



## ORIGINAL ARTICLE

UDK 615.03:613.2-099

**Robert L. Epstein**  
**Greg L. Epstein**

College of Applied Sciences  
 Mercy Center for Corrective Eye  
 Surgery  
 McHenry, Illinois

**Correspondence**

Robert L. Epstein, MD, MSEE  
 Mercy Center for Corrective Eye  
 Surgery  
 McHenry, IL USA  
 Email: rlepstein@aol.com

# Abbreviated UVA-Riboflavin Corneal Collagen Cross-linking for Keratoconus and Post-LASIK Ectasia

**ABSTRACT**

**Introduction.** To determine the effect of corneal collagen cross-linking treatment on keratoconus and post-LASIK ectasia particularly after an abbreviated exposure to ultraviolet light exposure.

**Materials and methods.** Fifty-one eyes of 34 patients were treated with epithelium-off UVA-riboflavin corneal collagen cross-linking for either 20 minutes or 30 minutes as part of a US.FDA clinical study. The study involved eyes with keratoconus but with no prior operation (virginal), patients who had undergone prior intracorneal ring segments, those with keratoconus regression after keratoplasty, and those with post-LASIK ectasia. We report follow up results from three months to one year.

**Results.** In the virginal keratoconus group all 83% of eyes having 20-minute UVA exposure and 75% of those having 30-minute of UVA exposure experienced corneal flattening or stabilization at 6 months post-operatively with visual improvement in both groups. The average patient age in the virginal keratoconus group was 34.5 years. Seventy five percent of virginal keratoconus eyes of patients under age 40 but only 33% of eyes of patients over age 40 experienced statistically significant corneal flattening at six months postoperatively. Average vision improved at six months post-operatively over pre-operative levels by -0.0744 logMAR units in the 20 minute group, and by -0.0869 logMAR units in the 30 minute group. Post-LASIK ectasia patients, with an average age of 58.2 years, had slight overall curvature flattening of -0.75D but without visual improvement one year post-operatively. No one experienced peri-operative complications. Topographic subtraction mapping revealed variations in the power of the cross-linking effect on different portions of the cornea

**Conclusion.** Cross-linking appears safe. It is effective in most young patients causing corneal flattening and can stabilize eyes with post LASIK ectasia but acts more slowly in older patients. The cross-linking effect may be more pronounced in individuals with darker pigmentation. Cross-linking can produce occasional very significant corneal flattening. The cross-linking effect increases with time.

**KEY WORDS**

Cross-linking, keratoconus, riboflavin, post-LASIK ectasia, collagen cross-linking

DOI: 10.7251/SMD1301019E

(*Scr Med* 2013;44:19-24)

Submitted: January 30, 2013

Accepted: March 28, 2013

Keratoconus is an important cause of visual loss that can severely affect relatively young and otherwise apparently healthy people. Also there is association of keratoconus with disease. Keratoconus is associated with eczema, allergy and asthma<sup>1</sup>, as well as with Marfan syndrome and with Down syndrome<sup>2</sup>. There is a high incidence of sleep

apnea among keratoconus patients<sup>3</sup> and keratoconus patients may have reduced life expectancy<sup>4</sup>.

Early visual decline may resemble the optical changes of youth. But what is not normal is the need for increasing astigmatic correction that is typically seen in developing

keratoconus. With disease progression eyeglasses cannot correct vision to normal. Visual loss from keratoconus is often misdiagnosed at first as being from amblyopia unless there is a search for and comparison with old records from previous eye doctors. Soft lenses and then rigid contact lenses become necessary for adequate vision, but when these lenses become increasingly uncomfortable and more poorly fitting, surgical treatment is necessary to improve vision. Vigorous eye rubbing makes the disease worse and patients should be discouraged from this practice.<sup>5,6</sup>

The mainstay of surgical treatment for keratoconus has included corneal transplantation with its long healing period, risk of rejection, infection, and corneal rupture. Commonly transplantation requires the patient to wear rigid contact lenses after surgery in order to achieve optimum vision. Surface excimer laser treatment of the cornea after healing may be indicated to help vision in some cases. Corneal grafting, either full thickness or deep anterior lamellar keratoplasty remains necessary for some cases of advanced keratoconus, yet even that may not stop visual decline because keratoconus persists in the host cornea.

More recently, the implantation into the corneal wall of two, or possibly more effectively just one<sup>7</sup>, polymethyl methacrylate ring segment has helped to regularize the shape of the keratoconus cornea. However, this bracing effect does not stop the basic disease process which usually continues.

A condition called post-LASIK ectasia can occur as a result of the normal sculpting of the cornea in laser refractive surgery, including either LASIK or the surface laser vision correction known as PRK. It closely mimics the visual distortion of keratoconus. Some of the victims of post-LASIK ectasia may have had an unrecognized early stage of keratoconus, or *forme fruste* keratoconus, but others show no signs of the disease whatsoever, even when tested by any method in current technology. Detection of risk factors for post-LASIK ectasia is a subject of considerable interest and research.<sup>8-14</sup> An increased number of patients with *forme fruste* keratoconus tend to seek laser vision correction; the incidence has been documented to be in some cases as high as 9%.<sup>15</sup> Fortunately, some years ago Spoerl, Huhle, and Seiler<sup>16</sup> published a procedure called corneal collagen cross-linking with riboflavin that provided a partial solution to the problem of ectatic and keratoconic corneas. Studies from their institute and many others have advanced the field with over 400 papers having been published since that time.

Although the complete mechanism of keratoconus is not known, it is due in part to inadequate cross-linkages between collagen fibrils in the cornea and further degradation by metalloproteinases.<sup>17,18</sup> Corneal collagen cross-linking with riboflavin is an oxidatative process that riboflavin promotes in the presence of ultraviolet light.

Cross-linking causes immediate corneal stiffening even in cadaver tissue. Along with that stiffening cross-linking causes actual keratocyte destruction, swelling and corneal stromal remodeling in living corneas.<sup>19,20</sup> Riboflavin presently is critical to the cross-linking process and riboflavin penetrates poorly<sup>21</sup> through an intact corneal epithelium, however much work is occurring to increase the epithelial permeability including recently the addition on an experimental basis of vitamin E TPGS to the riboflavin solution<sup>22</sup>.

Collagen cross-linking is a successful adjunct to the use of antibiotics in certain difficult corneal infections<sup>22</sup>, and there is evidence that cross-linking may actually reduce the degree of edema and improve vision in some patients with persistent corneal edema occurring after cataract surgery and corneal edema from Fuchs' dystrophy<sup>23</sup>. Corneal collagen cross-linking is not yet approved by the United States Food and Drug Administration (US FDA) although it is freely available in certain eye centers worldwide

#### Materials and Methods

Fifty-one eyes of 34 patients underwent UVA-riboflavin, corneal collagen cross-linking, with epithelial removal. This was the first part of a three year clinical study on the safety and effectiveness of cross-linking as well as a comparison of the relative effects of 30 minutes versus 20 minutes of ultraviolet exposure. Cross-linking was performed for eyes with advancing keratoconus, with post-LASIK ectasia, and with advancing keratoconus recurring years after corneal transplantation. This report details the results of the cross-linking in forty-five eyes where patients were re-evaluated with three months to one year of follow up.

All patients received complete eye exams at each visit including endothelial cell photography and also five Pentacam Scheimpflug photographs of each eye.

Individuals who would most likely benefit from cross-linking and also from intracorneal ring segments (ICRS) were given a choice of two protocols: either having ICRS first and cross-linking 90 days later or having cross-linking first, then ICRS one year later.

Because the measure, maximal anterior corneal curvature, Kmax, is the most sensitive indicator of corneal curvature change from cross-linking,<sup>24</sup> those values were tabulated as part of the current clinical study. We have shown<sup>25</sup> that based on a comparison of the average of five Kmax values taken at each visit, the 95% confidence level of true Kmax change is a measured difference of at least 0.678 D using the Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany). Thus, one reasonable criterion for judging the efficacy of cross-linking is a change of 0.678D or more Kmax based on five readings. That criterion is used here.

All eyes in the study had the cross-linking procedure following the removal of corneal epithelium. Then an initial

14 minute corneal soaking was done by dripping 0.1% riboflavin upon the cornea every two minutes. This step was followed by the application by random assignment of either 20 minutes or 30 minutes of ultraviolet light at 370 nm using the UV-X device (Peschke Meditrade, Huenenberg, Switzerland). Either Mediocross brand (Streuli Pharma distributed by Peschke Meditrade) isotonic riboflavin 0.1% in 20% dextran or the hypotonic 0.10% riboflavin in 0.9% saline was used based on the minimal corneal pachymetry readings. All patients signed detailed consent forms, and the clinical study was performed in a manner approved by both the U.S. Food and Drug Administration and by the Institutional Review Board of the Mercy Health System, the parent company of this surgical practice. SPSS 16.0 (IBM Armonk, New York, USA) and Excel 2007 (Microsoft Corp. Redmond, WA, USA) were used for the statistical analyses.

Cross-linking was done under sterile conditions. Pachymetry of each eye averaged at least 400 microns throughout the treatment. Any eye undergoing cross-linking that developed stromal corneal pachymetry less than 410 microns was treated with hypotonic riboflavin, and the thicker corneas were cross-linked with isotonic riboflavin. Ultrasonic pachymetry was measured at three minute intervals. Under rare circumstances when pachymetry dipped below 400 microns during cross-linking a single drop of sterile water was applied to the cornea. Within seconds this treatment increased the corneal thickness by 20 microns or more. Epithelium was removable gently with an Amoils brush but for post-surgical eyes just ten seconds of 70% ethanol and gentle rubbing with a WeckCell sponge was found to be sufficient. All eyes with post-LASIK ectasia had epithelium removed using alcohol rather than the Amoils brush. In general the epithelium in eyes with keratoconus was found to be less firmly attached than in normal eyes.

Eyes in our study included those with virginal keratoconus and no prior surgery, those with prior refractive surgery, those with prior intracorneal ring treatment, and those with prior corneal transplantation for keratoconus. Included in the study were a total of 41 eyes with virginal keratoconus, that is, keratoconus as distinguished from post-LASIK ectasia in eyes that had not had intracorneal ring placement or corneal transplantation. Of these 41 eyes, 36 were at least one month post cross-linking. The overall patient age in the study was 38.9 +/-13.7 years with the post-LASIK ectasia patients being considerably older at 58.2 +/-4.6 years and the keratoconus patients being 34.5 +/-11.5 years.

## Results

None of our patients had any operative or peri-operative complications. Corneal edema was common during the first week. Except in the younger patients, correctable vision typically was better pre-operatively than one month post-operatively

There was no tendency towards endothelial cell loss. In the combined group, the pre-operative average cell count was 2306 +/- 590. Cross-linking resulted in essentially no change in endothelial cell count. Cell count changes from the pre-operative level were -2.9%+/-13.2%, +1%+/-28.3%, -5.2% +/-14.1%, and -0.2% +/-17.4% at one month, three months, six months and one year postoperatively respectively.

There were no patient complaints of dry eye occurring after cross-linking that had not also been documented pre-operatively.

Tables 1 through 4 describe the behavior of the corneal curvature, as measured by maximal anterior equivalent keratometry, Kmax. Table 1 documents the number of statistically significant increases and decreases of Kmax at six months postoperatively. Based on the modest sample size, results from both the twenty and thirty minute UV-A riboflavin cross-linking treatments appeared to be equivalent six months postoperatively. In Table 2 shows that there was a general tendency for some reduction in the curvature of the cornea in most patients by six months postoperatively and this effect was first noticeable at three months postoperatively.

**Table 1. Behavior of Kmax at 6 months postoperative after collagen cross-linking in virginal keratoconus eyes (no LASIK, corneal transplant, or intracorneal rings)**

Group----->	20 minute	30 minute
Kmax		
Decrease(better)	9	6
Increase(worse)	2	3
Same	0	3

Note: "Same" is defined as having the five easurement post-operative Kmax average within 0.678D or pre-operative average

**Table 2. Behavior of Kmax after Collagen Cross-linking by Postoperative Time All eyes including virginal keratoconus, post-LASIK ectasia, post Intrstromal rings, and post corneal transplant**

	1 month	3 months	6months	1 year
Kmax				
Decrease(better)	13(28.3%)	15(41.7%)	18(52.9%)	7(53.8%)
Increase(worse)	19(41.3%)	12(33.3%)	11(32.4%)	4(28.6%)
Same	14(32.7%)	9(25%)	5(14.7%)	3(21.4%)

Note: Same=Five measurement Kmax average is within 0.678D or pre-operative average

Despite the small sample size, Table 3 shows that cross-linking reduces or stabilizes the maximal corneal curvature of post-LASIK ectasia eyes similarly to what is seen in keratoconic eyes. However, it had a slightly weaker effect

on the ectasia eyes that visible at all until six months. Table 4 lists results from the combined group of virginal keratoconic eyes and shows a continuing and increasing cross-linking effect on the maximal corneal curvature extending beyond six months.

Five eyes were cross-linked after having had intracorneal ring segments (ICRS) at least three months before. Four had ICRS for keratoconus and one had ICRS for post-LASIK ectasia. The Kmax values of those eyes decreased an average of -2.12 D (range -0.94 to -2.82 D) and one eye with post LASIK ectasia had no statistical change six months after cross-linking (Kmax change +0.08D).

**Table 3: Behavior of Kmax in Post LASIK Ectasia Eyes at one year (patient average age 58.2 years)**

	1 month	3 months	6 months	1 year
Kmax				
Decrease(better)	3(33.3%)	1(11.1%)	3(60%)	3(60%)
Increase(worse)	4(44.4%)	5(55.6%)	2(40%)	2(40%)
Same	2(22.2%)	3(33.3%)		

Note: Same=Five measurement Kmax average is within 0.678D or pre-operative average

**Table 4: Behavior of Kmax in Virginal Keratoconic Eyes**

	1 month	3 months	6 months	1 year
Kmax				
Decrease(better)	10(29.4%)	13(52%)	15(65.2%)	4(66.7%)
Increase(worse)	13(38.2%)	6(24%)	5(21.7%)	1(16.7%)
Same	11(32.4%)	6(24%)	3(13%)	1(16.7%)

**Table 5: Effect of Patient Age on Cross-linking Effect in Virginal Keratoconus Eyes At 6-month Postoperative**

	Age under 40	Age at least 40
Kmax		
Decrease(better)	13(76.5%)	2(33.3%)
Increase(worse)	3(17.6%)	2(33.3%)
Same	1(5.9%)	2(33.3%)

There appeared to be very minimal yet detectable reduction in corneal thickness after cross-linking. The pre-operative and postoperative corneal thickness measurements of the virginal keratoconus group were as follows. Pre-operative minimal pachymetry in the twenty minute group was 468.7+/-29.3 microns and was at six months postoperatively 466.38 +/- 3.94 microns and in the thirty minute group was pre-operatively 464.4 +/-28.3 and post-operatively was +/- 462.2 +/- 4.3 microns.

Preoperative maximal anterior equivalent keratometry, Kmax, was 55.3 +/- 4.2 D overall, with 55.3+/-4.D in the 20-minute group and 55.5+/-3.9D in the 30-minute group.

The Pentacam nuclear scale for detecting and quantifying

early cataract formation showed no changes in the eyes of patients followed for cross-linking. Clearly, the purpose of cross-linking is to stop visual loss. There was detectable visual improvement in virginal keratoconus corneas at six months. Some patients who had the cross-linking procedure had other problems that caused visual loss. For example, one patient had bilateral subluxated lenses, and another one had bilateral cataracts. The referring surgeon planned corrective operations after completion of the cross-linking one year follow up period.

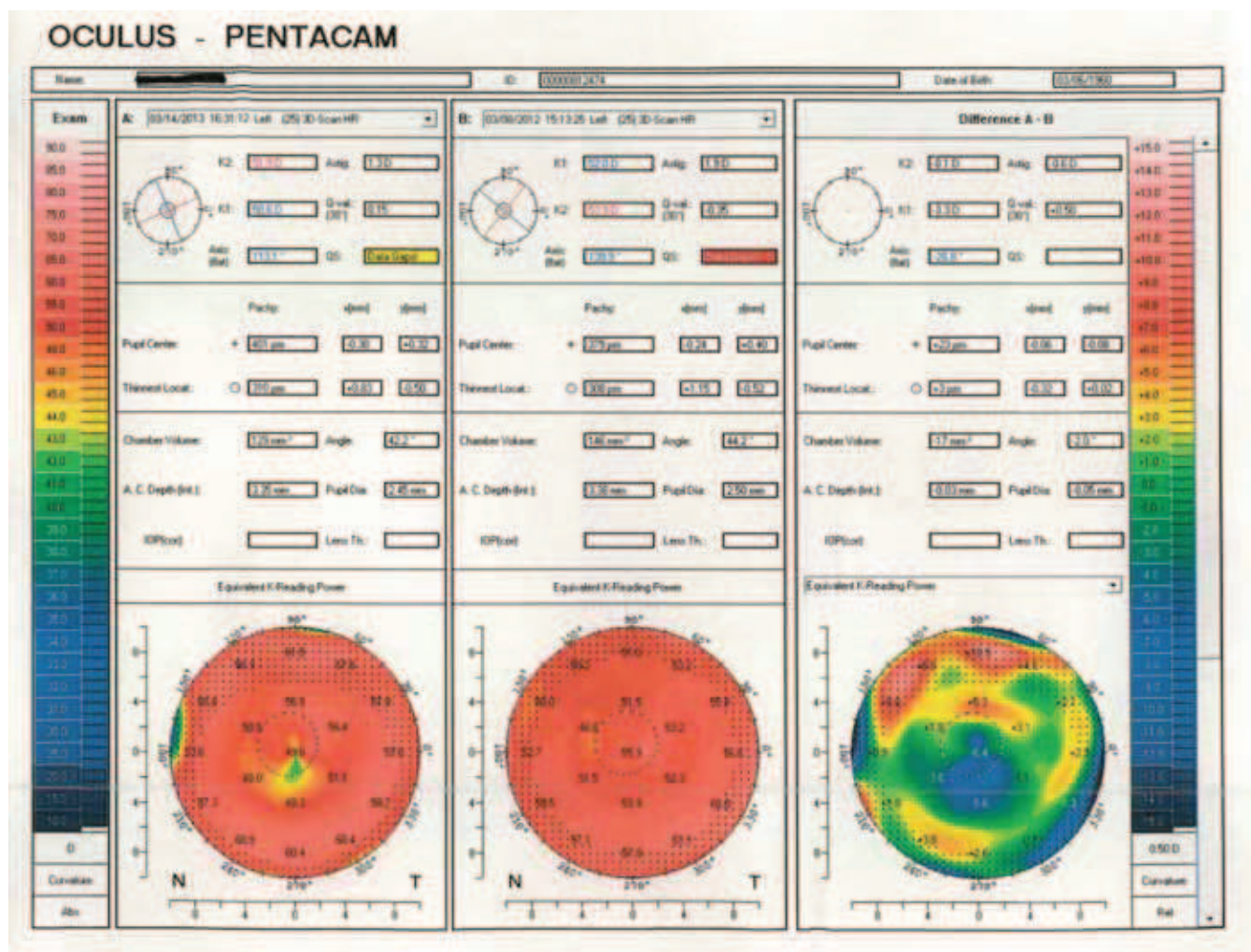
Comparing vision in virginal keratoconus treatment groups, the 20-minute exposure eyes improved from an average pre-operative vision of .3535 logMAR (Snellen 20/45.1) to .2791 LogMAR (Snellen 20/38) at six months postoperatively for a visual improvement of -0.0744 log units. In the 30 minute group vision improved from pre-operative .4044 LogMAR (Snellen 20/50.7) to .3175 logMAR (Snellen 20/40.5) for an improvement of -0.0869 log units at six month postoperative.

The small post-LASIK ectasia group improved slowly but had yet to recover pre-operative vision (an average of 0.3088 LogMAR 20/40.5) compared to an average vision at the one year follow up evaluation [0.419 LogMAR (20/52.9) ]. The average age of the post-LASIK ectasia group was 58.2 years compared with an average age of 34.5 years for the virginal keratoconus patients. Combination of data from the post-LASIK group and other smaller groups diminished the overall average visual change, with vision changing from a preoperative average of 0.3394 LogMAR (Snellen 20/43.7) to a six-month postoperative average of 0.3546 LogMAR (Snellen 20/45.25)

Age was also a factor in the cross-linking effectiveness in the virginal keratoconus eyes with 76.5% of eyes in patients under age 40 actually have corneal flattening as compared to only 33.3% of eyes in patients over age 40. Table 5 presents the details on that subject. One patient with post-LASIK ectasia had only slight improvement in Kmax yet a 6.4 diopter change in refraction due to flattening of most of the central cornea. Figure 1 shows the change in corneal curvature caused by cross-linking in this patient.

## Discussion

The patients enrolled in our study had experienced worsening of their keratoconus and post-LASIK ectasia prior to recruitment. Results from our clinical study, which is still in progress, indicate that corneal collagen cross-linking provides stabilization and partial reversal of the corneal irregularity resulting from keratoconus and post-LASIK ectasia. We also used cross-linking to stabilize corneas with keratoconus that had prior intracorneal ring segments, and we used it as well for previously transplanted corneas where initial good vision had gradually declined from residual keratoconus in the host tissue.



**Figure 1. Pentacam HR comparative topometric map of the anterior corneal curvature. At left are the postoperative contour maps. In the middle is the pre-operative map. The subtraction is shown at right. A significant change has occurred that has markedly improved the patients' unaided and spectacle corrected vision.**

The results of cross-linking are quite variable both with respect to which patients have the desired effect and also in the uniformity of the effect on parts of the cornea. Thus far, we lack predictors of which corneas will respond and whether additional treatment may be helpful. Generally the changes in curvature are toward more uniformity of curvature, but not always.

We noted good, but imperfect correlation in the effectiveness of cross-linking between two eyes of the same patient. The measure of Kmax is very useful in determining whether a keratoconic or post-LASIK ectasia cornea has worsened, but the Kmax metric does not always speak to the actual power of the cross-linking effect as in the patient illustrated in Figure 1. Two of the most highly responsive

corneas have been from people who were genetically either completely or partially African.

Because there is significant variability in the response to cross-linking, it would seem prudent to refrain from combine cross-linking with laser vision correction in the same operation until there is a way to predict the outcome of cross-linking. However, outside of clinical studies to determine the effect of cross-linking alone, combining cross-linking with insertion of intracranial ring segments is recommended.

The more vigorous response in younger eyes is not surprising. This observation only underscores the fact that cross-linking as treatment to reverse or stabilize keratoconus should be employed while patients are young.

The largest published study to date is by Vinciguerra et al. Their series of cross-linking of 401 eyes with data lasting as much as 4 years and with 53.5% of patients with one year or more of follow up, shows stabilization and some reversal of corneal curvature in patients under age 40 with visual improvement and shows stabilization with no aver-

age functional visual improvement on for patients over age 40. They publish on simK data rather than Kmax and sim K continues to decrease over a twenty four month period. They state that their results are best in the age range of 18 to 39 with lesser in the over 40 group possibly because age has already cross-linked the eyes and in the younger group because of the aggressiveness of the disease. These findings are not at odds with the findings of our younger study.

Our study is in its early stages at this point. We anticipate increased patient enrollment and extended follow up of all individuals, which should enable us to achieve greater statistical significance of the results.

#### Authorship statement

Both authors contributed equally.

#### Financial disclosure

No potential conflicts of interest was reported.

#### References

- Bawazeer AM, Hodge WG, Lorimer B. Atopy and keratoconus: a multivariate analysis. *Br J Ophthalmol* 2000;84:834-6.
- Kumar, Vinay. Eye: Cornea, Degenerations and Dystrophies. *Robbins Basic Pathology* (8th ed.). Philadelphia: Saunders/Elsevier, 2007. ISBN 978-1416029731.
- Saidel MA, Paik JY, Garcia C, et al. Prevalent of sleep apnea syndrome and high-risk characteristics among keratoconus patients. *Cornea*. 2012;31:600-3.
- McMonnies CW, Quo vadis older keratoconus patients? Do they die at younger ages? *Cornea*. 2013;32:496-502.
- Jafri B, Lichter H, Stulting RD. Asymmetric keratoconus attributed to eye rubbing. *Cornea* 23:560-4.
- Koenig SB. Bilateral recurrent self-induced keratoconus. *Eye Cont Lens* 2008;34:343-4.
- Chan CC, Sharma F, Wachler BS. Effect of inferior-segment Intacs with and with C3-R on keratoconus" *J Cataract Refract Surg* 2007;33:75-80.
- Randleman JB, Woodward M, Lynn MJ, et al. Risk assessment for ectasia after corneal refractive surgery. *Ophthalmology* 2008; 115:37-50.
- Reinstein DZ, Archer TJ, Gobbe M. Stability of LASIK in topographically suspect keratoconus confirmed non-keratoconic by Artemis VHG digital ultrasound epithelial thickness mapping: 1-year follow-up. *J Refract Surg*. 2009;25:569-77.
- Schweitzer C, Rogert CJ, Mahmoud AM, et al. Screening of forme fruste keratoconus with the ocular response analyzer. *Invest Ophthalmol Vis Sci* 2010; 51:2403-10.
- Saad A, Gatinel D, Topographic and tomographic properties of forme fruste keratoconus corneas. *Invest Ophthalmol Vis Sci* 2010 Nov;51(11):5546-55.
- Ambrosio R Jr, Caiado AL, Guerra FP, et al. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. *J Refract Surg* 2011;27:753-8.
- Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. *J Cataract Refract Surg*. 2012;38:2167-83.
- Fukuda S, Yamanari M, Lim Y, et al. Keratoconus Diagnosis Using Anterior Segment Polarization-Sensitive Optical Coherence Tomography. *Invest Ophthalmol Vis Science*, 2013;54:1385-91.
- Kozomara B, Boháč M, Potkonjak E, et al. Prevalence of keratoconus in candidates for refractive surgical procedures. *Scr Med* 2012;43:25-7.
- Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res* 1998;66:97-103.
- Zhang Y, Mao X, Schwend T, et al. Resistance of corneal RFU-VA-cross-linked collagens and small leucine-rich proteoglycans to degradation by matrix metalloproteinases *Invest Ophthalmol Vis Sci* 2013; IOVS 12-11277v1.
- Dudakova L, Liskova P, Trojek T, et al. Changes in lysyl oxidase (LOX) distribution and its decreased activity in keratoconus corneas, *Exp Eye Res* 2012;104:74-81.
- Martins SA, Combs JC, Noguera G, et al. Biomechanical evidence of the distribution of cross-links in corneas treated with riboflavin and ultraviolet A light. *J Cataract Refract Surg* 2006;32:279-83.
- Wollensak G, Spoerl E, Wilsch M, et al. Keratocyte apoptosis after corneal collagen cross-linking using riboflavin/UVA Treatment. *Cornea* 2004 ;23:43-9.
- Baiocchi S, Mazzotta C, Cerretani D, et al. Corneal cross-linking: riboflavin concentration in corneal stroma exposed with and without epithelium. *J Cataract Refract Surg*. 2009;35:893-9.
- Ostacolo C, Cafuso C, Tronimo D, et al. Enhancement of corneal permeation of riboflavin 5'-phosphate through vitamin E TPGS: a promising approach in corneal trans-epithelial cross linking treatment. *Int J Pharm* 2013; 440:148-53.
- Martins SA, Combs JC, Noguera G, et al. Antimicrobial efficacy of riboflavin/UVA combination (365 nm) in vitro for bacterial and fungal isolates: a potential new treatment for infectious keratitis. *Invest Ophthalmol Vis Sci*. 2008;49:3402-8.
- Hafezi F, Dejica P, Majo F. Modified corneal collagen cross-linking reduces corneal oedema and diurnal visual fluctuation in Fuchs dystrophy. *Br J Ophthalmol* 2010;94:660-1.
- Koller T, Iseli HP, Hafezi F, et al. Scheimpflug imaging of corneas after collagen cross-linking. *Cornea*. 2009;28:510-5.
- Epstein RL, Chiu YL, Epstein GL. Pentacam HR Criteria for Curvature Change in Keratoconus and Postoperative LASIK ectasia. *J Refract Surg*. 2012;28:890-4.
- Vinciguerra R, Romano MR, Camesasca FL, et al. Corneal Cross-Linking as a Treatment for Keratoconus: Four-Year Morphologic and Clinical Outcomes with Respect to Patient Age. *Ophthalmology* 2013 Epub prior to print January 2013.