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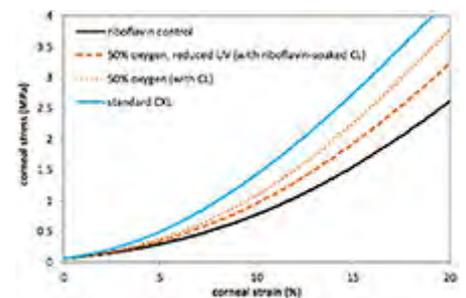
REFRACTIVE

## Research drills down into efficacy of crosslinking protocols for thin corneas

By Liz Hillman EyeWorld Staff Writer

### *Study further establishes essential role of oxygen for efficient biomechanical strengthening*

The essential role of oxygen in crosslinking to stiffen the cornea and halt progressive keratoconus is well-known, but the recipient of the Journal of Refractive Surgery Troutman Prize, presented at Refractive Surgery Subspecialty Day ahead of the 2016 American Academy of Ophthalmology annual meeting, described research that further established oxygen's necessity in the context of newer crosslinking protocols. Sabine Kling, PhD, Center for Applied Biotechnology and Molecular Medicine, University of Zurich, Zurich, Switzerland, presented research published in 2015 that investigated the role of oxygen in biomechanical stiffening in more detail.<sup>1</sup> "We found that reducing the available oxygen at the corneal surface by 50% (by means of a contact lens) ..., also reduces the biomechanical stiffening by about 50%," Dr. Kling told EyeWorld. "The results of this study therefore suggest that



Stress-strain curves in porcine corneas demonstrated that oxygen reduction significantly reduced the stiffening effect of crosslinking.



Two-dimensional mechanical characterization of corneal samples in a stress-strain extensometer Source (all): Sabine Kling, PhD

current crosslinking protocols are limited by the oxygen diffusion rate rather than UV intensity.” The original Dresden crosslinking protocol, described in the 1990s, includes scraping off the epithelium from corneas at least 400  $\mu\text{m}$  thick and instilling a riboflavin solution for 30 minutes, followed by UV-A irradiation for 30 minutes at 3 mW/cm<sup>2</sup>. Since then, different protocols have been proposed to shorten treatment time (e.g., pulse light accelerated crosslinking), to reduce pain (e.g., epithelium-on or transepithelial crosslinking), and to expand indications for corneas thinner than 400  $\mu\text{m}$  (e.g., swelling the cornea using a hypo-osmolar riboflavin or using a contact lens). Farhad Hafezi, MD, PhD, professor of ophthalmology, University of Geneva, Switzerland, and clinical professor of ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, who was the principle investigator in the research, said there is a large body of evidence supporting the efficacy and safety of the Dresden protocol. Other protocols have been rolled out with little evidence to support their biomechanical efficacy. As researchers stepped in to evaluate these protocols, Dr. Hafezi said many have been found less effective at stiffening the cornea. This study, he said, adds to that body of research. “All of these little puzzle pieces show us how a single element—oxygen—has major implications on this technique,” Dr. Hafezi said. In this study, the researchers used enucleated porcine eyes and murine eyes to represent standard corneas of 400  $\mu\text{m}$  in thickness and thinner corneas, respectively. The eyes were then treated with different crosslinking conditions: a standard crosslinking protocol, a contact lens-assisted protocol, and a corneal swelling protocol, as well as control conditions.

Contact lens-assisted protocols and corneal swelling could allow for crosslinking in thinner corneas that are too thin for safe application of the Dresden protocol. After treating the porcine and murine eyes under these conditions, biomechanical measurements of the corneas were taken using a stress-strain extensometer. “We saw in thin and thick corneas that crosslinking efficacy was equally limited by

oxygen, but thick corneas were more affected by UV reduction than thin corneas," Dr. Kling said in her presentation during Refractive Surgery Subspecialty Day. "In this study, we adapted the crosslinking protocol to the corneal thickness, so that the same UV energy per corneal volume was administered," Dr. Kling continued. "Therefore, we may conclude that crosslinking in thinner corneas is more effective due to faster oxygen diffusion into the stroma. ... In this study we have quantified this relationship." Dr. Kling noted that UV restriction decreased viscous components of the cornea while oxygen restriction did not. Because rigid materials have a small viscous component, which is typically related to the extracellular matrix and not collagen, Dr. Kling said this shows "oxygen is probably related to proteoglycan crosslinking." Dr. Kling told EyeWorld the results explain why transepithelial crosslinking, which is comparable to the contact lens protocol in the study, is less effective in the clinic. "[Our results] suggest that using a longer irradiation time and hence allowing for longer oxygen diffusion could partially compensate for the reduced diffusion rate. Also, increasing oxygen pressure could increase the efficacy of transepithelial crosslinking," she said. This latter point, Dr. Kling said, could be achieved by saturating the air with oxygen or increasing the ambient pressure by performing the treatment within a pressure chamber. According to the study, differences in crosslinking efficiency were seen among the protocols tested, but "we cannot draw a conclusion as to which is the minimal necessary increase of corneal stiffness to prevent keratoconus progression," Kling et al. wrote. "Currently, we speak of generalized standard, accelerated, or transepithelial crosslinking protocols," Dr. Kling said. "In the future, I think a patient-specific crosslinking treatment will become available using either corneal thickness or topography data to determine the treatment parameters. We have learned that crosslinking consists of three main components: UV energy, riboflavin, and oxygen. Algorithms will need to be developed in order to determine the best parameter set for a given patient." "Some of these new concepts are fascinating, but my professional advice is we should take a little longer to

validate them before we sell the machine to the patient," Dr. Hafezi said. "We have to make sure we have something that is effective." For now, Dr. Hafezi still prefers the Dresden protocol, although he does accelerate it to 10 minutes because there is a solid body of evidence supporting its efficacy. "I want to protect the technique because it works wonderfully," Dr. Hafezi said, noting that currently there is "total confusion" among his colleagues when it comes to the other, less established protocols.

## Reference

1. Kling S, et al. Increased biomechanical efficacy of corneal cross-linking in thin corneas due to higher oxygen availability. J Refract Surg. 2015;31:840–846.

***Editors' note:** Dr. Hafezi has financial interests with EMAGine (Zug, Switzerland) and is co-inventor of the PCT/CH2014/000075 application (UV light source). Dr. Kling has no financial interests related to her comments.*

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