International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2015): 6.391

# Cross-Linking Treatment for Progressive Keratokonus

**Teuta Haveri**

Eye Clinic, American Hospital Tirana Albania

**Abstract:** ***Background: Keratokonus is a degenerative disease, starting generally at 14- 25 years, causing progressive thinning, conical shape of the cornea and causing distortion of vision. Extreme advancement of keratokonus can cause corneal perforation, destroying the vision. To avoid this, corneal transplant is required to save the eye. Considering the young age of the patients, high cost of the of the corneal transplantation, and the risk of transplant reject, high priority is given to the early diagnose and treatment. Cross-linking is a non invasive procedure used to stop the natural progression of keratokonus. Aim: To assess the efficacy of cross-linking in stopping keratokonus progression. Method: Cross-linking procedure was applied in 75 patients, presenting progressive keratokonus. Patients were followed for a period of 3 years after treatment, recording the following parameters: keratometry readings: flattest, steepest, maximal; pachymetry central and thinnest; BCVA, UCVA. Results: Clear reduction in keratometry values, reduction in pachymetry values, increasing in BCVA, UCVA starting three months after procedure and continuing also 3 years after it. Conclusion: cross-linking is able to flatten the cornea, stopping the evolution of keratokonus and improving visual acuity***

**Keyword:** keratoconus, keratometry, pachymetry, cross-linking, cornea

## 1. Introduction

The cornea is a transparent interface covering the front of the eye. It has the function of protecting the eyeball and also is a powerful refracting surface, providing 2/3 of the eye's focusing power. The adult cornea has a thickness of 500 µm and is comprised of 5 layers: epithelium, Bowman's membrane, stroma, Descemet's membrane and the endothelium. The stroma is the thickest layer composed of collagen fibrils oriented parallel to each-other. It has also transversal fibrils which bond the parallel ones to each-other, giving to the cornea its natural strength. This phenomenon is known as natural cross-linking and it is responsible for the cornea's resistance against deformation. Keratokonus is a bilateral non- inflammatory disease which causes progressive corneal thinning, leading to protrusion, distortion, and scarring of the cornea[1] It is a naturally occurring ocular condition which leads to steepening of the central cornea, increasing myopia, irregular astigmatism, and loss of best spectacle-corrected visual acuity. Corneal thinning normally occurs in the infero-temporal or in the central cornea[2]. Exceptional case of superior localizations have also been described[3,4].Keratoconus becomes evident normally during puberty[6], although the disease has also been found to develop earlier[5] and latter in life[6].It potentially progresses until the fourth decade of life, when it usually stabilizes[6]. A study has determined that 50% of non-affected eyes of subjects with unilateral keratokonus will develop the disease in 16 years[7]. If left untreated, keratokonus frequently progresses to formation of descement's tears (known as Vogt's stries) and corneal perforation, seriously threatening the vision. At this point, corneal transplantation is required to restore useful vision and saving the eye. Collagen Cross-linking is a non invasive method used to stop the natural progression of keratokonus and able to preserve the own cornea. Its general principle is to strengthen the keratokonus cornea, combining the effect of riboflavin drops and irradiation with UVA.

The combination of riboflavin and UVA is able to:

- Increase the corneal rigidity with 300%
- Increase collagen fibers diameters 12,2 %
- Induce the formation of collagen polymers with high chemical stability
- Increase the numbers of transversal fibers of the cornea.

The result is a more stiffened and strong cornea[11,18] which contradict the natural deformation process of keratokonus, therefore stopping it.

Generally is applied by using Dresden protocol[8] requiring the removal of central 7- 9 nm of corneal epithelium layer, followed by 30 minutes of riboflavin administration, then UVA light is applied for 30 minutes. The corneal epithelial layer is generally removed to increase penetration of the riboflavin into the stroma.[11] During the UV light illumination, riboflavin acts also as a shield during irradiation on the cornea, protecting deeper ocular structures such as the endothelium, lens, and retina from UV-A irradiances that are too high[(12)] Another important role of riboflavin is to prevent corneal dehydration during exposure[(13)] The combination of riboflavin and UV-A light creates 80–95% absorption into the cornea during cross-linking depending on the concentration and the corneal thickness [(12)] Given the simplicity and minimal costs of the treatment, cross-linking treatment is also well-suited for developing countries[(8)]

In our hospital, cross-linking technique is applied from 2009. The patients presenting complains such as: progressive refractive changes, frequently change of glasses and not feeling comfortable with them, high astigmatism and myopia, are suspected for keratokonus. These patients are advised to undergo topographic examination with Pentacam instrument. This examination is based on the Scheimpflug working principle, taking 12–50 images of the cornea at different angles using a rotating camera. Anterior and posterior corneal elevations are then measured using topographic analysis, providing useful information in keratokonus diagnostic and grading the severity of

keratokonus[15.] IV-th grade of keratokonus with pachymetry lower than 360µm, Vogt's striae or corneal hydrops are immediately advised to undergo corneal transplant procedure. The patients, diagnosed in stage 1-3 of keratokonus, with no corneal changes are followed for 6 month to check the evidence of keratokonus progression and in this case, are advised to undergo cross-linking procedure. Others, already presenting clear evidence of progression in comparison of earlier topographic examination are immediately advised to the cross-linking procedure. The results of follow-up are collected and discussed in "Results and Discussion" showing evidence of flattening the cornea and stopping the progress of keratokonus.

## 2. Literature Survey

Corneal Collagen Cross-linking treatment is firstly developed at Dresden University in 1998[8], to treat keratoconus and other corneal ectasia. In this procedure ultraviolet (UV) light and riboflavin (vitamin B2) drops are used to strengthen the cornea's structure, which can slow or halt the progression of keratoconus, preventing deterioration of vision and the need for corneal transplantation. Firstly experimented in porcine and rabbits corneas, the results showed that riboflavin soaked and UVA irradiated corneas were stiffer and more resistant to enzymatic digestion. Investigations also proved that the treated corneas contained high molecular weight polymers of collagen due to fibril cross-linking[11.]Others, *in vitro* investigations, on human and porcine corneas examined the best treatment parameters for standard cross-liking, such as riboflavin concentration, intensity, wavelength of UV-A light, and duration of treatment.[9] Also it has been proved that UVA irradiation is not harmful for the endothelium, if the corneal thickness is above 400 µm [10] After the laboratory, clinical results were also encouraging. The pilot study included 16 patients with progressive keratoconus that were treated with cross-linking. All of them showed stopped progressing after treatment.70% had flattening of the steepest keratometry, decrease in average and maximum keratometric values and 65% had visual acuity improvement. No complication reported [8] After that, cross-linking became a worldwide used technique. Later and latest study[16], as the Siena Eye Study[14], investigates long-term effects of standard cross-linking. Three hundred and sixty-three eyes were treated and monitored over 4 years, producing reliable long-term results proving the efficacy of the procedure in terms of long-term stability of the cornea by halting the progression of keratokonus, and proving the safety of the procedure[14]

## 3. Methods

**Subjects**: 81 eyes (75 patients) with progressive keratoconus were included in the study. Average age was 23.54+5.2 years (the youngest 15 years old and the oldest 38 years old). 42.3% (32 patients) female and 57.3% (43 patients)

**Methods**: A rotating Scheimpflug camera (Pentacam HR, Oculus) is used to diagnose and follow-up the keratoconus before and post cross-linking treatment. The parameters recorded were: flattest steepest and, maximal keratometry, central and , thinnest pachymetry. UCVA (uncorrected visual acuity) and BCVA (best corrected visual acuity) were measured basing on Snellen chart.

The inclusion criteria were: evidence keratokonus progression (keratometry increasing at least 0,5 D in 6 months) decreasing visual acuity, complaining of uncomfortable vision and frequent changing of refraction),no previsious corneal surgeries, no corneal scars. Patients were treated according to Dresden protocol:

1) sol.proparacaine 0, 5% for 40 seconds on the cornea
2) Removal of central 7- 9 nm of corneal epithelium layer
3) 30 minutes of riboflavin administration (1 drop every 2 min)
4) UVA 370 µm light is applied for 30 minutes (adding also riboflavin drop every 2 min)
5) soft contact lens is applied for 5 days until re-epithelization process occurs
6) Sol. Antibiotic and anti-inflammatory (sol.ciprofloxacinum ophthalmic and sol.diclofenac ophthalmic and artificial tear is given every 4 hours as the post treatment) .

Patients are examined regularly after 1 week, 1 month,3 month, 6 month,1 year,2 year and 3 year after cross-linking treatment. Every time UCVA, BCVA are measured.. A topographic examination with the same instrument is performed (Pentacam HR, Oculus) and keratometry values (flattest, steepest, maximal) and pachymetry values ( central and thinnest) are recorded.
Also a careful examination of the cornea is performed on slit lamp.

## 4. Results

- Statistical Analysis Data were analyzed using the software, SPSS *(Statistical Package for Social Sciences 20.0)*
- For all numerical variables central and dispersion tendencies were calculated. For variables following the normal distribution, arithmetic medium value + standard deviation were calculated.
- Differences between groups were calculated with student test.
- Correlation between variables was analyzed through coefficients of Kendal's tau.
- The variables were presented in tables, graphics and diagrams, simple and linear.
- Statistically important were considered the values of $p \leq 0.05$.

Parameters before cross-linking treatment

| *Variables* | *Medium+SD* | *Minimum* | *Maximum* |
|---|---|---|---|
| Pak_central_preop_ | 467.09±33.70 | 341 | 554 |
| Pak_thinnest_preop | 444.83+33.52 | 313 | 526 |
| Kerat_flatest_preop | 46.68+4.41 | 39.2 | 62.4 |
| Kerat_steepest_preop | 50.58+4.93 | 42.3 | 67.9 |
| Kmax_preop | 56.46+6.30 | 45.4 | 78.2 |
| UCVA_preop | 0.20+0.18 | 0.01 | 1 |
| BCVA_preop | 0.41+0.21 | 0.01 | 1 |

Comparison of medium values of PAK (central corneal thickness) after cross-linking

| *Comparison groups* | | *Medium's* | *Value p** |
|---|---|---|---|
| Comparison couple I | Pak_central_preop | 466.99+34.14 | <0.001 |
| | Pak_central_1 week | 457.54+32.26 | |
| Comparison couple II | Pak_central_1 week | 457.54+32.26 | 0.004 |
| | Pak_central_1month | 452.47+34.00 | |
| Comparison couple III | Pak_central_1month | 452.26+33.93 | 0.169 |
| | Pak_central_3month | 450.39+35.50 | |
| Comparison couple IV | Pak_central_3month | 450.48+35.27 | 0.970 |
| | Pak_central_6month | 450.53+34.12 | |
| Comparison couple V | Pak_central_6month | 450.53+34.12 | 0.541 |
| | Pak_central_12month | 451.25+34.19 | |
| Comparison couple VI | Pak_central_12month | 451.25+34.19 | <0.001 |
| | Pak_central_24month | 445.05+36.57 | |
| Comparison couple VII | Pak_central_24month | 445.05+36.57 | <0.001 |
| | Pak_central_36month | 440.61+35.65 | |

* Student test for two couples

Analyzing the values through student test for 2 couples, the result is a statistically important difference between medium values of PAK central before treatment and after the first week (p<0.001), first week and first month after treatment (p=0.004), 12th month comparing to 24th month (p<0.001) and 24th month comparing to 36 th month after cross-linking(p<0.001), when a significant reduction in medium values of central pakimetry are evident (PAK central).

Comparison of medium values of thinnest pachymetry (PAK thinnest) after cross-linking

| *Comparison parameters* | | *Medium+SD* | *Values p** |
|---|---|---|---|
| Comparison couple I | Pak_thinnest_preop | 444.99+34.00 | <0.001 |
| | Pak_thinnest_1week | 436.06+34.86 | |
| Comparison couple II | Pak_thinnest_1month | 436.06+34.86 | 0.015 |
| | Pak_thinnest_1month | 431.52+33.74 | |
| Comparison couple III | Pak_thinnest_1month | 431.11+33.70 | 0.002 |
| | Pak_thinnest_3month | 427.39+34.75 | |
| Comparison couple IV | Pak_thinnest_3month | 427.63+34.58 | 0.449 |
| | Pak_thinnest_6month | 428.72+35.51 | |
| Comparison couple V | Pak_thinnest_6month | 428.72+35.51 | 0.432 |
| | Pak_thinnest_12month | 430.25+35.28 | |
| Comparison couple VI | Pak_thinnest_12month | 430.25+35.28 | 0.030 |
| | Pak_thinnest_24month | 426.43+37.73 | |
| Comparison couple VII | Pak_thinnest_24month | 426.43+37.73 | 0.012 |
| | Pak_thinnest_36month | 422.40+35.82 | |

*Student test for two sample couples

Basing on student test for two sample couples, there a statistically important difference between the medium values of PAK thinnest before cross-linking and one week after cross-linking (p<0.001), first week and first month after procedure (p=0.015), first month and third month (p=0.002), 12th and 24th month (p=0.030), 24th and 36th month after cross-linking(p=0.012), resulting in a significant reduction of medium values of PAK thinnest.

Comparison of the medium values of flattest keratometry after cross-linking

| *Comparison parameters* | | *Medium +SD* | *Value p** |
|---|---|---|---|
| Comparison couple I | Kerat_flatest_preop | 46.77+4.51 | 0.008 |
| | Kerat_flatest_1week | 47.13+4.38 | |
| Comparison couple II | Kerat_flatest_1week | 47.13+4.38 | 0.066 |
| | Kerat_flatest_1month | 46.89+4.59 | |
| Comparison couple III | Kerat_flatest_1month | 46.85+4.52 | <0.001 |
| | Kerat_flatest_3month | 46.20+4.31 | |
| Comparison couple IV | Kerat_flatest_3month | 46.17+4.29 | <0.001 |
| | Kerat_flatest_6month | 45.62+4.36 | |
| Comparison couple V | Kerat_flatest_6month | 45.62+4.36 | <0.001 |
| | Kerat_flatest_12month | 44.76+3.72 | |
| Comparison couple VI | Kerat_flatest_12month | 44.76+3.72 | <0.001 |
| | Kerat_flatest_24month | 44.05+3.55 | |
| Comparison couple VII | Kerat_flatest_24month | 44.05+3.55 | <0.001 |
| | Kerat_flatest_36month | 42.93+3.40 | |

*Student test for two sample couples

Basing on student test for two sample couples, there is a statistically important difference between the medium values of flattest keratometry before cross-linking and one week after cross-linking (p=0.008), 3rd month with 6th month (p<0.001), 6th month with 12th month (p<0.001),12th month with 24th 24 (p<0.001) and 24th month and 36th month after applying cross-linking procedure (p<0.001), when an statistically important reduction of flattest keratometry values is noted. Only the difference between first week and first month after procedure is not statistically important (p=0.066).

Comparison of steepest keratometry after cross-linking

| *Comparison of keratometry* | | *Medium+SD* | *Value p** |
|---|---|---|---|
| Comparison couple I | kerat_steepest_preop | 50.70+5.04 | 0.005 |
| | kerat_steepest_1week | 51.19+5.12 | |
| Comparison couple II | kerat_steepest_1week | 51.19+5.12 | 0.596 |
| | kerat_steepest_1month | 51.07+5.15 | |
| Comparison couple III | kerat_steepest_1month | 51.03+5.05 | <0.001 |
| | kerat_steepest_3month | 50.22+4.80 | |
| Comparison couple IV | kerat_steepest_3month | 50.18+4.78 | <0.001 |
| | kerat_steepest_6month | 49.57+4.93 | |
| Comparison couple V | kerat_steepest_6month | 49.57+4.93 | <0.001 |
| | kerat_steepest_12month | 48.71+4.51 | |
| Comparison couple VI | kerat_steepest_12month | 48.71+4.51 | <0.001 |
| | kerat_steepest_24month | 47.75+4.43 | |
| Comparison couple VII | kerat_steepest_24month | 47.75+4.43 | <0.001 |
| | kerat_steepest_36month | 46.34+4.39 | |

* Student test for two sample couples

Basing on student test for two sample couples, there is a statistically important difference between the medium values of steepest keratometry before cross-linking and one week after cross-linking (p=0.005), first month and 3rd month after procedure (p<0.001), 3rd month and 6th month (p<0.001), 6th month and 12th month (p<0.001), 12th month and 24th (p<0.001) and 24th and 36th month (p<0.001),where a statistically important reduction is seen in medium values of steepest keratometry. There is no evidence of a statistically important reduction between first week and first month after treatment (p=0.596).

Comparison of maximal keratometry after cross-linking

| *Comparison of keratometry* | | *Medium + SD* | *Values p** |
|---|---|---|---|
| Couple I | Kmax_preop | 56.57+6.42 | 0.001 |
| | Kerat_Kmax_1 week | 57.09+6.23 | |
| Couple II | Kerat_Kmax_1 week | 57.09+6.23 | 0.917 |
| | Kerat_Kmax_1 month | 57.11+6.19 | |
| Couple III | Kerat_Kmax_1 month | 57.07+6.07 | <0.001 |
| | Kerat_Kmax_3 month | 56.00+5.90 | |
| Couple IV | Kerat_Kmax_3 month | 55.94+5.89 | <0.001 |
| | Kerat_Kmax_6 month | 55.08+5.90 | |
| Couple V | Kerat_Kmax_6 month | 55.08+5.90 | <0.001 |
| | Kerat_Kmax_12 month | 53.14+5.15 | |
| Couple VI | Kerat_Kmax_12 month | 53.14+5.15 | 0.002 |
| | Kerat_Kmax_24 month | 52.24+5.00 | |
| CoupleVII | Kerat_Kmax_24 month | 52.24+5.00 | <0.001 |
| | Kerat_Kmax_36 month | 50.53+4.80 | |

*student test for two sample couples

Basing on student test for two sample couples, there is a statistically important difference between the medium values of maximal keratometry (Kerat_kmax) before cross-linking and one week after cross-linking (p=0.008), first and third month (p<0.001), third month and 6th month (p<0.001), 6th month and 12th month (p<0.001), 12th month and 24th month (p=0.002) and 24th and 36th month (p<0.001), where a statistically important reduction is seen in medium values of maximal keratometry (Kerat_Kmax). There is no evidence of a statistically important reduction between first week and first month after treatment (p=0.917).

Comparison of values UCVA (uncorrected visual acuity)

| *Comparing parameters* | | *Medium +SD* | *Values p** |
|---|---|---|---|
| Couple I | UCVA_preop | .19+0.18 | .754 |
| | UCVA_1week | .22+0.60 | |
| Couple II | UCVA_1week | .22+0.60 | .052 |
| | UCVA_1month | .23+0.59 | |
| CoupleIII | UCVA_1month | .17+0.14 | .001 |
| | UCVA_3month | .21+0.17 | |
| Couple IV | UCVA_3month | .22+0.17 | .214 |
| | UCVA_6month | .23+0.18 | |
| Couple V | UCVA_6month | .23+0.18 | .135 |
| | UCVA_12month | .25+0.18 | |
| Couple VI | UCVA_12month | .25+0.18 | .157 |
| | UCVA_24month | .26+0.19 | |
| Couple VII | UCVA_24month | .26+0.19 | .002 |
| | UCVA_36month | .29+0.18 | |

* student test for two sample couples

Basing on student test for two sample couples, there is a statistically important difference between the medium values of UCVA (uncorrected visual acuity)in first month and third month (p<0.001),) 24th month and 36th (p=0.002), where a statistically

important increasing is seen in medium values of UCVA. There is no evidence of a statistically important changes between first week and first month (p=0.052), 3rd month and sixth month (p=0.214), sixth month and 12th month (p=0.135),12th month and 24th month (p=0.157).

Comparison of BCVA(best corrected visual acuity)after cross-linking

| *Comparing parameters* | | *Medium+SD* | *Value p** |
|---|---|---|---|
| Couple I | BCVA_preop | 0.41+0.20 | <0.001 |
| | BCVA_1week | 0.27+0.19 | |
| Couple II | BCVA_1week | 0.27+0.20 | <0.001 |
| | BCVA_1month | 0.33+0.20 | |
| Couple III | BCVA_1month | 0.33+0.20 | <0.001 |
| | BCVA_3month | 0.43+0.20 | |
| Couple IV | BCVA_3month | 0.43+0.20 | <0.001 |
| | BCVA_6month | 0.51+0.19 | |
| Couple V | BCVA_6month | 0.51+0.19 | <0.001 |
| | BCVA_12month | 0.57+0.18 | |
| Couple VI | BCVA_12month | 0.57+0.17 | <0.001 |
| | BCVA_24month | 0.60+0.17 | |
| Couple VII | BCVA_24month | 0.60+0.17 | <0.001 |
| | BCVA_36month | 0.67+ 0.15 | |

* Student test for two sample couples

Basing on student test for two sample couples, there is a statistically important difference between the medium values of BCVA after cross-linking for all comparison period.

There is a tendency of continuous increasing of BCVA especially starting 6 months after procedure and continuing even after 3 years with 2/10 (Snellen chart)

## 5. Discussion

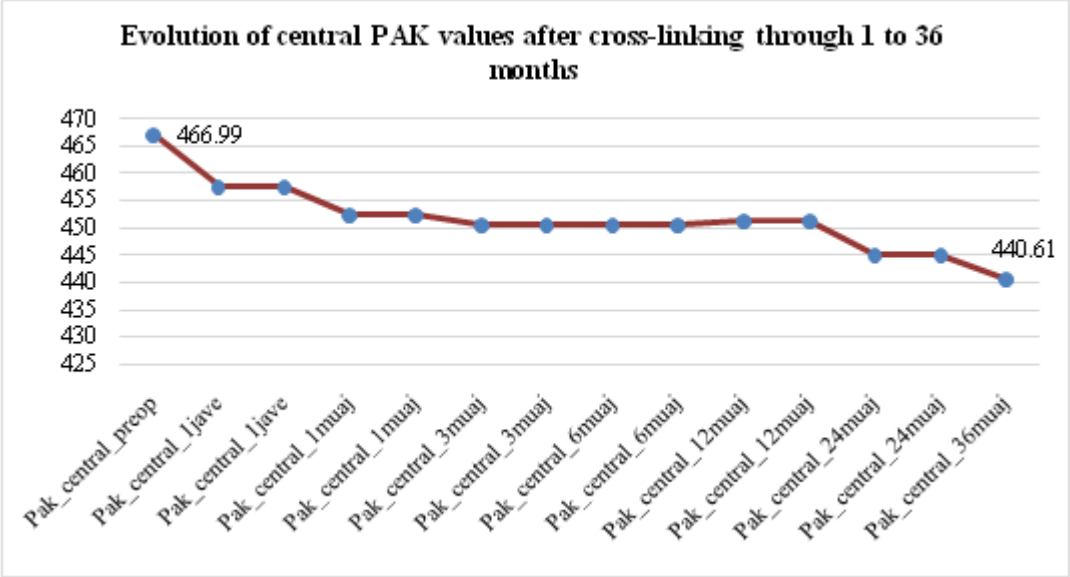
The main parameters which define the topographic corneal shape are the radius of corneal curvature. Generally 2 of them, perpendicular to each-other, are used to topographically characterize a certain cornea (the flattest and steepest keratometry).

Another keratometry value, corresponding to the apex of the cone or the point of maximal corneal elevation is recorded in Pentacam examination referring as maximal keratometry (Kmax)

In this study the flattest, steepest and maximal radius of the cornea are taken from the anterior curvature sagittal map of the cornea. The corneal thickness values, central and thinnest, are taken also from this map.

With the advancement ok keratokonus: steepest, flattest and Kmax increase. Central and thinnest values of pachymetry are decreasing.

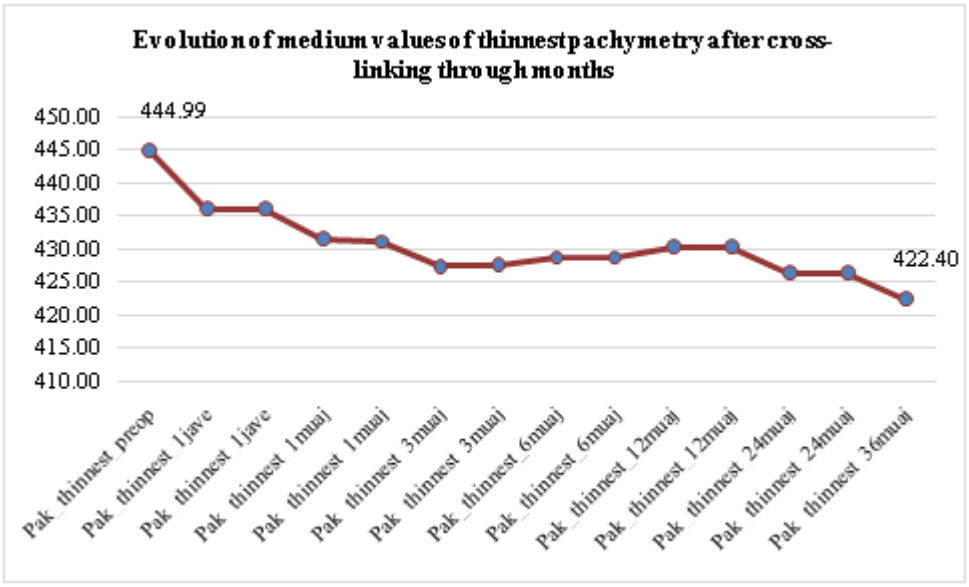
In the graphics below are presented the changes of each parameters after cross-linking




**Graph 1:** Evolution of central corneal thickening after cross-linking

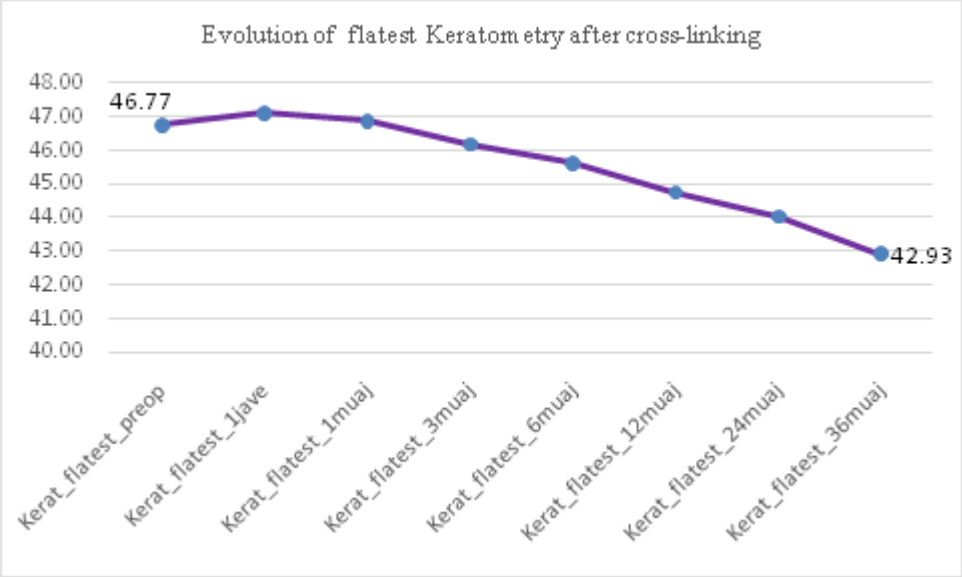
*Central pachymetry values continue to low until 3 years after cross-linking. This phenomenon is known as "Corneal shrinking". Cornea stiffens and became stronger, opposing to the deforming tendency of the keratokonus.*

***Graph. 6*** *Evolution of thinnest pachymetry after cross-linking*



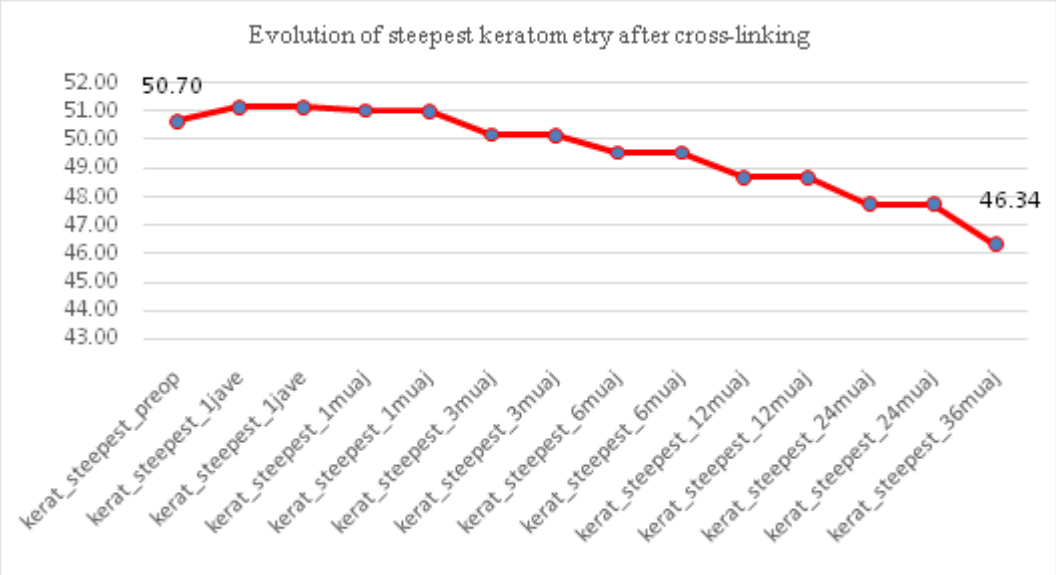

Thinnest pachymetry values follow the same tendency as central pachymetry. They continue to low until 3 years after cross-linking. Cornea stiffens and became stronger, opposing to the deforming tendency of the keratokonus.

**Graf. 7** Evolution of flattest keratometry after cross-linking (in Diopters)



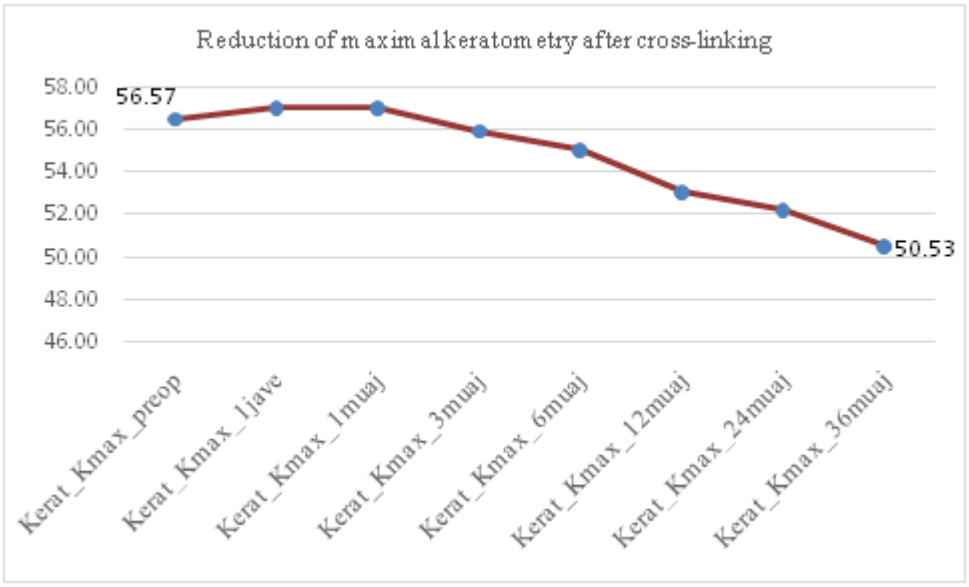

Flattest keratometry significantly reduces 6 months after cross-linking and continues to reduce even after 3 years (flattening 3.8 D)

**Graf. 8 Evolution** of steepest keratometry after cross-linking



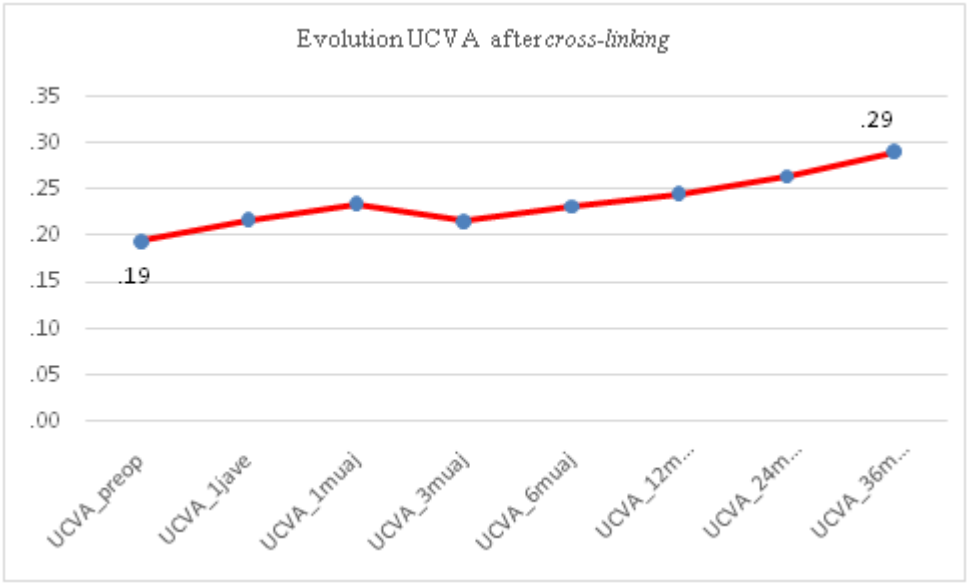

Steepest keratometry significantly reduces 6 months after cross-linking and continues to reduce even after 3 years (flattening 3.36 D)

**Graf. 9** Evolution of maximal keratometry Kmax after cross-linking

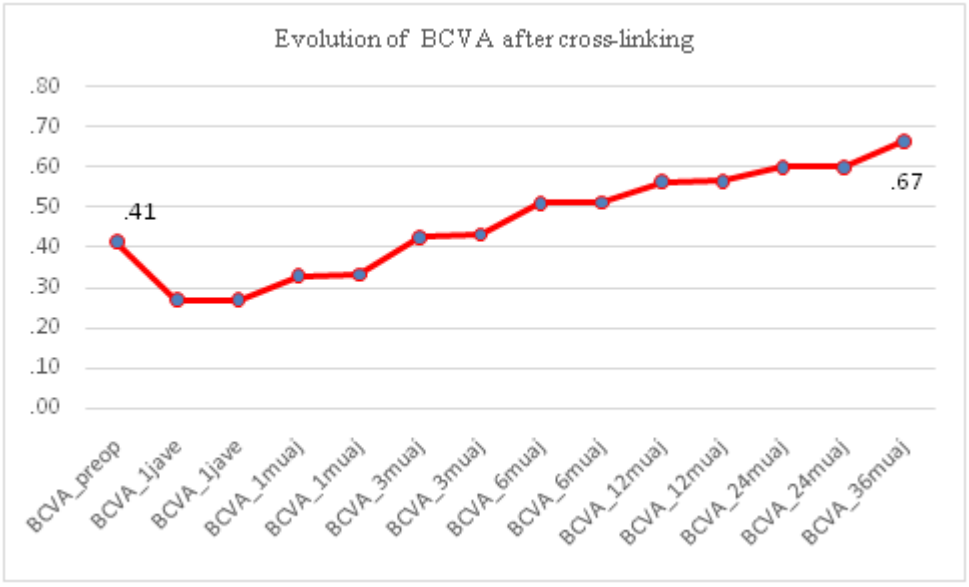



Maximal keratometry significantly reduces 6 months after cross-linking and continues to reduce even after 3 years (flattening 6 D)

**Graf. 9** Evolution of medium values of UCVA after cross-linking




There is a tendency of stabilizing UCVA after cross-linking and even an increasing 1/10, 3 years after procedure




There is a tendency of continuous increasing of BCVA especially starting 6 months after procedure and continuing even after 3 years with 2/10

## 6. Conclusions

Cross-linking procedure shows to be effective in reducing corneal radius (flattest, steepest, maximal). Having a flatter cornea, in a progressive keratokonus, mean that the progress of keratokonus is stopped and there is also a remodeling of its surface.

Remodeling the cornea, also stabilizes visual acuity and even improves best spectacles visual acuity.

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## Author Profile

**Teuta HAVERI** received her MD diploma at July 1999 and Specialization Diploma in Ophthalmology at January 2006 from Faculty of Medicine University of Tirana. Also she received a Diploma Universitaire in Strabismology at 2009 from University of Nantes, France. She is actually working as ophthalmologist surgeon at Eye Clinic, American Hospital of Tirana, Albania