The natural courses of keratometric, pachymetric and visual acuity outcomes during 1year follow up after corneal collagen cross-linking

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ABSTRACT

Background: As photochemical reaction that can stiffen the cornea, CXL is the only promising method of preventing progression of keratectasia such as KC and secondary ectasia following refractive surgery. The aim of CXL is to stabilize the underlying condition with a small chance of visual improvement.

Objective: To show the sequences of changes in visual acuity and topographic outcomes during 1 year post CXL for patients with progressive Keratoconus.

Type of the study: Cross sectional study

Methods: CXL procedure was done for 45 eyes with progressive KC. The following parameters had been monitored pre operatively, 1, 3, 6 and 12 months postoperatively: K apex, K2, corneal thickness at thinnest location, anterior and posterior elevation points, BCVA and UCVA. Placido -Scheimpflug topography (Sirius) device had been used to monitor the corneal parameters of the study. One -way ANOVA and Paired sample T test was used for statistical analysis.The study done in Lasik specialty center /Baghdad/Iraq

Results: At 1 year, an averages flattening of (2.11 D) diopter in K2 and (1.88 D) diopter in K apex were found. Mean BCVA improved by 1 line from (0.18) Log MAR to (0.13) Log MAR and mean UCVA improved by 3.5 lines from (0.89) to (0.64) log MAR. The corneal thickness at thinnest location was 5.71 Mm less than the baseline. All the above mentioned parameters showed a trend of worsening between the baseline and 1 month, and improvement thereafter. We found no statistically significant changes in the anterior elevation points while the posterior elevation point changed (increased) significantly.

Conclusions: Corneal collagen cross-linking seems to be effective in decreasing progression of KC , with improvements in optical measures in many patients. Post operative parameters discussed within this review followed a seemingly reproducible trend in there natural course over 12 months .Generally, the trend that observed was immediate worsening between baseline and 1 month resolution at approximately 3 months, and improvement thereafter.

Key words: Keratoconus, collagen cross-linking, K apex: keratometric value at the apex of the cone, K2: the steepest simulated K reading.

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Keratoconus is a degenerative, non inflammatory ectasia of the cornea with documented changes in the corneal epithelial basement membrane structure[1-3], in stromal collagen composition, distribution and organization leading to lamellar and /or fibrillar slippage[2-5] , in extracellular matrix component [3] , and in keratocyte morphology and cell -matrix interactions [6-8]. In addition, collagen loss , proteoglycan changes and up regulation of degenerative enzymes[8] has been shown in KC , all these changes lead to biomechanical instability and make it a progressive disease. Manifestations of the disease vary from slight irregular astigmatism to visual impairment secondary to corneal scarring. Progressive distortion and bowing of the cornea result in optical aberrations and in some cases inability to achieve functional vision [9] .Treatment option of KC based on refractive correction with spectacles, contact lens ,intracorneal ring implantation to correct astigmatism and restore visual acuity such modalities doesn't stop ectatic progression and further visual deterioration will ultimately necessitate corneal transplant in 10-20 % of cases[10] .

Corneal CXL using UV-A and riboflavin was first introduced by Wollensak et al. in 2003 as a method to halt progression of the disease.

The mechanism of CXL is that riboflavin as a photosensitizer which saturated cornea is exposed to UV-A light irradiation and excited into an activate state generating some reactive oxygen species which lead to formation of covalent bonds between collagen molecules that increase the stiffness the cornea [11, 12] .

It had been estimated that CXL result in strengthening of the human cornea by 328.9%. A beneficial side effect of CXL in many patients is flattening and regularization of conic corneal shape which in turn can cause reduction of myopia and astigmatism[13-16] .Given its relatively low treatment failure and complication rates , CXL has become widely accepted internationally ,as one of the front line treatment option for KC and postoperative ectasia .

The current study aimed to show the natural courses of keratometric, pachymetric and visual acuity outcomes during 1year follow up after CXL.

Patients and methods: Forty five eyes of 30 patients with progressive KC were enrolled in this prospective study; they were documented as having progressive KC as they had one or more of the following changes over 6 months period: An increase of 0.5 diopter (D) or more in the steepest simulated K value (K2) ,an increase of 0.25 diopter(D)or more in the manifest spherical equivalent or an increase of 0.5 diopter (D) or more in the manifest cylinder and decrease in patient's visual acuity by 1 or more Log MAR lines. For those under 20 years old no such documentation was required and they were

considered as progressive solely on the basis of their age as major determinant of KC progression.All patient provided informed consent .

Inclusion criteria:

1. Age from 11 to 40 years.
2. No opacities or scaring on slit lamp
3. Pachymetry reading >400 Mm at thinnest point of the cornea as measured by the corneal topography.

Exclusion criteria:

1. Pregnancy or nursing
2. Background systemic disease such as diabetes or collagen tissue diseases.
3. Any other previous or current treatment(s) for keratoconus except contact lens.
4. Unwilling patient to enroll into the study.

The following parameters were examined preoperatively and at 1, 3 , 6 and 12 months postoperatively :

UCVA, BCVA and topographic analysis by Scheimpflug-Placido corneal topography included: the steepest simulated keratometry (**K2**), apex keratometry (**K apex**), corneal thickness at thinnest (within 9 mm area) point of the cornea, anterior and posterior elevation points values.

CXL Treatment Protocol:

We treated all the 45 eyes using the surgical protocol first described by Wollensak et al [14].

After application of topical anesthesia, mechanical debridement of corneal epithelium was performed over the central 9mm zone.

Initial loading dose of riboflavin (0.1% in 20% Dextran T500 solution; Medio-Cross; Peschke Miditrade GmbH, Switzerland) by applying topical riboflavin in 2 -min interval during the initial 30 min . At conclusion of the loading phase stromal riboflavin saturation was confirmed by slit lamp examination. For those eyes with CCT <400 Mm after epithelial removal hypotonic riboflavin used (0.1% in sterile water MedioCross hypotonic) it was installed each 10 -s intervals over 2-min session and can repeated until US pachymetry at thinnest location measured 400 Mm .Once adequate thickness confirmed corneal treatment zone was exposed to UVA source emitting selective WL of 365 nm at irradiance 9mW/cm² for 10 minutes.

At the end of treatment antibiotic-steroid; tobramycin-dexamethasone eye drops (tobradex) installed before placement of bandage contact lens which was removed at 5th post-operative day .While the antibiotic-steroid eye drop continues for 2 weeks 4 times daily.

Statistical analysis:

Statistical data are presented as mean ±SD. Statistical analysis was performed using Minitab17. P value less than 0.05 was considered to be of significance. Preoperative (baseline) and postoperative parameters were compared by using One- way ANOVA , then the baseline and the 12 months outcome parameters compared by using paired -T- test.

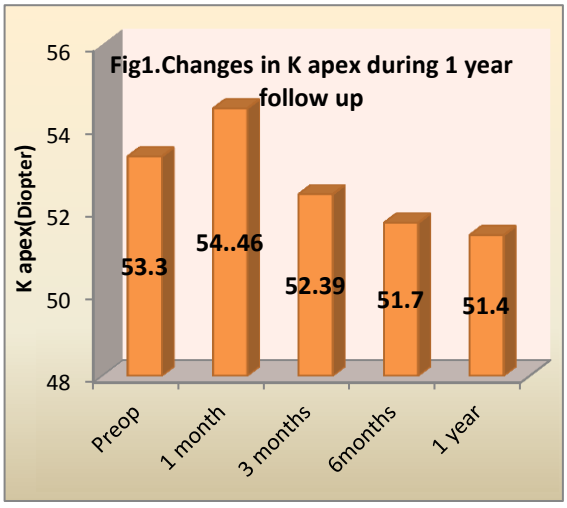
Results: Demographics: forty-five eyes of 30 patients were enrolled in this study .Out of 30 patients: 17 were female and 13 were male .The mean age of the patients was 25.26±6.11 (range 11 to 40 years): Table 1 showed the patients preoperative and postoperative parameters.

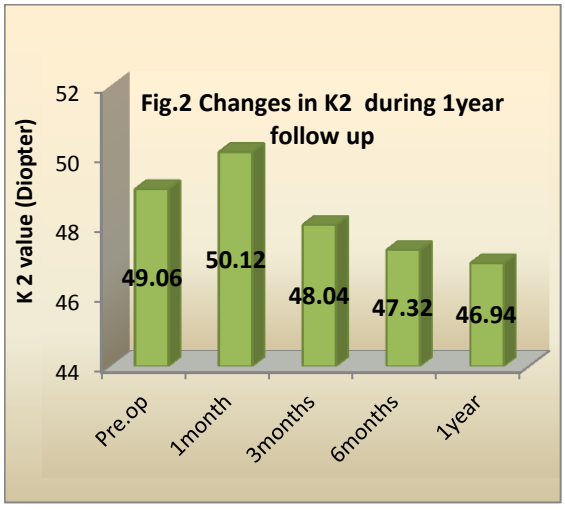
Table 1 : visual acuity and topographic parameters at baseline and during follow- up

parameters	baseline	1 month	3 months	6 months	12 months
K apex(D)	53.30±6.26	54.46±7.08	52.39±6.90	51.70±5.68	51.40±5.55
K2(D)	49.06±3.56	50.12±3.73	48.04±3.80	47.32±3.88	46.94±3.83
Pachymetry(Mm)	469±30.72	441.82±34.02	456.65±31.94	462.39±29.24	463.29±30.02
Ant.elevation (Mm)	34.17±13.61	34.75±14.74	34.70±14.23	34.80±15.20	34.23±13.55
Post.elevation(Mm	74.11±25.71	78.81±23.44	78.99±.24.45	80.82±25.66	80.39±24.33
UCVA (Log MAR)	0.89±0.58	1.08±0.54	0.81±0.52	0.68±0.45	0.64±0.43
BCVA (Log MAR)	0.18±0.21	0.37±0.23	0.19±0.20	0.15±0.18	0.13±0.17

K apex :keratometric value at apex of the cone ,K2: steepest simulated k, pachymetry: thickness at thinnest corneal location, BCVA: best corrected visual acuity, UCVA: un corrected visual acuity

The natural course in keratometric values can be shown in figures 1 and 2.





Keratometric data that collected by Scheimpflug-Placido topography across all time period (baseline, 1 month,3 months,6 months and 12 months) included K apex and K2. We noticed a statistically significant changes K apex and K2 during the whole follow up period P value 0.005, 0.001 respectively. A significant steepening in K apex and K2 at 1 month post CXL by 1.16 D and 1.06 D respectively with p value(<0.005) for both. This steepening succeeded by significant keratometric flattening between the study interval 1 to 3 months,3 to 6 months and 6 to 12 months. The mean flattening of K apex at 12 months post CXL was 1.88 D which was statistically significant reduction (p value =0.000).

While the mean flattening of K2 at 12 months post CXL was 2.11 D which was statistically significant reduction p value=0.000.

Corneal thickness outcomes:

A statistically significant thinning (P value =0.000) was found at 1 month which was followed by a meaningful corneal thickening was observed between 3 and 6 months (p=0.001)

While no statistical significant difference in pachymetry at interval between 6 to 12 months (p value=0.17).

It was noticed that pachymetry data at 1 year remained slightly decreased compared to the base line pachymetry (p value 0.000). The trend of natural pachymetry course can be seen in figure3.

Elevation points changes:

Anterior elevation point values at 1 year not changed significantly (p value =0.142) from the baseline while the posterior elevation points changed significantly (increased) with p value=0.000 .

Visual acuity outcomes:

The mean BCVA improved by (1 line) from 0.18 Log MAR at baseline to 0.13 log MAR at 12 months post CXL. Which reached a statistical significance p value =0.001. A review of BCVA time course (fig.4) showed a statistically significant worsening (2 lines decrease) at 1month (p =0.000) followed by significant improvement between study intervals 3 to 6months (p =0.000) and 6 to 12 months (p =0.013). There was an average (3.5 lines) line improvement in UCVA from 0.89 log MAR at baseline to 0.64 Log MAR at 12 months (P= 0.000) post CXL. The time course of UCVA mirrored the trend of BCVA, where a statistical significant worsening at 1month (p = 0.000) followed by improvement thereafter as figure 5 showed

.**Discussion**: Though not approved by FDA in the United States, corneal collagen-cross linking, internationally, has emerged as a frontline treatment option for KC and ectasia, particularly in those patients with documented disease progression. Corneal collagen-cross linking has been purported to enhance corneal biomechanics[13],[17] and stabilize these corneal ectatic disorders with good safety profile[14,15,18,19]

Improvement in topographic , visual , refractive and aberrometric parameters have also been reported ;notwithstanding ,continual disease progression and further loss of vision have been observed in some patient after CXL treatment.[15,16,20–22]

According to the results of the current study an average of (2.11 D),(1.88 D) flattening in K 2 and K apex respectively were found at 1year.Ourfinding support findings of other studies that also have reported K apex flattening ranging from 1.42 to 2.01 D[14,16,23] .

While monitoring the course of postoperative keratometric responses in this study, we further observed a trend of significant steepening in K2 and K apex at 1month that was succeeded by significant flattening between 1 to 3 months, 3 to 6 months and 6 to 12 months. This is in agreement with findings reported by Raiskup -Wolf et al .[16], and Caporossi et al [22]. Who described continual flattening of K values even beyond 1 year and in contrast to result reported by Chang CY et al [24] who described no further changes in k readings after 6months.

Visual acuity outcomes: Clinical studies have shown that CXL may also ameliorate VA in addition to topographic and aberrometric outcomes [16,20,22].

Changes in visual outcomes were carefully documented over time because a comprehensive understanding of postoperative time course in visual responses will greatly help physicians in setting realistic patient expectations after CXL.

The time courses of UCVA and BCVA mirrored each other; again, both followed a similar trend as other postoperative parameters discussed earlier .Worsening in VA can be observed at 1month;thereafter ,a trend of significant improvement was observed between 1 to3 months,3 to 6months and 6 to 12 months thus we found continual improvement after 1month post CXL treatment.

Corneal thickness: Progressive corneal thinning has generally been regarded as a sign of worsening in keratectatic diseases, and yet, such events have been described in many cases after CXL treatment [19,20,22,25].

Therefore understanding the natural history of corneal pachymetry after CXL can serve as foundation for proper evaluations of this procedure's efficacy and safety.

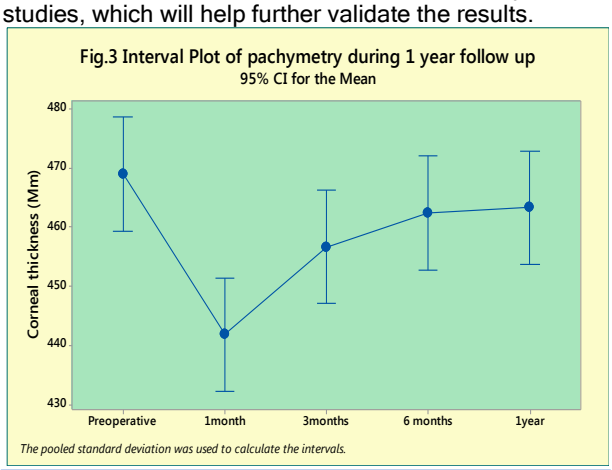
The natural course of the pachymetric changes across the 12months corresponded well with the time courses of corneal haze :significant thinning between base line and 3 months with significant improvement between 3 to 12 months ;however, pachymetric data at 1 year still remained lower than the baseline .The underlying mechanisms of corneal thickness changes in its postoperative course are yet unclear but it may be attributed to corneal de-epithilization that was performed during the operative procedure, postoperative keratocyte apoptosis and structural changes in collagen fibrils and extracellular matrix[26]. Our result similar to that conducted by Caporossi et al .[22] and Chang CY et al [24].

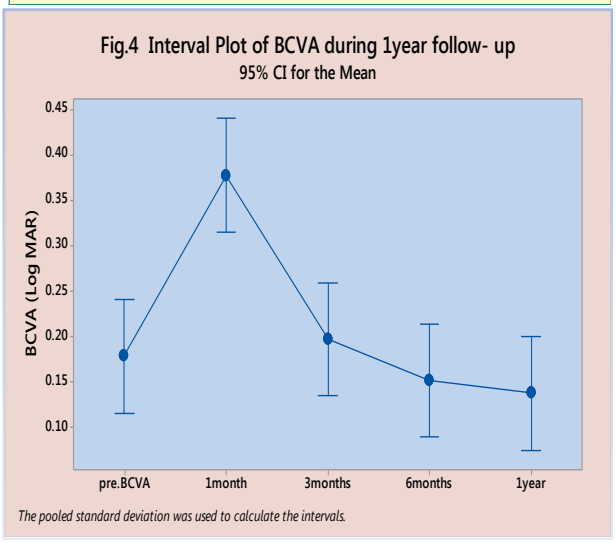
Topographic analysis of anterior elevation points values showed no significant change but the posterior elevation points values changed significantly (increased) provided that the elevation data gained by the optical devices may not be reliable after CXL procedure .The corneal haze and demarcation line present after the procedure may disturb data acquisition by the instrument as Koller et al [25,27]had shown.

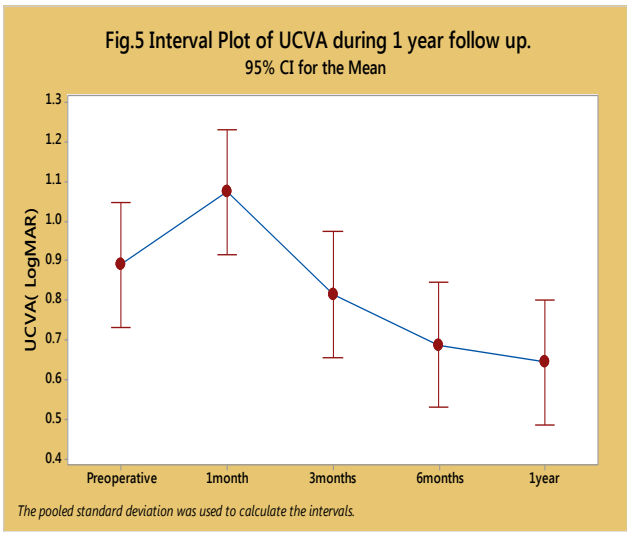
These data acquisition artifacts may also affect pachymetric measurement as well. Beside, US pachymetry in these instances, is not absolutely valid as thickness measurements are questionable in moderate and sever KC which had been shown in various studies.[25,28,29] Our results in topographic analysis of the elevation points post CXL support the results of Mirzaei M et al. [30] while Grewal et al [31]. didn't observe significant changes in anterior or posterior elevation points.

Conclusions :to conclude, from our study, we reached an understanding that CXL provides a new hope for patients with progressive KC. There is increases evidence that CXL not only halt the progression in the keratoconic eye by corneal tissue strengthening, but also improve visual outcomes.

Recommendations: CXL is the only treatment aimed to the original pathology in these patients; thus, we think that it should be performed as a standard treatment for all cases provided following the exclusion criteria mentioned before .As proved by our study visual acuity and corneal shape still didn't reach the normal standards; we thus recommended combining CXL with other procedures such as corneal ring insertion or the newly arouse topography-guided photorefractive keratectomy with CXL according to need. A longer duration of follow- up is recommended for any further studies, which will help further validate the results.







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