# Efficacy and Safety of Biodegradable Collagen–Glycosaminoglycan Polymer as a Material for Scleral Buckling

*Wei-Chi Wu,*[1,2] *Chi-Chun Lai,*[1,2,3] *Henry Shen-Lih Chen,*[1,2] *Ming-Hui Sun,*[1] *Lien-Min Lee,*[1] *Chia-Pang Shih,*[4] *Howard Wen-Hao Lee,*[5] *and Wei-Cherng Hsu*[6,7]

**Purpose.** To test the efficacy and safety of a biodegradable collagen-glycosaminoglycan (CG) polymer as the material for scleral buckling in rabbit eyes.

**Methods.** Segmental scleral buckling was performed by using a silicone sponge in one eye and a biodegradable CG polymer in the other eye of 20 rabbits. Wound and conjunctival reactions were evaluated by external photographs 1 day and then every week after surgery. Echography was used to evaluate the extent of the buckling effect. Electroretinograms were used to evaluate the retinal function after scleral buckling. Histology and immunohistochemistry were used to check the tissue reaction and distribution of myofibroblasts during wound healing. Scanning electronic microscopy of buckling materials was used to analyze structural changes after episcleral implantation.

**Results.** Biodegradable collagen initially achieved a buckling effect comparable to a silicone sponge; the buckling effect decreased after 1 month. Within 8 to 12 weeks, the collagen was gradually absorbed. After implantation, the collagen matrix degraded, and the pore size decreased as a result of compression and degradation. In contrast, no major structural changes were observed in silicone sponges, except some cell debris, fibrin, and blood cells were detected inside the porous structure of the sponge. The inflammatory responses were comparable between sponge and collagen in most areas of peribuckling histology. In areas of degraded collagen, a foreign body reaction was observable. Electroretinography revealed no detectable difference in retinal function between control and experimental eyes.

**Conclusions.** Biodegradable collagen was used effectively and safely as a material for scleral buckling. (*Invest Ophthalmol Vis Sci.* 2008;49:2673–2678) DOI:10.1167/iovs.07-1594

From the [1]Department of Ophthalmology, Chang Gung Memorial Hospital, Taoyuan, Taiwan; the [2]College of Medicine, the [3]Chang Gung Institute of Technology, and the [4]Department of Business Administration, Chang Gung University, Taoyuan, Taiwan; the [5]Department of Ophthalmology, Li Shin Hospital, Taoyuan, Taiwan; the [6]Department of Ophthalmology, Buddhist Tzu Chi General Hospital, Taipei, Taiwan; and the [7]Department of Ophthalmology, Tzu Chi University, Hualien, Taiwan.

Supported by Life Spring Biotech Co. Ltd.

Submitted for publication December 14, 2007; revised February 4, 2008; accepted April 23, 2008.

Disclosure: **W.-C. Wu**, None; **C.-C. Lai**, None; **H.S.-L. Chen**, None; **M.-H. Sun**, None; **L.-M. Lee**, None; **C.-P. Shih**, None; **H.W.-H. Lee**, None; **W.-C. Hsu**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Wei-Cherng Hsu, Department of Ophthalmology, Buddhist Tzu Chi General Hospital, Taipei, Taiwan; cyao@seed.net.tw.

Retinal detachment is a serious ocular disease that can cause severe visual dysfunction. It occurs more frequently after ocular trauma, after ocular surgeries, and in high myopia. Scleral buckling with permanent materials has served well for repair of uncomplicated retinal detachment for more than 40 years.[1] Although the success rate is high, complications can occur with scleral-buckling procedures. Some complications are related to the use of permanent scleral buckling materials and include anterior segment ischemia,[2,3] intrusion of buckling materials,[4,5] refractive errors,[6–8] chronic infection,[9,10] buckle extrusion,[11,12] and diplopia caused by disturbance of the normal function of ocular muscles.[13] Temporary scleral buckling with absorbable materials may be able to reduce these undesired side effects.

Collagen and collagen copolymers have been applied in skin wound healing,[14–16] inhibition of conjunctival scarring,[17] and control of filtering bleb structure.[18] These materials are biodegradable, and tissue reactions have been widely investigated. The purpose of the present study was to evaluate the efficacy and biocompatibility of collagen matrix polymers used in scleral buckling surgery and to compare these materials with commonly used silicone sponge implants.

## Materials and Methods

### Collagen-Glycosaminoglycan (CG) Matrix Production

CG copolymer matrices were produced as previously described, with modifications.[14,19] Type 1 CG was prepared as a weak acidic aqueous solution and was stirred at high speed to form a slurrylike composition. After lyophilization for 36 hours, it was cross-linked via thermal dehydration at 105°C for 24 hours in a vacuum, followed by exposure to UV light. Additional cross-linkage was made by using genipin or glutaraldehyde to elevate the physical strength of the scleral buckling band.

### Animals and Surgical Procedures

Twenty male New Zealand rabbits weighing 2.5 to 3 kg were used. The animals were handled in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The rabbits were anesthetized with intramuscular injections of 1.5 mL/kg of an equal-volume mixture of 2-(2,6-xylidino)-5.6-dihydro-4H-1.3-thiazine-hydrochloride, methylparaben (Rompun; Bayer AG, Leverkusen, Germany), and 50 mg/mL ketamine (Ketalar; Parke-Davis, Morris Plains, NJ). Before surgical implantation, all episcleral implants were soaked in a 40-mg/mL solution of gentamicin. After topical application of benoxinate hydrochloride (Novesin; Novartis, Hettlingen, Switzerland), a lid retractor was used to allow a clear view of the site of implantation. The conjunctiva was dissected along the limbus at the superior temporal quadrant of the eyeball between the superior and lateral rectus muscles. After the superior and lateral rectus muscles were separated with a muscle hook, segmental scleral buckling was performed with the explant placed and maintained by one U-shaped scleral mattress suture of 5-0 plaited polyester (Dacron; Alcon Pharma, Fort Worth, TX), 5 mm from the limbus. The sutures were 7 mm apart, and each one was 2 to

3 mm long. The episcleral implants were approximately 10 mm long, and the sutures were tightened enough to produce a visible scleral invagination. The conjunctiva was closed with 7-0 polyglactin sutures (Vicryl; Ethicon, Somerville, NJ). At the end of the surgery and for the following 28 days, ophthalmic antibiotic ointment (tobramycin) was applied to the surgical eyes. Absorbable collagen explants were implanted in the right eyes, and silicone sponges (506 sponge; Mira Inc., Waltham, MA) were implanted in the left eyes as the control (Fig. 1).

### External Photos

Each week, animals were anesthetized and external photographs were taken by a digital camera. The degree of conjunctival congestion and buckle absorption were recorded. Conjunctival congestion was evaluated according to the Cornea and Contact Lens Research Unit (CCLRU) grading scale.[20] The severity of conjunctival redness ranged from very slight (grade 1), to slight (grade 2), to moderate (grade 3), to severe (grade 4). Signs of wound infection, buckle migration, and buckle exposure were also recorded.

### Echographic Examinations

The effect of scleral indentation was recorded by echographic examinations each week according to previously published methods.[21,22] After systemic anesthetization of animals, topical anesthetic agent (Novesin; Novartis, Hettlingen, Switzerland) was applied to the eye. An echographic machine (B-5500; Sonomed Inc., Lake Success, NY) was used to examine the effect of explant indentation on the sclera. The echographic probe (frequency: 10 MHz ± 10%) was directed toward the area of the scleral explants. B-scan mode was used to document the effect of scleral indentation while, A-scan mode was used to confirm the site of scleral indentation. A high spike was expected in the A-scan if the proper area of explants was recorded. The distance of the greatest indentation was measured as the buckling effect.

### Histologic and Immunohistochemical Staining

From 4 to 8 weeks after surgery, one rabbit was killed each week for histology. After fixation and dehydration of the eye cups, the samples were embedded in paraffin, serially sectioned (6 mm thickness), and stained for light microscopy with hematoxylin and eosin. The sections were examined in areas around the scleral explants. Additional tissue sections were used for immunohistochemistry to identify the distribution of myofibroblasts.[17] Myofibroblasts synthesize collagen fibers in a direction parallel to their orientation and are actively involved during wound healing.[23] Myofibroblasts contain the contractile apparatus of smooth muscle cells, α-smooth actin (SMA), which was the species targeted by immunohistochemistry.

### Electron Microscopy (EM)

Before and 6 weeks after implantation, the scleral explants were scanned via electron microscopy. After an intravenous overdose of pentobarbital sodium (100 mg/mL; Sigma-Aldrich, St. Louis, MO), the eyeballs were enucleated for morphology. The scleral explants were fixed in 3% glutaraldehyde in sodium phosphate buffer for 1 hour at 4°C, postfixed in 1% osmium tetroxide, dried to the critical point, sputter-coated in platinum, and photographed by microscope (model S-5000; Hitachi, Tokyo, Japan).

### Electroretinograms

Some absorbable buckling materials, such as gelatin, may cause a low-grade inflammatory reaction with vitreous haze and even macular edema.[1] Therefore, the ERG was used to evaluate retinal functional changes after implantation of buckling materials in the rabbits. One week after the scleral implants were placed and immediately before death, flash ERGs were recorded (UTAS-E 300; LKC Technology, Gaithersburg, MD) to assess the retinal function of collagen-implanted and control eyes. The rabbits were dark-adapted for 1 hour before the ERG. After they were anesthetized, the rabbits were placed on a heating pad. The recording Ag:AgCl electrode was placed on the cornea with 0.5% methyl cellulose as a conductive medium. A reference electrode was attached to the shaven skin of the head, and a ground electrode was clipped to the ear. A single-flash light (duration, 100 ms) 30 cm from the eye was used as the light stimulus. The responses were amplified with a gain setting ±500 μV and filtered with an amplifier (low, 0.3 Hz; high, 500 Hz). Data were acquired, digitized, and analyzed (EM) for Windows, ver. 2.6; LKC Technology) running on an IBM-compatible computer. The amplitudes and the implicit times of the a- and b-waves were measured and averaged.

### Statistical Analysis

The Wilcoxon signed-ranks test was used to test for significant differences in the buckle effects and ERG results between collagen-implanted and control eyes. The data were obtained and analyzed with statistical software (SPSS ver. 11.0; SPSS Inc., Chicago, IL) and are expressed as the mean ± SD, with $P < 0.05$ considered to be significant.

## Results

### External Photos

The degree of conjunctival congestion was similar between eyes implanted with silicone sponges and those implanted with collagen polymers (Fig. 2A). After surgery, moderate to severe conjunctival congestion lasted for ~4 to 5 weeks. After that, the redness decreased gradually. There was no significant difference between the two groups in the degree of conjunctival redness assessed by the CCLRU grading scale up to 10 weeks after surgery (Fig. 2B). None of the eyes developed buckle extrusion, intrusion, or infection.

### Buckle Height Determination

After surgery, the silicone sponges maintained a very stable buckle height. In contrast, the buckling effect of the CG matrix degreased gradually (Fig. 3). The buckle created by each material was noted immediately after surgery; the buckling effect was similar between the two materials. One week after implantation, there was still no significant difference in buckle height between the silicone sponge and the collagen matrix (3.79 ± 0.25 mm vs. 3.64 ± 0.31 mm, $n = 20$ each; $P = 0.07$). One month after implantation, 72% of the buckle height remained in the collagen-implanted eyes (3.68 ± 0.24 mm vs. 2.42 ± 0.55 mm, $n = 7$ each; $P = 0.017$). Six weeks after implantation, 43% of the buckle height remained in the collagen-implanted eyes (3.59 ± 0.23 mm vs. 1.59 ± 0.87 mm, $n = 8$; $P = 0.17$). Eight weeks after implantation, only 18% of the buckle height remained in the collagen-implanted eyes (3.7± 0.11 mm vs. 0.60 ± 0.58 mm, $n = 5$, $P = 0.043$; Fig. 3). Most of the CG matrices were reabsorbed 8 to 12 weeks after episcleral implantation.

### Electroretinograms

The ERG amplitude and the implicit time of the b-wave of the collagen-implanted eyes were not significantly different from those of the sponge-implanted eyes eyes, either at 1 week after surgery or immediately before death (Fig. 4). There was no noticeable change in ERG a-wave amplitude or implicit time between the two groups (data not shown).

### Histology and Immunohistochemistry

The histology and immunohistochemistry results are shown in Figure 5. In eyes implanted with silicone sponges, the tissues around the sponge formed a pseudocapsule (a capsule with endothelial lining). The pseudocapsule was mainly composed of fibroblast-like cells. There were a few neutrophils and lymphocytes scattered around the buckle material and in areas

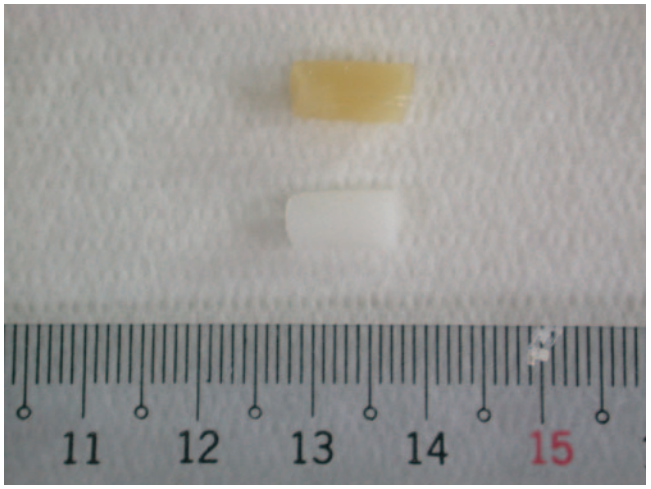


**FIGURE 1.** Gross appearance of collagen matrix (*top*) and 506 silicone sponge (*bottom*).

with stitches. In some areas, plasma cells were also detected. No foreign body giant cells were found. In eyes implanted with CG matrix, more inflammatory reactions were noted in areas inside the collagen material. No capsule formed around the CG matrix. In CG-degraded areas, there was less inflammation than in areas inside the CG matrix undergoing active degradation. The degree of inflammation was compatible with that in the eyes implanted with silicone sponges. Some foreign body giant cells were clustered around the collagen and around the area of the stitches. There was more neutrophil and lymphocyte infiltration in the pericollagen areas, indicating a mixed acute and chronic inflammatory reaction. Some plasma cells were also detected. The choroid and retina adjacent to the implant appeared to be intact, except for signs of compression.

In CG-implanted eyes, immunostaining for $\alpha$- SMA showed randomly distributed myofibroblasts adhering to the remaining CG matrix. In contrast, SMA-positive cells were found only in the structure of vessel walls inside the capsule in the sponge-implanted eyes. The randomly distributed myofibroblasts that produced collagen in the random alignment were different from the uniaxial orientation of the myofibroblasts and collagen in scar tissue. No retinal edema or retinal inflammation was noted. Only retinal compression was noted in the area directly underneath the scleral buckling.

## Scanning Electronic Microscopy (SEM)

SEM of the silicone sponge revealed numerous porous structures on the surface of the silicone sponge. The size of these porous structures ranged from 20 to 400 $\mu$m. After the sponge was implanted as an episcleral buckling agent, no major structural changes were observed, except for some cell debris, fibrin, and blood cells detected inside these porous structures.

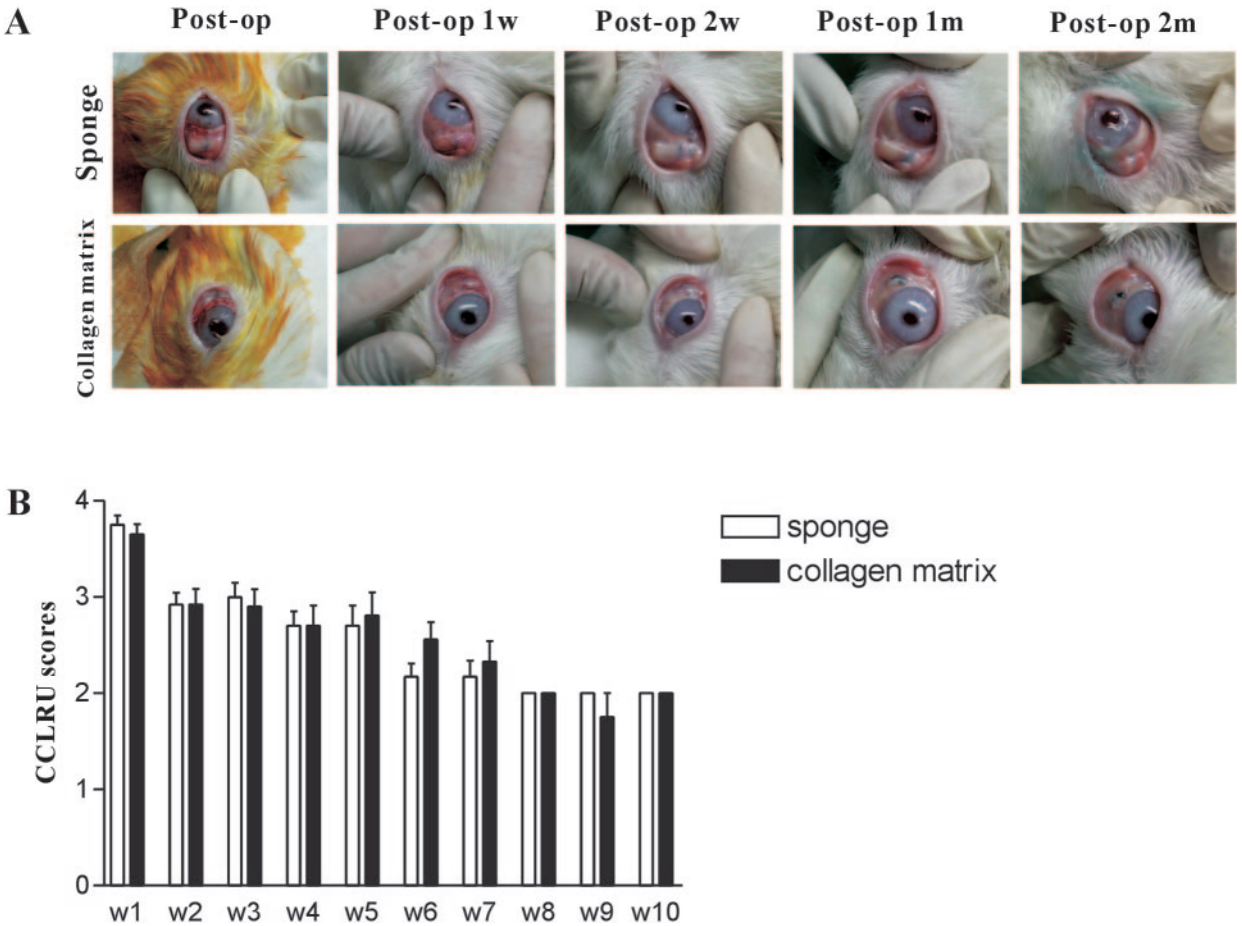


**FIGURE 2.** External photographs and conjunctival congestion scores of eyes after implantation of CG matrix and silicone sponge. (**A**) Collagen matrix was implanted in the right eye and a silicone sponge in the left eye. The degree of conjunctival congestion was comparable between these two groups. Buckling in eyes implanted with silicone sponges remained stable after surgery, whereas the collagen matrix was reabsorbed gradually. (**B**) There was no difference in conjunctival congestion scores between these two treatment groups up to 10 weeks after surgery.

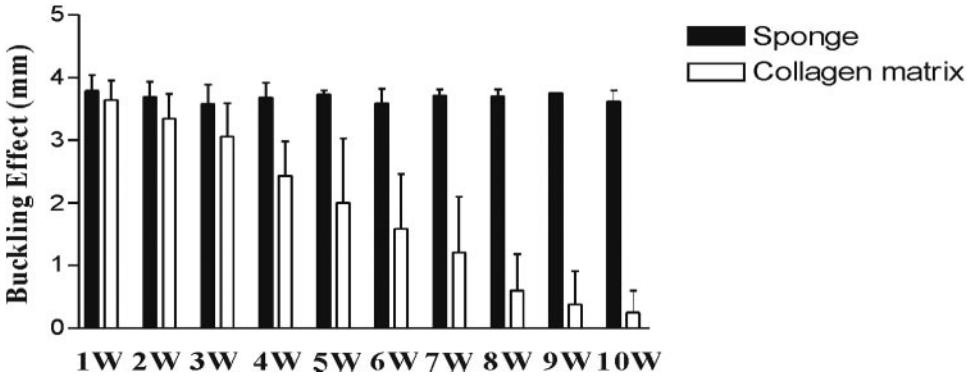


**FIGURE 3.** Buckling effect after implantation of collagen matrix in one eye and silicone sponge in the other eye. The buckling effect remained stable in eyes implanted with silicone sponges, but decreased gradually in eyes implanted with collagen matrix.

SEM of the CG matrix revealed that the collagen matrix consisted of collagen plates loosely packed together. Randomly oriented pore walls were observed on the collagen matrix surface. The pore size of the collagen matrix ranged from 20 to 200 $\mu$m. After the sponges were implanted episclerally for 6 weeks, the morphology of the collagen matrix changed significantly. The collagen matrix degraded partially and the pore size decreased as a result of compression and degradation (Fig. 6).

## DISCUSSION

Buckling implants close retinal tears and provide mechanical support until the retina and choroid have reattached with chorioretinal scar formation. Permanent implants have been used for decades for scleral buckling in retinal detachment surgery. In cases with a fixed retinal fold, multiple breaks, or advanced proliferative vitreoretinopathy (PVR), permanent support to reattach the retina is usually needed. Permanent implants can cause long-term complications such as intrusion, extrusion through the conjunctiva, infection, pain, or diplopia.[2–13] In retinopathy of prematurity–induced retinal detachment treated with scleral buckling, additional procedures must be performed early in infancy to sever or remove the permanent buckling materials, to prevent the inhibition of normal eye growth.[6] In simple uncomplicated cases of retinal detachment, the need for a buckling effect is temporary.[24]

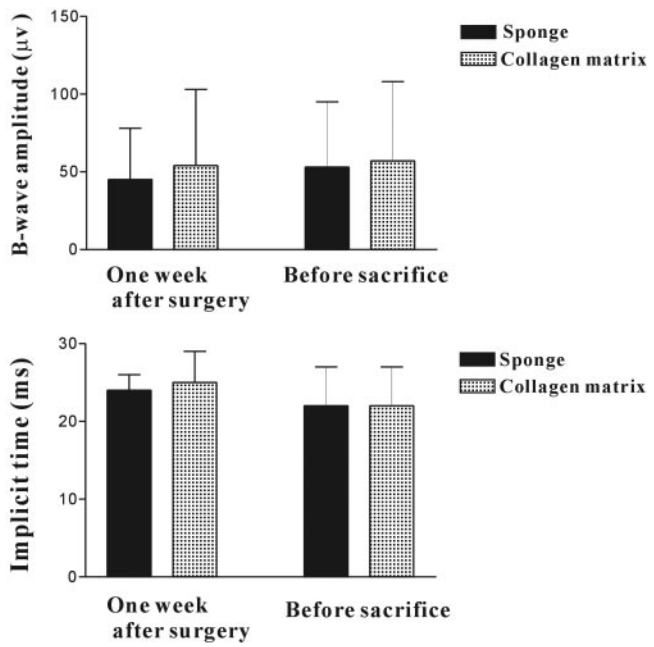


**FIGURE 4.** ERG results in eyes implanted with collagen matrix or silicone sponges. There was no significant difference between the two treatment groups in b-wave amplitude or implicit time, either 1 week after surgery or immediately before the animals were killed.

An optimal implant for patients who need only temporary scleral buckling could be made of a slowly biodegradable material with good biocompatibility, such as donor tissue or specially prepared materials. Donor tissues, such as fascia lata[25] and sclera,[26,27] are derived from either autogenous or cadaveric sources. The drawbacks of using these tissues are the additional surgery necessary to obtain autologous tissues or the risk of infection or other unknown risks when using donor tissues. Specially prepared materials, such as gelatin[28–31] and bovine fibrin,[32] have been used as scleral implants. Gelatin is somewhat brittle and must be implanted under the scleral flap.[1] Once implanted, it gradually liquefies and is replaced by a thin layer of granulation tissue. Because of this tissue reaction, gelatin may cause a low-grade inflammatory reaction with vitreous haze and even macular edema.[1]

Because temporary buckling materials are sometimes desirable and because of the shortcomings of available temporary buckling materials, biodegradable scleral implants comprised of a CG copolymer were developed and tested in this rabbit animal model. The CG copolymer is a biocompatible material that undergoes biodegradation during the wound healing process in vivo. The rate of degradation of the CG copolymer depends on the tissue reaction and the dosage of anti-inflammatory medication.[33–35] Beyond passive degradation, the CG copolymer matrix can even induce partial regeneration of the injured dermis in humans and animals.[36–38] Implantation of the CG copolymer in these models inhibited wound contraction and stimulated regeneration of a nearly physiological dermis. Implantation of CG copolymer matrix in a surgery-induced conjunctival defect drastically reduced wound contraction and guided the healing of subconjunctival stroma with a more physiological collagen deposition.[17] Conjunctival scarring was inhibited and fornix shortening was prevented after implantation.[18] In agreement with these other research reports, our study also shows that application of CG copolymer can lead to random and relatively loose reorganization of regenerating myofibroblasts, that might reduce scar formation.[17] These findings suggest that the CG matrix provides a physiological structure for tissue repair, inducing a conjunctival wound to heal more in a physiological than a pathologic process.

Potential complications associated with CG copolymers are comparable with those of silicon sponges before they are degraded. These complications include infection, extrusion, anterior segment ischemia, changes in refractive error, choroidal detachment, motility disturbance, and failure to reattach. However, CG copolymers are reabsorbed within a couple of months after implantation, which might reduce the complications of chronic infection, motility disturbance, and induced

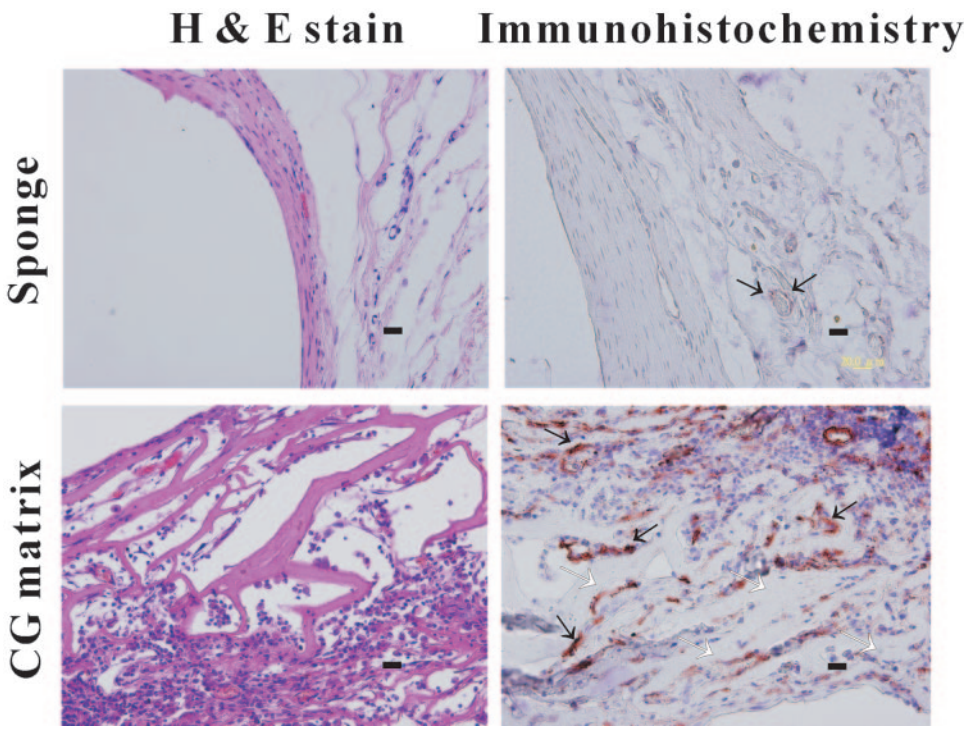


**FIGURE 5.** Histology and immunohistochemistry results after implantation of sponges or CG copolymers. H&E staining showed numerous neutrophils and lymphocytes inside the degrading CG matrix. In sponge-implanted eyes, pseudocapsule formation around sponge was noted, with fewer neutrophils and lymphocytes. In CG-implanted eyes, immunostaining for α-SMA showed randomly distributed myofibroblasts (*black arrows*) adhering to the degrading CG matrix (*white arrowheads*). In contrast, SMA-positive cells were found only in the structure of vessel walls inside the capsule in the sponge-implanted eyes (*black arrows*). Scale bar, 20 μm.

refractive error. If the underlying etiology that induces PVR and retinal redetachment after the CG copolymer has degraded, then permanent scleral buckling materials will be needed because they could provide a persistent vitreous base support to counter the tractional force.

CG polymer, implanted on top of the sclera like a sponge, is easier to handle, less brittle, and less antigenic than gelatin. Therefore, simple retinal detachment may be treated more safely and with more physiologic wound healing by using this material as a biodegradable implant. The stiffness of the CG material and the rate of its degradation can be adjusted according to each patient's particular need by changing the level of collagen cross-linkage and the concentration of collagen.[39] Thus, CG matrix could be a good biodegradable material for scleral buckling procedures in the future. These promising results justify controlled clinical trials with this biodegradable material, which might allow the combined advantages of precise localization similar to silicone sponge explants, reversibil-

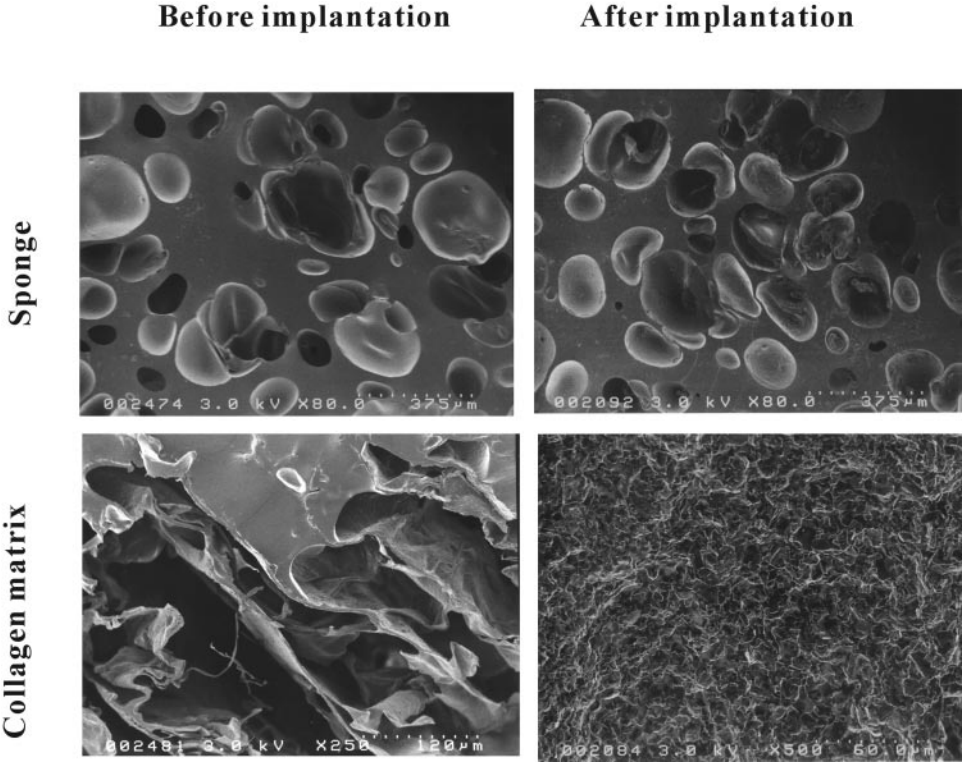


**FIGURE 6.** SEM of silicone sponge and collagen matrix before and after episcleral implantation. Cut end of collagen-CG matrixes shows irregularly shaped cells (interstices) 20 to 400 μm in size before implantation. After implantation, the morphology of the collagen matrix changed significantly. The collagen matrix degraded, and the pore size decreased as a result of compression and degradation. SEM of the silicone sponge revealed numerous porous structures on the surface of the silicone sponge. After implantation of the sponge as an episcleral buckling agent, no major structural changes were observed, except for some cell debris, fibrin, and blood cells detected inside these porous structures.

ity similar to inflatable balloon treatment, and perhaps even enhanced wound healing.

## *References*


1. Schepens CL, Acosta F. Scleral implants: an historical perspective. *Surv Ophthalmol*. 1991;35:447–453.
2. Doi N, Uemura A, Nakao K. Complications associated with vortex vein damage in scleral buckling surgery for rhegmatogenous retinal detachment. *Jpn J Ophthalmol*. 1999;43:232–238.
3. Barile GR, Chang S, Horowitz JD, Reppucci VS, Schiff WM, Wong DT. Neovascular complications associated with rubeosis iridis and peripheral retinal detachment after retinal detachment surgery. *Am J Ophthalmol*. 1998;126:379–389.
4. Shami MJ, Abdul-Rahim AS. Intrusion of a scleral buckle: a late complication of retinal reattachment surgery. *Retina*. 2001;21:195–197.
5. Nguyen QD, Lashkari K, Hirose T, Pruett RC, McMeel JW, Schepens CL. Erosion and intrusion of silicone rubber scleral buckle: presentation and management. *Retina*. 2001;21:214–220.
6. Chow DR, Ferrone PJ, Trese MT. Refractive changes associated with scleral buckling and division in retinopathy of prematurity. *Arch Ophthalmol*. 1998;116:1446–1448.
7. Sato T, Kawasaki T, Okuyama M, Ideta H. Refractive changes following scleral buckling surgery in juvenile retinal detachment. *Retina*. 2003;23:629–635.
8. Smiddy WE, Loupe DN, Michels RG, Enger C, Glaser BM, deBustros S. Refractive changes after scleral buckling surgery. *Arch Ophthalmol*. 1989;107:1469–1471.
9. Roldan-Pallares M, Castillo Sanz JL, Awad-El Susi S, Refojo MF. Long-term complications of silicone and hydrogel explants in retinal reattachment surgery. *Arch Ophthalmol*. 1999;117:197–201.
10. Smiddy WE, Miller D, Flynn HW Jr. Scleral buckle infections due to atypical mycobacteria. *Retina*. 1991;11:394–398.
11. Deokule S, Reginald A, Callear A. Scleral explant removal: the last decade. *Eye*. 2003;17:697–700.
12. Yoshizumi MO. Exposure of intrascleral implants. *Ophthalmology*. 1980;87:1150–1154.
13. Spencer AF, Newton C, Vernon SA. Incidence of ocular motility problems following scleral buckling surgery. *Eye*. 1993;7:751–756.
14. Yannas IV, Lee E, Orgill DP, Skrabut EM, Murphy GF. Synthesis and characterization of a model extracellular matrix that induces partial regeneration of adult mammalian skin. *Proc Natl Acad Sci USA*. 1989;86:933–937.
15. Yannas IV. Tissue regeneration by use of collagen-glycosaminoglycan copolymers. *Clin Mater*. 1992;9:179–187.
16. Yannas IV. Studies on the biological activity of the dermal regeneration template. *Wound Repair Regen*. 1998;6:518–523.
17. Hsu WC, Spilker MH, Yannas IV, Rubin PA. Inhibition of conjunctival scarring and contraction by a porous collagen-glycosaminoglycan implant. *Invest Ophthalmol Vis Sci*. 2000;41:2404–2411.
18. Chen HS, Ritch R, Krupin T, Hsu WC. Control of filtering bleb structure through tissue bioengineering: an animal model. *Invest Ophthalmol Vis Sci*. 2006;47:5310–5314.
19. Yannas IV, Burke JF, Gordon PL, Huang C, Rubenstein RH. Design of an artificial skin. II. Control of chemical composition. *J Biomed Mater Res*. 1980;14:107–132.
20. Cornea and Contact Lenses Research Unit. *C.C.L.R.U. Grading Scales.* Sydney, Australia: University of New South Wales; 1996
21. Irvine AR, Stone RD. An ultrasonographic study of early buckle height after sponge explants. *Am J Ophthalmol*. 1981;92:403–406.
22. Stone RD, Irvine AR, Santos E. An ultrasonographic study of the persistence of buckle height three years after segmental sponge explants. *Am J Ophthalmol*. 1977;84:508–513.
23. Gabbiani G, Ryan GB, Majne G. Presence of modified fibroblasts in granulation tissue and their possible role in wound contraction. *Experientia*. 1971;27:549–550.
24. Lincoff HA, Kreissig I, Hahn YS. A temporary balloon buckle for the treatment of small retinal detachments. *Ophthalmology*. 1979;86:586–596.
25. Minning CA Jr, Havener WH. Host tolerance of homologous fascia lata in retinal detachment surgery. *Arch Ophthalmol*. 1983;101:475–478.
26. Thompson FB. Scleral reinforcement for severe myopia: case report demonstrating long-term viability of scleral implant. *Ann Ophthalmol*. 1982;14:94–95.
27. Cibis PA, Knobloch WH. Scleral implants with preserved human sclera. *Bibl Ophthalmol*. 1967;72:293–318.
28. King LM Jr, Margherio RR, Schepens CL. Gelatin implants in scleral buckling procedures. *Arch Ophthalmol*. 1975;93:807–811.
29. Tanenbaum HL, Chandra G. Gelatin implants in retina surgery. *Can J Ophthalmol*. 1976;11:52–54
30. Levit R, Seelenfreund MH, Freilich DB. Use of ophthalmic gelfilm in retinal surgery. *Ann Ophthalmol*. 1975;7:1613–1616.
31. Daniele S, Jacklin HN, Schepens CL, Freeman HM. Gelatin as an absorbable implant in scleral buckling procedures. *Arch Ophthalmol*. 1968;80:115–119.
32. Grosz ID, Vereb K, Kerenyi G. Scleral buckling with Bioplast fibrin in retinal detachment. *Acta Ophthalmol* (*Copenh*). 1976;54:408–416.
33. Bryniarski K, Maresz K, Szczepanik M, Ptak M, Ptak W. Modulation of macrophage activity by proteolytic enzymes: differential regulation of IL-6 and reactive oxygen intermediates (ROIs) synthesis as a possible homeostatic mechanism in the control of inflammation. *Inflammation*. 2003;27:333–340.
34. Daniels JT, Cambrey AD, Occleston NL et al. Matrix metalloproteinase inhibition modulates fibroblast-mediated matrix contraction and collagen production in vitro. *Invest Ophthalmol Vis Sci*. 2003;44:1104–1110.
35. Huang C, Yannas IV. Mechanochemical studies of enzymatic degradation of insoluble collagen fibers. *J Biomed Mater Res*. 1977;11:137–154.
36. Burke JF, Yannas IV, Quinby WC Jr, Bondoc CC, Jung WK. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. *Ann Surg*. 1981;194:413–428.
37. Heimbach D, Luterman A, Burke J, et al. Artificial dermis for major burns: a multi-center randomized clinical trial. *Ann Surg*. 1988;208:313–320.
38. Yannas IV, Burke JF, Orgill DP, Skrabut EM. Wound tissue can utilize a polymeric template to synthesize a functional extension of skin. *Science*. 1982;215:174–176.
39. Lee CR, Grodzinsky AJ, Spector M. The effects of cross-linking of collagen-glycosaminoglycan scaffolds on compressive stiffness, chondrocyte-mediated contraction, proliferation and biosynthesis. *Biomaterials*. 2001;22:3145–3154.