Long-term follow-up of repeated corneal cross-linking for progressive keratoconus in young patients

Acompanhamento a longo prazo do retratamento com *cross-linking* corneano para ceratocone em progressão em pacientes jovens

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ABSTRACT

Objective: To evaluate the long-term safety and efficacy of repeated corneal cross-linking in eyes of children and adolescents with progressive keratoconus.

Methods: This retrospective study included nine eyes of nine consecutive patients with progressive keratoconus who underwent repeated corneal cross-linking 3.9 (range of 1.6 to 5.6) years after a primary one. All patients were followed for a mean period of 9.11 (range of 6 to 11) years after first treatment and 5.44 (range of 4 to 9) years, after corneal cross-linking retreatment.

Results: Nine eyes of nine patients (six male) with progressive keratoconus underwent primary corneal cross-linking from 2009 to 2011. Despite the stability achieved with the epi-off corneal cross-linking, keratoconus continued to progress after some time. Mean time to documented evidence of keratoconus progression after primary corneal cross-linking was 3.9 (range of 1.6 to 5.6) years. All eyes were retreated as soon as progression was noted. At the last follow-up visit, 5.44 (range of 4 to 9) years after repeated corneal cross-linking, there was a significant decrease of 2.02 D in mean maximum topographic K-value (p = 0.045) and 1.95D in mean topographic K-value (p = 0.007).

Conclusion: Repeated corneal cross-linking seems to be a safe and effective procedure to halt keratoconus progression after a primary corneal cross-linking failure.

RESUMO

Objetivo: Avaliar a segurança e a eficácia a longo prazo da repetição do *cross-linking* corneano em olhos de crianças e adolescentes com ceratocone progressivo.

Métodos: Estudo retrospectivo que incluiu nove olhos de nove pacientes consecutivos com ceratocone progressivo, que foram submetidos a retratamento com *cross-linking* corneano de 3,9 (variação de 1,6 a 5,6) anos após tratamento primário com *cross-linking* corneano. Todos os pacientes foram acompanhados por um período médio de 9,11 (variação de 6 a 11) anos após o primeiro tratamento e 5,44 (variação de 4 a 9) anos após retratamento com *cross-linking* corneano.

Resultados: Nove olhos de nove pacientes (seis homens) com progressão do ceratocone foram submetidos a *cross-linking* corneano primário de 2009 a 2011. Apesar da estabilidade alcançada com o *epi-off cross-linking* corneano, o ceratocone continuou a progredir após algum tempo. O tempo médio para evidência documentada de progressão do ceratocone após *cross-linking* corneano primário foi de 3,9 (intervalo de 1,6 a 5,6) anos. Todos os olhos foram retratados com *cross-linking* corneano, assim que a progressão foi observada. Na última consulta de acompanhamento, 5,44 (variação de 4 a 9) anos após a repetição do *cross-linking* corneano, houve diminuição significativa de 2,02 D na média da curvatura máxima (p = 0,045) e 1,95 D na média da curvatura média (p = 0,007).

Conclusão: O retratamento com *cross-linking* corneano parece ser um procedimento seguro e eficaz para interromper a progressão do ceratocone após falha primária do *cross-linking* corneano.

INTRODUCTION

Keratoconus (KC) is a bilateral, asymmetric, and progressive corneal ectasia, which causes corneal thinning and steepening because of its biomechanical instability. This leads to irregular astigmatism and subsequent decrease in visual acuity.[1]

Keratoconus usually manifests in adolescence or pre-adolescence, but in many cases, it can manifest at a much younger age. Some studies have shown that KC is more severe and aggressive in children and adolescents than in adults.[2,3]

Knowledge about the evolution of the disease is essential for early diagnosis, identification of progression, and staging KC. This information greatly helps in deciding the ideal time and the best treatment option to be indicated. In addition, it is important to decide on whether the treatment benefits outweigh the risks.[4-7]

Corneal cross-linking (CXL) increases the biomechanical strength and stability of the cornea by an interaction of ultraviolet (UV) light, riboflavin, and oxygen, which are used to halt or decline the progression of KC.[8-12]

Although there are variations in the CXL technique, the Dresden protocol is still the gold standard for the treatment of progressive KC, both in pediatric and adult patients.[13] This procedure includes removal of the corneal epithelium and subsequent irradiation with 3 mW/cm² of UVA light for 30 minutes.[8] However, even with the good results described over time,[8,9,13] some patients, especially children and adolescents, continue to show progression of KC despite treatment.[2,3,14-17] In these cases, repeated CXL may be indicated to achieve disease stabilization.[18-20]

There is little information in the literature on the long-term results of repeated corneal CXL for progressive KC. This study aims to evaluate the long-term safety and efficacy of repeated CXL in eyes of children and adolescents with progressive KC, who experienced treatment failure with subsequent KC progression, despite having achieved stability for some time after a first CXL.

METHODS

This retrospective study included nine eyes of nine young patients (six men), with low stage progressive KC. All patients underwent epithelium-off CXL according to the standard Dresden protocol, to stabilize the disease. Mean age at the time of first treatment was 12.77 ± 2.99 (range of 9 to 17) years. Five (55.5%) of the nine patients reported a history of allergic conjunctivitis and eye rubbing and were adequately treated before CXL.

All procedures were performed at the *Instituto de Olhos de Goiânia*, Goiania (GO), Brazil, by a single surgeon, from January 2009 to December 2011. According to the Amsler-Krumeich classification[21] of KC disease, all eyes were classified as low stage KC: four eyes (44.4%) were stage I and five eyes (55.5%) were stage II.

An increase of 1.00 diopter (D) in maximum topographic K-value (Kmax; the most curved point on the entire cornea) or a 5% reduction in corneal thickness with or without changes in uncorrected visual acuity (UCVA) and best-spectacle corrected visual acuity (BSCVA) within the last year, were considered as indications of progression.

Inclusion criteria for both, the initial CXL and retreatment were: progressive KC, endothelial cell density higher than 2.000 cell/mm², a minimum de-epithelialized corneal thickness of 330 μm and age under 18 years old.

Exclusion criteria were severe vernal keratoconjunctivitis, severe dry eye, history of herpetic keratitis, concurrent autoimmune disease, previous ocular surgery other than primary CXL, and central or paracentral opacities. Patients using contact lenses were asked to discontinue lens use for at least three weeks before each examination.

Preoperative examination

Preoperative and postoperative examinations included: uncorrected and best spectacle corrected distant visual acuity (UCVA and BSCVA), manifest and cycloplegic refraction, slit-lamp biomicroscopy, specular microscopy (Konan, Hyogo, Japan), corneal topography and pachymetry (Orbscan IIz, Technolas Perfect Vision GmbH). Visual acuity was measured using a standard Snellen acuity chart at 6 m and measured in feet/logmar.

The study was approved by the institutional ethics committee and conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from the patient (aged 18 years and over) or one of the parents, after receiving a detailed description of the nature and risks of the procedure.

Cross-linking procedure

Primary and repeated CXL were performed using the conventional Dresden protocol.

All patients received a mild oral sedative (diazepam 5 mg) 30 minutes before surgery and two drops of topical 0.5% proximetacaine, 2 to 5 minutes before surgery. A wire eyelid speculum was placed for exposure. Corneal epithelium was removed by mechanical scraping over the central cornea (9.0-mm) with a blunt Paton spatula (Storz

Ophthalmic Instruments, St Louis, USA). The lid speculum was removed. Iso-osmolar 0.1% riboflavin solution (400 mOsmol/L), which was generated by diluting vitamin B2-riboflavin-5-phosphate 0.5% with dextran T500 20%, was instilled to the cornea every 3 minutes for 30 minutes.

The lid speculum was replaced. Central corneal thickness (CCT) was measured using ultrasound pachymetry (CompuScanTM P, Storz, St. Louis, MO, United States). A minimum de-epithelialized corneal thickness of 330 µm before CXL was verified. In eyes with a CCT (without epithelium) less than 400 µm, additional hypo-osmolar riboflavin 0.1% drops (200 mOsmol/L) were applied until the thinnest corneal thickness (TCT) reached 400 µm.

Fixation during irradiation was achieved by instructing the patient to focus on the light emitting diode on the UVA emitter. Ultraviolet-A radiation was performed for 30 minutes using a commercially available UVA system (UV-X; Peschke Meditrade GmbH, Hunenberg, Switzerland) at a working distance of 5 cm, with an irradiance of 3mW/cm^2, corresponding to a surface dose of 5.4 J/cm^2. During irradiation, iso-osmolar 0.1% riboflavin drops were applied every 5 minutes to ensure saturation of the cornea with riboflavin. A topical anesthetic agent (0.5% proxymetacaine) was applied as needed. CCT was monitored throughout the irradiation period. In cases that pachymetry was less than 400 µm, hypo-osmolar riboflavin was instilled to maintain the minimum thickness of 400 µm required by the Dresden protocol. After treatment, patients were medicated with topical moxifloxacin 0.3% drops four times a day for 5 days, and ketorolac tromethamine three times a day for 3 days. A soft therapeutic lens was applied until complete re-epithelialization of the cornea. Unpreserved artificial tears were recommended for mild irritation. Paracetamol-codeine pain medication was also prescribed, as needed, for the first 2 to 3 days. Fluorometholone eye drops were then applied three times a day for 2 weeks.

Postoperative examinations

Follow-up examinations were scheduled daily until complete re-epithelialization. Subsequent examinations were performed at 1, 6, and 12 months after primary and repeated CXL, and then once a year. Every single time, a complete ophthalmic examination was performed.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows, version 21.0. Descriptive statistics were performed as means and standard deviations. Then, Friedman's repeated measures analysis test was performed. In addition, a Spearman correlation was performed. The level of statistical significance was considered when the p-value was less than 0.05.

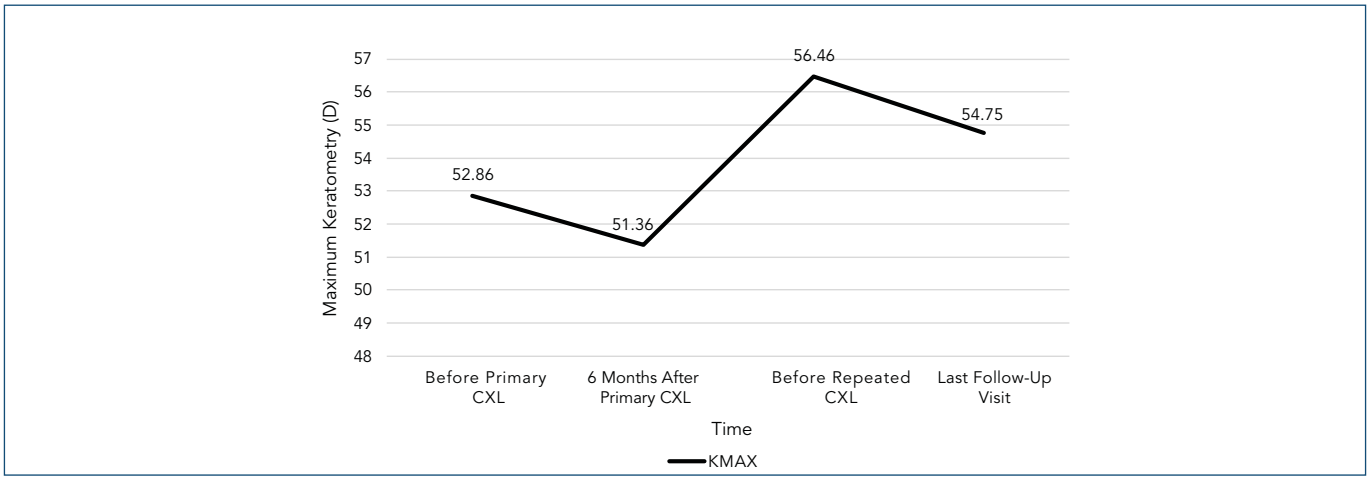
RESULTS

Nine eyes of nine patients with progressive KC underwent primary CXL from 2009 to 2011. Mean patient age at first CXL was 12.7 ± 2.9 (range of 9 to 17) years. All treated eyes had early to moderate KC, according to the Amsler-Krumeich classification. Four eyes (44.4%) were grade I, and five eyes (55.5%) were grade II KC, with a mean central keratometry reading lower than 53 diopters (D), absence of corneal scaring, and minimum corneal thickness greater than 400 µm.

Six months after the initial CXL, all nine eyes (100%) showed KC stability. There was a significant decrease in maximum keratometry (Kmax), from 52.86 D (range of 47.6 to 57.2 D) to 51.36 D (range of 46.6 to 55.2 D; p = 0.01) (Figure 1). Also, a significant decrease in median keratometry (Kmean) from 49.31 D (range of 45.0 to 52.4 D) to 47.64 D (range 44.4 to 51.0D; p = 0.001) was noted. The average pachymetry decreased from 436 (range of 402 to 476) µm to 422 (range of 401 to 450) µm, (p = 0.001) (Figure 2). Due to slight corneal haze, 3 patients (33.3%) lost one Snellen line of the best-corrected visual acuity (BCVA) (Table 1).

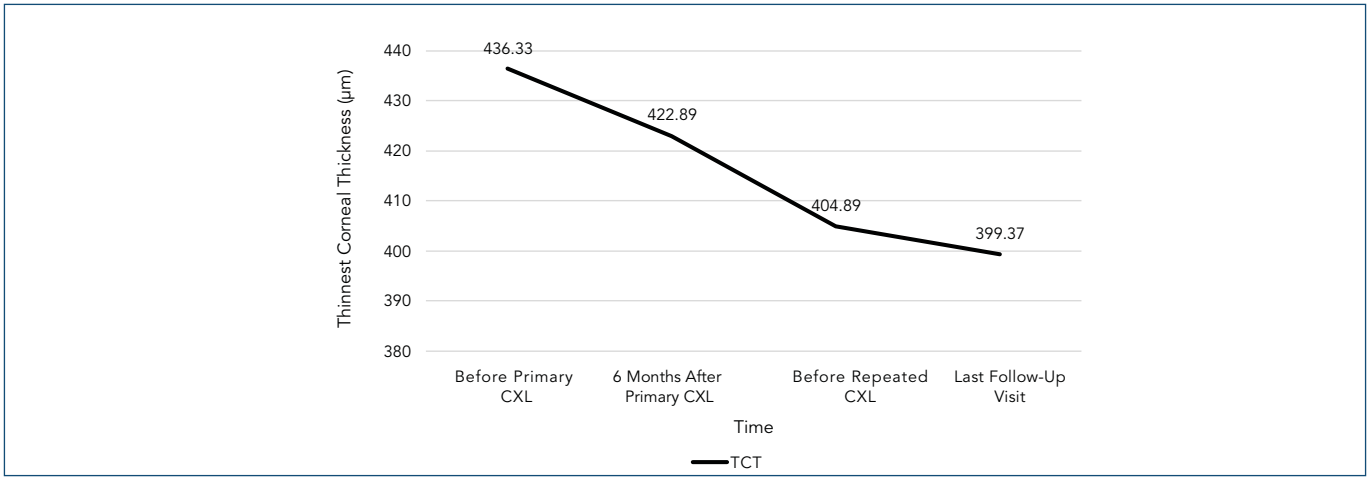
Despite the stability achieved with the epi-off CXL, KC continued to progress sometime later. Mean time to documented evidence of KC progression after primary CXL was 3.9 (range of 1.6 to 5.6) years. All eyes were retreated as soon as progression was noted. Due to KC progression, at this time, seven eyes (77.7%) were classified as stage II and two eyes (22.2%) as stage III KC. Mean patient age at CXL retreatment was 16.4 ± 3.8 (range of 11 to 21) years. All patients were followed for a mean of 5.44 (range of 4 to 9) years after repeated CXL.

Comparing the data when the new KC progression was identified (before CXL retreatment) with those months after the primary CXL, there was a mean statistically significant increase in Kmax, from 51.36D (range of 46.6 to 55.2D) to 56.46D (range of 51.0 to 58.4 D; p = 0.004), and in Kmean from 47.64 D (range of 44.4 to 51.0) to 52.04 D (range of 48.2 to 54.4; p = 0.008). There was an average pachymetry decrease from 422 (range of 401 to 450) µm to 404 (range of 368 to 420) µm, (p = 0.005). The BCVA reduced from logmar 0.075 (range of zero to 0.1) to logmar 0.087 (range of zero to 0.1). One eye (11.1%) lost one Snellen line of the BCVA.



CXL: corneal cross-linking; Kmax: maximum topographic K-value.

Figure 1. Maximum keratometry over time.



CXL: corneal cross-linking; TCT: thinnest corneal thickness.

Figure 2. Thinnest corneal thickness over time.

Table 1. Changes in topographic parameters

	Before primary CXL	6 months after primary CXL	Before repeated CXL	Last follow-up visit
BCVA, logmar	0.037 ± 0.05	0.075 ± 0.05	0.087 ± 0.04	0.112 ± 0.06
Kmax	52.86 ± 4.07	51.36 ± 4.06	56.46 ± 2.99	54.75 ± 2.58
Kmean	49.31 ± 2.80	47.64 ± 2.68	52.04 ± 2.11	50.10 ± 2.06
TCT	436.33 ± 26.72	422.89 ± 18.92	404.89 ± 15.29	399.37 ± 7.19

CXL: corneal cross-linking; BCVA: best corrected visual acuity; Kmax: maximum keratometry; Kmean: median keratometry; TCT: thinnest corneal thickness.

At the last follow-up visit, 5.44 (range of 4 to 9) years after repeated CXL, there was a significant reduction of 2.02 D in mean Kmax (p = 0.045), and 1.95 D in mean Kmean (p = 0.007), compared to the data before CXL retreatment. The thinnest point of the cornea had decreased from 404 (range of 368 to 420) µm to 399 (range of 384 to 406) µm, but this difference was not statistically significant (p = 0.75) (Table 2). Best corrected visual acuity had decreased from logmar 0.087 (range of zero to 0.1) to logmar 0.112 (range of zero to 0.2). Due to corneal haze, two eyes (22.2%) lost one Snellen line of the BCVA. Keratoconus stability was noted in eight (88.8%) eyes. According to the Amsler-Krumeich classification, one eye (11.1%) was classified as stage I, six eyes (66.6%) as stage II, and one eye (11.1%) as stage III KC. One eye (11.1%) showed further KC progression 4 years after repeated CXL, with a loss of 2 Snellen lines of the best spectacle-corrected visual acuity. At that time point, the patient was 15 years old. To improve his BCVA, he underwent intrastromal corneal ring segment implantation to address corneal surface irregularity. Three months after corneal ring implantation, he underwent a third CXL and remained stable until the last follow-up visit. It is interesting to note that the two youngest patients at the time of first treatment, both 9

years old, with grade I KC, were the two who had the worst evolution, since the first CXL. Both also had a history of allergic conjunctivitis and were adequately treated before the first CXL and throughout the follow-up.

Table 2. Data before repeated corneal cross-linking versus last follow-up visit

	Before repeated CXL	Last follow-up visit	p-value
BCVA, logmar	0.087 ± 0.04	0.112 ± 0.06	0.02
Kmax	56.46 ± 2.99	54.75 ± 2.58	0.04
Kmean	52.04 ± 2.11	50.10 ± 2.06	0.007
TCT	404.89 ± 15.29	399.37 ± 7.19	0.75

CXL: corneal cross-linking; BCVA: best corrected visual acuity; Kmax: maximum keratometry; Kmean: median keratometry; TCT: thinnest corneal thickness.

Comparing the data found before primary CXL and those found at the last follow-up visit, 9.1 (range of 6 to 11) years later, there was an increase in Kmax from 52.86 D (range of 47.6 to 57.2 D) to 54.75 D (range of 50.1 to 56.5 D; p=0.10), and in Kmean, from 49.31 D (range of 45.0 to 52.4 D) to 50.10 D (range of 47.2 to 51.4 D; p=0.80). The average pachymetry was reduced from 436.3 (range of 402 to 476) µm to 399.3 (range of 384 to 406) µm, (p=0.6). Also, the BCVA reduced from logmar 0.037 (range of 0 to 0.1) to logmar 0.112 (range of 0 to 0.2). However, none of these changes were statistically significant (Table 3). Due to persistent corneal haze, 2 patients (22.2%) lost 2 lines of the best corrected visual acuity.

Table 3. Data before primary corneal cross-linking versus last follow-up visit.

	Before primary CXL	Last follow-up visit	p-value
BCVA, logmar	0.037 ± 0.05	0.112 ± 0.06	0.01
Kmax	52.86 ± 4.07	54.75 ± 2.58	0.1
Kmean	49.31 ± 2.80	50.10 ± 2.06	0.8
TCT	436.33 ± 26.72	399.37 ± 7.19	0.6

CXL: corneal cross-linking; BCVA: best corrected visual acuity; Kmax: maximum keratometry; Kmean: median keratometry; TCT: thinnest corneal thickness.

Although all five patients (55.5%) with a history of allergic conjunctivitis were adequately treated, all of them reported occasional episodes of eye itching during the 9.1 (range of 6 to 11) years of follow-up, since primary CXL. Therefore, allergic conjunctivitis and eye scratching, as well as young age, were identified as risk factors for the progression of KC after CXL.

DISCUSSION

In recent years, CXL technique has been successfully used to prevent the progression of KC.[8,9,13] However, in some eyes, especially in children and adolescents, in whom the disease is more aggressive, treatment may fail. After the first CXL, even though KC has remained stable for some time, further KC progression may occur.[2,3,14-17] Raiskup et al.[22] reported recurrences of progressive corneal ectasia at 5 and 10 years after the initial treatment in their 10-year follow-up study.

The current study evaluated the clinical and topographical corneal parameters of nine young patients, 17 years older or younger, who had progressive low stage KC and underwent CXL treatment. All of them showed disease stabilization for an average period of 3.9 (range of 1.6 to 5.4) years. However, after this time, a new progression was identified. All patients were retreated and were followed up for a long period of time. In fact, this is the great contribution of this study: the long-term follow-up. On both occasions, the standard Dresden protocol was used.

A previous study by our group[3] evaluated 16 eyes of 11 patients (8 male) aged between 9 and 14 years, with progressive KC. Patients underwent CXL with the standard Dresden protocol. The mean follow-up time was 26 months (ranging from 12 to 60 months). On the last outpatient follow-up visit, UCVA improved by at least one Snellen line in six eyes (37.5%) and remained stable in nine eyes (56.25%). Two eyes (12.5%) of patients who frequently scratched their eyes required retreatment due to KC progression, 15 and 28 months after the first CXL. These data showed that while CXL is a safe and effective option for treating progressive KC, the effect may not be long-lasting, and additional treatment may be necessary.

There is limited information on the safety and efficacy of repeated CXL for controlling the progression of KC despite previous treatment.[18-20] Antoun et al.[18] demonstrated that CXL retreatment using the conventional epi-off CXL protocol (Dresden protocol) was safe and effective in an adult population. They found stability one year after CXL retreatment in seven eyes of five patients with progressive ectasia. Four eyes had stage II KC, two eyes had stage IV and one eye had post-LASIK ectasia. Mean time to KC progression after the original CXL was 29.14 months. Only two eyes (from a single patient) were treated with CXL alone. Four eyes had already undergone intrastromal corneal ring segment implantation at the time of repeated CXL and one eye underwent CXL retreatment simultaneously with PRK. They noted that allergic conjunctivitis and eye rubbing were the only risk factors associated with KC progression after CXL. In the study by Turhan et al.,[20] all eyes presented Kmax > 57 D before the first CXL, more advanced cases than those in our study. In the first CXL, they used the epi-on technique in 9 of the 12 treated eyes and in the repeated CXL, the epi-off

accelerated technique. Both CXL techniques have shown lower effectiveness than that obtained with the conventional epi-off Dresden protocol.[23,24] After 36 months of follow-up, they observed stability or regression of KC in 11 of the 12 treated eyes. Only one eye showed progression. Corroborating our findings, this patient also had a history of ocular allergy.

After CXL retreatment, patients were followed for a mean time of 5.44 years. Eight eyes achieved KC stability. The corneal flattening observed in these eight eyes suggests that repeated CXL has an additive effect to increase corneal rigidity and biomechanical stability, despite failure of the first treatment. These data corroborate those presented by Turhan et al.[20], who followed patients for 35.9 months (2.9 years) after repeated CXL. Their data have shown a significant decrease in Kmax values in 66.6% of the operated eyes, no change in 16.6% and an increase in 16.6%. They have suggested that patients should be followed up for at least 2 years after a primary CXL to confirm corneal stability. In our study, we observed progression of KC at a mean follow-up time of 3.9 (range of 1.6 to 5.6) years after first treatment. One eye showed progression 4 years after repeated CXL. We can conclude that, in children and adolescents, KC may continue to progress, even after several years of the first or second treatment. Therefore, we suggest that patients undergoing CXL, especially at a young age, be closely monitored for a long period of time.

In the present study, five (55.56%) patients reported eye allergy and the habit of constantly scratching/rubbing their eyes before the first CXL. All of them were properly treated and instructed on the importance of not scratching their eyes. Despite that, all five patients reported isolated episodes of itching during the 9.1 (range of 6 to 11) years of follow-up between the first CXL and the last recorded eye exam. Eye rubbing leads to biochemical and biomechanical changes and therefore plays an important role in disease recurrence.[25-27] Other risk factors for progression, determined by previous studies, include age, pregnancy, paracentral cones, and Kmax greater than 58.0 D.[14-16] Another important observation in our study is that all nine patients (100%) were right-handed. Six of them (66.6%) showed progression of KC in the right eye. McMonnies et al.[27] showed a significant relationship between intense eye rubbing and KC on the same side as hand dominance. However, Santos et al.[28] have shown that the association between higher keratometry values and sleeping position appears to be more significant than that reported between keratometry and itching, or manual dexterity. On the other hand, Bral et al.[29] reported a case of unilateral ectasia in a healthy male patient after persistent unilateral eye rubbing by the nondominant hand. They suggested that this case supports the hypothesis of mechanical fatigue of the cornea due to repetitive shear stress on the corneal surface caused by eye rubbing.

Hafezi et al.[19] described a case of a 32-year-old man that showed a central corneal flattening of up to 4D after a standard Dresden protocol primary CXL and a further flattening effect of another 4D, after accelerated-CXL retreatment, with a total flattening effect of 8 D, 2 years after repeated CXL.

Kymionis et al.[30] also reported a case of a 23-year-old woman who showed a significant progressive corneal flattening, corneal thinning, and hyperopic shift 5 years after a second CXL. The identified causative factor was the extremely higher steep preoperative keratometry. In our study, a mean reduction of 2.012 D in Kmax was observed in eight eyes with a mean follow-up of 5.44 years after repeated CXL. No patient had excessive or continuous corneal flattening. The smaller effect found in our patients may be related to the low age of the patients. Since KC is more severe and aggressive in children and adolescents, CXL may be less effective in this group of patients. Besides, unlike Kymionis et al.,[30] our patients had low stage KC at first treatment, and only 2 eyes were grade III KC, at CXL retreatment.

In a recent study, Kuechler et al.[14] suggested that Kmax greater than 58 D is one of the main risk factors for KC progression after CXL. On the other hand, a study by Sarac et al.[15] concluded that the best individual predictors of treatment outcome 2 years after CXL in pediatric patients were cone location and thinner corneal pachymetry. Pediatric patients with paracentral cones or thin corneas were more likely to progress 2 years after CXL. Similarly, another study conducted by Wisse et al.[17] concluded that extreme corneal thinning (< 330 µm) and more eccentric cones may be additional risk factors for disease progression. At the first CXL, mean thinnest corneal thickness of our patients was 436.33 (range of 402 to 476) µm and mean Kmax was 52.86 (range of 47.6 to 57.2) D. At the time of CXL retreatment, the thinnest pachymetry was 404.89 (range of 368 to 420) µm and Kmax was 56.46 (range of 51.0 to 58.4) D. Therefore, in our patients, there was no extreme elevated keratometry or corneal thinning to account for the progression observed 3.9 (range of 1.6 to 5.6) years after the original CXL or the progression developed by one of the eyes 4 years after repeated CXL. The identified causal factor that justifies the

progression in this group of patients were low age, ocular allergy and the habit of scratching the eyes.

Beshtawi et al.[31] explored the biomehanical changes induced by repeated cross-linking using scanning acoustic microscopy in 30 ex vivo human corneas. The mean donor age was 75 (range of 55 to 88) years. They concluded that no further cross-linkings are induced when CXL is repeated. However, older corneas are stiffer due to the natural stiffness of collagen fibers that occurs with aging. In contrast, in our study, with a population of very young patients, the corneas have not yet reached natural stiffness, which explains the increase in stiffness observed throughout the follow-up period. Also, 20% of the elderly show high glycemia that goes along with increased biomechanical stiffness.[32]

Tabibian et al.[33] have evaluated whether repeated collagen CXL performed in vivo, in mice, shows an additive effect on mechanical corneal stiffness. They concluded that repeated CXL, 3 days after the first procedure, did not increase corneal stiffness. In our study, the mean time interval between the primary and repeated treatment was 3.9 years. Our results show that after this period, repeated CXL proved to be effective.

Kling et al.[11] have investigated the effect of oxygen availability on the biomechanical changes induced by various clinically applied thin cornea CXL protocols, in both thin (murine) and thick (porcine) corneas. They provided evidence that thin corneas have a higher oxygen availability than corneas of standard thickness. Richoz et al.[12] also concluded that the biomechanical effect of CXL seems to be oxygen dependent, which may explain more efficient results of CXL in thin corneas. Our patients had a mean pachymetry of 436.3 (range of 402 to 476) µm at first treatment and 404.89 (range of 368 to 420) µm, at repeated CXL. Probably this low pachymetry justifies the good result observed over the years in 8 (88.8%) eyes, after repeated CXL.

Sarac et al.[15] evaluated 72 eyes of 52 patients with a mean age of 14.8 (9 to 17) years, with progressive KC, for a period of 2 years after CXL. They observed that approximately half of the eyes with thin corneas (≤ 450 µm) showed progression of KC after 2 years of follow-up. Corneas with a pachymetry of less than 400 µm after removal of the epithelium were treated with hypo-osmolar riboflavin to induce artificial edema that would allow the corneas to reach the thickness of 400 µm required by the Dresden protocol. This corneal swelling, artificially induced by hypo-osmolar riboflavin, may lead to a less effective effect of CXL in stabilizing KC. Furthermore, as discussed earlier, the natural history of KC shows higher rates of progression in young patients. In the present study, we also used hypo-osmolar riboflavin to obtain the 400 µm pachymetry required by the conventional Dresden protocol. Hypo-osmolar riboflavin was used in four (44.4%) eyes in the first treatment and in all eyes (100%) in CXL retreatment. Like Sarac et al.,[15] we also observed progression of KC after the initial CXL. However, the mean time to progression observed in our group of patients took longer than the 2 years to occur. On average, our patients showed KC progression 3.9 (range of 1.6 to 5.6) years after the original CXL. Only one patient (11.1%) showed progression 1.6 year after the primary CXL. At this time, he was 9 years old and the thinnest point on his cornea was 456 µm. He underwent repeated CXL at age 11 and, at that time, the thinnest pachymetry was 368 µm. This same patient presented another progression, 4 years after CXL retreatment, when he was 15 years old, with a loss of 3 Snellen lines of his best corrected visual acuity. He was then submitted to intrastromal corneal ring segment implantation to correct corneal irregularity and rehabilitate visual acuity. Probably, the young age, ocular allergy, and the habit of scratching the eyes, justify the continuous progression of the disease in this patient. The other eight eyes (88.8%) showed KC stability at the last follow-up visit. It is interesting to note that, the two youngest patients in the study, both 9 years old at the time of the first CXL, were the ones with the earliest progression: 1.6 and 2.4 years after primary CXL. Mean time to KC progression after the first CXL in the other seven patients was 4.4 years.

These data corroborate studies that suggest that there is an inversely proportional correlation between patient age and KC aggressiveness.[2,3] Therefore, after CXL for progressive KC, a close follow up of the patients is mandatory over a long period of time, so that any suspected topographic changes may be identified and, if progression is confirmed, a new treatment can be performed safely and effectively in time to prevent the progression of the disease and consequent visual impairment.

CONCLUSION

Repeated corneal cross-linking is a safe and effective procedure to stop the progression of keratoconus in young patients in whom the first procedure has failed. The additive effect obtained on corneal stiffness can recover the biomechanical strength achieved, for some time, after the original corneal cross-linking. The slight flattening of the anterior surface of the cornea and the increase in resistance seen in this series of patients proved to be long lasting. However, not all eyes respond equally to corneal

cross-linking. Therefore, close and frequent monitoring of these patients must be performed over a long period of time.

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