Corneal Collagen Crosslinking and Vision-Related Quality of Life: Outcomes in Keratoconus Patients

Crosslinking Corneano e Qualidade de Vida Relacionada com a Visão: Resultados em Doentes com Queratocone

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Recebido/Received: 2024-10-18 | **Aceite/Accepted:** 2025-02-05 | **Published online/Publicado online:** 2025-06-04 | **Published/Publicado:** 2025-09-29

DOI: https://doi.org/10.48560/rspo.38322

ABSTRACT

INTRODUCTION: Keratoconus (KC) is a progressive corneal ectatic disorder that significantly impacts patients' quality of life. This study aims to evaluate the effect of corneal collagen crosslinking (CXL) on vision-related quality of life in keratoconus patients using the Portuguese version of the Keratoconus Outcomes Research Questionnaire (KORQ).

METHODS: Prospective observational study including patients with progressive KC who underwent CXL, as well as a group of stable KC patients without indications for treatment. Patients undergoing CXL completed the KORQ before treatment and six months after. Patients not receiving any treatment also answered the questionnaire at the same time points. A comparison between the KORQ scores of both groups was performed. Relations between KORQ scores and best-corrected visual acuity (BCVA), keratometric and refractive parameters were also assessed.

RESULTS: In the CXL group, the Activity Limitation (AL) subscale improved from 50.86 preoperatively to 52.09 (p=0.746) six months after treatment, while the Symptoms subscale showed a greater increase from 46.86 to 54.80 (p=0.080). The BCVA significantly improved from 0.327 to 0.157 logMAR (p<0.05). Significant reductions (p<0.05) were also observed in maximum keratometry (Kmax), flattest keratometry (K1), and steepest keratometry (K2). In contrast, untreated patients exhibited minimal changes in both visual parameters and KORQ scores. A significant interaction (p=0.036) was observed between time and treatment in the Symptoms subscale, indicating that the CXL group experienced a greater improvement in symptom perception over time.

CONCLUSION: This study underscores the effectiveness of CXL in treating keratoconus by stabilizing the disease and seeming to improve symptom perception. Using patient-reported outcome measures like KORQ is crucial for accurately assessing the impact of the disease and its treatments on patients' quality of life.

KEYWORDS: Corneal Cross-Linking; Keratoconus; Quality of Life; Surveys and Questionnaires.

RESUMO

INTRODUÇÃO: O queratocone é uma doença ectásica progressiva da córnea com um impacto significativo na qualidade de vida dos doentes. Este estudo tem como objetivo avaliar o efeito do *crosslinking* (CXL) na qualidade de vida relacionada com a visão em doentes com queratocone, utilizando a versão portuguesa do *Keratoconus Outcomes Research Questionnaire* (KORQ).

MÉTODOS: Estudo observacional prospetivo que incluiu doentes com queratocone progressivo com indicação para CXL, bem como um grupo de doentes sem indicação para tratamento. Os doentes submetidos a CXL preencheram o KORQ antes do tratamento e seis meses depois. Os doentes não submetidos a tratamento responderam ao questionário nos mesmos momentos. Foi efetuada uma comparação entre as pontuações do KORQ de ambos os grupos. Foram também avaliadas as relações entre as pontuações do KORQ e a melhor acuidade visual corrigida (MAVC), parâmetros queratométricos e refrativos.

RESULTADOS: No grupo de doentes submetidos a CXL, a subescala de Limitação da Atividade (AL) melhorou de 50,86 no pré-operatório para 52,09 (p=0,746) seis meses após o tratamento, enquanto a subescala de Sintomas mostrou um maior aumento, de 46,86 para 54,80 (p=0,080). A MAVC melhorou significativamente de 0,327 para 0,157 logMAR (p<0,05). Foram também observadas reduções significativas (p<0,05) na queratometria máxima (Kmax), na queratometria mais plana (K1) e na queratometria mais curva (K2). Por outro lado, os doentes não tratados apresentaram alterações mínimas tanto nos parâmetros visuais como nas pontuações do KORQ. Observou-se uma interação significativa (p=0,036) entre o tempo e o tratamento na subescala de Sintomas, indicando que o grupo CXL registou uma melhoria superior na perceção dos sintomas ao longo do tempo.

CONCLUSÃO: Este estudo sublinha a eficácia do CXL no tratamento do queratocone, estabilizando a doença e parecendo melhorar a perceção dos sintomas. A utilização de medidas de resultados reportadas pelos doentes, como o KORQ, é crucial para avaliar adequadamente o impacto da doença e dos seus tratamentos na qualidade de vida.

PALAVRAS-CHAVE: Crosslinking Corneano; Inquéritos e Questionários; Qualidade de vida; Queratocone.

INTRODUCTION

Keratoconus is the most common corneal ectatic disease, characterized by localized corneal thinning and protrusion. It typically affects both eyes, though in an asymmetrical way.[1] While the exact etiology is not fully understood, both genetic and environmental factors are believed to contribute to keratoconus development. Key risk factors include eye rubbing, a positive family history, and atopic conditions such as allergies, asthma, or eczema.[2] Diagnosis is usually made during childhood or adolescence, progressing until the third or fourth decade of life.[1,3] Patients with keratoconus often experience poor visual acuity that is difficult to correct with glasses.[1] Besides reduced visual acuity, ectasia-induced refractive errors, such as irregular astigmatism, further contribute to a decline in overall visual quality.[4]

Corneal collagen crosslinking (CXL) is a surgical technique that combines ultraviolet-A light and riboflavin effects to strengthen corneal collagen fibers. By increasing the cornea's biomechanical stability, CXL slows ectasia's progression and prevents further degeneration, delaying the need for a corneal transplant.[1,5] Several studies have reported not only a significant reduction in disease progression but also improvements in best-corrected visual acuity and a flattening of the cornea on topography in patients who underwent CXL.[6,7]

Keratoconus is a chronic condition that significantly affects patients' daily lives, not only due to visual impairment but also the ongoing need for ophthalmologic care. Vision-related quality-of-life (VR-QoL) reflects an individual's level of satisfaction with their vision and how it affects overall life activities.[8] Previous studies showed that the VR-QoL in keratoconus patients is not only lower than that of healthy individuals but also worse when compared to those with other ocular diseases, such as age-related macular degeneration.[9] This is particularly significant in KC as it primarily affects adolescents and young adults. Loss of visual capacity at such an early age can lead to lifelong repercussions on academic and professional achievements. Moreover, VR-QoL deteriorates further as the disease advances.[10]

Over the years, patient-reported outcome (PRO) measures for keratoconus patients have been assessed using tools originally designed for other conditions, such as cataracts or

refractive errors.[11] Given the unique nature of keratoconus, it is essential to use high-quality, condition-specific PRO measures to evaluate VR-QoL in these patients accurately. The Keratoconus Outcomes Research Questionnaire (KORQ) is the first validated, keratoconus-specific questionnaire and serves as a psychometrically robust tool to assess the impact of the disease and its treatments on activity limitation and symptoms.[12] KORQ has been translated and validated in multiple languages, including Portuguese.[13]

While CXL has demonstrated effectiveness in halting keratoconus progression,[5,6] there is still a gap in understanding its impact on patient's perceived quality of life. It is crucial to determine whether CXL offers significant advantages over no treatment at all in relation to daily functioning and overall well-being. Although stabilizing the cornea and achieving visual improvements are important, these outcomes do not always translate into meaningful benefits in quality of life, which is essential for assessing the overall success of the intervention.

This study aims to evaluate the impact of corneal collagen crosslinking on vision-related quality of life in keratoconus patients, using the validated Portuguese version of the KORQ (Appendix A).

MATERIAL AND METHODS

STUDY DESIGN

A prospective observational study, conducted at the Ophthalmology Department of a Portuguese medical center. The study was performed in accordance with the Declaration of Helsinki as revised in 2024.

PARTICIPANTS

Patients diagnosed with keratoconus who had proven clinical progression that were scheduled for CXL were invited to participate. Additionally, a group of stable patients, without indications for CXL, was also invited to answer the questionnaire. Patients were excluded if they presented any of the following: inability to give informed consent or to fully understand the study questions, age <18 years, corneal opacities or scarring, other significant ocular diseases or serious systemic or psychiatric conditions.

SURGICAL PROCEDURE

Surgeries were performed by two experienced corneal surgeons (A.R. and J.G). All patients underwent an accelerated epithelium-off CXL protocol, previously described in the literature.[14] Epithelium removal was achieved using phototherapeutic keratectomy (PTK) to perform a 50 µm debridement. Following epithelial removal, a 0.1% isoosmolar riboflavin solution was applied to the stromal surface for 10 minutes to ensure adequate impregnation. UV-A light irradiation was then performed (KXL 1 UVA system, 10 mW/cm^2, 10 minutes, total dose 6 J/cm^2, Avedro).

DATA COLLECTION

Patients were invited to participate in the study through a phone call. Following their agreement, the questionnaire was sent via email as a Google Forms link, enabling them to complete it online.

The KORQ consists of two subscales: an "Activity Limitation" scale (18 items) and a "Symptoms" scale (11 items). Each of those items has a 4-point rating scale and an additional "not applicable" option. Each patient's score was obtained using a ready-to-use Microsoft Excel scoring spreadsheet for the two subscales. A Rasch analysis was performed to convert the ordinal raw scores into interval-level measurements. This helps to assess the fit of each item to the underlying construct being measured and ensures that the scale operates consistently across different levels of severity, ensuring the validity and reliability of the responses.[12] For better reading and understanding, person-measure data were rescaled from the original logit scale to a 0-100 scale, with higher scores meaning higher ability for daily activities or less symptoms.

All patients proposed for CXL completed the translated and validated Portuguese version of the KORQ before and six months after undergoing CXL. The group of stable patients performed the questionnaire twice, with a similar time interval.

Data including demographics, best-corrected visual acuity (BCVA) and topographic parameters were collected at the same time points. The BCVA was reported as logarithm of minimum angle of resolution (logMAR).

In the group that underwent crosslinking, relationships between demographic and clinical features were assessed and reported based on the treated eye. For untreated patients, analyses were conducted using the better eye, classified according to Kmax, in line with recommendations from the existing literature.[15–17]

STATISTICAL ANALYSIS

Statistical analysis was conducted using IBM SPSS Statistics® for Windows (version 29).

Demographic and clinical variables were summarized using means, standard deviations and frequencies for both the CXL and untreated groups. Independent t-tests were employed to assess differences in continuous variables and chi-squared tests were used for categorical variables. Changes in the activity limitation (AL) and symptoms (S) subscale scores over time were compared between groups using repeated measures ANOVA tests. Additionally, correlation analyses were performed to evaluate relationships between the AL and S scores and keratometric parameters, spherical equivalent, and BCVA. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 31 patients completed the Portuguese version of the KORQ. Of these, 17 underwent CXL and answered

Appendix A. Keratoconus Outcomes Research Questionnaire (KORQ)

Keratoconus Outcomes Research Questionnaire (KORQ)

LIMITAÇÃO DA ACTIVIDADE

(*Por favor, selecione o resposta que melhor descreve como considera que o estado da sua visão afecta a sua capacidade de executar estas atividades*)

1. Quanto é que a sua visão interfere com a utilização do monitor do computador?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

2. Quanto é que a sua visão interfere com a condução durante o dia?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

3. Quanto é que a sua visão interfere com a condução durante a noite?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

4. Quanto é que a sua visão interfere com a leitura de sinais de trânsito?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

5. Quanto é que a sua visão interfere ao ver TV?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

6. Quanto é que a sua visão interfere com a subida/descida de degraus?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

7. Quanto é que a sua visão interfere com evitar colidir com objectos no seu caminho?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

8. Quanto é que a sua visão interfere com a sua aptidão para fazer o seu trabalho?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

9. Quanto é que a sua visão interfere com ver ao longe?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

10. Quanto é que a proximidade de luzes interfere com a sua visão na execução de tarefas?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

11. Quanto é que a sua visão interfere com a execução de tarefas de destreza manual fina ao perto?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

12. Quanto é que a sua visão interfere com a execução dos seus passatempos?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

13. Quanto é que a sua visão interfere com o reconhecimento de caras?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

14. Quanto é que a sua visão interfere com ver quando há pouca luz?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

15. Quanto é que a sua visão interfere com a execução de tarefas domésticas (p.ex., limpar, passar a ferro, lavar a louça)?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

16. Quanto é que a sua visão interfere com a percepção de profundidade?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

17. Quanto é que a sua visão interfere com ver objectos pequenos ao longe (p.ex., bola de golf, dardos)?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

18. Quanto é que a sua visão interfere com a execução de tarefas de observação (p.ex., máquina fotográfica, microscópio, binóculos, etc)?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

SINTOMAS

1. Quanto é que a alteração da sua visão o(a) incomoda?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

2. Quanto é que o brilho e usar sempre óculos de sol o(a) incomoda?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

3. Quanto é que um dia de sol intenso interfere com a sua visão na execução de tarefas?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

4. Quanto é que o uso de lentes de contacto rígidas permeáveis a gás o(a) incomoda?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

5. Quanto é que as dores de cabeça causadas pelo uso de óculos/lentes de contacto o(a) incomodam?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

6. Quanto é que o olho seco o(a) incomoda?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

Relativamente aos seus olhos e à sua visão:
7. Quanto é que dias com muito vento o(a) incomodam?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

Relativamente aos seus olhos e à sua visão:
8. Quanto é que o cansaço o(a) incomoda?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

Relativamente aos seus olhos e à sua visão:
9. Quanto é que dias secos o(a) incomodam?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

Relativamente aos seus olhos e à sua visão:
10. Quanto é que dias com poeiras o(a) incomodam?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

Relativamente aos seus olhos e à sua visão:
11. Quanto é que ambientes com fumo o(a) incomodam?
Não se aplica ☐ Nada ☐ Pouco ☐ Bastante ☐ Muito ☐

the questionnaire again six months after the procedure. The remaining 14 patients, who did not receive any treatment, also completed the baseline and the follow-up questionnaire. Table 1 outlines the demographic and treatment characteristics of both groups.

Among the patients who underwent CXL, the majority were male (70.6%, n=12). The mean age at diagnosis was 20.27 ± 5.81 years old (ranging from 13 to 38) and the mean age at the time of surgery was 23.18 ± 6.79 years (ranging from 14 to 44). Based on the Amsler-Krumeich classification, 5.9% (n=1) of patients were categorized as stage I, 23.5% (n=4) as stage II, 23.5% (n=4) as stage III, and 47.1% (n=8) were classified as having the most advanced form of the disease (stage IV).

In the group that did not receive any treatment, a total of 8 women and 6 men completed the questionnaire. The mean age at diagnosis was 23.58 ± 5.99 years (ranging from 17 to 36), with a current mean age of 32.50 ± 5.61 years (ranging from 24 to 40). The distribution of patients across the four severity stages of the Amsler-Krumeich classification revealed a predominance of individuals in the earlier stages, as 35.7% (n=5) were classified as stage I, and 42.9% (n=6) were at stage II. Only 2 patients were classified as stage III, and 1 patient presented with stage IV keratoconus.

Table 1. Demographic characteristics of both groups.

	Crosslinking group (n=17)	Untreated group (n=14)
Sex		
Male (%)	70.6	57.1
Female (%)	29.4	42.9
Age		
Mean (SD)	23.18 (6.79)	32.50 (5.99)
Severity stage (Amsler-Krumeich classification)		
Stage I (%)	5.9	35.7
Stage II (%)	23.5	42.9
Stage III (%)	23.5	14.3
Stage IV (%)	47.1	7.1
Optical correction		
Glasses (%)	64.7	64.3
Soft contact lenses (%)	0	7.1
Glasses and soft contact lenses (%)	0	21.4
RGP contact lenses (%)	5.9	0
None (%)	29.4	7.1

SD: standard deviation; RGP: rigid gas permeable.

TREATMENT OUTCOMES

In the CXL group, the AL subscale score slightly improved from 50.86 ± 7.46 preoperatively to 52.09 ± 10.90 six months after treatment, although this change was not statistically significant (p=0.746). The Symptoms (S) subscale score demonstrated a more notable increase from 46.86 ± 14.31 to 54.80 ± 12.13 (p=0.080) (Fig. 1). A statistically significant improvement in BCVA was observed, with logMAR values changing from 0.327 ± 0.200 to 0.157 ± 0.151 (p=0.004). Both the flattest keratometry (K1) and steepest keratometry (K2) values showed significant reductions after treatment, with K1 decreasing from 46.95 ± 5.08 diopters (D) to 45.16 ± 4.52 D (p=0.03) and K2 decreasing from 50.22 ± 6.13 D to 48.60 ± 1.14 D (p=0.028). Additionally, maximum keratometry (Kmax) also exhibited a significant decrease, from 57.97 ± 10.41 D to 53.28 ± 10.78 D (p<0.001).

In the untreated group, both AL and Symptoms subscale scores showed a slight decline between the evaluations (Fig. 1). The AL score decreased from 55.83 ± 15.70 to 53.16 ± 7.49 (p=0.597), while the Symptoms score dropped from 51.07 ± 13.92 to 44.63 ± 9.76 (p=0.443). Neither change was statistically significant. The visual acuity of the better eye showed only a minimal variation, changing from 0.064±0.093 to 0.060±0.02 logMAR. Similarly, keratometric parameters exhibited remarkable stability, with K1, K2 and Kmax remaining almost unchanged over time.

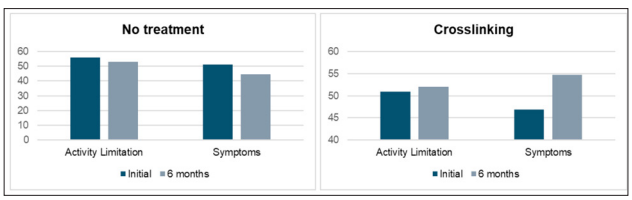

Figure 1. Activity Limitation and Symptoms subscales scores at initial assessment and after 6 months for No Treatment group (left) and Crosslinking group (right).

COMPARISON OF GROUPS

The initial KORQ scores were comparable between groups, with no significant differences observed in the AL (p=0.256) and Symptoms (p=0.252) subscales. In contrast, significant differences were noted in BCVA, with the untreated group demonstrating significantly better vision (p<0.001). As expected, a chi-squared test revealed a significant difference in keratoconus severity (p=0.03) between groups, with patients proposed for crosslinking presenting more advanced stages. The age at keratoconus diagnosis did not differ significantly between the groups (p=0.159), but both current age (p<0.001) and disease duration (p<0.001) were significantly higher in the untreated group, with a mean disease duration of 8.58 ± 4.10 years compared to 2.60 ± 2.66 years in the group proposed for CXL.

The interaction between time and treatment was evaluated using a Repeated Measures ANOVA. No significant difference (p=0.529) was observed in AL score variation over time between groups, and similarly, no significant time effect was detected (p=0.816). In contrast, the Symptoms subscale revealed a significant interaction between time and treatment (p=0.036), indicating that the crosslinking group experienced a greater improvement in symptoms perception over time. However, no overall significant time effect was found for symptoms (p=0.819). Despite the lack of a significant difference in symptoms scores between groups (p=0.391), suggesting a non-significant overall effect of treatment on symptoms, CXL lead to a notable change in symptom perception.

CORRELATIONS BETWEEN KORQ SCORES AND CLINICAL PARAMETERS

Spearman's correlation results are presented in Table 2.

In the CXL group, prior to treatment, there were significant (p<0.05) positive correlations between the Symptoms subscale and keratometric values (K1, K2, and Kmax). Additionally, AL was positively correlated with K2. In the untreated group, no significant correlations were observed at baseline. Later, a significant (p<0.05) negative correlation was found between the Symptoms subscale score and BCVA (logMAR), suggesting that patients with better visual acuity reported fewer symptoms, even without undergoing CXL.

DISCUSSION

This study aimed to evaluate the impact of CXL on vision-related quality of life (VR-QoL) in patients with keratoconus through the Portuguese version of the Keratoconus Outcomes Research Questionnaire. Our findings suggest that CXL not only contributes to significant improvements in keratometric parameters and visual acuity but has also some positive influence on patients' perception of their symptoms.

The KORQ is the most appropriate questionnaire for evaluating the outcomes of interventions in keratoconus patients, as it was specifically designed to address the unique aspects and challenges of this condition.[12,15] With its two subscales (Activity Limitation and Symptoms), the KORQ allows an accurate assessment of the impact of keratoconus and its treatments on patients' daily lives and symptoms.

CXL is an effective and safe surgical technique aimed at increasing biomechanical stability and rigidity of the cornea, to prevent keratoconus progression.[1] Several studies support the role of CXL at stabilization of the disease and improvement of both corneal topographic parameters and visual outcomes, with sustained results at long-term follow-ups.[6,18] Pinto *et al* reported that CXL is the only intervention significantly associated with functional scores.[8] We observed significant corneal flattening after corneal CXL, with notable reductions in maximum keratometry (Kmax), steepest keratometry (K2), and flattest keratometry (K1), indicating an overall improvement in corneal shape and stability.

Table 2. Correlations between KORQ subscales and clinical parameters.

		K1		K2		Kmax		BCVA		Spherical equivalent	
		CXL	Ø tx	CXL	Ø tx	CXL	Ø tx	CXL	Ø tx	CXL	Ø tx
AL	Initial	0.457	-0.280	**0.490**	-0.358	0.398	-0.464	0.039	-0.232	0.072	-0.293
	6m	-0.248	0.249	-0.315	0.222	-0.125	0.557	0.304	0.072	-0.094	0.009
S	Initial	**0.614**	0.156	**0.668**	0.275	**0.551**	0.064	0.233	0.092	0.220	-0.187
	6m	0.253	-0.196	-0.020	-0.389	-0.150	-0.328	0.293	**-0.634**	**-0.562**	0.029

Spearman's correlation coefficients between KORQ subscales and clinical parameters for both groups at initial evaluation and six months follow-up. Significant correlations ($p < 0.05$) are highlighted in bold.

AL: activity limitation; S: symptoms; Initial: initial evaluation; 6m: six months evaluation; CXL: crosslinking group; Ø tx: untreated group; K1: flattest keratometry; K2: steepest keratometry; Kmax: maximum keratometry; BCVA: Best Corrected Visual Acuity (logMAR)..

Our study revealed that both the Activity Limitation and Symptoms scores seemed to improve following CXL. Although neither change reached statistical significance, the improvement in symptoms perception was notably more pronounced. The modest improvement in the AL score suggests that, compared to symptom perception, the effects on broader aspects of daily functioning may take longer to become evident and could be influenced by factors beyond visual acuity and corneal shape. A similar study by Ferrini et al. reported only a minimal and non-significant improvement in the Activity Limitation subscale six months after CXL, with the Symptoms subscale showing scores that were either unchanged or slightly worse.[3] Cingu *et al* evaluated the quality of life in keratoconus patients one year after CXL using a combination of questionnaires and reported improvements in both VR-QoL and overall health-related quality of life. These enhancements appeared to be associated not only with keratometric and visual outcomes but also with a reduction in anxiety levels related to the disease.[19]

The correlations between KORQ subscales and clinical parameters in our study reveal interesting associations. In the CXL group, stronger positive correlations were found between initial keratometric readings and Symptoms scores. While the association of higher keratometric values with fewer reported symptoms may seem unexpected, this may be due to patient adaptation to advanced disease, where compensatory mechanisms reduce symptom reporting despite severe corneal steepening. Additionally, symptom perception varies and may not directly correlate with clinical measures. The lack of a significant correlation between BCVA and symptoms in the CXL group likely reflects the stabilizing effect of CXL, which prevents further visual decline. Even if BCVA does not significantly improve, the stabilization itself may reduce the perception of worsening symptoms. The use of customized crosslinking protocols, tailored to individual patient characteristics, may contribute to the observed improvements in visual outcomes and symptoms after CXL. A study by Seiler et al compared the one-year outcomes of customized versus standard CXL protocols, demonstrating a stronger flattening effect, better corneal regularization, and improved epithelial healing with customized CXL.[20] These personalized approaches optimize the effectiveness of the procedure, potentially leading to enhanced visual outcomes, even in the absence of significant changes in BCVA. A randomized clinical trial found improvements in symptoms such as glare, halos, night driving, and starbursts one year after CXL. Interestingly, none of these improvements correlated with BCVA, indicating that patients can experience significant relief in symptoms and overall visual quality that may not be reflected in measurable changes in BCVA.[21]

The comparison of initial KORQ scores between the CXL and untreated groups revealed no significant differences in both subscales, despite notable disparities in clinical parameters such as BCVA and keratoconus severity. This aligns with previous research indicating that symptom perception and functional limitations do not always correlate with objective visual metrics like BCVA. The untreated group, exhibiting a longer disease duration and better BCVA, suggests a more stable condition, justifying their lack of proposed treatment. We consider that the absence of significant differences in baseline scores between the groups may have been influenced by lifestyle and demographic factors. The broad age range within both groups, for example, suggests that certain questionnaire items may not have been equally applicable to all patients, potentially impacting the overall results.

Our findings support the idea that CXL is a worthwhile intervention for keratoconus patients. Although initial KORQ scores were similar, we found a significant interaction between time and treatment in the Symptoms subscale, with the CXL group experiencing a greater improvement in symptom perception over time. The lack of a significant time effect on AL scores suggests that broader functional improvements may require longer follow-up periods to be observed.

It is important to note that, similarly to the group of patients who underwent CXL, the untreated group was also evaluated twice with the KORQ questionnaire. This not only allows for a comparison of baseline and follow-up scores but also serves to evaluate the repeatability of the questionnaire. This repeated measurement enhances the reliability of the results and helps assess the consistency of symptom perception and activity limitations over time in the absence of intervention.

Our study has some limitations. The small sample size may restrict the generalizability of our findings and reduce the statistical power needed to detect significant changes.

We believe that with a larger sample, the observed improvement trend could potentially reach statistical significance. Additionally, the six-month follow-up period might be insufficient to observe long-term effects on quality of life and activity limitations. Although both groups had similar KORQ scores at baseline, differences in demographic features and disease severity could influence the results and complicate comparisons, highlighting the need for careful interpretation of the findings.

In conclusion, corneal collagen crosslinking is a critical intervention for managing keratoconus, with established effectiveness in halting disease progression while enhancing keratometric and visual outcomes. Our study further reveals a significant improvement in patients' symptom perception and overall vision-related quality of life following CXL. This underscores the importance of integrating patient-reported outcome measures, such as the KORQ, into routine assessments, for capturing the true impact of the disease and evaluating treatment effectiveness from the patient's perspective.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

MF: Conceptualization, formal analysis, data collection, writing the manuscript.

EG: Data collection.

JG: Conceptualization, formal analysis, writing – review and editing.

EC, AR, CT, MJQ, JM: Critical revision.

All authors approved the final version to be published.

MF: Conceptualização, análise formal, recolha de dados, redação do manuscrito.

EG: Recolha de dados.

JG: Conceptualização, análise formal, redação – revisão e edição.

EC, AR, CT, MJQ, JM: Revisão crítica

Todos os autores aprovaram a versão final a ser publicada.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

REFERENCES

1. Santodomingo-Rubido J, Carracedo G, Suzaki A, Villa-Collar C, Vincent S, Wolffsohn J. Keratoconus: An updated review. Contact Lens and Anterior Eye. 2022;45:101559. doi:10.1016/j.clae.2021.101559.
2. Hashemi H, Heydarian S, Hooshmand E, Saatchi M, Yekta A, Aghamirsalim M, et al. The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis. Cornea. 2020;39:263. doi:10.1097/ICO.0000000000002150.
3. Ferrini E, Aleo D, Posarelli C, Figus M, Miccoli M, Gabbriellini G. Impact of corneal collagen cross-linking on vision-related quality of life measured with the keratoconus outcomes research questionnaire (KORQ) in patients with keratoconus. Contact Lens and Anterior Eye. 2023;46:101746. . doi:10.1016/j.clae.2022.101746.
4. Kurna S, Altun A, Gencaga T, Akkaya S, Sengor T. Vision Related Quality of Life in Patients with Keratoconus. 2014;2014:694542. doi:10.1155/2014/694542.
5. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003;135:620-7. doi:10.1016/S0002-9394(02)02220-1.
6. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat L. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: Long-term results. J Cataract Refract Surg. 2008;34:796-801. doi:10.1016/J.JCRS.2007.12.039
7. Chan C, Sharma M, Wachler B. Effect of inferior-segment Intacs with and without C3-R on keratoconus. J Cataract Refract Surg. 2007;33:75-80. doi:10.1016/J.JCRS.2006.09.012.
8. Pinto R, Abe R, Gomes F, Barbisan P, Martini A, Borges D, et al. Quality of life in keratoconus: evaluation with Keratoconus Outcomes Research Questionnaire (KORQ). Sci Rep. 2021;11:12970. doi:10.1038/s41598-021-92346-1
9. Kymes S, Walline J, Zadnik K, Gordon M, Collaborative Longitudinal Evaluation of Keratoconus study group. Quality of life in keratoconus. Am J Ophthalmol. 2004;138:527-35. doi:10.1016/j.ajo.2004.04.031.
10. Kymes S, Walline J, Zadnik K, Sterling J, Gordon O, Collabo-

rative Longitudinal Evaluation of Keratoconus study group. Changes in the Quality of Life of People with Keratoconus. Am J Ophthalmol. 2008;145:611. doi:10.1016/J.AJO.2007.11.017
11. Ortiz-Toquero S, Perez S, Rodriguez G, De Juan V, Mayo-Iscar A, Martin R. The influence of the refractive correction on the vision-related quality of life in keratoconus patients. Qual Life Res. 2016;25:1043-51. doi:10.1007/s11136-015-1117-1.
12. Khadka J, Schoneveld P, Pesudovs K. Development of a keratoconus-specific questionnaire using rasch analysis. Optom Vis Sci. 2017;94:395-403. doi:10.1097/OPX.0000000000001035.
13. Pinto R, Gomes F, Arieta C, Alves M. Translation and validation of the Portuguese version of the Keratoconus Outcomes Research Questionnaire (KORQ). Arq Bras Oftalmol. 2021;84:430-5. doi:10.5935/0004-2749.20210067.
14. Kanellopoulos AJ, Asimellis G. Keratoconus management: long-term stability of topography-guided normalization combined with high-fluence CXL stabilization (the Athens Protocol). J Refract Surg. 2014;30:88-92. doi:10.3928/1081597X-20140120-03.
15. Kandel H, Pesudovs K, Nguyen V, Chen J, Poon A, Mills R, et al. Patient-Reported Outcomes in Keratoconus: A Save Sight Keratoconus Registry Study. Cornea. 2023;42:590-7. doi:10.1097/ICO.0000000000003119.
16. Kandel H, Nguyen V, Piermarocchi S, Ceklic L, Teo K, Arnalich-Montiel F, et al. Quality of life impact of eye diseases: a Save Sight Registries study. Clin Exp Ophthalmol. 2022;50:386-97. doi:10.1111/CEO.14050.
17. Sahebjada S, Fenwick E, Xie J, Snibson G, Daniell M, Baird P. Impact of Keratoconus in the Better Eye and the Worse Eye on Vision-Related Quality of Life. Invest Ophthalmol Vis Sci. 2014;55:412-6. doi:10.1167/IOVS.13-12929.
18. Taşçı Y, Taşlıpınar G, Eyidoğan D, Saraç Ö, Çağıl N. Five-Year Long-Term Results of Standard Collagen Cross-Linking Therapy in Patients with Keratoconus. Turk J Ophthalmol. 2020;50:200. doi:10.4274/TJO.GALENOS.2020.53810.
19. Cingu A, Bez Y, Cinar Y, Turkcu F, Yildirim A, Sahin A, et al. Impact of Collagen Cross-linking on Psychological Distress and Vision and Health-Related Quality of Life in Patients With Keratoconus. Eye Contact Lens. 2015;41:349-53. doi:10.1097/ICL.0000000000000129.
20. Seiler TG, Fischinger I, Koller T, Zapp D, Frueh BE, Seiler T. Customized Corneal Cross-linking: One-Year Results. Am J Ophthalmol. 2016;166:14-21. doi:10.1016/j.ajo.2016.02.029.
21. Brooks N, Greenstein S, Fry K, Hersh P. Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia. J Cataract Refract Surg. 2012;38:615-9. doi:10.1016/J.JCRS.2011.11.029.

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