• Clinical Research •

Corneal densitometry changes after SMILE Xtra versus SMILE for moderate to high myopia

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Abstract

● **AIM:** To investigate the changes in corneal densitometry (CD) after small incision lenticule extraction combined with accelerated corneal cross-linking (SMILE Xtra) for correcting moderate to high myopia and to analyze their correlation.

● **METHODS:** In this non-randomized retrospective comparative study, participants who underwent surgery were enrolled in the standalone SMILE group and SMILE Xtra group, respectively. Preoperative and postoperative uncorrected visual acuity, spherical equivalent (SE), and CD values were recorded at 1, 3, 6, and 12mo. Measurements were taken in the central (0–2 mm), paracentral (2–6 mm), and peripheral (6–10 mm) zones, as well as in the anterior 120 μm, central, and posterior 60 μm layers of the cornea. A generalized linear mixed model (GLMM) was used to compare CD values between groups and at different time points, and the correlation between postoperative CD values and residual bed thickness (RBT) was analyzed.

● **RESULTS:** Totally 31 participants (62 eyes, mean age 20.32±2.76y) were in the standalone SMILE group and 28 participants (53 eyes, mean age 20.45±2.08y) in SMILE Xtra group. At 12mo postoperatively, there were no statistically significant differences in uncorrected visual acuity or SE between the two groups (P>0.05). Preoperative CD values in all regions showed no significant differences between groups (all P>0.05). In the central (0–2 mm) and paracentral (2–6 mm) zones, and the anterior, central, and total stromal layers, group, time, and interaction effects were all significant (all P<0.001). At 1, 3, and 6mo postoperatively, CD values in the SMILE Xtra group were significantly higher than those in the SMILE group within the 0–2 mm and 2–6 mm diameter ranges, as well as in the anterior, central, and total layers (all P<0.05). At 12mo postoperatively, CD values in the anterior layer remained significantly higher in the SMILE Xtra group compared to the SMILE group (P=0.007), whereas no statistically significant differences were observed in other diameter ranges or stromal layers (all P>0.05). Correlation analysis revealed that at 12mo postoperatively, CD values in all regions of both groups showed a significant positive correlation with RBT (all P<0.05), except for the anterior layer in the SMILE group, which showed no significant correlation with RBT (r=0.114, P=0.380).

● **CONCLUSION:** SMILE Xtra induces transient early increase in CD, primarily in the anterior and central layers. Although values stabilize or decline by 12mo postoperatively, the clinical significance of these long-term patterns requires cautious interpretation, considering the potential influence of post-surgical structural changes. Further research is necessary to fully elucidate the underlying contributions to these densitometric changes.

● **KEYWORDS:** small incision lenticule extraction; accelerated corneal cross-linking; corneal densitometry; myopia

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INTRODUCTION

Corneal transparency primarily depends on the regular arrangement of stromal collagen fibers and the uniformity of the tissue microstructure[1]. Following refractive surgery, corneal healing responses, including keratocyte activation and collagen remodeling, can induce abnormal increases in backscattered light[2]. Traditional slit-

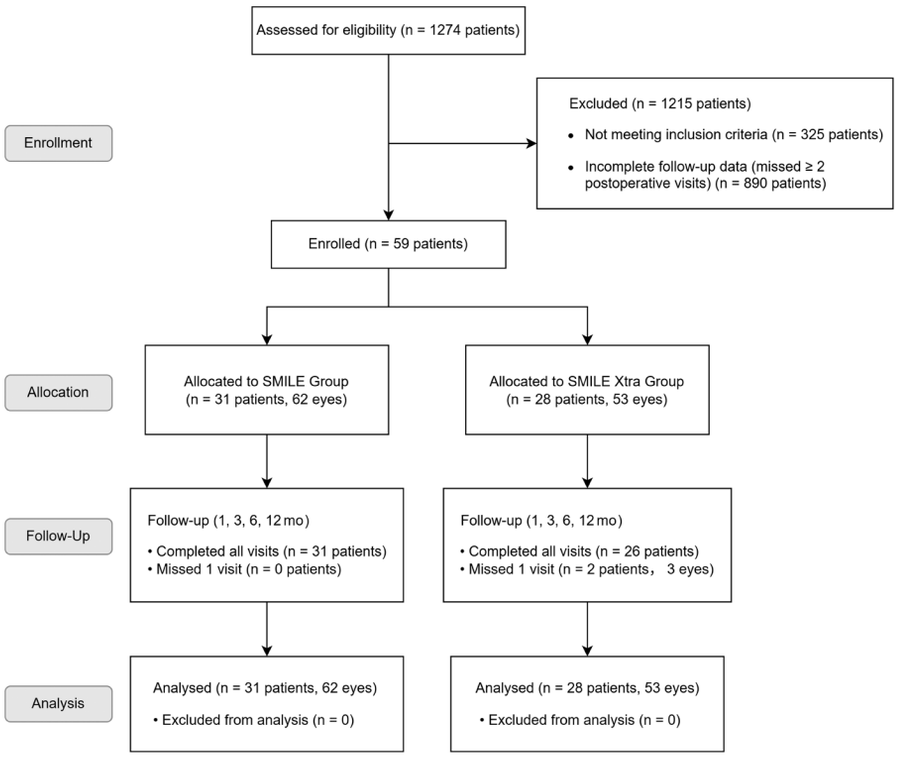


Figure 1 Flow diagram of patient enrollment, allocation, and follow-up SMILE Xtra: Small incision lenticule extraction combined with accelerated corneal cross-linking.

lamp microscopy is highly subjective when assessing corneal transparency, making it difficult to identify subtle changes in the cornea and their spatial distribution characteristics, especially when no obvious opacity is observed clinically. In recent years, quantitative analysis technology for corneal densitometry (CD) based on the Scheimpflug imaging principle has been widely applied in clinical practice. This technique captures backward scattered light generated by corneal tissue and digitally maps its signal intensity to standard grayscale units (GSU), thereby providing a highly repeatable quantitative basis for evaluating corneal transparency[3-4]. Accelerated corneal cross-linking is a surgical method based on the photochemical oxidative reaction induced by ultraviolet irradiation of riboflavin. It promotes the formation of new covalent bonds between and within corneal collagen fibers, enhancing their structural stability and mechanical strength[5-6]. The application of accelerated corneal cross-linking as an adjunct to corneal refractive surgery is primarily intended to mitigate the risk of long-term refractive regression and secondary corneal ectasia, particularly in patients with high myopia or relatively thin corneas postoperatively[5-8]. However, the cross-linking process also triggers keratocyte apoptosis, transient edema, and microstructural remodeling[9]. Clinical evidence suggests that these early tissue responses often manifest as mild stromal haze, with CD values significantly higher than those observed after standalone refractive surgery[10]. Despite these observations, comprehensive reports on corneal transparency following small incision lenticule extraction combined with accelerated corneal cross-linking (SMILE Xtra) remain scarce. In particular, the spatial and depth-specific patterns of stromal transparency changes lack medium- to long-term quantitative clarification. Therefore, this study aims to objectively quantify CD values across different corneal depths and regions after SMILE Xtra versus SMILE, providing a clinical basis for evaluating tissue transparency following this combined procedure.

PARTICIPANTS AND METHODS

Ethical Approval The research protocol adhered to the tenets of the Declaration of Helsinki, and was approved by the Institutional Ethics Committee of the Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine (No. HEC-HY-2024029KY). All patient data were de-identified and patient's informed consent was waived by the Ethics Committee.

Participants This retrospective, non-randomized case-control study enrolled consecutive patients scheduled for SMILE or SMILE Xtra at our hospital between January 2021 and January 2024. The detailed participant selection and enrollment process is illustrated in the participant flow diagram (Figure 1). Both eyes of eligible patients were included in the study where applicable. Ultimately, 31 patients (62 eyes) were included in the SMILE group, and 28 patients (53 eyes) were included in the SMILE Xtra group.

Inclusion criteria were patients over 18 years of age with

moderate to high myopia, stable refraction for more than 2y [with a change in spherical equivalent (SE) ≤0.50 D in the past year], and a residual corneal stromal bed thickness of 300 μm or more. Patients with any history of ocular diseases other than myopia or astigmatism, such as keratoconus, trauma, severe amblyopia, dry eye (evidenced by ≥5 punctate spots or confluent corneal fluorescein staining, or significant meibomian gland dysfunction signs such as eyelid margin hyperemia, telangiectasia, and lipid caps or plugs upon preoperative slit-lamp examination), and a history of recurrent corneal diseases (such as herpes simplex keratitis or recurrent corneal erosion syndrome).

Due to the retrospective design, group allocation was not randomized; rather, it was based on clinical indications (confounding by indication). Based on preoperative examinations, patients meeting two or more of the following criteria were included in the SMILE Xtra group: 1) cylinder ≥3.00 D; 2) corneal topography showing an asymmetric bowtie pattern, inferior steepness/radial axis tilt, with an inferior-superior (I-S) value ≤1.4 D; 3) tomographic biomechanical index (TBI) measured by visual corneal biomechanical analyzer (Corvis ST, Oculus, Germany) between 0.3 and 0.5[11]. Furthermore, patients in the SMILE Xtra group underwent anterior segment optical coherence tomography (AS-OCT)[12], with inclusion based on epithelial mapping criteria, superonasal-inferotemporal (SN-IT) thickness <50 μm, superior-inferior (S-I) thickness <45 μm, and a minimum thickness location Y-coordinate <-0.75 mm. All patients diagnosed with keratoconus were strictly excluded. Patients who did not exhibit these high-risk features underwent standalone SMILE.

All patients underwent a comprehensive ophthalmic evaluation, including assessments of sphere, cylinder, SE, uncorrected distance visual acuity (UDVA), and corrected distance visual acuity (CDVA). Additional examinations included intraocular pressure measurement, slit-lamp biomicroscopy of the anterior segment, and fundus examination. Furthermore, corneal topography was performed using the Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany), and corneal biomechanical properties were evaluated with the Corvis ST.

Sample Size Estimation Sample size estimation was performed based on the anterior CD at 1mo postoperatively. Assuming an expected difference between groups of δ=1.94 and a pooled standard deviation of S=2.8, a minimum of 44 eyes per group was required to achieve a statistical power of 1-β=0.90 (t_β=1.282) at a two-sided significance level of α=0.05 ($t_{\alpha/2}$=1.96). In this study, 62 eyes in the SMILE group and 53 eyes in the SMILE Xtra group were ultimately included, providing a sufficient sample size and ensuring reliable statistical power.

$$n = \frac{2\ \left(\mathrm{t}_{\frac{\alpha}{2}} + t_\beta\right)^2\ \cdot S^2}{\delta^2}$$

Surgical Procedure All patients underwent the SMILE procedure under topical anesthesia with 0.4% oxybuprocaine hydrochloride. Corneal photodisruption was performed using a 500-kHz VisuMax femtosecond laser system (Carl Zeiss Meditec, Jena, Germany) with a pulse energy of 130 nJ. The cap thickness was set at 110–120 μm with a diameter of 7.5 mm. The lenticule diameter ranged from 6.0 to 6.6 mm, including a 0.1–0.2 mm transition zone. A 2-mm side cut was created at the 120° position.

For the SMILE Xtra group, 0.23% Vibex Xtra riboflavin (Avedro, Inc., Waltham, MA, USA) was instilled into the corneal pocket immediately after lenticule extraction and allowed to diffuse for 80s. The pocket was then irrigated with a balanced salt solution. Accelerated collagen cross-linking was performed using the KXL system (Avedro, Inc., Waltham, MA, USA) with an ultraviolet-A irradiance of 30 mW/cm² for 80s, resulting in a total energy dose of 2.4 J/cm². Corneal hydration was maintained throughout the irradiation. Postoperatively, the cornea was examined *via* slit-lamp biomicroscopy. The lenticule thickness, optical zone (OZ) diameter, and residual bed thickness (RBT) were recorded for all cases. All procedures were performed by the same experienced surgeon. Both groups received a strictly identical, standard postoperative medication regimen, which consisted of topical antibiotics, topical corticosteroids, and preservative-free artificial tears.

Corneal Densitometry Measurement CD was quantified using the Pentacam HR system and reported in GSU, where 0 represents maximum transparency and 100 indicates total opacity. The mean densitometry was evaluated in three annular zones (0–2, 2–6, and 6–10 mm) centered on the corneal apex. Regarding depth-dependent analysis, the cornea was partitioned into three segments: the anterior (superficial 120 μm), posterior (innermost 60 μm), and central (intervening tissue) layers. Changes in CD values were analyzed across these distinct anatomical regions and depths.

To ensure data reliability, all scans were performed by a single experienced technician to eliminate inter-observer variability. All measurements were conducted in a standardized darkened room under scotopic conditions (ambient light <5.0 lx) to minimize the impact of external stray light on the Scheimpflug imaging system. To account for diurnal variation in corneal parameters, all examinations were scheduled during the morning hours. For repeatability, each eye was measured three consecutive times, and only scans with a “Quality Specification” of “OK” were accepted.

Statistical Analysis Statistical analyses were performed using SPSS software (version 27.0; IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed data are presented as mean±standard deviation. Comparisons of baseline characteristics between the two surgical groups were conducted using the independent *t*-test. Generalized linear mixed model (GLMM) was used to compare the differences in CD values between groups and across various follow-up time points. In this model, group, time, and the interaction between group and time were set as fixed effects.

Individual subjects were set as a random intercept to control for the inter-eye dependency (clustering effect) of including both eyes of the same patient. Furthermore, to control for confounding by indication stemming from the non-randomized design, gender, age[13], preoperative SE, cylinder, central corneal thickness (CCT), TBI, OZ, lenticule thickness, and RBT were directly incorporated as covariates in the GLMM. Post-hoc pairwise comparisons were adjusted using the Bonferroni correction. Spearman correlation tests were used for correlation analysis. All statistical tests were two-sided, and a $P<0.05$ was considered statistically significant.

RESULTS

A total of 1274 consecutive patients were initially assessed for eligibility. After excluding 1215 patients who did not meet the inclusion criteria or had incomplete follow-up records, 59 eligible patients were finally enrolled. Based on clinical indications (presence of high-risk features for ectasia), patients were non-randomly allocated to the SMILE group (31 patients, 62 eyes) or the SMILE Xtra group (28 patients, 53 eyes). Minor intermittent missing data during follow-up were retained and statistically handled by GLMM.

There were no significant differences between the two groups in terms of age, preoperative refraction, CCT, or surgical parameters (Table 1). At 12mo postoperatively, 96% (51/53 eyes) in the SMILE Xtra group and 98% (61/62 eyes) in the SMILE group achieved UDVA of 0.1 logMAR or better (Figure 2).

Furthermore, the mean SE at 12mo was -0.19±0.50 D in the SMILE Xtra group and -0.22±0.50 D in the SMILE group, with no statistically significant difference observed between the two groups ($P>0.05$; Figure 3).

Comparison of Corneal Densitometry GLMM was utilized to analyze the longitudinal changes in CD values across different annular zones and stromal depths. In the central (0–2 mm) zone, paracentral (2–6 mm) zone, anterior layer, central layer, and total stromal layer, the GLMM revealed significant main effects for both group and time ($F_{group}=37.340$, $F_{time}=73.436$; $F_{group}=34.293$, $F_{time}=72.933$; $F_{group}=23.708$, $F_{time}=38.896$; $F_{group}=10.005$, $F_{time}=27.716$; $F_{group}=17.119$, $F_{time}=31.060$, all $P<0.001$). Crucially, a significant group-by-time interaction was observed in these regions ($F=42.085$; $F=37.202$; $F=24.086$; $F=8.586$; $F=15.911$; all $P<0.001$).

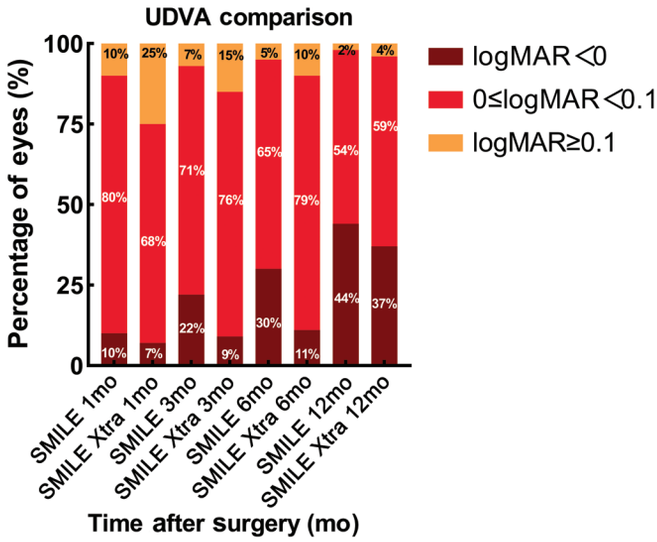


Figure 2 Distribution of postoperative UDVA SMILE Xtra: Small incision lenticule extraction combined with accelerated corneal cross-linking; UDVA: Uncorrected distance visual acuity.

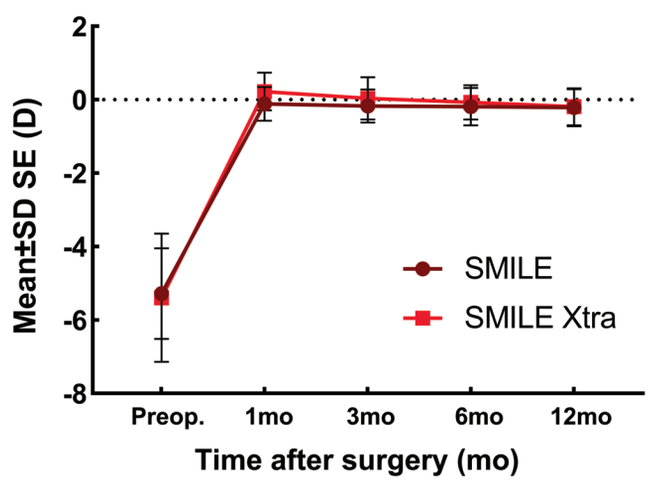


Figure 3 Stability of SE over time SMILE Xtra: Small incision lenticule extraction combined with accelerated corneal cross-linking; SE: Spherical equivalent; SD: Standard deviation.

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

Parameters	SMILE (62 eyes)	SMILE Xtra (53 eyes)	*P*
Age, y	20.32±2.76	20.45±2.08	0.779
Sphere, D	-4.50±1.26	-4.65±1.77	0.600
Cylinder, D	-1.56±0.76	-1.50±1.18	0.721
Spherical equivalent, D	-5.28±1.23	-5.39±1.74	0.676
CCT, μm	538.71±17.99	533.57±24.76	0.201
LT, μm	106.44±14.26	103.85±19.66	0.417
OZ, mm	6.22±0.16	6.16±0.19	0.063
RBT, μm	317.35±15.23	314.92±12.47	0.356

SMILE Xtra: Small incision lenticule extraction combined with accelerated corneal cross-linking; CCT: Central corneal thickness; LT: Lenticule thickness; OZ: Optical zone; RBT: Residual bed thickness; SD: Standard deviation.

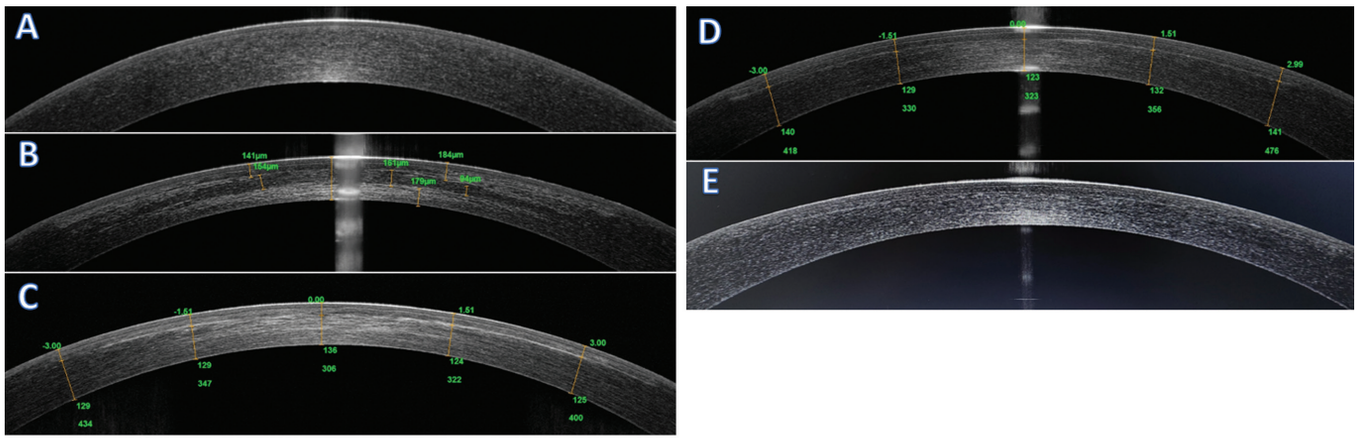


Figure 4 Representative longitudinal imaging and corresponding corneal densitometry maps from preoperative to 12mo postoperatively A: Preoperative; B: 1mo postoperative; C: 3mo postoperative; D: 6mo postoperative; E: 12mo postoperative.

In the peripheral zone (6–10 mm), the model revealed a significant main effect of time. However, neither the main effect of group nor the group-by-time interaction reached statistical significance (F_{group}=3.535, P=0.064; F_{time}=27.451, P<0.001; $F_{interaction}$=1.428, P=0.223). In the posterior layer, the main effect of group was not statistically significant, both the main effect of time and the group-by-time interaction were significant (F_{group}=1.868, P=0.176; F_{time}=11.334, P<0.001; $F_{interaction}$=5.617, P<0.001).

Preoperatively, there were no statistically significant differences in CD values between the two groups across various diameter ranges and stromal depths (all P>0.05). At 1 and 3mo postoperatively, CD values in the SMILE Xtra group were significantly higher than those in the SMILE group within the 0–2 and 2–6 mm diameter ranges, as well as in the anterior layer, central layer, and total layers (all P<0.05). Notably, at 3mo postoperatively, statistically significant intergroup differences also emerged in the 6–10 mm diameter range and the posterior layer (all P<0.05). At 6mo postoperatively, CD values remained significantly higher in the SMILE Xtra group within the 0–2, 2–6, and 6–10 mm diameter ranges, as well as in the anterior layer, central layer, and total layers (all P<0.05); however, the intergroup difference in the posterior layer was no longer significant (all P>0.05). At 12mo postoperatively, CD values in the anterior layer remained significantly higher in the SMILE Xtra group compared to the SMILE group (P=0.007), whereas no statistically significant differences were observed in other diameter ranges or stromal layers (all P>0.05; Table 2).

To visually illustrate these quantitative findings, Figure 4 provides representative AS-OCT images and corneal densitometry maps from the SMILE Xtra group. These images visually corroborate the transient early postoperative elevation of CD, predominantly in the anterior and central zones (Figure 4).

Correlation Analysis Between Corneal Densitometry and RBT At 12mo postoperatively, CD values in the SMILE group across the 0–2, 2–6, and 6–10 mm zones, as well as in the central, posterior (60 μm), and full-thickness layers, were significantly and positively correlated with RBT (r=0.342, 0.318, 0.364, 0.349, 0.317, 0.264, P<0.05; Figure 5). However, no significant correlation was observed between the anterior layer CD values and RBT in the SMILE group at 12mo (r=0.114, P=0.380; Figure 5).

At 12mo postoperatively, CD values in the SMILE Xtra group across all annular zones (0–2, 2–6, and 6–10 mm) and all anatomical layers (anterior 120 μm, central, and posterior 60 μm) showed significant positive correlations with RBT (r=0.307, 0.305, 0.318, 0.389, 0.493, 0.331, 0.479, P<0.05; Figure 5).

DISCUSSION

Previous studies utilizing *in vivo* confocal microscopy have confirmed that the photo-oxidative effect of ultraviolet A combined with riboflavin triggers keratocyte apoptosis in the anterior stroma, accompanied by transient early-stage stromal edema and the formation of a localized acellular zone[14]. These histological alterations lead to an inhomogeneous refractive index within the stroma, increasing backscattered light and manifesting as a significant postoperative elevation in CD.

In the current study, the increase in CD values in the SMILE Xtra group was primarily concentrated in the central and paracentral zones, as well as the anterior stroma, which correlates with the cross-linking effect and the anatomical location of the surgical interface. First, the ultraviolet A irradiation energy decreases gradually as it penetrates deeper into the corneal stroma; combined with the more compact collagen arrangement in the anterior stroma, the cross-linking effect is significantly more robust in the anterior layer than in the deeper stroma[7]. Second, as the riboflavin solution infiltrates both the anterior and posterior surfaces of the stromal lenticule, the cross-linking reaction is notably enhanced at these interfaces and their adjacent tissues. In

Table 2 Differences in corneal densitometry values (GSU) between the two groups

Parameters	SMILE mean (95%CI)	SMILE Xtra mean (95%CI)	*P*	β (95%CI)	Effect size (*d*)
0–2 mm					
Preop.	12.46 (12.06, 12.86)	12.86 (12.43, 13.30)	0.184	0.40 (-0.20, 1.00)	0.31
Postop. 1mo	12.79 (12.39, 13.19)	14.80 (14.37, 15.24)	<0.001	2.01 (1.41, 2.62)	1.58
Postop. 3mo	12.00 (11.60, 12.40)	15.12 (14.68, 15.55)	<0.001	3.12 (2.51, 3.72)	2.44
Postop. 6mo	12.09 (11.69, 12.49)	14.04 (13.61, 14.47)	<0.001	1.95 (1.35, 2.56)	1.53
Postop. 12mo	11.64 (11.24, 12.04)	12.05 (11.62, 12.49)	0.177	0.42 (-0.19, 1.02)	0.33
2–6 mm					
Preop.	11.44 (11.11, 11.76)	11.72 (11.37, 12.07)	0.262	0.27 (-0.22, 0.77)	0.26
Postop. 1mo	11.85 (11.53, 12.18)	13.61 (13.26, 13.96)	<0.001	1.75 (1.26, 2.25)	1.67
Postop. 3mo	11.27 (10.94, 11.59)	13.68 (13.33, 14.04)	<0.001	2.41 (1.92, 2.90)	2.30
Postop. 6mo	11.47 (11.15, 11.80)	12.79 (12.44, 13.14)	<0.001	1.31 (0.82, 1.81)	1.25
Postop. 12mo	10.98 (10.66, 11.31)	11.32 (10.96, 11.67)	0.182	0.34 (-0.16, 0.83)	0.32
6–10 mm					
Preop.	11.60 (11.23, 11.98)	11.92 (11.51, 12.33)	0.287	0.31 (-0.26, 0.88)	0.26
Postop. 1mo	11.98 (11.61, 12.36)	12.30 (11.89, 12.71)	0.283	0.31 (-0.26, 0.88)	0.26
Postop. 3mo	11.40 (11.02, 11.77)	12.15 (11.74, 12.56)	0.011	0.75 (0.18, 1.32)	0.63
Postop. 6mo	11.60 (11.23, 11.98)	12.20 (11.79, 12.61)	0.043	0.59 (0.02, 1.16)	0.49
Postop. 12mo	10.81 (10.43, 11.18)	11.20 (10.79, 11.61)	0.180	0.39 (-0.18, 0.96)	0.33
Anterior layer					
Preop.	18.56 (17.87, 19.25)	19.21 (18.48, 19.95)	0.221	0.65 (-0.38, 1.68)	0.31
Postop. 1mo	18.13 (17.44, 18.82)	21.05 (20.31, 21.79)	<0.001	2.91 (1.88, 3.94)	1.38
Postop. 3mo	17.22 (16.54, 17.91)	21.18 (20.44, 21.92)	<0.001	3.95 (2.92, 4.98)	1.87
Postop. 6mo	17.46 (16.77, 18.15)	19.84 (19.10, 20.58)	<0.001	2.37 (1.34, 3.40)	1.12
Postop. 12mo	16.70 (16.01, 17.39)	18.13 (17.39, 18.88)	0.007	1.43 (0.40, 2.46)	0.68
Central layer					
Preop.	12.24 (11.87, 12.61)	12.55 (12.15, 12.95)	0.285	0.31 (-0.25, 0.86)	0.26
Postop. 1mo	12.00 (11.63, 12.37)	13.33 (12.93, 13.73)	<0.001	1.32 (0.77, 1.88)	1.14
Postop. 3mo	11.71 (11.34, 12.08)	12.88 (12.48, 13.28)	<0.001	1.16 (0.60, 1.72)	1.00
Postop. 6mo	11.87 (11.50, 12.24)	12.53 (12.13, 12.93)	0.023	0.65 (0.09, 1.21)	0.56
Postop. 12mo	11.34 (10.97, 11.71)	11.82 (11.41, 12.22)	0.098	0.47 (-0.09, 1.03)	0.41
Posterior layer					
Preop.	8.85 (8.58, 9.12)	9.06 (8.77, 9.36)	0.309	0.20 (-0.21, 0.62)	0.23
Postop. 1mo	8.98 (8.71, 9.25)	9.25 (8.95, 9.55)	0.199	0.26 (-0.16, 0.67)	0.29
Postop. 3mo	8.68 (8.41, 8.95)	9.29 (8.99, 9.58)	0.004	0.59 (0.18, 1.01)	0.68
Postop. 6mo	8.94 (8.67, 9.21)	9.28 (8.99, 9.58)	0.106	0.33 (-0.09, 0.74)	0.38
Postop. 12mo	8.71 (8.43, 8.98)	8.49 (8.19, 8.79)	0.292	-0.22 (-0.64, 0.19)	-0.25
Total layer					
Preop.	13.44 (13.04, 13.83)	13.91 (13.48, 14.33)	0.123	0.46 (-0.13, 1.04)	0.38
Postop. 1mo	13.29 (12.90, 13.69)	14.69 (14.27, 15.12)	<0.001	1.39 (0.81, 1.98)	1.15
Postop. 3mo	12.74 (12.34, 13.13)	14.62 (14.20, 15.04)	<0.001	1.87 (1.29, 2.46)	1.55
Postop. 6mo	12.96 (12.56, 13.36)	14.14 (13.72, 14.56)	<0.001	1.17 (0.59, 1.76)	0.97
Postop. 12mo	12.58 (12.19, 12.98)	13.14 (12.72, 13.57)	0.064	0.56 (-0.03, 1.15)	0.46

β represents the regression coefficient (the estimated mean difference between the SMILE Xtra and SMILE groups) calculated using generalized linear mixed models. Effect size (*d*) refers to Cohen's *d*, where 0.2, 0.5, and 0.8 represent small, medium, and large effects, respectively. *P*<0.05 was considered statistically significant. CI: Confiderce interval; SMILE Xtra: Small incision lenticule extraction combined with accelerated corneal cross-linking; GSU: Grayscale units.

this study, the corneal cap thickness was set at 110–120 μm, meaning the anatomical location of the lenticule extraction fell precisely within the measurement range of the anterior layer (0–120 μm). Since the anterior stroma is the most active site for postoperative wound healing, keratocyte activation, and microstructural remodeling, the superposition of these factors collectively led to the marked increase in CD values in the anterior layer. This anatomical predilection also explains why the anterior layer was the only zone with a persistent inter-group difference at 12mo, underscoring that the anterior stroma is the primary and most durable site of the cross-linking effect.

Regarding the temporal trend, the SMILE Xtra group exhibited a significant elevation of CD in the central (0–2 mm) and paracentral (2–6 mm) zones, as well as the anterior stroma,

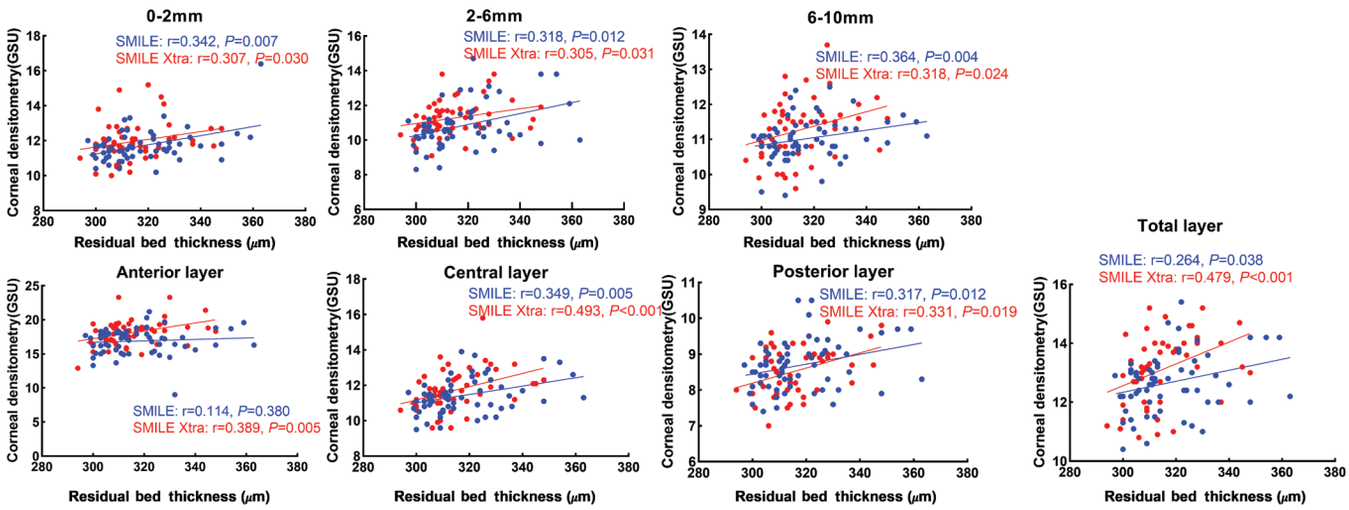


Figure 5 Correlations between RBT and corneal densitometry at 12mo postoperatively Correlations between RBT and corneal densitometry values are evaluated across different zones (0–2, 2–6, and 6–10 mm) and layers (anterior, central, posterior, and total layer). Blue dots and lines represent the SMILE group; red dots and lines represent the SMILE Xtra group. SMILE Xtra: Small incision lenticule extraction combined with accelerated corneal cross-linking; RBT: Residual bed thickness; GSU: Grayscale units.

during the early postoperative period (1–3mo). This increase substantially exceeds the published repeatability coefficients for the Pentacam HR in corresponding regions of healthy corneas[15]. Although measurement variability may differ between postoperative and healthy eyes, this substantial magnitude suggests that the early elevation predominantly represents genuine biological microstructural changes induced by cross-linking, and cannot be solely attributed to instrument measurement noise. However, by 12mo postoperatively, although the residual inter-group difference in the anterior layer remained statistically significant, its absolute magnitude had decreased considerably, approaching the instrument's measurement variability range for these specific layers[16]. Therefore, careful consideration is required when interpreting the clinical significance of this minute long-term difference, and over-interpretation should be strictly avoided.

Regarding the distribution across concentric zones, the increase in CD was primarily concentrated in the central and paracentral regions, which highly coincided with the programmed lenticule diameter (6.0–6.6 mm) and the ultraviolet irradiation area in this study. Since lenticule extraction, riboflavin infiltration, and ultraviolet irradiation were all localized within the region covered by the lenticule, the impact of this combined procedure on CD was predominantly restricted to the central and paracentral concentric zones[17]. These findings align with a 5-year follow-up by Wei *et al*[18], which confirmed that CD changes after SMILE are closely aligned with the anatomical depth of the surgical interface. In contrast, the peripheral zone (6–10 mm) and the posterior layer remained largely unaffected by cross-linking, with no significant CD changes observed throughout the follow-up period. This is consistent with Kosekahya *et al*[19], who noted that accelerated CXL has limited impact on the posterior layer, although minor fluctuations may occur early on, no significant long-term abnormalities were identified.

At 12mo postoperatively, CD values in both groups returned to or dropped below baseline levels; however, this decrease should be primarily attributed to optical path-length shortening from stromal thinning and device measurement variability, rather than being overinterpreted as a substantive improvement in corneal biological transparency[20]. This explanation is further supported by the correlation analysis, which demonstrated that CD values were significantly positively correlated with the RBT in most regions. This association suggests that CD values are modulated by the physical characteristics of the residual corneal geometry rather than pathological haze. These findings are consistent with the long-term follow-up study of SMILE by Han *et al*[21], which attributed the downward trend in CD during the late postoperative period to the thinning of total corneal thickness following lenticule extraction and the subsequent corneal wound healing response.

In the present study, the recovery of CD at 12mo post-SMILE Xtra differed from the long-term lack of recovery observed by some researchers. The 2.4 J/cm^2 protocol was supported by the study of Kanellopoulos *et al*[22-23], who demonstrated that this accelerated high-fluence corneal collagen crosslinking procedure could provide significant corneal stability with minimal biological stress. Different from the therapeutic protocol for keratoconus, prophylactic corneal collagen crosslinking in refractive surgery aims to strengthen the corneal lamellar structure rather than induce extensive tissue remodeling. The conservative dose of 2.4 J/cm^2 can minimize the

risk of clinically significant corneal haze. When comparing our findings with other studies, we noted that Osman *et al*[24], using a 3.2 J/cm^2 protocol, reported a significant increase in CD that failed to return to baseline even at 24mo postoperatively. Conversely, Piyacomn *et al*[25] utilized 2.7 J/cm^2 in patients undergoing SMILE Xtra, LASIK Xtra, and PRK Xtra. Their results showed a highly consistent trend across all procedures: CD in the anterior and central layers increased during the early postoperative period, but largely recovered in the central 0–6 mm zone by 6mo, with only a slight but significant increase persisted in the peripheral 6–10 mm zone. These discrepancies suggest that the variation in energy protocol settings between studies is likely one of the primary factors contributing to the inconsistent recovery times of CD[26]. Brar *et al*[26] further confirmed in a long-term study that SMILE and SMILE Xtra exhibited comparable safety, efficacy, and predictability, with no long-term hyperopic shift observed contrary to previous concerns. Liu *et al*[27] conducted a prospective cohort study comparing SMILE Xtra with FS-LASIK Xtra over 12mo, demonstrating comparable safety, efficacy, predictability, and stability between the two procedures, with 98% and 99% of eyes achieving UDVA of 20/20 or better, respectively. Chabib *et al*[28] also reported no significant differences in UDVA, safety index, or efficacy index between SMILE Xtra and SMILE at 24mo. Collectively, these studies support the favorable long-term safety and stability of SMILE Xtra in high-risk populations.

Several limitations of the present study should be acknowledged. First, this study was limited by its retrospective, non-randomized design, which introduced unavoidable selection bias. Patients in the SMILE Xtra group were assigned according to preoperative risk criteria (including high astigmatism, borderline corneal thickness, or increased ectasia risk) rather than by random allocation. While this design reflects real-world clinical decision-making in which prophylactic intervention is reserved for biomechanically "high-risk" eyes, and although we adjusted for relevant baseline risk factors in our GLMM, residual confounding by indication cannot be entirely ruled out, preventing definitive causal interpretation of between-group differences.

Second, the evaluation indices were not exhaustive. Specifically, advanced functional visual-quality metrics (such as contrast sensitivity, higher-order aberrations, and intraocular straylight), endothelial cell density, demarcation line depth which are essential for a comprehensive evaluation of optical quality after refractive surgery. Ganesh and Brar[29] have reported contrast sensitivity outcomes after SMILE Xtra, demonstrating a transient decrease that remained within normal limits and trended toward recovery by 12mo. Liu *et al*[27] reported a temporary decrease in straylight that gradually returned to preoperative levels. However, systematic data on these functional outcomes specifically after SMILE Xtra remain scarce. Third, the long-term effects of the cross-linking protocol necessitate further validation. There is currently no unified international or domestic consensus on the standardized parameter settings for corneal refractive surgery combined with cross-linking; thus, the long-term impact of various radiant energies and riboflavin soaking durations on corneal transparency remains to be further explored. Finally, the relatively small sample size and limited follow-up duration represent a constraint. Future multicenter, large-scale, and long-term randomized controlled trials are warranted to further evaluate the long-term impact of the SMILE Xtra protocol on enhancing corneal biomechanical stability, as well as its influence on visual acuity and corneal histological evolution.

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