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Cornea & External Disease

Twelve-Month Clinical and Histopathological Performance of a Novel Synthetic Cornea Device in Rabbit Model

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Purpose: To report the biological stability and postoperative outcomes of a second-generation, single-piece, flexible synthetic cornea in a rabbit model.

Methods: Device materials and design were amended to enhance biointegration. Optic skirt design devices were made from compact perfluoroalkoxy alkane with porous expanded polytetrafluoroethylene ingrowth surface overlying the skirt and optic wall. Sixteen devices were implanted into intrastromal pocket in rabbit eyes. Rabbits were randomly assigned to 6- and 12-month follow-up cohorts ($n = 8$ in each) postoperatively. Monthly examinations and optical coherence tomography assessed cornea–device integration, iridocorneal angle, optic nerve, and retina.

Results: There were no intraoperative complications. All devices were in situ at exit, with clear optics. No retroprosthetic membrane, glaucoma, cataract formation, or retinal detachment was observed. Two rabbits in the 6-month group had mild, focal anterior lamella thinning without retraction adjacent to the optic near tight sutures. Three postoperative complications occurred in the 12-month group. One rabbit diagnosed with endophthalmitis was euthanized on day 228. Mild sterile focal retraction of anterior lamella occurred in two rabbits, which were terminated on days 225 and 315. Light microscopic examination of enucleated globes demonstrated fibroplasia with new collagen deposition into the porous scaffold without significant inflammation, encapsulation, or granuloma formation.

Conclusions: Clinical evaluations, imaging, and histopathological findings indicate favorable outcomes of this synthetic corneal device in a rabbit model. Early feasibility studies in humans are being planned.

Translational Relevance: Favorable 12-month results of the device in rabbits demonstrate vision-restoring potential in corneally blind individuals at high risk of failure with donor keratoplasty.

Introduction

Penetrating keratoplasty has been the mainstay of donor corneal transplantation for decades. At the turn of the twenty-first century, widespread adoption of endothelial keratoplasty to address corneal edema owing to Fuchs' endothelial dystrophy or postsurgical bullous keratopathy, and later introduction of corneal cross-linking for early treatment of keratoconus, led to significant changes in the modern keratoplasty landscape.[1,2] Although 98.8% of all corneal transplants in the United States were penetrating keratoplasties in 2000, this percentage decreased to

33.1% in 2021.[3,4] Prior graft failure is now the leading preoperative indication for penetrating keratoplasty in North America and Europe.[3,5–7] The outcomes of penetrating keratoplasty have historically been excellent with graft survival rates between 99% and 93% at 5 and 25 years, respectively.[8–10] However, current results might not be as favorable owing to a greater proportion of penetrating keratoplasty surgeries being repeat grafts.[11] Unfortunately, both the graft survival and the visual outcomes worsen with each successive graft.[12]

Prosthokeratoplasty, also known as artificial corneal transplantation, is considered in cases where donor corneal transplantation does not have a reasonable expectation of success, such as for patients with inflammatory ocular surface diseases and dry eye, intraocular inflammation, or patients who have had prior glaucoma surgeries. The Boston type I keratoprosthesis (Massachusetts Eye and Ear Infirmary, Boston MA) is the most commonly implanted prosthetic corneal device globally. Despite the superior outcomes of this device in comparison with repeat penetrating keratoplasty in patients with complex corneal problems,[13–15] there has been a downward trend in the number of devices implanted yearly, largely owing to worsening outcomes over longer term follow-up, even with frequent postoperative care.[16,17] These postoperative complications are, unfortunately, caused by design flaws that cannot be completely overcome.[18] Owing to the rigidity and compact nature of its materials (polymethyl methacrylate and titanium), the Boston type I keratoprosthesis does not integrate into the recipient corneal stroma, which poses a risk for intraocular invasion of micro-organisms through the perioptic space, even in the absence of epithelial defects. In addition, the perpetual micro-oscillation of the device within the corneal stroma with every blink triggers inflammation leading to sterile keratolysis, retroprosthetic membrane, iris synechiae, and glaucoma. Moreover, a donor cornea as a carrier is a requisite, which limits its use in the developing world, where corneal blindness is most prevalent.

With the goal of creating a corneal prosthesis with more favorable outcomes, we designed a single-piece, fully synthetic, flexible, suturable optic skirt configuration device prototype. The feasibility of this novel surgical technique, biocompatibility of the materials used, and short-term clinical outcomes of a previous version have been published.[19] We herein report the longer term performance and clinical outcomes of the modified, second-generation design in a healthy rabbit model.

Materials and Methods

All study protocols were approved by a credentialed committee (protocol # 2635SC by The W. L. Gore & Associates Institutional Animal Care and Use Committee [Flagstaff, AZ], protocol #: RB17M34, and RB23M12 by Johns Hopkins University Institutional Animal Care and Use Committee [Baltimore, MD]). The ARVO statement for the Use of Animals in Ophthalmic and Vision Research and the tenets of the Declaration of Helsinki regarding the ethical treatment of animal subjects were adhered to throughout the study.

Prosthesis

The device is a single-piece, fully synthetic corneal button with an optic and skirt design. It is made out of a flexible and compact fluoropolymer, perfluoroalkoxy alkane, that is optically clear (W.L. Gore & Associates, Inc., Newark, DE). The skirt and the optical wall are covered with semitransparent porous expanded polytetrafluoroethylene (ePTFE) for tissue integration. The two materials are fused through compression molding using heat and pressure. The specifications of the previous device version and 6- month clinical results were published elsewhere.[19] In order to improve the previously reported clinical outcomes, several revisions were made to the device design as summarized in this article.

Enhancing Biointegration

To optimize the adhesion of recipient corneal fibroblasts and collagen deposition, four different prototype lenticules made of the ePTFE material with varying microstructures were evaluated. Disc-shaped lenticules, measuring 4 mm in diameter and 100 microns in thickness, were implanted into manually created intrastromal corneal pockets at various depths (40%–70%) in New Zealand adult white rabbits. Rabbits were euthanized at day 45, and enucleated globes were submitted for histopathological evaluations. Light microscopy was performed on formalin fixed and paraffin embedded specimens using hematoxylin and eosin (H&E) stains to evaluate inflammatory response. Masson's trichrome stain was used to assess fibroblast invasion and collagen deposition.

The results revealed that:

a. An implantation depth of less than 50% and peripheral placement resulted in extrusion,

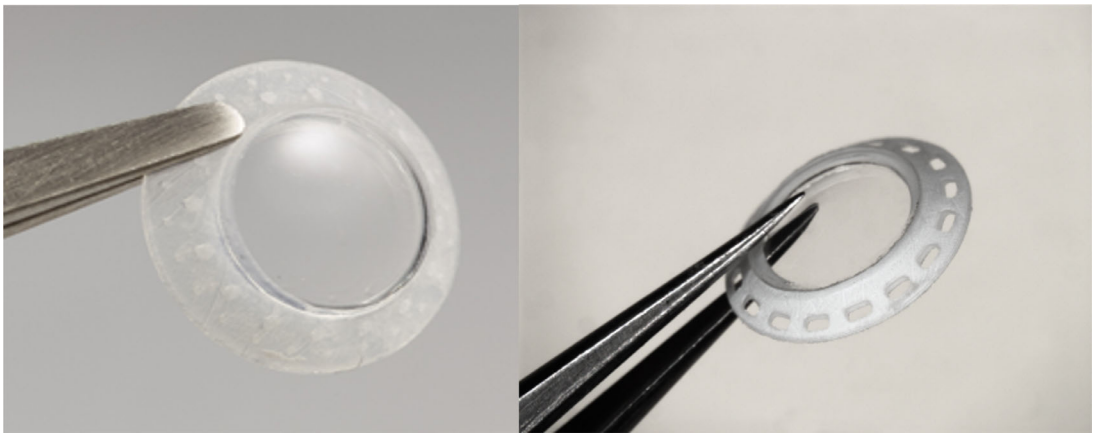

Figure 1. External appearance of the previous device design with the solid skirt with partial thickness microperforations (left) versus the revised second-generation prototype with full-thickness macroapertures designed to enhance biointegration (right).

whereas the lenticules implanted deeper and more centrally were observed to be free of vascularization, edema, and extrusions.

b. Larger pore size with open structures measuring 50 microns in diameter demonstrated the greatest fibroblast infiltration and collagen deposition.

Based on these results, the implantation depth of 60% to 70% of corneal thickness and the ingrowth surface ePTFE material with a pore size of 50 microns with 50 micron thickness were selected.

Device Design Modifications

To improve the compliance of the device with the recipient cornea and enhance clinical outcomes, several modifications to the device constructs were tested.

a. Instead of the partial thickness microperforations (24 circular holes of 200 microns in diameter and additional 16 circular holes of 300 microns in diameter through the skirt but not the ingrowth surface), full-thickness macroapertures (16 oval holes measuring 650 by 333 microns in diameter through the skirt as well as the ingrowth surface) were placed circumferentially around the skirt for better nutrition and hydration of the overlying anterior corneal lamella (Fig. 1). Light microscopic examination of enucleated rabbit globes implanted with the enhanced device constructs confirmed the presence of recipient fibroblasts and collagen deposition through the entirety of these macroapertures (Fig. 2).

b. The optic wall was revised. It was built vertical to the skirt for a tighter fit within the trephination opening. Porous ePTFE ingrowth surface was fused onto the optic wall to allow for biointegration and prevent the potential peri-optic space. A microflange was placed around the anterior perimeter of the optic for protection of the corneal epithelium at the optic–cornea junction. Histopathological sections of the enucleated rabbit eyes demonstrated a tight seal at the device–cornea junction with growth of the stromal fibroblasts along the optical wall (Fig. 2, yellow arrow).

c. The device dimensions were reduced (from 6 mm optic × 9.5 mm outer skirt diameter to 4.75 mm optic × 6.9 mm outer skirt diameter) to be able to implant the device in eyes with failed donor corneal transplants.

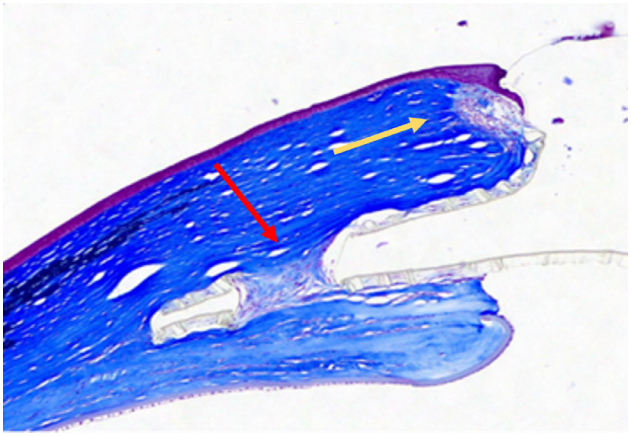

Figure 2. Light microscopic appearance of the recipient rabbit cornea, with revised second-generation prototype with full-thickness macroapertures in the skirt. Significant fibroblast infiltration and new collagen deposition through the entirety of the full-thickness aperture (red arrow) is evident (Masson's trichrome staining; original magnification ×10).

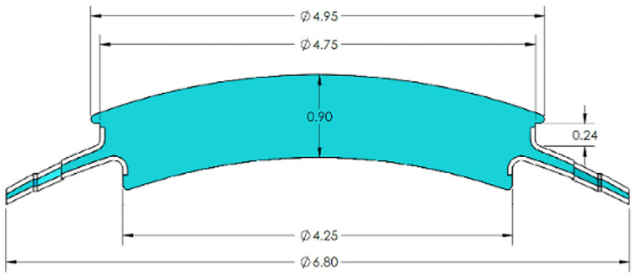

Figure 3. Diagram of the second-generation novel synthetic cornea device. The blue color indicates the compact and optically clear material, and the white color indicates the porous ingrowth surface.

Final Device Constructs

The prototypes were fabricated manually using precision fixtures providing secure mounting during machining. The final device optic diameter measures 4.75 mm anteriorly and 4.25 mm posteriorly and has a central thickness of 0.9 mm (Fig. 3). The skirt has an outer diameter of 6.9 mm (240 microns thick adjacent to the optic with taper to 170 microns thick distally). The ingrowth surfaces are rendered hydrophilic with a temperature-resistant polyvinyl alcohol-based coating and become translucent when wetted. The optic is shaped according to the calculated rabbit corneal curvature (47.4 D). The device weighs about 38 mg, which is less than the weight of an 8-mm human corneal button (50 mg) or Boston type I KPro with an 8.5-mm titanium plate (80 mg), without the donor corneal carrier.

Surgical Technique and Postoperative Care

Details of the surgical technique and postoperative care have previously been reported and a short video is included (Supplementary Video 1).[19] New Zealand white rabbits aged 12 months and older were used for the experiments. The surgery was performed in the right eye of each rabbit using an operating microscope with built-in optical coherence tomography (OCT) (Proveo 8 Ophthalmic Microscope, Leica Microsystems, Wetzlar, Germany). A scleral fixation ring and stay sutures were used to stabilize the globe. The cornea was marked for centration using a sterile surgical marker. Partial thickness trephination was made using a 4.0-mm disposable, handheld metal trephine (Surgistar, Vista, CA). An intrastromal lamellar pocket measuring 8 mm in diameter at 60% to 70% of the corneal thickness was created 360° manually, using a disposable 2.2-mm angled, double-bevel spoon blade (Unique Technologies, Mohnton, PA). The anterior chamber was then penetrated through a paracentesis using a surgical blade (I-Knife, Alcon, Fort Worth, TX). The anterior chamber was irrigated using heparin 20 IU/ml (Heparin sodium USP; Sagent Pharmaceuticals, Schaumburg, IL) and filled with an ophthalmic viscoelastic material (Healon, Johnson & Johnson Surgical Vision, Santa Ana, CA). The corneal button was removed using a pair of curved microscissors (Vannas capsulotomy scissors, Ambler Surgical, Exton, PA). The device was then folded and inserted within the intrastromal pocket and sutured in place using 16 interrupted 10-0 nylon sutures (CS160-6, Ethicon, Cornelia, GA) with the knots buried into the host stromal rim. The viscoelastic material was removed from the anterior chamber via the paracentesis and replaced with balanced salt solution. The paracentesis was closed using a single 10-0 nylon suture.

The rabbits were treated with a topical antibiotic and steroid combination ointment (tobramycin 0.3% and dexamethasone 0.1%; Bausch & Lomb, Bridgewater, NJ) four times daily with weekly taper to once a day and kept on a once daily regimen during the entire length of the follow-up. External examinations were performed daily. Rabbits were randomly assigned to the 6-month ($n = 8$) and 12-month ($n = 8$) follow-up cohorts postoperatively and euthanized at those predetermined time points, with the exception of early terminations owing to complications.

Imaging and Data Collection

A full ophthalmological examination was performed under general anesthesia using the operating microscope with OCT at monthly intervals. The entire anterior chamber, with a 9-micron depth resolution and 16-micron lateral resolution, was imaged to assess the 360° anterior and posterior corneal lamellar apposition and the positioning of the device within the corneal stroma. The full chamber view was used to examine the entire anterior chamber depth, iris plane, and the iridocorneal angle. The optic nerve head, retinal nerve fiber layer, and macula were visualized at 4, 6, and 12 months (if applicable). The OCT scans and color images were obtained using BIOM5 (Oculus Surgical Inc., Fort Pierce, FL) with a high-definition lens mounted on the operating microscope. Images were obtained in the operative and contralateral eyes at 6 months and 12 months (if applicable).

Histopathology

The eyes were enucleated after having been marked for orientation, fixed in Bouin's solution for 48 hours, and preserved in 10% neutral buffered formalin until trimming. The implant in situ was trisected on the

perpendicular plane and embedded in paraffin and serially sectioned at 200-µm intervals through the entire block. Two 5-µm-thick slides were made at each section: one stained with H&E and one stained with Masson's trichrome. Additionally, a cross section of the lens and optic nerve from each globe was embedded in paraffin, and sections were stained with H&E and Masson's trichrome.

Results

Summary of Clinical Outcomes

The intraoperative and postoperative outcomes are summarized in Table. All surgeries were completed without complication. The lens and iris were left untouched in all cases. The mechanical strength of the device was excellent, with no tears or scratching during or after surgery. As soon as the device was inserted into the pocket, even before suturing, the wound was watertight, likely owing to undersizing of the trephination (4.00 mm vs 4.75 mm anterior device diameter).

The device was retained in situ in all 16 implanted eyes as of the last study visit. Other than a mild, superficial, whitish amorphous material deposit that could be easily removed using surgical sponges, no spoliation, discoloration, or opacification was noted by 12 months. The optic remained clear, allowing for fundus examination through the operating microscope using the fundus lens at all study visits (Fig. 4).

Almost all rabbits (13/16) underwent suture replacement, starting from 4 weeks, owing to loosening. Replacements were performed during the regularly scheduled monthly examinations. Some rabbits underwent suture replacement procedures at multiple time points (Table). In only one rabbit, a single suture was removed but not replaced.

Three of the 16 rabbits developed focal thinning of the anterior corneal lamella at 6 months with mild retraction, but no epithelial defect; the retraction corresponded with tight sutures (Fig. 5). There were three (3/8) late complications (12-month cohort) that are detailed elsewhere in this article. None of the animals (0/16) were noted to have an elevation in intraocular pressure (assessed by digital palpation), retroprosthetic membrane, cataract formation, or retinal detachment. Serial OCT images of the anterior segment showed good anatomical positioning of the device in the recipient midstroma (Fig. 6), without alterations in the anterior chamber depth or iridocorneal angle. No difference between the operated versus fellow eyes with regards to the optic nerve head or the retinal nerve fiber layer thickness was noted. Afferent pupillary defect was assessed and not detected in any of the 16 rabbits at the exit exam before euthanizing.

Detailed Report on Late Complications

Three of the eight rabbits in the 12-month cohort had late complications. One rabbit (4) underwent multiple suture replacements. One of the replacement sutures was a mattress suture at day 252. At day 273, another replacement had to be performed in the same area. Moderate (30% of skirt width) focal (measuring 3 clock-hours) retraction was noted at day 308 localized to the suture area. A topical antibiotic and steroid combination (neomycin/polymyxin/dexamethasone 0.1%, Maxitrol, Alcon Laboratories, Fort Worth, TX) at four times daily dosing was added at day 308. No change was noted by day 313. The decision was made to terminate early at day 315 (Fig. 7). Histopathological examination did not demonstrate any infectious etiology. Moderate inflammation mediated by polymorphonuclear leukocytes with occasional foreign body reaction was observed around the area of retraction. The remainder of the anterior and posterior lamellae were quiescent.

Another rabbit (8) was diagnosed with infectious keratitis at day 224 postoperatively (Fig. 8) and sacrificed early at day 228 after unsuccessful treatment with topical moxifloxacin administered eight times daily for 4 days. Before that, the last examination on day 189 was entirely unremarkable. Bacterial endophthalmitis (cocci in clusters) and significant inflammation with polymorphonuclear leukocytes, lymphocytes, macrophages, and multinucleated giant cells within the corneal lamellae and anterior chamber were noted. Hypopyon with cocci was present in the anterior chamber. Posterior segment was within normal limits. The OCT did not demonstrate tissue thinning adjacent to the optic or obvious perioptic space.

One other rabbit (12) was noted to have localized mild (50% of the skirt width, for 1 clock-hour) to moderate (30% of skirt width, for 1 clock-hour) retraction of the anterior lamella without an infiltrate or anterior chamber reaction on day 225 (Fig. 9). There was a small area of anterior synechia as well measuring approximately 1 clock-hour. The animal was terminated at day 225. Sterile moderate inflammation mediated by polymorphonuclear leukocytes with occasional foreign body reaction around the area of retraction was noted on the histopathological examinations. The remainder of the anterior and posterior lamellae were quiescent.

Table. Summary of Clinical and Histopathological Results of a Second-Generation Novel Synthetic Cornea Device Implantation in 16 Healthy Rabbit Eyes

Rabbit	Intraoperative Complications	Device-related Complications	Postoperative Complications	Final Outcome	Days	Histopathological Findings
1	None	Mild debris	Mild focal tissue thinning without epithelial defect next to a tight suture	Unremarkable Terminated at term	181	No significant inflammation
2	None	Mild debris	Small area of epithelial island trapped in the peripheral stroma	Unremarkable Terminated at term	181	No significant inflammation
3	None	Trace debris	None	Unremarkable Terminated at term	364	No significant inflammation
4	None	Mild debris	Mattress replacement suture at day 252. At day 273 another mattress replacement suture placed at the same area. Moderate (30% of skirt width) focal (measuring 3 clock-hours) retraction was noted at day 308 localized around the suture	Topical antibiotic+ steroid ointment at 4× daily was added at day 308. No improvement was noted by day 313. Decision was made to early terminate	315	No micro-organism were noted Moderate inflammation mediated by polymorphonuclear leukocytes with occasional foreign body reaction around the area of retraction Remainder of the anterior and posterior corneal lamellae, anterior chamber and posterior segment were unremarkable
5	None	Trace debris	None	Unremarkable Terminated at term	351	No significant inflammation
6	None	Trace debris	None	Unremarkable Terminated at term	351	No significant inflammation
7	None	Mild debris	None	Unremarkable Terminated at term	181	No significant inflammation
8	None	Mild debris	All findings were unremarkable at 189 Infectious keratitis was noted at day 224	Topical moxifloxacin at 8× daily was added at day 224. No improvement was noted by day 228 Decision was made to early terminate	228	Bacterial endophthalmitis (cocci in clusters) with significant inflammation with polymorphonuclear leukocytes, lymphocytes, macrophages, and multinucleated giant cells within the corneal lamellae. Hypopyon noted in the anterior chamber. Posterior segment was unremarkable

Table. Continued

Rabbit	Intraoperative Complications	Device-related Complications	Postoperative Complications	Final Outcome	Days	Histopathological Findings
9	None	Trace debris	One suture was removed and not replaced at day 336 Mild (20% of skirt width) focal (measuring 1 clock-hour) retraction at the removed suture area noted at day 364	Unremarkable Terminated at term	364	No significant inflammation
10	None	Mild debris	None	Unremarkable Terminated at term	188	No significant inflammation
11	None	Mild debris	Mild focal tissue thinning without retraction measuring 1 clock-hour adjacent to a tight suture	Unremarkable Terminated at term	189	No significant inflammation
12	None	Trace debris	Mild guttering with haze around a loose suture was noted at day 190 At day 225, two sutures were exposed Mild (50% of the skirt width, for 1 clock-hour) to moderate (30% of skirt width, for 1 clock-hour) retraction of the anterior lamella without an infiltrate or anterior chamber reaction was observed Anterior synechiae at 12 o'clock was noted	Decision was made to early terminate	225	No micro-organisms were noted Moderate inflammation mediated by polymorphonuclear leukocytes with occasional foreign body reaction around the area of retraction. Remainder of the anterior and posterior corneal lamellae, anterior chamber and posterior segment were unremarkable
13	None	Trace debris	None	Unremarkable Terminated at term	188	No significant inflammation
14	None	Trace debris	None	Unremarkable Terminated at term	188	No significant inflammation
15	None	Trace debris	None	Unremarkable	350	No significant inflammation Terminated at term
16	None	Moderate debris	None	Unremarkable Terminated at term	182	No significant inflammation

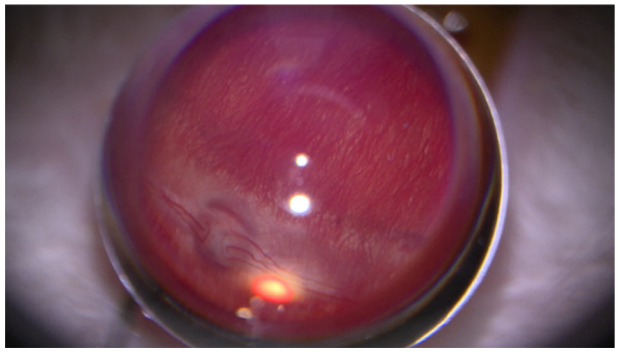

Figure 4. Rabbit 15. Fundus appearance through the novel synthetic cornea device demonstrating a clear view of the optic nerve and retina. The photograph was taken at 12 months postoperatively using the operating microscope (Proveo 8 Ophthalmic Microscope, Leica Microsystems, Wetzlar, Germany) and the BIOM5 HD fundus lens (Oculus Surgical, Inc., Fort Pierce, FL).

Tissue Response and Biointegration

In the 13 rabbit eyes without significant complications ($n = 8$ at 6 months and $n = 5$ at 12 months), the recipient cornea was quiescent without any appreciable inflammation, edema, or neovascularization. The porous ingrowth material around the optic wall and the skirt along with the macroapertures were invaded by the host fibroblast with new collagen laid. No thinning or epithelial defects overlying the anterior stroma were observed. Light microscopic examination of the globes also confirmed a lack of retroprosthetic membrane, anterior or posterior synechiae, or optic nerve atrophy. There was no epithelial growth overlying the optic. Histopathological examination of the retina and optic nerve did not demonstrate any obvious abnormal findings in any of the study eyes in comparison to the fellow eyes of the animals.

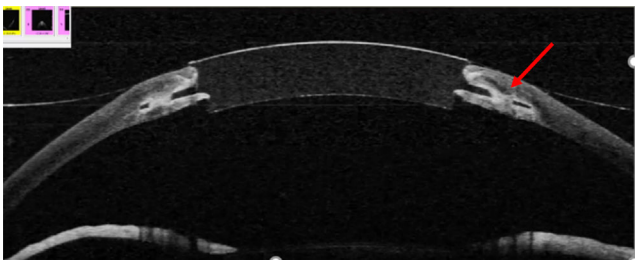

Figure 6. Rabbit 15. Optical coherence tomographic view of a rabbit eye at 12 months demonstrating good apposition of the device within the recipient corneal midstroma and healing response (lighter color) around the optical wall and skirt and through the macroapertures (red arrow). The anterior chamber depth and corneal curvature are unchanged.

Discussion

This experimental study demonstrated favorable outcomes of a novel one-piece optic skirt configuration, flexible, suturable synthetic cornea device in a healthy rabbit model over a 12-month follow-up. Clinical examination using an operating microscope did not reveal corneal neovascularization, edema, haze, retraction, retroprosthetic membrane, anterior or posterior synechiae formation, cataract, glaucoma, or retinal detachment. Anterior segment OCT demonstrated good apposition of the device without distortion of the anterior chamber or iridocorneal angle. Histopathological sections demonstrated significant fibroblast invasion and new collagen deposition into the interstices of the porous ingrowth material coating the optical wall and the skirt and through the entirety of the macroapertures. No significant inflammation, foreign body reaction with multinucleated giant cell formation, or encapsulation was noted. In the 6-month cohort, there were three rabbits with focal tissue

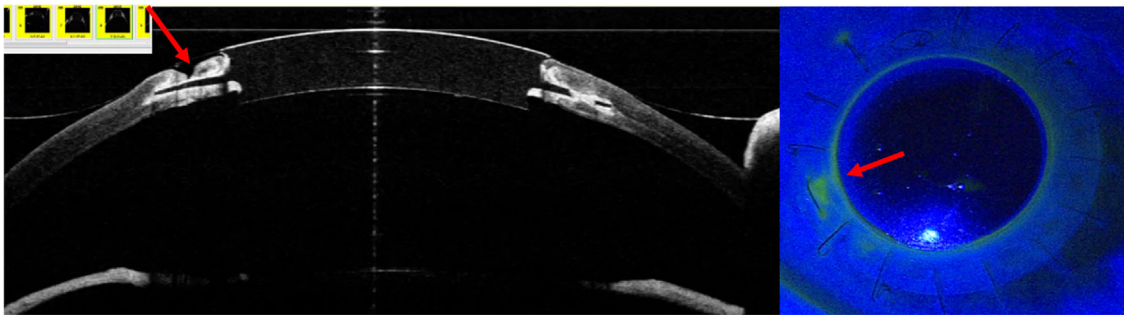

Figure 5. Rabbit 11. Mild focal anterior lamellar thinning at 6 months (red arrow) associated with a tight mattress suture after novel synthetic cornea device implantation in a healthy rabbit eye. The picture on the left depicts the anterior segment's optical coherence appearance. The picture on the right was taken under the operating microscope using external cobalt blue light after topical fluorescein instillation.

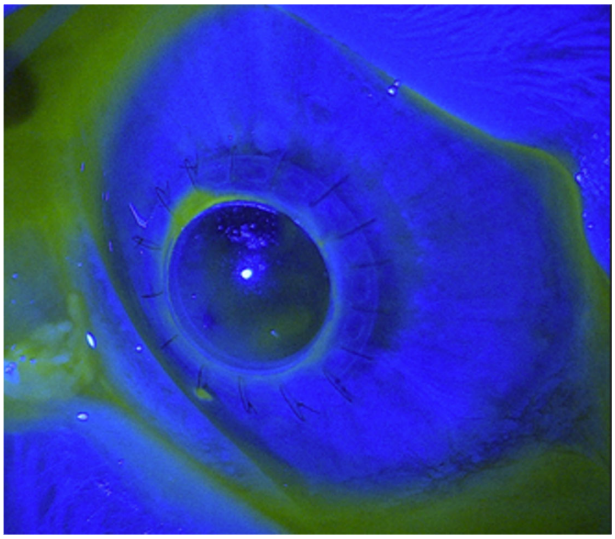

Figure 7. Rabbit 4. Clinical appearance of an area of localized anterior lamellar focal retraction without an infiltrate. This picture was taken under the operating microscope using an external cobalt blue light source and with topical fluorescein drops at day 315.

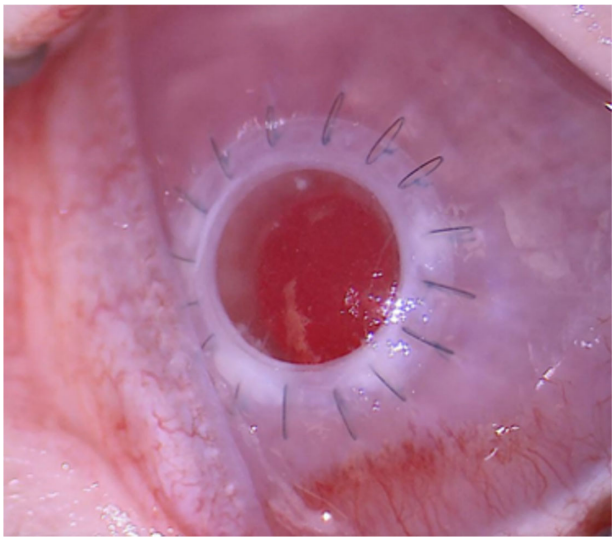

Figure 8. Rabbit 8. Clinical appearance of an area of the anterior segment under the operating microscope showing an infiltrate approximately 360° in the recipient cornea overlying the device skirt that preceded endophthalmitis.

thinning without epithelial defects or retraction. These areas corresponded with the location of tight mattress sutures. In the 12-month cohort, there was one case of endophthalmitis that had to be terminated early. Two rabbits had moderate tissue retraction without infection. Complications related to the device cornea integration were thought to be suture related. We did not note neovascularization of the recipient cornea in any of the rabbits except the one with endophthalmitis. This finding is a clinically relevant, because significant neovascularization would decrease the success of future conventional penetrating keratoplasty in the case of device failure.

Indeed, we encountered multiple sutures becoming loose throughout the follow-up starting from the 4-week time point. Although the sutures were meticulously replaced during the regularly scheduled monthly evaluations, we hypothesize that, in between visits, microepithelial or macroepithelial defects associated with the loose sutures may have led to the late postoperative complications. A literature review was indeed helpful in understanding the potential reasons why we encountered such suture issues. One consideration is that the rabbit cornea is thinner than the human cornea (380 µm vs. 550 µm).[20–22] In addition, owing to the scarcity of the collagen fibers and lack of collagen intertwining, the rabbit cornea is markedly less stiff with a lower elasticity modulus (1.1 kPa vs. 33 kPa) than the human cornea, which translates into decreased tensile strength.[23,24] In addition, the rabbit corneal epithelium is substantially thinner than human corneal epithelium peripherally, where the sutures are placed (45–47 µm vs. 51–55 µm centrally and 37.6 µm vs. 79.6 µm peripherally).[21] The 10-0 nylon suture used in these experiments (9000G, Ethicon, Raritan, NJ) has a diameter of 20 microns, and the difference in epithelial thickness between the two species approximates to 200% of the suture thickness. Suture-related issues are also very common in the pediatric donor corneal transplantation field,[25] but not in adult recipients.[26] This factor could be due to the fact that the pediatric cornea is structurally similar to the rabbit cornea as both are less stiff and thinner than the adult human cornea.[27] Further, the human cornea shows negligible extensibility under low stresses, such as a normal intraocular pressure. The rabbit tissue, however, undergoes a 9% strain under low pressures with a curvilinear relationship between stress and strain. At higher pressures the relationship is linear, and the tissue shows creep.[28] Additionally, we have observed the suture issues in normal rabbit eyes after syngeneic donor penetrating keratoplasty, which we performed as a control group.[19] Last, other authors also reported suture issues in rabbits after the initial phase of wound healing in the first 3 months.[29,30] Interestingly, mattress sutures were noted to cause more significant thinning of the tissue attributed to the greater fibrosis induced.[31]

In the United States, the Boston type 1 keratoprosthesis has been the last resort alternative to traditional penetrating keratoplasty in patients who are at high risk for failure. Although it has the potential to provide almost instant vision in patients who would otherwise not be offered corneal surgery, there has been a downward trend in the number of surgeries performed yearly both within the United States and overseas,[32]

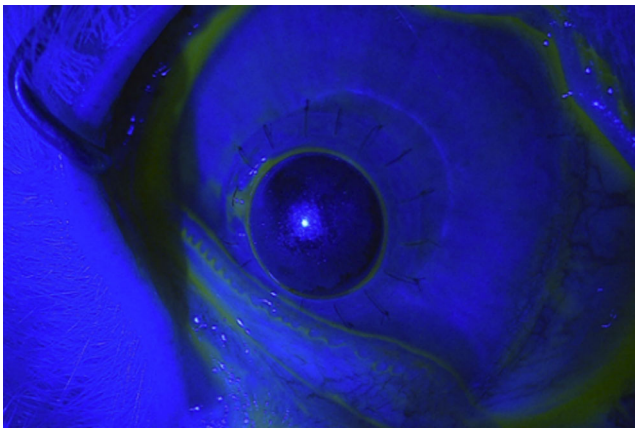

Figure 9. Rabbit 12. Clinical appearance of an area of localized anterior lamellar retraction without an infiltrate. The picture was taken under the operating microscope using an external cobalt blue light source and with topical fluorescein drops.

largely owing to continually worsening outcomes over longer term follow-up.[16,17] Although retroprosthetic membrane, infectious keratitis or endophthalmitis, sterile stromal keratitis, and device extrusion are all unwanted postoperative complications that can lead to loss of vision, glaucoma is the leading cause of permanent blindness after Boston type I keratoprosthesis surgery.[33] Otherwise, a reasonable visual acuity can be expected after a repair procedure or repeat keratoprosthesis surgery performed primarily or after an interim therapeutic keratoplasty[34] after those complications.

The exact pathway leading to extensive optic nerve damage and profound vision loss after Boston type I keratoprosthesis has yet to be elucidated. However, the immediate changes in the anterior chamber anatomy owing to the curvature mismatch between the posterior plate of the device and native cornea and the volume it occupies along with the bulky optical cylinder may play a role in crowding of the chamber and angle closure.[35,36] Inflammation is now considered the prime mechanism of glaucoma after the Boston keratoprosthesis. Chronic inflammation, mediated by tumor necrosis factor alpha and IL-beta in the tear film, the donor cornea, posterior segment, and peripheral circulation has previously been documented.[37–40]

We have not encountered glaucoma after the implantation of our novel flexible synthetic corneal device in healthy rabbit eyes assessed by tactile pressure measurement, OCT imaging of the optic nerve and retinal nerve fiber layer, or pupil light reflex at the exit visit, as well as histology of the optic nerve in the explanted globes. We hypothesize that this finding is due to the lack of inflammation elicited by the device. Although a rabbit is not a good model for glaucoma owing to the myelinization of the axons penetrating through the sparsely developed lamina cribrosa into the nerve fiber layer that changes the mechanical reactivity in the optic nerve head region,[41] the lack of anterior or posterior synechia and the presence of an entirely open angle in all of the animals were reassuring findings.

Structurally, the cornea is a thin elastic membrane made largely out of water.[42] There is a constant outward tension owing to the intraocular pressure and an inward force by the upper eyelid.[43] The Boston type I keratoprosthesis is a rigid device with no tissue integration around the optical wall. Therefore, with each blink, significant flexural oscillation of the prosthetic within the corneal wound occurs with irritation and substantial kinetic energy being generated, which is consequently absorbed by the surrounding corneal stroma and leads to thinning.[18] Otherwise, both polymethyl methacrylate and titanium, the materials that comprise the Boston keratoprosthesis device, are known to be inert with excellent biocompatibility. In fact, polymethyl methacrylate lens implants, whether implanted into the capsular bag or sulcus, are not known to cause inflammatory reactions unless there is constant movement. In addition, intermittent or constant separation of the stroma from the optic wall, periprosthetic gap, and loss of tight seal can occur owing to lack of device compliance and forms an entry point for debris or microbes, triggering idiopathic vitritis or endophthalmitis.[44]

For a thin plate, bending stiffness is directly related to the modulus of the material and the cross-sectional moment of inertia. Our novel prosthetic device is constructed with biocompatible and flexible materials that are compliant with the native human cornea. The porous ingrowth surface promotes bioadhesion of the recipient fibroblasts and collagen production. These two factors allow for strong bonding between the optic wall and the recipient cornea with high tensile strength (resistant to spontaneous separation or leak of less than 1000 mm Hg intraocular pressure [unpublished data on file, 2022]). Thus, the device seems to check two of the three most important requirements for an ideal artificial cornea: compliance and biointegration.[45] Although the long-term outcomes of the device–cornea integration without sutures are unknown. Studies for epithelization of the device optic are currently underway.

In conclusion, based on 12-month favorable results in rabbits, this novel synthetic cornea device has the potential to restore vision in corneally blind individuals who are otherwise at high risk of failure with donor keratoplasty. An early feasibility study in human patients is currently being planned.

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Supplementary Material

Supplementary Video 1.