Keratoconus is a non-inflammatory corneal dystrophy in which the cornea deforms due to thinning and protrusion. The biomechanical strength of the cornea depends on the lamellar organization of the collagen fibers that comprise the corneal stroma, regulated by an interconnecting network of proteoglycans. Although the pathogenesis of keratoconus remains unclear, it appears that a primary event leads to the loss and/or slippage of collagen fibrils and changes to the extracellular matrix in the corneal stroma.

Recently, the corneal collagen cross-linking procedure (CXL) has been developed. CXL is accomplished by instilling riboflavin drops onto the cornea and then irradiating the cornea with ultraviolet-A (365-nm) light (Figure 1). CXL aims to halt the keratoconus disease process by stabilizing the collagen lamellae, mimicking the age-related cross-linking that occurs in the cornea due to the accumulation of non-enzymatic glycation end products over time. The treatment results in mechanical stiffening of the cornea, with the clinical goal being a consequent decrease in progression of the disease process. In vitro studies show that stress measurement increases immediately after CXL in human corneas by more than 300%.

When activated with ultraviolet-A light in the presence of oxygen, riboflavin is converted into excited singlet and triplet states, which then undergo a series of chemical reactions resulting in the formation of reactive species that interact with corneal proteins and lead to the formation of chemical bonds. Several different pathways lead to the formation of cross-link bonds, driven by the relative availabilities of oxygen, riboflavin, and ultraviolet light. Under aerobic conditions, singlet oxygen and hydroxyl radicals are the reactive oxygen species produced that react with the collagen to form these bonds. Under anaerobic conditions, radical riboflavin may also lead to the production of cross-link bonds. Balancing the competing aspects of the reaction by controlling the rate of oxygen consumption allows for control of the distribution of cross-link bonds formed in the cornea.

Several changes have been reported in both in vitro and clinical studies of the cornea after CXL. These include increased collagen fiber diameter,
keratocyte apoptosis and subsequent keratocyte changes, resistance to thermal shrinkage, change in corneal swelling properties, and increased resistance to collagenase degradation. CXL has no effect on any collagen structural parameter measured by x-ray scattering except the uniformity of nearest neighbor interfibrillar spacing. Therefore, it is believed that cross-links are formed predominantly at fibril surfaces and within the proteoglycan network surrounding the collagen.

Corneal haze has been noted after CXL and a demarcation line is commonly seen in the corneal stroma in the clinical setting, delineating the posterior extent of the cross-linking effect. The biomechanical strength of the cornea resides predominantly in the anterior stroma, where the microarchitecture of the collagen fibrils are more interwoven in the anterior-stromal axis. Similarly, CXL appears to have its predominant effect in the anterior 300 µm of the cornea.

In clinical trials, CXL appears to be effective in decreasing progression of keratoconus due to its effect on corneal stiffness. Studies report that, in addition to stabilizing the cornea, there is, on average, improvement in topographic and visual acuity outcomes. For example, in our previous report of 1-year CXL outcomes, the topography-derived maximum keratometry value flattened by 1.70 diopters and patients had an improvement in corrected distance visual acuity from 20/45 to 20/34 and in uncorrected distance visual acuity from 20/137 to 20/117. Moreover, there was a general improvement in several corneal topography indices, corneal and total eye higher order aberrations, and subjective patient visual symptoms. Thus, CXL offers great promise in the treatment of keratoconus and ectatic corneal disease.

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