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# Epithelium-On Versus Epithelium-Off Corneal Collagen Cross-Linking for The Management of Keratoconus

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## ABSTRACT

**Background:** Keratoconus is a noninflammatory, bilateral, frequently asymmetrical, and most common corneal ectatic disorder characterized by central corneal thinning, biomechanical weakening, and steepening of the corneal curvatures leading to substantial distortion of vision. The estimated prevalence worldwide is 54.5 cases/100,000.

**Objective:** The aim of the work was to compare epithelium-on and epithelium-off corneal collagen cross-linking for the management of keratoconus as regards keratoconus progression and visual outcome.

**Patients and methods:** In this study, 20 eyes of 11 keratoconus patient were included. All were having keratoconus and presented with diminution of vision, increasing myopia and / or astigmatism. Cases with corneal scarring, corneal thickness less than 400 μm at the thinnest point and active corneal infections were excluded. The preoperative evaluation of patients showed UCVA, In epithelium-on (group 1) ranging from 0.05 to 0.60 with a mean 0.29 ± 0.21 and in epithelium-off (group 2) UCVA ranging from 0.05 to 0.50 with a mean 0.23 ± 0.13.

**Results:** The postoperative results revealed improvement of UCDVA and BSCVA at 6 month postoperative in both groups. The postoperative manifest refraction spherical equivalent showed stability with mild improvement in both groups. Keratometric readings showed a decrease in curvature in both groups in the follow up period. Corneal hysteresis (CH) and corneal resistance factor (CRF) showed no significant difference after 6 months of follow up.

**Conclusion:** It could be concluded that UVA/Riboflavin cross-linking of ectatic cornea by its two techniques is effective, safe, stable and do not affect corneal biomechanical characteristics, that leads in the majority of the cases to a halt the progression of ectasia.

**Keywords:** Epi-Off cross-linking, Epi-On Cross-Linking, Corneal, Keratoconus

## INTRODUCTION

Corneal ectasia is a synonym to a group of disorders characterized by an inherent state of tectonic corneal weakness and /or thinning, leading to protrusion, irregular astigmatism, leading to reduction of visual acuity, and rarely a risk of perforation [(1)].

These disorders comprise both primary conditions such as keratoconus, keratoglobus, posterior keratoconus and pellucid marginal degeneration, and secondary or iatrogenic corneal ectasia, which may occur after refractive procedures such as LASIK [(1)].

Management of keratoconus has always been a challenge. Glasses, contact lenses and intracorneal rings can correct refractive errors due to keratoconus, in advanced cases with severe corneal irregularity and stromal opacities, keratoplasty may constitute the last surgical alternative[(1)].

The primary ectatic corneal disorders are to a great extent similar in clinical presentation. keratoconus, pellucid marginal degeneration and keratoglobus may actually represent variations in the phenotypic expression of the same pathogenetic mechanism [(2)].

Keratoconus, pellucid marginal degeneration, and keratoglobus have a basic treatment algorithm. Visual correction starts with glasses, then by contact lens fitting. Failing these modalities, a surgical approach, designed to arrest the progression and/or restore a more normal corneal contour is planned [(2)].

The aim of the work was to compare epithelium-on and epithelium-off corneal collagen cross-linking for the management of keratoconus as regards keratoconus progression and visual outcome.

## SUBJECTS AND METHODS

This a prospective comparative interventional clinical trial included a total of 20 eyes of 11 keratoconic patients attending at Al-Azhar University Hospitals.

**Approval of the ethical committee and a written informed consent from all the subjects were obtained.** This study was conducted between 2018 and 2019.

All patients were presented with diminution of vision, increasing myopia and / or astigmatism. All patients underwent corneal collagen cross linking, 10 eyes for epithelium-on CXL and the others 10 eyes for eptithelium- off CXL.

**Inclusion criteria:**

1- Documented keratoconus by pentacam.
2- Amsler Krumeich classification graded stage1 to 3.
3- Best corrected distance visual acuity( BCDVA) is 6/36 or more.
4- Manifest refractive spherical equivalent is 6 D or less.



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5- Corneal thickness 400-450µm at the thinnest point.
6- Age range from 18 to 35.

**Exclusion criteria**

1- Corneal thickness <400µm at the thinnest point.
2- Past history of herpes simplex viral keratitis.
3- Severe dry eye.
4- Active corneal infections or ocular surface inflammations.
5- Corneal scarring.

**All patients were subjected to:**

1- A detailed ocular and medical history
2- Complete ophthalmic examination including:
   a. Uncorrected visual acuity (UCVA)
   b. Manifest refraction
   c. Best spectacle-corrected visual acuity (BSCVA).
   d. Slit lamp examination to exclude corneal opacity or inflammation.
   e. Fundus examination to report any posterior segment abnormalities
   f. Scheimpflug imaging with pentacam (Allegro® Oculyzer, WaveLight AG, Germany) to measure keratometric,elevation front,elevation back readings , corneal thickness at thinnest location, coma and spherical aberration.

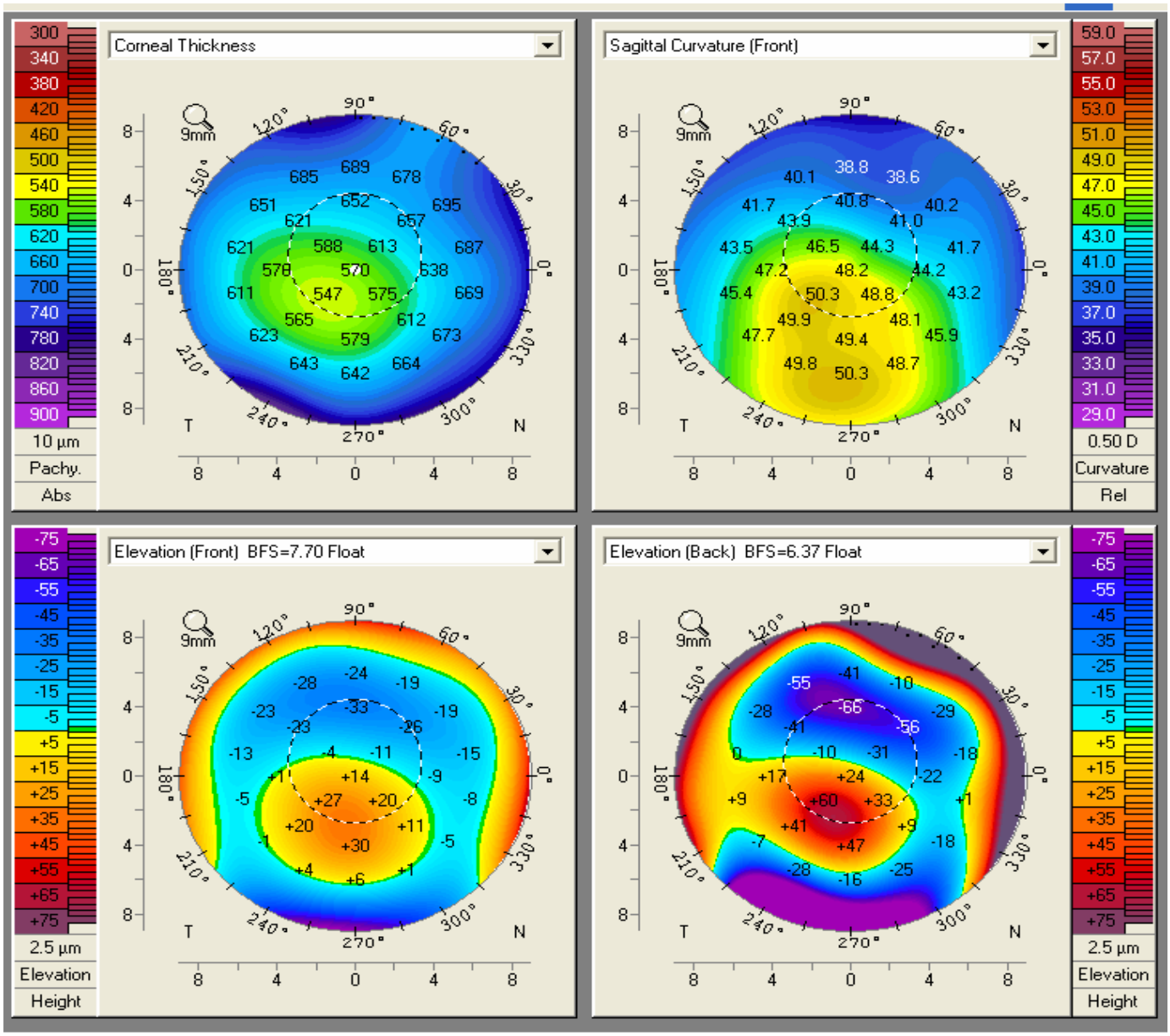


**Figure 1:** Preoperative measurement of keratometric, elevation front, elevation back readings and corneal thickness at thinnest location by Scheimpflug imaging with pentacam (Allegro® Oculyzer, WaveLight AG, Germany)

**Operative procedures**

One eye of 20 consecutive patients with keratoconus was randomly assigned to epithelium-off (Group A= 10 eyes) or epithelium-on cross-linking (Group B = 10 eyes).

For epithelium-off cross-linking, a riboflavin 0.1%, dextran20% solution (RICROLIN ® ) instilled over the cornea for 30 minutes after removal of epithelium.

For epithelium-on cross-linking, a riboflavin 0.1% , dextran 15%, EDTA 0.1%, Tris (Trishydroxymethylaminomethane) 0.05% solution (RICROLIN TE ®) instilled over the cornea for 30 minutes without removal of epithelium.

The cornea was then irradiated with UVA (18mW/cm2) for 5 minutes.

**Surgical Techniques:**

**Treatment after Epithelial Debridement:**

1- Topical anaesthesia (Benoxinate eye drops every 5 minutes for 3-5 times).
2- Sterilization of both eyes with bovidone iodine followed by draping and speculum applied to the eye to be treated
3- With an 8-mm diameter trephine blade, the central mark is placed over the epithelium.
4- Mechanical epithelial debridement of the previously marked central 8 mm of the cornea is carried out gently using an iris repositor or merocel sponge, or with an Amoils brush without disturbing the subepithelial components.
5- As a photosensitizer, RICROLIN ® was instilled onto the cornea every 5 min for 30 min before irradiation to allow sufficient saturation of the stroma.
6- The eye was examined at the slit lamp just prior to the application of the UV light to ensure that the cornea and the anterior chamber are saturated by riboflavin.
7- An 8.0-mm diameter of central cornea is irradiated with UVA light of 370 nm wavelength and an irradiance of 18 mW/cm$^2$ for 5 min.
8- At the end of the procedure, a combination of topical steroid and antibiotic drops (moxifloxacin eye drops 0.5%, prednisolone acetate 1% eye drops) were administered followed by a bandage contact lens application.

**Transepithelial Technique:**

1- The procedure was done under topical anaesthesia (Benoxinate eye drops every 5 minutes for 3-5 times).
2- Sterilization of both eyes with bovidone iodine followed by draping and speculum applied to the eye to be treated.
3- As a photosensitizer RICROLIN TE ® solution was instilled onto the cornea every 5 min for 30 min before irradiation to allow sufficient saturation of the stroma.
4- The eye was examined at the slit lamp just prior to the application of the UV light to ensure that the cornea and the anterior chamber are saturated by riboflavin.
5- An 8.0-mm diameter of central cornea is irradiated with UVA light of 370 nm wavelength and an irradiance of 18 mW/cm$^2$ for 5 min.
6- At the end of the procedure, a combination of topical steroid and antibiotic drops (moxifloxacin eye drops 0.5%, prednisolone acetate 1% eye drops) were administered followed by a bandage contact lens application.

**Post-operative treatment:**

Topical antibiotics, moxifloxacin, steroids in the form of prednisolone and artificial tears eye drops every one hour during the first day then antibiotics dose decreases to be every 4 hours for 10 days only . gradual tapering of steroid dose was carried out while use of artificial tears every 4 hours continues for about 1 month .Analgesics were prescribed ,Patient instruction to avoid eye rubbing was done in all cases. Contact lenses were removed once epithelial healing is complete (average 3$^{rd}$ day after surgery). All cases were asked to come for follow up after 1 week,1,3and 6 months .during each follow-up complete ophthalmic examination, visual acuity measurement, refraction and pentacam were made.

***Statistical analysis***

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

***The following tests were done:***

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square ($x^2$) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)

- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

**RESULTS**

This study included 20 eyes (11 keratoconus patients) divided in two groups, 10 eyes each, from both sexes who were asked to be followed up for 6 months. Only those complete 6 months follow up were included in the statistical analysis.

**Table (1):** shows **Patient's demographic data;** age, gender and the affected eye of both groups.
Group I = EPI-ON Group II = EPI-OFF

**Table (1): Comparison between the studied groups according to demographic data**

| | Group I (n=10) | | Group II (n=10) | | Test of Sig. | p |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Gender<br>**Male**<br>**Female** | <br>**6**<br>**4** | <br>**60.0**<br>**40.0** | <br>**2**<br>**8** | <br>**20.0**<br>**80.0** | **$\chi^2$=3.333** | **$^{FE}$p=0.170** |
| Age<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | <br>**19.0 – 36.0**<br>**27.0 ± 6.07**<br>**26.50** | | <br>**18.0 – 30.0**<br>**22.80 ± 4.73**<br>**20.0** | | **t=1.725** | **0.102** |
| Affected eye<br>**OD**<br>**OS** | <br>**5**<br>**5** | <br>**50.0**<br>**50.0** | <br>**5**<br>**5** | <br>**50.0**<br>**50.0** | **$\chi^2$=0.0** | **1.000** |

$\chi^2$: value for Chi square
FE: Fisher Exact test
t: Student t-test

**Visual outcome**

**1- Uncorrected visual acuity (UCVA)**

Table (2) show comparison between the preoperative and postoperative UCVA.
In Group I (EPI-ON) : Preoperative UCVA ranged from 0.05 to 0.60 with a mean 0.29 ± 0.21., at 6 month the mean change to 0.32 ± 0.20.
In Group II (EPI-OFF): Preoperative UCVA ranged from 0.05 to 0.50 with a mean 0.23 ± 0.13., at 6 month the mean change to 0.24 ± 0.13.
There is no statistically significant difference between UCVA in different periods of follow-up in the two Groups except in Group II at 1 month where is a statistically significant difference as UCVA decreased to mean 0.16 ± 0.11.

**Table (2): Comparison between the studied groups according to UCDVA**

| | **UCDVA** | | | |
|---|---|---|---|---|
| | **Before** | **1 Month** | **3 Month** | **6 Month** |
| **Group I**<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | <br>**0.05 – 0.60**<br>**0.29 ± 0.21**<br>**0.25** | <br>**0.05 – 0.60**<br>**0.28 ± 0.20**<br>**0.25** | <br>**0.05 – 0.60**<br>**0.32 ± 0.20**<br>**0.30** | <br>**0.05 – 0.60**<br>**0.32 ± 0.20**<br>**0.30** |
| **P** | | **0.317** | **0.083** | **0.083** |
| **Group II**<br>**Min. – Max.**<br>**Mean ± SD.**<br>**edian** | <br>**0.05 – 0.50**<br>**0.23 ± 0.13**<br>**0.20** | <br>**0.04 – 0.40**<br>**0.16 ± 0.11**<br>**0.15** | <br>**0.04 – 0.50**<br>**0.24 ± 0.14**<br>**0.25** | <br>**0.05 – 0.50**<br>**0.24 ± 0.13**<br>**0.25** |
| **P** | | **0.005*** | **1.000** | **0.317** |
| Z (p) | 0.504 (0.614) | 1.502 (0.133) | 1.044 (0.297) | 0.892 (0.372) |

Z: Z for Mann Whitney test for comparing between group I and II
p: p value for Wilcoxon signed ranks test for comparing between before with each other stages
*: Statistically significant at $p \leq 0.05$

**2- Best spectacle corrected visual acuity (BSCVA)**

Table (3) shows that in Group I (EPI-ON): Preoperative BCVA ranged from 0.60 to 0.90 with a mean 0.74 ± 0.11., at 6 month the mean change to 0.79 ± 0.12.
In Group II (EPI-OFF): Preoperative BCVA ranged from 0.30 to 0.90 with a mean 0.63 ± 0.19., at 6 month the mean change to 0.70 ± 0.26.
There was no statistically significant difference between the two groups.

**Table (3): Comparison between the studied groups according to BCDVA**

| | BCDVA | | | |
|---|---|---|---|---|
| | **Before** | **1 Month** | **3 Month** | **6 Month** |
| **Group I** | | | | |
| **Min. – Max.** | **0.60 – 0.90** | **0.60 – 0.90** | **0.60 – 0.90** | **0.60 – 0.90** |
| **Mean ± SD.** | **0.74 ± 0.11** | **0.74 ± 0.11** | **0.79 ± 0.12** | **0.79 ± 0.12** |
| **Median** | **0.80** | **0.80** | **0.80** | **0.80** |
| **P** | | **1.000** | **0.313** | **0.251** |
| **Group II** | | | | |
| **Min. – Max.** | **0.30 – 0.90** | **0.20 – 0.90** | **0.30 – 1.0** | **0.30 – 1.0** |
| **Mean ± SD.** | **0.63 ± 0.19** | **0.57 ± 0.24** | **0.67 ± 0.27** | **0.70 ± 0.26** |
| **Median** | **0.70** | **0.60** | **0.80** | **0.80** |
| **P** | | **0.843** | **0.963** | **0.397** |
| **t (p)** | **1.564 (0.140)** | **2.040 (0.063)** | **1.281 (0.224)** | **1.397 (0.179)** |

t: Student t-test for comparing between group I and II

p: Stands for adjusted Bonferroni p-value for ANOVA with repeated measures for comparing between before with each other stages

*: Statistically significant at $p \leq 0.05$

**Keratoconus index (K I)**

Table (4) shows that using pentacam, KI was measured before, 1, 3 & 6 month after the operation in the 2 groups as demonstrated in table 12.

In Group I (EPI-ON) : Preoperative KI ranged from 1.05 to 1.36 with a mean 1.14 ± 0.09, there was no statistically significant difference at 1,3 and 6 month as the mean of KI was 1.14 ± 0.09, 1.13 ±0.09, 1.14 ± 0.10 at 1,3 & 6 month.

In Group II (EPI-OFF): Preoperative KI ranged from 1.04 to 1.24 with a mean 1.15 ± 0.07, there was no statistically significant difference at 1, 3 & 6 month as the mean of KI was 1.16 ± 0.08, 1.16 ± 0.08, 1.15 ± 0.09 at 1,3 &6 month. There was no statistically significant difference between the two groups at 1, 3 & 6 month of follow up.

**Table (4): Comparison between the studied groups according to KI**

| | KI | | | |
|---|---|---|---|---|
| | Before | 1 Month | 3 Month | 6 Month |
| Group I | | | | |
| **Min. – Max.** | **1.05 – 1.36** | **1.05 – 1.35** | **1.04 – 1.35** | **1.04 – 1.35** |
| **Mean ± SD.** | **1.14 ± 0.09** | **1.14 ± 0.09** | **1.13 ± 0.09** | **1.14 ± 0.10** |
| **Median** | **1.13** | **1.12** | **1.12** | **1.12** |
| p | | **1.000** | **1.000** | **1.000** |
| Group II | | | | |
| **Min. – Max.** | **1.04 – 1.24** | **1.04 – 1.28** | **1.05 – 1.29** | **1.04 – 1.30** |
| **Mean ± SD.** | **1.15 ± 0.07** | **1.16 ± 0.08** | **1.16 ± 0.08** | **1.15 ± 0.09** |
| **Median** | **1.16** | **1.17** | **1.18** | **1.18** |
| p | | **0.951** | **0.921** | **0.978** |
| t (p) | **0.242 (0.811)** | **0.550 (0.589)** | **0.592 (0.561)** | **0.457 (0.653)** |

t: Student t-test for comparing between group I and II

p: Stands for adjusted Bonferroni p-value for ANOVA with repeated measures for comparing between before with each other stages

*: Statistically significant at $p \leq 0.05$

**Central keratoconus index (CKI)**

Table (5) shows that using pentacam, CKI was measured before, 1, 3 & 6 month after the operation in the 2 groups as demonstrated in table 13.

In Group I (EPI-ON) : Preoperative CKI ranged from 0.98 to 1.15 with a mean 1.03 ± 0.05, there was no statistically significant difference at 1,3 and 6 month as the mean of CKI was 1.04 ± 0.06, 1.05 ±0.09, 1.04 ± 0.07 at 1,3 & 6 month.

In Group II (EPI-OFF): Preoperative CKI ranged from 1.00 to 1.08 with a mean 1.03 ± 0.03,there was statistically significant difference at 1 & 3 & 6 month as the mean of CKI was 1.04 ± 0.03, 1.04 ± 0.03, 1.04 ± 0.03at 1,3 &6 month.
There was no statistically significant difference between the two groups at 1, 3 & 6 month of follow up.

**Table (5): Comparison between the studied groups according to CKI**

| | CKI | | | |
|---|---|---|---|---|
| | Before | 1 Month | 3 Month | 6 Month |
| Group I<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **0.98 – 1.15**<br>**1.03 ± 0.05**<br>**1.03** | **0.97 – 1.20**<br>**1.04 ± 0.06**<br>**1.03** | **0.98 – 1.31**<br>**1.05 ± 0.09**<br>**1.03** | **0.98 – 1.24**<br>**1.04 ± 0.07**<br>**1.03** |
| p | | **0.414** | **0.180** | **0.317** |
| Group II<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **1.0 – 1.08**<br>**1.03 ± 0.03**<br>**1.02** | **1.01 – 1.09**<br>**1.04 ± 0.03**<br>**1.04** | **1.0 – 1.09**<br>**1.04 ± 0.03**<br>**1.03** | **1.0 – 1.10**<br>**1.04 ± 0.03**<br>**1.03** |
| p | | **0.026*** | **0.011*** | **0.036*** |
| Z (p) | **0.344 (0.731)** | **0.383 (0.702)** | **0.038 (0.969)** | **0.076 (0.939)** |

Z: Z for Mann Whitney test for comparing between group I and II
p: p value for Wilcoxon signed ranks test for comparing between before with each other stages
*: Statistically significant at $p \leq 0.05$

**Spherical aberration**
Table (6) shows that using pentacam, Spherical aberration was measured before, 1, 3 & 6 month after the operation in the 2 groups as demonstrated in table 15.
In Group I (EPI-ON) : Preoperative Spherical aberration ranged from 0.48 to 2.25 with a mean 1.28 ± 0.66, there was no statistically significant difference at 1,3 and 6 month as the mean of Spherical aberration was 1.25 ± 0.63, 1.25 ±0.62, 1.26± 0.66 at 1,3 & 6 month.
In Group II (EPI-OFF): Preoperative Spherical aberration ranged from 0.52 to 2.17 with a mean 1.20 ± 0.61, there was no statistically significant difference at 1, 3 & 6 month as the mean of Spherical aberration was 1.13 ± 0.68, 1.18 ± 0.64, 1.19 ± 0.62 at 1,3 & 6 month.

There was no statistically significant difference between the two groups at 1, 3 & 6 month of follow up.

**Table (6): Comparison between the studied groups according to spherical aberration**

| | Spherical Aberration | | | |
|---|---|---|---|---|
| | Before | 1 Month | 3 Month | 6 Month |
| Group I<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **0.48 – 2.25**<br>**1.28 ± 0.66**<br>**1.27** | **0.52 – 2.22**<br>**1.25 ± 0.63**<br>**1.21** | **0.55 – 2.23**<br>**1.25 ± 0.62**<br>**1.18** | **0.56 – 2.36**<br>**1.26 ± 0.66**<br>**1.15** |
| p | | **0.092** | **0.202** | **0.799** |
| Group II<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **0.52 – 2.17**<br>**1.20 ± 0.61**<br>**0.93** | **0.22 – 2.19**<br>**1.13 ± 0.68**<br>**1.03** | **0.28 – 2.28**<br>**1.18 ± 0.64**<br>**1.08** | **0.48 – 2.35**<br>**1.19 ± 0.62**<br>**0.98** |
| p | | **0.475** | **0.767** | **0.878** |
| Z (p) | **0.076 (0.940)** | **0.529 (0.597)** | **0.151 (0.880)** | **0.302 (0.762)** |

Z: Z for Mann Whitney test for comparing between group I and II
p: p value for Wilcoxon signed ranks test for comparing between before with each other stages
*: Statistically significant at $p \leq 0.05$

**Corneal biomechanics**

Table (7) shows that using ocular response analyzer (ORA) corneal hysteresis (CH) and corneal resistance factor (CRF) were measured before and 6 months after the operation in the 2 groups as demonstrated in table (16) and (17)

In Group I (EPI-ON) : Preoperative corneal hysteresis ranged from 6.96-9.2 with a mean 8.18±.88, there was no statistically significant difference at 6 month as the mean of corneal hysteresis was 8.2±.88 at 6 month.

In Group II (EPI-OFF): Preoperative corneal hysteresis ranged from 6.62-9.12 with a mean 7.96±.99, there was no statistically significant difference at 6 month as the mean of corneal hysteresis was 7.97±.99 at 6 month.

There was no statistically significant difference between the two groups at 6 month of follow up.

**Table (7): comparison between the studied groups according to the corneal hysteresis**

| | Corneal hysteresis | |
|---|---|---|
| | Before | 6 Month |
| Group I<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **6.96-9.2**<br>**8.18±.88**<br>**8.31** | **6.98-9.22**<br>**8.2±.88**<br>**8.33** |
| p | | **0.063** |
| Group II<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **6.62-9.12**<br>**7.96±.99**<br>**8.02** | **6.6-9.11**<br>**7.97±.99**<br>**8.03** |
| p | | **0.063** |
| Z (p) | **0.076 (0.940)** | **0.529 (0.597)** |

Table (8) shows that using In Group I (EPI-ON) : Preoperative corneal resistance factor ranged from 5.78-8.21with a mean 7.16±.94, there was no statistically significant difference at 6 month as the mean of corneal resistance factor was 7.16±.95 at 6 month.

In Group II (EPI-OFF): Preoperative corneal hysteresis ranged from 4.95-8.3 with a mean 7.03±1.15, there was no statistically significant difference at 6 month as the mean of corneal resistance factor was 6.75±1.18 at 6 month.

**Table (8): Comparison between the studied groups according to the corneal resistance factor**

| | Corneal resistance factor | |
|---|---|---|
| | Before | 6 Month |
| Group I<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **5.78-8.21**<br>**7.16±.94**<br>**7.38** | **5.76-8.23**<br>**7.16±.95**<br>**8.33** |
| p | | **0.3** |
| Group II<br>**Min. – Max.**<br>**Mean ± SD.**<br>**Median** | **4.95-8.3**<br>**7.03±1.15**<br>**7.3** | **4.96-8.25**<br>**6.75±1.18**<br>**6.87** |
| p | | **0.072** |
| | | |

**DISCUSSION**

In this study, 20 eyes of 11 keratoconus patient were included. All patients underwent corneal collagen cross linking, 10 eyes for epithelium-on CXL and the others 10 eyes for eptithelium- off CXL. All patients had mild to moderate keratoconus with clear central cornea. Cases of post Lasik ectasia were not included in this study.

In this study the results of UCVA, BSCVA, MRSEQ and K max showed that:

Comparison of UCVA at different periods in the two studied groups demonstrated that: In Group I (EPI-ON): Preoperative UCVA ranged between 0.05 – 0.60 with a mean 0.29 ± 0.21. Improved after 6 month to mean 0.32 ± 0.20, In Group II (EPI-OFF): Preoperative UCVA ranged between 0.05 – 0.50 with a mean 0.23 ± 0.13. improved after 6 month to mean 0.24 ± 0.13, there were no statistically significant differences between UCVA in different periods of follow-up in the two Groups except in Group II after 1 month there was a statistically significant difference with p value <0.05 as UCVA decreased to mean 0.16 ± 0.11.

Comparison of BSCVA at different periods in the both groups demonstrated that, In Group I (EPI-ON): Preoperative BSCVA ranged between 0.60 – 0.90 with a mean 0.74 ± 0.11. Improved after 6 month to mean 0.79 ± 0.12., In Group II (EPI-OFF): Preoperative BCVA ranged between 0.3 – 0.9 with a mean 0.63 ± 0.19. Improved after 6 month to mean 0.70 ± 0.26, there were no statistically significant differences in BSCVA between the two groups in the different periods of follow up.

Regarding manifest refraction spherical equivalent (MRSEQ) demonstrated that, In Group I (EPI-ON): Preoperative SEQ ranged between -6 – -

1.25 with a mean -3.13 ± 1.82. Improved after 6 month to mean -2.98 ± 1.87. In Group II (EPI-OFF): Preoperative SEQ ranged between -9.5 – -2.25 with a mean -4.28 ± 2.43. Improved after 6 month to mean -3.98 ± 2.39, there were improvement of MRSEQ of all patients has been noticed in the two groups at all periods of follow up but, there were no statistically significant differences in BSCVA between the two groups in the different periods of follow up.

As regards K max in the two studied groups demonstrated that, In Group I (EPI-ON): Preoperative Kmax ranged between 45.5 – 58.5 D with a mean 50.85 ± 5.36 improved slightly after 6 month to mean 50.75 ± 4.99.

In Group II (EPI-OFF): Preoperative Kmax ranged between 45.80 – 57.20 D with a mean 51.61 ± 4.21 improved after 6 month to mean 50.81 ± 4.72, there were no statistically significant differences at different periods of follow-up and between the two groups.

These results demonstrate that the spherical equivalent error were reduced in all cases. The UCVA were better than preoperatively at all period of follow up except at

1 month in group 2 (EPI-OFF technique) there is significant decrease of vision. The BSCVA had an improvement of 1 or 2 lines after 6 months of follow up in the two groups. No eye lost BSCVA lines. The k max decreased approximately by 1 D, Patient satisfaction was encountered in all patients

Other similar studies confirm the results of ours, these studies are the following:

**Studies show the effect of EPI-OFF CXL in halting progression of keratoconus and improving vision:**

The first in vivo controlled clinical study by **Wollensak *et al,*** which included 23 eyes of 22 patients with moderate or advanced progressive keratoconus, showed an arrest of progression of keratoconus in all treated eyes, A reduction in maximal keratometry (K) readings of 2.01 D and of the refractive error of 1.14 D over a mean follow-up period of 23 months was found in 70% of cases, with slight visual acuity improvement in 65% of cases [(3)].

**Caporossi *et al.*** reported the long term results of an open case series of 44 keratoconic eyes treated with CXL. Keratoconus was stabilized in 44 treated eyes after 48 months while 65% of the untreated fellow eyes showed a progression of 1.5 diopers at 24 months, prior to cross-over treatment. In the treatment group, mean best corrected visual acuity improved by 1.9 Snellen lines, and uncorrected visual acuity improved by 2.7 Snellen lines [(4)].

**Agrawal** found similar results in 37 eyes of Indian subjects 1 year after treatment. Agrawal reported that 54% of the eyes gained at least one line of BCVA, astigmatism decreased by a mean of 1.2 D in 47% of the eyes, the keratometry value at the apex decreased by a mean of 2.73 D in 66% of the eyes and the maximum K value decreased by a mean of 2.47 D in 54% of the eyes [(5)].

A study by **Jankov *et al.*** found that progression of keratoconus stopped in all patients who were actively progressing 6 months prior to treatment.After treatment, no eyes lost lines of best spectacle-corrected visual acuity (BSCVA), 12 maintained BSCVA, one gained one line of BSCVA, five gained two lines of BSCVA and one patient gained three lines of BSCVA [(6)].

**Studies to compare the effect of transepithelial CXL and epithelial-off CXL on keratoconic eyes show similar results support the efficacy of transepithelial CXL:**

A Prospective study by **Antonio and Islam** [(7)] on 51 keratoconic eyes. The eye with more severe keratoconus was treated; the fellow eye served as the control. To evaluate the clinical effects of transepithelialcorneal cross-linking (CXL) on Keratoconic eyes pre-treated with substances enhancing epithelial permeability showed that: Mean corrected distance visual acuity improved by 0.036 logMAR after CXL and worsened by 0.039 logMAR in the control eyes (*P*_.05). Safety index was 1.05 after CXL and 0.96 in the control group.Mean spherical equivalent refraction decreased by 0.35 D (less myopic) after CXL and increased by 0.83 diopters (D) in the control eyes (*P*_.05). Mean apex curvature on tangential videokeratography increased by 0.51 D after CXL and by 1.61 D in the control eyes (*P*=.16). Mean average simulated keratometry decreased by 0.10 D after CXL and increased by 0.88 D in the control eyes (*P*_.05). Mean index of surface variance increased (worsened) by 0.9 after CXL and 5.3 in the control eyes (*P*_.05). Conclusions: A limited but favorable effect of transepithelial CXL was noted on keratoconic eyes, without complications [(7)].

While good results have been reported with transepithelial CXL for the treatment of keratoconus [(8)], other clinical & laboratory studies have reported weaker effect of transepithelial CXL [(9)].

In this study, as regard pachymetry values at thinnest location at the different periods in the studied groups using pentacam showed that marked decrease of thickness noticed in group II (EPI-OFF) at 1&3 month which gain thickness again at 6 month. There were statistically significant differences between the two groups at 1 & 3 month but not at 6 month as marked decrease of thickness noticed in group II at 1&3 month.

In Group I (EPI-ON): Preoperative pachymetry ranged from 414.0 to 446.0 with a mean 435.7±9.45, there was statistically significant difference at 1 month and 3 month as the mean of thickness was 429.9±9.21, 430.4±8.99, 430.9±10.59 at 1,3 & 6 month., In Group II (EPI-OFF): Preoperative pachymetry ranged from

431.0 to 530.0 with a mean 478.50 ± 28.10, there was statistically significant difference at 1, 3 & 6 month as the mean of thickness was 431.30 ± 25.31, 454.70 ± 30.87, 466.10 ± 27.58 at 1,3 &6 month.

Regarding Elevation front at BFS, 8 mm diameter Using pentacam, there were no statistically significant difference between the two groups at 1, 3 & 6 month of follow up.

Regarding Elevation back at BFS, 8 mm diameter Using pentacam, there were no statistically significant differences between the two groups at 1, 3 & 6 month of follow up.

Regarding keratoconus index( KI) and central keratoconus index (CKI) using pentacam, there were no statistically significant differences between the two groups at 1, 3 & 6 month of follow up.

Regarding corneal high order aberrations (coma & spherical equivalent) using pentacam, there were no statistically significant differences between the two groups at 1, 3 & 6 month of follow up.

A study by **Ziad and Laszlo** on thirty-one eyes of 31 keratoconus patients treated with XCL, found that the anterior and posterior corneal surfaces show no significant deviations in respect to corneal HOA, LOA or elevation data obtained between the 3.0-6.0 mm corneal zones compared to preoperative values in a follow up period of 7 months and CCT also showed no difference at the end of the postoperative period Consequently, cross-linking treatment can stabilize not only refraction value, but also anterior and posterior corneas including corneal HOA **[10].**

Regarding the effect on biomechanical properties of the cornea we compared between corneal hysteresis (CH) and corneal resistance factor (CRF) using ORA, which showed no statically significance difference after the operation in the two groups same results were found by **Hallahan KM *et al.*[11] and Greenstein *et al.* [12] .**

## CONCLUSIONS

In conclusion, corneal collagen crosslinking using epi-on or epi-off technique seems to be easy procedure, effective treatment with good visual and refractive outcomes. However epi-on technique is less invasive, less painful and with less risk of infection in comparable to epi-off technique. Future larger comparative studies of both techniques are needed.

- UVA/Riboflavin cross-linking of ectatic cornea is effective, safe and stable modality that can halt the progression of ectasia.
- Transepithelium corneal collagen cross-linking is as effective as the traditional epithelium- off method of cross-linking, but long term studies are required to ensure stability.
- Transepithelium corneal collagen cross-linking preserves corneal thickness in comparison with traditional epithelium- off method of cross-linking.
- The transepithelium method causes no pain and has a lower risk of infection as the epithelium is intact.

## RECOMMENDATIONS

- Further long-term studies are recommended in the future to confirm the stability and efficacy of transepithelium CXL.
- Transepithelium corneal collagen cross-linking can be preserved mainly for pediatric patients and patients having a corneal thickness less than 400 um.

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