

# Progressive keratoconus and cross-linking. Reporting our long-term results

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## Keywords

keratoconus, keratometry,  
pachymetry, cross-linking,  
cornea

## Abstract

**Aims:** To analyze the data and to assess the efficacy of cross-linking in stopping keratoconus progression.

**Patients and methods:** 81 eyes with progressive keratoconus were treated with epithelium off cross-linking method. Patients were followed for a period of 3 years after treatment, recording the following parameters: flattest, steepest and maximal keratometry; central and thinnest pachymetry, uncorrected visual acuity (UCVA), and best corrected visual acuity (BCVA).

**Results:** Clear reduction in keratometry values, increasing in BCVA, UCVA starting 6 months after procedure and continuing also 3 years after it.

**Conclusion:** Cross-linking seems to be effective in flattening the keratoconic cornea and stabilizing the corneal structure and therefore improving visual acuity.

## Introduction

Keratoconus is a non-inflammatory degenerative disease of the cornea, which affects mostly young people from 14 - 30 years old (1). Usually it is a progressive situation, which leads to steepening and thinning of the inferior part of the cornea (2) and causing progressive loss of vision (3). These young patients, very exigent for their visual acuity, are always changing their correction (glasses or contact lenses) but not feeling comfortable with them. Extreme advancement of the keratoconus can cause extreme thinning of the cornea and risk of perforation. To avoid this devastating complication, in advanced stage keratoconus, corneal transplant is required to save the eye and the vision. It is already known that hot weather and sun is an envi-

ronmental factor contributing in high incidence of keratoconus (4,5,6,7). Albania, as a Mediterranean country, offering this climate, has a relatively high incidence of keratoconus. Still not having exact statistical data for keratoconus incidence in Albania, we diagnose almost every week young patients with keratoconus which comparing to our population of 3 million habitants, shows a non-negligible incidence of the disease. Also, it is not very rare to diagnose younger children with keratoconus (8), having the youngest one diagnosed with 3-4th stage of keratoconus at 10 years old. It is not very rare also to find adults, after 35 years old, showing clear evidence of progressive keratoconus. Another fact that should be mentioned is the finding of an increased number of children 5-10 years old with high astigmatisms 4-5 diopters or more, with corneal

thickness less than 500  $\mu\text{m}$ , which can develop to keratoconus later. These general considerations are mentioned to underline the importance of keratoconus disease in our country and therefore showing the importance of early diagnosis and treatment with cross-linking. Nowadays, cross-linking is the only procedure used to halt the natural progression of keratoconus, Spoerl et al. were the first to report its use on stabilizing the cornea (9). After that, a great number of clinical studies supported its efficacy in halting the progression of keratoconus. Its simplicity in application and its low cost makes this treatment easily applicable.

In Albania, cross-linking procedure is applying since 2009. In this paper we would like to present our results of the follow-up of patients underwent cross-linking procedure.

### Patients and Methods

81 eyes of 75 patients with progressive keratoconus were included in the study. Average age was 23.5 +/- 5.2 years (the youngest was 15 years old and the oldest 38 years old). Altogether 42.3% (32 patients) were female and 57.3% (43 patients) were male. The diagnosis of progressive keratoconus was based on: 1. History of the patients, astigmatismus and/or myopia, frequently changing the refraction, young age. 2. Objec-

tive examination: high keratometry values above 47 diopters in autorefractometer measurement. 3. Slit lamp examination: presence of Fleischer ring on the cornea. 4. Lens, retina and optic nerve examination to rule out any other accompanying pathology. 5. Evaluation of corneal topography with Pentacam (Oculus HR) which establishes the diagnosis and keratoconus stage according to Krumeich classification. Cross-linking technique. Patients were treated with epithelium off technique, according to Dresden Protocol. 1. Sol. proparacaine 0.5% for 4 times on the cornea. 2. Removal of corneal epithelium (6-8 mm diameter). 3. 30 minutes of riboflavin administration (1 drop every 2 minutes). 4. UVA light is applied for 30 minutes (adding also riboflavin drop every 2 minutes). 5. Bandage soft contact lens is applied for 3-5 days until re-epithelization process occurs. 6. Antibiotic and anti-inflammatory eye drops (sol. ciprofloxacinum ophthalmic and sol. diclofenac ophthalmic) and artificial tear were given every 4 hours as the post treatment. Postoperative assessments. Patients were examined regularly after 1 week, 1 month, 3 months, 6 months, 1 year, 2 years and 3 years after cross-linking treatment. Every time uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) were measured using Snellen chart. A topographic examination with the same instrument was performed (Pentacam HR, Ocu-

**Table 1. 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	

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 ( $p=0.008$ ), 3<sup>rd</sup> month with 6<sup>th</sup> month ( $p<0.001$ ), 6<sup>th</sup> month with 12<sup>th</sup> month ( $p<0.001$ ), 12<sup>th</sup> month with 24<sup>th</sup> 24 ( $p<0.001$ ) and 24<sup>th</sup> month and 36<sup>th</sup> 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 ( $p=0.066$ ).

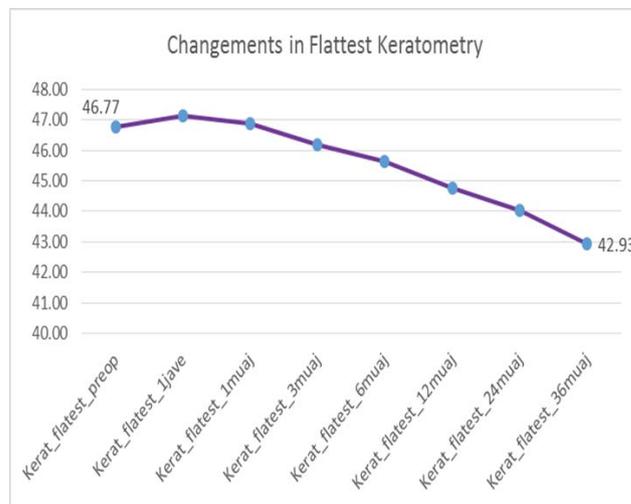


Figure 1. Evolution of medium values of flattest keratometry 1 week and 1, 3, 6, 12, 24, 36 months after treatment

**Table 2. Comparison of the medium values 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	

Based 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 ( $p=0.596$ ).

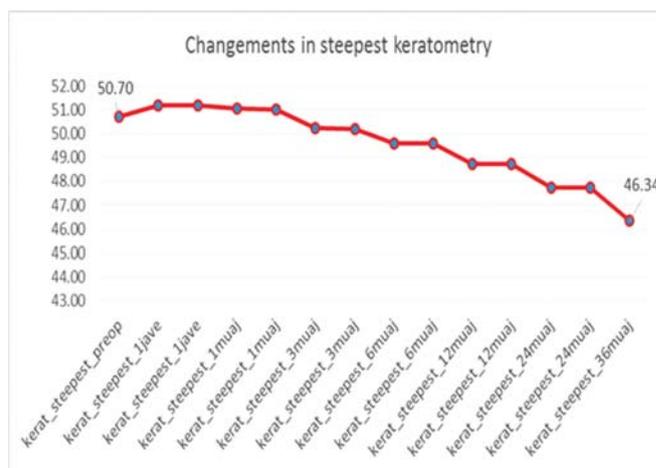


Figure 2. Evolution of medium values of steepest keratometry 1 week and 1, 3, 6, 12, 24, 36 months after treatment

**Table 3. Comparison of the medium values 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	
Couple VII	Kerat_Kmax_24 month	52.24+5.00	<0.001
	Kerat_Kmax_36 month	50.53+4.80	

Based 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 ( $p=0.917$ ).

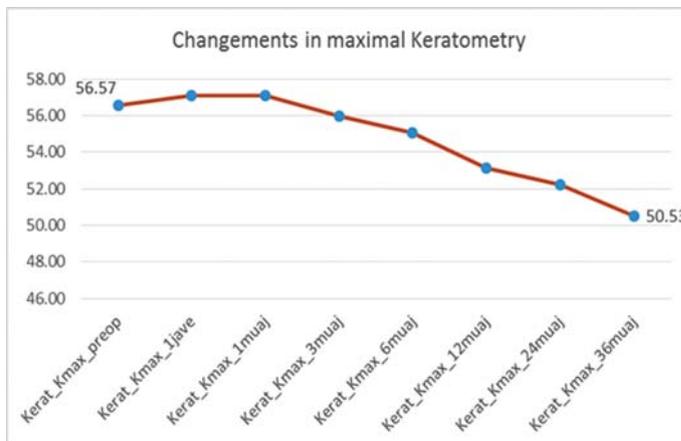


Figure 3. Evolution of medium values of maximal keratometry 1 week and 1, 3, 6, 12, 24, 36 months after treatment

Table 4. Comparison of the medium values of BCVA 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	

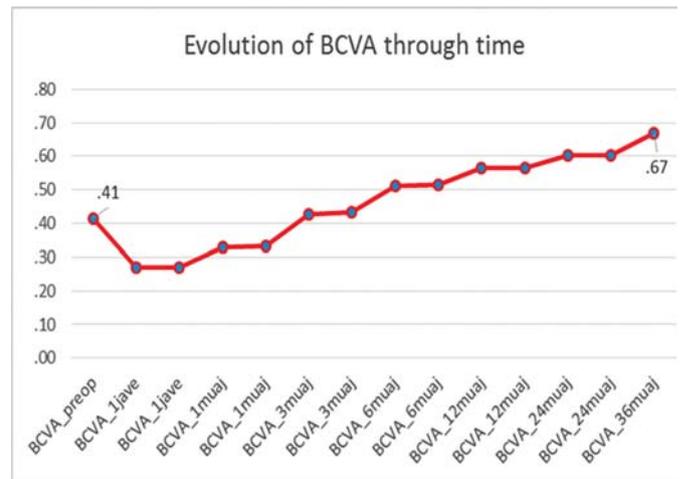


Figure 4. Evolution of medium values of BCVA 1 week and 1, 3, 6, 12, 24, 36 months after treatment

Based 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)

Table 5. Comparison of the medium values of UCVA after cross-linking			
	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	
Couple III	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	

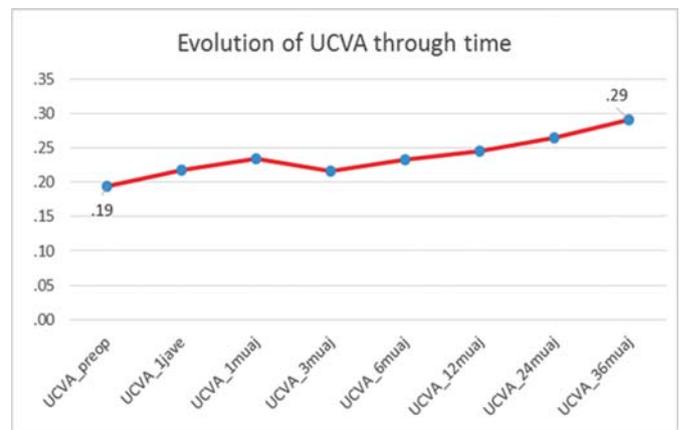


Figure 5. Evolution of medium values of UCVA 1 week and 1, 3, 6, 12, 24, 36 months after treatment

Based 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 ( $p < 0.001$ ), 24<sup>th</sup> month and 36<sup>th</sup> ( $p = 0.002$ ), 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 ( $p = 0.052$ ), 3<sup>rd</sup> month and sixth month ( $p = 0.214$ ), sixth month and 12<sup>th</sup> month ( $p = 0.135$ ), 12<sup>th</sup> month and 24<sup>th</sup> month ( $p = 0.157$ ).

**Table 6. Comparison of the medium values of thinnest pachymetry 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	

Based 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 ( $p = 0.002$ ), 12<sup>th</sup> and 24<sup>th</sup> month ( $p = 0.030$ ), 24<sup>th</sup> and 36<sup>th</sup> month after cross-linking ( $p = 0.012$ ), resulting in a significant reduction of medium values of PAK thinnest.

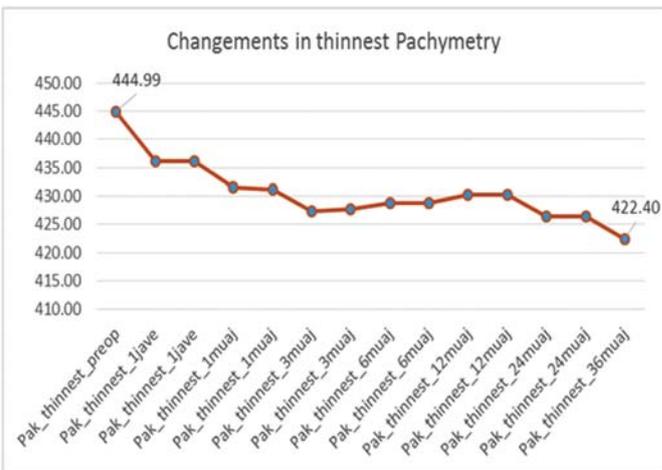


Figure 6. Evolution of medium values of thinnest pachymetry 1 week and 1, 3, 6, 12, 24, 36 months after treatment

**Table 7. Comparison of the medium values of central pachymetry 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	

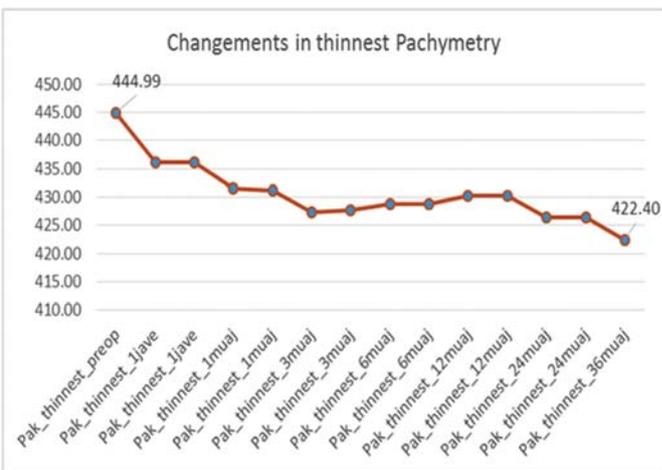


Figure 7. Evolution of medium values of central pachymetry 1 week and 1, 3, 6, 12, 24, 36 months after treatment

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 ( $p = 0.004$ ), 12<sup>th</sup> month comparing to 24<sup>th</sup> month ( $p < 0.001$ ) and 24<sup>th</sup> month comparing to 36<sup>th</sup> month after cross-linking ( $p < 0.001$ ), when a significant reduction in medium values of central pachymetry are evident (PAK central).

lus) and keratometry values (flattest, steepest, maximal) and pachymetry values (central and thinnest) were recorded. Also a careful examination of the cornea was performed on slit lamp.

Statistical analysis. Statistical analysis data were analyzed using the SPSS software (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 and standard deviation were calculated. Differences between groups were calculated with student test. Correlation between variables was analyzed through coefficients of Kendal's tau. Statistically significant differences were considered when the values of  $p \leq 0.05$ .

## Results

The tendency of progression of parameters after cross-linking are presented in the following graphics. Each graphic presents the medium value of each parameters and its evolution through time starting with pre-treatment values and the medium values 1 week after treatment and also 1, 3, 6, 12, 24 and 36 months after cross-linking treatment.

The following parameters were recorded: flattest keratometry, steepest keratometry, maximal keratometry, UCVA, BCVA, central pachymetry, thinnest pachymetry. The reduction of keratometries became visible mostly after 6 months and continued even after 36 months. The most affected is maximal keratometry. Changes in visual acuity became also visible after 6 months, mostly affecting BCVA. Reduction in pachymetry values start at 12 months mostly due to the phenomenon of "corneal shrinking". The changes are presented in the tables and figures.

## Discussion

The main parameter which define the topographic corneal shape is 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 ( $K_{max}$ ). 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 of keratoconus steepest, flattest and  $K_{max}$  increase. Central and thinnest values of pachymetry are decreasing.

After cross-linking procedure we noted the following changes:

- the flattest keratometry significantly reduces 6 months after cross-linking and continues to reduce

even after 3 years (flattening 3.8 D).

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

In other studies, visual acuity generally starts to improve 3 months after cross-linking (10) following a temporary reduction in early phase due probably to corneal haze and edema. Visual acuity improvement has been reported from 1 to 2 Snellen line 1- 4 years after treatment (11,12).

The reduction in keratometric values by 2 diopters and gradually improving in UCVA and BCVA has been reported in long term studies (11). Other randomized clinical studies have shown evidence of arrested keratoconus with improvements in keratometry values and visual acuity (13).

In our study the most important findings were the reduction of 3 diopters and more in flattest and steepest keratometry and a reduction of 6 diopters in maximal keratometry. Also an increase in 1/10 in UCVA and 2/10 in BCVA is noted.

## Conclusion

Cross-linking procedure shows to be effective in reducing corneal radius (flattest, steepest, maximal). Having a flatter cornea in a progressive keratoconus means that the progress of keratoconus is stopped and there is also a remodeling of its surface. Remodeling of the cornea, also stabilizes visual acuity and even improves best spectacles corrected visual acuity.

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