Cross-Linking: Asking the Tough Questions

by Christopher Kent, Senior Editor

Four surgeons discuss the risks and address the unanswered questions still associated with this procedure.

While many American surgeons remain frustrated at the lack of Food and Drug Administration approval of collagen cross-linking—in which riboflavin is applied to the (usually) de-epithelialized cornea followed by exposure to UV light, resulting in a measureable stiffening of corneal tissue—the procedure continues to be refined and tested around the world. Most of the conversation in the United States has been focused on the benefits of the procedure, causing some surgeons to worry that limitations and downsides are being overlooked. Here, four surgeons with extensive experience in cross-linking discuss the procedure and address some of the questions that still surround it.

How Risky Is the Procedure?

"Cross-linking is a real surgical procedure, which in most forms involves removal of the corneal epithelium," notes A. John Kanellopoulos, MD, clinical associate professor of ophthalmology at NYU Medical School and director of the Laservision.gr Institute in Athens, Greece. "Unfortunately, it carries all the risks that such procedures carry.

Problems that have been associated with cross-linking include delayed epithelial healing and some epithelial haze, including late epithelial haze a year postop in one patient who had intense UV exposure. In a few cases we've seen stromal scarring, and there have been reports of herpetic keratitis, assumed to be a recurrence incited by the cross-linking procedure. There have also been reports of infectious keratitis."

Dr. Kanellopoulos notes that the occasional case of delayed epithelial healing could be a collateral effect of the cross-linking. "It could be a toxicity effect caused by the procedure itself; the postop medications used on the stroma that's going to be epithelialized; and/or the shock to the limbal stem cells that repopulate the surface of the cornea," he says. "This is something that needs to be studied to find out what the long-term effect on limbal stem cells might be. As far as scarring, anytime you de-epithelialize the cornea this is a risk, especially if there's delayed epithelial healing or excessive cross-linking in the corneal stroma. And we still have to keep an eye out for a potential increase in the risk of carcinoma in the conjunctiva and corneal epithelial cells due to the UV light. It's a known risk for sun exposure; theoretically, it has to be a potential risk for cross-linking as well."

Roy S. Rubinfeld, MD, MS, clinical associate professor at Georgetown University Medical Center, and in private practice in Chevy Chase, Md., believes that most of the risks associated with collagen cross-linking have been a result of the removal of the epithelium in the original version of the procedure. "Any time you make a large, 9- or 10-mm epithelial abrasion you then have the risks of infection, haze and delayed epithelial healing," he points out. "In a handful of cases worldwide, delayed epithelial healing after cross-linking has also caused corneal melts."

(continued on next page)

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As far as characteristics associated with increased risk, Dr. Rubinfeld notes that one study authored by Theo Seiler, MD, PhD, found that patients with very steep corneas had a higher chance of problems or failure—at least when using the epi-off technique.[1] "So far, our work with the epi-on approach [leaving the epithelium intact] has not found that to be the case," he says. "In our study, out of more than 1,200 eyes treated to date, I'm only aware of two patients whose keratoconus progressed in spite of treatment, and those individuals can be retreated. Adverse events have been extremely rare in our studies."

Despite the risks, Dr. Kanellopoulos doesn't believe the procedure is dangerous. "In general, these cases represent a very small percentage of the total number of cases done," he says. "This procedure is performed globally at thousands of centers, and the majority of cases are relatively uneventful. Using our Athens protocol, consisting of topography-guided PRK and cross-linking, delayed epithelial healing—meaning healing delayed more than four days—happens in about 5 percent of cases, as we reported in a paper presentation at the 2011 annual meeting of the American Academy of Ophthalmology. We've seen some minor anterior scarring in less than 1 percent of the cases. We haven't encountered any infectious keratitis in the 420 cases we've done. I think that if one is aware of these risks and able to diagnose them early, cross-linking isn't any more dangerous than PRK or pterygium removal, or any other well-evaluated procedure that we perform on the anterior surface of the eye."

Dr. Rubinfeld adds that cross-linking risks, which are uncommon to begin with, need to be taken in context. "The alternative to cross-linking is progressive vision loss, hybrid contact lenses and in many cases, corneal transplant," he points out. "Corneal transplants work, but I don't know a single corneal specialist who would rather have a transplant performed on himself than have collagen cross-linking. Even with the removal of the epithelium, cross-linking remains a relatively safe procedure, resulting in approval in all 25 European Union nations by 2006. The United States remains the only developed country I'm aware of that has not approved this procedure."

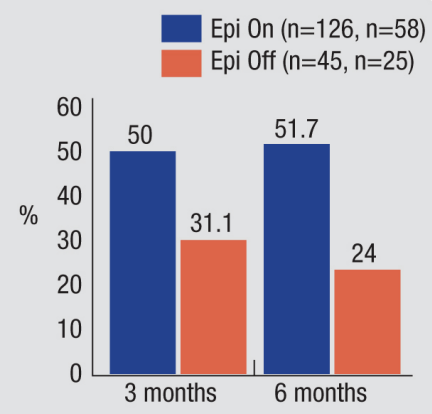
Epithelium On or Off?

Dr. Rubinfeld is a member of the CXLUSA research group. "One of the things our organization has done since 2009 is set up multiple protocols via physician-sponsored, institutional-review-board-approved studies," he says.

"We've done this for two reasons: first, to make the technology available on an investigational basis to patients in the United States; and second, to discover ways to improve the procedure. Starting in May 2010 our multicenter trial has also included epithelial-on cross-linking treatments, and we've had excellent success rates.

"Leaving the epithelium on has numerous benefits, including speeding the patient's visual recovery," he continues. "Recovery often takes weeks or months when the epithelium is removed, but may take less than a day when the epithelium is left on. Perhaps more important, it eliminates most of the risks associated with the original Dresden protocol. If you don't remove the epithelium, you won't develop problems associated with delayed epithelial healing; your risk of infection is enormously reduced; and haze and scarring seem to be markedly reduced as well."

Epi-on vs Epi-off: Percentage of Patients w/Improved BCVA At Three and Six Months



Preliminary results from a multicenter study being conducted by CXLUSA indicate that epi-on cross-linking could be even more effective than epi-off.

Dr. Rubinfeld says that some mixed results from early attempts at epi-on cross-linking may have resulted from issues relating to the riboflavin. "Some of the early work in this area used a formulation of riboflavin that didn't penetrate the epithelium very well," he explains. "It had high molecular weight components, so it was a real challenge to get the riboflavin into the corneal stroma, and that has to happen in order for effective cross-linking to occur. Using our current formulation, we're finding that our epi-on cross-linking is just as effective at three months and six months postop—or more so—than our prior work with epi-off cross-linking." (See chart, above.)

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Many surgeons are still hesitant to try this approach without seeing clinical evidence supporting it. Arturo S. Chayet, MD, who practices at the CODET Vision Institute in Tijuana, Mexico, is concerned that leaving the epithelium on is unproven and could lead to patients not getting the corneal stiffening they need. "So far, there's little scientific data showing that it works to leave on the epithelium," he says. "So I think it's risky to try to do this with the epithelium intact, especially with a patient who really needs the cornea to be stiffened." He adds that individual case reports can be misleading. "If you do cross-linking with the epithelium on in a 35-year-old patient and you document that there wasn't any increase in the keratoconus, that doesn't mean it was because of the cross-linking," he points out. "Plenty of individuals with keratoconus at that age don't progress."

Other Questions

• ***Does it improve vision, and if so, for whom?*** Dr. Rubinfeld notes that cross-linking does improve vision in a number of patients. "We've found that about 50 percent of the time patients achieve a significant improvement in vision," he says. "Nearly all studies have found some improvement in corneal curvature and some flattening after cross-linking.

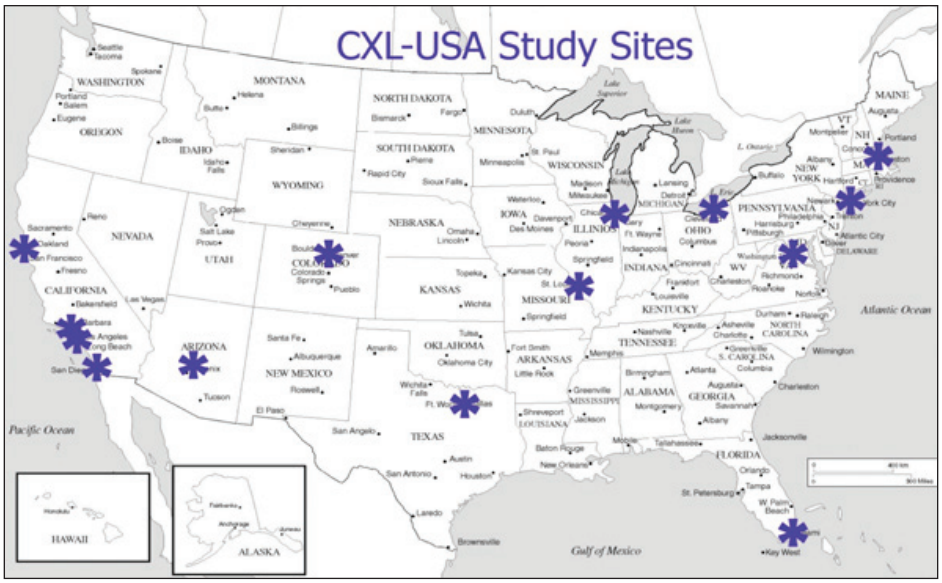
"However, the reasons for the improvement in vision may be more complex than that," he continues.

"For example, Cynthia Roberts, PhD, has noted that cross-linking changes the cornea's index of refraction. All of our investigators have seen cases in which the topography doesn't look particularly different after cross-linking, but patients go from 20/200 uncorrected to 20/40 uncorrected with markedly reduced astigmatism and better BCVA. One possible explanation is that the cross-linking process is changing the index of refraction.

"So far," he adds, "we haven't determined which patients will end up with a significant improvement in visual acuity, or the optimum means of achieving that. Of course, this is not LASIK. When we discuss what we think we can accomplish with patients in our study, we tell them that the most important goal, the one we achieve 98 or 99 percent of the time, is to stop their loss of vision."

• ***When will American surgeons have access to the procedure?*** Dr. Rubinfeld notes that the cost of an FDA study is the issue holding up approval of cross-linking in the United States. "An FDA study can cost $50 million because it's a pre-market approval study, with all that entails," he says.

Despite the lack of FDA approval, many patients may be able to receive treatment, thanks to efforts such as the physician-sponsored multicenter trial being conducted by CXLUSA at 12 centers spread across the United States, "We tried to achieve a broad geographic distribution so no one would have to travel across the country to have access to this technology," notes Dr. Rubinfeld. "The easiest way to find the nearest location of a participating center is to go to our website, CXLUSA.com. The study is still open and enrolling patients."



Despite the lack of FDA approval, many individuals in need may be able to receive cross-linking. A physician-sponsored multicenter trial is being conducted by CXLUSA at 12 geographically diverse centers across the United States; the study is still enrolling patients. To find the nearest location of a participating center, visit CXLUSA.com.

1. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal cross-linking. J Cataract Refract Surg 2009;35:8:1358-62.