Review Article

Contact lens assisted corneal cross linking in thin ectatic corneas – A review

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Contact lens-assisted corneal cross-linking (CACXL) was introduced by Jacob *et al*. in 2012 for treating thin keratoconic corneas using riboflavin soaked soft contact lens to artificially increase the functional corneal thickness. It is advantageous over other thin corneal cross-linking techniques as it works independent of swelling properties of the cornea, is an epi-off technique and does not require additional time, additional expensive equipments or special solutions. The only additional requirement as compared to all other techniques is a UV barrier-free soft contact lens (Soflens™, B&L) which is easily available and inexpensive. Advantages include simplicity, easy adaptability, early visual rehabilitation, good visual outcomes, safety, and efficacy. Progression rates are acceptable and the need for re-treatment has been low. CACXL can help regularize corneal shape and may be used in isolation or synergistically with Intracorneal ring segments (ICRS) or Corneal allogenic intrastromal ring segments (CAIRS). It gives about 70% stiffening as compared to standard Dresden protocol CXL in less ideal porcine eye studies. Murine eye models that closely mimic thin corneas and show greater cross-linking effect as compared to porcine eyes may be a better model for evaluation of CACXL, however further studies are needed. Care should be taken in selecting the right kind of contact lens. Proper technique should be followed, especially by confirming thinnest functional pachymetry to be above 400 microns intra-operatively before application of UV-A. The sub-contact lens riboflavin film should be avoided as also an excessively thick supra-contact lens riboflavin film and too many re-applications.

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Keratoconus is a bilateral asymmetric condition which causes progressive corneal thinning and protrusion leading to irregular astigmatism and visual deterioration.[1] It typically begins at puberty and tends to progress until the 3–4th decade of life.[2] Progression of keratoconus is defined as increase in steepest keratometry (Kmax) by >1 Diopter (D), increase in flattest Keratometry (Kmin) by >1D, increase in mean keratometry (Kmean) by >0.75D, increase in manifest spherical equivalent >0.5D and decrease in central corneal thickness by >2%.[3]

Cross-linking (CXL) was introduced by Wollensak *et al*. in 2003 to arrest the progression of keratoconus.[4] The introduction of cross-linking has significantly altered the management of keratoconus, preventing irreversible corneal damage and the need for keratoplasties.[5] The standard Dresden protocol (conventional CXL) involves removal of central 8–10 mm of the epithelium, followed by application of an iso-osmolar riboflavin solution (riboflavin-5-phosphate 0.5% with dextran T500 20%) every 3 minutes for 30 minutes followed by UV-A (370-nm wavelength) exposure of irradiance 3 mW/cm^2 for 30 minutes.[4] Riboflavin acts as a photosensitizer in the photo-polymerization process when exposed to UV-A irradiation resulting in the formation of intrafibrillar and interfibrillar covalent bonds in the anterior 250–300 μm of corneal stroma, thus increasing the overall biomechanical strength (usually upto 300%).[4,6-8] Nevertheless, conventional CXL has the limitation that it can be safely performed only when the corneal thickness after de-epithelialisation is >400 microns.[9] Wollensak *et al*. showed an irradiance of 0.37 mW/cm^2 and above to be cytotoxic to the endothelial cell layer.[9] In a 400 microns thick cornea saturated with riboflavin, the irradiance at the endothelial level is 0.18 mW/cm^2, which is 2-fold lesser than the damage threshold. Therefore 400 microns is considered as the safe limit to protect the endothelium and intraocular structures from the adverse effects of UV-A irradiation. CXL in thinner corneas with the standard protocol is of concern considering the possible complications such as permanent endothelial damage, stromal scarring, and the subsequent need for keratoplasty.[10,11]

In the past few years, various techniques have been introduced for treating thinner corneas. These include use of a higher riboflavin concentration or an increase in the thickness of the riboflavin film, decreasing surface irradiance, inducing stromal swelling by using hypo-osmolar

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solutions, localized and customized epithelial debridement, transepithelial cross-linking and contact lens assisted cross-linking (CACXL).[12,13]

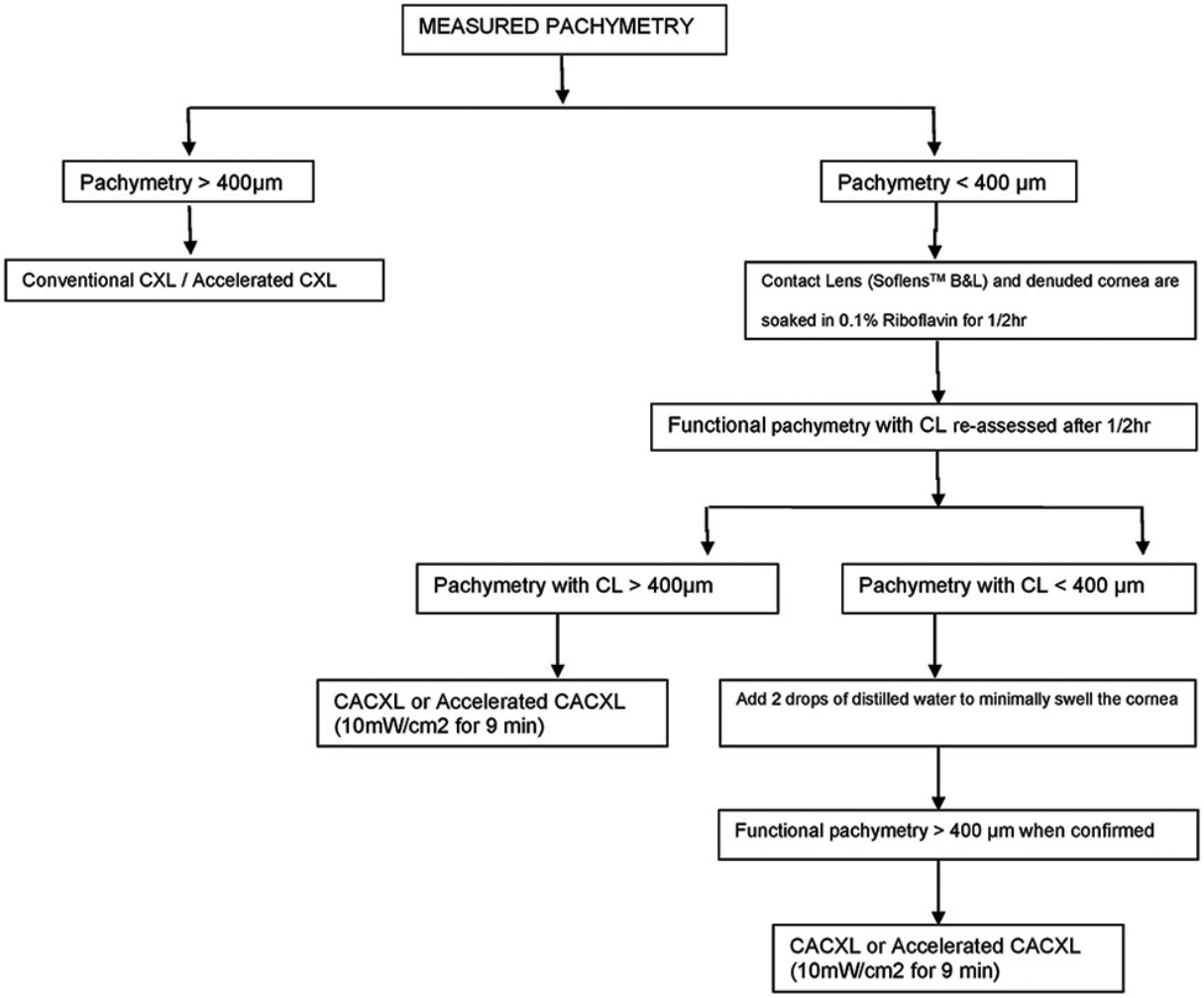
Contact Lens-Assisted CXL (CACXL)

One of the authors (Jacob S) introduced the technique of the contact lens-assisted corneal cross-linking (CACXL) in 2012 for treating thinner corneas using a riboflavin-soaked soft contact lens to artificially increase the corneal thickness.[14] The contact lens provided the functional pachymetry necessary to overcome the two major potential complications that are associated with cross-linking thin corneas, namely - ultraviolet-related endothelial cell damage and permanent stromal haze. This technique was initially employed for treating patients with progressive keratoconus with the thinnest pachymetry ranging from 350-400 µm (after epithelial removal) but has subsequently been used for even thinner corneas.

Surgical technique

Routine evaluation including visual acuity, rigid gas permeable (RGP) contact lens corrected visual acuity, corneal topography, specular microscopy, anterior segment OCT (ASOCT), slit-lamp examination, and dilated fundus evaluation are performed pre-operatively. Pilocarpine 2% eye drops are applied pre-operatively to constrict the pupil in order to decrease the potential for any UV damage to deeper structures. Proparacaine 0.5% eye drops are also applied for anesthetic effect as well as to aid in easier epithelial removal. After the epithelium is removed, minimum corneal thickness is measured using ASOCT pachymetry or ultrasound pachymeter. For the sake of simplicity, it may also be calculated by deducting 50 microns from the pre-operative epi-on thinnest pachymetry. The decision on further management is then as shown in the flowchart [Fig. 1].

The contact lens is soaked in 0.1% riboflavin for the same half an hour that the de-epithelialized cornea is soaked. Riboflavin is applied every 3 minutes for 30 minutes to maintain a uniform film over the corneal surface and prevent corneal desiccation. At the end of 30 minutes penetration of riboflavin through corneal layers is confirmed by visualization of green flare in the anterior chamber. The functional pachymetry achieved may be measured after placing the contact lens over the cornea. Alternatively, it may be calculated by measuring the thinnest



CXL: Cross linking; CACXL: Contact lens assisted cross linking; CL: Contact Lens

Figure 1: Flowchart on decision making for CACXL and accelerated CACXL

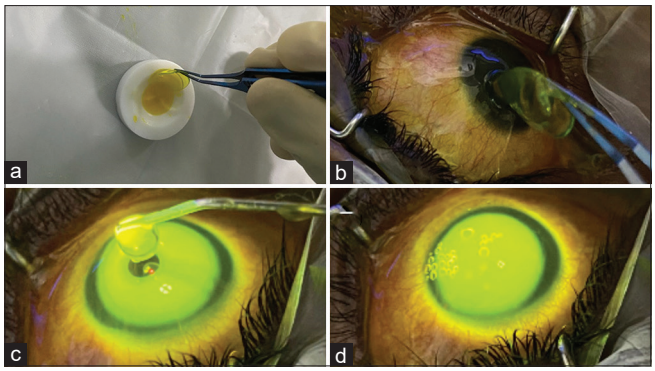


Figure 2: (a) Soft Contact lens soaked in riboflavin solution (b) Riboflavin soaked contact lens placed over the cornea before UV application (c) Infrequent application of a thin layer of riboflavin over the contact lens during UV exposure (d) Application of UV light (with contact lens over the cornea)

pachymetry and adding 100 microns that is provided by placing the contact lens to the measured value. Once the functional pachymetry at the thinnest zone is confirmed to be above 400 microns, UV-A application is done either following the classical Dresden protocol of 3 mW/cm2 for 30 min or accelerated CXL protocol using an irradiance of 10 mW/cm2 for 9 minutes. At the end of the treatment, the contact lens is removed, riboflavin washed off and a fresh bandage contact lens is applied until complete epithelial healing [Fig. 2a-d].

If the functional pachymetry achieved is less than 400 microns, a few drops of distilled water is applied over the cornea to achieve the small amount of swelling that may be required to take the functional pachymetry (with the soft contact lens on) to safe levels. In our experience, the number of cases where this is required is low and the increase in thickness required is also lesser and easily and rapidly achieved.

Which contact lens may be used?

A UV barrier-free contact lens must be used for the treatment to be effective. UV transmittance of a contact lens may be checked in the product literature or by checking the UV irradiance that passes through the contact lens using a digital UV meter. The contact lens used by the authors is the B&L Soflens™ Daily Disposable (made of Hilafilcon B) which has absent or negligible UV filter. A lens of negligible power is selected. The Soflens™ has a thin lens design with a central thickness of 90 µm and a diameter of 14 mm. It follows the shape of the cornea and is hydrophilic in nature. Other contact lenses which have been studied for high UV-A transmission include filcon IV, nelfilcon A, enfilcon A, lotrafilcon A and lotrafilcon B and can be the treatment choice for CACXL technique in thin corneas though their efficacy and safety profiles need to be studied in animal and human models first.[15] Hydrophilicity and thickness of the contact lens are also important factors as discussed later.[16]

Our experiments showed absorption of riboflavin into the substance of the soft lens as demonstrated by staining of the filter paper over which riboflavin filled soft contact lens is placed. [Fig. 3] Our experiments also showed that application of the riboflavin-soaked contact lens gave an average of 107.9 ± 9.4 microns of additional corneal thickness. An average of 100 microns may be taken for quick calculation and to maintain errors towards safety.

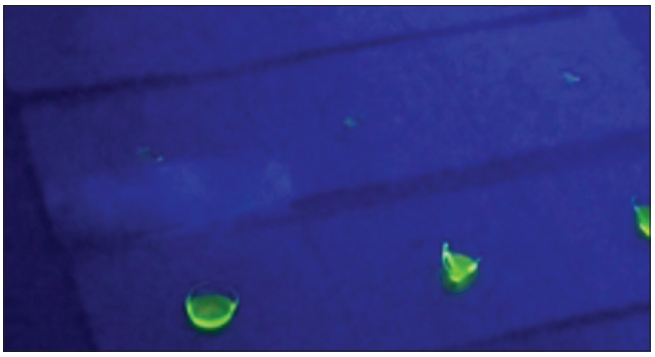


Figure 3: Absorption of riboflavin into the soft contact lens

Which riboflavin may be used?

Iso-osmolar riboflavin 0.1% in 20% dextran T500 was used, in view of easy availability. Dextran in iso-osmolar riboflavin is known to cause intra-operative dehydration of the cornea and therefore, riboflavin in HPMC 1.1% may be utilized to avoid this disadvantage in already thin corneas. Malhotra *et al*. reported that HPMC based riboflavin may be associated with a deeper demarcation line than dextran based riboflavin. However, they also reported that both solutions were safe for the endothelium.[17] The deeper demarcation line with HPMC based riboflavin could be explained by the difference in the properties of the two molecules. HPMC enhances the stromal penetration of riboflavin, whereas dextran, because of its high viscosity, retards this diffusion. As mentioned earlier, riboflavin acts as a photosensitizer for the formation of collagen covalent bonds by generation of reactive oxygen species. Thus cross-linking tends to occur more where there is higher concentration of riboflavin explaining the deeper demarcation line in HPMC group as against shallower demarcation line in dextran group. As explained previously, HPMC-based riboflavin solutions (such as VibexRapid™, Avedro) also reduces intra-operative deturgescence and prevents corneal thinning and ensures greater endothelial safety.[17]

Safety profile Of CACXL

The rationale of applying the riboflavin-soaked contact lens is to increase the total functional corneal thickness to 400 microns or more. In our study the contact lens contributed to an increase in functional corneal thickness by 107.9 ± 9.4 µm as measured by ASOCT. The pre-contact lens riboflavin film along with the contact lens contributes to UV-A attenuation allowing about 60–70% UV transmittance. Thus, the irradiance at the level of endothelium is below the endothelial toxic level which ensures adequate safety of the CACXL procedure. This was supported by the fact that there was no significant endothelial loss, pleomorphism, polymegathism or loss of corneal clarity post CACXL in any of the studies.[12,17-19]

Efficacy of CACXL

The demarcation line is considered as a measure of efficacy of the cross-linking procedure. It can be seen as early as 2 weeks postoperatively and can be appreciated till 3-6 months. Kymionis *et al*. showed that the stromal demarcation line represented the transition zone between anterior acellular treated zone with reduced number of keratocytes (due to cellular apoptosis) and posterior cellular untreated zone with

unaffected keratocyte population, on examination by confocal microscopy after CXL.[20,21]

Seiler and Hafezi reported a demarcation line at 300 μm in eyes with a minimum corneal thickness greater than 400 μm and showed it to be an effective tool for assessment of extent of CXL.[22] Doors *et al*. showed a mean central depth of the stromal demarcation line of 313 μm ± 66 μm one month after corneal cross-linking with a range of 225 to 448 μm in normal thickness corneas after iso-osmolar CXL.[23]

Our pilot study included 14 eyes of 12 patients with maximum and minimum keratometric values of 50.9 ± 3.1 D and 45 ± 1.9 D. Preoperative corneal thickness after epithelial removal ranged from 350 to 398 μm. The mean postoperative depth of stromal demarcation line in our study measured with ASOCT was observed at 252.9 ± 40.8 μm (range: 208 to260 μm). There was no progression of keratectasia seen in any patients. Regression was observed in 4 eyes. Corneas remained clear and there was no significant endothelial loss.[12] Since this pilot study, our un-published data of a much larger number of patients who underwent CACXL has been very encouraging with good safety and efficacy results. These results have now been replicated from other centers worldwide. Malhotra *et al*. in their study on CACXL showed a mean demarcation line depth of 308.22 μm ± 84.19 in the HPMC group and 235.33 ± 64.87 in the dextran group ($P < 0.04$).[17] *In vivo* confocal microscopy (IVCM) performed on 10 eyes treated with CACXL by Mazzotta *et al*. showed that cytotoxic effects of CACXL are similar to IVCM changes seen in standard CXL and were concentrated in anterior and mid stroma up to 300 ± 30 microns. Corneal endothelium did not show any morphological changes between pre-and post-operative follow-up. The importance of intraoperative pachymetry to ensure that functional pachymetry is above 400 microns before starting UV light treatment was stressed on.[19]

A recent study by Randleman *et al*. that compared the biomechanical efficacy of CACXL and standard CXL in enucleated porcine eyes using brillouin microscopy and extensometry testing showed that CACXL achieved 70% stiffening effect of the standard CXL group. Both the groups showed significant stiffening in the anterior and middle corneal regions and no effect on the posterior corneal region. They also noted that there was a significant difference in the stiffening effect between the two groups only in the anterior one-third of the cornea, with CACXL achieving 71% effect of standard CXL. However, statistically significant difference was not noted in the other two regions between the groups. They concluded that the contact lens did not shift the CXL effect anteriorly but rather only blunted the effect of CXL in the anterior corneal region. In thin corneas, as the primary concern is endothelial protection, even a blunted response may be sufficient.[24]

In a study on post mortem porcine eyes, Wollensak *et al*. assessed the biomechanical efficacy of CACXL comparing it with standard CXL and found it to be about one-third less than standard CXL.[16] They also tested CACXL with and without an adherent precorneal riboflavin film of up to 100 μm thickness and tested three different soft contact lenses (Air Optix Aqua®, SofLens® and Galifa®) with different degrees of hydrophilic properties. Among the lenses studied, the Air Optix Aqua® has less hydrophilicity and stained less (33% hydration, 80 microns thickness) and the Galifa® lens had a considerably higher thickness of about 160 microns and hydration of 72%.[16] The third lens studied was the Soflens® which has been used in previous published studies on CACXL (hydration 59% and thickness 90 microns).[12,17,18,24] Their experiments showed that very highly hydrophilic contact lenses absorb more riboflavin and consequently also more UV-A and thereby lead to less cross-linking effect. When riboflavin soaked, the Air Optix Aqua®, SofLens® and Galifa® lens had a UV-A absorption of 12%, 27% and 50% respectively showing the importance of the choice of contact lens used. The subcontact lens film in the porcine eyes in their experiments was measured to be between 80-116 microns and the supra-contact lens film between 102-124 microns unlike the measurement in human eyes *in vivo* which was between 10-15 microns and 60–100 microns, respectively. They omitted the supra-contact lens film. Addition of a subcontact lens riboflavin film did not cause a significant biomechanical cross-linking effect. This is important while performing CACXL and riboflavin should not be instilled under the contact lens. The supra contact lens film should also not be replenished too often or made excessively thick. A lower viscosity riboflavin film with less thickness may be beneficial. Biomechanical measurements by Wollensak *et al*. in their experiments without both the sub-and pre-contact lens riboflavin film showed Young's modulus and stress at 8% strain in the Air Optix Aqua® group to reach 92.4% and 86.35% respectively of the standard CXL value whereas it was lesser (67.04% and 65.28% in the SofLens® group; 68.48% and 75.52% in the Galifa® group). Their experiments clearly show the significance of selecting the right type of contact lens, avoiding a thick riboflavin film and the importance of following the right technique intraoperatively. The Galifa® lens is thicker and more hydrophilic, thereby absorbing more riboflavin and therefore causing a greater shielding effect than what is required by virtue of both its increased thickness and greater riboflavin content. The Air Optix Aqua® is a thinner lens and also has lesser hydration than the contact lens (SofLens®) used by us and other authors, therefore probably resulting in a greater biomechanical effect. This is obviously an advantage. Biomechanical effect needs to be balanced by endothelial protective effect and further *in vivo* human eye studies are required to show endothelial protection with the Air Optix Aqua®.[16] SofLens® has already proven endothelial protection and good biomechanical effect in in-vivo studies.[12,17] The hydrothermal shrinkage pattern in their study as shown by Wollensak *et al*. with the Galifa® lens would be expected to be less due to the thicker profile and greater hydrophilicity and thereby greater UV-A absorbing effect of the Galifa® lens. Published *in vivo* human eye data from multiple centers as well as our un-published data has shown good endothelial protection as well as biomechanical efficacy with the SofLens®, however, the need for further *in vivo* human eye studies with Air Optix Aqua® and other contact lenses to determine the best contact lens to be used cannot be denied. It should be noted here that results of porcine eye studies cannot be directly extrapolated as having equivalent results in thin cornea human eye cross-linking studies. This was shown by Hafezi *et al*. in their study that showed that cross-linking was more efficient in thin cornea models like murine cornea than thick cornea models like porcine corneas.[25] In another study, Kling and Hafezi also similarly showed a linear decrease in the effect of standard corneal collagen cross-linking (CXL) treatment with increasing corneal thickness in different species, with thinner corneas

achieving more stiffening.[26] Thus the stiffening effect obtained in human thin keratoconic corneas may possibly be more than that reported in porcine experimental eye models, and further experiments are needed to know the exact effects.

Oxygen availability

A study by Kling *et al*. compared different CXL treatment protocols for high corneal thickness (porcine eyes) representing standard corneas with a thickness >400 microns and low corneal thickness (murine eyes) representing keratoconic corneas with a stroma less than 400 microns. This study showed that the efficacy of cross-linking was different in thick (porcine) and thin (murine) corneas and that thin corneas cross-link better than thicker corneas. They postulated the different effect of CACXL in porcine (thick) and murine (thin) corneas to be due to a higher oxygen availability in the murine cornea resulting from faster oxygen diffusion and hence oxygen replenishment during UV irradiation. Although it was found that cross-linking was equally limited by oxygen in both thick and thin corneas, it was more efficient in thinner corneas. It is probable that oxygen availability and therefore the biomechanical stiffening effect of CXL may be greater in thin corneas. They also found that the amount of absorbed UV light was much more important in thick (porcine) than thin (murine) corneas. They reported a decrease in the long-term modulus after CACXL by 15-20% compared to standard CXL.[25]

The oxygen transmissibility (Dk) of the contact lens used may also play an important role in the effectiveness of cross-linking attained. The Dk of the SofLens™ is similar to the oxygen permeability of corneal stroma. The treatment efficacy of CACXL may therefore be further improved by using a contact lens with higher oxygen transmissibility or by increasing the oxygen supply.

Accelerated CACXL

Since late 2013, we have been doing accelerated CACXL using UV power of 10 mW/cm2 for 9 minutes to give a total energy level of 5.4 J/cm2. Advantages over Dresden protocol include a decrease in the intraoperative dehydration which is of significance in these already thin corneas. It also makes the procedure shorter for patient and surgeon.[27]

Knyazer *et al*. performed accelerated CACXL on 24 eyes with keratoconus. This study showed that accelerated CACXL halted keratoconus progression in 80%, led to flattening in 45% and significantly improved uncorrected distance visual acuity (UDVA), maximum keratometry, anterior steep keratometry, anterior astigmatism and posterior astigmatism without any evidence of damage to the corneal endothelium or any permanent side effects. Five eyes (20.8%) showed progression which was defined as an increase of 1D or more in maximum keratometry or 1.5D or greater in mean keratometry. Four out of these five eyes with progression had stable or improved uncorrected distance visual acuity and therefore did not undergo additional treatment. The authors mention their success rate of 80% in halting progression to the fact that they included advanced cases of keratoconus and also that during UV irradiation, instillation of the riboflavin solution was done both above and below the contact lens. Success rate could have been better still if the sub-contact lens riboflavin film had been omitted.[18]

Corneal Allogenic Intrastromal Ring Segments (CAIRS)

In severe keratoconus (with maximum K up to 80D) and where there is enough thickness available for CACXL, a new technique was described by one of the authors (Jacob S) - corneal allogenic intrastromal ring segments (CAIRS), which can be inserted as a first step to flatten the cornea and also increase the corneal thickness in the zone of implantation, following which CACXL can be safely performed to arrest the progression.[28] This can avoid the need for DALK and its associated disadvantages in many advanced cases of keratoconus.

Advantages of CACXL

CACXL is advantageous over other thin corneal cross-linking techniques in that it works independent of the swelling properties of the cornea, is an epi-off technique and does not require additional time, additional expensive equipments or special solutions to perform the procedure. The SMILE lenticule assisted CXL is another technique recently proposed that employs the same principle as CACXL and uses a riboflavin soaked SMILE lenticule for artificially increasing functional corneal thickness.[29] Though similar in principle, this technique has disadvantages of limited access to donor SMILE lenticule; need for a lenticule of sufficient thickness (generally 7-8 Dioptres of refractive correction would be needed to get a lenticule of sufficient thickness to provide shielding effect for CXL); unpredictability and variability of donor tissue pachymetry depending on cylindrical correction performed in donor, days post-harvest of lenticule and storage medium used; erroneous shifts in pachymetry in case of edema or dehydration of the lenticule; variable riboflavin absorption based on hydration status of the donor lenticule; dependency on human donor tissue, need for serology of donor lenticule and need for storage and eye banking facilities.

The additional requirement for CACXL as compared to all other techniques is only a UV barrier-free soft contact lens which is easily available and inexpensive. It is a simple technique to perform and can be easily adapted to the surgical protocol. It provides early visual rehabilitation and in our experience (unpublished data) and that of others, it can be safely performed in pediatric patients as well.[30] CACXL has been proven to be effective in regularising the corneal shape and simultaneously preventing the progression of keratoconus in isolation and also with synergistic effect when combined with Intracorneal segments (INTACS) or Corneal allogenic intrastromal ring segments (CAIRS). CACXL has about 70% stiffening as compared to standard Dresden protocol CXL in the less ideal porcine eye studies. Murine eye models that closely mimic thin corneas and show greater cross-linking effect as compared to porcine eyes may be a better model for evaluation of CACXL, however further studies are needed.

Conclusion

The safety and visual outcomes of CACXL have been comparable to conventional CXL. Progression rates are acceptable and the need for re-treatment has been low. Care should be taken in selecting the right kind of contact lens in terms of oxygen transmissibility, material, thickness, hydrophilicity, and riboflavin absorption properties to increase effectiveness of

cross-linking and to decrease an excessive shielding response. Proper technique should be followed, especially by confirming that the thinnest functional pachymetry has gone above 400 microns intra-operatively before application of UV-A. The subcontact lens riboflavin film should be avoided as also an excessively thick supra-contact lens riboflavin film and too many re-applications. Further *in vivo* human eye studies are needed to assess the safety of omitting the riboflavin film altogether, changing the riboflavin concentration within the cornea, using different types of contact lenses, increasing oxygen availability by using lenses with better oxygen transmissibility, increasing oxygen concentration in the atmosphere, etc. Future studies should aim at improving biomechanical efficacy further while maintaining the proven safety of this technique.

Financial disclosure

Soosan Jacob has a patent pending for special trephines, devices and processes used to create CAIRS segments as well as for various types of shaped corneal segments

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Conflicts of interest

There are no conflicts of interest.

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