Ultrastructural changes of corneal stromal lenticule after laser shaping

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Abstract. With the aim to improve the application of stromal lenticules derived from small-incision lenticule extraction (SMILE) surgery in treating refractive and corneal diseases, a technique was developed in the present study to reshape these lenticules by modifying their thickness distribution. For this, the ultrastructural changes in SMILE-derived corneal stromal lenticules following excimer laser reshaping were examined. SMILE was performed on 40 myopia using the VisuMax femtosecond laser system. In the experimental group, 20 corneal stromal lenticules were reshaped using an excimer laser, while the remaining 20 lenticules were left untreated as the control group. A total of 14 lenticules from both groups were used to measure changes in absorbance and light transmittance, while six from each group were histologically examined by HE staining and evaluation under an optical microscope to assess their morphological structure. No visible edema was observed in the central cornea before or after laser reshaping, and the stromal fiber layers remained regularly arranged. No abnormalities were found in the two groups. A significant improvement in lenticule light transmittance was observed after reshaping. In conclusion, excimer laser plasticity did not alter the regular arrangement of corneal stromal lenticule fibers but significantly enhanced their light transmittance.

Introduction

A corneal stromal lenticule is a valuable biological material obtained through small-incision lenticule extraction (SMILE). It has been reported that SMILE-derived corneal stromal lenticules can be used to treat corneal ulcers and perforations, to effectively repair corneal defects and to improve the local inflammatory response, and they have good surgical reproducibility (1,2). Optical coherence tomography (OCT) can be used to assess the depth and extent of corneal lesions, and it may be possible to change the shape of the implant according to the cornea condition as measured by OCT to improve surgical treatment outcomes.

Keratoconus is a common progressive, non-inflammatory corneal degenerative disease that usually occurs in early adolescence (3). Corneal collagen crosslinking can be used to control the progression of keratoconus (4,5). However, certain patients with advanced keratoconus do not have a corneal thickness of 400 μm, which is the minimum thickness required for corneal crosslinking surgery (6). Corneal thickness can however be increased through the implantation of corneal stromal lenticules. Corneal stromal lenticules have achieved good clinical results in the treatment of keratoconus, but the curvature of patients after lenticule implantation has been reported to increase as a result (7-11). The implantation of a convex lenticule derived from SMILE for myopia causes a steeper curvature in patients with keratoconus, which may lead to postoperative glass intolerance, poor rigid gas permeable contact lens matching, difficulty in refractive reconstruction and poor patient satisfaction. Nubile *et al* (12) found that customizing lenticules by increasing their asymmetry and tailoring their re-shaping may improve implantation outcomes in cases of eccentric keratoconus.

Presbyopia is the most common visual condition affecting people over 40 years of age. Studies such as that by Liu *et al* (13) suggested that corneal stromal lenticule implantation may be a feasible and safe treatment for presbyopia (14,15). However, a major limitation is the thickness of the corneal stromal lenticule, which depends on the refractive status of the donor undergoing SMILE surgery. The number of available lenticules with lower refraction is limited. A study indicated that only 15 out of 424 patients (3.54%) with presbyopia had lenticules suitable for reimplantation (16). In addition, in patients with high myopia and thin corneas who are unwilling to undergo implantable collamer lens treatment, the corneal stromal lenticule can also be remodeled into a concave lens or a 'donut' and then implanted into a capsule created using a femtosecond laser to correct refractive error. Therefore, if corneal stromal

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lenticule implantation is a useful treatment for refractive and corneal diseases, it would be beneficial to develop a technique that meets the clinical need for corneal stromal lenticule thickness distribution and enables its remodeling.

The corneal stromal lenticule is the anterior layer of the central corneal stromal layer. It is composed of collagen fibers arranged regularly. Its normal anatomical structure and physiological function maintain the light transmittance and biomechanics of the cornea; therefore, it has good plasticity. Luft *et al* (17) assessed wound healing, inflammation and tissue ultrastructure in the human corneal stroma after SMILE and femtosecond laser-assisted *in situ* keratomileusis (FS-LASIK), and found that both procedures elicited virtually identical and minimal keratocyte activation, cell death or inflammation, with the stromal bed exhibiting a smoother surface texture after LASIK. This demonstrates that the excimer laser has little effect on the matrix and can therefore be used to reshape the corneal stromal lenticule according to the patient's needs. However, there are few available studies on ultrastructural changes after corneal stromal lenticule shaping. The microstructure and light transmittance of the corneal stromal lenticule after excimer laser shaping are essential for predicting postoperative patient satisfaction, as they may be associated with better optical quality, reduced inflammatory responses and faster recovery. Therefore, this study used microcode to observe changes in the light transmittance and morphological structure of corneal stromal lenticules after shaping under an optical microscope.

Patients and methods

Study subjects and groups. This study involved 30 patients aged 19.68±1.79 years (range, 18 to 27 years) who underwent SMILE surgery at Jinan Mingshui Eye Hospital (Jinan, China) during July 2024, including a total of 40 eyes. All patients voluntarily came to Jinan Mingshui Eye Hospital (Jinan, China) for refractive surgery, and none of them had received any treatment for any eye condition. A complete ophthalmological examination was performed before the surgery. Eyes were grouped according to the experimental design; the same thickness was required to be ascertained for experimental group 1 and control group 1 before corneal stromal lenticules shaping, and for experimental group 2 and control group 2 the same thickness was required to be ascertained after shaping. The removed corneal stromal lenticules were divided into an experimental group requiring excimer cutting and a control group without excimer cutting. Tissues from experimental group 1 and control group 1 were examined under an optical microscope after hematoxylin and eosin (HE) staining (6 eyes in each group). The diopters of both groups were consistent before laser shaping [experimental group 1: -5.04±0.69 (range: -5.88 to -4.25D), control group 1: -5.23±0.65 (range: -6.13 to -4.38D)]. Light transmittance was measured for experimental group 2 and control group 2 (14 eyes in each group) using a microcoder to ensure that lenticule thickness was comparable between the two groups after laser plasticity. The equivalent spherical lens for experimental group 2 was -6.511±0.412 (range, -7.25 to -5.50D). The equivalent spherical mirror for the control group was -3.843±0.405 (range, -4.38 to -3.25D). The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Jinan Mingshui Eye Hospital (Jinan, China; Ref. Ethics/2024/004). All participants or their legal guardians consented to the use of the corneal stromal lenticules produced during their surgery for this study.

The inclusion criteria were as follows: i) The patient had a desire to discoutinue glasses and had reasonable expectations regarding surgical outcomes; ii) age, 17-30 years; iii) stable dioptric state and an annual increase of the myopia dioptric number within two years not exceeding 0.5D; iv) column lens degree ≤1.00D; v) adequate pupil diameter (bright pupil ≤5 cm, dark pupil ≤8 cm); vi) the patient had discontinued the use of soft contact lenses for at least 10 days, of hard contact lenses for at least a month and of orthokeratology lenses for at least three months.

The following exclusion criteria were applied: i) The patient was unable to place the head in a normal position; ii) previous cornea-related surgery; iii) presence or family history of keratoconus or glaucoma; iv) pregnancy or being at the breastfeeding stage; v) other eye diseases or diabetes, systemic immune diseases or neuropsychiatric disorders.

Corneal stromal lenticule acquisition process. All patients underwent detailed ophthalmological examinations and all procedures were performed by the same experienced physician. Levofloxacin eye drops (Levofloxacin Bromofenac sodium, Ruilin) were routinely used 1 day before the operation. After routine conjunctival sac irrigation and periocular disinfection before surgery, promecaine hydrochloride eye drops (Unitel Nanjing Pharmaceutical Co., Ltd) were used for surface anesthesia. Femtosecond laser for lenticule and small incision was performed with a Visumax 500 kHz femtosecond Laser System (Carl Zeiss AG); the energy was 130 nJ, the lenticule cutting diameter was 6.5 mm, the corneal cap thickness was 120 μm and the length of the small incision was 2 mm.

Corneal stromal lenticule laser remodeling. The stromal lenticule was placed on the plate and 1-2 drops of 0.09% saline were applied to flatten it. Excess water was quickly absorbed and the stromal lenticule was placed on the Amaris excimer machine (Schwind Amaris 500E; Schwind) for excimer cutting. The cutting optical area was set to 4 mm and excimer cutting with refractive parameter 1:1 (that is, the diopter of the excimer cutting design is equal to the effective diopter of the lenticules) was performed based on the lenticule's equivalent spherical power. The entire process was completed within two minutes.

Fixation of corneal stromal lenticule and optical observation. After the corneal stromal lenticule was removed, it was fixed with 10% paraformaldehyde at 20˚C for 24 h and dehydrated using an ethanol gradient. The tissue was encased in wax blocks and sections (thickness, 3-5 μm) were prepared with a microtome. A group of good slices was taken up with tweezers and placed on the surface of the water in the slot of a sheet spreading machine (water temperature, 40-45˚C); they were allowed to stretch naturally and after the slices were flattened, the best slice was separated. A clean slide of the corresponding tissue, which had been numbered, was inserted into the water near the slice at an angle, and it was slowly lifted to make

Table I. Basic information statistics of patients undergoing optical microscopy.

Variable	Totals (n=12)	Experimental group 1 (n=6)	Control group 1 (n=6)	t/Z -value	P-value
Age[a], years	18.92±0.79	18.5±0.55	19.33±0.82	-1.791	0.073
Sex				0	>0.999
Males	8 (66.7)	4 (66.7)	4 (66.7)		
Females	4 (33.3)	2 (33.3)	2 (33.3)		
Diopters	-5.138±0.664	-5.043±0.68521	-5.232±0.649	-0.489	0.636

Values are expressed as the mean ± standard deviation or n (%). [a]The normal distribution and homogeneity of variance are not met.

Table II. Basic information statistics of patients with light transmittance measurements.

Variable	Totals (n=28)	Experimental group 2 (n=14)	Control group 2 (n=14)	t/Z-value	P-value
Age[a], years	20±2.00	20.5±2.35	19.5±1.50	-1.636	0.102
Sex				0	>0.999
Males	18 (64.3)	9 (64.3)	9 (64.3)		
Females	10 (35.7)	5 (35.7)	5 (35.7)		
Diopters[a]	-5.18±1.42	-6.51±0.41	-3.84±0.41	-4.521	<0.001
Predicted thickness[a], μm	89.82±5,80	90.36±4.09	89.29±7.24	-0.254	0.799
Actual measured thickness, μm	164.536±9.143	162.857±166.214	166.214±12.04	-0.970	0.341

Values are expressed as the mean ± standard deviation or n (%). [a]The normal distribution and homogeneity of variance are not met.

the slice adhere to the slide. The slide was baked at 37˚C for 24-48 h. Dewaxing and rehydration were performed with xylene, an ethanol series and steaming water. The sample was stained with hematoxylin and eosin according to standard methods and sealed with neutral gum for light microscopic observation.

Corneal stromal lenticule light transmittance measurement. To ensure that the predicted thickness of the two groups of corneal stromal lenticules was the same and to prevent lenticule thickness from affecting light transmittance, the predicted thickness of the control group was the thickness of the corneal stromal lenticule calculated according to the Zeiss full femtosecond laser surgery system (Carl Zeiss AG). The predicted thickness of experimental group 2 was the thickness of the corneal stromal lenticule calculated using the Zeiss full femtosecond laser surgery system minus the laser cutting thickness calculated using the Amaris excimer laser surgery system. The prepared corneal stromal lenticule was placed in front of the OCT to measure its actual thickness (the measurement was completed within one minute). After the measurement was completed, 0.09% normal saline was immediately placed into the corneal stroma lenticules, which were then placed flat in a 96-well plate, and three drops of 0.09% normal saline were added to completely cover the corneal stromal lenticule. The absorbance of the corneal stromal lenticule was measured using a microcoder at wavelengths of 350, 450 and 600 nm, and each lens was measured three times. Measurements were completed within 2 h. A greater absorbance measured was associated with a worse light transmittance of the corneal stromal lenticule, while a smaller absorbance, was associated with a better light transmittance of the corneal stromal lenticule.

Statistical analysis. All data were analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp.). The normality of data distribution was assessed with the Shapiro-Wilk test. If a normal distribution and homogeneity of variance were met, an independent-samples t-test was used. If not consistent with a normal distribution and homogeneity of variance, the Mann-Whitney U-test was used. Nonparametric values were expressed as n (%) and compared using Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Basic information statistics of patients. Demographic data and clinical statistics of patients analyzed via optical microscopy revealed no significant differences in age, sex or refraction between experimental group 1 and control group 1 (Table I). For patients undergoing light transmittance measurements, no statistically significant differences were observed in age,

Table III. Comparison of absorbance [l/(g x cm)] between control group 2 and experimental group 2.

Wavelength, nm	Experimental group 2	Control group 2	t/Z-value	P-value
350	0.243±0.023	0.261±0.016	2.307	0.029
450[a]	0.095±0.01	0.105±0.008	-2.924	0.003
600	0.069±0.006	0.075±0.005	3.205	0.004

Values are expressed as the mean ± standard deviation. [a]The normal distribution and homogeneity of variance are not met.

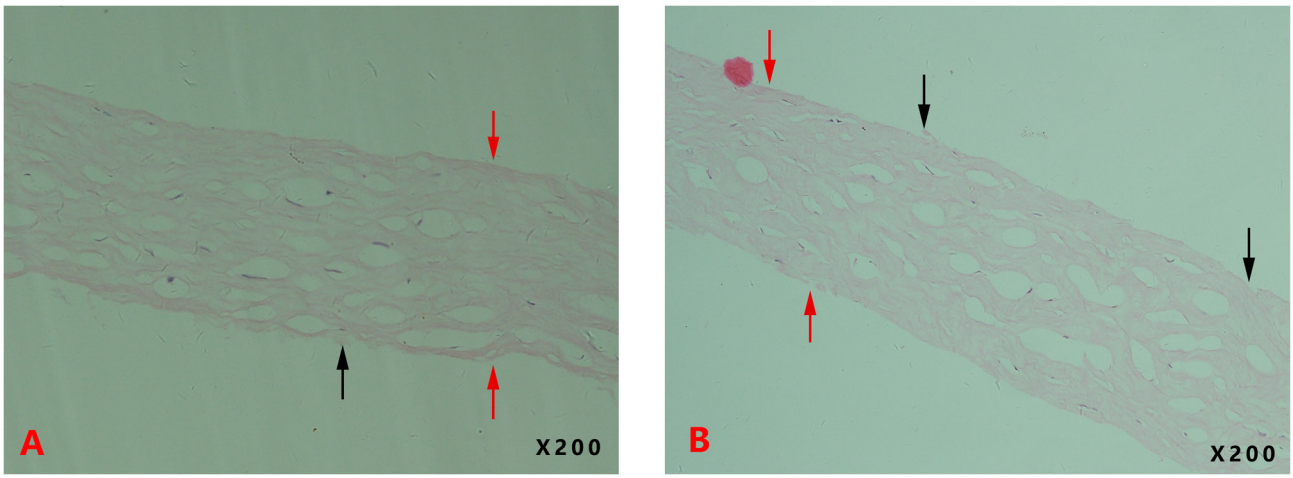

Figure 1. (A) Experimental group 1 of corneal stromal lenticules and (B) Control group 1 of corneal stromal lenticules observed under an optical microscope. Certain burrs and broken fibers (black arrows) were observed at the edge of the cross section. Part of the edge tissues were deeply stained (red arrows) and numerous bubbles of different sizes were present (magnification, x200).

sex, predicted thickness or actual measured thickness between experimental group 2 and control group 2, while there were statistically significant differences in diopters (Table II).

Optical microscopy results. The surface of the corneal stromal lenticules was observed to exhibit burrs, broken fibers and bubbles under the optical microscope. In experimental group 1, there was no visible edema in the central area of the cornea and the stromal layer fibers were arranged regularly (Fig. 1A). Control group 1 showed no significant edema in the central cornea and the stromal layer fibers were also arranged regularly. A comparison between experimental group 1 and control group 1 revealed no obvious abnormalities (Fig. 1B).

Microplate reader results. The difference in absorbance between experimental group 2 and control group 2 was statistically significant ($P<0.05$; Table III). The absorbance of the corneal stromal lenticule in control group 2 was greater than that in experimental group 2, indicating improved light transmittance of the reshaped corneal stromal lenticule.

Discussion

In corneal refractive surgery, femtoseconds achieve a high energy density within a small area due to the strong focusing ability of their ultrashort laser pulses. At high energy density, the electrons and atoms in matter are separated, producing light blasting inside the tissue, thus generating bubbles to separate the tissue (18). The corneal stromal lenticule is the anterior layer of the central corneal stromal layer. It is composed of orderly arranged collagen fibers. Its normal anatomical structure and physiological functions ensure corneal light transmittance and biomechanics, providing excellent plasticity. Numerous studies have shown that the smooth surface of the corneal stromal lenticule prepared using the femtosecond laser system exhibits predictable and high surface quality (19,20). Excimer laser can cut the corneal tissue with high precision, does not affect the tissue outside the cutting area and is safe (21); therefore, the excimer laser is used to reshape the corneal stromal lenticule. Currently, there is a lack of research on the corneal stromal lenticules after molecular shaping. In this experiment, an optical microscope was used to observe the HE-stained tissue sections and the absorbance of the microcode to explore whether the corneal stromal lenticule microstructure changed after excimer laser remodeling.

The surface of the lenticules was observed under the optical microscope to exhibit burrs, broken fibers and bubbles, in agreement with the results of previous studies (22-24). During SMILE surgery, the lenticule surface is the ablating focus of the femtosecond laser, and the photo-decomposing function of the femtosecond laser makes it possible to break the chemical bonds between molecules, resulting in a number of bubbles. Once the bubbles expand and merge to form a separate plane in the corneal tissue, the corneal stroma may be separated (18,25). Some of the bubbles may be partially absorbed by the surrounding corneal tissue or diffuse into

the air, while the remaining ones tend to become fixed in the tissue, as observed in the corneal stroma lens under optical microscopy. Under optical microscopy, the presence of edema of the corneal stromal lenticule and the fiber arrangement of the stroma were observed. Thermal damage to corneal tissue, if present, would be indicated by deep staining or tissue loss in HE-stained tissue sections. No significant differences in the degree of edema and stromal layer fiber arrangement were noted between the two groups. The reasons why there is no difference between the two groups are speculated to be the low excimer laser energy, emitted energy in the order of nanojoules and a very short time of action. Therefore, when the laser thermal effect and heat transfer focused on the tissue are small, the instantaneous thermal damage and mechanical damage to the corneal tissue can be minimized, so the excimer laser shaping minimally damages the corneal stromal lenticule.

Corneal light transmittance is a critical property of a healthy cornea, reflecting changes such as edema or inflammation, which may lead to opacity, increased corneal density and reduced corneal light transmittance. Therefore, corneal light transmittance serves as a valuable indicator of early corneal pathological changes and can be used to monitor the postoperative stromal response and keratinocyte activation. It is a reliable predictor of visual acuity and visual quality (26,27). In the present study, the absorbance of the corneal stromal lenticules was measured using a microcoder and the light transmittance of the stromal lenticules was evaluated. The results indicated that the lenticule light transmittance after excimer shaping was better under the condition that there was no statistically significant difference in lenticule thickness between the experimental group 2 and the control group 2 after excimer shaping. Before Agca *et al* (28) used live confocal microscopy and compared SMILE with FS-LASIK, it was found that corneal light transmittance after FS-LASIK was better than that after SMILE. On the one hand, this may be due to a smoothing effect of the excimer laser ablation that is implicit in the FS-LASIK technique. On the other hand, the less straightforward surgical dissection of the lenticule plane in SMILE through a 3-mm incision compared with the flap-lifting maneuver in FS-LASIK must not be overlooked as a contributing factor to the increased roughness of the lenticule bed. Lazaridis *et al* (29), Han *et al* (30) and Wei *et al* (31), using Scheimpflug corneal densitometry, compared the corneal light transmittance after SMILE and FS-LASIK and found a shorter postoperative corneal density and more transparent cornea after FS-LASIK. These findings are consistent with the present results, which showed improved lenticule light transmittance following excimer laser shaping. This discrepancy may result from the differing mechanisms of action between the two surgical methods. In SMILE, femtosecond lasers primarily use photo disruption to generate plasma, shock waves and cavitation bubbles. However, in FS-LASIK, in the process of excimer laser photoablation, when the excimer laser destroys the organic molecular bond in the corneal tissue, unlike the femtosecond laser, the 193 nm wavelength light pulse is absorbed by the corneal tissue, causing thermal and secondary radiation damage. The total energy applied to the corneal stroma during SMILE was higher than that applied to the corneal stroma during LASIK using the same platform.

In summary, to better use corneal stromal lenticule implantation as a treatment method for refractive and corneal diseases in the future, an excimer laser was selected in the present study to cut the corneal stromal lenticule. The convex lenticule of the corneal matrix can be shaped into a parallel or a concave lenticule. In this way, the thickness of the cornea in patients with keratoconus can be increased and curvature of the cornea can be avoided, which is more conducive to refractive reconstruction. The corneal matrix lenticule can also be shaped and reused according to the needs of individual patients, and instead of thinning and weakening, corneal laser surgery can be used instead to thicken and strengthen the tissue, providing a new treatment alternative for patients with thin corneal ametropia. In the present study, optical microscopy and light transmittance detection of the cut corneal stromal lenticule were performed. The degree of edema and the regularity of the matrix fiber arrangement did not change after excimer cutting. The absorbance decreased and the light transmittance improved. However, this study only examined the corneal stromal lenticule *in vitro* and did not explore a series of changes after implantation into the receptor pouch. Further studies are needed to determine whether the ideal refractive correction effect can be achieved after excimer shaping and whether corneal biomechanics can be effectively increased.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YL contributed to the conception and design of the study. ML, JH, JZ, LY, XL and XW acquired and interpreted study data. XW conducted statistical analysis and drafted the manuscript. YL and JH provided critical manuscript revisions, as well as administrative and technical support. YL supervised the study. All authors read and approved the final manuscript. YL and XW checked and confirmed the authenticity of the raw data.

Ethics approval and consent to participate

The study protocol conformed to the tenets of Declaration of Helsinki and was approved by the Human Ethics Committee of Jinan Mingshui Eye Hospital (Jinan, China; approval no. Ethics/2024/004). All of the adult study participants consented to the use of the corneal stromal lenticules obtained during their surgery for this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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