Corneal Cross-linking for Keratoconus and Post-LASIK Ectasia and Failure Rate: A 3 Years Follow-up Study

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Abstract

PURPOSE: To report the response of keratoconus(KC) and post-LASIK ectasia (referred as "ectasia") to the corneal crosslinking(CXL) and to compare the rate of progression between KC and ectasia at 3 years.

METHODS: Retrospective cohort study of patients undergoing CXL for either KC or ectasia. 54 eyes(31 patients) with ectasia and 111 eyes(67 patients) with KC were included in the study. Corrected distance Visual acuities(CDVA), refraction, keratometry(K) and pachymetry were followed over 3 years. Simultaneous Photorefractive keratectomy(PRK) and CXL was performed on 20 KC and 20 ectasia eyes. Intrastromal Corneal Ring Segments(ICRS) was performed on 51 KC and 6 ectasia eyes.

RESULTS: In KC, CDVA, spherical equivalence, sphere, cylinder and mean K improved at 3 years post-CXL(p-value<0.05), but, these values improved without reaching a statistical significance in ectasia. 12 of 54 eyes with ectasia(22.2%) and 4 of 111 eyes(3.6%) with KC had progression post CXL(p-value:0.0001). Ectasia patients diagnosed with progression were older at presentation (36.1 years) than non-progressive ectasia patients(31 years)(p-value:0.02), and also older than KC patients.

Sub-analysis excluding PRK and ICRS cases showed that there was an improvement in mean sphere (from -5.23±4.2D to-4.46±3.89D) (p-value:0.03) cylinder(from 2.54±1.68D to 1.97±1.51D)(p-value:0.03) mean keratometry(from 46.81±3.78D to 46.01±3.25D)(p-value:0.006) in KC patients 3 years post CXL(40patients). Compared to baseline, all the mean refractive and tomographic variables deteriorated at 3 years post CXL in ectasia(28 patients)(p-value>0.05). Also, 2 of 40 patients with KC(5%) vs. 7 of 28 patients with ectasia(25%) had progression 3 years post-CXL and the difference between both groups remained statistically significant(p-value:0.027).

CONCLUSION: Eyes with post-LASIK ectasia seems to be less responsive to CXL than KC.

Introduction

Keratectasias are progressive, non-inflammatory corneal diseases defined by thinning, bulging and distortion of the cornea leading to irregular astigmatism and loss of visual acuity.[1] Early progressive disease is treated with corneal crosslinking (CXL) to stabilize the cornea while end stage cases are treated with penetrating or deep anterior lamellar keratoplasty. Visual rehabilitation of stable corneas include spectacle correction, hard contact lens or scleral contact lens, intrastromal corneal ring segment implantation (ICRS), phakic intraocular lens and photorefractive keratectomy (PRK).[1]

After the introduction of CXL with riboflavin in 2003, it became the primary treatment to reduce the keratoconus and post LASIK ectasia progression.[2] Ultraviolet-A light induces a photochemical reaction in the corneal stroma in the presence of riboflavin, leading to more covalent connection between collagen fibers and hence, stabilizing the cornea and improving collagen structure.[3] (For the sake of simplicity, we will be using from here on the term "ectasia" to signify post-LASIK ectasia).

Recently, PRK and ICRS insertion were used in combination with CXL(simultaneously or staged procedures) to improve the uncorrected and best corrected visual acuity of the patients and strengthen their corneas at the same time.[4,5]

Multiple studies proved the effectiveness of CXL and reported good outcomes in terms of visual acuity, refraction, corneal curvature and keratometry on the short and long term follow up in patients with keratoconus and ectasia.[3,6-8]. However, many corneas failed to stabilize after CXL and had progressive steepening. Failure rate was variable between studies, in patients with keratoconus it was reported to be between 3.17% and 33%.[3,9-13] On the other hand, in the smaller studies conducted on patients with ectasia, the failure rate ranged between 0 to 27.5%.[14, 15]

Ectasia and keratoconus response to CXL were previously compared over a one-year period. It was postulated that the reduced effect of CXL post-LASIK may be caused by the flap, which may inhibit the diffusion of riboflavin, or due to the anterior stromal behavioral change by the CXL process.[16] Most of the comparative studies were performed on a small sample of patients or for a short period of time.[14-16] Therefore we decided to investigate the effect of CXL on keratoconus and ectasia groups simultaneously and to calculate the difference in the rate of progression between both groups on the long term follow up, in addition to the characteristics and the risk factors of CXL failure in each group.

Materials

A retrospective cohort study conducted at Beirut Eye and ENT Specialist Hospital (Lebanon) between January 2010 and June 2015

Patients who underwent CXL surgery for progressive keratoconus and ectasia were followed for 3 years. Review board approved the study which complies with the Declaration of Helsinki.

Study population

Charts of all the patients receiving CXL between January 2010 and June 2015 were reviewed, 158 patients with keratoconus and 62 patients with ectasia were identified.

Inclusion criteria: - Progressive keratectasia (keratoconus or ectasia) based on refraction and topography changes in two consecutive visits (criteria discussed in the following section)

- Patients who presented for follow up at 6 months, 1 year and 3 years

- Minimal central corneal thickness of 330 µm[17]

- All age groups

Exclusion criteria: - loss of follow up

- Ocular surface pathologies

- Pregnancy during the 3 years of follow up

- Eyes implanted with implantable Collamer lens (ICL) during the follow up period

165 eyes of 98 patients met the inclusion criteria. 54 eyes (31 patients) had ectasia and 111 eyes (67 patients) had keratoconus. Since keratoconus is more prevalent than ectasia a higher number of patients was included. In both keratoconus and ectasia groups, some patients were subject to combined procedures, ICRS or PRK. In order to avoid biased statistics, statistical analysis was first carried in all patients comparing both groups and then patients who had ICRS or/and PRK were excluded from the final analysis comparing ectasia and CXL at different follow up period.**(Figure 1)**

Keratoconus andEctasia progression

Progression in patients diagnosed with keratoconus and ectasia is suspected if there is deterioration in the visual acuity or the manifest refraction, after an increase in maximum keratometry readings or a decrease in corneal thickness[13,18-20]. Until now there is no clear definition of progression. The global consensus on Keratoconus and Ectatic Diseases (2015) defined progression by a change in at least two of the following parameters: progressive steepening of the anterior corneal surface, steepening of the posterior corneal surface, and/or thinning or changes in the pachymetric rate of change.[18]

In our study the progression before and after CXL was diagnosed based on the presence of two or more of the following criteria on two consecutive visits:

- Increase in K values (K1, K2, K max and K mean) >1D
- A change in the map difference between two consecutive readings >1D
- ≥ 2 % decrease in central thickness
- A deterioration of CDVA or uncorrected visual acuity defined as a drop of one or more lines on Snellen chart and that is not attributed to other ocular disorders
- Any significant changes in the magnitude of spherical equivalence, myopic or astigmatic refraction (>1.0D) that is not attributed to any other optical system disorders.

Surgical Procedure

CXL-epithelium off was used for all the surgeries. Proparacaine hydrochloride 0.5% drops were used to anesthetize the eye. After the insertion of a lid speculum, a bunt spatula was used to remove the central 9 mm corneal epithelium. The riboflavin 0.1% dextran solution (Collagex, isotonic 0.1%, Lightmed USA Inc.) was instilled every 2 minutes for 30 minutes. The ultraviolet A (UVA) lamp (UV-X illumination system, version 1000; IROC AG, Zurich, Switzerland) was then focused on the cornea with a radiant energy of 3.0 ± 0.3 mW/cm^2 for 30 minutes following Dresden protocol.[2] During UVA administration, riboflavin drops were applied to the cornea every 2 minutes. The thinnest and central pachymetry were continuously monitored through the procedure using Accutome AccuPach VI 24-6200 Pachymeter Digital Signal Analysis (Accutome, Inc, USA). Eyes with a pre-operative Central corneal thickness between 330 and 400 µm, application of a hypo-osmolar riboflavin for 5 minutes (1 drop every 20 second) was performed until adequate corneal thickness was reached (>400 µm).[17]

After treatment, gatifloxacin 0.5% (Zymaxid®; Allergan, Inc.) eye drops were instilled, followed by the placement of a bandage soft contact lens (ACUVUE®, Johnson & Johnson Vision Care, Inc.) for 5 days. Postoperatively, patients were given gatifloxacin 0.5% four times daily for 7 days, Tobramycin-dexamethasone 0.1% (TOBRADEX® Alcon Laboratories, Inc) four times daily for 10 days, followed by Loteprednol (LOTEMAX® Bausch & Lomb .Inc) 0.5% 5 times daily, tapered over 5 weeks. [11]

Some patients in both groups were subject to combined procedure, ICRS and PRK. ICRS (Intacs® Addition Technology™, Inc) were implanted 4 weeks prior to CXL in both group if the patient had a decreased CDVA (<20/30) , contact lens intolerance and irregular astigmatism on topography. A total of 57 eyes were implanted with ICRS using Intralase femtosecond laser (IntraLase, Abbott Medical Optics Inc., Santa Ana, California, USA) to create the tunnels at 400µm depth (different ring segment arc length and thickness were used following our published algorithm in each case[21]). Also, a simultaneous PRK using eximer laser (ALCON WAVELIGHT® EX500 Alcon Laboratories, Inc.) was performed at the same day prior to CXL if the patient had a CDVA > 20/30, a minimum preoperative thinnest pachymetry of 480µm and a calculated ablation depth limited to <50µm over the cone. The 9 mm central corneal epithelium was removed using a blunt spatula. PRK was performed on 40 eyes. (Figure 1)

Data collection and Outcome Measures

Patients' charts were reviewed. Assessment of their uncorrected distance visual acuity, corrected distance visual acuity (CDVA) and manifest refractions using Snellen charts was performed preoperatively, 6months, 1 year and 3 years post treatment. Logarithm of the minimum angle of resolution (logMAR) system was used to document and analyze visual acuity.

Also, slit lamp exam, fundus evaluation and corneal tomography maps were performed during each visit. The WaveLight® Allegro Oculyzer™ (WaveLight, GmbH, Erlangen, Germany) was used to record keratometry (K1, K2, K mean, K max) and pachymetry.

Statistical analysis

SPSS 19.0 (SPSS, Inc, Chicago, IL) was used to analyze data. Continuous variables (visual acuity, spherical equivalence, keratometry, pachymetry) were analyzed as mean and SD (standard deviation), while categorical variables (gender, ICRS, PRK) were presented as percentages. The progression rate was calculated for both keratoconus and ectasia. Pared sample t-test was used to explore relationships between continuous variables while chi-square test (Fisher's Exact Test) was used to compare categorical variables and progression rate. p-value was considered significant if less than 0.05.

Results

Of the 165 eyes included in the study. 111 eyes of them (67 patients) had keratoconus with a mean age of 26.2 ±8.3 years (67 males and 44 females) and 54 eyes (31 patients) had ectasia with a mean age of 32.4 ± 7.8 years (26 males and 28 females).

It is well known that PRK and ICRS may be a source of bias due to the unpredictable changes of the tomographic parameters. Therefore, analysis of keratoconus and ectasia response to CXL at 3 years was performed with and without the exclusion of simultaneous PRK or ICRS implantation cases

Analysis including all patients: Keratoconus patients had progressive improvement of the mean CDVA over 3 years (improvement by 0.07 logMAR). Although the improvement is statistically significant, it is not clinically relevant. Also, spherical equivalence, sphere, cylinder and mean keratometry decreased reaching statistical significance after 6 months while the maximum keratometry was significantly different at 3 years, the thinnest pachymetry did not show any difference 3 years post CXL. Ectasia patients had minimal

improvement in CDVA, spherical equivalence, sphere, cylinder and mean keratometry and results did not reach significance at 3 years post-CXL (p-value>0.05). Only pachymetry deteriorated by 16.7µm at 3 years (p-value:0.04). **(Table 1)(Table 2)**

Analysis excluding PRK and ICRS patients: At 3 years post CXL, the mean CDVA and spherical equivalent were not statistically different from baseline in keratoconus and ectasia groups, 7 patients with keratoconus (17.5%) and 5 patients with ectasia (17.8%) lost 1 or more lines of CDVA. Also, 6 patients with keratoconus (15%) and 8 patients with ectasia (28.5%) had a deterioration of 1 or more diopters of spherical equivalence. (**Table 1) (Figure 2)**

Keratoconus patients had progressive decrease in the mean sphere and cylinder up to 3 years post CXL (p-value: 0.03). On the contrary, ectasia patients had progressive increase in the mean sphere and cylinder without reaching significance. (**Table 1)**

In keratoconus, the mean keratometry decreased significantly by 0.8 D at 3 years post-CXL (p-value: 0.006) and the maximum keratometry decreased by 0.44 D without reaching statistically significant difference (p-value: 0.26). In ectasia, mean and maximum keratometry increased reaching a difference of 0.29D and 1.02 D respectively, at 3 years compared to baseline (p-value>0.05) **(Table 2)**

Over 3 years of follow up, the changes in the mean corneal thickness at the thinnest location were not statistically significant in keratoconus and ectasia. 10 patients with keratoconus (25%) and 7 with ectasia (25%) lost more than 2% of their corneal thickness during follow up period. **(Table 2)(Figure 2).**

Keratoconus and post-LASIK Ectasia progression post CXL:

Of the total 165 eyes that were included in the study, 111 eyes had keratoconus of which 4 eyes (3.6%) had progression. 54 eyes had ectasia of which 12 eyes (22.2%) met the criteria for progression 3 years post CXL. The difference was statistically significant (p-value: 0.0001)**.**

Patients diagnosed with progressive keratoconus at 3 years post CXL were younger at the first presentation than patients with stable keratoconus (23±8.4 vs. 26.3±8.3 years respectively), but this was not significantly different (p-value: 0.43; CI: [-5.1; 11.7]). Patients who had progression of their ectasia 3 years post CXL were older at presentation than those with a stable ectasia (36.1±6.4 vs. 31±7.7 years respectively) and this difference was significant (p-value: 0.02; CI: [-10.7; -0.7]).

After excluding all the patients who received PRK or ICRS: 2 of 40 patients with keratoconus (5%) vs. 7 of 28 patients with ectasia (25%) had progression 3 years post CXL and the difference between both groups remained statistically significant (p-value: 0.027). The 9 patients with progression included in the subgroup analysis had 2 or more of the previously mentioned criteria indicating failure of CXL (2 patients with keratoconus and 7 with ectasia) **(Table 3)**.

Procedure Complications: of the total pool of patients, only 1 patient operated with CXL without ICRS or PRK presented with late post-operative haze. Infectious keratitis or healing defect were not reported in our series.To note that 10 patients (8 with keratoconus and 2 with ecatsia) had a central corneal thickness between 340 and 400 to which a hypo-osmolar riboflavin solution was used during CXL procedure without any complication.

Discussion

Up to present time, corneal crosslinking has been proved to be the most effective method used to halt the progression of keratoconus and other corneal ectatic diseases.[13,22, 23]

Multiple studies have shown long-term stability post CXL in keratoconus patients with minimal risk of progression.[3,9-12] Other newly published studies have shown a relative stability post-CXL in patients with ectasia. in a US based Multicenter Clinical Trial of CXL for Treatment of post Lasik ectasia, 91 patients who received CXL showed improvement of the maximum keratometry compared to the sham group at one year, 4% of the treated patients had significant deterioration of their maximum keratometry and CDVA.[24] In another longer report, 13 of the 17 treated eyes had stable or improved CDVA over an 80 months mean follow up period.[25] In a study, 2 of 14 patients with ectasia had keratometric deterioration between one and 3 years of follow up.[14] Moreover, another report showed that 27.5% of patients with ectasia had lost Snellen lines over a two-year period.[15]

On the other hand, few comparative studies have been published. Over a one year follow up, 3 of the 22 patients with ectasia lost two Snellen lines compared with 3 of 49 eyes with keratoconus.[16] The later study actually found that there was no difference between

keratoconus and ectasia response to CXL.[16] Unfortunately, these studies were performed either on a small population or over a short period of time and most of them were non comparative and failed to identify the number of patients who met the criteria for progression after CXL, defined by the global consensus on Keratoconus and Ectatic Diseases. Therefore, it is difficult to compare KC and post-Lasik ectasia from different studies on different populations and using different treatment protocols.

In our study, progression rate post CXL was significantly higher in ectasia patients compared to keratoconus over a 3 year period. To mention that progression was diagnosed at least 1 year after the CXL, because we consider that the response corneal remodeling after CXL is mostly achieved at 6 months post-surgery and the topography stabilizes at 6 months post CXL which is considered as a baseline data after CXL that will be used for further analysis. To explain the higher rate of ectasia progression after CXL, we hypothesize that progression in ectasia patients could be due to the presence of a small bio-mechanically effective residual stromal bed post-LASIK procedure, and the fact that the anterior flap does not contribute to the biomechanical stability restoration after CXL.[26] On the contrary, the flap itself may form a barrier to hinder riboflavin and UV light penetration to the deeper residual stromal bed tissue.[16] Hence, photosensitization of the deep stromal tissue in the residual stromal bed post LASIK happens at much lower effective rate than in the upper part of the stromal tissue in keratoconus during CXL procedure. Moreover, the histopathological and ultra-structural differences between ectasia and keratoconic corneas have been previously described.[27] In a study, both pathologies were similar in terms of having fewer and thinner than normal lamellae in the region of ectasia. But, only the residual stromal bed in post-LASIK corneas showed these changes while all the corneal thickness was affected in keratoconus.[27] And since the anterior corneal stroma –which represents the strongest region- has been ablated by the flap; the cornea post- LASIK, was expected to have a different response to the biomechanical treatments, such as those used in ICRS placement or CXL.[27,28]

Our analysis showed that older age at presentation in patients with ectasia may be a factor in the development of progression. This could be explained by the progressive deterioration of these corneas over a long period of time reaching a threshold of clinical significance at older ages.

PRK procedure along with CXL has been proved to be safe and effective in patients with keratoconus.[29] In this study, the rate of performed PRK in progressive and non-progressive cases (in keratoconus and ectasia groups) were comparable. But, because of a possible selection bias, no conclusion can be drawn concerning the safety of PRK in keratectasia and its contribution to the progressive deterioration of some cases.

In the subgroup analysis excluding patients who received PRK or ICRS: the mean CDVA, SE, mean and maximum keratometry had continuous improvement from 6 months post CXL up to 3 years in keratoconus patients (though not always reaching statistical significance or clinical significance). These results are in concordance with the published literature about the long term outcomes of CXL in keratoconus patients.[30,31] On the other hand, the mean CDVA, SE, mean and maximum keratometry deteriorated in patients with ectasia at 3 years post-CXL.

The significance of the changes in CDVA and refractive outcomes at 3 years compared to baseline, decreased after eliminating PRK and ICRS cases in keratoconus patients. This suggests that the changes reported in the total population were not caused by the crosslinking, they are most likely the result of the ICRS which are known to improve the CDVA and decrease the spherical equivalence.

Maximum keratometry was more indicative of progression in ectasia patients than keratoconus patients, a possible explanation to this difference can be attributed to keratoconus being a disease that affects the entire cornea while ectasia is more of a localized entity. In our study, we tried to correlate the amount of historical LASIK ablation depth and the original refraction to the progression of ectasia, but the data was nonexistent in most of the patients, since it was performed in other centers and it could not be concluded from the available data due to ectasia. Moreover, in light of the higher rate of CXL failure in ectasia patients, the proposed treatment for ectasia by inducing fibrogenesis and new interfibrillary bonds using deep stromal puncturing to restore the flap's contribution to the biomechanical corneal stability sounds as very effective alternative to conventional CXL in ectasia patient.[32]

There are some limitations to the current study. First, it was performed in a single center and the surgeries were conducted by the same surgeon. Second, the number of patients decreased after excluding ICRS and PRK patients. Third, a selection bias is present since many patients with keratoconus and post-Lasik ectasia were loss to follow up and were excluded from the study.

In conclusion, post-LASIK ectasia showed lower stability post CXL compared with keratoconus. Older patients and males with post-LASIK ectasia showed progression more than younger ones. The effect of CXL on the cornea can continue up to 3 years post CXL

while ectasia patients showed progression after 6 months.

What was known:

CXL is proved effective in halting the progression of both post-Lasik ectasia and keratoconus.

What this paper adds:

Post-LASIK ectasia patients had non-significant changes of refraction and topographic parameters post CXL

Post-Lasik ectasia has a higher progression rate than keratoconus at 3 years.

Abbreviations

CDVA: Corrected Distance Visual Acuity

CXL: Corneal Crosslinking

D: Diopters

Ectasia : post-LASIK ectasia

ICRS: Intrastomral Corneal Ring Segments

K: Keratometry

LASIK: Laser-assisted in situ keratomileusis

Declarations

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Tables

Table 1: Pre and post cross-linking refractive measurements (corrected distance visual acuity, spherical equivalence, sphere and cylinder).

Group	Factor	Patients	Pre-CXL	6 months Post-CXL	1 year Post-CXL	3 years Post-CXL	P-value (at 3years)	CI (at 3years)
Including all cases (with ICRS and PRK)	CDVA (logMAR)	KC (n=111)	0.16±0.21	0.15 0.14	0.1±0.11**	0.09±0.21**	**0.001**	0.04; 0.11
		Ectasia (n=54)	0.1±0.14	0.11 0.18	0.09±0.1	0.09±0.11	0.4	-0.02; 0.05
	Spherical equivalence (diopters)	KC (n=111)	-3.4±3.37	-2.39±3.57**	-2.39±3.63**	-2.38±3.8**	**0.001**	-1.48; -0.54
		Ectasia (n=54)	-2.64±3.73	-2.35±4.35	-2.49±4.09	-2.29±3.72	0.15	-0.82; 0.13
	Sphere (diopters)	KC (n=111)	-4.7±3.74	-3.37±3.92**	-3.36±3.98**	-3.29±4.14**	**0.001**	-1.92; -0.89
		Ectasia (n=54)	-3.5±3.75	-3.12±4.5	-3.24±4.25	-3.05±3.93	0.08	-0.96; 0.05
	Cylinder (diopters)	KC (n=111)	2.6±1.73	1.94±1.48**	1.93±1.59**	1.84±1.53**	**0.001**	0.45; 1.07
		Ectasia (n=54)	1.72±1.32	1.55±1.55	1.49±1.55	1.5±1.55	0.27	-0.17; 0.59
Excluding ICRS and PRK cases	CDVA (logMAR)	KC (n=40)	0.14±0.23	0.14±0.13	0.11±0.12	0.1±0.13	0.24	-0.02;0.09
		Ectasia (n=28)	0.11±0.12	0.13±0.23	0.12±0.12	0.12±0.12	0.35	-0.45;0.01
	Spherical equivalence (diopters)	KC (n=40)	-3.96±3.89	-3.36±3.77**	-3.22±3.66**	-3.48±3.71	0.11	-1.08;0.12
		Ectasia (n=28)	-4±4.58	-4.14±5.4	-4.58±4.68	-4.25±4.29	0.49	-0.48;0.98
	Sphere (diopters)	KC (n=40)	-5.23±4.2	-4.45±4.07**	-4.26±3.82**	-4.46±3.89**	**0.03**	-1.48;-0.04
		Ectasia (n=28)	-4.9±4.48	-5.09±5.4	-5.62±4.66	-5.26±4.31	0.3	-0.35;1.08
	Cylinder (diopters)	KC (n=40)	2.54±1.68	2.15±1.63	2.08±1.6	1.97±1.51**	**0.03**	0.05;1.08
		Ectasia (n=28)	1.79±1.53	1.9±1.65	2.07±1.68	2.02±1.76	0.41	-0.8;0.34

CDVA: Corrected distance visual acuity

CI: confidence interval

CXL: collagen cross-linking.

KC: keratoconus

n: number of patients

ICRS: intrastomal corneal ring segments

PRK: photorefractive keratectomy

P-value: using paired sample T-test comparing 3 years with pre-CXL data

**significant changes with p-value <0.05 compared to pre-CXL data

Table 2: Pre and post cross-linking tomographic measurements (mean keratometry, maximum keratometry and thinnest corneal pachymetry).

Group	Factor	Patients	Pre-CXL	6 months Post-CXL	1 year Post-CXL	3 years Post-CXL	P-value (at 3years)	CI (at 3years)
Including all cases (with ICRS and PRK)	K Mean (diopters)	KC (n=111)	47.46±4.4	46.4±4.23**	46.16±4.13**	46.1±4.12**	**0.001**	0.85; 1.7
		Ectasia (n=54)	44.07±3.29	43.38±3.75**	43.54±4.07	43.47±3.85	0.08	-0.08; 1.28
	K Maximum (diopters)	KC (n=111)	54.49±7.99	54.66±8.44	53.97±7.92	53.36±7.56**	**0.001**	0.49; 1.76
		Ectasia (n=54)	48.77±8.74	49.33±5.07	49.49±5.65	49.83±5.65	0.34	-3.28; 1.16
	Thinnest Pachymetry (µm)	KC (n=111)	462.5±45.38	455.8±7.99**	456.8±42.2**	458.5±41.37	0.13	-1.23; 9.39
		Ectasia (n=54)	464.3±60.72	446.7±72.85**	448.3±82.35	447.6±79.47**	**0.04**	0.14; 33.1
Excluding ICRS and PRK cases	K Mean (diopters)	KC (n=40)	46.81±3.78	46.23±3.36**	46.1±3.31**	46.01±3.25**	**0.006**	0.24;1.34
		Ectasia (n=28)	44.11±3.63	44.24±4.38	44.29±4.25	44.4±4.44	0.365	-0.94;0.35
	K Maximum (diopters)	KC (n=40)	52.14±6.63	52.51±6.98	52.1±6.79	51.7±6.42	0.26	-0.34;1.21
		Ectasia (n=28)	50.99±6.35	51.13±5.87	51.54±6.61	52.01±6.31	0.106	-2.26;0.23
	Thinnest Pachymetry (µm)	KC (n=40)	461.9±45.3	464.1±36.2	463.9±42.3	463.4±42.8	0.699	-8.97;6.08
		Ectasia (n=28)	463.1±57.9	448.8±74.3	459.5±69.4	460.8±59.9	0.553	-5.61;10.25

CI: confidence interval

CXL: collagen cross-linking

K: keratometry

KC: keratoconus

n: number of patients

ICRS: intrastomal corneal ring segments

PRK: photorefractive keratectomy

P-value: using paired sample T-test.

**significant changes with p-value <0.05 compared to pre-CXL data

Table 3: variables changes at 3 years of follow up compared to baseline in each of the patients diagnosed with progression and failure of crosslinking (excluding cases with intrastomal rings and PRK).

Patient number	1	2	3	4	5	6	7	8	9
Pathology	ectasia	ectasia	ectasia	ectasia	ectasia	ectasia	ectasia	KC	KC
CDVA	-	+	-	-	+	+	-	-	+
SE	+	+	-	-	+	+	+	+	-
Sphere	+	+	-	+	+	+	+	+	-
Cylinder	-	-	+	+	+	-	-	+	-
Mean K	-	+	-	-	+	+	-	-	+
Max K	+	+	+	+	+	-	-	-	-
Thinnest pachymetry	+	+	-	+	-	-	-	+	-

+ indicates significant deterioration suspicious of progression according to our criteria

- Indicates improvement or minimal changes compared to baseline

CDVA: corrected distance visual acuity

K: keratometry

SE: spherical equivalence

Figures

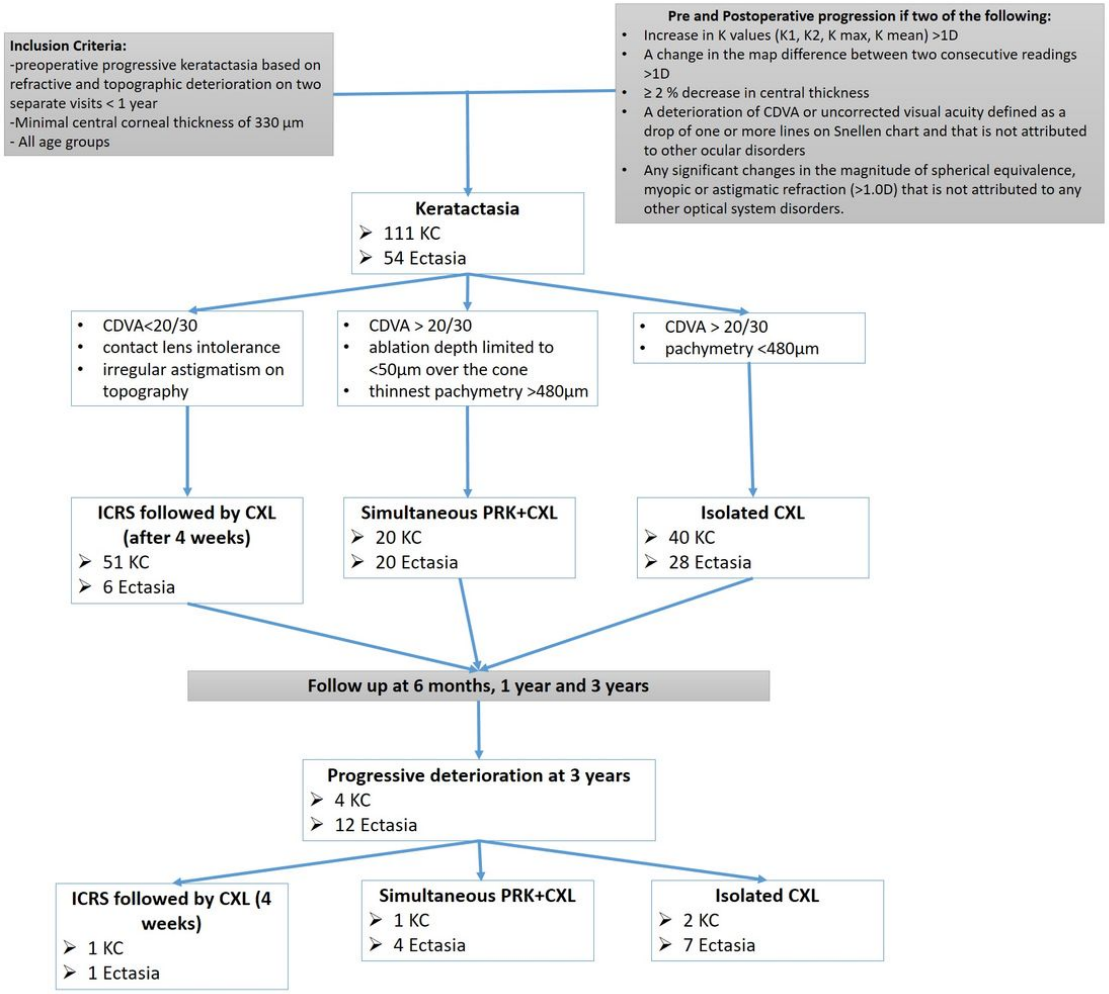

Figure 1

inclusion criteria, pre and post operative patient's distribution

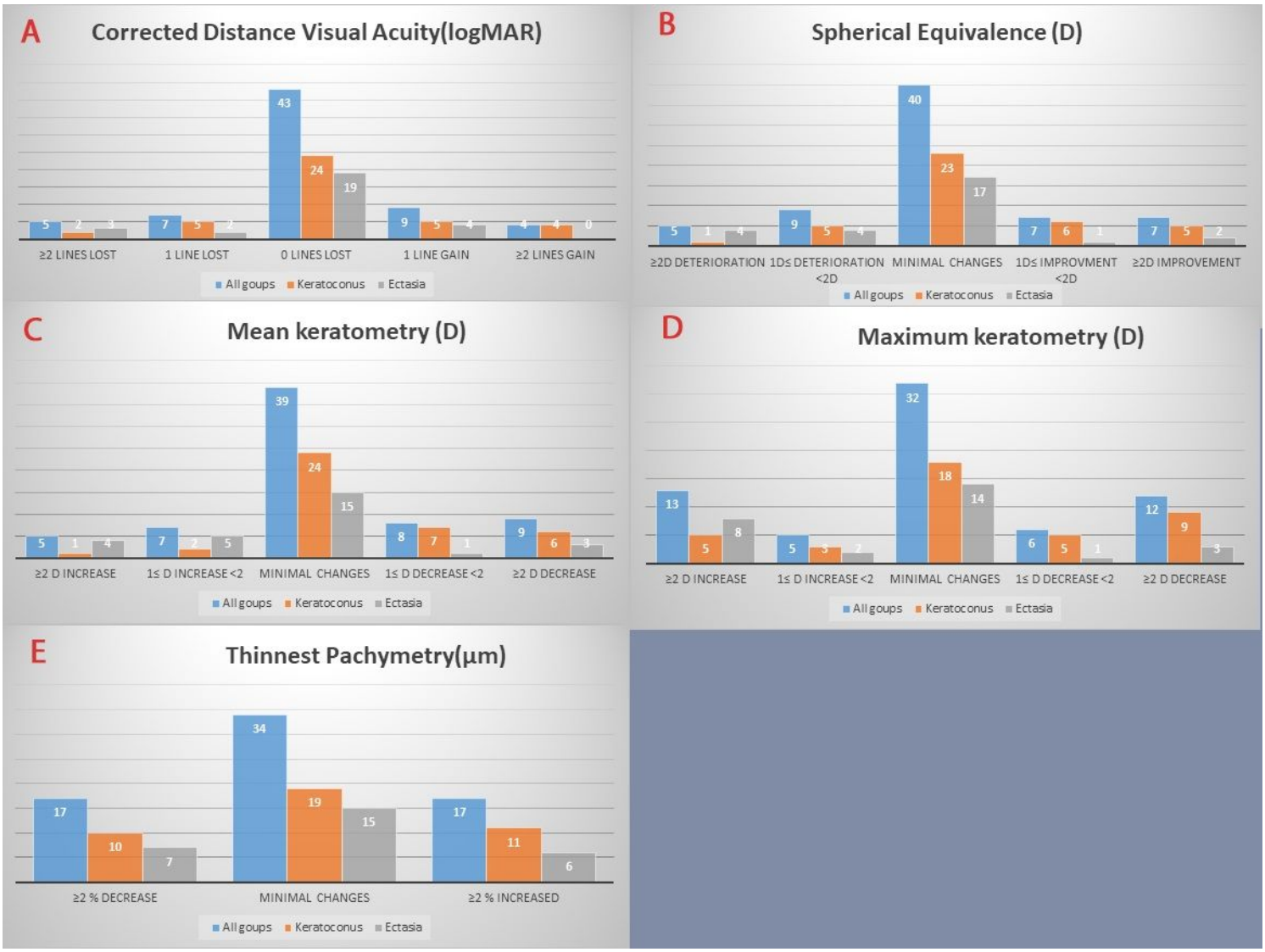

Figure 2

Changes in "Corrected Distance Visual Acuity (A), spherical equivalence (B), mean keratometry (C), Maximum keratometry(D), thinnest corneal pachymetry(F)" between baseline and 3 years post-CXL. (Excluding PRK and ICRS cases)