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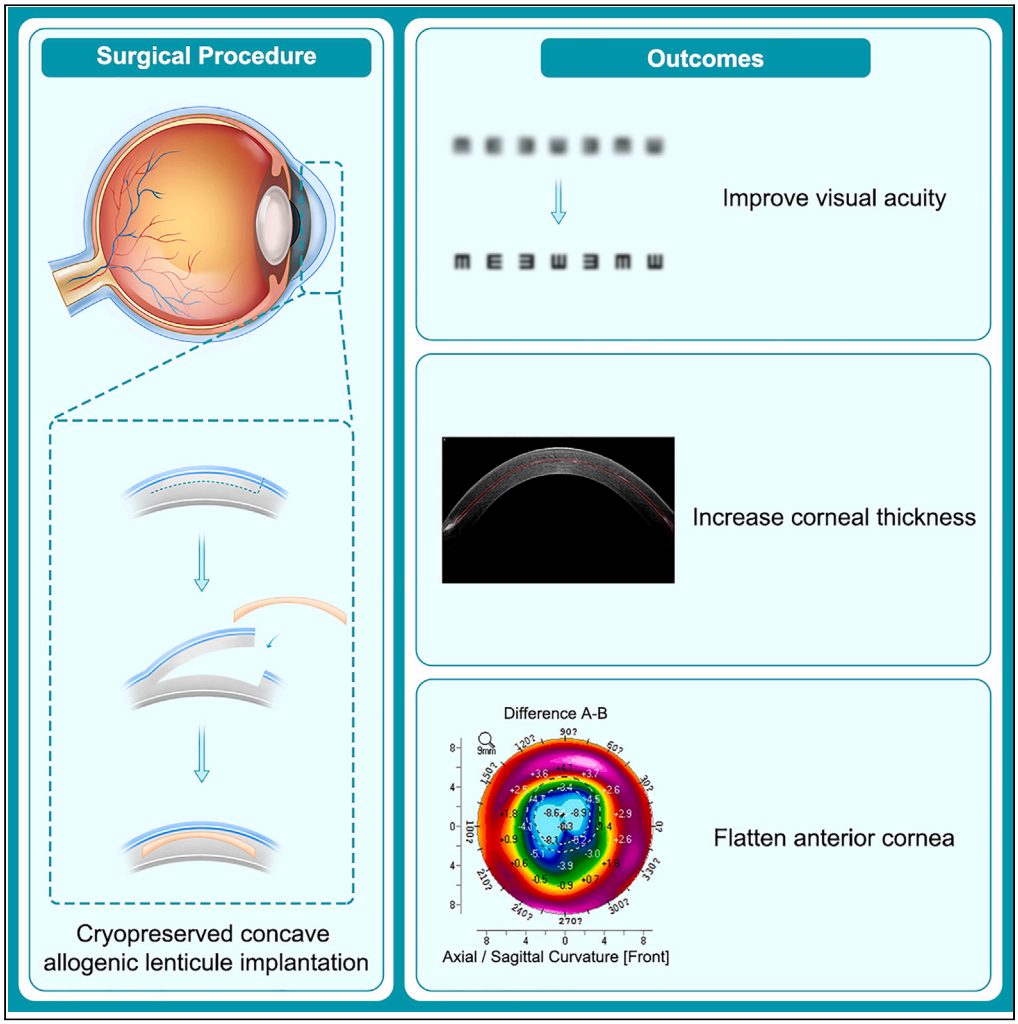

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Highlights

Cryopreserved concave allogenic lenticules are effective for treating post-LASIK ectasia

The lenticule can increase corneal thickness and decrease anterior K values

Long-term outcomes demonstrate improved visual acuity and refractive status

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Long-term results of allogenic corneal lenticule of hyperopic SMILE for post-LASIK ectasia

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SUMMARY

Post-laser-assisted *in situ* keratomileusis (LASIK) corneal ectasia is a severe complication of corneal refractive surgery, and cryopreserved lenticules from hyperopic small incision lenticule extraction (SMILE) may offer a promising treatment though their long-term safety and efficacy are still under investigation. In this prospective case series, six eyes from six patients with post-LASIK ectasia received lenticules (mean cryopreserved time: 63 days). The procedure involved lifting the corneal flap, implanting the lenticule, and repositioning the flap. Over a follow-up period of at least one year, uncorrected distance visual acuity (UDVA) improved from 1.52 ± 0.40 preoperatively to 0.74 ± 0.28 LogMAR. Two eyes gained one line of corrected distance visual acuity (CDVA), three gained two lines, and one gained over three lines. Spherical equivalents decreased from −14.67 ± 2.36 D to −8.75 ± 4.03 D ($p = 0.02$). Mean anterior K and total corneal refractive power decreased ($p < 0.05$). Thinnest corneal thickness increased from 359.2 ± 39.3 μm to 401.7 ± 53.4 μm ($p = 0.02$). These findings support the potential of cryopreserved lenticules for treating post-LASIK ectasia, though further refinement in refractive predictability is needed.

INTRODUCTION

Postoperative corneal ectasia, a rare but severe complication of corneal refractive surgery, was first reported by Seiler et al.[1] in 1998, and its incidence has been reported to range from 0.04% to 0.66%.[1] It is characterized by a progressive corneal steepening and marked visual impairment following refractive surgery. Although the risk factors and prognosis for corneal ectasia after corneal refractive surgeries have been extensively investigated,[2–4] the disease still occurs.[2,5]

Traditional treatments for corneal ectasia include a rigid gas permeable contact lens (RGP), corneal crosslinking (CXL), an intracorneal ring segment, and a corneal graft. As small incision lenticule extraction (SMILE) continues to advance, the millions of corneal lenticules extracted possess potential as a source for treating corneal diseases.[6,7] Corneal lenticule implantation has emerged as an alternative for the treatment of keratoconus[8–14] or post-LASIK ectasia.[15–18] While fresh lenticules from myopic SMILE are more commonly used for implantation due to their accessibility, the advancement of cryopreservation techniques shows promise for the widespread use of cryopreserved lenticules in the future. One significant advantage of cryopreserved lenticules is that they can be used without limitations on time or place. Moreover, lenticules from hyperopic SMILE are potentially more suitable for corneal ectasia compared to those from myopic SMILE, as they can theoretically decrease corneal power and enhance visual quality. However, clinical data supporting this assertion are currently lacking.[16] Therefore, obtaining long-term data on the implantation of cryopreserved concave corneal lenticule from hyperopic SMILE is crucial in investigating its safety, efficacy, and potential application in the treatment of corneal ectasia.

In a prior case report, we presented the 10-month outcomes after lenticule implantation from a hyperopic donor to treat post-LASIK ectasia.[15] Additionally, we conducted a 3-year study with *in vivo* confocal microscopy.[18] In this prospective pilot study, we now present results from a long-term follow-up involving the implantation of a cryopreserved concave lenticule.

RESULTS

The patient demographic and refractive outcomes are presented in Table 1. There were no intraoperative or postoperative complications such as corneal infection, lenticule dissolution, rejection, or haze throughout the follow-up.

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Table 1. Patient demographic and refractive data

Case No	Gender/ age	Pre-op UDVA	Pre-op refraction	Lenticule parameters	Central flap thickness, μm	Maximum lenticule thickness, μm	Programmed Lens Dia, mm	Cryopreservation duration, day	Last visit, year	Last visit UDVA	Last visit refraction	Change in CDVA, line
1[a]	M/29	0.01	−13.50/-6.00* 10 (0.3)	+5.75/-0.50*15	91	116	6.7	0	7	0.4	−4.00/-0.50* 165 (0.4)	1
2[a,b]	M/28	0.1	−11.25/-8.75* 140 (0.4)	+3.50/-0.50*5	200	71	7.3	50	2	0.15	−11.25/-6.00* 145 (0.6)	2
3[b]	M/42	0.01	−12.75/-4.50* 130 (0.3)	+8.00/-2.00*165	212	116	7.5	27	5	0.15	−4.50/-6.50* 125 (0.4)	1
4[a,b]	M/25	0.04	−10.00/-2.75* 180 (0.3)	+6.11/-1.95*145	156	119	8.2	21	3	0.1	−7.00/-5.50* 15 (0.5)	2
5[b]	F/50	0.04	−17.00/-0.50* 135 (0.3)	+4.75	348	76	7.3	42	1	0.1	−11.75/-0.50* 160 (0.5)	2
6[b]	M/24	0.05	−9.25/-6.00* 170 (0.1)	+5.25/-1.14*180	73	106	8.3	240	2	0.4	−4.50 (0.7)	8

[a]with documented ectasia progression before lenticule implantation.
[b]underwent corneal cross-linking (CXL) before lenticule implantation (cases 2–4) or simultaneously underwent lenticule implantation and CXL (cases 5 and 6).

Table 2. Changes in corneal topography and optical coherence tomography

	Anterior K values (mean, D)			Posterior K values (mean, D)			Back elevation, μm				TCRP, D			Thinnest corneal thickness, μm			Lenticule maximum thickness, μm		
Case no	Preop	last visit	Δdiff	Pre-op	last visit	Δdiff	Pre-op	Post-1 day	last visit	Δdiff	Pre-op	last visit	Δdiff	Pre-op	last visit	Δdiff	Pre-op	last visit	Δdiff
1[a]	50.1	45.0	−5.1	−8.9	−8.5	0.4	94	99	89	−5	51.4	43.9	−7.5	329	358	29	116	118	2
2[a,b]	53.9	53.6	−0.3	−8.4	−7.9	0.5	60	77	153	93	51.5	51.5	0	400	416	16	71	87	16
3[b]	46.7	42.5	−4.2	−8.5	−8.2	0.3	66	81	76	10	47.4	40.5	−6.9	353	424	71	116	121	5
4[a,b]	64.5	62.2	−2.3	−10.5	−11.0	−0.5	118	145	157	39	62.5	59.3	−3.2	301	332	31	119	120	1
5[b]	48.4	46.2	−2.2	−8.5	−8.6	−0.1	90	133	111	21	47.1	43.7	−3.4	398	484	86	76	93	17
6[b]	49.2	47.4	−1.8	−8.3	−8.6	−0.2	78	88	79	1	/	47.7	/	374	396	22	106	96	−10

Preop: preoperative; Δdiff: changes between last visit and preoperative value.

[a]with documented ectasia progression before lenticule implantation.

[b]underwent corneal cross-linking (CXL) before lenticule implantation (cases 2–5) or simultaneously underwent lenticule implantation and CXL (cases 6 and 7).

Visual outcomes

On the last visit, all treated eyes showed improvement in uncorrected distance visual acuity (UDVA), improving from preoperative values of 1.52 ± 0.40 (LogMAR) to postoperative values of 0.74 ± 0.28 (LogMAR). Two eyes (33%) gained one line of corrected distance visual acuity (CDVA), 3 eyes gained (50%) two lines of CDVA, and 1 eye (17%) gained three or more lines of CDVA. No eyes lost more than two lines of CDVA. The safety index (postop CDVA/preop CDVA) was 2.42 ± 2.25 (range, 1.33–7.0), and the efficacy index (postop UDVA/preop CDVA) was 1.15 ± 1.45 (range, 0.33–4.0). Spherical error decreased from preoperative values of −12.29 ± 2.81 D to postoperative values of −7.17 ± 3.52 D ($p = 0.02$) while cylindrical error decreased from preoperative values of −4.75 ± 2.87 D to postoperative values of −3.17 ± 3.13 D ($p = 0.35$). Spherical equivalent (SE) decreased from preoperative values of −14.67 ± 2.36 D to postoperative values of −8.75 ± 4.03 D ($p = 0.02$).

Concerning the patient satisfaction survey, all patients reported moderate improvement. All patients responded "yes" to the questionnaire item, "Would you recommend this treatment to others?". In addition, all patients reported moderate improvement in performing near work without spectacles.

Corneal topographic changes

Changes in anterior and posterior mean K and greatest posterior elevation are presented in Table 2. Five eyes (83.3%) showed a decrease in anterior K values greater than 1.0 D. No eyes showed an increase in anterior K values greater than 1.0 D.

Figures 1A and 1B shows the time-dependent changes in mean anterior K and posterior K values. Mean anterior K values changed from preoperative values of 52.13 ± 6.52 D to postoperative values of 49.48 ± 7.25 D ($p = 0.01$). Mean posterior K values were −8.85 ± 0.83 D preoperatively and −8.80 ± 1.11 D postoperatively ($p = 0.78$).

Figure 1C shows the time-dependent changes in mean total corneal refractive power (TCRP). Mean TCRP decreased from 51.98 ± 6.25 D preoperatively to 47.78 ± 7.60 D at the last visit ($p = 0.04$).

The thinnest corneal thicknesses at different time points are presented in Figure 1D. They increased significantly from preoperative values of 359.2 ± 39.3 μm to postoperative values of 401.7 ± 53.4 μm at the most recent visit ($p = 0.02$).

We further investigated the relationship between the changes in mean anterior K (ΔK) and SE of implanted lenticules. The regression equation was as follows: ΔK = -1.17*SE (lenticule) +3.28 ($R^2 = 0.69$, $p = 0.04$).

Corneal epithelium changes on optical coherence tomography

Central, maximum, and minimum corneal epithelium thicknesses are presented in Figure 2. There were no statistically significant differences in either central corneal epithelium thickness, maximum corneal thickness, or minimum corneal epithelium thickness between preoperative values and those at the last visit (all $p > 0.05$).

Lenticular maximum thicknesses measured by optical coherence tomography (OCT) are presented in Table 2. The maximum lenticule thicknesses in all eyes on the most recent visit were similar to pre-implantation values.

The OCT images (Figure 3) show a clear lenticule at the periphery of all eyes on the most recent visit, but the lenticule demarcation lines were difficult to identify in the central cornea. The lenticule density was similar to that of the surrounding corneal stroma in all eyes.

Fibrillar ultrastructure

Transmission electron microscopy (TEM) demonstrated that the collagen fibrils of the lenticules remained regular after 1, 2, and 4 weeks of cryopreservation (Figure S1). There was no significant difference in the density and diameter of collagen fibrils (all $p > 0.05$).

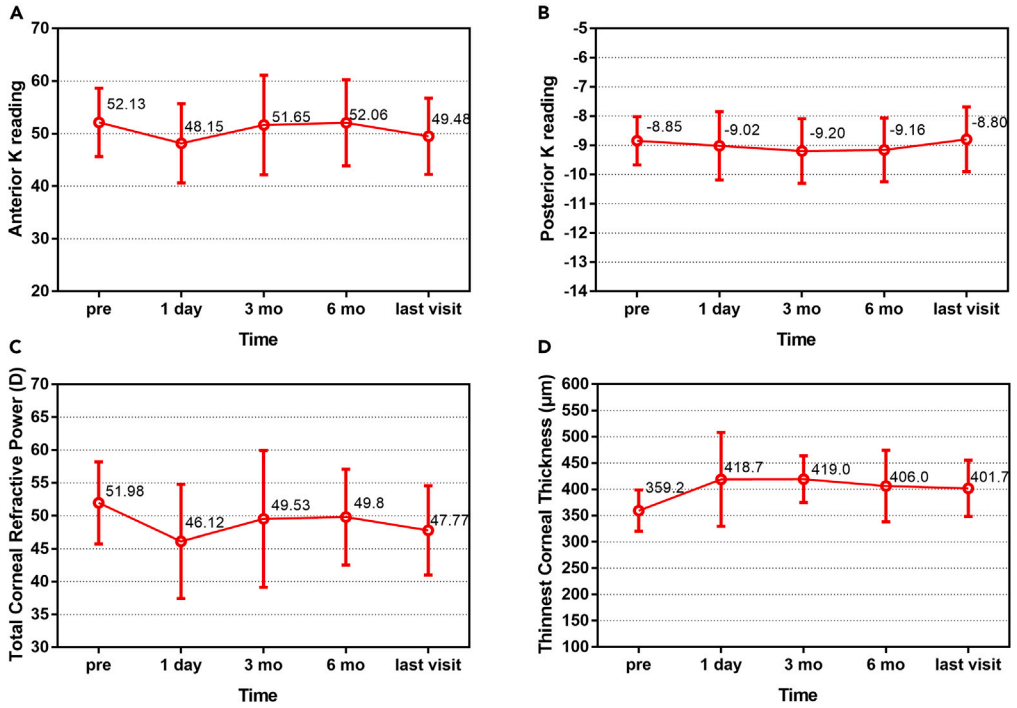

Figure 1. Time-dependent changes in corneal tomography

(A) Anterior K.

(B) Posterior K.

(C) Total corneal refractive power.

(D) Thinnest corneal thickness.

Data are represented as mean ± SD.

DISCUSSION

Stromal lenticules, which are extracted through SMILE, have been utilized for diverse applications. Prior research has revealed that implanting autologous lenticules in rabbit eyes[19] and allogeneic lenticules in monkey eyes[20] increased corneal stromal thickness and modified corneal refractive power. Human lenticule xenograft implantation in rabbits was also found to be safe.[21,22] Our findings suggest that intrastromal lenticule implantation may offer a promising alternative remedy for addressing corneal disorders and refractive errors.

Our results indicated that cryopreserved autologous or allogenic intrastromal lenticule implantation may serve as a potential alternative treatment for refractive errors and corneal diseases. The application of lenticule in presbyopia,[23–25] hyperopia,[26–28] and corneal perforation[29] was reported in human eyes. Since fresh lenticules are not always accessible, it is crucial to maintain the integrity of the lenticule after long-term storage and to ensure the safety and efficacy of implantation with preserved lenticules. Cryopreservation allows for extended storage, providing resources for future medical use or research, and reduces the risk of disease transmission. It also helps maintain structural integrity and consistent tissue quality, despite the technical complexity and cost. In the current study, lenticules remain regular ultrastructure after cryopreservation for up to 1 month and no intraoperative or postoperative complication was detected for long term after cryopreserved lenticule implantation, indicating the safety of the procedure. In accordance with our results, Ganesh et al.[30] used cryopreserved lenticules (mean duration of cryopreservation = 96 days) from myopic SMILE to correct 8 hyperopic eyes, with no eyes showing any evidence of rejection throughout a mean follow-up period of 155 days. Although risks such as epithelial ingrowth may occur, we have implemented careful monitoring and preventive measures, including drying the stromal bed, flattening the lenticule, and ensuring proper flap alignment and closure. Further investigation is advised to explore the outcomes of lenticule implantation utilizing different cryopreservation techniques.

In the study, we also demonstrated the efficacy of cryopreserved lenticule implantation in post-LASIK ectasia. The application of corneal lenticules in keratoconus[8–14] or post-LASIK ectasia[15–18] with convex or concave lenticules has been reported. In 2015, Ganesh et al.[9] reported a 6-month result of convex intrastromal lenticule implantation combined with accelerated transepithelial CXL (ATE-CXL) in 6 eyes with progressive keratoconus. The UDVA, CDVA, and manifest refraction improved after the surgery. In 2017, Jiang et al.[17] implanted myopic SMILE lenticules into 3 eyes with post-LASIK ectasia. Although corneal thickness increased, the central cornea was steepened, worsening patients' manifest refraction. In 2018, Mastropasqua et al.[8] reported the 6-month results of negative meniscus-shaped stromal lenticule addition keratoplasty in 10 eyes with stage III and IV stable keratoconus and concluded that negative meniscus-shaped lenticule addition flattened the cone and increased corneal thickness. Recently, Doroodgar et al.[11] customized lenticules with a necklace or necklace-with-ring based on the corneal thickness and topographic shape to treat advanced keratoconus. Here, we applied the cryopreserved hyperopic lenticules for

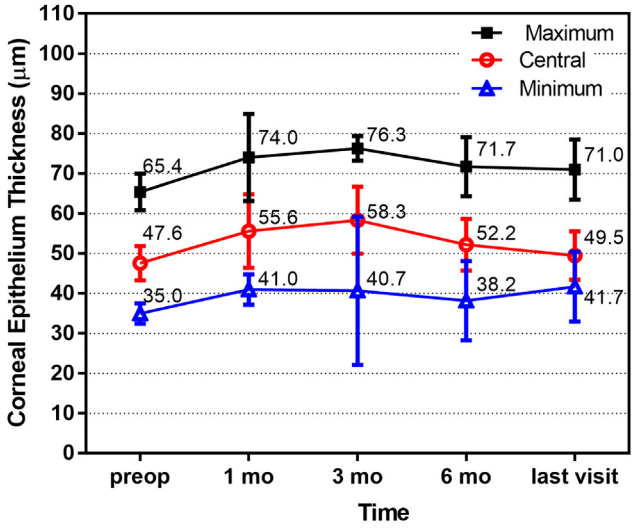

Figure 2. Time-dependent changes in central, maximum, and minimum epithelium thicknesses. Data are represented as mean ± SD.

post-LASIK ectasia. As expected, the implanted lenticules had refractive effects, and significant differences were found between preoperative and postoperative mean anterior K readings on the recent visit. However, one progressive eye (case 2) did not show an obvious decrease in anterior K values (Δdiff = −0.3, Table 2) but showed a significant increase in corneal back elevation as well as a significant decrease in thinnest corneal thickness throughout a 2-year postoperative period. This may suggest that this technique may not be favorable in aggressive keratoconus. Similar to our results, Ganesh et al.[9] found that, in patients with progressive keratoconus, eyes with advanced keratoconus did not show a reduction in mean keratometry following femtosecond intrastromal lenticular implantation combined with ATE-CXL.

In the present study, we also attempted to investigate the relationship between changes in anterior K values (ΔK) and SE of implanted cryopreserved lenticules. A regression equation ($R^2 = 0.69$) was obtained, indicating that the addition of tissue can flatten the anterior cornea. Because of the small sample size in the present study, other important factors were not taken into account when generating the regression equation. Many factors that we considered have been associated with changes in corneal keratometry, including but not limited to lenticule diameter, lenticule thickness, flap thickness, the corneal thickness of recipient cornea, and anterior corneal curvature. Future studies on predictive formulas are therefore recommended to improve the predictability of the procedure.

In conclusion, the present study findings suggest that implantation of a concave cryopreserved allogenic lenticule may be an alternative in the treatment of post-LASIK ectasia, although this prediction should be further refined.

Limitations of the study

A limitation of this study is the relatively small sample size, despite a statistical power of 0.99. However, the reported incidence of ectasia after LASIK ranges from 0.04%[4] to 0.6%,[31] and since cryopreserved allogeneic lenticule implantation is a new technique for treating corneal ectasia,

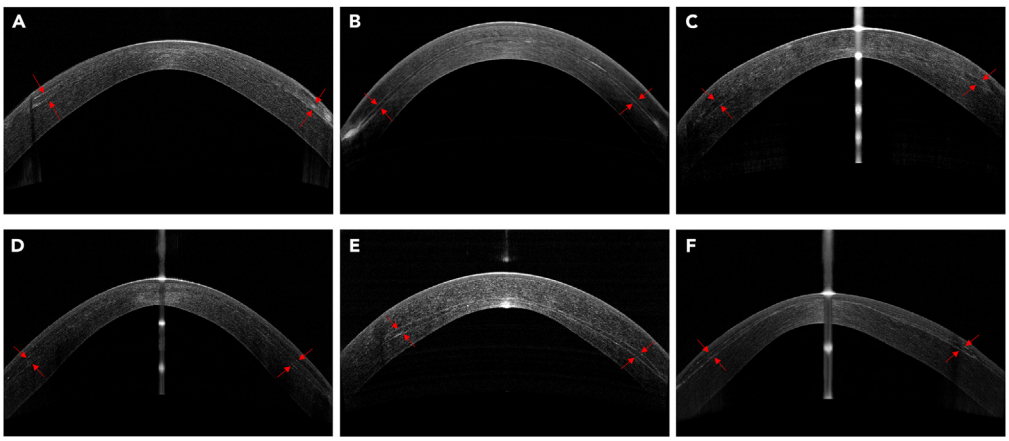

Figure 3. RTVue optical coherence tomography (Optovue,Inc., Fremont, CA) 8-mm diameter horizontal scan on the last visits
(A–F) (A) Case 1, year 7; (B) Case 2, year 2; (C) Case 3, year 2; (D) Case 4, year 3; (E) Case 5, year 1; (F) Case 6, year 2. Red arrows indicate lenticule demarcation lines.

there are even fewer patients who have undergone this procedure, making it challenging to recruit a larger cohort. Further prospective studies with larger sample sizes are needed to provide more robust evidence.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Xingtao Zhou (doctzhouxingtao@163.com).

Materials availability

The data that support these findings of the study are available upon request from the corresponding authors.

Data and code availability

- All data reported in this paper, including parameters of lenticules and patients, will be shared by the lead contact upon request.
- The paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript. Research concept and design (X.T.Z.); data collection and performance of the research (all authors); analysis and interpretation of data (M.Y.L., R.Y.W., and B.Q.); writing of the manuscript (M.Y.L. and R.Y.W.); critical revision of the manuscript (X.T.Z., Q.B., and J.C.); supervision (X.T.Z.).

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
SMILE lenticules of patients	Eye and ENT Hospital, Fudan University, Shanghai, China	Not applicable
Software and algorithms		
GraphPad Prism	GraphPad Software	https://www.graphpad.com, RRID:SCR_002798
R Project for Statistical Computing, version 4.0.5	R Foundation for Statistical Computing	http://cran.rproject.org, RRID:SCR_ 001905

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Six patients diagnosed with post-LASIK ectasia were enrolled between 2015 and 2018 at the Department of Ophthalmology of Fudan University Eye & ENT Hospital. Patient demographics were listed in Table 1. All patients were Chinese, with 5 males and 1 female. The mean age was 39.6±10.5 years.

The study complied with the Ethics Committee of the Fudan University Eye and ENT Hospital Review Board approved the study (No.2016039). Every patient approved an informed consent.

METHOD DETAILS

Patients

This prospective case series included six patients diagnosed with post-LASIK ectasia between 2015 and 2018 at the Department of Ophthalmology of Fudan University Eye & ENT Hospital. All subjects received a full preoperative evaluation, consisting of uncorrected and corrected distance visual acuity (UDVA and CDVA), slit lamp examination, manifest refraction, corneal topography, and OCT assessments.

The inclusion criteria for patients were as follows: (1) post-LASIK ectasia with or without documented evidence of progression. The criteria for progression included an increase in K_{max} of 1 diopter (D) within a year, a mean central K reading change > 1.5 D, or a mean central corneal thickness decrease > 5% per three consecutive topographies in the previous 6 months; (2) inability to tolerate RGP lens; (3) transparent cornea; (4) normal endothelial cell density (ECD); (5) age equal to or greater than 18 years old.

Patients with any of the following conditions were excluded: (1) a history of herpetic keratitis or concurrent corneal infections; (2) severe dry eye; (3) other eye diseases such as glaucoma, cataract, or vitreoretinal disorders; (4) concomitant autoimmune diseases; (5) pregnancy or lactation.

Before the surgery, all subjects provided written informed consent, and the risks, benefits, and alternatives of the procedure were fully explained to them. The Ethics Committee of the Fudan University Eye and ENT Hospital Review Board approved the study (No.2016039).

Five out of the six eyes had a history of accelerated (45 mW/cm^2) transepithelial CXL before lenticule implantation (cases 2-4) or had undergone both transepithelial CXL and lenticule implantation simultaneously (cases 5 and 6).

Surgical procedures

All surgical procedures were performed by a single experienced surgeon (XZ). Before performing the SMILE procedure on the hyperopic donor eyes, blood samples were collected and evaluated for several conditions, such as blood glucose levels, HBV, HCV, HIV, *Treponema pallidum* particle agglutination, and rapid plasma reagin. The hyperopic donor patient was scheduled for a standard hyperopic SMILE procedure using a VisuMax femtosecond laser (Carl Zeiss Meditec, Jena, Germany).[32] The repetition rate was set to 500 kHz, the pulse energy to 130 nJ. The programmed lenticule diameter ranged from 6.7 to 8.3 mm and the optical zone diameter of lenticule ranged from 5.3 to 6.5 mm. The intended lenticule thickness was 71 to 119 μm on the periphery and 20 to 25 μm in the center. The side cut was made at 90°, and the lenticule was then separated and extracted through the incision. To distinguish the front and back sides of the lenticule and to ensure accurate future astigmatism correction through its implantation, the edge of the lenticule was stained with crystal violet at the 10 o'clock position (small dot) and the 12 o'clock position (large dot) after complete extraction from the incision. The extracted lenticule was then washed and transferred into a 2 ml sterile freezing tube using smooth forceps. The tube was placed into a refrigerator at -80°C without preservation media.

For the recipient eyes, the goal of lenticule implantation was to improve refractive status. To select the appropriate lenticule, those with equivalent spherical refraction to that of the recipient eye were chosen. Following the completion of standard sterile draping and insertion of the eye speculum, the edge of the microkeratome flap was opened using a Sinskey hook and the flap was then lifted. The cryopreserved corneal lenticule was thawed to room temperature by immersion in phosphate-buffered saline (PBS). Subsequently, it carefully placed onto the exposed stromal bed, with the steepest part of the astigmatic axis of the lenticule aligned to the flattest astigmatic axis of the

recipient eye, and spread until flat. Our previous study has described the detailed rotation method, which was used during this process.[26] The PBS solution was examined for microbiological testing to evaluate the risk of bacterial and fungal infections. Finally, the flap was carefully repositioned.

For cases 2-4, ATE-CXL was performed before lenticule implantation.[33] Briefly, a trephine was placed on the central cornea and ParaCel Solution (Medio-Haus-Medizinprodukte GmbH, Kiel, Germany) was applied for 240 seconds, followed by VibeX Xtra (Avedro, Waltham, MA, USA, containing 0.25% riboflavin-5-phosphate) for 6 minutes. After removing the trephine, ATE-CXL was carried out with the KXL system (Avedro) using 45-mW/cm^2 pulsed irradiation for 320 seconds (7.2 J/cm^2). Balanced salt solution was used every 40 seconds to prevent dehydration.

For cases 5 and 6, after flap lifting, the lenticule extracted from the SMILE donor was briefly immersed in VibeX Xtra for 2 seconds. It was then placed onto the exposed stromal bed as described above, and flatten out. The flap was then placed back into position. The KXL system was used to execute ATE-CXL, whereby pulsed illumination with an energy of 45 mW/cm^2 was delivered for 1-second on and 1-second off intervals. The procedure delivered a total of 7.2 J/cm^2 with a duration of 320 seconds.

Finally, a bandage contact lens (Acuvue Oasys; Johnson & Johnson, Jacksonville, FL, USA) applied after surgery until the following day. Postoperative topical medication consisted of 0.5% levofloxacin, dexamethasone, 0.1% fluorometholone, and a tear supplement.

Measurements

All subjects underwent the following examinations before and after surgery. Patients had regular follow-ups for 1 day, 1 month, 3 months, 6 months, 1 year, and then annually.

(1) Slit-lamp examination.
(2) Intraocular pressure and ECD.
(3) UDVA and CDVA measured by standard logarithmic visual acuity charts, manifest refraction.
(4) Corneal topography by Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany). Curvature changes were measured with the average sagittal keratometer readings on the 15° ring around the corneal apex for both the anterior and posterior corneal surfaces. Corneal power was obtained from the total corneal refractive power (TCRP) map calculated by the PENTACAM software based on Snell's law of refraction with real refractive indices (1 for air, 1.336 for aqueous humor, and 1.376 for cornea). Our analysis of TRCP covered a 3 mm range from the apex.
(5) Fourier-domain OCT (RTVue OCT; Optovue, Inc., Fremont, CA) augmented with the adaptor lens (CAM-L mode). Corneal pachymetry and epithelium maps were acquired. Lenticule dimensions were measured with the caliper tool on horizontal and vertical scans. Corneal tomography was acquired in a single 8-mm scan length mode on the horizontal and vertical meridians. Maximum lenticule thickness was measured by averaging the four values of the scans.[6]
(6) Patient satisfaction was evaluated with an established questionnaire on the last visit.[34]

TEM

Fresh or preserved corneal stromal lenticules were cut into small segments (approximately 1 mm^3) and fixed in 2.5% glutaraldehyde at 4°C overnight. The tissue segments were washed with PBS three times, then fixed with 1% osmium acid for 2 hours, followed by three PBS washes. The samples were dehydrated in increasing concentrations of ethanol (30%, 50%, 70%, 80%, 85%, 90%, 100%) and infiltrated with a mixture of epoxy resin and acetone (1:2, 1:1, and pure epoxy resin) at 37°C. The samples were then embedded in epoxy resin and polymerized in a 60°C oven for 48 hours. Ultrathin sections (80 to 100nm) were cut and double stained with 2% uranyl acetate and lead citrate. The collagen fibrils were visualized using TEM.

QUANTIFICATION AND STATISTICAL ANALYSIS

All statistical analyses were performed using R version 4.0.5 (R Project for Statistical Computing, http://cran.rproject.org/). Data were reported as means ± standard deviation (SD). A general linear regression model was used to investigate the relationship between changes in anterior mean keratometric readings (differences between preoperative values and values from the last visit) (ΔK) and lenticule spherical equivalent refractive power. The difference between baseline values and those on the last visit was evaluated with a paired *t*-test. A $P < 0.05$ was considered statistically significant.

We calculated the sample size with a significance level of 0.05 and power of 0.9, based on the effect size (Cohen's d) derived from Ganesh et al.'s prior study.[9] A sample size of 4 was calculated to be sufficient.

ADDITIONAL RESOURCES

No additional resources.