Collagen cross linking: Current perspectives

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Keratoconus is a common ectatic disorder occurring in more than 1 in 1,000 individuals. The condition typically starts in adolescence and early adulthood. It is a disease with an uncertain cause and its progression is unpredictable, but in extreme cases, vision deteriorates and can require corneal transplant surgery. Corneal collagen cross-linking (CCL) with riboflavin (C3R) is a recent treatment option that can enhance the rigidity of the cornea and prevent disease progression. Since its inception, the procedure has evolved with newer instrumentation, surgical techniques, and is also now performed for expanded indications other than keratoconus. With increasing experience, newer guidelines regarding optimization of patient selection, the spectrum of complications and their management, and combination procedures are being described. This article in conjunction with the others in this issue, will try and explore the uses of collagen cross-linking (CXL) in its current form.

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Keratoconus is a long recognized condition that affects teens and young adults in the productive phase of their lives. It is therefore a cause of significant morbidity, both from the ocular and economic perspective, especially in India, where it appears to have a higher prevalence compared to the neighboring Asian populations. Being a corneal problem, it creates significant optical imperfections in the affected eye, and except in the very early stages, is not amenable to correction using spectacles. The irregular corneal profile also precludes the use of soft contact lenses and hence, there is a need for a rigid lens to achieve clear vision. With the advent of special contact lenses such as the Rose K system, with an aspheric back optical surface, our ability to fit even advanced cones with contact lenses has improved considerably. There have also been other major paradigm shifts in the management of this condition in the past decade and these include the use of intracorneal implants to correct the shape of the cone, and the use of lamellar surgical approaches to replace only the anterior stromal layers of the cornea. While the former has had limited success in correcting keratoconus, the use of lamellar surgery has greatly improved the prognosis for corneal transplants in these eyes, as there is no risk of endothelial rejection with this procedure. However, the surgery is technically complex and has a steep learning curve. Hence, the advent of a procedure that can stabilize keratoconus and prevent it from progressing to an extent that surgical corneal replacement is required, is an important addition to the armamentarium of the corneal surgeon dealing with keratoconus.

The first studies in photobiology began in early 1990s, with attempts to identify biological glues that could be activated by heat or light to increase the resistance of stromal collagen.[1] It was discovered that the gluing effect was mediated by an oxidative mechanism associated with hydroxyl radical release. A similar mechanism of natural hardening and thickening of collagen fibers has been demonstrated in corneal aging, related to glycosylation of age-dependent tropocollagen molecules. Clinical use of collagen cross-linking (CXL) can also be supported by the fact that young diabetics seldom have progressive keratoconus due to the natural cross-linking effect of glucose, which increases corneal resistance.

CXL results in an increase in intra- and interfibrillar covalent bonds by photosensitized oxidation, and causes a biomechanical stabilization of the cornea. Wollensak has reported a significant increase by 328.9% in biomechanical rigidity of the cornea, and a 4.5 fold increase in Young's modulus after CXL.[2] It thus, treats the underlying pathophysiological mechanism in keratectasia. The treatment procedure is conducted in sterile conditions, using topical anesthesia. A central 7-8 mm epithelial debridement is done either mechanically or with the use of alcohol, followed by instillation of topical 0.1% riboflavin (10 mg riboflavin-5-phosphate in 10 ml dextran-T-500 20% solution). Riboflavin plays a dual role in this procedure; it acts as a photosensitizer for the photooxidative cross-linking and also shields the lens and other ocular structures from ultraviolet mediated damage. Initially, riboflavin is instilled at every 2 min for the first 30 min (15 times). The patient may be examined on a slit lamp to confirm adequate penetration of riboflavin in the eye, wherein a yellowish-green fare is seen in the anterior chamber. Following this the cornea is subjected to ultraviolet-A (UVA) radiation (365-370 nm) from a distance of 50 cm for the next 30 min, delivering a total dose of 3 mW/cm^2 (5.4 J/cm^2). During this period, topical riboflavin is instilled at 5 min intervals. On completion of the treatment, a sterile eye pad may be applied with antibiotic eye ointment or alternatively a bandage contact lens may be used. Usually complete reepithelization occurs in 2-4 days. Patients are prescribed topical antibiotics for the first week along with tear substitutes for 3-4 weeks. Patients may experience mild pain and discomfort for the first 2-3 days,

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for which oral analgesics are also prescribed to keep them comfortable. Variations in procedure include performing the treatment without removing the epithelium and the use of surface steroids for the first 4 weeks in tapering doses to modulate corneal scarring.

A mild epithelial haze with transient mild stromal edema may be seen in some cases, which disappear in 2-3 weeks. There is no damage to the endothelium, but a dose-dependent keratocyte apoptosis is seen in human corneas down to a depth of 300 μm using a surface UVA dose of 5.4 J/cm^2. Histopathologically, it has been demonstrated that there is a significant increase in collagen fiber diameter after CXL. It has been well-documented that the corneal epithelium attains a regular morphology and density within 5 days. Initially, disappearance of subepithelial stromal nerve fibers is observed in the treated area, with reinnervation starting at 1 month after the procedure. Complete recolonization of the anterior subepithelial stroma is observed in 6 months, with restoration of corneal sensitivity. After CXL, the cornea shows increase in thermomechanical stability as well as a markedly increased resistance to collagen digesting enzymes.[3,4]

Since its inception in India, CXL has gained increasing popularity, and is now performed in many centers in the country. This is in part, due to the ease of performing the procedure. Various terms have been used to describe the procedure—like corneal collagen cross-linking (CCL), CXL, etc., but the term C3R is generally used for the technique where UVA irradiation is performed without epithelial removal.[5] While the general consensus is that it is successful in halting the occurrence of further changes in the corneas of eyes with keratoconus, evidence that it flattens the cone and improves the corneal shape is less unequivocal. At the moment, there is also no data that allows the physician to predict the extent of effect that is possible in an individual eye. Other areas of uncertainty include the optimal treatment protocol, the role of this procedure in thin corneas, its use for expanded indications like post laser-assisted *in situ* keratomileusis (LASIK) ectasia and pellucid marginal degeneration, and the long-term outcomes; including the possible need for "touch-up" procedures if corneal remodeling gradually removes the cross-links created by the procedure. Even more exciting is the use of this modality in conjunction with other options like intrastromal rings and excimer surgery, which attempt not just to stabilize the cone, but reverse some of the optical imperfections, to allow the patient a better quality of vision. This article is an attempt to address some of these issues, which however, do not detract from the relevance of the CXL procedure in the management of keratoconus.

Collagen Cross Linking in Post LASIK Ectasia

Corneal ectasia, the progressive steepening and thinning of the cornea that reduces the uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA), is one of the most feared complications that may occur after a seemingly successful uncomplicated lamellar refractive surgery. Although rare, this complication can have devastating consequences. While spectacles and semisoft rigid glass permeable (RGP) contact lenses can help in early ectasia, corneal transplantation may be required in more advanced cases. However, none of these options try to arrest the progression of corneal thinning and ectasia. With the advent of CCL, this is now possible, with available evidence suggesting that it may be a useful modality and is probably better if performed earlier rather than later.

During the procedure in post-LASIK eyes, care must be exercised to remove epithelium by using strokes in the axis of the LASIK flap hinge, to avoid disturbing the flap. Care is also taken to stay within the edge of the flap, for the same reason. Although the anterior 300 μm of the cornea is affected by CXL, in a case of post LASIK ectasia, there is an altered biomechanical corneal structure due to the creation of the flap. It however appears that there is not much difference in the post cross-linking corneal topographic changes in eye treated for LASIK ectasia or primary keratoconus. Corneal pachymetry may decrease, but the change is not statistically significant, and no significant change in endothelial cell counts is seen. The decrease in corneal thickness might be expected as a result of collagen fibril thickening and consequent shortening as well as a transient loss of keratocytes.

The need for corneal transplants may be significantly reduced in these patients with corneal ectasia. Given the simplicity of the treatment, it might also be well suited for developing countries. Long-term results are necessary to evaluate the duration of the stiffening effect and to exclude long-term side effects. After cross-linking, most of the patients who were preoperatively intolerant to contact lenses can wear them after surgery. In general, UCVAs and BCVAs improved as compared to preoperatively assessment. It is possible that the combination of cross-linking with other modalities like intrastromal corneal rings may further enhance outcomes in these eyes.[6-8]

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