ORIGINAL RESEARCH

Three-year Results of Customized Corneal Collagen Cross-linking for Keratoconus Patients in Oman

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Abstract

Purpose: This 3-year study examined the safety and efficacy of customized corneal collagen cross-linking (CuRV) for keratoconus in patients from Oman.

Methods: Corneal collagen cross-linking was initiated by the application of 0.1% riboflavin. Targeted ultraviolet-A light was applied to the treatment area, and the energy levels were customized according to the topographic findings. Efficacy assessments were conducted preoperatively and postoperatively at 1, 6, 12, 24, and 36 months. Uncorrected distance visual acuity (UCVA), best corrected distance visual acuity (BCVA), maximum keratometry (Kmax), mean keratometry (Kmean), and corneal pachymetry were measured.

Results: Most eyes (17/20 or 85% and 15/20 or 75%) improved or remained stable in UCVA or BCVA, respectively, between baseline and 36 months. Mean changes in Kmax from baseline were significant at 6–36 months, ranging from −1.4 to −2.1 D of flattening. Most (80%) eyes demonstrated ≥1 D of flattening at 36 months compared with baseline. At 36 months, mean pachymetry values showed corneal thinning at 6 and 24 months compared with baseline values ($p < 0.05$). In terms of safety, 15 and 25% of eyes showed small deteriorations of UCVA and BCVA, respectively.

Conclusions: Overall, CuRV was safe and effective for long-term stabilization of keratoconus progression. Stable improvement in visual function and corneal flattening were observed over the 3-year follow-up period.

Keywords: Corneal collagen cross-linking, Customized, Customized, Customized corneal collagen cross-linking, Epi-off, Keratoconus.

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Introduction

Keratoconus is a bilateral ocular disease that is characterized by progressive corneal thinning and steepening.[1] The disease typically exhibits an asymmetric profile with one eye being affected more than the other.[2] Progression of keratoconus can lead to irregular astigmatism, reduced visual acuity, and the need for corneal transplantation in severe cases.[1,3] Corneal steepening and decreased visual acuity in the eye with better vision correlate with decreased vision-related quality of life (including the indicators of near activity, distance activity, driving, role difficulty, and mental health).[4] Environmental factors that increase risk for keratoconus development include atopy, eye rubbing, sun exposure, and geography.[5]

The global prevalence of keratoconus has been estimated at between 2,000 and 4,790 per 1,00,000 individuals, with the highest prevalence occurring in the 20–30 year-old age-group.[1,5–7] The disease exhibits a higher prevalence in people of Arab, Asian, and Indian descent compared with those of European descent.[8] A study in Saudi Arabia found the keratoconus prevalence among 12–21-year-olds to be 4.8%.[9] Another study from that country found the prevalence of keratoconus among individuals seeking laser refractive surgery to be as high as 19.7%.[10] A retrospective study from the Ministry of Defense Hospital in Oman reported 458 new keratoconus patients (893 eyes) in a 5-year period from January 2011 to December 2015.[8] A recent cross-sectional study in Oman showed an overall keratoconus prevalence of 3.49% in individuals aged 20–34 years, with certain Omani regions exhibiting rates up to 16.8%, and a significant proportion of cases already in advanced stages upon detection.[11]

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Treatments for keratoconus vary with the stage of the disease—stable vs progressive.[1,12] Stable keratoconus is typically managed using spectacles, rigid contact lenses, topography-guided photorefractive keratectomy, intracorneal ring segments, corneal allogenic intrastromal ring segments, or posterior-chamber intraocular lens or intraocular lens.[1,12] Corneal collagen cross-linking (CXL) is the preferred treatment for progressive keratoconus.[1,12] In severe cases, corneal transplantation with penetrating keratoplasty or deep anterior lamellar keratoplasty may be required.

Corneal collagen cross-linking is a surgical procedure that promotes the formation of covalent bonds between collagen molecules to strengthen the tissue and slow or halt progression of keratoconus.[1,13,14] Conventional CXL involves the removal of the corneal epithelium followed by the application of riboflavin and ultraviolet (UV) radiation (termed epi-off CXL).[14] The technique is well-established as an effective treatment for halting

keratoconus progress.[14,15] Transepithelial ("epithelium-on") methods of CXL also have become available in recent years with the potential for reduced postoperative pain, although in some cases it may not be as effective as traditional epithelium-off cross-linking at normalizing the corneal surface and improving higher-order aberrations, or flattening Kmax.[16–18]

Recently, modifications have been introduced with both transepithelial and epithelium-off CXL procedures, including reducing treatment times.[19,20] Reduced treatment times can require increased energy and, therefore, may cause increased oxygen consumption.[20–22] As a result, oxygen supplementation has been used to promote more stable bonds between collagen fibers, thereby increasing corneal strength and allowing for the shorter treatment times.[16,20,23]

Biomechanical modeling of the cornea has demonstrated that excellent results can be obtained by treating only the weak sections of a cornea with keratoconus. In other words, it is not necessary to strengthen the entire corneal surface.[24] In this more customized approach, more energy can be focused on weaker parts of the cornea while stable areas can receive less or even no UV energy.[22,24] Customized corneal collagen cross-linking (CuRV) employs targeted activation using riboflavin with customized UV energy shapes and defined intensity profiling. This induces more targeted stiffening of the cornea in the weakest areas. Customized CXL has been shown to have comparable safety with faster epithelial healing and stronger flattening in Kmax than standard CXL.[22] The current study examines 3-year safety and efficacy outcomes with customized corneal collagen cross-linking for keratoconus treatment in patients from Oman.

Methods

Study Design and Participants

This was a prospective study conducted at the Ministry of Defense Hospital Ophthalmology Center in Muscat, Oman. The follow-up period started on September 2, 2018 and has been extended to 3 years postoperatively. Ethical approval was obtained prior to the research initiation. Informed consent was obtained prior to the CXL procedure.

For inclusion into the study, all patients had to be 13–30 years old (as of treatment date), and could be of any race or gender. An established diagnosis of keratoconus with recorded progression was required. Keratoconus progression was defined as an increase in the Kmax by ≥1 D over 1 year. Prior to the procedure, patients had to cease contact lens wear for either 1 week (soft contact lenses) or 2 weeks (rigid gas-permeable lenses) prior to their screening visit. Patients had to be willing and able to provide written informed consent and comply with all study instructions.

Patients were excluded from participation for corneal pachymetry < 400 microns (thinnest point); a known sensitivity or allergy to investigational product; a concurrent history of any other ocular pathologies; a history of previous refractive surgery; or pregnancy and/or lactation during the study period.

Surgical Procedures

Topical anesthesia, consisting of 1% tetracaine one drop every minute for 15 min, was applied. Epithelial debridement over the specific targeted area was performed using a crescent blade. Corneal collagen cross-linking was initiated by the application of riboflavin (VibeX Rapid 0.1% Riboflavin; Avedro—now Glaukos Corp., Aliso Viejo, CA). Targeted UVA light (UV-A system; Mosaic™ System, Glaukos Corp.) was applied to the treatment area, and the energy levels were customized according to the topographic findings. The greatest energy dose was applied over the area of steepest posterior curvature, encompassing the area of steepest anterior elevation as well. Treatment zones of 10, 7.2, and 5.4 J with 30 mW/cm^2 continuous illumination were used.

Postoperative topical medications included moxifloxacin 4 times per day for 1 week; fluorometholone 4 times per day for 1 week and tapered weekly over 1 month; ketorolac 3 times per day for 5 days; cyclopentolate 3 times per day for 5 days; and artificial tears 2 hourly for 1 week, then 4 times per day for 1 month.

Table 1: Demographics

Category	*Value*
N	20
Age (mean ± SD)	19.7 ± 4.6
Gender, *n* (%)	
Male	11 (55)
Female	9 (45)
Eye, *n* (%)	
Right eye	13 (65)
Left eye	7 (35)

Outcomes and Statistical Analysis

Efficacy assessments were scheduled preoperatively and postoperatively at 1, 6, 12, 24, and 36 months. These measurements included: Uncorrected distance visual acuity (UCVA), best corrected distance visual acuity (BCVA), corneal topography (including maximum keratometry (Kmax) and mean keratometry (Kmean), and corneal pachymetry. A Pentacam HR machine was used for corneal topography. Keratoconus progression was defined as an increase in the Kmax by ≥1 D over 1 year. Safety assessments included adverse events and any worsening of UCVA or BCVA. Differences in efficacy assessments vs baseline were analyzed using a paired *t*-test. The threshold for statistical significance was set at $p < 0.05$.

Results

Demographics

Fifty-four eyes with keratoconus were originally treated in 2018. Data for 20 eyes from 20 patients were available out to 36 months. The average age of these 20 patients was 19.7 ± 4.6 years and 55% were males (Table 1).

Efficacy

Table 2 shows the numerical outcomes for key efficacy parameters measured through 36 months.

Visual Acuity

Significant improvements compared with baseline were observed for the overall mean UCVA values at 12 and 24 months ($p < 0.05$; Table 2; Fig. 1). Most (17 of 20; 85%) eyes improved in UCVA or remained stable between baseline and 36 months (Fig. 2).

The overall mean BCVA significantly improved at 12, 24, and 36 months compared with baseline ($p < 0.05$; Table 2; Fig. 3). The BCVA of most (15 of 20; 75%) eyes improved or remained stable between baseline and 36 months (Fig. 4).

Table 2: Efficacy results

Category	*Preop*	*1 month*	*6 months*	*12 months*	*24 months*	*36 months*
UCVA mean (decimal)	0.254	0.260	0.284	0.328	0.320	0.290
p-value vs preop		0.888	0.147	0.003	0.032	0.192
BCVA mean (decimal)	0.505	0.507	0.557	0.590	0.634	0.656
p-value vs preop		0.864	0.172	0.030	0.031	0.010
Kmax mean (diopters)	56.720	56.558	55.345	55.321	55.195	54.600
p-value vs preop		0.493	0.0009	0.0008	4.926e-05	4.083e-05
Anterior Kmean (diopters)	48.8400	49.047	48.290	48.347	48.416	47.915
p-value vs preop		0.766	0.002	0.003	0.010	0.004
Posterior K mean (Diopters)	–7.17	–7.24	–7.19	–7.25	–7.2	–7.17
p-value vs preop		0.144	0.199	0.064	0.09	0.353
Pachymetry mean (µm)	445.6	437.9	436.6	435.4	430.7	431.4
p-value vs preop		0.081	0.019	0.069	0.032	0.059

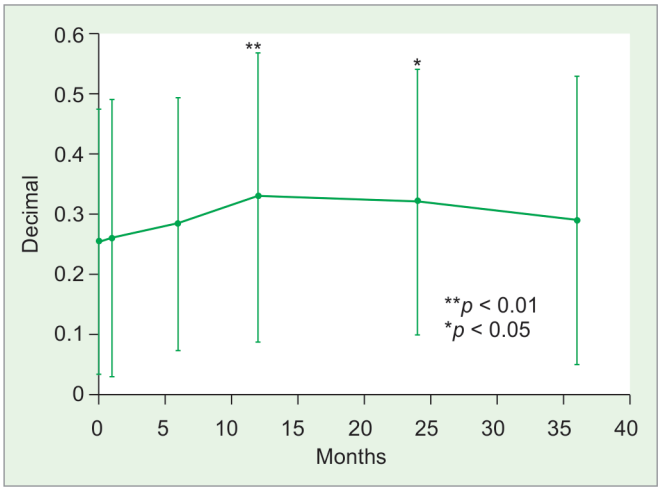

Fig. 1: Mean uncorrected visual acuity (decimal) following customized corneal collagen cross-linking treatment for keratoconus ($n = 20$)

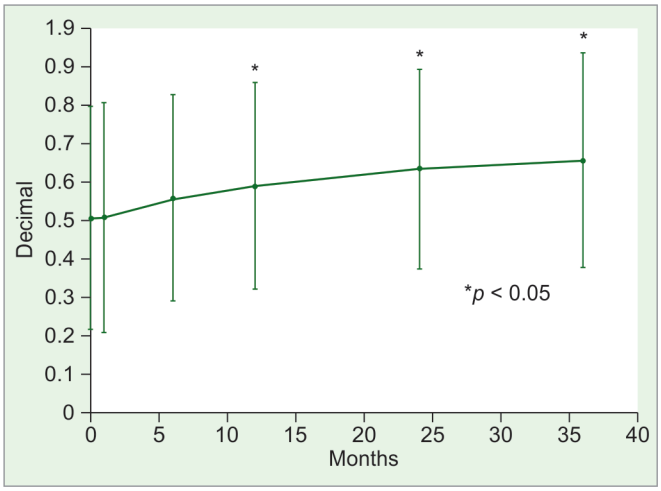

Fig. 3: Mean best corrected visual acuity (decimal) following customized corneal collagen cross-linking treatment for keratoconus ($n = 20$)

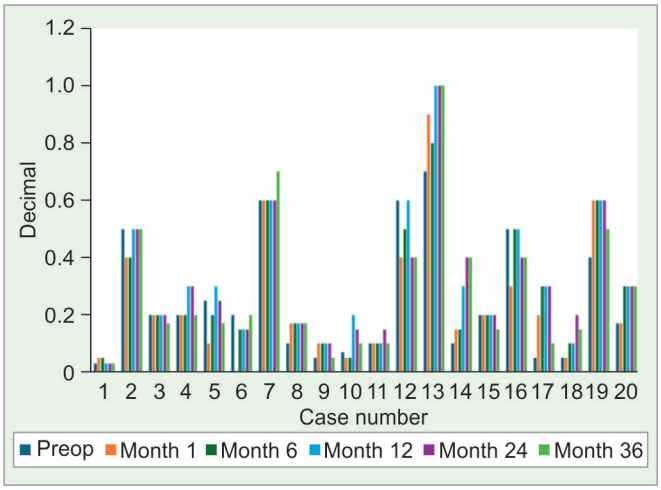

Fig. 2: Uncorrected visual acuity (decimal) following customized corneal collagen cross-linking treatment for keratoconus (results from individual eyes are shown)

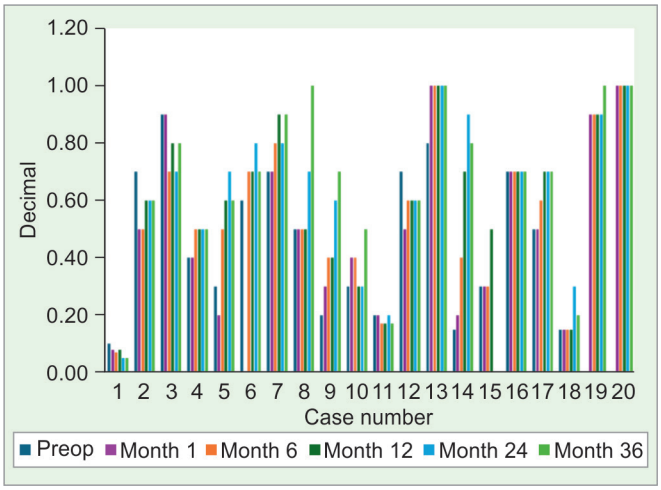

Fig. 4: Best corrected visual acuity (decimal) following customized corneal collagen cross-linking treatment for keratoconus (results from individual eyes are shown)

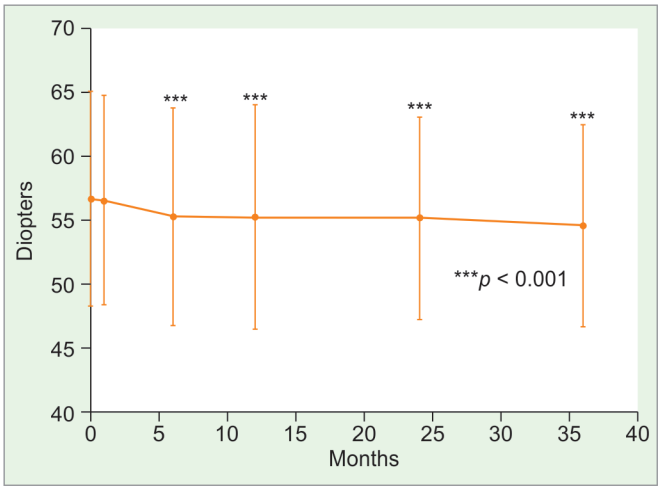

Fig. 5: Mean Kmax values following customized corneal collagen cross-linking treatment for keratoconus ($n = 20$)

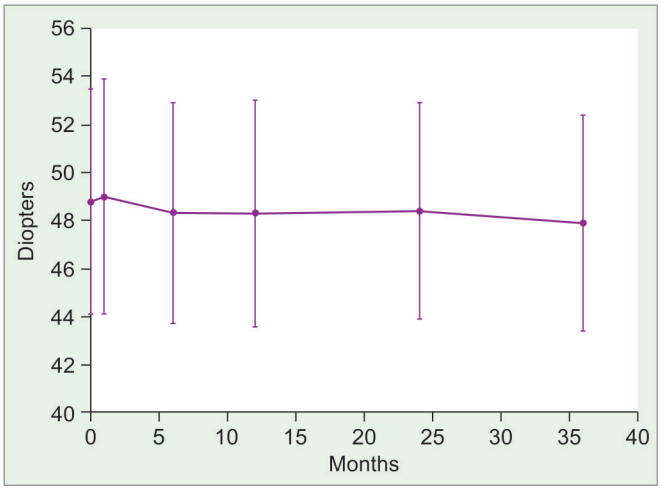

Fig. 7: Kmean values following customized corneal collagen cross-linking treatment for keratoconus ($n = 20$)

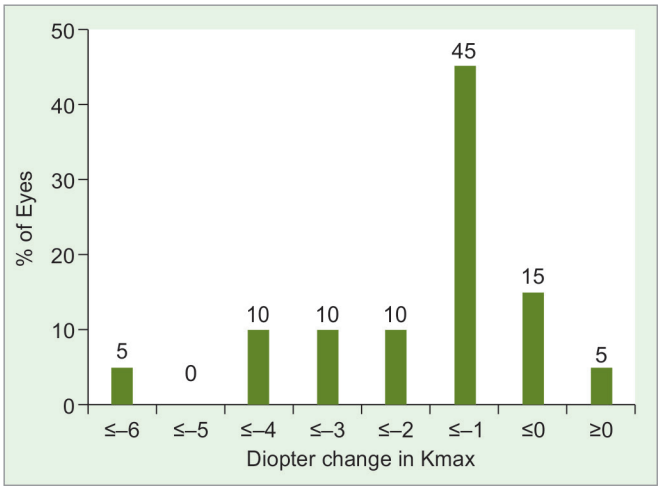

Fig. 6: Change in Kmax values following customized corneal collagen cross-linking treatment for keratoconus ($n = 20$)

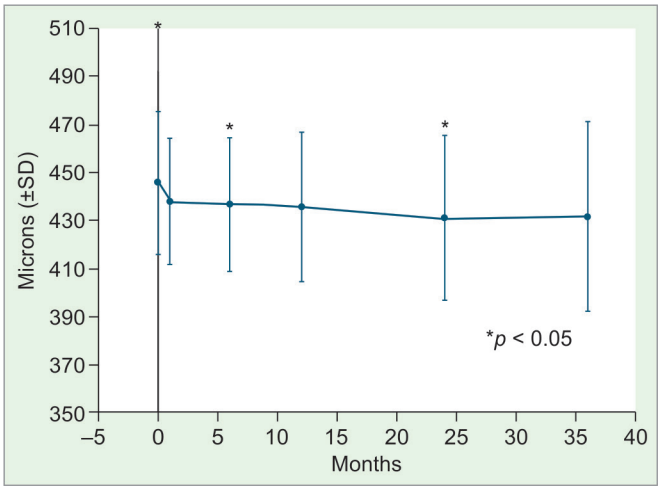

Fig. 8: Mean corneal pachymetry following customized corneal collagen cross-linking treatment for keratoconus ($n = 20$)

Corneal Topography

Significant reductions from baseline (indicating flattening or normalization of the corneal curvature) in the overall mean Kmax were observed at 6, 12, 24, and 36 months (Fig. 5). Mean changes in Kmax from baseline over this timeframe ranged from –1.4 to –2.1 D. Mean change in Kmax from baseline at 36 months was –2.1 D. Most (80%) eyes demonstrated ≥1 D of flattening at 36 months compared with baseline, while 35% showed ≥2 D of flattening (Fig. 6). Only one eye (5%) had slight worsening of 0.1 D at 36 months. No worsening of ≥1 D was reported for any eye between baseline and 36 months.

Overall average anterior Kmean values showed significant improvement at 6, 12, 24, and 36 months ($p < 0.05$) (Fig. 7). Additionally, 14 of 20 (70%) of the eyes showed improvement, two (10%) were stable with no change, and four (20%) had a slight ≤0.4 D worsening at 36 months.

Overall average posterior Kmean values did not show any statistical significant differences at 1, 6, 12, 24 and 36 months ($p > 0.05$) (Table 2).

Pachymetry

Mean pachymetry values showed corneal thinning at 6 and 24 months compared with baseline values ($p < 0.05$; Table 2; Fig. 8). Stable but nonsignificant trends toward thinning ($p < 0.081$) were also observed at 1, 12, and 36 months. Only four of 20 (20%) eyes did not show corneal thinning compared with baseline over the course of the 36-month study.

Safety

Safety observations included adverse events and loss of UCVA and BCVA. Delayed epithelial healing was noted in one patient at 1 week postoperative; no resultant sequelae or complications were recorded. Mild (grade I) corneal haze was noted in five patients at 1 week postoperative, and persisted in one patient at 1 month postoperative; no eyes had haze at 3 months postoperative. A small proportion of eyes (three of 20; 15% and five of 20; 25%) showed a slight deterioration of UCVA or BCVA, respectively, between

baseline and 36 months. No secondary procedures were completed in any eye.

Discussion

Customized corneal collagen cross-linking was safe and effective for stabilizing keratoconus progression for up to 36 months in most eyes. Stable improvement in UCVA and BCVA were reported, with some eyes showing further improvements at 24 and/or 36 months. Significant reductions from baseline in the overall mean Kmax, indicating flattening or normalization of the corneal curvature, were observed up to 36 months. Safety events were mild and minimal, and only a small proportion of eyes showed minor deteriorations of UCVA and BCVA, respectively.

The present results can be appreciated in the context of prior studies on customized cross-linking. Lang et al. conducted a study with three epithelium-off protocols (standard, accelerated with equivalent total irradiance, and accelerated with increased total irradiance) that showed improvements in BCVA and Kmax compared with baseline.[25] Our results also showed stable improvements in UCVA, BCVA, Kmax, and Kmean following the customized cross-linking procedure. Seiler et al. conducted a study in 40 eyes to compare the efficacy of customized corneal cross-linking with standard CXL ($n = 20$ per group).[22] The improvement in Kmax was significantly better at 1 year in the customized CXL group vs standard CXL, with favorable safety, including low rates of delayed epithelial healing. The study authors concluded that customized CXL was as safe as standard CXL with greater flattening in Kmax, with the added benefit of faster epithelial healing.[22] Within the customized group of the Seiler et al. study (the appropriate comparator for our present customized cross-linking cohort), change in Kmax was –1.7 D at 12 months. In comparison, our study showed comparable flattening at 12 months, but more pronounced flattening by 36 months (–2.1 D); safety outcomes were similarly favorable in the two studies, including very low incidence of delayed epithelial healing.

Balidis et al. conducted a study in 54 eyes using customized transepithelial CXL combined with sustained oxygen delivery.[19] This 2-year follow-up study showed significant improvements in visual function and corneal curvature, with a favorable safety profile. These results suggest that oxygen supplementation may be a valuable addition to the customized CXL treatment protocol for keratoconus.

This study is not without limitations. Data through 3 years was not available for all patients. Anterior and posterior corneal curvature data were not available. Sample size was modest. There was no concurrent control group of no cross-linking, as all patients had progressive keratoconus and needed treatment. Future research could include larger prospective studies using customized CXL and oxygen supplementation with pulsed, higher dose UVA. Comparative studies could also be done to compare the efficacy and safety of customized vs standard CXL.

Customized CXL utilizes targeted activation using riboflavin with customized UV energy shapes and defined intensity profiling. In our study, customized CXL was safe and effective for long-term stabilization of keratoconus progression. Stable improvement in visual function and corneal flattening was observed over the 3-year follow-up period, with favorable safety. These results support the clinical utility of this treatment in halting keratoconus progression.

References

1. Santodomingo-Rubido J, Carracedo G, Suzaki A, et al. Keratoconus: An updated review. Cont Lens Anterior Eye 2022;45(3):101559. DOI: 10.1016/j.clae.2021.101559.
2. Nichols JJ, Steger-May K, Edrington TB, et al. The relation between disease asymmetry and severity in keratoconus. Br J Ophthalmol 2004;88(6):788–791. DOI: 10.1136/bjo.2003.034520.
3. Li X, Rabinowitz YS, Rasheed K, et al. Longitudinal study of the normal eyes in unilateral keratoconus patients. Ophthalmology 2004;111(3):440–446. DOI: 10.1016/j.ophtha.2003.06.020.
4. Jones-Jordan LA, Walline JJ, Sinnott LT, et al. Asymmetry in keratoconus and vision-related quality of life. Cornea 2013;32(3):267–272. DOI: 10.1097/ICO.0b013e31825697c4.
5. Gordon-Shaag A, Millodot M, Shneor E, et al. The genetic and environmental factors for keratoconus. Biomed Res Int 2015;2015:795738. DOI: 10.1155/2015/795738.
6. Flockerzi E, Xanthopoulou K, Goebels SC, et al. Keratoconus staging by decades: A baseline ABCD classification of 1000 patients in the Homburg Keratoconus Center. Br J Ophthalmol 2021;105(8):1069–1075. DOI: 10.1136/bjophthalmol-2020-316789.
7. Hashemi H, Heydarian S, Hooshmand E, et al. The prevalence and risk factors for keratoconus: A systematic review and meta-analysis. Cornea 2020;39(2):263–270. DOI: 10.1097/ICO.0000000000002150.
8. Al-Mahrouqi HH, Al-Shamli N, Mohan NR, et al. Clinical profile of Omani keratoconus patients: An experience from a tertiary referral centre in Muscat. Oman J Ophthalmol 2018;11(3):259–264. DOI: 10.4103/ojo.OJO_203_2017.
9. Netto EAT, Al-Otaibi WM, Hafezi NL, et al. Prevalence of keratoconus in paediatric patients in Riyadh, Saudi Arabia. Br J Ophthalmol 2018;102(10):1436–1441. DOI: 10.1136/bjophthalmol-2017-311391.
10. Althomali TA, Al-Qurashi IM, Al-Thagafi SM, et al. Prevalence of keratoconus among patients seeking laser vision correction in Taif area of Saudi Arabia. Saudi J Ophthalmol 2018;32:114–118. DOI: 10.1016/j.sjopt.2017.11.003.
11. Al Saidi R, Almahroqi H, Bandara A, et al. Prevalence of keratoconus among young adults in Oman: A cross-sectional study using retinoscopy and corneal tomography. Int J Kerat Ect Cor Dis 2023;10(1–2):20–25. DOI: 10.5005/jp-journals-10025-1195.
12. Deshmukh R, Ong ZZ, Rampat R, et al. Management of keratoconus: An updated review. Front Med (Lausanne) 2023;10:1212314. DOI: 10.3389/fmed.2023.1212314.
13. Raiskup F, Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A. I. Principles. Ocul Surf 2013;11(2):65–74. DOI: 10.1016/j.jtos.2013.01.002.
14. Hersh PS, Stulting RD, Muller D, et al. United States multicenter clinical trial of corneal collagen crosslinking for keratoconus treatment. Ophthalmology 2017;124(9):1259–1270. DOI: 10.1016/j.ophtha.2017.03.052.
15. Wollensak G. Crosslinking treatment of progressive keratoconus: New hope. Curr Opin Ophthalmol 2006;17(4):356–360. DOI: 10.1097/01.icu.0000233954.86723.25.
16. Matthys A, Cassagne M, Galiacy SD, et al. Transepithelial corneal cross-linking with supplemental oxygen in keratoconus: 1-year clinical results. J Refract Surg 2021;37(1):42–48. DOI: 10.3928/1081597X-20201111-01.
17. Arance-Gil A, Villa-Collar C, Perez-Sanchez B, et al. Epithelium-off vs. transepithelial corneal collagen crosslinking in progressive keratoconus: 3 years of follow-up. J Optom 2021;14(2):189–198. DOI: 10.1016/j.optom.2020.07.005.
18. D'Oria F, Palazon A, Alio JL. Corneal collagen cross-linking epithelium-on vs. epithelium-off: A systematic review and meta-analysis. Eye Vis (Lond) 2021;8(1):34. DOI: 10.1186/s40662-021-00256-0.
19. Balidis M, Koronis S, de Politis PB, et al. Two-year outcomes of transepithelial customized cross-linking for mild to moderate keratoconus. Int J Kerat Ect Cor Dis 2023;10(1–2):26–31. DOI: 10.5005/jp-journals-10025-1196.

20. Hill J, Liu C, Deardorff P, et al. Optimization of oxygen dynamics, UV-A delivery, and drug formulation for accelerated epi-on corneal crosslinking. Curr Eye Res 2020;45(4):450–458. DOI: 10.1080/02713683.2019.1669663.
21. Lim WK, Soh ZD, Choi HKY, et al. Epithelium-on photorefractive intrastromal cross-linking (PiXL) for reduction of low myopia. Clin Ophthalmol 2017;11:1205–1211. DOI: 10.2147/OPTH.S137712.
22. Seiler TG, Fischinger I, Koller T, et al. Customized corneal cross-linking: One-year results. Am J Ophthalmol 2016;166:14–21. DOI: 10.1016/j.ajo.2016.02.029.
23. Kluger R, Alagic A. Chemical cross-linking and protein-protein interactions – A review with illustrative protocols. Bioorg Chem 2004;32(6):451–472. DOI: 10.1016/j.bioorg.2004.08.002.
24. Roberts CJ, Dupps Jr WJ. Biomechanics of corneal ectasia and biomechanical treatments. J Cataract Refract Surg 2014;40(6):991–998. DOI: 10.1016/j.jcrs.2014.04.013.
25. Lang PZ, Hafezi NL, Khandelwal SS, et al. Comparative functional outcomes after corneal crosslinking using standard, accelerated, and accelerated with higher total fluence protocols. Cornea 2019;38(4):433–441. DOI: 10.1097/ICO.0000000000001878.