Original Article

# Corneal Cross-Linking for Keratoconus at Tripoli University Hospital, Libya

## عملية تثبيت القرنية في حالات القرنية المخروطية في مشفى طرابلس الجامعي في ليبيا

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## Abstract

**Objective:** Keratoconus is a progressive, noninflammatory corneal disorder where the normally spherical corneal structure progressively assumes a cone shape, thereby distorting vision and decreasing the quality of life from a young age. Cross-linking remains the only procedure for keratoconus that can be used to halt the progression of the disease. The aim of this study was to evaluate the outcome of corneal cross-linking in Tripoli University Hospital, Libya in patients between the ages of 13 and 35 years. **Methods:** A retrospective study on patients from the Tripoli University Hospital records the cross-linking procedures performed for keratoconus conducted between February 2017 and October 2019. Population size of 49 patients (54 eyes) was selected from patients attending cornea clinic at Tripoli University Hospital between February 2017 and October 2019. **Results:** A total of 54 eyes from 49 patients were analyzed from the records, 2 eyes progressed postcross-linking on both K-max and pachymetry values. Twelve eyes showed an increase in K-max readings only and 16 showed progression on pachymetry only. **Conclusions:** The study showed that cross-linking for keratoconus is an effective method of treating progressive keratoconus but seems less effective than comparative studies done in other places elsewhere.

**هدف البحث:** تعتبر القرنية المخروطية اضطراباً مترقياً غير التهابي في القرنية تتحول فيه بنية القرنية الكروية في الأصل إلى شكل مخروطي، الأمر الذي يؤدي إلى خلل في الرؤية وتراجع في جودة الحياة لدى المرضى بعمرٍ مبكر. يعتبر تثبيت القرنية هو الإجراء الوحيد في تدبير القرنية المخروطية الذي يمكن استخدامه لوقف تقدم المرض. تهدف هذه إلى تقييم نتائج عمليات تثبيت القرنية في مستشفى طرابلس الجامعي لدى المرضى بأعمار بين 13 و35 سنة. **طرق البحث:** تم إجراء دراسة راجعة على السجلات الطبية لمرضى عمليات تثبيت القرنية في حالات القرنية المخروطية خلال الفترة بين شهري شباط 2017 وتشرين الأول 2019، حيث بلغ حجم العينة المدروسة 49 مريضاً (54 عيناً) تم اختيارهم من المرضى المراجعين لعيادة القرنية في مشفى طرابلس الجامعي. **النتائج:** شملت الدراسة حالة 54 عيناً لدى 49 مريضاً تم عزلها من السجلات الطبية للمرضى. حدث تطور على قيم K-max وpachymetry بعد إجراء عملية تثبيت القرنية في عينين فقط، بينما أظهرت 12 عيناً زيادة في قراءات K-max فقط، كما أظهرت 16 عيناً حدوث ترقٍ من خلال قياس pachymetry. **الاستنتاجات:** أظهرت هذه الدراسة أن عملية تثبيت القرنية المخروطية هي عملية آمنة وفعالة في علاج حالات القرنية المخروطية، لكنها فعاليتها الملاحظة في هذه الدراسة أقل من تلك التي أوردتها دراسات مقارنة أخرى أجريت في أماكن أخرى من العالم.

**الكلمات المفتاحية:** عملية تثبيت القرنية Cross-linking، القرنية المخروطية، pachymetry، ectasia، riboflavin.

**Keywords:** Cross-linking, ectasia, keratoconus, pachymetry, riboflavin

## Introduction

The cornea is the transparent anterior portion of the fibrous coat of the eye.[1] In humans, the cornea averages 0.52 mm in thickness at the center and is about 0.65 mm thick at the periphery.[2–4] The human cornea traditionally consists of five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium.[2–4] The newly discovered Dua's layer will not be discussed. The stroma makes up approximately 90% of the thickness of the cornea and is the major structural component. The cornea's strength, shape, and transparency can be attributed to the anatomic and metabolic properties of the stroma.[2,3] The stroma consists of

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collagen, glycosaminoglycans, keratocytes, and nerves. Two to three percent of the stroma consists of cellular components (keratocytes). Collagen makes up approximately 70% of the dry weight of the cornea. Type I collagen makes up the majority of the collagen in the stroma with types III, IV, and VI also being present.[3]

Keratoconus is a well-known ecstatic condition of the cornea. *Cline et al*.[5] defined keratoconus as, "a developmental or dystrophic deformity of the cornea in which it becomes cone-shaped due to a thinning and stretching of the tissue in its central area". It is the most common corneal dystrophy affecting one in 2000 people. It is an ecstatic corneal disorder characterized by a progressive corneal thinning that causes irregular astigmatism and decreasing visual acuity.[3] It is often associated with allergic conjunctivitis and seems to also have a degree of familial inheritance. It usually manifests itself during puberty, is usually bilateral, and is more common in women than men.

A clinical description of keratoconus might include the following, a non-inflammatory, bilateral, asymmetric progressive ectasia of the cornea associated with thinning, protrusion, and distortion of the cornea.[6–8] Clinical signs of keratoconus include Vogt's striae, Fleischer's ring, corneal thinning, corneal scarring, increased visibility of corneal nerves, characteristic topographical changes, protrusion and rupture/folding in the area of Descemet's membrane.[7–9]

Keratoconus has a prevalence of between 50 and 230 people per 100 000 of the population depending on the criteria used to diagnose the condition.[10]

Keratoconus is an ectatic, noninflammatory corneal disorder characterized by progressive corneal thinning that causes irregular astigmatism and decreasing visual acuity. It is often associated with allergic conjunctivitis and seems to also have a degree of familial inheritance. Onset is during the first decade and it progresses until the third decade of life when it often stabilizes. Amongst the corneal ectatic diseases, it remains the most common cause of debilitating progressive visual impairment in the childhood and young adult phases of life.

Individuals with keratoconus form a significant proportion of patients for an eye practitioner managing corneal diseases. Yet, it is a disease where the pathogenesis is poorly understood and until recently there has been no treatment (apart from corneal transplantation) that could be offered that was curative or even capable of slowing down the progression of the disease.[11] Collagen cross-linking treatment using riboflavin and ultraviolet (UV) light was developed in an attempt to address this need and the initial results were promising.[12] Different ways of cross-linking assessment were experimentally compared regarding safety and efficacy. The most promising comprised of UVA (370 nm) and riboflavin as a photomediator and was tested in pilot studies on human eyes with progressive keratoconus. Stromal keratocytes were killed up to 320 μ deep in the stroma but the delicate endothelium appeared unaffected.

In 2003, the first results of these pilot studies were published.[12] Surprisingly, not only a halt in progression was found, but in more than half of the eyes treated, regression toward a more regular-shaped cornea occurred. So far, very few complications have been reported. Progression of 2D or more keratometry value (corneal steepening), the need for a new contact lens fit, or "if a patient reports of decreasing visual acuity" were used in following and monitoring keratoconus progression in the German study by Carus.[13]

The sustained effect of cross-linking as a treatment of keratoconus was proven later in the Siena Eye Cross Study[14] and again in the Australian study of keratoconus[15] using the three parameters: K-values, visual acuities, and pachymetry.

The aim of this study was to evaluate the outcomes of corneal cross-linking in a public tertiary hospital, that is, at Tripoli University Hospital, Tripoli, Libya.

The objectives of this study include:

(1) To study the preprocedural values of K-readings and pachymetry.
(2) To look and compare the postprocedural values of the same parameters at two consecutive values after the procedure.
(3) To prove that the corneal cross-linking procedure is an effective method of treatment in patients with progressive keratoconus.

## Materials and Methods

This study is a descriptive, quantitative chart review project. Charts from all patients with keratoconus, treated once with corneal cross-linking were reviewed from the time of the procedure up to 2 years after the procedure. The patients were taken from recorded data from the Tripoli University Hospital. Each eye was treated as an "individual" and was given a unique study number. Preoperative readings were compared with visits taking place within 180 days (early) of the procedure and visits taking place 180 days after the procedure (late). The reasons for dividing the visits into early and late groups are as follows:

(1) Visits for the different patients did not occur at regular intervals. Some patients complete three visits within the first 6 months then default further follow-up, while others might only come late due to transport and other reasons.
(2) The researchers wanted to see the difference between pretreatment and end-results, but also whether further changes occur in this population later than 6 months after the treatment.

The inclusion criteria included keratoconic eyes that had received a corneal cross-linking procedure at Tripoli University Hospital, between February 2017 and October 2019.

The sample consisted of both males and females between the ages of 13 and 35 years. The following patients were excluded:

(1) Patients who had less than three follow-ups since the procedure, irrespective of the time after treatment.
(2) Cross-linking done in patients for any other indication other than for keratoconus.
(3) Ocular or central nervous system disease other than keratoconus which prevents good vision.

The study looked at the corneal steepness, keratometry, K-values (D), and pachymetry (μm) as primary outcome indices to determine whether corneal cross-linking improves corneal stability in the profile of patients.

(1) A pachymetric failure-of-treatment is defined as a loss of at least 25 μm in thickness from baseline thinnest area of the cornea.
(2) A keratometric failure-of-treatment is defined as a gain of at least 2 diopters steepening in the K-maximum.

## Measurements

**K-values:** Steepest, flattest, and average curvature of the cornea measures in mm radius by TMS-5 from Tomey Company (the smaller the value the steeper the cornea). Pachymetry (corneal thickness) measured as thinnest point by the Pentacam and/or anterior segment Optical Coherence Tomography (OCT) (in microns).

The researchers used the Liu method to determine optimal cut-points. When looking at the data for prediction, the researchers were searching for variables before the corneal cross-linking procedure that could predict treatment failure. The age was tested, pretreatment keratometry, and pretreatment pachymetry readings using logistic regression. The analysis aimed to predict combination (pachymetry + keratometry) as well as failure-of-treatment of the individual indices (pachymetry fail or keratometry fail, separately).

Permission to conduct the study was granted by Tripoli University Hospital. Signed consent was taken from all patients.

## Results

Fifty-four eyes of 49 patients were found to fulfill the criteria for entrance into the study [Figure 1].

Follow-up times in the study cohort were not regular; therefore, all follow-up visits were divided into one of the two time frames: <180 days (early) and >180 days (late). This also allowed us to get an idea of whether stabilization of the cornea keeps increasing >6 months after the treatment.

The average age in the "early group" of visits was 22.3 years with a standard deviation (SD) of 4.94 years presurgery, the average keratometry was 57.1 D (SD = 3.89 D), and average corneal thickness was 425.94 μm, with an average follow-up of 114.19 days. The average postsurgery keratometry was 56.93 diopter and the pachymetry was 415.06 μm. The Wilcoxon signed-rank test shows that there is no difference between these two groups for diopters ($P = 0.582$) or pachy ($P = 0.4367$) values pre and postprocedure. Only five eyes out of 42 showed worsening of diopter values and four out of 36 showed further thinning based on pachymetric values. Of the above eyes that worsened, only one eye failed to stabilize on both indices [Tables 1 and 2].

The "late group" had an average age of 21 years at first visit (SD = 4.95 years). Average baseline keratometry was 56.78 D (SD = 5.8 D), and pachymetry was 425 μm. The changes in

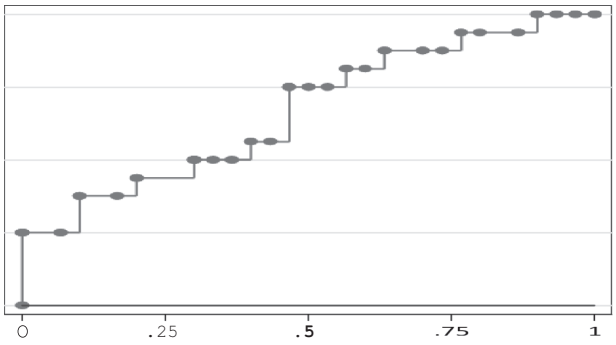


**Figure 1:** ROC prediction curves displaying the predictive effect of baseline pachymetry on treatment failure.

**Table 1: Summary of population in the group with early follow-up**

| Variables | Obs. | Mean | Std. dev. | Minimum | Maximum |
|---|---|---|---|---|---|
| Age | 42 | 22.1 years | 5.53733 | 13 years | 39 years |
| Pre-km | 42 | 50.16 diopter | 3.890907 | 43.3 diopter | 58.9 diopter |
| Prepacky | 42 | 428.7 μm | 45.59622 | 304 μm | 523 μm |
| Follow-up period | 42 | 121.4 days | 39.70136 | 31 days | 185 days |
| Post-km | 42 | 50.94 diopter | 5.035051 | 43.2 diopter | 70.95 diopter |
| Postpacky | 42 | 415.07 μm | 50.40538 | 297 μm | 498 μm |
| K-change | 42 | 0.7850002 | 2.925887 | −5.10 D | 12.05 D |
| Pack-change | 42 | −13.69 μm | 46.23349 | −160 μm | 82 μm |

Km, kilometer.

**Table 2: Summary of population in the group with >180 days follow-up**

| Variables | Obs. | Mean | Std. dev. | Minimum | Maximum |
|---|---|---|---|---|---|
| Age | 41 | 21.31 years | 4.951964 | 13 years | 29 years |
| Pachy base | 41 | 425 μm | 42.57229 | 327 μm | 543 μm |
| km base | 41 | 56.77 D | 9.022625 | 44.6 D | 81.4 D |
| Pachy-change | 41 | 11.73 μm | 36.00766 | −62 μm | 109 μm |
| K-change | 41 | −0.37 D*J* | 3.4 D*J* | −8.2 D* | 9.4 D* |

**Table 3: Of combined failure (K reading and pachy)**

| | Freq. | Percent (%) | Cum |
|---|---|---|---|
| 0 | 23 | 56.10 | 56.1 I |
| 1 | 18 | 43.90 | 100.0 f |
| Total | 41 | 100.00 | |

pachymetry and keratometry postprocedure was 11.73 qm and the diopter change was −0.373, both the changes are not significant (pachy: $P = 0.0551$; and keratometry: $P = 0.3747$).

### Failure rates

An analysis of the failure rate of treatment in the long-term group revealed that looking at the overall failures of this group it was observed that when it comes to keratometry there were seven eyes out of 41 that failed and 12 out of 41 eyes continued to progress on pachymetry, only one eye failed in both.

### Combination failure

Results using age, pretreatment diopter, and pretreatment pachymetry readings gave no variables to use as predictors for combined indices failure. For the outcome on diopter failure, only the diopter baseline value is a statistically significant variable. When looking at the outcome of pachymetry failure on its own, the baseline pachymetry seems to be most important but is not statistically significant [Table 3] .

(1) ROC curves summarize the trade-off between the true positive rate and false positive rate displaying the predictive effect of baseline pachymetry on treatment failure using different probability thresholds.
The optimal discrimination point for pachymetry in this study is at 450 μm thickness and is the value that best separates the study population into two groups, failure and success. This implies that stability is more likely to occur with an initial corneal thickness of >450 μm than with thinner corneas. The age of 20.5 years is also a threshold but not nearly as powerful as pachymetry in predicting treatment failure and probably has no significance in clinical practice. The sensitivity at cut-point was determined at 0.44 and the specificity at 0.78.

(2) There was overall stability in the keratometry and pachymetry measured between the three time periods. Stabilization or improvement was seen in 28 out of the 36 eyes in the early follow-up group and in 23 out of 41 patients in the late follow-up group. Failures generally occurred in only one of the indices and only one patient had a treatment failure on both thinning and steepening of the cornea.

## Discussion

The main finding in this study was that only eight eyes had failed out of the sample group of 36 and seven eyes out of the 41 had a longer follow-up period. There was no statistical difference of treatment failures between the two groups. In this study, therefore, the cornea did not seem to increase or decrease in stability >6 months after the treatment.

We found that most failures came from the continued thinning of the cornea while the diopters were still steady. This was considered as statistically significant for this study. Of the above numbers, only one eye progressed in both the K-max and pachymetry parameters. This was considered statistically significant for the study. Age did not seem to have a significant contribution in terms of those who seemingly progressed but perhaps that also speaks to the criteria that the patients were only between the ages of 13 and 35 years and not falling within the pediatric age bracket.

A study of 23 patients by Wollensak *et al.*[12] on collagen cross-linking showed that in all treated eyes, the progression of keratoconus was at least stopped, 16 eyes (70%) showed regression of the ectasia with a reduction of the maximal keratometry readings by at least 2 diopters and improvement of the refractive error by 1.14 diopters was found. These results are substantially better than the results on the current study population group [Tables 4 and 5].

A study done by Raiskup-Wolf *et al.*[13] showed that the best corrected visual acuity improved significantly (z1 line) in 53% of 142 eyes in the first year, 57% of 66 eyes in the

**Table 4: ROC table combo-fail age**

| Obs. | ROC area | Std. err. | Asymptotic normal (95% confidence interval) |
|---|---|---|---|
| 41 | 0.5435 | 0.0931 | 0.36100–0.72595 |

**Table 5: ROC table combo-fail pbase**

| Obs. | ROC area | Std. err. | Asymptotic normal (95% confidence interval) |
|---|---|---|---|
| 41 | 0.5459 | 0.0978 | 0.35414–0.73765 |

second year, and 58% of 33 eyes in the third year or remained stable (no lines lost) in 20%, 24%, and 29%, respectively.

Similar observations were made by Hersh *et al*.[14] The results of cross-linked eyes showed that maximum K-value worsened between baseline and 1 month, followed by improvement between the first and third month and stabilization thereafter. The above phenomena were also observed in the current study aligning with previous findings in studies done on the subject.

A considerable number of the patients seen with keratoconus at our hospital also have allergic conjunctivitis or vernal keratoconjunctivitis as it has been found that there is a proven association between keratoconus and chronic ocular allergies. Among the points of concern the researchers speculated whether keratoconus and ocular allergies in the African population give the same outcomes as other populations where there is less ocular allergy involved. In the study researchers suggested that atopy, positive family history, and smoking are not independent factors affecting corneal cross-linking outcomes.

Poli *et al*.[16] conducted a study in which they looked at patients who had cross-linking for keratoconus and showed that from 1 month up to 6 years in some patients the results may not be as favorable as one expects. They noted that after 1 year moving toward the 6-year period there was a notable improvement in the patients' parameters including visual acuity. The above study prompts for a study looking at long-term effects of corneal cross-linking on these current patients.

Chunyu *et al*.[17] did a meta-analysis where they concluded that cross-linking for keratoconus in patients followed for 1 year showed a statistical significance at 12 months postprocedure. In the current study, the above behavior was seen with a significant stabilization in K-max and pachymetry values.

The outcome of this study was not as favorable as the other prominent studies although the results were significant enough to support the hypothesis.

## Limitations and strengths

Tripoli University Hospital is one of the public hospitals that offers corneal cross-linking for the general people and it is a referral hospital. Despite many challenges including late referrals, poor transport systems, financial constraints, and staff shortages the team at Tripoli University Hospital continues to manage keratoconus to the abovementioned in spite of the abovementioned difficulties.

Limitations for this study included having a fairly small sample group with varying dates for follow-up; therefore, the comparison between them is not as accurate as the researchers desired it to be. Dividing the visits into early and late visits aimed to standardize the data more effectively.

The sample included patients who had cross-linking done using the hypotonic riboflavin solution and there is no indication of how many of these patients were included in the study. All patients, however, had "epi-off" cross-linking, where riboflavin is administered to the cornea after a portion of the epithelium had been removed.

Another limitation is that the data from the patients during the time of consultation and examination were taken by different medical officers that worked in the department at the time; therefore, there is a chance of positional variations on the parameters depending on the skill of the officer. Most data, however, were taken directly from the TMS-5 Scheimpflug topography equipment which adds a degree of objectivity.

Some patients who had the procedure done had mild to moderate ocular allergies and they were marked during the period of the procedure or collection to see if the presence of ocular allergies made a difference in the outcome of cross-linking in those individuals.

Lack of visual acuities as a measure of the procedure outcome is possibly the biggest limitation of this study since our aim in treating is to preserve/improve visual function in our patients.

## Implications and recommendations

Corneal cross-linking for keratoconus is still a safe and valid means of halting progression of the disease. A longer follow-up study to determine the behavioral pattern postprocedure will reveal more in terms of the outcome.

The threshold of 450 μm corneal thickness in predicting stability after treatment is, at least partly, to be expected since thicker corneas should logically be more stable from the outset. It might, however, be prudent when counseling patients about the relative success of corneal cross-linking depending on initial corneal thickness.

This study leaves us with many questions in terms of contributors to the rate of success or failure in the African setting. It would be of interest to look at the effect of ocular allergies and the outcome of cross-linking in the Libyan population as a research topic in the future. The effect of earlier referral, larger age differences, treatment with hypotonic versus isotonic riboflavin, and "epi-on" corneal cross-linking still require researching in a Libyan population.

## Conclusions

These results show that cross-linking for keratoconus is a useful conservative treatment modality to halt the progression of keratoconus. The need for corneal graft procedures is subsequently significantly reduced. The fairly minimal costs involved in this procedure compared to corneal graft procedures are also an important point to consider. Results in African patients might, however, be poorer than in Caucasian eyes for as yet unknown reasons.

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### Conflicts of interest

There are no conflicts of interest.

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