**Research Article**

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# An effective treatment for progressive keratoconus with two-year outcomes: accelerated epithelium-on corneal cross-linking

## *Progresif keratokonus için etkili bir tedavinin iki yıllık sonuçları: hızlandırılmış epi-on korneal çapraz bağlama*

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**Abstract**

**Purpose:** Corneal collagen cross-linking (CXL) is a surgical technique for progressive keratoconus. There are several technical modifications with varying clinical outcomes. This study aimed to evaluate the long-term outcomes of the accelerated epithelium-on CXL.

**Materials and methods:** A retrospective study was performed on progressive keratoconus patients treated via the accelerated epithelium-on CXL who completed the 24$^{th}$-month follow-up. We included 111 eyes of 77 patients. Clinical variables, including visual acuity, aberrometry, topographic measurements, and refractive outcomes, were evaluated at the postoperative 12$^{th}$ and 24$^{th}$ months.

**Results:** There was a significant improvement in postoperative visual acuity in 50.4% of patients ($p$<0.001). Baiocchi Calossi Versaci total index and lower low-order aberration values determined at the 12$^{th}$-month and 24$^{th}$-month follow-up visits were significantly higher than the baseline values ($p$=0.044 and $p$=0.033). The depths of the anterior chapter and its aqueous part, the anterior chamber volume, front apical keratometry, and the mean power of the pupil were significantly lower in the 12$^{th}$ and 24$^{th}$-month evaluations than the baseline values ($p$<0.05). For the 12$^{th}$-month evaluation, significant increments in the central corneal thickness ($p$=0.043) and back apical keratometry ($p$=0.034) were detected than the baseline values. The horizontal anterior chamber diameter ($p$=0.005) and the keratoconus area ($p$=0.001) were significantly different in the 24$^{th}$-month evaluation than in the preoperative period.

**Conclusion:** The study findings indicated that accelerated epithelium-on CXL stabilized disease progression and significantly improved visual acuity. Therefore, accelerated epithelium-on CXL stands out as one of the better options among the modified CXL techniques to treat progressive keratoconus surgically.

**Keywords:** Aberrometry, corneal topography, epithelium-on corneal cross-linking, keratoconus, visual acuity.

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**Öz**

**Amaç:** Korneal kollajen çapraz bağlama (CXL), progresif keratokonus için cerrahi bir tekniktir. Farklı klinik sonuçlara sahip çeşitli teknik modifikasyonları vardır. Bu çalışmada, hızlandırılmış epitelyum-on CXL'nin uzun vadeli sonuçlarını değerlendirmeyi amaçladık.

**Gereç ve yöntem:** Hızlandırılmış epitelyum-on CXL ile tedavi edilen ve 24. ay takibini tamamlayan progresif keratokonus hastaları üzerinde retrospektif bir çalışma yaptık. 77 hastanın 111 gözünü dahil ettik. Görme keskinliği, aberrometri, topografik ölçümler ve kırma kusurları gibi klinik değişkenleri cerrahi sonrası 12. ve 24. aylarda değerlendirdik.

**Bulgular:** Hastaların %50,4'ünde ameliyat sonrası görme keskinliğinde anlamlı artış görüldü ($p$<0,001). 12. ay ve 24. ay takiplerinde belirlenen Baiocchi Calossi Versaci total indeksi ve alt düşük dereceli aberasyon değerleri, başlangıç değerlerinden anlamlı derecede yüksekti ($p$=0,044 ve $p$=0,033). Ön kamara derinliği, ön kamara hacmi, ön apikal keratometri ve gözbebeğinin ortalama gücü, 12. ve 24. ay değerlendirmelerinde başlangıç değerlerine göre anlamlı derecede düşüktü ($p$<0,05). 12. ay değerlendirmesinde santral kornea kalınlığında ($p$=0,043) ve arka apikal keratometride ($p$=0,034) başlangıç değerlerine göre anlamlı artışlar tespit edildi. Horizontal ön kamara çapı ($p$=0,005) ve keratokonus alanı ($p$=0,001) 24. ay değerlendirmesinde ameliyat öncesine göre anlamlı olarak farklıydı.

**Sonuç:** Çalışma bulguları, hızlandırılmış epitelyum-on CXL'in görme keskinliğini önemli ölçüde artırdığını ve hastalığın progresyonunu durdurduğunu gösterdi. Böylece, hızlandırılmış epitelyum-on CXL'in, progresif keratokonusun cerrahi tedavisinde modifiye CXL yöntemleri arasında iyi bir seçenek olduğu ortaya konuldu.

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**Anahtar kelimeler:** Aberometri, görme keskinliği, Epi-on korneal çapraz bağlama, keratokonus, korneal topografi.

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## Introduction

Keratoconus is a bilateral progressive, noninflammatory degenerative ectasia of the cornea characterized by the conical protrusion, progressive thinning, and changes in biomechanical properties [1-3]. Although spectacles can be used in the early stages of the disease, hard corneal lenses are often needed to achieve good visual acuity due to increased myopia and irregular astigmatism in the later stages [1]. On the other hand, some patients with progressive keratoconus might require corneal collagen cross-linking (CXL) [2]. Several studies have addressed the long-term effectiveness of various technically modified versions of CXL in overcoming keratectasia in patients with keratoconus [1].

Among the technically modified versions of CXL, the epithelium-on (epi-on CXL, transepithelial) and the epithelium-off (epi-off CXL) stand out as the most common CXL techniques [1, 4, 5]. The difference between the two methods is whether the corneal epithelium is removed in the final state. Among these two techniques, the epi-off CXL technique has been associated with a higher risk of postoperative morbidity in some studies [6] but not in others [4, 7]. It has been accepted that the epi-on CXL technique is as effective as the epi-off CXL and, at the same time, a less invasive alternative to the epi-off CXL technique [8, 9]. The standard or accelerated CXL technique has been developed, taking into consideration that the irradiation time is part of the operation [2, 5, 10, 11]. It is widely believed that accelerated protocols are associated with a shorter duration of surgery and lower complication rates [12]. However, the data on which CXL method is the most effective in terms of postoperative visual results remain controversial.

There are a number of studies on the postoperative changes in tomographic, densitometric, visual, and aberrometry parameters, including maximum keratometry, central corneal thickness, visual acuity, spherical equivalent, and corneal biomechanical properties in the eyes with keratoconus after CXL [2]. However, the number of studies evaluating the long-term outcomes of accelerated epi-on CXL is limited.

In this context, this study was carried out to investigate the long-term outcomes of the accelerated epi-on CXL on patients with keratoconus.

## Material and methods

### Study design

The material of this retrospective study consisted of the eyes of all consecutive patients with progressive keratoconus who were treated with the accelerated epithelium-on CXL technique and followed up for 24 months at the eye diseases department of our hospital between January 2013 and July 2016. Patients with biomicroscopic, retinoscopic, and tomographic findings suggestive of keratoconus, Krumeich keratoconus stages of 1 to 3, absence of deep scar formation in the central cornea, and the thinnest pachymetric measurements of ≥400 μm were deemed to have keratoconus [13]. Patients with a central corneal thickness thinner than 400 μm at the thinnest point, pregnancy or lactation, systemic autoimmune or collagen tissue disorders, neurodermatitis, sequelae of hydrops fetalis, recurrent corneal erosion, dystrophia of the cornea, lacrimal gland dysfunction, history of herpes virus keratitis, deep corneal scarring visible on the slit-lamp examination, and untreated eyelid disorders were excluded from the study. In the end, 111 eyes of 77 patients were included in the study sample.

The study was approved by the Recep Tayyip Erdogan University Non-Interventional Clinical Research Ethics. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. The written informed consent could not be taken from the patients due to the retrospective design of the study and the unanimity of data.

**Data collection process**

A standardized diagnostic, therapeutic, and follow-up protocol was applied to all patients. All data were prospectively recorded into a predesigned worksheet.

All patients underwent a complete ocular assessment with slit-lamp biomicroscopy and ocular fundus examinations prior to CXL. The visual acuity measurements were performed based on a logarithm of the minimum angle of resolution (LogMAR) Snellen chart [14]. The Bailey-Lovie (logMAR) chart was used to measure visual acuity from a testing distance of six meters under standardized lighting conditions.

The anterior segment examination was performed using biomicroscopy. Corneal topography was performed using Placido disc topography (Sirius 1.2, CSO, Florence, Italy, combined with Scheimpflug camera) under standardized lighting conditions. The average of three consecutive measurements was recorded.

Corneal densitometry was obtained using Sirius 1.2, CSO, Florence, Italy. The grayscale units of backscattered light were used to express densitometry that was calculated automatically by the respective software. A scale ranging from 0 (completely transparent) to 100 (completely opaque) was used in all measurements.

All measurements were performed without pupil dilatation during the daytime between 1.00 PM and 5.00 PM [14].

**Surgical procedure**

Patients who have been using contact lenses were asked to stop to do so at least one month before the clinical examination and the CXL procedure. The same experienced surgeon performed all procedures.

Under sterile conditions, the eye was anesthetized with 0.5% proparacaine hydrochloride (Alcaine, Alcon Laboratories, Puurs, Belgium). A speculum was placed between the eyelids. The corneal epithelium was left intact. Riboflavin solution was applied to the corneal surface for ten minutes at one-minute intervals without removing the cornea. The first four of these ten applications were performed using the Paracel solution (ParaCel™, Avedro Inc., Massachusetts, USA) containing 0.25% riboflavin, hydroxypropyl methylcellulose, and benzalkonium chloride, and the subsequent six applications were performed using the VibeX Xtra solution (VibeX Xtra™, Avedro Inc., Massachusetts, USA) containing 0.22% riboflavin and NaCl.

Ultraviolet A was applied with the Avedro KXL system (Avedro Inc., Waltham, MS, USA). The parameters for accelerated CXL are an ultraviolet power of 45mW/cm², a UV irradiation time of 2 minutes, pulsed illumination of 40 seconds (45mW/cm$^2$, 1 sec on/1 sec off), and a surface dose of 7.20 J/cm² [15]. Subsequently, the cornea and conjunctiva were washed with Ringer's lactate, and the eye was closed.

**Follow-up procedure**

Patients were recommended to close their eyes with EYE PATCH for one day and then use sodium hyaluronate drops (Eyestil 0.15% eye drops, four times a day) for one week.

All patients were examined postoperatively at the 1$^{st}$, 12$^{th}$, and 24$^{th}$ months.

**Outcomes of the study**

Based on the patients' medical records and the data entered into the predesigned worksheets, the following data were determined as the primary outcomes of the study:

i. visual acuity data,

ii. aberrometry measurement data (low-order, high-order, longitudinal, total, longitudinal spherical aberrations, Baiocchi Calossi Versaci front, back, and total indexes, Root Mean Square Front and Back Areas (RMSf A and RMSb A),

iii. topographic measurement data (anterior chamber aqueous and total depths, anterior chamber volume, horizontal anterior chamber diameter, iridocorneal angle, central corneal thickness, corneal volume, thickness of the thinnest part of the cornea, curvature asymmetry-front value, curvature asymmetry-back value, apical keratometry front and back values, keratoconus vertex front and back values, keratoconus area, keratoconus volume), and

iv. refractive outcomes (cylindrical dioptric power and cylindrical value axis).

### Statistical analysis

SPSS 20.0 (Statistical Product and Service Solutions for Windows, Version 20.0, IBM Corp., Armonk, NY, U.S., 2011) software package was used to analyze the collected data statistically. Descriptive statistics obtained from the collected data were expressed as numbers (n), and percentage (%) values in the case of categorical variables and as mean and standard deviation values in the case of normally distributed numerical variables. Kolmogorov-Smirnov test and graphics were used to determine whether the numerical variables conformed to the normal distribution. The paired t-test were used to compare dependent groups featuring normally-distributed. Probability (*p*) values of <0.05 were deemed to indicate statistical significance.

## Results

### Visual acuity

The preoperative and postoperative 24$^{th}$-month visual acuity of 111 eyes were 0.33±0.33 and 0.26±0.30 logMAR, respectively. Accordingly, there was a significant difference in the visual acuity between the preoperative and postoperative measurements ($p$<0.001). There was a significant improvement in 56 (50.4%) eyes, whereas there was no significant change in 32 (28.9%) eyes. On the other hand, there was a significant decrease in visual acuity in 23 (20.7%) eyes.

### Aberrometric measurements

The results of the preoperative and postoperative aberrometry measurements are given in Table 1. There were no significant differences between the baseline, 12$^{th}$, and 24$^{th}$-month measurements except for Baiocchi Calossi Versaci total index and low-order aberration ($p$<0.05). The Baiocchi Calossi Versaci total index values measured at the 12$^{th}$-month follow-up visit were significantly higher than the baseline values ($p$=0.044). Additionally, the low-order aberration values measured at the 24$^{th}$-month follow-up visit were significantly lower than the baseline values ($p$=0.033).

**Table 1.** Comparison of preoperative and postoperative 24$^{th}$-month aberrometric measurements

| | Preoperative | Postoperative 12$^{th}$ month | *t* | *p* | Postoperative 24$^{th}$ month | *t* | *p* |
|---|---|---|---|---|---|---|---|
| **Low-order aberration** | 2.16±1.22 | 2.26±1.23 | -1.89 | 0.060[a] | 2.28±1.16 | -2.04 | 0.043[a] |
| **High-order aberration** | 2.22±0.93 | 2.22±0.92 | -0.65 | 0.948[a] | 2.21±0.95 | 0.46 | 0.644[a] |
| **Total aberration** | 3.21±1.29 | 3.53±2.90 | -1.24 | 0.216[a] | 3.52±2.85 | -1.19 | 0.235[a] |
| **Longitudinal spheric aberration** | -0.59±2.65 | -0.72±2.34 | 1.05 | 0.296[a] | -0.53±2.42 | -0.21 | 0.834[a] |
| **Baiocchi Calossi Versaci front index** | 3.33±1.43 | 3.42±1.50 | -1.92 | 0.057[a] | 3.39±1.46 | -1.26 | 0.210[a] |
| **Baiocchi Calossi Versaci back index** | 3.50±1.30 | 3.58±1.36 | -1.818 | 0.720[a] | 3.58±1.37 | -1.89 | 0.061[a] |
| **Baiocchi Calossi Versaci total inde**x | 3.38±1.31 | 3.49±1.39 | -2.70 | 0.008[a] | 3.45±1.37 | -1.91 | 0.059[a] |
| **Root mean square front area** ($mm^2$) | 0.221±0.083 | 0.318±0.948 | -1.054 | 0.294[a] | 0.368±1.43 | -1.04 | 0.300[a] |
| **Root mean square back area** ($mm^2$) | 0.482±0.144 | 0.491±0.151 | -1.725 | 0.087[a] | 0.489±0.151 | -1.83 | 0.069[a] |

All values were given as mean ± standard deviation, [a]: Paired sample t test

### Corneal topography

The baseline depths of the anterior chapter and its aqueous part, the anterior chamber volume, front apical keratometry, and the mean power of the pupil were significantly higher than the respective values measured at the 12th- and 24th-month follow-up visits ($p<0.05$) (Table 2). The central corneal thickness and back apical keratometry values determined at the 12th-month follow-up visit were significantly higher than the baseline values ($p=0.043$ and $p=0.034$, respectively). In addition, the horizontal anterior chamber diameter and the keratoconus area values determined at the 24th-month follow-up visit were significantly different than the baseline values ($p=0.005$ and $p=0.001$, respectively). There was no significant difference between the baseline and postoperative measurements in other corneal topographic measurements ($p>0.05$).

**Table 2.** Preoperative and postoperative 24th-month corneal topographic measurements

| | Preoperative | Postoperative 12th month | *t* | *p* | Postoperative 24th month | *t* | *p* |
|---|---|---|---|---|---|---|---|
| **Anterior chamber aqueous depth (µm)** | 3.366±0.282 | 3.352±0.280 | 2.490 | 0.014[a] | 3.350±0.289 | 3.061 | 0.003[a] |
| **Anterior chamber depth (µm)** | 3.835±0.278 | 3.817±0.275 | 3.720 | <0.001[a] | 3.815±0.285 | 4.47 | <0.001[a] |
| **Anterior chamber volume** ($mm^3$) | 184.3±33.876 | 181.75±32.812 | 3.788 | <0.001[a] | 181.48±34.117 | 3.567 | <0.001[a] |
| **Horizontal anterior chamber diameter (µm)** | 12.34±0.57 | 12.51±2.52 | -.896 | 0.372[a] | 12.077±1.33 | 2.061 | 0.042[a] |
| **Iridocorneal angle (°)** | 46.3±7.3 | 45.5±5.6 | 1.408 | 0.162[a] | 45.64±5.64 | 1.431 | 0.155[a] |
| **Central corneal thickness (µm)** | 463±38 | 466±39 | -2.247 | 0.027[a] | 464.7±38.9 | -0.484 | 0.629[a] |
| **Corneal volume** ($mm^3$) | 54.87±3.45 | 55.10±3.32 | -1.553 | 0.27[a] | 59.71±3.30 | -1.046 | 0.298[a] |
| **Corneal thinnest point** | 444.8±55.83 | 444.8±56.43 | .012 | 0.990[a] | 448.2±37.5 | -0.827 | 0.410[a] |
| **Curvature asymmetry-front** | 6.53±2.99 | 6.71±3.06 | -1.493 | 0.138[a] | 6.69±3.09 | -1.351 | 0.180[a] |
| **Curvature asymmetry-back** | 1.76±0.63 | 1.81±0.68 | -1.861 | 0.065[a] | 1.79±0.68 | -1.382 | 0.170[a] |
| **Apical keratometry front** | 56±4.27 | 55.64±3.99 | 2.842 | 0.005[a] | 55.53±4.05 | 2.488 | 0.014[a] |
| **Apical keratometry back** | -9.70±1.07 | -9.13±1.08 | -9.709 | <0.001[a] | -9.12±1.06 | -1.812 | 0.73[a] |
| **Mean power of the pupil** | 46.18±2.19 | 46.02±2.01 | 2.090 | 0.039[a] | 45.99±1.94 | 2.625 | 0.01[a] |
| **Keratoconus vertex front** | 32.12±12.15 | 32.64±12.337 | -1.476 | 0.143[a] | 32.60±12.49 | -0.991 | 0.324[a] |
| **Keratoconus vertex back** | 75.29±24.92 | 76.40±24.81 | -1.720 | 0.088[a] | 76.62±25.626 | -1.720 | 0.088[a] |
| **Keratoconus area** ($mm^2$) | 5.82±1.49 | 6.24±5.86 | -0.777 | 0.439[a] | 5.94±1.44 | -2.253 | 0.026[a] |
| **Keratoconus volume** ($mm^3$) | 0.105±0.0407 | 0.1125±0.0977 | -0.863 | 0.390[a] | 0.1072±0.0452 | -0.883 | 0.379[a] |

All values were given as mean ± standard deviation, [a]: Paired sample t test

### Dioptric power measurements

Although the cylindrical dioptric power values increased in the postoperative 12th and 24th-month evaluations compared to baseline values, the differences were insignificant ($p$=0.113 and $p$=0.053, respectively) (Table 3).

There were no intra- or postoperative complications or adverse reactions in the study group during and after the CXL procedure.

**Table 3.** Preoperative and postoperative cylindrical dioptric power measurements.

| | Preoperative | Postoperative 12th month | *t* | *p* | Postoperative 24th month | *t* | *p* |
|---|---|---|---|---|---|---|---|
| **Cylindrical dioptric power** | -3.43±1.34 | -2.42±1.42 | -0.94 | 0.347[a] | -2.46±1.29 | -0.90 | 0.367[a] |

All values were given as mean ± standard deviation, [a]: Paired sample t test

## Discussion

The findings of this study suggest that the accelerated epithelium-on corneal collagen cross-linking (CXL) technique may have the potential to prevent the progression of keratoconus. This is based on the observed significant improvement in visual acuity at the 24th-month evaluation, as well as the absence of significant changes in the topographic parameters over the same time period.

The epi-off CXL is generally considered a superior treatment modality for halting progressive keratoconus [16, 17]. On the other hand, the transepithelial CXL approaches have also been proposed in the context of reduced postoperative complication risks [9, 15, 18-22]. Several authors recommended that a thin cornea, poor corneal endothelial function, and slowly progressing keratoconus might indicate the epi-on CXL [17]. Faster visual recovery and decreased postoperative pain were cited among the other advantages of the epi-on CXL. Nevertheless, compared to epi-off CXL, a higher degree of pain was reported in patients who underwent epi-on CXL [15, 23]. In comparison, no acute or chronic complications were observed in this study that could be attributed directly related to the surgical technique used. Then again, the time required for visual recovery and postoperative pain were not evaluated within the scope of this study. Additionally, the epi-on CXL's efficacy in terms of not leading to any morbidity and stopping the progression of keratoconus could not be evaluated since there was no control group. Yet, the findings have been deemed sufficient to conclude that the epi-on CXL is a viable surgical alternative to epi-off CXL in stopping the progression of keratoconus.

The original CXL procedure, as described by Wollensak et al. [24] in 2003, used UVA light at 3 mW/cm$^2$ intensity for 30 minutes leading to a total radiant exposure of 5.4 J/cm$^2$ [15]. Accordingly, since then, a total UVA energy of 5.4 J/cm$^2$ has been deemed sufficient and non-toxic for the epi-off CXL [23, 25]. However, the upper limit of total energy dose for epi-on CXL has been questioned on multiple occasions. In this context, several authors suggested a total UVA energy of 7.2 J/cm$^2$ for the UVA energy needed in epi-on CXL [23]. The relatively long duration of surgery, which can be as long as one hour, has been deemed the main disadvantage of epi-on CXL [15]. Several authors tried to develop new approaches using high-intensity UVA irradiation to shorten the duration of epi-on CXL surgery. Although all these approaches utilized different high-intensity protocols with various intensities and employed different cutoff values of duration of surgery [11, 12, 26-28], the outcomes were favorable.[15] Among these approaches, the approach developed by Kır et al. [15], who proposed using UVA irradiation at 45 mW/cm$^2$ for 2 minutes and 40 seconds, was utilized in this study. Consequently, significant differences were recorded in the measurements related to the anterior chamber, central corneal thickness, the corneal thinnest point, and front and back apical keratometry performed throughout the follow-up period. Although these measurements did not provide sufficient data indicative of the cessation of disease progression by the epi-on CXL technique, they provided sufficient data suggestive of the stabilization effect of the epi-

on CXL technique on the pathological process in the cornea in these patients.

The surgical outcomes of the epi-on CXL technique in patients with keratoconus remain controversial. Based on the corrected distance visual acuity (CDVA) measurements and topographic parameters, some studies reported improvement, whereas others reported worsening or stabilization with the use of the epi-on CXL. The assessment of the efficacy of CXL procedures was commonly based on visual acuity data. Nevertheless, it was speculated that the keratometry scores might be more sensitive in assessing progressive keratoconus compared to visual acuity data [12]. In addition, disturbances in the visual acuity caused by the transparency of the refractive media and retinal and optic nerve conditions might act as late effects. In sum, the cylindrical dioptric power measurements did not indicate a significant improvement.

Topographic parameters have also been used to quantify the changes following CXL procedures in patients with keratoconus. The mean corneal thickness at the thinnest point might indicate the corneal stroma's degree of lamellar remodeling [15]. There are contradictory findings on postoperative corneal thickness following CXL procedures in the literature. In comparison, no change was detected in the corneal thickness between the baseline measurements and those performed at the 12$^{th}$ and 24$^{th}$-month follow-up visits. The mean and maximum keratometry values are among the other topographic parameters used to quantify the changes following CXL procedures in patients with keratoconus [16]. Significant reductions were observed in both mean and maximum keratometry values measured at 12 and 18 months after the epi-on and epi-off CXL procedures [11, 23, 25]. These reductions were attributed to decreased corneal curvature and distortion [25]. Similarly, in this study, a significant decrease was observed in the apical keratometry values. However, prospective large-scale studies are needed to establish an optimum topographic parameter indicating the efficacy of the CXL procedures.

Changes in the central cornea and corneal thickness at the thinnest point are among the other parameters used to assess the efficacy of CXL procedures. The thinning of the cornea is generally considered an early event, followed by an increase in the thickness of the cornea. Nevertheless, no significant thinning in the cornea was reported after the epi-on CXL procedure [8]. In contrast, significant reductions in the thickness of the central cornea and corneal thickness at the thinnest point were reported in other studies featuring follow-up periods of up to 24 months. A significant increase was reported in the central corneal thickness at the 12$^{th}$-month measurement, and a significant difference between the baselines and 24$^{th}$-month measurements [11, 12]. Given the conflicting results, several authors concluded that corneal pachymetry might not be considered a reliable assessment tool for predicting the progression of the disease after CXL [25].

High-order aberration was another parameter indicating disturbed visual function and contrast sensitivity. Post-CXL changes in the high-order aberrations might be used to evaluate keratoconus's progression. Previous studies reported increases in this type of refraction error in the early phases, followed by decreases up to the baseline values in the following period [2]. Other studies revealed a close relationship between the baseline values and the postoperative changes [29]. In contrast, improvements were detected in high-order aberrations for up to one year after the accelerated epi-off CXL [30]. However, no significant changes were detected in this study in the low-order or high-order aberrations after CXL. Methodological differences between the studies might be implicated in the differences in the quality of postoperative visual functions.

Several technical modifications related to the type of epi-on approach, riboflavin solutions, and adjunctive agents were reported in the literature [15]. Some authors recommended using benzalkonium chloride, ethylenediaminetetraacetic acid-Tris, iontophoresis, sodium chloride, and proxymetacaine hydrochloride 0.5% to increase the transepithelial absorption of riboflavin [15, 23]. For this purpose, a chemical solution containing hydroxypropyl methylcellulose and benzalkonium chloride was used in this study, as in other studies [15]. Oxygen supplementation was another maneuver used to increase the riboflavin permeability of the corneal epithelium [3, 19]. The variable outcomes of

the epi-on CXL procedure might be attributed to such differences between the methodologies employed in different studies.

### Limitations of the study

Apart from its strengths, such as its relatively larger sample size and extended follow-up duration, there were also some limitations to this study, the primary ones being its retrospective design and lack of a control group. Secondly, the fact that different CXL methods were not addressed in this study might be deemed another limitation as a comparison between these methods could not be made.

In conclusion, the study findings indicated that accelerated epithelium-on CXL stabilized disease progression and significantly improved visual acuity. Therefore, accelerated epithelium-on CXL stands out as one of the best options among the modified CXL techniques to treat progressive keratoconus surgically. However, prospective controlled studies are needed to corroborate the findings of this study based on patients with better clinical outcomes.

**Conflict of interest:** The authors have no relevant financial or non-financial interests to disclose.

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### Authors' contributions to the article

M.K. formulated the primary concept and hypothesis for the research. M.K. conceptualized the theory and organized the materials and methods section. M.K. conducted the data analysis for the results section. M.K authored the discussion section of the article. M.O, H.F. and F.U. reviewed, revised, and provided approval. Additionally, all authors engaged in comprehensive discussions regarding the study and endorsed the final version.