combined with accelerated corneal cross-linking; GSU: Grayscale units.

Table 3 Corneal densitometry in different diameter ranges in FS-LASIK and FS-LASIK Xtra groups

Different diameters (GSU)	FS-LASIK	FS-LASIK Xtra	*t*	*P*
0–2 mm				
Preop.	13.10±0.61	13.22±1.05	0.26	0.614
Postop. 1mo	12.69±0.89	14.31±1.43	65.48	<0.001
Postop. 3mo	12.52±0.86	13.57±1.71	22.15	<0.001
Postop. 6mo	12.41±0.80	12.56±0.85	1.12	0.292
2–6 mm				
Preop.	12.12±0.51	12.13±0.92	0.11	0.745
Postop. 1mo	11.77±0.73	12.82±0.96	48.24	<0.001
Postop. 3mo	11.73±0.80	12.49±1.15	16.99	<0.001
Postop. 6mo	11.96±0.88	12.04±0.64	0.39	0.532
6–10 mm				
Preop.	12.32±1.42	12.24±1.30	0.37	0.545
Postop. 1mo	12.21±1.34	12.72±1.02	3.35	0.039
Postop. 3mo	12.20±1.43	12.35±1.21	0.11	0.737
Postop. 6mo	12.19±1.25	12.06±1.17	0.61	0.543

FS-LASIK: Femtosecond assisted laser *in situ* keratomileusis; FS-LASIK Xtra: FS-LASIK combined with accelerated corneal cross-linking; GSU: Grayscale units.

The fabrication of a corneal flap and the ablation of corneal stroma in FS-LASIK procedure disrupt the original structure of corneal tissue, leading to a reduction in biomechanical stability. Previous studies have demonstrated the efficacy of CXL in improving the biomechanical stability in patients with keratoconus[13-14]. In recent years, several studies have investigated the combination of prophylactic accelerated CXL with LASIK, aiming to enhance postoperative safety and efficacy, and have achieved favorable outcomes[15-17]. However, it should be noted that varying degrees of corneal superficial stromal layer clouding may occur after CXL[18-20]. Based on the aforementioned research background, the present study was conducted using corneal densitometry measured with the Pentacam to investigate corneal transparency after FS-LASIK Xtra procedure. The study aimed to explore the changes in corneal transparency following surgery.

In this study, the corneal densitometry in the FS-LASIK group exhibited a decrease compared to the preoperative measurements at various thickness stratifications, which aligns with the findings of previous investigations[8,21]. The corneal densitometry in the anterior 120 μm, central, and total layer regions of the FS-LASIK Xtra group demonstrated a tendency to initially increase and then decrease after surgery, with similar patterns observed in the posterior region compared to conventional FS-LASIK. Upon analyzing the underlying factors, it was observed that the corneal flap thickness in this study was 100 μm. The Pentacam anterior layer was divided into a 120 μm area adjacent to the epithelium, and the riboflavin-impregnated area primarily resided in the anterior and central layers. Consequently, the most significant postoperative changes were observed in the anterior 120 μm and central layer, which corresponded to the high reflectance within the superficial anterior stroma observed under slit-lamp examination during the postoperative period. It is worth noting that the CXL effects did not extend to the posterior layers of the cornea. Zhang *et al*[22] reported an increase in corneal densitometry in the anterior 120 μm, middle, and posterior 60 μm layers at 3mo after small incision lenticule extraction (SMILE) combined with accelerated CXL, consistent with the changes observed in the anterior 120 μm and middle layers at 3mo post-surgery in our study. The differences in the posterior layers are speculated to be attributed to variations in surgical techniques and energy transmission.

Analyze the results of densitometry measurements for a range of corneal diameters, it was observed that corneal densitometry within various diameters in the FS-LASIK group exhibited a slight decreasing trend postoperatively, while the FS-LASIK Xtra group demonstrated an initial increase followed by a decrease. Cankaya *et al*[23] reported that a healthy human cornea displayed higher densitometry at 0–2 mm due to the closer arrangement of corneal collagen fibers in the central optical zone, resulting in higher densitometry at 0–2 mm compared to 2–6 mm. In both groups of patients in our study, the change in densitometry at 0–2 mm was greater than at 2–6 mm and 6–10 mm, possibly due to the tightly arranged stromal collagen fibers at 0–2 mm, which were more affected by the excimer laser. Corneal transparency is influenced by the arrangement of corneal collagen fibers and the spacing between them[24]. The process of corneal stromal repair after excimer laser involves breaking down damaged collagen fibers and synthesizing irregularly arranged new collagen fibers, resulting in a decrease in postoperative corneal transparency[25].

The increase in corneal densitometry after FS-LASIK Xtra can be attributed to the thickening of stromal collagen fiber diameter following CXL, which induces the formation of additional chemical bonds between collagen molecules. These additional chemical bonds enhance the connections between collagen fibers[26], resulting in a grayish white hyperreflective corneal stroma. The corneal flap diameter of 8.1 mm falls within the range of 6–10 mm, and only a portion of the stroma between 6 and 8.1 mm are impregnated with riboflavin, which is less affected by CXL under ultravoilet (UV) irradiation. Additionally, the incision can only be repaired with fibers, leading to scar formation[27], which can also contribute to a decrease in corneal transparency within this range.

In this study, we observed that corneal densitometry increased and corneal transparency decreased during the early postoperative period following FS-LASIK Xtra. However, as the observation time extended, the densitometry values started to decrease at 3mo after surgery. At 6mo, there was no statistically significant difference in densitometry compared to conventional FS-LASIK. It is worth noting that a transient turbidity in the superficial stroma, resulting from the combined accelerated CXL (Figures 2 and 3), was commonly observed at one month postoperatively and typically resolved within 20wk[28].

In summary, FS-LASIK combined with accelerated CXL resulted in an increase in corneal densitometry and a decrease in transparency in the early stages, with the most significant increase being in the superficial central zone, which was comparable to that of conventional FS-LASIK at 6mo postoperatively. This study did not combine anterior segment optical coherence tomography (OCT) and confocal microscopy for a more comprehensive observation, and should continue to expand the sample size and prolong the follow-up time in the later stage to explore the corneal densitometry more comprehensively in combination with CXL lines, with a view to providing experience for clinical implementation.

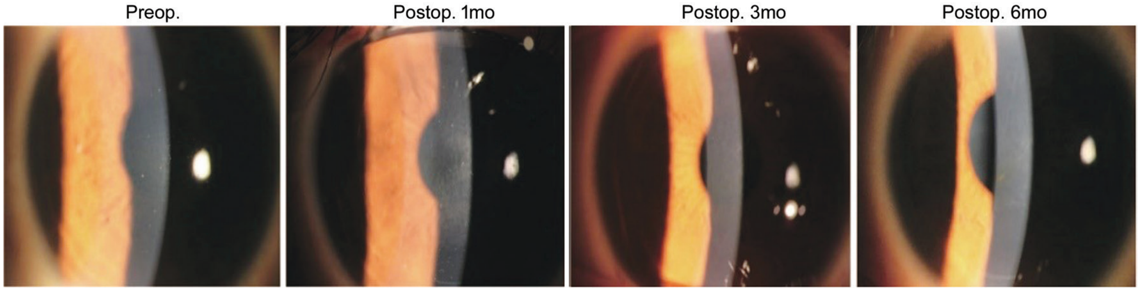

Figure 2 A 24-year-old patient underwent FS-LASIK Xtra in July 2021 Highly reflective light in the superficial corneal stroma seen under slit-lamp in the early postoperative period. FS-LASIK Xtra: Femtosecond assisted laser *in situ* keratomileusis combined with accelerated corneal cross-linking.

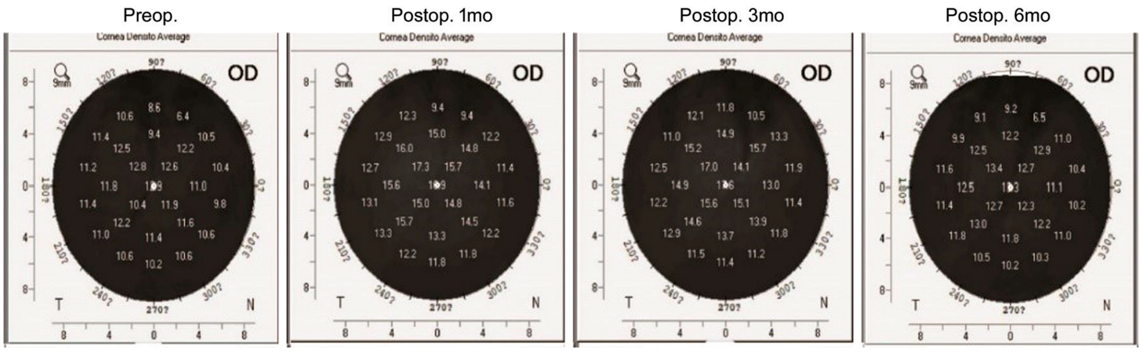

Figure 3 Pentacam exams of the same patient preoperatively and at 1, 3, and 6mo postoperatively FS-LASIK Xtra: Femtosecond assisted laser *in situ* keratomileusis combined with accelerated corneal cross-linking.

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REFERENCES

1 Holden BA, Fricke TR, Wilson DA, *et al*. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016;123(5):1036-1042.

2 Kanellopoulos AJ, Asimellis G, Karabatsas C. Comparison of prophylactic higher fluence corneal cross-linking to control, in myopic LASIK, one year results. *Clin Ophthalmol* 2014;8:2373-2381

3 Tan J, Lytle GE, Marshall J. Consecutive laser *in situ* keratomileusis and accelerated corneal crosslinking in highly myopic patients: preliminary results. *Eur J Ophthalmol* 2014:0.

4 Rajpal RK, Wisecarver CB, Williams D, *et al*. Lasik Xtra® provides corneal stability and improved outcomes. *Ophthalmol Ther* 2015;4(2): 89-102.

5 Shajari M, Wanner E, Rusev V, Sefat SMM, Mayer WJ, Kohnen T, Priglinger S, Kook D. Corneal densitometry after femtosecond laser-assisted *in situ* keratomileusis (fs-LASIK) and small incision lenticule extraction (SMILE). *Curr Eye Res* 2018;43(5):605-610.

6 Otri AM, Fares U, Al-Aqaba MA, Dua HS. Corneal densitometry as an indicator of corneal health. *Ophthalmology* 2012;119(3):501-508.

7 Alnawaiseh M, Zumhagen L, Wirths G, Eveslage M, Eter N, Rosentreter A. Corneal densitometry, central corneal thickness, and corneal central-to-peripheral thickness ratio in patients with fuchs endothelial dystrophy. *Cornea* 2016;35(3):358-362.

8 Alio Del Barrio JL, Parafita-Fernandez A, Canto-Cerdan M, Alio JL, Teus M. Evolution of corneal thickness and optical density after laser *in situ* keratomileusis versus small incision lenticule extraction for myopia correction. *Br J Ophthalmol* 2021;105(12):1656-1660.

9 Alnawaiseh M, Rosentreter A, Eveslage M, Eter N, Zumhagen L. Changes in corneal transparency after cross-linking for progressive keratoconus: long-term follow-up. *J Refract Surg* 2015;31(9):614-618.

10 Kim BZ, Jordan CA, McGhee CNJ, Patel DV. Natural history of corneal haze after corneal collagen crosslinking in keratoconus using Scheimpflug analysis. *J Cataract Refract Surg* 2016;42(7):1053-1059.

11 Piyacomn Y, Kasetsuwan N, Puangsricharern V, Reinprayoon U, Satitpitakul V, Chantaren P. Topometric indices and corneal densitometry change after corneal refractive surgery combined with simultaneous collagen crosslinking. *Clin Ophthalmol* 2019;13:1927-1933.

12 Osman IM, Helaly HA, Abou Shousha M, AbouSamra A, Ahmed I. Corneal safety and stability in cases of small incision lenticule extraction with collagen cross-linking (SMILE Xtra). *J Ophthalmol* 2019;2019:6808062.

13 Sedaghat MR, Momeni-Moghaddam H, Ambrósio R Jr, *et al*. Long-term evaluation of corneal biomechanical properties after corneal cross-linking for keratoconus: a 4-year longitudinal study. *J Refract Surg* 2018;34(12):849-856.

14 Hashemi H, Asgari S, Mehravaran S, Miraftab M, Ghaffari R, Fotouhi A. Corneal biomechanics after accelerated cross-linking: comparison between 18 and 9 mW/cm^2 protocols. *J Refract Surg* 2017;33(8):558-562.

15 Lim L, Lim EWL, Rosman M, Koh JCW, Htoon HM. Three-year outcomes of simultaneous accelerated corneal crosslinking and femto-LASIK for the treatment of high myopia in Asian eyes. *Clin Ophthalmol* 2020;14:2865-2872.

16 Kanellopoulos AJ. Collagen cross-linking in early keratoconus with riboflavin in a femtosecond laser-created pocket: initial clinical results. *J Refract Surg* 2009;25(11):1034-1037.

17 Kohnen T, Lwowski C, Hemkeppler E, de'Lorenzo N, Petermann K, Forster R, Herzog M, Böhm M. Comparison of femto-LASIK with combined accelerated cross-linking to femto-LASIK in high myopic eyes: a prospective randomized trial. *Am J Ophthalmol* 2020;211:42-55.

18 Greenstein SA, Hersh PS. Corneal crosslinking for progressive keratoconus and corneal ectasia: summary of US multicenter and subgroup clinical trials. *Transl Vis Sci Technol* 2021;10(5):13.

19 Stein R, Ong Tone S, Lebovic G, Singal N, Hatch W. Subjective and objective evaluation of corneal haze after accelerated corneal crosslinking for corneal ectasias. *Acta Ophthalmol* 2023;101(5):568-574.

20 Serrao S, Lombardo G, Lombardo M. Adverse events after riboflavin/UV-a corneal cross-linking: a literature review. *Int Ophthalmol* 2022;42(1):337-348.

21 Li JF, Peng H, Li JJ *et al*. Comparison of corneal optical density at different time after different lase keratomileusis. *Recent Advances in Ophthalmology* 2022,42(04):294-298.

22 Zhang Y, Lei YL, Ma ZX, *et al*. Early clinical observation of corneal densitometry after SMILE combined with rapid corneal cross-linking. *Journal of Otorhinolaryngology and Ophthalmology of Shandong University* 2021;35(6):52-58.

23 Cankaya AB, Tekin K, Kiziltoprak H, Karahan S, Yilmazbas P. Assessment of corneal backward light scattering in the healthy cornea and factors affecting corneal transparency. *Jpn J Ophthalmol* 2018;62(3):335-341.

24 O'Donnell C, Wolffsohn JS. Grading of corneal transparency. *Cont Lens Anterior Eye* 2004;27(4):161-170.

25 Yuan Q, Liu L, Zhang YL, *et al*. Effect of SMILE and FS-LASIK on corneal densitometry after myopic correction. *Chin J Optom Ophthalmol Vis Sci* 2018;20(12):719-724.

26 Angelo L, Gokul Boptom A, McGhee C, Ziaei M. Corneal crosslinking: present and future. *Asia Pac J Ophthalmol (Phila)* 2022;11(5):441-452.

27 Stramer BM, Zieske JD, Jung JC, Austin JS, Fini ME. Molecular mechanisms controlling the fibrotic repair phenotype in cornea: implications for surgical outcomes. *Invest Ophthalmol Vis Sci* 2003;44(10):4237-4246.

28 Ziaei M, Gokul A, Vellara H, Patel D, McGhee CNJ. Prospective two year study of changes in corneal density following transepithelial pulsed, epithelium-off continuous and epithelium-off pulsed, corneal crosslinking for keratoconus. *Cont Lens Anterior Eye* 2020;43(5):458-464.