Corneal Collagen Cross-Linking for Keratoconus and Corneal Ectasia

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6.1 Introduction

Corneal collagen cross-linking (CXL) is a treatment designed to decrease the progression of keratoconus (Wollensak et al. 2003a), in particular, and other corneal thinning processes such as post LASIK and PRK ectasia (Vinciguerra et al. 2009b; Seiler et al. 1998; Salgado et al. 2011; Hafezi et al. 2007). Studies have suggested that cross-linking also can have beneficial visual and optical effects such as decrease in corneal steepness, decrease in refractive error and astigmatism, improvement in best corrected and uncorrected visual acuity, and improvement in topography irregularity indices in some patients.

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6.2 Pathophysiology

An understanding of corneal biomechanics may help to elucidate the cause and natural history of keratoconus and other ectatic processes. The cornea is a viscoelastic structure with both viscous and elastic components (Roberts 2000). In response to stress, there is an immediate elastic response of the cornea followed by a prolonged, time-dependent, viscoelastic recovery. Early studies measured a decrease in elasticity in corneas with keratoconus (Edmund 1988). Currently, while 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 (Meek et al. 2005). These changes are thought to cause biomechanical instability of the corneal stroma with consequent changes in both the cornea's anatomic and topographic architecture (Gefen et al. 2009).

The progression of keratoconus slows as patients age, secondary to a natural cross-linking of the stromal collagen and consequent stiffening of the cornea with age. In the corneal collagen cross-linking procedure, riboflavin (vitamin B_2) is administered in conjunction with ultraviolet A (UVA 370 nm) irradiation. Riboflavin acts as a

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photosensitizer for the production of reactive oxygen species (singlet oxygen). Both the free radicals produced by this interaction as well as UVA-excited molecules of riboflavin result in the cross-linking effect and cause mechanical stiffening of the cornea (Wollensak et al. 2003b). Whether the actual "cross-links" are between or within collagen molecules, or involve corneal proteoglycans, remains unclear (Sawaguchi et al. 1989, 1991; Wollensak and Buddecke 1990). Wollensak et al. (2003b) reported that immediate in vitro stress measurements increased by 71.9 and 328.9 % in porcine and human corneas, respectively, after CXL. In rabbit corneas, these increases in stress measurements were maintained between 69.7 and 106 % at 8 months postoperatively (Wollensak and Iomdina 2009). Such postoperative increases in Young's modulus have been further demonstrated with collagen hydrogels exposed to UVA/riboflavin therapy (Ahearne et al. 2008).

The biomechanical strength of the cornea resides, predominantly, in the anterior stroma, where the microarchitecture of the collagen fibrils is more interweaved in the anteroposterior axis. The collagen cross-linking procedure, similarly, appears to have its predominant effect in the anterior 300 μm of the cornea (Wollensak et al. 2004b). In studies of the cornea after cross-linking, a number of changes have been reported. These include increased collagen fiber diameter (Wollensak et al. 2004b), keratocyte apoptosis and subsequent keratocyte changes (Wollensak et al. 2004a), resistance to thermal shrinkage (Spoerl et al. 2004a), change in corneal swelling properties (Dohlman et al. 1962), and increased resistance to collagenase degradation (Spoerl et al. 2004b). On clinical examination, corneal haze has been noted after the cross-linking procedure (Greenstein et al. 2010), and a demarcation line is commonly seen in this corneal stroma, delineating the posterior extent of the cross-linking effect (Seiler and Hafezi 2006). Although the exact mechanism of corneal collagen cross-linking has not been elucidated, it is clear from laboratory and clinical studies that the combination of riboflavin with UV light stiffens and strengthens the biomechanically unstable ectatic cornea.

6.2.1 The Cross-Linking Procedure

The general technique of corneal collagen cross-linking is based on the original corneal cross-linking procedure described by Seiler and colleagues (Wollensak et al. 2003a). In brief, a topical anesthetic is administered and the central 9 mm epithelium is removed by mechanical debridement. Riboflavin is then administered topically every 2 min for a total of 30 min. Following riboflavin administration, riboflavin absorption is confirmed on slit lamp examination (Fig. 6.1a). At this time, pachymetry measurements are performed, and if the cornea is <400 μm, hypotonic riboflavin is administered, one drop every 10 s for 2-min sessions, after which pachymetry measurements are performed again, to confirm that the stroma had swelled to ≥400 μm. The goal of this is to provide adequate corneal thickness to absorb the incoming UV light in order to protect the endothelium from damage by the UV-riboflavin interaction. The cornea is aligned and exposed to UVA 365 nm light for 30 min at an irradiance of 3.0 mW/cm^2 (Fig. 6.1b). While the cornea is exposed to UVA light, riboflavin administration is continued every 2 min. Postoperatively, antibiotic and corticosteroid drops are administered, a soft contact lens bandage is placed, and the eye is reexamined by slit lamp examination. The contact lens is removed after the epithelial defect had closed.

6.3 Clinical Outcomes

6.3.1 Visual Acuity and Refractive Outcomes

Generally, CXL appears to stabilize visual acuity and in many cases offers a modest improvement to patient's uncorrected and best correct vision. Previous work has shown that, on average, at 1 year postoperatively, uncorrected vision changed by 0–2.7 Snellen lines (Caporossi et al. 2010; Vinciguerra et al. 2009a; Hersh et al. 2011). In a study of 71 eyes, performed by one of the authors (PSH) as a part of the US multicenter clinical trial of collagen cross-linking, about 25 % of

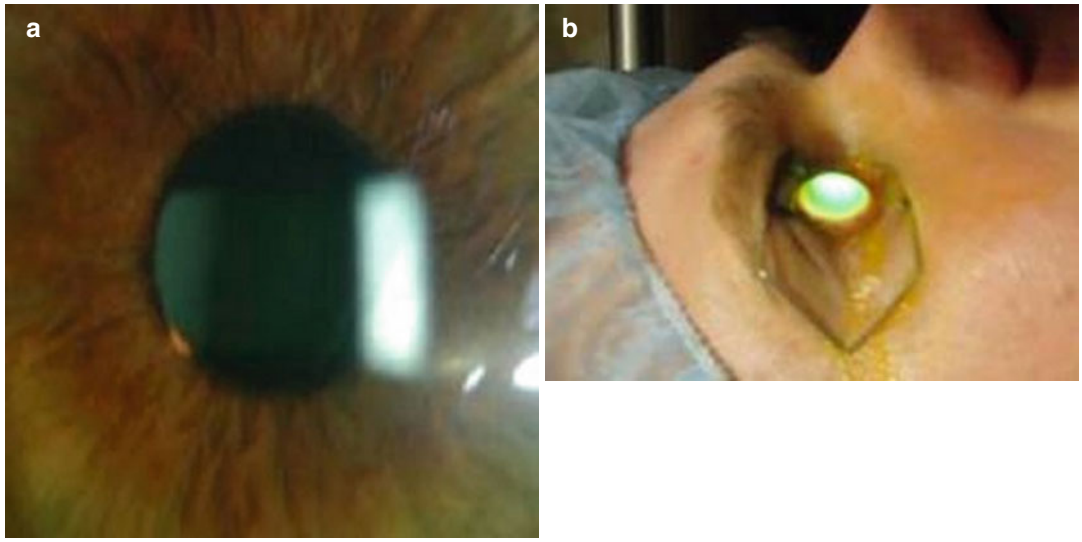


Fig. 6.1 (**a**) Slit lamp image confirming corneal riboflavin uptake and anterior chamber flare. (**b**) Photograph of patient being treated with UVA 365 nm light at an irradiance of 3.0 mW/cm^2

patients gained two or more Snellen lines of uncorrected vision, and about 8.5 % patients lost two or more lines of uncorrected visual acuity at 1 year (Fig. 6.2a) (Hersh et al. 2011).

In our study, while improvement of patient's uncorrected visual acuity after CXL was notable, more clinically significant was the improvement of best corrected visual acuity. Mean 1 year best corrected visual acuity significantly improved by about 1 Snellen line, from logMAR 0.35 ± 0.24 (Snellen acuity = 20/45) to 0.23 ± 0.21 (Snellen acuity = 20/34). Postoperative improvement of best corrected visual acuity has been noted in numerous other CXL studies as well. Vinciguerra et al. (2009a, b) found that in patients with stage III keratoconus, mean best corrected vision (logMAR) improved from 0.28 to 0.14 at 12 months postoperatively. At 1-year follow-up, Raiskup-Wolf et al. (2008) and Caporossi et al. (2010) reported significant improvements in best corrected vision of logMAR 0.08 and 1.34 Snellen lines, respectively, with continued improvement after 1-year follow-up. In our study (Hersh et al. 2011), about 21 % of patients gained two or more Snellen lines of best corrected visual acuity, and only one patient (1.4 %) lost two or more lines of best corrected visual acuity (Fig. 6.2b). More recently, another study reported about 40 % of patients gained two or more lines postoperatively; however, 12 % of patients in this study lost two or more lines of best corrected vision as well (Asri et al. 2011).

Regarding refractive outcomes, significant changes in manifest astigmatism of 0.93 D (Raiskup-Wolf et al. 2008) and 0.26 D (Vinciguerra et al. 2009a) have been reported. However, in other studies, mean manifest astigmatism essentially remained unchanged following CXL (Hersh et al. 2011). A vector and double-angle plot analysis, performed 1 year after CXL, revealed that mean induced astigmatism at 12 months, compared with preoperative values, was 0.75 D × 76°. Mean induced astigmatism was 0.99 × 88.8 and 0.65 × 44.7, in the right and left eyes, respectively. These refractive analyses suggest that there are directional changes in the cones and cylinder of keratoconus patients following CXL; however, the changes are random and unpredictable (Hersh et al. 2011).

6.3.2 Topographic Outcomes

Maximum keratometry is a key topographic indicator of the success of CXL, since it

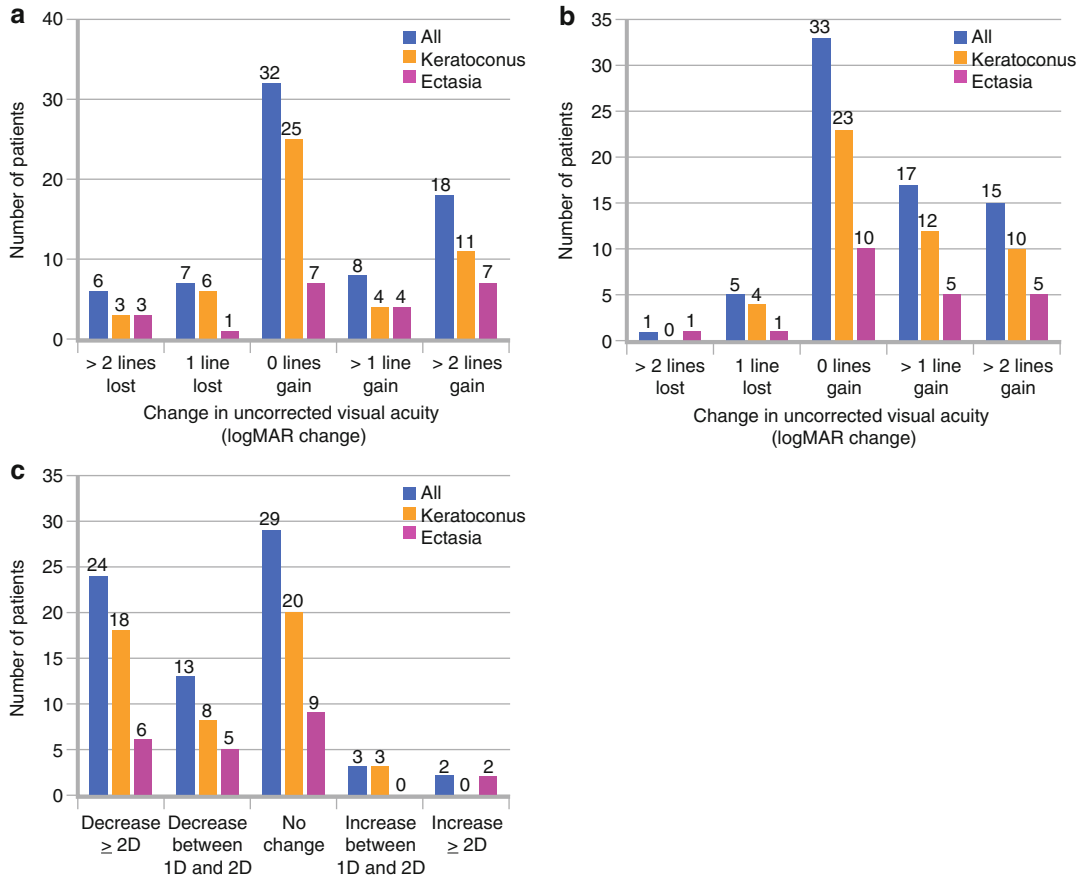


Fig. 6.2 (**a**) Number of individual patients who experienced a change in UCVA Snellen lines between baseline and 12 months after CXL. (**b**) Number of individual patients who experienced a change in BSCVA Snellen lines between baseline and 12 months after CXL. (**c**) Number of individual patients who experienced a change in maximum keratometry (D) between baseline and 12 months after CXL (Hersh et al. 2011)

measures, to some extent, the severity of the keratoconic cone. In the literature, average flattening of maximum keratometry ranges from about 1D to 3D, 1 year after CXL (Wollensak et al. 2003a; Caporossi et al. 2010; Vinciguerra et al. 2009a; Hersh et al. 2011; Caporossi et al. 2006; Koller et al. 2011). Furthermore, Raiskup-Wolf et al. (2008) and Caporossi et al. (2010) reported a continued flattening of maximum keratometry after 1-year follow-up. Individually, maximum keratometry decreased by 2D or more in 21 to 35 % of patients, change between −2D and 2D in 62.0 to 68 % of patients (essentially remaining stable), and steepen by 2D or more in 3 to 6 % of patients (Fig. 6.2c) (Hersh et al. 2011; Asri et al. 2011).

6.3.3 Topographic Keratoconus Indices

In general, topographic keratoconus indices (Table 6.1) are elevated over normal in patients with keratectasia and, therefore, a significant decrease in any of these postoperative measurements after CXL may indicate improvement in the contour of the cornea. Koller et al. (2011) reported a significant improvement in four of seven Pentacam topography indices [central keratoconus index (CKI), keratoconus index (KI), index of height asymmetry (IHA), and minimum radius of curvature (R_{min})] 1 year after CXL. Similarly, we noted an improvement in four of seven indices, including KI and R_{min} as in

Table 6.1 List of the abnormal and pathological values for the Pentacam topographic indices (User manual for the Pentacam Oculus, Wetzlar, Germany)

Index	Description of index	Abnormal	Pathological
ISV	A general measure of corneal surface irregularity	≥37	≥41
IVA	A measure of the difference between superior and inferior curvature in the cornea	≥0.28	≥0.32
KI	As determined by the Pentacam	≥1.07	≥1.07
CKI	As determined by the Pentacam	≥1.03	≥1.03
R_{min}	A measurement of the smallest radius of curvature of the cornea	<6.71	<6.71
IHA	A similar measurement to IVA, but based on corneal elevation	≥19	>21
IHD	A calculation with Fourier analysis of corneal height to quantify the degree of vertical decentration	≥0.014	≥0.016

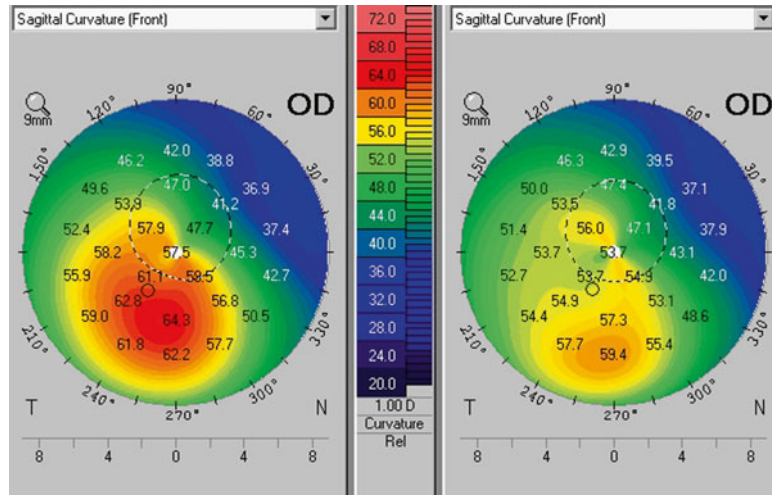


Fig. 6.3 Corneal topography before (*left*) and 1 year after CXL (*right*). Note improvement in corneal contour

the aforementioned study, but additionally, our study revealed improvements of index of surface variance (ISV) and index of vertical asymmetry (IVA) (Greenstein et al. 2011). The improvements observed in ISV indicate a decrease of the curvature variation compared to the mean curvature of the cornea, and IVA, a measurement of the difference between the superior and inferior curvature of the cornea, which may be analogous to an improvement in the more commonly used I-S ratio (Rabinowitz 1995). Furthermore, improvement in KI may indicate that there is a normalization of the keratoconic topographic appearance postoperatively (Fig. 6.3). The overall improvements in the above indices suggest, in general, that the cone is flattening and that the post-CXL cornea is becoming more optically regular and symmetric; however, it is unclear why, in the previous two studies, the improvements were demonstrated, in part, by different Pentacam indices.

6.3.4 Higher-Order Aberrations

Increased anterior corneal, posterior corneal, and total ocular higher-order aberrations are optical sequelae of keratoconus which contribute to the diminished visual function found in these corneal disease processes (Lim et al. 2007; Schlegel et al. 2009). Corneal collagen cross-linking, although developed primarily to mitigate progression of ectatic corneal processes, as discussed previously, has been found to improve visual acuity in many patients as well. Detailed analyses of higher-order aberrations showed significant improvements in ocular and anterior corneal higher-order

aberrations 1 year after CXL (Fig. 6.4a–c) (Vinciguerra et al. 2009a; Hersh et al. 2011; Greenstein et al. 2012a). This finding corroborates the improvement in corneal topography seen. Although improvement both in topography and in aberration profile would be expected to improve vision, interestingly, neither the corneal nor total ocular aberrations were statistically associated with the improvements of postoperative visual acuity in our study. Furthermore, there did not appear to be any clinically relevant associations between improvement of higher-order aberrations and improvement of any subjective visual symptoms (e.g., glare, halos, sunbursts, etc.) after cross-linking as well (Greenstein et al. 2012a). Notwithstanding these statistical analyses, a general decrease in higher-order aberrations and improvement in corneal topographic contour would be expected to have overall beneficial effects to the patients visual function.

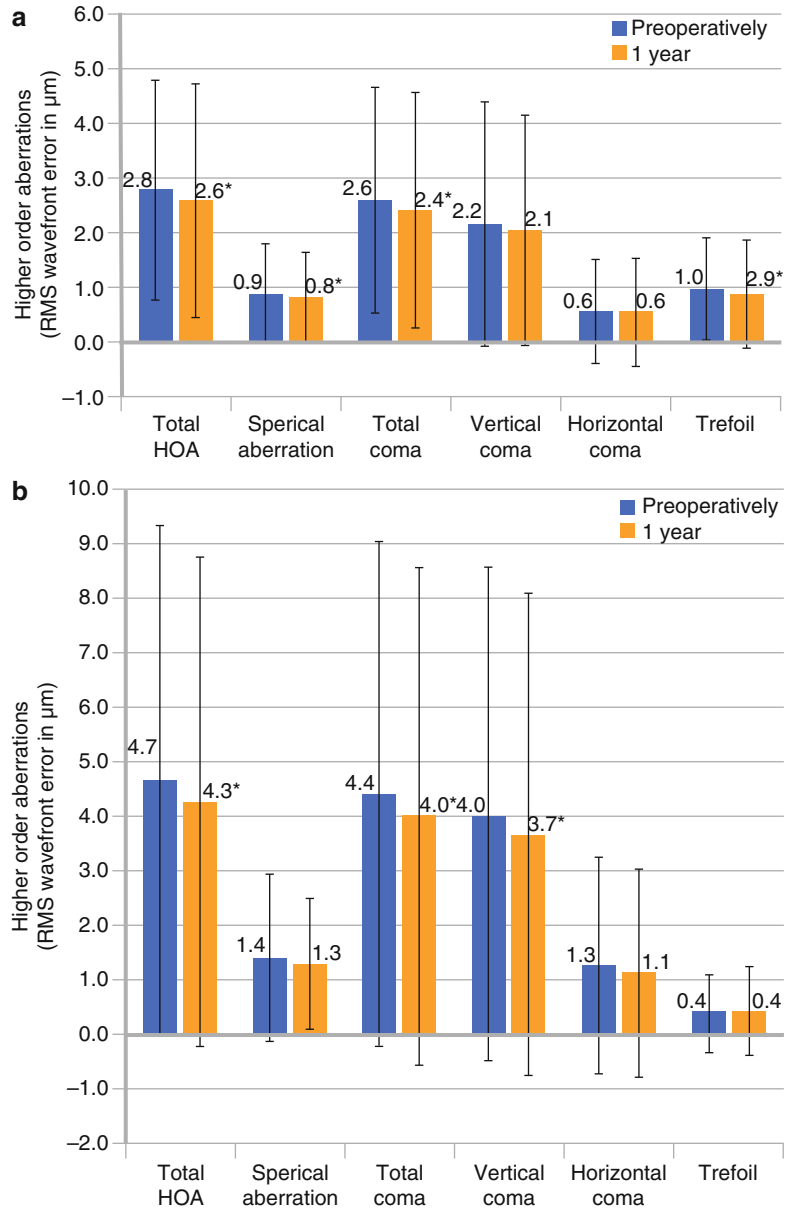
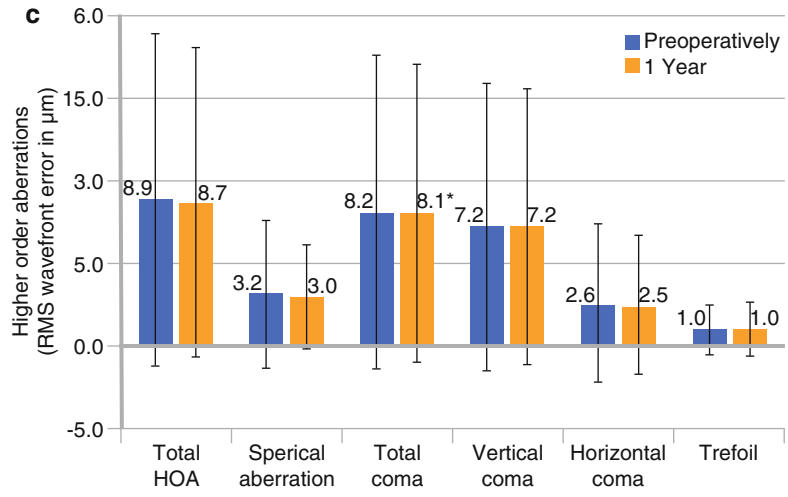


Fig. 6.4 Higher-order aberrations (root mean squared wave front error), measured preoperatively and at 1 year after CXL. *Error bars* represent 2 standard deviations from the mean. *Indicates a significant change compared to preoperative measurements ($P<0.05$). (**a**) Total ocular aberrations. (**b**) Anterior corneal aberrations. (**c**) Posterior corneal aberrations (Greenstein et al. 2012a)

Fig. 6.4 (continued)



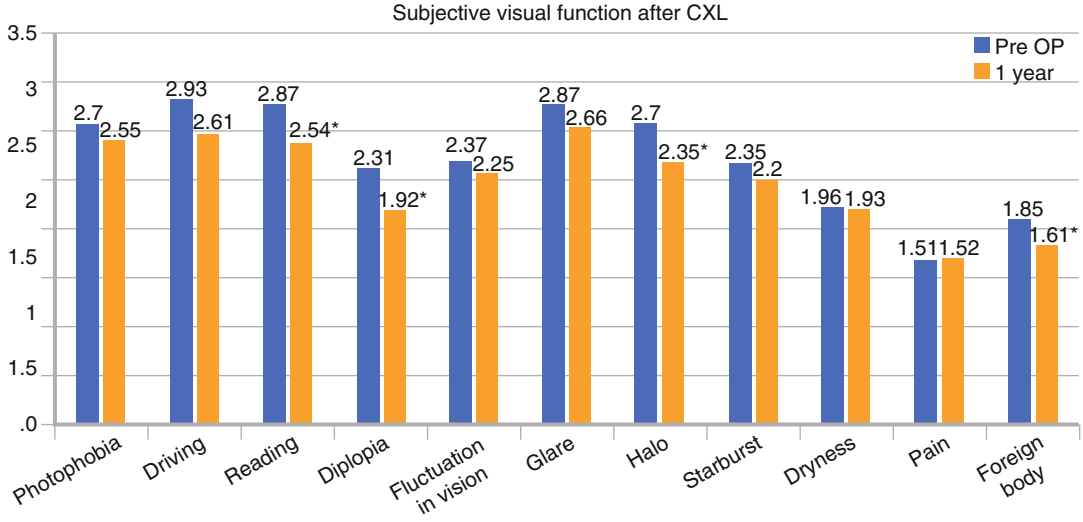


Fig. 6.5 Average rating of subjective visual parameters for keratoconus subgroup preoperatively and at 12 months after CXL. Subjective scale 1–5 (1 = no symptoms, 5 = severe symptoms). *Statistically significant ($p < 0.05$) (Brooks et al. 2012)

6.3.5 Patient Satisfaction

In an effort to expand on the objective postoperative assessment of the cross-linking procedure and to further elucidate the expected clinical response, a self-reported analysis of patients' optical symptoms and visual function was instructive. In our study, we found that patients generally noted subjective improvement in visual symptoms. Specifically, night driving, difficulty reading, diplopia, glare, halo, starbursts, and foreign body sensation were all improved 1 year after CXL (Fig. 6.5) (Brooks et al. 2012). In addition to corroborating the objective postoperative improvements after corneal collagen cross-linking, this speaks to the positive subjective patient satisfaction after the procedure.

6.3.6 Postoperative Timecourse

Looking at the clinical timecourse after cross-linking, there was a significant worsening of vision and steepening of the keratoconic cones at 1 month postoperatively. These changes appear to improve

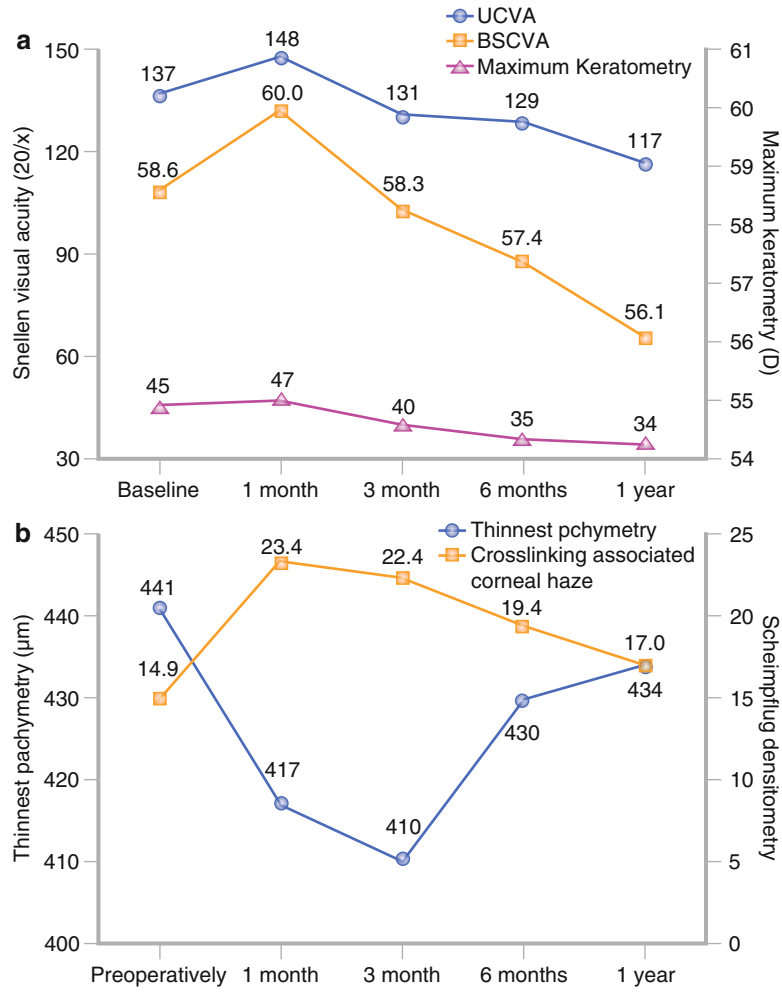


Fig. 6.6 (**a**) Change in UCVA, BSCVA, and maximum keratometry over time. (**b**) Change in thinnest pachymetry and cross-linking-associated corneal haze over time (Hersh et al. 2011)

at about 6 months and plateau thereafter (Fig. 6.6a). Interestingly, these postoperative outcomes appear to be congruous with the postoperative thinning and cross-linking-associated corneal haze changes over time (Fig. 6.6b). It is unclear whether this suggests a remodeling occurring during a "desired" haze and thinning process or if this time course suggests a natural process of corneal would healing irrespective of the changes in cross-linking-associated corneal haze and postoperative thinning (see Sect. 6.5).

6.4 Biomechanical Changes

In vitro, corneal collagen cross-linking has been reported to increase the biomechanical stability of the ecstatic cornea in keratoconus (see Sect. 6.2). Currently, the Ocular Response Analyzer (ORA, Reichert Inc., Buffalo, NY, USA) is one of the few commercially available tools to measure in vivo corneal biomechanics. Two core metrics are used to describe the biomechanical strength of the cornea: corneal hysteresis (CH) and corneal resistance factor (CRF). CH is a measurement of the viscous dampening in corneal tissue, and CRF is a measurement of the entire viscoelastic response of the cornea, in response to both the graded and time-dependent applanation pressures applied by the ORA. To measure CH and CRF, a tube is automatically aligned with the patient's eye, and an air puff is released of a specific time and pressure gradient. Concomitant with the air pulse, the ORA measures two applanation pressures: the first pressure is measured when the cornea is moving inward, and the second pressure is measured

when the cornea returns to its original position. In addition, a waveform of this temporal corneal deformation is captured. Measurements derived from the waveform signal such as peak amplitudes, timing of peaks, width of peaks, and others, have been used to determine the biomechanical properties of individual corneas (Kerautret et al. 2008; Fry et al. 2008; Gatinel and Luce 2009; Lam et al. 2010).

In vivo biomechanical measurements, CH and CRF appear to remain unchanged 1 year after CXL (Fournie et al. 2009; Goldich et al. 2009; Vinciguerra et al. 2010; Greenstein et al. 2012). Interpreting these results is challenging, since postoperative changes to either the viscous or elastic components of the cornea may be too subtle for these ORA metrics to capture and may in part contribute to the lack of significant results (Touboul et al. 2008; Glass et al. 2008). Moreover, the surface optical irregularity of these ectatic corneas may introduce error and variability into the ORA signal that may prevent meaningful quantitative comparison of preoperative and postoperative CH and CRF (Vinciguerra et al. 2009a; Shah et al. 2006). It is also possible that the biomechanical changes after CXL are inherently different than those measured by CH and CRF, and therefore, these metrics may not capture the true biomechanical effect of CXL over time. Development of interpretive models of the waveform itself, similar to those used to grade keratoconus, may better capture the true biomechanical properties of the cornea after CXL (Fry et al. 2008; Gatinel and Luce 2009). Moreover, development of new instrumentation to assess corneal biomechanics will help to better assess the stiffening effects of the cross-linking procedure clinically.

6.5 Complications

6.5.1 Postoperative Haze

On clinical examination, corneal haze has been noted after the cross-linking procedure (Fig. 6.7). Cross-linking-associated corneal haze is different in clinical character from haze after other procedures such as excimer laser photorefractive keratectomy. The former is a dustlike change in the corneal stroma or a mid-stromal demarcation line (Seiler and Hafezi 2006), whereas the latter has a more reticulated subepithelial appearance. Cross-linking-associated corneal haze is most likely a measure of backscattered and reflected light, causing decreased corneal transparency (Caporossi et al. 2010). This haze can be graded at the slit lamp (Wollensak and Iomdina 2009); however, grading slit lamp haze is subject to observer interpretation and is difficult to measure objectively. Moreover, corneal haze has been confirmed using confocal microscopy as well and can be objectively quantified using Scheimpflug densitometry (Fig. 6.8) (Mazzotta et al. 2007).

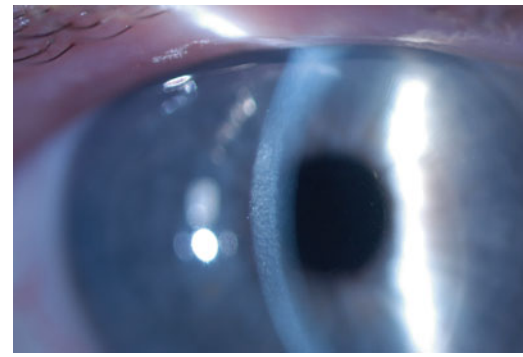


Fig. 6.7 Typical corneal stromal haze after collagen cross-linking

Similar to the timecourse of clinical outcomes after cross-linking, there appears to be an increase in haze, which peaks at 1 month and plateaus between 1 and 3 months. Between 3 and 6 months, the cornea begins to clear and continues to return toward baseline at 1 year (Fig. 6.6b) (Greenstein et al. 2010).

To date, it remains unclear whether this postoperative haze is a true complication or rather a desired wound healing effect demonstrating the efficacy of the cross-linking procedure. Transparency of the cornea is a result of the regular spacing, small uniform diameter of the collagen fibrils (Vinciguerra et al. 2009a), and the cellular structure of stationary keratocytes (Hersh et al. 2011). Increased spacing and changes in fibril diameter could cause increased light scatter and decreased transparency. Furthermore, stationary keratocytes have crystallins in their cytoplasm that have a refractive index similar to that of the extracellular matrix. During wound healing,

Fig. 6.8 Scheimpflug images of cross-linking-associated corneal haze over time

migratory keratocytes have decreased crystallins, leading to an increase in refracted light and a subsequent increase in haze (Hersh et al. 2011). In vitro and ex vivo studies have shown that collagen cross-linking led to an almost immediate loss of keratocytes in the corneal stroma (Gefen et al. 2009; Raiskup-Wolf et al. 2008). Confocal microscopy, in patients with keratoconus, revealed activated keratocytes repopulating the corneal stroma starting at 2 months, and stromal repopulation was almost complete at 6 months (Mazzotta et al. 2007). It is possible that these activated keratocytes contribute to the development of haze, as seen on Scheimpflug imagery. Additionally, a significant increase in collagen fibril diameter, with increased spacing between collagen fibrils, following UVA/riboflavin therapy may play an important role in the decreased corneal transparency as well (Wollensak et al. 2004b; Hersh et al. 2011).

6.5.2 Corneal Pachymetry

Corneal thinning is a general concomitant of the early CXL postoperative course (Fig. 6.6a). Previous studies have noted that intraoperative ultrasound pachymetry decreased after the initial 30 min of riboflavin administration (Wollensak et al. 2004a), and several others have noted corneal thickness changes after CXL (Seiler et al. 1998; Salgado et al. 2011; Hafezi et al. 2007; Roberts 2000; Wollensak and Iomdina 2009; Ahearne et al. 2008; Wollensak et al. 2004a, b). Postoperatively, similar to the timecourse of cross-linking-associated corneal haze, and cross-linking clinical outcomes, the cornea appears to thin at 1 and 3 months and to re-thicken between 3 and 12 months (Greenstein et al. 2011). At 1 year, cornea treated with standard dextran riboflavin alone remained slightly thinner than preoperative measurements.

The physiology of this initial thinning and subsequent re-thickening is, as yet, unclear. Epithelial remodeling is a possible early factor in corneal thickness changes. Although reepithelialization after CXL generally is complete at 4–5 days after surgery (Sawaguchi et al. 1989), continued epithelial remodeling could influence total corneal thickness over time (Fig. 6.9a, b). For instance, the native epithelium may mask underlying stromal contour irregularities, with thicker epithelium over the lower stromal regions and thinner epithelium overlying the cone itself. Thus, removing the epithelium may unmask a greater stromal irregularity, resulting in steeper corneal topography, which then resolves as the epithelium heals and remodels. Aside from epithelial healing, anatomic and structural changes of corneal collagen fibrils such as compression of collagen fibrils (especially the more transverse-oriented anterior fibrils) (Wollensak et al. 2003b; Vinciguerra et al. 2009a), changes in corneal hydration (Hersh et al. 2011) and edema (Raiskup-Wolf et al. 2008; Asri et al. 2011), keratocyte apoptosis (Sawaguchi et al. 1989; Caporossi et al. 2006; Koller et al. 2011), changes in glycosaminoglycans (Rabinowitz 1995), and other processes might be implicated in the distinct clinical timecourse after CXL.

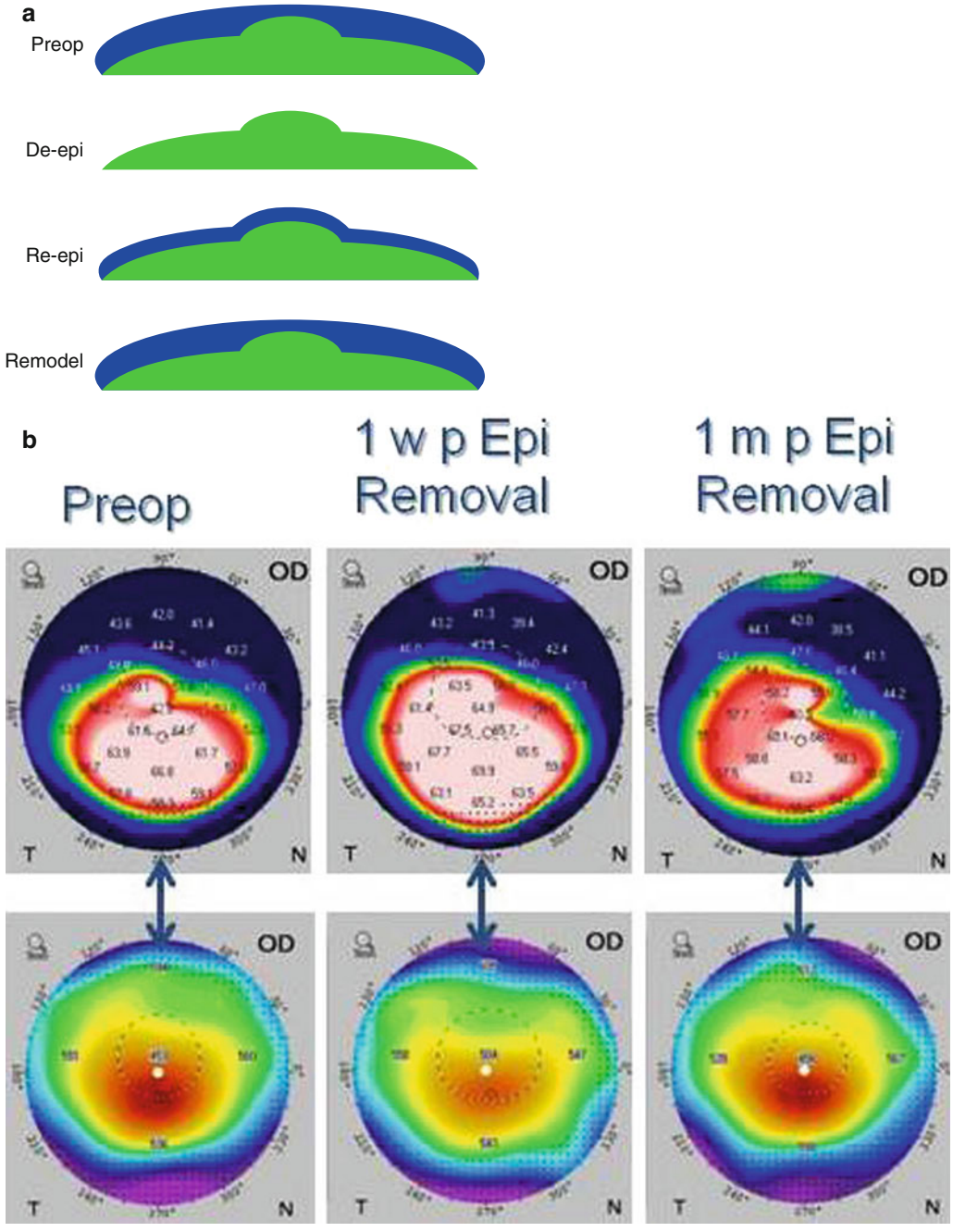


Fig. 6.9 (**a**) Epithelial remodeling as a possible cause of early topography cone steepening after CXL. Note "unmasking" of cone with epithelial removal and subsequent improvement of anterior contour as epithelium remodels, filling in low topographic regions. (**b**) Corneal topography and corresponding thickness preop, at 1 week, and at 1 month. Note the increased cone and thickening over the apex 1 week after de-epithelialization and the improvement in the cone height with thinning of the pachymetry 1 month post-op

6.6 Predictors of Outcomes

The essential goal of collagen cross-linking is to stabilize the progression of the ectatic cornea. With regard to this disease stabilization, cross-linking indeed appears efficacious; 98.1 % of eyes showed <2D and 91.6 % showed <1.0D of topographic progression over 1 year postoperatively. In addition, specific predictors of not only stabilization but rather positive and negative cross-linking outcomes have begun to be elucidated. Two studies from Seiler's group deserve attention (Spoerl et al. 2004b). In the first, of 105 eyes, 3 lost 2 Snellen lines of best corrected vision at 1 year. Two characteristics, age >35 years and best corrected vision better than 20/25, were identified as risk factors for this loss of vision. Eight eyes (7.6 %) showed continued progression of keratoconus 1 year after CXL, defined as an increase in maximum *K* of ≥1.0D. Two preoperative characteristics, maximum *K* >58.0 D and female gender, were identified as risk factors for continued disease progression. In a second study by this group, they found that a preoperative *K* >54.0 D was associated with a greater likelihood of postoperative flattening of >1.0D, a finding corroborated by our study (Greenstein and Hersh 2013). With regard to clinical decision-making, their latter study conflicts somewhat with their earlier conclusion that the *K* >58.0 was associated with greater risk of continued disease progression.

These results may have important implications for patient outcomes after cross-linking. Our multivariate analyses revealed the only independent predictor of a change in postoperative best corrected vision after CXL was preoperative best corrected visual acuity. Those eyes with worse preoperative best corrected visual acuity were more likely to experience an improvement of ≥2 Snellen lines. Specifically, eyes with a preoperative Snellen visual acuity of 20/40 or worse were 5.9 times more likely to improve by two lines or more; 43 % of eyes with best corrected vision 20/40 or worse had an improvement of ≥2 lines compared with only 11 % of eyes who were better than 20/40 (Fig. 6.10a, b). With regard to eyes which lost vision from the procedure, the most salient indicator of an unwanted outcome, there was no independent preoperative indicator.

With regard to postoperative topography, eyes with a maximum *K* ≥55D were 5.4× more likely to have topographic flattening ≥2D after CXL compared with eyes with flatter corneas. However, with regard to eyes in which corneal topography continued to steepen, that is, those in which the cross-linking procedure failed to stabilize the disease, there were no independent predictors of continued topographic steepening even at the more refined ≥1D level (Greenstein and Hersh 2013). All eyes were equivalently likely to be stabilized by the CXL procedure. Specifically, in patients with an initial maximum *K* ≥55D, 40/44 (90 %) eyes showed less than 1.0 D of progression, 1 year after CXL; similarly, in patients with initial maximum *K* <55.0D, 55/60 (92 %) eyes were stable (Fig. 6.11a, b).

From the viewpoint of clinical decision-making, since no independent predictors of failure of cross-linking to stabilize topographic disease progression were identified, it is reasonable that all eyes with progressive keratoconus or corneal

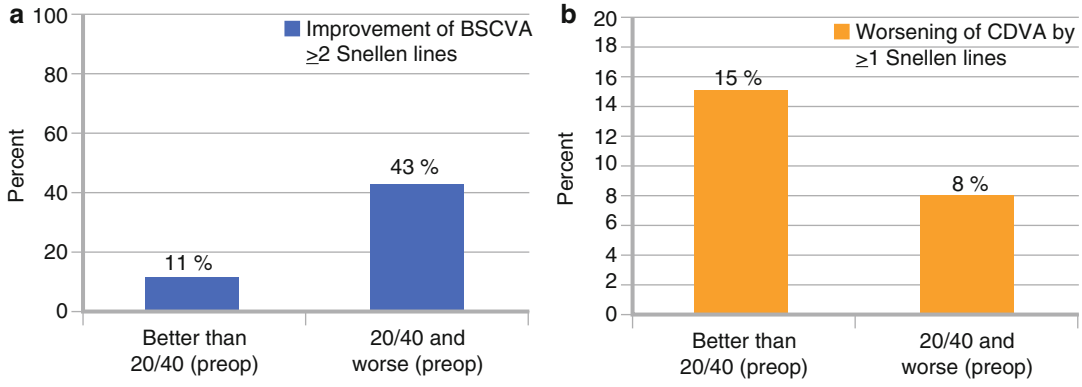


Fig. 6.10 The effect of preoperative BSCVA on CXL outcomes. (**a**) (*Blue*) Percentage of eyes in which BSCVA improved by ≥2 Snellen lines 1 year after CXL. (**b**) (*Orange*) Percentage of eyes in which BSCVA worsened by ≥1 Snellen line 1 year after CXL

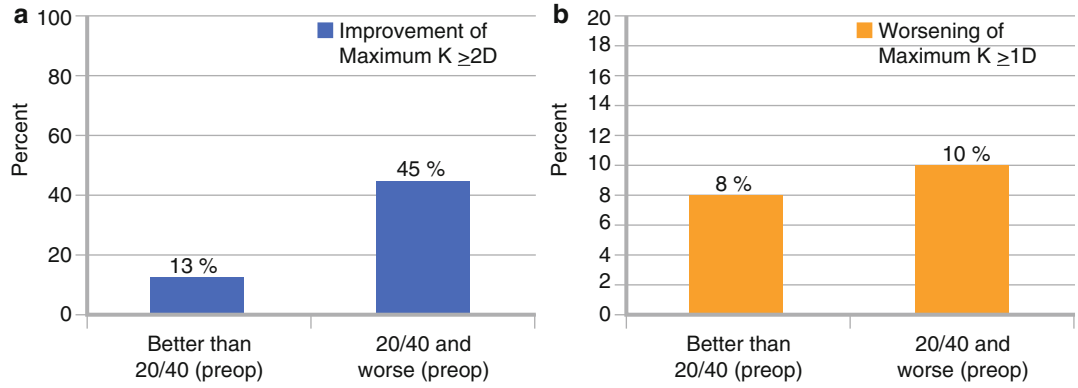


Fig. 6.11 The effect of preoperative maximum keratometry on CXL outcomes. (**a**) (*Blue*) Percentage of eyes in which maximum *K* flattened by ≥2D 1 year after CXL. (**b**) (*Orange*) Percentage of eyes in which maximum *K* steepened by ≥1D 1 year after CXL

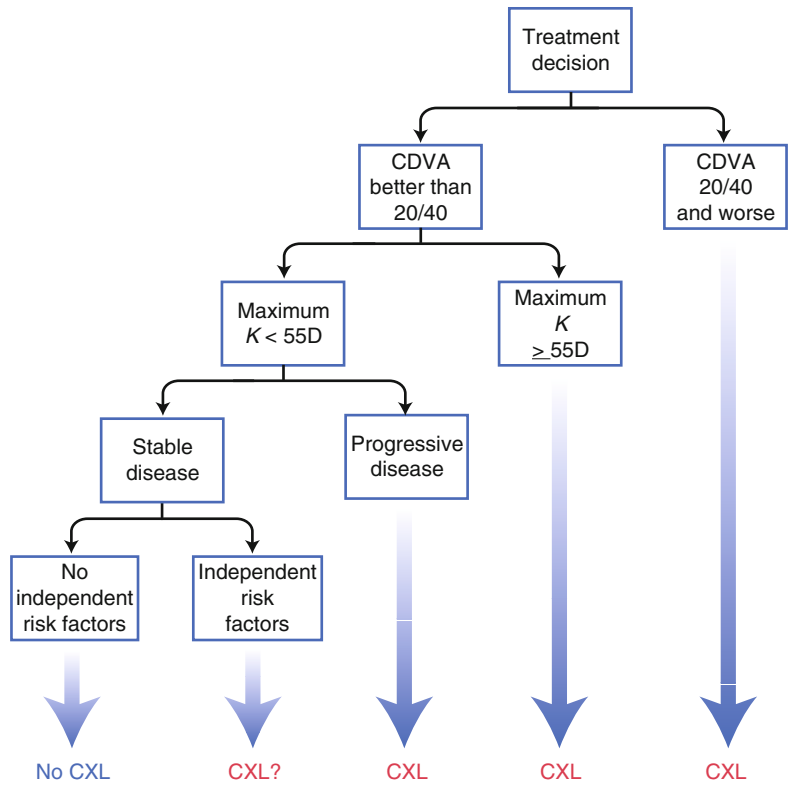


Fig. 6.12 Treatment algorithm for CXL patient selection

ectasia should be considered for cross-linking treatment, with the goal of diminishing disease progression. With regard to postoperative best corrected vision, from our current knowledge, it might be reasonable to conclude that eyes with worse vision initially would expect the greatest chance of actual visual improvement, and all eyes are equally likely to remain stable within 2 lines of best corrected visual acuity, although eyes with initially good vision (better than 20/40) may be somewhat more susceptible to a loss of 1 line (Fig. 6.12). Therefore, eyes with good visual acuity and progressive disease may still benefit from cross-linking treatment but the ophthalmologist should be aware of this possible visual complication and the patient properly counseled.

Finally, preoperative cone location may play an important role in the efficacy of the cross-

linking procedure (Greenstein et al. 2012b). There appears to be more topographic flattening in those eyes with centrally located cones. In our previous work, maximum keratometry flattened by 2.6D in eyes with centrally located cones and by only 1.0D and 0.05D in those eyes with paracentral and peripheral cones, respectively. This difference in topographic outcomes may be explained by a number of mechanisms. The treatment delivered by the current UV technique may not be homogeneous over the entire treatment zone, the "cosine effect" (Hersh et al. 2003) may diminish the relative treatment of the peripheral cornea by cross-linking, and hypothetically, the more symmetric cross-linking effect in centrally located cones may lead to more equal compression of collagen fibrils in all directions, and therefore increased flattening in those patients with centrally located cones. Furthermore, it was noted that patients with post LASIK ectasia (included in the above study) were more likely to have peripheral cones, and therefore, the above study may be elucidating a difference in the disease response to cross-linking rather than the cone location itself.

While the mechanism for the greater improvement of centrally located cones remains uncertain, the effect of preoperative cone location on cross-linking outcomes may be important as cross-linking continues to evolve. With regard to the delivery system, assuring consistent energy over the face of the beam may give more consistent treatment to the corneal periphery. Moreover, topographically guided treatments, either with the beam directed at the cone apex directly or more elegantly delivered as a true topographically guided treatment, could improve cross-linking results independent of cone location. With regard to other procedures to enhance the cross-linking effect, efforts to "centralize" the cone, for instance, by intracorneal ring segments or by conductive keratoplasty (Hersh et al. 2005), could possibly lead to more robust cross-linking results as well.

6.7 Future of Corneal Collagen Cross-Linking

Transepithelial cross-linking, a variation of the standard cross-linking procedure in which the corneal epithelium is not removed, offers several possible advantages. Firstly, it improves patient comfort in the early postoperative reepithelialization phase. Secondly, it reduces the risk for infection, and thirdly, it offers faster visual recovery with an earlier potential return to contact lens wear. The approach to transepithelial cross-linking is evolving. Standard riboflavin in a dextran solution does not penetrate the corneal epithelium well. Therefore, many investigators utilize riboflavin without dextran and also use a solution containing benzalkonium chloride (BAK) to increase the permeability of the corneal epithelium and allow for the penetration of the riboflavin into the corneal stroma before exposure to the UV light (McCarey and Edelhauser 2007). Early results of transepithelial cross-linking have been mixed, as are the long-term results for this procedure (Caporossi et al. 2012, 2013; Zhang and Zhang 2012; Koppen et al. 2012). Further long-term studies are required to determine the efficacy of this procedure and, more importantly, to determine the ideal riboflavin and coupling solutions, as well as the application method and optimum UV power to achieve desired results.

Another variation of the standard cross-linking procedure is accelerated corneal collagen cross-linking. In this procedure, the cornea is exposed to a higher power of UV light over a significantly shorter period of time. In vitro studies have shown that despite delivering a higher power of UV light, the safety and integrity of the corneal endothelium remains intact secondary to the very short exposure time. Clinical studies of accelerated cross-linking are now underway.

Finally, there has been increasing focus on the use of corneal collagen cross-linking as part of a larger treatment algorithm for patients with keratoconus. While there are many patients who may benefit from cross-linking alone, there are other patients who may benefit from cross-linking as an adjunct procedure to stabilize the cornea. Other procedures, such as intracorneal ring segments (Vega-Estrada et al. 2013; Saelens et al. 2011; Alio et al. 2006; Kwitko and Severo 2004), PRK (Spadea 2012), topography-guided photorefractive keratectomy, and microwave thermokeratoplasty (Keraflex) (Barsam et al. 2010), are starting to be preformed and studied for patients with more severe keratoconus. These procedures may induce more initial flattening of steeper cones and improve

the contour of the ectatic cornea; however, corneal collagen cross-linking may be required to better stabilize these changes over time.

Conclusions

Corneal collagen cross-linking is a promising new treatment to stabilize and even improve the visual acuity and topography of patients with keratoconus. In the future, faster and more precisely guided UV light delivery systems, as well as new forms of riboflavin, may continue to improve the safety and efficacy of this new procedure. Further studies being conducted will likely continue to reveal the patients who will most benefit from corneal collagen cross-linking whether it is as a standalone procedure or in conjunction with other procedures designed to improve the contour and optical quality of the ectatic cornea.

Compliance with Ethical Requirements

Conflict of Interest

Dr. Greenstein declares that he has no conflict of interest.

Dr. Hersh is a consultant for Avedro, Inc.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Animal Studies

No animal or human studies were carried out by the authors for this article.

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