Long-Term Results of Sterile Corneal Allograft Ring Segments Implantation in Keratoconus Treatment

Fatma Feyza Nur Keskin Perk, MD, Cafer Tanriverdi, MD,† Zeki Yigit Karaca, MD,† Khoa D. Tran, PhD,‡ and Aylin Kilic, MD§*

Purpose: To evaluate the efficacy and safety of sterile corneal allograft ring segments implantation for the treatment of keratoconus by analyzing long-term visual, refractive, and tomographic clinical outcomes.

Methods: This prospective study included 62 eyes of 49 patients with keratoconus who underwent corneal allograft ring segments implantation at Istanbul Medipol University Faculty of Medicine between February 2020 and August 2022. Surgical outcomes using the Istanbul nomogram were evaluated in patients preoperatively and postoperatively at 1 month, 6 months, 1 year, and 3 years. Outcomes measured were uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), spherical equivalent (SE), spherical refraction (SR), cylindrical refraction (CR), topographic keratometric values, and corneal thickness at the thinnest point.

Results: Preoperative mean UDVA and CDVA (LogMAR) were 0.96 ± 0.50 and 0.72 ± 0.47, respectively, and increased to 0.41 ± 0.34 and 0.22 ± 0.19 at the last visit ($P < 0.001$). There was a significant decrease in SE, SR, and keratometric values postoperatively ($P < 0.001$). There was no difference in CR and thinnest corneal thickness values ($P = 0.333$ and 0.154, respectively). The stromal and epithelial thicknesses measured by anterior segment optical coherence tomography were stabilized at 6 months and 1 year, respectively. No major complications or side effects were observed intraoperatively or postoperatively.

Conclusions: This study demonstrated that sterile corneal allograft ring segments implantation is a safe and feasible treatment for keratoconus, yielding notable long-term visual outcomes with minimal implant-related complications.

Key Words: keratoconus, corneal allograft ring, CAIRS, sterile allograft ring segments

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In the visual rehabilitation of keratoconus, intracorneal ring segments (ICRSs) have been used for many years.[1,2] All existing ICRSs are made of synthetic materials.[3,4] Although successful results have been achieved, there have been reports of long-term complications such as segment migration, recurrent corneal epithelial defects, vascularization and infectious keratitis, broken ring segments, corneal melting, ring extrusion, and perforation.[5–9] Allograft or xenograft rings can be used as an alternative to synthetic materials to avoid potential complications. Allogeneic intracorneal ring segments are currently used to treat keratoconus,[10–15] and the more biologically compatible tissue-derived products reduce complications caused by synthetic materials of ICRSs.

The corneal allogeneic intrastromal ring segments (CAIRS) technique, which was first described by Jacob et al,[12] involves the surgeon cutting the donor corneal tissue into ring segments in the operating room and placing them in the intrastromal tunnel. This study includes patients with progressive keratoconus between Amsler–Krumeich stages 1 and 4 with sufficient minimum corneal thickness to allow crosslinking treatment. The clinical outcomes from such studies indicated good visual outcomes for patients during 12 to 18 months of follow-up, suggesting that intervention using donor corneal tissues was tolerated in the short term.[12,16] However, complications with synthetic materials used in ICRS can occur at both early and later postoperative time points, suggesting that it may be important to examine more long-term clinical outcomes for tissue-based products as well.

A newer iteration of the CAIRS technique includes the use of sterile allograft rings, KeraNatural (VisionGift, Portland, OR), where corneal tissue from human donors is precut to shape, sterilized by electron beam irradiation, and prepared so that the tissues can be stored at room temperature for up to 2 years, ready for surgical use. Each package contains full-thickness corneal stromal tissue (approximately 500 μm) cut into 1-mm wide full or half rings.[17] The advantages of using sterile, ready-to-use grafts include increased graft availability for planned procedures, reduced procedural complexity in the operating room, and increased patient safety benefits as a result of tissue sterilization. The use of sterile tissues for

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From the *Department of Ophthalmology, Diyadin Government Hospital Istanbul, Ağrõ, Turkey; †Department of Ophthalmology, Istanbul Medipol University, Faculty of Medicine, Istanbul, Turkey; ‡VisionGift, Portland, OR; and §Swiss Vision Clinic, Istanbul, Turkey.

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Correspondence: Fatma Feyza Nur Keskin Perk, MD, Nişanca District, Abdurrahman Şerefbey St, Akarçeşme Site 18/3 Flat 13, 34050, Eyüpsultan, İstanbul, Türkiye (e-mail: feyzakeskinn1@gmail.com).

ophthalmic procedures have been previously described for other indications including corneal patch grafts, corneal lamellar grafts, and glaucoma drainage device covers with positive long-term clinical outcome results.[18–20] However, long-term surgical outcomes of the use of sterile allograft rings and segments for the treatment of keratoconus have not been described.

Previously, we have reported positive short-term results of the use of sterile ring segments for the treatment of keratoconus.[17] In this study, we assess the effectiveness, stability, and safety of sterile allograft rings in patients with keratoconus for up to 3 years after surgical intervention.

MATERIALS AND METHODS

This prospective study involved 62 eyes of 49 patients with keratoconus who received sterile corneal allograft ring implants (KeraNatural; VisionGift) at Istanbul Medipol University Faculty of Medicine between February 2020 and August 2022. Before the operation, all patients were provided with comprehensive information about the keratoconus disease and signed a preoperative informed consent form. Following the approval of the Ethics Committee of Istanbul Medipol University Research Evaluation Commission (decision number 346, dated April 13, 2023), the study was initiated in accordance with the International Declaration of Helsinki.

Patient Criteria

The study included patients with stage 1, 2, and 3 keratoconus aged 18 years and older with contact lens intolerance, corrected visual acuity less than 0.5 Snellen, and a clear cornea. The operation required a corneal thickness of 350 μm or more at the implantation site and the absence of additional ocular diseases other than keratoconus. Exclusion criteria for the study included patients with central or paracentral corneal scarring, a history of herpetic keratitis, severe dry eye, previous corneal or intraocular surgery, and autoimmune or connective tissue disease and pregnant or lactating patients. Furthermore, patients who had previously undergone cross-linking treatment or who had a double-ring segment implanted because of a central cone were excluded from the study.

Surgical Technique

All surgeries were performed by the same surgeon (A.K.) under topical anesthesia (0.5% proparacaine; Alcaine, Alcon Laboratories, Inc., Fort Worth, TX). The visual axis was marked with an ink-stained Sinskey under a WaveLight EX500 biomicroscope (Alcon Laboratories, Inc.) with the first Purkinje reflex as a reference. Following centralization based on the reference point, docking was performed with an iFS 150 kH Intralase femtosecond laser platform (Abbott Medical Optics Inc, CA) and an intrastromal tunnel was created. The parameters of the Istanbul nomogram defined by our clinic were used to create the intrastromal circular tunnel (Table 1). The tunnel was dissected through the incision site with a blunt-tipped semicircular dissector. Allograft rings (KeraNatural; VisionGift) were cut to an arc length of approximately 160 degrees using surgical scissors. The rings were then inserted into the tunnel using a modified forceps and placed according to the cone localization. Suturing was not required in any of the cases. Topical moxifloxacin 0.5% (Vigamox, Alcon Laboratories) and dexamethasone 0.1% (Dexasine SE, Liba, Istanbul, Turkey) eye drops were administered, ending the surgery.

Postoperative topical moxifloxacin 0.5% (Vigamox, Alcon Laboratories) was prescribed 4 times daily for 1 week, and nonpreservative artificial tear drops were given 5 times daily for 8 weeks. Topical dexamethasone 0.1% (Maxidex, Alcon Laboratories, Belgium) eye drops were given 5 times daily for 4 weeks and tapered for the following 4 weeks. Dexamethasone 0.1% drops were used for a total of 2 months.

Clinical Examination

Visual acuity, detailed biomicroscopic examination (SL D7, Topcon Med. Sys, Japan), and fundus examinations were performed on preoperative and postoperative first day and in the postoperative first week, first month, third month, sixth month, first year, and third year. Visual acuities were measured as Snellen and then converted to LogMAR for statistical analysis. In addition, autorefractometer (Topcon KR8900, Topcon Med. Sys), tonometry, and Scheimpflug corneal tomography (Pentacam HR, Oculus Optikgeräte, Wetzlar, Germany) measurements were performed at each visit. Anterior segment optical coherence tomography (OCT) (Heidelberg Engineering, Germany) was used to assess the status of the rings and cornea at each visit from the first postoperative day. Corneal tomography was used to evaluate the flat keratometry (K1), steep keratometry (K2), mean keratometry (Kmean), maximum keratometry (Kmax), and thickness of the thinnest point of the cornea (pachymetry). Using anterior segment OCT, stromal thickness above the graft (upper stromal thickness [UST]), graft thickness (GT),

TABLE 1. İstanbul Nomogram Parameters

Istanbul Protocol Nomogram
Allograft ring
Approximately 160-degree arc
Full-thickness corneal tissue (around 500 μm)
1-mm wide
Channel diameters and depth
Inner diameter: 4 mm
Outer diameter: 7.5 mm
Depth: 200–250 μm (approximately 35–40% depth)
Incision cut energy: 1.3 μj
Ring energy: 1.3 μj
Incision
Cut length: 1.5 mm
Localization: perpendicular to the implantation site
Implantation site: tomographic cone localization
Number of ring segments
Asymmetric cone: single-segment implantation
Central cone: symmetric double-segment implantation

stromal thickness below the graft (lower stromal thickness [LST]), tunnel depth (TD), epithelial thickness above the graft (Gep), and epithelial thickness peripheral to the graft were measured (Pep) (Fig. 1). All measurements were analyzed throughout the entire 3-year follow-up period, and the process of corneal stabilization was investigated.

Statistical Analysis

Data analysis was conducted using SPSS version 20.0 (IBM) software. The suitability of the data for normal distribution was examined using the Shapiro–Wilk test. The Friedman test was used to compare nonnormally distributed data. The Wilcoxon test with Bonferroni correction was used to determine differences between repeated measurements. Analysis of variance (repeated ANOVA) was used to compare normally distributed data. A *t* test with Bonferroni correction was used to compare the repeated measurements of these groups. Pairwise group comparisons considered $P < 0.05$ as significant while repeated measurements requiring Bonferroni correction considered $P < 0.01$ as significant.

RESULTS

This prospective study included 62 eyes of 49 patients who underwent corneal allograft ring implantation. The patients were regularly followed up for a minimum of 6 and a maximum of 36 months, with a mean follow-up period of 23.23 ± 13.46 months. Of the 62 eyes that were monitored, 32 (52%) had a follow-up of 36 months, 50 (81%) had a follow-up of 12 months, and all 62 (100%) had a follow-up of 6 months. The patients consisted of 33 men (67%) and 16 women (33%), with a mean age of 29.04 ± 8.13 years (ranging from 18 to 52). There were a total of 29 eyes with stage 1, 17 with stage 2, and 16 with stage 3 keratoconus, classified using the Amsler–Krumeich scale.

Visual Acuity and Refraction

The uncorrected distance visual acuity (UDVA, LogMAR) was 0.96 ± 0.50 before allograft ring implantation. At 1 month, it improved to 0.40 ± 0.34, and at 6 months, 1 year, and 3 years after implantation, it remained stable at 0.44 ± 0.34, 0.44 ± 0.35, and 0.41 ± 0.34, respectively. The increase in UDVA was significant throughout the follow-up period compared with the preoperative period ($P < 0.01$); no significant difference in UDVA was observed at any visit after the first month ($P > 0.01$). Comparing the preoperative and final visit, UDVA increased by 3 or more lines in 39 eyes (63%), 2 lines in 11 eyes (18%), and 1 line in 6 eyes (10%). UDVA did not change in 6 eyes (10%) while no patient (0%) had a decrease in UDVA. There were no patients with preoperative visual acuity equal to or better than 20/40. In the first postoperative year, 60% of the eyes had UDVA ≥20/40, 20% had ≥20/25, and 2% had ≥20/20. At the third postoperative year, 47% of eyes exhibited an UDVA of at least 20/40, 25% had UDVA of at least 20/25, and 6% had UDVA of at least 20/20. There was a significant increase in corrected distance visual acuity (CDVA) at all visits compared with the preoperative period ($P < 0.01$), but there was no difference between the other visits ($P > 0.01$). Comparing the preoperative and final visit, CDVA increased by 3 or more lines in 45 eyes (73%), 2 lines in 8 eyes (13%), and 1 line in 4 eyes (6%). There were 5 eyes (8%) with unchanged CDVA at the last follow-up visit and no cases with a decrease in CDVA. At the one-year postoperative follow-up, the CDVA was ≥20/40 in 82% of eyes, ≥20/25 in 38% of eyes, and ≥20/20 in 12% of eyes. At the end of the third year, the CDVA was ≥20/40 in 81% of eyes, ≥20/25 in 38% of eyes, and ≥20/20 in 16% of eyes. The mean refractive spherical equivalent (SE) was −7.54 ± 5.54 diopters (D) preoperatively, −2.92 ± 5.27 D at month 1, −2.66 ± 4.74 D at month 6, −2.31 ± 4.89 D at year 1, and −2.10 ± 4.90 D at year 3 postoperatively. There was a significant decrease in the mean refractive SE in all postoperative control eyes compared with the preoperative period ($P < 0.01$) while no difference was found in the mean refractive SE after the first month ($P > 0.01$). A total of 57% of eyes exhibited cylindrical refraction (CR) of ≥4D preoperatively while 47% of eyes demonstrated this at 3 years postoperatively. The preoperative CR was ≥6D in 22% of eyes and 21% of eyes 3 years after surgery.

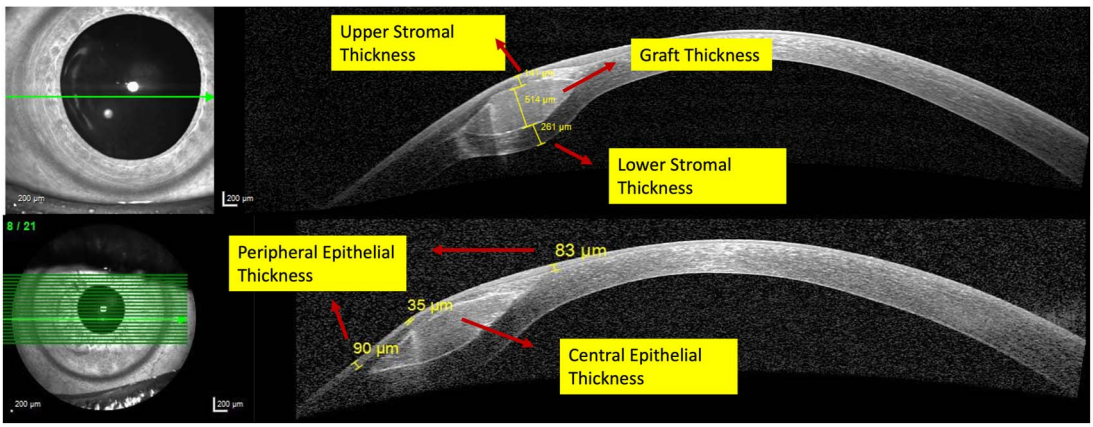

FIGURE 1. Anterior segment OCT measurements. (The full color version of this figure is available at www.corneajrnl.com.)

Tomographic Findings

There was a significant decrease in keratometric values in all control eyes compared with preoperative values ($P < 0.01$), but there was no difference after 1 year ($P > 0.01$). No difference was found in the thinnest corneal thickness measured at any visits ($P > 0.01$) (Table 2).

Allograft rings were not visible to the naked eye in any of the patients. They could only be seen under a biomicroscope (Fig. 2A).

Anterior Segment OCT Findings

Anterior segment OCT showed well-placed anterior stromal rings. No signs of rejection such as melting, necrosis, edema, or inflammation were observed in any segment or the surrounding host stroma at any follow-up time points (up to 3 years). No other major intraoperative or postoperative complications were observed. In 1 patient, graft displacement toward the incision site and an opening at the tunnel entrance were observed during the first week of surgery and the graft was repositioned.

After 6 months, according to anterior segment OCT measurements, the thickness of the allograft ring, upper and lower stromal thickness, and tunnel depth were unchanged. The change in measured epithelial thickness after 1 year was not significant ($P > 0.01$) (Table 3). PE was found to be thicker than GE ($P < 0.05$) at all visits.

Dry eye findings such as punctate epitheliopathy and shortened tear breakup time were noted in 7 patients with early burning and stinging complaints. The findings improved with medical treatment, and the symptoms regressed. In 6 cases, yellow–white deposits were observed in the segment tunnels after 6 months (Fig. 2B). These channel deposits did not affect the performance or visual quality of the segment rings.

DISCUSSION

This study examined clinical outcomes of patients implanted with a sterile allograft ring segment for up to 3 years. Comparing the preoperative visual acuity of patients with that at their last visit, there was an increase of 0.34 ±

TABLE 2. Long-Term Visual Acuity, Refraction, and Topographic Outcomes of Patients Included in the Study

	Preop (N = 62)	1st mo (N = 62)	6th mo (N = 62)	1st year (N = 50)	3rd year (N = 32)
UDVA (LogMAR)	0.96 ± 0.50	0.40 ± 0.34	0.44 ± 0.34	0.44 ± 0.35	0.41 ± 0.34
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 1.000$	$P_2 = 1.000$	$P_2 = 1.000$
CDVA (LogMAR)	0.72 ± 0.47	0.28 ± 0.22	0.25 ± 0.24	0.23 ± 0.21	0.22 ± 0.19
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 1.000$	$P_2 = 1.000$	$P_2 = 1.000$
SE (D)	−7.54 ± 5.54	−2.92 ± 5.27	−2.66 ± 4.74	−2.31 ± 4.89	−2.10 ± 4.90
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 0.914$	$P_2 = 0.284$	$P_2 = 0.190$
SR (D)	−4.81 ± 4.96	−1.22 ± 5.17	−0.50 ± 4.57	−0.30 ± 4.39	−0.01 ± 4.65
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 0.166$	$P_2 = 0.180$	$P_2 = 0.165$
CR (D)	−5.19 ± 2.51	−3.32 ± 2.19	−4.35 ± 2.40	−4.64 ± 2.72	−4.77 ± 2.69
		P_1 0.002	$P_1 = 0.054$	$P_1 = 0.102$	$P_1 = 0.333$
			$P_2 = 0.001$	$P_2 = 0.063$	$P_2 = 0.498$
K1 (D)	47.15 ± 4.65	44.51 ± 4.88	43.90 ± 4.24	43.61 ± 4.16	43.61 ± 4.18
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 0.122$	**$P_2 = 0.008$**	$P_2 = 0.952$
K2 (D)	51.42 ± 5.51	48.09 ± 5.25	47.79 ± 4.96	47.88 ± 5.00	48.00 ± 4.87
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 0.76$	$P_2 = 0.389$	$P_2 = 0.493$
Kmean (D)	49.17 ± 4.97	46.22 ± 4.98	45.75 ± 4.47	45.63 ± 4.44	45.68 ± 4.41
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 0.055$	$P_2 = 0.385$	$P_2 = 0.767$
Kmax (D)	58.51 ± 7.55	56.34 ± 7.43	55.27 ± 6.17	55.17 ± 5.87	55.31 ± 5.34
		$P_1 < 0.001$	**$P_1 < 0.001$**	**$P_1 < 0.001$**	**$P_1 < 0.001$**
			$P_2 = 0.172$	$P_2 = 0.467$	$P_2 = 0.573$
Pachymetry (μm)	449.68 ± 49.48	446.32 ± 40.26	445.70 ± 47.35	444.38 ± 50.15	441.09 ± 49.06
		$P_1 = 0.974$	$P_1 = 0.662$	$P_1 = 0.153$	$P_1 = 0.154$
			$P_2 = 0.615$	$P_2 = 0.412$	$P_2 = 0.370$

Bold indicates visual, refractive, and topographic results.
P_1 is compared with preop; P_2 is compared with the previous visit. $P < 0.01$ is defined as statistically significant.
D, diopters, pachymetry: thickness of the thinnest point of the cornea.

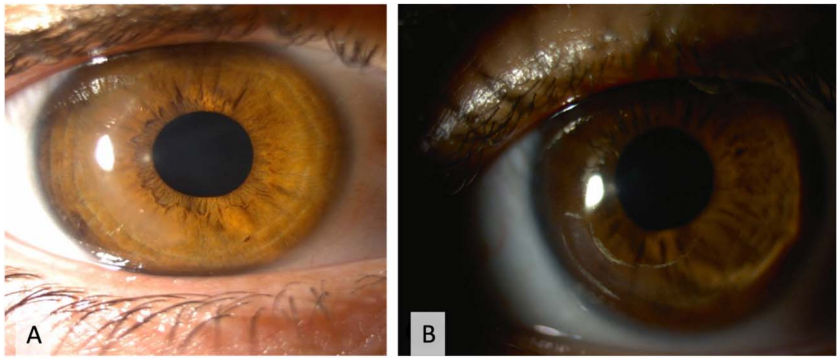

FIGURE 2. A, Biomicroscopic image of an eye with corneal allograft ring implantation. B, Yellow–white deposits inside the tunnel in another eye. (The full color version of this figure is available at www.corneajrnl.com.)

0.22 (0–0.85) in UDVA and 0.38 ± 0.21 (0–0.90) in CDVA. There was no decrease in visual acuity in any of the patients, but there were 3 patients who had no increase in UDVA and CDVA despite topographic improvement. As the patients were satisfied, the ring was not removed from any of the patients. Comparing the preoperative refractions with those at the last visit, the decrease in SE was 5.41 ± 3.40 D, spherical refraction (SR) was 4.86 ± 3.24 D, and CR was 0.53 ± 2.80 D. When the topographic difference maps were analyzed, a flattening of the topography was observed where the allograft ring had been implanted (Fig. 3). Comparing the preoperative keratometric values with those at the last visit, K1 was flattened 3.73 ± 2.58 D, K2 3.50 ± 2.16 D, Kmean 3.67 ± 2.17 D, and Kmax 2.59 ± 4.04 D.

TABLE 3. Anterior Segment OCT Measurements

	1st day (N = 62)	1st mo (N = 62)	6th mo (N = 62)	1st year (N = 50)	3rd year (N = 32)
UST (μm)	178.73 ± 54.82	165.03 ± 39.30 **P_1 < 0.001**	161.06 ± 38.78 **P_1 < 0.001** P_2 = 0.083	165.27 ± 37.38 **P_1 < 0.001** P_2 = 0.028	165.63 ± 42.35 **P_1 = 0.001** P_2 = 0.862
GT (μm)	532.70 ± 114.42	495.67 ± 95.93 **P_1 < 0.001**	486.90 ± 86.54 **P_1 < 0.001** P_2 = 0.029	476.47 ± 94.33 **P_1 < 0.001** P_2 = 0.051	462.23 ± 94.20 **P_1 < 0.001** P_2 = 0.165
LST (μm)	356.46 ± 79.30	335.70 ± 72.98 **P_1 < 0.001**	328.50 ± 64.61 **P_1 < 0.001** **P_2 = 0.007**	326.50 ± 65.28 P_1 = 0.615 P_2 = 0.316	325.27 ± 66.12 **P_1 < 0.001** P_2 = 0.794
TD (μm)	212.40 ± 42.77	210.53 ± 39.89 **P_1 = 0.006**	214.33 ± 38.51 P_1 = 0.292 P_2 = 0.331	214.63 ± 36.41 P_1 = 0.464 P_2 = 0.935	212.63 ± 36.57 P_1 = 0.905 P_2 = 0.368
Gep (μm)	45.67 ± 11.24	43.93 ± 8.86 **P_1 = 0.006**	42.80 ± 6.80 P_1 = 0.050 P_2 = 0.661	42.57 ± 5.20 P_1 = 0.166 P_2 = 0.995	41.13 ± 6.48 P_1 = 0.034 P_2 = 0.324
Pep (μm)	70.27 ± 13.07	71.03 ± 12.03 P_1 = 0.041	76.50 ± 19.27 **P_1 = 0.001** P_2 = 0.033	78.73 ± 19.31 **P_1 = 0.002** P_2 = 0.157	73.87 ± 15.04 P_1 = 0.365 P_2 = 0.404

Bold indicates visual, refractive, and topographic results.

P_1 is compared with preop; P_2 is compared with the previous visit. $P < 0.01$ is defined as statistically significant.

In the first series of 24 eyes with a mean follow-up of approximately 12 months published by Jacob et al, UDVA increased from 0.22 ± 0.16 to 0.36 ± 0.22 decimal and CDVA increased from 0.59 ± 0.21 to 0.79 ± 0.19 decimal ($P < 0.001$). The spherical equivalent decreased from −5.35- ± 3.17 D to −1.28 ± 5.61 D ($P < 0.001$); no significant difference was found in refractive astigmatism ($P = 0.87$). The steep keratometry decreased from 57.61 ± 5.42 to 54.83 ± 4.33 D ($P < 0.001$).[12] In the newly described customized CAIRS technique by Jacob et al, to personalize the flattening effect according to individual topography, 32 eyes of 29 patients were examined over a 1-year follow-up period. UDVA and CDVA increased from 0.22 to 0.47 ($P = 0.000$) and from 0.76 to 0.89 ($P = 0.001$), respectively. Significant improvements were seen in K1, K2, Kmean, Kmax, topographic astigmatism, sphere, cylinder, and spherical equivalent ($P < 0.01$).[16] The visual acuity and topographic results of both studies were similar to ours, and we report longer term results of the allograft rings. In addition, we have not observed any of the possible complications such as melting and extrusion even after 3 years of use.

Hacõağaoğlu et al reported the 6-month results of 44 eyes of 32 patients who underwent sterile allogeneic corneal ring implantation using the Istanbul nomogram. UDVA and CDVA increased from 0.19 ± 0.17 and 0.29 ± 0.20 preoperatively to 0.45 ± 0.26 and 0.56 ± 0.26 at 6 months postoperatively, respectively ($P < 0.001$). SE decreased from −7.77 ± 4.89 to −2.79 ± 5.22 ($P < 0.001$); K1, K2, Kmean, and Kmax values decreased significantly ($P < 0.001$). There was no significant change in the thinnest corneal thickness ($P = 0.537$). In our study, we evaluated the long-term results of the patients operated with this nomogram developed in our clinic. We found that the long-term results were similar to those reported by Hacõağaoğlu et al.[17]

Another study by Nacaroğlu et al also presented results at one-year postoperatively. Here, the authors examined safety and efficacy of the implantation of allograft rings using the Istanbul nomogram. UDVA increased from 0.91 ±

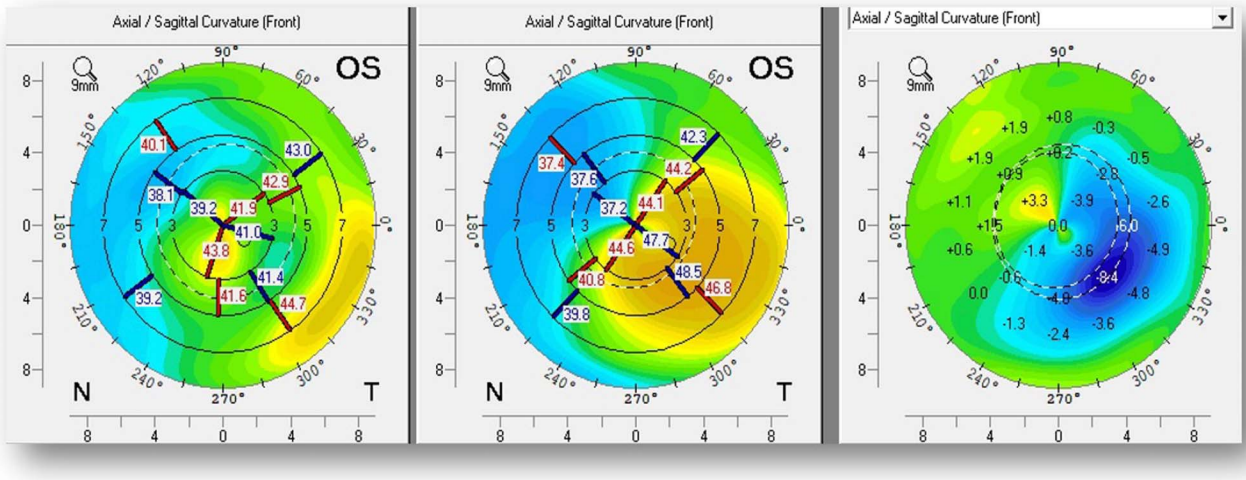

FIGURE 3. Topographic difference map. The figure shows the 3-year postoperative, preoperative, and difference maps. (The full color version of this figure is available at www.corneajrnl.com.)

0.50 LogMAR to 0.36 ± 0.25 LogMAR; CDVA increased from 0.87 ± 0.20 LogMAR to 0.36 ± 0.15 LogMAR ($P < 0.001$). SE decreased from −8.82 ± 4.57 D to −2.32 ± 4.95 D ($P < 0.001$). K1, K2, Kmean, and Kmax also decreased significantly ($P < 0.001$), and keratometric and refractive changes and visual acuity remained stable over the 1-year follow-up. The results were also similar to ours. Nacaroğlu et al also evaluated anterior and posterior corneal elevation. Anterior elevation showed a significant decrease from the first month and remained stable ($P < 0.001$), whereas posterior elevation decreased at the first month ($P < 0.01$) but started to increase after the third month. At 6 months and 1 year, there was no difference between the preoperative values ($P > 0.05$).[21] The similarity of this study with the results of previous studies reporting early results of the Istanbul nomogram suggests that stabilization is achieved over a period of 6 months to 1 year.

Comparing the results from this study with those of previous studies reveals that visual acuity stabilizes between 6 and 12 months postoperatively and remains consistent for at least 3 years. Therefore, future studies can use the 6-month and 1-year results to measure visual recovery success. In addition, our long-term study provides valuable data on the safety of using sterile ring segments to treat keratoconus, being the first to document the absence of serious complications in a large cohort over a span of up to 3 years.

Surgical success can be achieved without the use of a laser-cut tunnel. Parker et al performed CAIRS implantation with manual dissection in 26 eyes of 25 patients with keratoconus and reported the mean 2-month follow-up results. Kmax decreased from 70.4 D to 64.6 D ($P = 0.47$) in inferior cone cases with single-segment implantation and from 86 D to 78.6 D ($P = 0.22$) in central cone cases with double-segment implantation. This study demonstrated the feasibility of the manual technique but did not assess refraction and visual acuity.[13]

In our study, we analyzed the patients who underwent corneal allograft ring implantation using anterior segment OCT for up to 3 years. To our knowledge, there is no study in the published literature describing the shape and behavior of allograft ring segments after implantation using OCT. Previous OCT studies with ICRSs compared the targeted implantation depth with the achieved implantation depth and investigated the relationship of the implantation depth with the effect of the ring and the long-term stabilization of the position of the ring in the stroma. By contrast, our study used the OCT to investigate the possible shape change and movement of the ring in the stroma, stromal melting, and epithelial remodeling in the long term.

We measured the shortest distance between the 2 points from the same part of the graft. On day 1, there were gaps around the allograft ring in the tunnel and it maintained its own shape. At 1 month, the allograft ring had spread to fill the gap in the tunnel and had a fusiform shape. It appeared stable at subsequent visits (Fig. 4). The graft thickness measured on the first day was higher than the other control eyes. We thought that this was due to the spreading of the graft in the tunnel during the first month and possible edema in the graft in the early period.

There was no change in upper stromal thickness and tunnel depth after month 1 and lower stromal thickness after month 6. We attributed the fact that the measured upper stromal thickness was less than the tunnel depth to the compression of collagen fibrils by the increase in pressure in the stroma above the graft. Similarly, studies using ICRS reported that the implantation depth after surgery was shallower than the targeted implantation depth.[22,23]

Some studies using ICRS have investigated the effect of implantation depth on ring effectiveness. It has been shown in the studies by Hashemi et al and Sadigh et al that rings implanted at a depth of more than 80% lose their effectiveness. Both studies argued that ICRSs should be implanted superficially enough to exert their effect, but deep enough to

avoid extrusion.[24,25] We performed a more superficial implantation because allograft rings are softer than synthetic rings and are less likely to affect the metabolic balance of the recipient cornea. As we implanted at a fixed depth of 200 or 250 μm, we were unable to investigate the impact of implantation depth on visual acuity and topographic change. However, we observed that all parameters stabilized after the sixth month and were maintained for the 3-year follow-up period, and there were no evidence of corneal melting or extrusion.

In measurements of epithelial thickness, we observed a thinning of the epithelium in the ring area and a thickening of the epithelium at the periphery on both sides of the ring. This situation may be related to the elevation in the stroma caused by allograft ring implantation, due to the volume effect. It is believed that compensation is provided by epithelial remodeling to create a smooth ocular surface after stromal remodeling. It was observed that epithelial remodeling was completed within the first month and remained stable during subsequent follow-ups. The results of the study by Clémentine et al using the ICRS also support our study. Using epithelial mapping, the authors demonstrated epithelial thickening in the cone area after implantation. They argued that this resulted in a more regular corneal surface.[26] As epithelial mapping was not available at our clinic, we were unable to investigate any epithelial changes on the cone or central cornea.

In a meta-analysis of 64 studies using the ICRS procedure, UDVA (LogMAR) increased from 0.96 (0.86–1.06) to 0.44 (0.38–0.50) and CDVA increased from 0.28 (0.24–0.32) to 0.19 (0.15–0.22). SE decreased from −5.27 (−6.14 to −4.40) D to −2.24 (−2.86 to −1.62) D.[27] The findings of the ICRS study are comparable with those of this study, and it can be concluded that allograft rings may prevent complications that may be caused by synthetic material.

Another potential avenue for the treatment of keratoconus is keratoplasty procedures. There have been documented instances of successful outcomes following penetrating keratoplasty and deep anterior lamellar keratoplasty. Publications that have compared ICRS with lamellar keratoplasty have indicated that keratoplasty may be associated with superior visual outcomes.[28,29] Nevertheless, long-term follow-ups have demonstrated that the rejection rate in the first 2 years following keratoplasty ranges from 5.8% to 41%.[30–32] It is important to consider the possibility of long-term rejection and recurrence in patients with keratoconus, given that they are relatively young. Although keratoplasty procedures are always an important option for patients with advanced keratoconus, suitable patients may be given the opportunity for a less invasive method, the corneal ring.

No complications were encountered except for dry eye findings in the early period and intratunnel deposits in the long term. No patients presented with complaints such as halo or glare. It is believed that the similarity in the refractive index between allogeneic segments and the recipient cornea, as well as the lack of rigidity and sharp edges in the implants (unlike synthetic types), may contribute to this phenomenon. But, there was no specific questionnaire/test to assess these symptoms. Additional investigation into patients' visual quality and symptoms such as halo, glare, and contrast sensitivity will be examined in the future studies.

We believe that our study has some limitations. Anterior segment OCT measurements are dependent on the accuracy of the examiner. To overcome this limitation, we increase reliability by averaging repeated measurements by a different investigator. The use of epithelial mapping in the

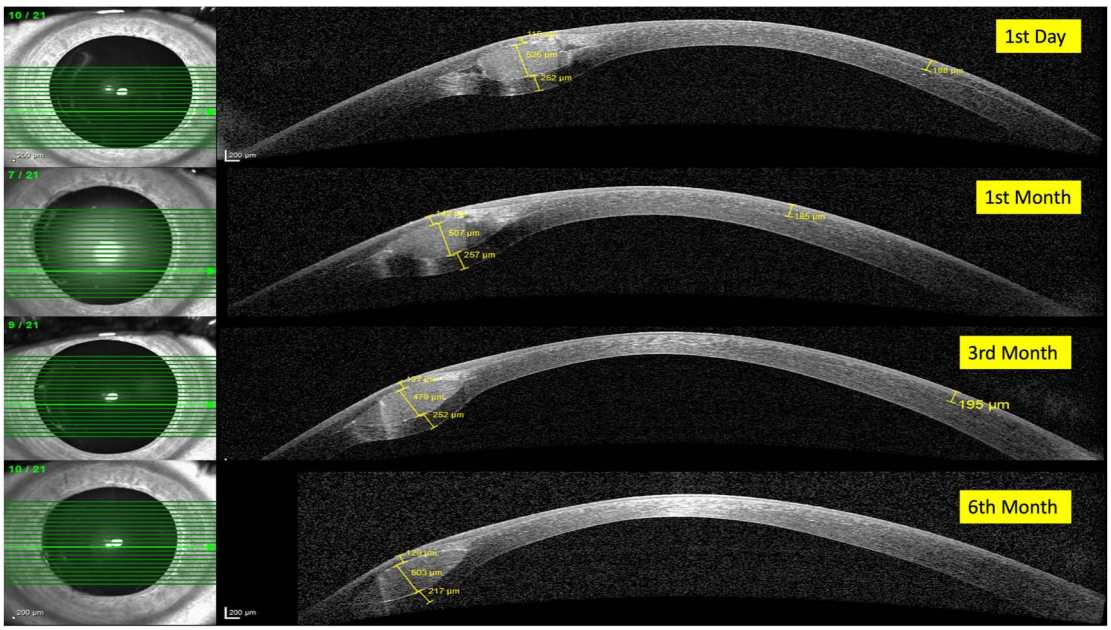

FIGURE 4. Examination of the allograft ring by anterior segment OCT over time. (The full color version of this figure is available at www.corneajrnl.com.)

future studies will provide more precise results, especially in epithelial thickness measurements.

In conclusion, our study shows that sterile allograft ring segments can be used to improve the visual performance of patients with keratoconus with a more biocompatible material. This study presents the longest follow-up to date on the use of allograft rings (sterile or nonsterile), demonstrating their effectiveness and safety.

REFERENCES

1. Colin J, Cochener B, Savary G, et al. Correcting keratoconus with intracorneal rings. *J Cataract Refract Surg.* 2000;26:1117–1122.
2. Alió JL, Shabayek MH, Artola A. Intracorneal ring segments for keratoconus correction: long-term follow-up. *J Cataract Refract Surg.* 2006;32:978–985.
3. Deshmukh R, Ong ZZ, Rampat R, et al. Management of keratoconus: an updated review. *Front Med (Lausanne)*. 2023;10:1212314.
4. Zare MA, Hashemi H, Salari MR. Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy. *J Cataract Refract Surg.* 2007;33:1886–1891.
5. Park S, Ramamurthi S, Ramaesh K. Late dislocation of intrastromal corneal ring segment into the anterior chamber. *J Cataract Refract Surg.* 2010;36:2003–2005.
6. Kugler LJ, Hill S, Sztipanovits D, et al. Corneal melt of incisions overlying corneal ring segments: case series and literature review. *Cornea*. 2011;30:968–971.
7. Coskunseven E, Kymionis GD, Tsiklis NS, et al. Complications of intrastromal corneal ring segment implantation using a femtosecond laser for channel creation: a survey of 850 eyes with keratoconus. *Acta Ophthalmol.* 2011;89:54–57.
8. Kanellopoulos AJ, Pe LH, Perry HD, et al. Modified intracorneal ring segment implantations (INTACS) for the management of moderate to advanced keratoconus: efficacy and complications. *Cornea*. 2006;25:29–33.
9. Bautista-Llamas MJ, Sánchez-González MC, López-Izquierdo I, et al. Complications and explantation reasons in intracorneal ring segments (ICRs) implantation: a systematic review. *J Refractive Surg.* 2019;35:740–747.
10. Awwad ST, Jacob S, Assaf JF, et al. Extended dehydration of corneal allogenic intrastromal ring segments to facilitate insertion: the corneal jerky technique. *Cornea*. 2023;42:1461–1464.
11. Parker JS, Dockery PW, Jacob S, et al. Preimplantation dehydration for corneal allogenic intrastromal ring segment implantation. *J Cataract Refract Surg.* 2021;47:E37–E39.
12. Jacob S, Patel SR, Agarwal A, et al. Corneal allogenic intrastromal ring segments (CAIRS) combined with corneal cross-linking for keratoconus. *J Refractive Surg.* 2018;34:296–303.
13. Parker JS, Dockery PW, Parker JS. Flattening the curve: manual method for corneal allogenic intrastromal ring segment implantation. *J Cataract Refract Surg.* 2021;47:E31–E33.
14. Parker JS, Dockery PW, Parker JS. Trypan blue-assisted corneal allogenic intrastromal ring segment implantation. *J Cataract Refract Surg.* 2021;47:127.
15. Dapena I, Parker JS, Melles GRJ. Potential benefits of modified corneal tissue grafts for keratoconus: bowman layer 'inlay' and 'onlay' transplantation, and allogenic tissue ring segments. *Curr Opin Ophthalmol.* 2020;31:276–283.
16. Jacob S, Agarwal A, Awwad ST, et al. Customized corneal allogenic intrastromal ring segments (CAIRS) for keratoconus with decentered asymmetric cone. *Indian J Ophthalmol.* 2023;71:3723–3729.
17. Haciagaoglu S, Tanriverdi C, Keskin FFN, et al. Allograft corneal ring segment for keratoconus management: Istanbul nomogram clinical results. *Eur J Ophthalmol.* 2022;33:689–696.
18. Utine CA, Tzu JH, Akpek EK. Lamellar keratoplasty using gamma-irradiated corneal lenticules. *Am J Ophthalmol.* 2011;151:170–174.e1.
19. Passo RM, Hoskins ZB, Tran KD, et al. Electron beam irradiated corneal versus gamma-irradiated scleral patch graft erosion rates in glaucoma drainage device surgery. *Ophthalmol Ther.* 2019;8:421–426.
20. Mathews PM, Fogla R, Samayoa E, et al. Long-term clinical outcomes of keratoplasty using gamma-irradiated corneal lenticules. *BMJ Open Ophthalmol.* 2019;4:e000396.
21. Nacaroglu SA, Yesilkaya EC, Perk FFNK, et al. Efficacy and safety of intracorneal allogenic ring segment implantation in keratoconus: 1-year results. *Eye*. 2023;37:3807–3812.
22. Barbara R, Barbara A, Naftali M. Depth evaluation of intended vs actual intacs intrastromal ring segments using optical coherence tomography. *Eye*. 2016;30:102–110.
23. Shahhoseini S, Hashemi H, Asgari S. Intracorneal ring segment depth in keratoconus patients: a long-term follow-up study. *Int Ophthalmol.* 2018;38:1379–1383.
24. Hashemi H, Yazdani-Abyaneh A, Beheshtnejad A, et al. Efficacy of intacs intrastromal corneal ring segment relative to depth of insertion evaluated with anterior segment optical coherence tomography. *Middle East Afr J Ophthalmol.* 2013;20:234–238.
25. Sadigh AL, Aali TA, Sadeghi A. Outcome of intrastromal corneal ring segment relative to depth of insertion evaluated with scheimpflug image. *J Curr Ophthalmol.* 2015;27:25–31.
26. David C, Reinstein DZ, Archer TJ, et al. Postoperative corneal epithelial remodeling after intracorneal ring segment procedures for keratoconus: an optical coherence tomography study. *J Refract Surg.* 2021;37:404–413.
27. Benoist D'Azy C, Pereira B, Chiambaretta F, et al. Efficacy of different procedures of intra-corneal ring segment implantation in keratoconus: a systematic review and meta-analysis. *Transl Vis Sci Technol.* 2019;8:38.
28. Rocha G, Vieira BV, Mendes BMS, et al. Visual outcomes in advanced keratoconus using different strategies: scleral lens, intracorneal ring segment and lamellar keratoplasty. *Eur J Ophthalmol.* 2021;31:1563–1570.
29. Özertürk Y, Sari ES, Kubaloglu A, et al. Comparison of deep anterior lamellar keratoplasty and intrastromal corneal ring segment implantation in advanced keratoconus. *J Cataract Refract Surg.* 2012;38:324–332.
30. Choi JA, Lee MA, Kim MS. Long-term outcomes of penetrating keratoplasty in keratoconus: analysis of the factors associated with final visual acuities. *Int J Ophthalmol.* 2014;7:517–521.
31. Javadi MA, Motlagh BF, Jafarinasab MR, et al. Outcomes of penetrating keratoplasty in keratoconus. *Cornea*. 2005;24:941–946.
32. Niziol LM, Musch DC, Gillespie BW, et al. Long-term outcomes in patients who received a corneal graft for keratoconus between 1980 and 1986. *Am J Ophthalmol.* 2013;155:213–219.e3.