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REFRACTIVE EYECARE®

SPECTACLES, CONTACT LENSES, AND CORNEAL AND LENTICULAR REFRACTIVE SURGERY FOR PRACTICE GROWTH

Collagen Crosslinking Enters US Clinical Trials

R. Doyle Stulting, MD, PhD

With an FDA clinical trial now in progress, collagen crosslinking may become a new option for treating keratoconus and post-LASIK ectasia.

Currently, patients with keratoconus and other progressive ectatic conditions often face a grim prognosis. While spectacles and contact lenses may correct their vision for a time, invasive surgeries—typically Intacs® (Addition Technology, Inc.) or penetrating keratoplasty—often become necessary as the ectasia progresses.

Fortunately, recent research into collagen crosslinking could soon provide another option. A relatively noninvasive procedure that enhances the biomechanical strength of the cornea, collagen crosslinking has already shown promise for treating keratoconus and post-LASIK ectasia; and the procedure may have other applications as well, from augmenting the safety and efficacy of existing refractive procedures to treating corneal ulcers.

To pave the way for clinical use of collagen crosslinking in the US, I recently began an FDA trial to assess its safety and efficacy. If the results of this study confirm the positive findings of research performed in other countries, patients with keratoconus and post-LASIK ectasia may gain a new treatment option that could not only alleviate the need for some corneal transplants but also significantly improve vision.

Collagen Crosslinking with Riboflavin and UV Light

Procedurally, collagen crosslinking is fairly straightforward. The technique employed by most researchers—which is also the

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Optimizing the Athlete's Vision

Rolando Toyos, MD

Ophthalmologists have much insight to offer elite athletes, and the recreational athlete may be interested, too.

Comprehensive eye practices of the future can expect to see more of a certain kind of patient in their exam rooms, patients for whom an eye exam is much more than routine body maintenance. In a sports-crazed nation, weekend warriors and student athletes will want ophthalmologists to give them a specialized vision tune-up—an exam to find the tiny, unique quirks of a person's visual system that might be interfering with their game.

This new breed of patient will have high expectations for the quality of vision they achieve with corrective lenses or refractive surgery. "Good enough" corrections will of necessity become a thing of the past; 0.25 D of residual sphere or cylinder will not satisfy them.

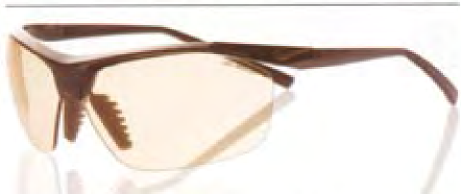

FIGURE 1 Nike's tinted Impel wrap sunglass is designed to reduce glare for runners. (Photo courtesy Marchon.)

Lessons Learned

Sports ophthalmologists like myself encounter such patients today, and I expect a growing number of others to percolate through the ophthalmic community over the next several years and beyond. As president of the Sports Ophthalmic Society of the Americas (www.sosas.org), my hope is that the knowledge to better

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technique being used in the FDA study—uses riboflavin and ultraviolet (UV) light to trigger a biochemical reaction between collagen fibers.

Once the epithelium is removed, the cornea is first pretreated and then saturated with a solution of riboflavin, which is allowed time to soak into the stroma. Then the surgeon exposes the eye to UVA light for 30 minutes, while reapplying riboflavin every few minutes throughout the procedure (Figure 1). Because the intensity of the UV light is carefully calibrated prior to the procedure, the UV irradiation affects only the riboflavin-soaked stroma and does not damage tissues deeper in the eye.

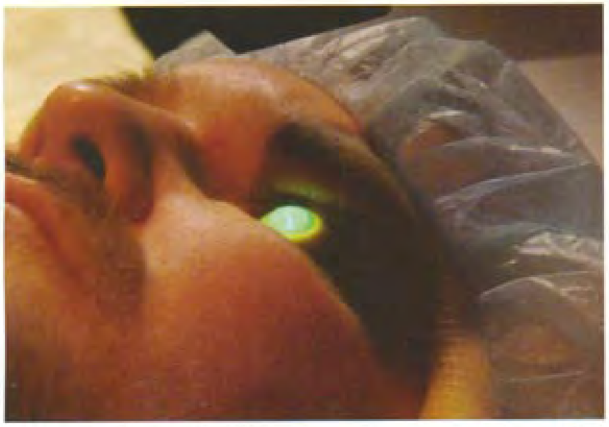

FIGURE 1 During the collagen crosslinking procedure, ultraviolet light is shone on the cornea for approximately 30 minutes. The green color is fluorescence from the riboflavin that has been applied to the eye.

During this process, chemical bonds between collagen fibers in the stroma are formed. These crosslinks help to stabilize and strengthen the tissue, thus enhancing the eye's biomechanical stability. Since ectatic conditions result from corneal weakness—whether due to a degenerative process as in keratoconus or a surgically induced weakening as in LASIK—enhancing the biomechanical strength of the cornea promises to be an effective means for treating weakened corneas.

Early Research and Ongoing Studies

While the current FDA trial is the first study in the US to rigorously evaluate collagen crosslinking, researchers abroad have already published positive results.[1,2] So far, research has focused primarily on the use of collagen crosslinking for treating keratoconus and post-LASIK ectasia, but other applications, such as treating corneal ulcers, have also been evaluated.

In a 2006 study evaluating the efficacy of collagen crosslinking for the treatment of keratoconus, researchers in Siena, Italy, treated 10 eyes of 10 patients with bilateral keratoconus.[1] After treatment, topography showed that the power of the central 3 mm of the cornea had decreased by over 2 D, and the researchers observed a trend towards increasing corneal symmetry. The mean spherical equivalent correction also decreased from −4.7 ± 3.35 D preoperatively to −2.495 ± 3.06 D at the 3-month follow-up visit.

ONGOING FDA TRIAL FOR COLLAGEN CROSSLINKING

- Lead Researcher: R. Doyle Stulting
- Study aim is to evaluate collagen crosslinking for two indications:
  — Keratoconus
  — Post-LASIK ectasia
- Multicenter study will enroll 160 patients per indication
- First patients were treated in early January 2008

Another recent study conducted at sites in Switzerland and Greece found positive results using collagen crosslinking to treat eyes with post-LASIK ectasia.[2] In half of the 10 patients treated in this study, progressive keratoectasia had *regressed* by the 12-month follow-up; in the remaining patients, keratoectasia was halted. Most patients showed an improvement in best spectacle-corrected visual acuity and a decrease in the amount of cylinder. This study also showed that the effect of the treatment appears to be long-term; one patient showed continuous improvement of the maximum K readings out to 25 months, with a best spectacle-corrected visual acuity going from 20/60 at baseline to 20/25 at 25 months.

So far, research has focused primarily on the use of collagen crosslinking for treating keratoconus and post-LASIK ectasia, but other applications, such as treating corneal ulcers, have also been evaluated

Building on these findings, my study will evaluate the safety and efficacy of collagen crosslinking for treatment of both keratoconus and post-LASIK ectasia. Using the riboflavin and UV light technique described previously, the multicenter study will enroll 160 patients for each indication. Change in corneal curvature is the primary endpoint. Although the completion of the study and FDA review could take some time, the first patients were treated in early January of this year and the study is ongoing.

Other Potential Applications

While most current research on collagen crosslinking focuses on treating keratoconus and post-LASIK ectasia, several other uses remain to be explored. In addition to applications that involve strengthening corneal tissue,

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Implications for Surgeons

Because of the relative simplicity of the collagen crosslinking procedure and its potential applications for treating conditions for which few good therapeutic options currently exist, it may become an important treatment modality. Not only would FDA approval of this technique provide surgeons with a new option for treating keratoconus and post-LASIK ectasia, it would also increase the importance of screening for these conditions, since identifying these conditions early would allow collagen crosslinking treatments to provide the greatest benefit.

THE BOTTOM LINE

An ongoing FDA trial to evaluate collagen crosslinking may soon give surgeons a new treatment option for halting or even reversing the ectatic progression in keratoconus and post-LASIK ectasia. In addition, this procedure may also have applications in the treatment of edema, corneal ulcers, and infections.

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References

1. Caporossi A, Baiocchi S, Mazzotta C, et al. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced crosslinking of corneal collagen: preliminary refractive results in an Italian study. *J Cataract Refract Surg.* 2006 May;32(5):837-45.
2. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg.* 2007;33(12):2035–40.
3. Spoerl E, Wollensak G, Seiler T. Increased resistance of crosslinked cornea against enzymatic digestion. *Curr Eye Res.* 2004 Jul; 29(1):35-40.

ATHLETE'S VISION continued from page 1

serve these patients will come from those of us who currently care for the vision of elite athletes.

Already, the ophthalmic world has seen how much influence athletes can have on our patients' choices. When high-profile professional athletes like golfer Tiger Woods (a −10 D myope) had LASIK surgery and then began a long winning streak, the publicity helped to inspire confidence in refractive surgery among prospective patients who had been leery of the microkeratome speeding up the laser vision correction revolution.

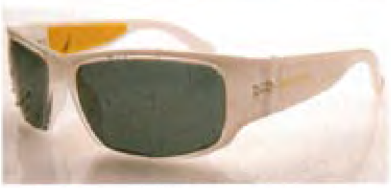

FIGURE 2 The Nautica Drifter frame, which has polarized lenses and floats if dropped in water, is aimed at athletes who compete in outdoor water sports. (Photo courtesy Marchon.)

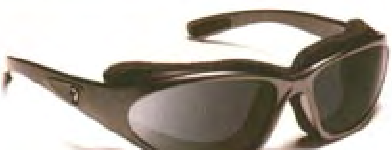

FIGURE 3 The ColorTec Gray lens in Panoptx' Bora sunglass enhances the colors red, green, and yellow. Note the protective eyecups. (Photo courtesy Panoptx.)

Tools to See Better

Since then, we have seen developments such as sports-specific sunglass and contact lens tints, and even multifocal intraocular lenses that some believe are ideal for sports like golf.

Meanwhile, the crackdown on performance-enhancing drugs in sports has forced pro players to look elsewhere for their next competitive advantage. One of these has been "vision coaching," which uses our field's basic knowledge of how humans see to teach athletes ways to improve the big-picture aspects of vision, such as eye-body coordination, tracking of moving objects, and peripheral vision.

Athletes of All Ages

The burgeoning interest in individually optimized vision cuts across all age groups. Who among us has not had at least one active retiree ask about an IOL or special sunglasses that might shave a few strokes off his golf score? (Figures 1-3)

PROFESSIONAL ATHLETES

- ✓ Demand perfect vision correction
  - — 0.25 residual sphere or cylinder is not good enough
- ✓ Create demand in patients who aren't professional athletes
  - — For example, Tiger Woods' endorsement of LASIK
- ✓ May be reluctant to treat existing visual impediments
  - — Fear adapting to different vision
- ✓ Looking for an edge
  - — Sharper vision
  - — Vision coaching (learning to use vision better)
- ✓ High risk for ocular injury, but
- ✓ Typically reject protective eyewear
- ✓ May be improved beyond 20/20 by HOA elimination
- ✓ Require doctor's time to determine exact visual needs

When I examine rookies on a professional sports team for the first time, I have been surprised to find that some of them never had an eye exam during their school years. Some have had undiagnosed cataracts, amblyopia, glaucoma, keratoconus, and uncorrected refractive error. But it is not uncommon for these players to refuse treatment or refractive correction for fear that a prolonged adaptation period would hurt their game.

In contrast, I recall the case of a baseball player I treated, a myope whose best-corrected visual acuity (BCVA) with spectacles and contact lenses was 20/20. He wanted to know why his .317 daytime batting average dropped to .250 during night games. Aberrometry (WaveScan Wavefront®, LadarWave Aberrometry, Visx/AMO) showed that his eyes had high levels

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the procedure could also prove useful for treatment of infectious keratitis and sterile corneal melts.

Perhaps the most exciting unexplored use of the procedure might be to *prophylactically* crosslink eyes vulnerable to surgically induced ectasia. Currently, most surgeons consider an irregular or thin cornea to be a contraindication for LASIK; if surgeons could use collagen crosslinking to strengthen these eyes before a planned LASIK procedure, these patients could potentially enjoy the benefits of a refractive procedure without undue risk.

Collagen crosslinking may also be able to aid in the treatment of corneal edema secondary to conditions such as Fuchs endothelial dystrophy. Preliminary results indicate that collagen crosslinking causes at least some of the edema to resolve and the cornea to thin, resulting in improved visual acuity. If early results are borne out, collagen crosslinking could potentially be used to treat patients with pseudophakic corneal edema and other corneal abnormalities, in addition to Fuchs dystrophy.

The ability of collagen crosslinking to stiffen the cornea could also enhance the benefits of orthokeratology. If patients who receive adequate, although temporary, vision correction from orthokeratology were to wear their lenses overnight and then undergo collagen crosslinking before the cornea returned to its unaltered shape, the effect of the orthokeratology lenses could potentially become long-term, if not permanent.

Enhancing the biomechanical strength of the cornea promises to be an effective means for treating weakened corneas

Finally, collagen crosslinking may also have applications for treating corneal ulcers or drug-resistant infections. Because some research has shown that collagen crosslinking makes the cornea resistant to enzymatic degradation, it could help stabilize the cornea in cases in which a corneal ulcer occurs as a result of autoimmune disease or when corneal melting occurs due to inflammatory disease.[3] In addition, because the collagen crosslinking reaction produces free radicals that can kill microbes, the procedure could conceivably aid in the treatment of drug-resistant infections.

How Collagen Crosslinking Improves Corneal Stability

Stephen D. Klyce, PhD

In a normal human eye, the anterior cornea's radius of curvature is about 7.8 mm. When the cornea is weakened through disease or surgery, however, it can become ectatic and bulge out, increasing the corneal curvature and, as a consequence, increasing the cornea's refractive power. Because of this intrinsic connection between corneal curvature and refractive power, normal vision requires that the cornea maintain a constant shape, making the biomechanical stability of the cornea a crucial factor for vision.

Not only must the cornea maintain its shape, it must also remain transparent. This requirement puts some unique constraints on corneal tissue that increase its vulnerability to biomechanical destabilization. Unlike tissues that are composed of interconnected fibers of different diameters, collagen fibers in the cornea are uniform in diameter and run virtually uninterrupted from limbus to limbus. This ordered arrangement of fibers is one of the unique features of the cornea that makes corneal transparency possible. However, the lack of connections between collagen fibers makes the cornea weaker than tissues in which the fibers can crosslink and form a matrix. Because of its lack of crosslinks, the cornea can be critically weakened by physiologic processes, such as those that take place in keratoconus, as well as by the flap cutting and tissue ablation of LASIK. In either case, thinning in one part of the cornea can affect the shape of the entire tissue.

Collagen crosslinking addresses biomechanical weakening by using riboflavin and ultraviolet light to trigger bonding between collagen fibers. Chemically, the process is similar to the reaction that occurs during the tanning of animal hides, and the result is analogous: the tissue is made stronger and more stable. By creating chemical bridges between collagen fibers, collagen crosslinking increases the biomechanical strength of the cornea, allowing it to better withstand the eye's intraocular pressure. As a result, localized tissue weakness has less effect on the overall shape of the cornea. Because crosslinking the corneal stroma with riboflavin maintains the basic structure of the collagen — uniform diameter and even spacing—the stroma is able to maintain its transparency Because collagen crosslinking can strengthen and stabilize the cornea, surgeons may soon have a new option for treating conditions in which corneal tissue becomes weakened. As a result, they may soon be able to halt, and possibly even reverse, the progression of keratoconus or surgically induced ectasia.

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