The Mystery of Collagen Cross-linking When it Comes to In Vivo Biomechanical Measurements

To the Editor:

Bak-Nielsen et al. recently reported on the dynamic assessment of keratoconus and the effects of corneal cross-linking (CXL).[1] The authors described the corneal deformation during rapidly applied force via an air jet using ultra high-speed Scheimpflug technology (Corvis ST; Oculus Optikgeräte GmbH, Wetzlar, Germany).[1] Patients with both untreated and CXL-treated keratoconus were significantly different from normal patients with respect to some deformation parameters. However, no significant differences were found between patients with untreated keratoconus and CXL-treated keratoconus. The absence of significant change in corneal hysteresis and corneal resistance factor provided by the Ocular Response Analyzer (Reichert, Buffalo, NY) has previously been documented in patients with progressive keratoconus undergoing CXL.[2] To account for these surprising results, one might propose the possibility that biomechanical changes induced by CXL are too subtle to be measured by the Ocular Response Analyzer and Corvis ST, or have attributes not well characterized by these technologies. Alternately, a more provocative yet plausible explanation for these findings is that CXL simply does not induce significant changes to corneal biomechanical properties when performed in vivo on corneas with progressive keratoconus.

The Ocular Response Analyzer and Corvis ST have the capacity to record subtle biomechanical differences in non-treated keratoconic corneas of different ectatic degree.[3,4] The observation of the reduction in corneal hysteresis and corneal resistance factor values after LASIK and surface ablation has also been demonstrated.[5] This logically suggests that if CXL would significantly alter the biomechanics of progressive keratoconus corneas, these instruments would be able to identify changes. It is possible that in vivo human corneas of patients with progressive keratoconus do not respond in the same manner to CXL as in animal models. It is also possible that the improvements in keratometric readings and visual quality reported after CXL may be due to non-biomechanical changes: similar effects, along with significant gains in corrected distance visual acuity, occur frequently after phototherapeutic keratectomy, even when shallow ablation with no refractive correction is performed. Based on Munnerlyn's simplified equation, a reduction of 2 diopters of the central 3-mm keratometry reading could result from an increase of less than 10 µm in the epithelial thickness. Interestingly, the prevalent role of epithelium re-growth in postoperative CXL changes is underlined by the fact that the effects of transepithelial CXL appear to be less pronounced than the effects of CXL with deepithelialization as described in the literature.

The absence of measurable biomechanical change in living keratoconus corneas after CXL could be due to the fact that the creation of new chemical bonds may result in insignificant mechanical strengthening compared to the weakening caused by the preexisting alteration of the collagen structure, the disorganization of collagen fiber intertwining, and compromised structural–mechanical homogeneity induced by the keratoconus disease. These alterations may be too overwhelming in corneas with progressive keratoconus to be improved by CXL in its current in vivo modalities. I believe that the mysterious discrepancy between the in vivo and in vitro biomechanical changes of the cornea after CXL requires further investigation.

REFERENCES

1. Bak-Nielsen S, Pedersen IB, Ivarsen A, Hjortdal J. Dynamic Scheimpflug-based assessment of keratoconus and the effects of corneal cross-linking. *J Refract Surg*. 2014;30:408-414.
2. Goldich Y, Marcovich AL, Barkana Y, et al. Clinical and corneal biomechanical changes after collagen cross-linking with riboflavin and UV irradiation in patients with progressive keratoconus: results after 2 years of follow-up. *Cornea*. 2012;31:609-614.
3. Saad A, Lteif Y, Azan E, Gatinel D. Biomechanical properties of keratoconus suspect eyes. *Invest Ophthalmol Vis Sci*. 2010;51:2912-2916.
4. Ali NQ, Patel DV, McGhee CN. Biomechanical responses of healthy and keratoconic corneas measured using a noncontact Scheimpflug-based tonometer. *Invest Ophthalmol Vis Sci*. 2014;55:3651-3659.
5. Kamiya K, Shimizu K, Ohmoto F. Time course of corneal biomechanical parameters after laser in situ keratomileusis. *Ophthalmic Res*. 2009;42:167-171.

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Reply:

We would like to thank Dr. Gatinel for his interest in our article,[1] and the area of corneal cross-linking and corneal biomechanics.

It may well be that instruments based on fast deformation of the cornea, such as the Corvis ST (Oculus Optikgeräte GmbH, Wetzlar, Germany) and Ocular Re-

sponse Analyzer (Reichert, Buffalo, NY) are too insensitive to the changes in biomechanics induced by corneal cross-linking. We agree that further investigations into the mysterious discrepancy between in vivo and in vitro biomechanical changes after corneal cross-linking are required.

REFERENCE

1. Bak-Nielsen S, Pedersen IB, Ivarsen A, Hjortdal J. Dynamic Scheimpflug-based assessment of keratoconus and the effects of corneal cross-linking. *J Refract Surg.* 2014;30:408-414.

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