Summary

In recent years, reduced corneal biomechanics have been identified as an important element in the pathogenesis of various corneal diseases. Intra- and intermolecular cross-links between collagen molecules are essential elements of these biomechanical properties,Accordingly, collagen cross-links occur physiologically in all tissues .

A number of techniques can be used to induce additional cross-links: exposure to aldehydes, enzymatic treatment (lysyloxydase), and photo-polymerization using UV light.

The most promising technique should have the following characteristics: it should absorb ultraviolet (UVA) light, strong enough to generate free radicals that induce cross-links and should protect deeper ocular structures from the potential hazards of free radical formation. These parameters were achieved by using a 0.1% aqueous solution of riboflavin-phosphate (vitamin B2).

Since riboflavin is a macromolecule (molecular weight of 376.37 g/mol), the corneal epithelium represents a barrier that decreases the absorption rate. The corneal epithelium should therefore be removed prior to instillation of riboflavin solution. The intensity of UVA irradiation was set to 3 mW/cm2, corresponding to a surface dose of 5.4 J/cm2. These parameters induce corneal cross-links to a depth of 310 μm. A stromal thickness of at least 400 μm should be respected in CXL.

Besides the biomechanical effect, a biochemical effect also contributes to the increased resistance of cross-linked corneas. Changes

in the tertiary structure of the collagen molecule may explain the stabilizing biochemical effect of cross-linking. These changes prevent proteolytic enzymes to access their specific cleavage sites.

After an abrasion of the corneal epithelium of 9 mm, isoosmolar 0.1% riboflavin solution with Dextrane T500 is applied on the cornea every three minutes for 30 minutes.

Successful penetration of riboflavin through the cornea ("riboflavin shielding") is assured by visualization of riboflavin in the anterior chamber by slit lamp biomicroscopy (using blue light). Prior to treatment, ultrasound pachymetry (five repetitive measurements) is performed on the deepithelialized cornea at the thinnest point to ensure a minimal corneal thickness of 400 μm. Thereafter, the eye is irradiated for 30 minutes with UVA at a working distance of 5 cm with an irradiance of 3 mW/cm2 corresponding to a surface dose of 5.4 J/cm2.

Modified technique using hypoosmolar riboflavin solution is used to induce stromal swelling, thus increasing the stromal thickness prior to CXL in cases with preoperatively thin corneas. Hypoosmolar riboflavin solution was administered repeatedly until the minimal corneal thickness reached 400 μm, which usually occurred within five to 15 minutes.

The techniques used to monitor successful CXL are corneal topography, corneal pachymetry (ultrasound or optical) and corneal confocal microscopy.

Wollensak and coworkers have shown even a regression of maximal

K-values by an average of 2 diopters (D) in 70% of all patients treated. Regression took up to 30 months to stabilize.

CXL in keratoconus and pellucid marginal degeneration

Between 1999 and 2002, 22 patients with progressive keratectasia were treated in a clinical phase one study and were followed for an average of two years (range three months to four years). A distinction of clinical subentities such as keratoconus and pellucid marginal degeneration was not performed. The progression halted in every case, and no side effects were observed except for slight corneal edema, photophobia, and minimal intrastromal scarring in the early postoperative phase.

CXL in iatrogenic keratectasia after refractive laser surgery

Kohlhaas and coworkers reported the first CXL in a case of iatrogenic keratectasia after LASIK. The keratectasia occurred one month after LASIK, and the progression was documented for the following ten months.

CXL in corneal melting processes

The first report on clinical use of CXL in the corneal ulcer was when Schnitzler et al reported four cases of corneal melting ulcers that were resistant to other conventional therapies in 2000. In three of the four cases, the melting process could be stopped, and a keratoplasty was at least temporarily avoided. The aim of CXL in these cases is to arrest the melting process and to avoid a keratoplasty .

Potential future applications of CXL

CXL of collagen may not only improve the aforementioned conditions. Additionally, a number of potential applications can be envisioned.

Bullous Keratopathy

Krueger et al., showed that staged UV-A CXL (15mW/cm2) with femtosecond—laser-facilitated intrastromal 0.1% riboflavin administration may be a safe and effective method for managing bullous keratopathy.

Progressive myopia

Wollensak et al have demonstrated successful cross-linking of scleral collagen in the rabbit by UVA irradiation. Once all issues regarding potential cytotoxicity to the underlying choroid and outer retina is overcome, this technique may open new experimental approaches in the treatment of progressive myopia.

In ***penetrating keratoplasty for keratoconus***, the rate of keratoconus recurrence is increasing with time after surgery. CXL prior to penetrating keratoplasty for keratoconus might be a means to prevent the recurrence of keratoconus.

A combination of Intacs and CXL might be beneficial for patients. Chan and coworkers have reported a significant reduction in postoperative cylinder in patients that were treated with Intacs and subsequent CXL when compared to Intacs implantation alone.

Kanellopoulos et al have performed ***a topography-guided surface ablation following CXL*** for keratoconus. The aim was to homogenize the irregular corneal surface. With a follow-up of 18 months, the patient showed no signs of keratoconus recurrence and corneal topography, K-readings, and refraction were stable.

Ultimately, in ***cataract surgery***, continuous curvilinear capsulorhexis (CCC) might be facilitated in selected cases. A combination of Trypan Blue as a chromophore and illumination with diffuse white light of 6000 lux intensity increases the stiffness of the anterior capsule, thus making CCC easier

CXL safety issues and potential complications

Spoerl et al have demonstrated that the UVA intensity used during CXL is far below the damage threshold for the corneal endothelium, the iris, lens and retina.

Nevertheless, various cases with complications after CXL were reported by several groups and at the 4th CXL congress in Dresden in 2008.

Conclusion

Cross-linking of corneal collagen is a promising approach for the treatment of various corneal disorders. In progressive ectatic corneal diseases, it reduces the need for penetrating keratoplasty. The ease-of-use and inexpensiveness make it particularly interesting for countries where penetrating keratoplasty is difficult due to donor availability and/or financial reasons.