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ORIGINAL PAPER

The effects of collagen cross-linking on corneal density: a comparison between accelerated and conventional methods

Ali Mahdavi Fard · Rana Daei Sorkhabi · Mojtaba Khazaei · Nader D. Nader

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Abstract

Purpose To compare the corneal density before and after accelerated versus conventional corneal cross-linking (CXL).

Methods Pentacam densitometry and corneal mapping were performed before and 6 months following the randomly assigned intervention. Corneal density was measured over different zones and layers of the cornea by two independent ophthalmologists. Total corneal density was calculated. The patients were followed up for the occurrence of procedure-related and unrelated complication 1 week, 1 month and a final visit around 6 months (180 ± 10 days) after the procedure, during which the corneal density was remeasured and recorded.

Results Twenty-three patients were enrolled. There was a significant increase in corneal density over the anterior layer ($P < 0.001$) and middle corneal layer ($P = 0.035$). Additionally, the corneal density significantly increased in 0–2 and 2–6 mm zones ($P < 0.001$), as well as total density ($P = 0.002$) following corneal CXL. Although there was no significant difference in the corneal density between the two CXL groups, the increase in corneal density was only significant in group A for the 6–10 mm zone and the posterior corneal layer.

Conclusion Both the conventional and accelerated CXL methods increase the overall corneal density with exception of posterior central corneal layer and the 6–10 mm zone, which is only increased in the accelerated method.

Keywords Keratoconus · Densitometry · Cross-linking

A. Mahdavi Fard · R. Daei Sorkhabi · M. Khazaei
Nikookari Hospital (Eye Center), Tabriz University of Medical Sciences, Tabriz, Iran
e-mail: alimahdavifard@gmail.com

R. Daei Sorkhabi
e-mail: Sorkhabi_r@yahoo.com

M. Khazaei
e-mail: mkhazaei0456@gmail.com

N. D. Nader (✉)
Department of Anesthesiology, State University of New York at Buffalo, 77 Goodell Street, Suite 550, Buffalo, NY 14203, USA
e-mail: nnader@buffalo.edu; nadernd@gmail.com

Introduction

Keratoconus (KCN) refers to the conical shape of the cornea due to progressive thinning and bulging of the central or pericentral cornea. KCN is a common disorder with a prevalence of approximately 54 in 100,000 in general population [1]. A combination of genetic as well as several environmental risk factors

such as eye rubbing, corneal inflammation due to atopic reactions or hard contact lens, with activation of oxidative stress may play a role in the onset and progression of KCN [2]. The hereditary pattern is not prominent, while positive family history has been reported in 6–8% of cases. Clinically unaffected first-degree relatives have a higher chance of showing subclinical topographic abnormalities associated with KCN than the general population. Although multiple chromosomal loci have been linked to development of KCN, identification of specific genes that directly contribute to the pathology remains elusive [3, 4]. Nearly all cases are bilateral although the severity of the disease may vary from one side to another. The disease tends to progress during the adolescent years and into the second and third decades of life. As the disease progresses, the apical thinning of the central cornea worsens, and extreme degrees of irregular astigmatism may develop.

Computerized corneal topography (CT) algorithms are used to diagnose the whole range of KCN and the effectiveness of proposed corrective procedures. Scanning slit and other elevation-based systems continue to be improved to measure deviation above a "best-fit sphere" [5]. Penetrating keratoplasty (PK) is still the most widely performed surgical procedure for KCN with an excellent outcome [6]. Collagen cross-linking (CXL) of the cornea has recently become popular and is commonly used to prevent corneal ectasia. In contrast to other treatment modalities, the corneal CXL increases the rigidity of corneal collagen fibers by radiating with ultraviolet-A (UV-A) rays following injection of 0.1% riboflavin (conventional method) [7]. According to Bunsen–Roscone law, a delivery of higher dose of UV-A radiation can achieve the same therapeutic results in a shorter duration (accelerated CXL method) [8, 9].

In vivo studies have shown that accelerated CXL carries similar profile on the corneal epithelium healing time and limbal cell morphology as the conventional method [7, 10]. Due to intangible difference in the cost and duration of exposure to radiation, it is important to examine whether the accelerate method is inferior to the conventional method in altering corneal density and the associated safety profile. The primary endpoint of this study was the measure of corneal density, and the secondary outcome variable was the need to repeat procedure and the loss of peripheral visual acuity. We hypothesize that accelerated CXL is non-inferior to the conventional CXL technique in altering corneal density.

Patients and methods

The study protocol was reviewed and approved by the institutional review board for its scientific merit and ethical suitability according to the Helsinki Declaration. All consecutive patients < 20 years old with KCN and patients between 20 and 30 years old with progressive KCN undergoing collagen CXL were screened for enrollment. Only one eye was treated from each patient. Progressive KCN was defined an increase $\geq$ one unit in the maximum K value (K-max) during the follow-up period. Following screening, a study team member approached all eligible patients to obtain an informed consent was obtained. For patients under the age of 18 years old, an informed consent was obtained. Patients were excluded, if they refused to sign an informed consent or if they had one or more of the following conditions: a prior procedure on the cornea, history of herpetic keratitis, autoimmune disease with or without severe ocular surface disorder (Sjögren Syndrome) and presence of severe corneal opacity or corneal thickness < 400 microns. Patients with history of delayed epithelial healing of the cornea were also excluded.

Primary endpoint and sample size determination

The study design was before and after measurement of the primary outcome following two different types of corneal CXL. The measured corneal density before and after CXL was the primary endpoint of this study. The secondary endpoint included the occurrence of major adverse event related to the corneal CXL. The primary endpoint was used for power analysis and sample size determination. The corneal density was reported to be 16.3 ± 1.9 that increased to 18.5 ± 2.5. A total of 23 patients were needed in each group to detect a mean difference of 2.1 units increase in the corneal density with a power of 80%.

Study design and randomization

The experimental design was prospectively randomized study of two different treatment modalities for correcting the corneal density for KCN. Factorial

analysis design (Accelerated vs. Conventional CXL) was used to examine the difference in corneal density before and after two CXL treatment arms. The patients were randomly assigned to either arm using computer-generated numbers at 1:1 ratio using a "block of 4" method.

Collagen cross-linking methods

In the conventional group (group C), CXL was performed based on the modified technique that was originally described by Dresden et al. [11]. In this arm of the study, the central 7 mm of corneal epithelium was debrided and removed and riboflavin 0.1% in 20% dextran solution was then applied every 3 min for 30 min. Upon confirming the presence of riboflavin in the anterior chamber by slit lamp examination, an 8-mm diameter of central cornea was exposed to the ultraviolet-A light with a wavelength of 370 nm of 3 mW/cm^2 irradiance for 30 min. UV-A radiation was done using IROC-Innocross AG® (Avedro, Waltham, MA). Riboflavin containing solution was applied every 5 min throughout UV-A irradiation. After completion of the CXL procedure, topical antibiotic and corticosteroids were applied and a bandage contact lens was inserted. This contact lens was removed 3 days after the procedure.

In accelerated group (group-A), corneal debridement and riboflavin application processes were similar to that in group C. The only difference was the UV-A radiation was set at a higher energy level of 9 mW/cm^2 for a shorter duration of 10 min. Post-procedural care of the patients was the same in both groups for the entire follow-up period that included clinic visits on the 30th and 180th days after the procedure; however, the corneal density was only measured 6 months after the CXL procedure.

Measurement of the corneal density and pentacam analysis

Pentacam analysis was performed using the specific optional module of Pentacam Oculus (Innova Medical Ophthalmics, Laval, QC, Canada) device. The output is expressed in gray scale units (GSU). The GSU scale is calibrated by proprietary software, which defines a minimum light scatter of 0 (maximum transparency) and maximum light scatter of 100 (minimum transparency). Corneal densitometry was completed over various radial zones of the cornea: (a) central zone 0–2 mm; (b) radial 2–6 mm zone; (c) radial 6–10 mm; and (d) radial 10–12 mm zone and calculated total corneal density. Furthermore, the corneal density was separately measured at the anterior (120 μm front), middle and posterior (60 μm rear) layers of the cornea before and after the CXL procedure (Fig. 1). The mean corneal density was calculated for each case before and after the CXL procedure. All patients were scheduled for a follow-up visit 6 months (180 ± 10 days) after the procedure, during which the measurements were performed and used for repeated measure analyses.

Statistical analysis

Raw data from the corneal densitometry were exported into an excel worksheet and the Statistical Program for Social Sciences (SPSS ver. 24.0; IBM Inc. Chicago, IL) for analysis. In Brief, pre- and post-procedural changes of the corneal density were assessed by paired *t* test and data were expressed as mean ± standard deviation. In order to examine the effect that the type of CXL procedure affected the changes in the corneal density, repeated measure analysis was used and the type of CXL was the only independent factor in the univariate analysis. Multivariate analysis included, gender, age and the laterality (OS vs. OD) as independent factors in addition to the type of CXL procedure using a linear regression model. The coefficient for each factor is provided with 95% confidence interval.

Results and major findings

A total of 46 eyes from 46 (29 male and 17 female) patients with KCN were equally randomized to undergo either conventional (group C; $N = 23$) or accelerated (group A; $N = 23$) corneal CXL procedure. CXL was done on the left eye in 27 patients and on the right eye in 19 patients. There is no difference between group C and group A in laterality of CXL procedure. The average age was 23.5 ± 5.6 years old in group C and it was 24.3 ± 5.8 years old in group A. Overall corneal density was 17.6 ± 2.2 GSU prior to the procedure which increased to 19.3 ± 2.5 GSU after CXL ($P < 0.001$). Similarly, the corneal density increases by 3.4 GSU over the anterior layer

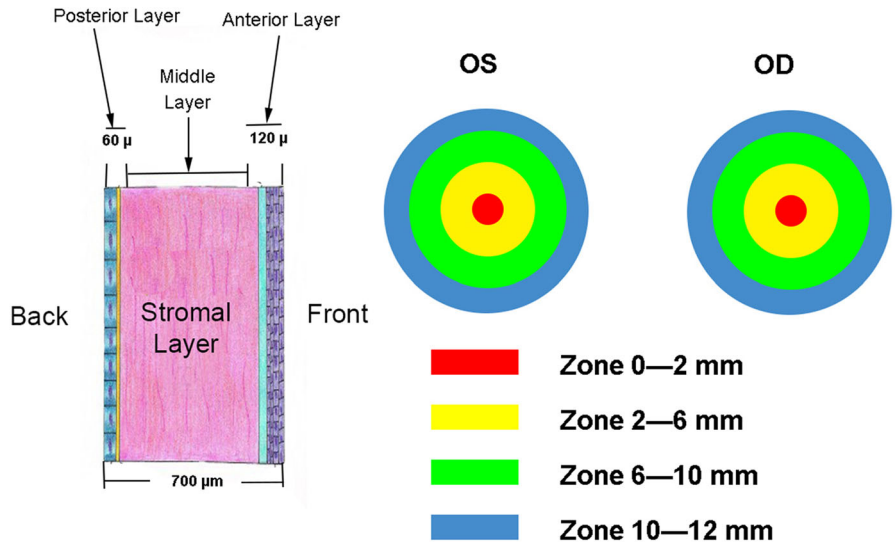

Fig. 1 A schematic guide for the corneal layers and the zones

($P < 0.001$) and by 1.0 GSU over the middle layer ($P = 0.035$). From the topographical zones, central 0–2 and 2–6 mm radial zones had significant increase in the corneal density ($P < 0.001$) (Table 1).

Baseline total density of the cornea was 17.5 ± 2.3 GSU in group C while it was 17.7 ± 2.1 GSU in group A. After the CXL procedure, the corneal density increased by 1.2 ± 3.4 GSU in group C and increased by 2.0 ± 3.3 GSU in group A ($P = 0.421$) (Fig. 2). Despite a lack of significant changes in overall corneal density, the regional thickness of the cornea differed from one zone to another (Table 2). Maximum level of increase in the corneal density was in the central 0–2 mm zone, where it increased from the baseline value of 20.5 ± 2.3–25.8 ± 5.1 GSU after CXL procedure ($P < 0.001$). However, the method of CXL did not affect the change in the corneal density of this zone.

Multivariate linear regression model was constructed to include all factors that may affect the increases in overall corneal density in response to CXL procedure. We included patient factors such as gender, age and the laterality of the involved eye in addition to the method of the CXL procedure. Table 3 depicts the individual effects of these factors on the changes in overall corneal density in the top panel. None of the patient factor stated above independently affected the net change in overall corneal density. However, the baseline densities of the cornea over the anterior, middle and posterior layers were all

Table 1 Corneal density in grayscale unit (GSU) is shown for various corneal layers and topographical zones before and after cross-linking (CXL) procedures

Topographical zones of the cornea	Before CXL ($N = 46$)	After CXL ($N = 46$)	Mean diff	95% Confidence interval	T value	P value
Anterior layer (120 µm)	24.7 ± 3.6	28.0 ± 3.9	3.4	1.9–4.8	− 4.71	< 0.001
Middle layer	15.4 ± 2.0	16.4 ± 2.3	1.0	0.1–1.9	− 2.18	0.035
Posterior layer (60 µm)	12.9 ± 1.9	13.3 ± 2.2	0.4	− 0.5–1.3	− 0.92	0.364
Zone (0–2 mm)	20.5 ± 2.3	25.8 ± 5.1	5.3	3.6–7.0	− 6.20	< 0.001
Zone (2–6 mm)	17.7 ± 2.0	20.4 ± 3.1	2.6	1.5–3.8	− 4.55	< 0.001
Zone (6–10 mm)	14.9 ± 2.4	14.9 ± 2.4	0.0	− 0.9–0.8	0.09	0.927
Zone (10–12 mm)	20.2 ± 6.4	19.3 ± 5.5	− 0.8	− 2.9–1.2	0.82	0.417
Overall density	17.6 ± 2.2	19.3 ± 2.5	1.6	0.6–2.6	− 3.32	0.002

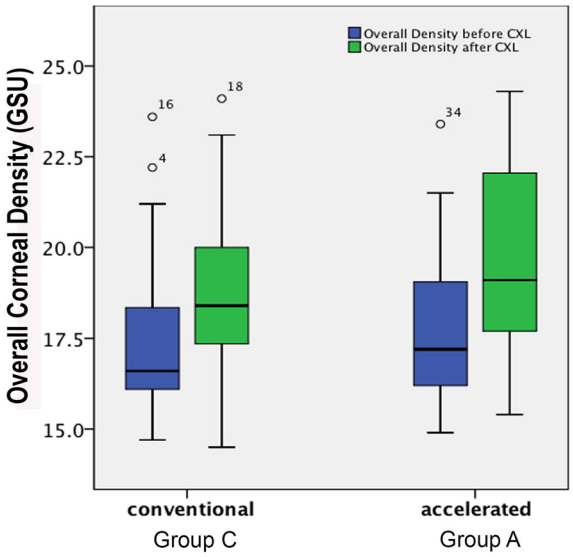

Fig. 2 Overall corneal density is compared between groups A and C

significant predictors of the CXL-related changes in the corneal density. Changes in the corneal density ranged from 0.5 to 1.2 GSU for every one unit of baseline density of all three layers.

Discussion

In the present study, we measured corneal density before and after corneal collagen CXL with conventional and accelerated methods. Similar to previous studies on this field, we found that both methods of CXL procedures result in significant increases in corneal density [10, 12, 13]. We also measured changes in corneal density in 2, 2–6, 6–10 and 10–12 mm zones, as well as the anterior, middle and posterior layers of the cornea in both groups. Similar to study by Bernardo et al. in which there was a significant rise in corneal density in 2 and 2–6 mm zones, we found a significant increase in corneal density in both of the mentioned zones of the cornea. We additionally reported significant increases in total corneal density in both groups following CXL.

In addition to its use in KCN, corneal densitometry is considered an important diagnostic tool where a vast area of the cornea is amenable to ablation in refractive surgery. It is important to obtain an accurate information on density of different zones of the cornea after CXL procedures [14, 15]. Several studies have shown the efficacy of CXL by measuring the corneal biomechanics and so far, corneal CXL is considered the best available treatment for KCN [16, 17]. Measurement of the corneal biomechanics is the only means of assessing the efficacy of the treatment in many centers. In this study, we measured the corneal density and properties over the various zones and layers of the cornea before and after the corneal CXL along with its clinical efficacy. This information is valid and is globally used to examine the efficacy of the corneal CXL. However, we acknowledge that its reproducibility of the results is inferior to ocular response analyzer ® (ORA) in assessment of the corneal biomechanics.

In contrast, Pircher et al. have reported an increase in corneal density only in the anterior layer of cornea, while Alnawaiseh et al. have shown significant augmentations of density over the anterior and middle layers of the cornea after conventional CXL [12, 18].

Table 2 Corneal densities are shown in grayscale unit (GSU) over various zones before and after conventional or accelerated cross-linking procedure

Density of layers and zones of the cornea (GSU)	Group C (N = 23)		Group A (N = 23)		P value
	Before	After	Before	After	
Anterior layer (120 μm)	24.7 ± 4.3	27.7 ± 3.8	24.7 ± 2.8	28.4 ± 4.1	0.728
Middle layer	15.5 ± 1.9	16.0 ± 1.8	15.4 ± 2.1	16.8 ± 2.7	0.304
Posterior layer (60 μm)	12.7 ± 1.7	12.6 ± 1.7	13.1 ± 2.1	14.0 ± 2.4	0.024
Zone (0–2 mm)	20.1 ± 2.0	26.2 ± 5.0	20.8 ± 2.6	25.4 ± 5.3	0.398
Zone (2–6 mm)	17.5 ± 1.8	20.2 ± 3.1	18.0 ± 2.2	20.5 ± 3.1	0.894
Zone (6–10 mm)	14.9 ± 2.7	14.1 ± 1.8	14.9 ± 2.1	15.6 ± 2.7	0.067
Zone (10–12 mm)	20.6 ± 7.7	17.9 ± 4.7	19.8 ± 4.9	20.8 ± 6.0	0.072

Table 3 Multivariate linear regression analysis models that examined the effect of the cross-linking methods, gender, age and laterality of the involved eye on the changes in overall (total) corneal density after the cross-linking procedure. All independent variables were tested against the baseline density of the cornea over the anterior, middle and posterior layers

	Coefficients	St err	Correlation	*P* value	Lower CI	Upper CI
Constant	− 0.373	3.355		0.912	− 7.148	6.403
Accelerated/conventional CXL	0.826	1.007	0.125	0.417	− 1.209	2.860
Female/male	1.310	1.134	0.192	0.255	− 0.981	3.601
Age (year)	− 0.091	0.092	− 0.155	0.324	− 0.277	0.094
OD/OS	0.817	1.095	0.122	0.460	− 1.395	3.030
Regression adding baseline anterior layer density						
Constant	12.585	4.293		0.006	3.909	21.262
Accelerated/conventional CXL	0.833	0.859	0.127	0.338	− 0.903	2.569
Female/male	0.573	0.984	0.084	0.564	− 1.417	2.562
Age (year)	0.020	0.083	0.035	0.807	− 0.147	0.188
OD/OS	− 0.314	0.975	− 0.047	0.749	− 2.284	1.657
Baseline thickness of ant. layer	− 0.528	0.130	− 0.574	< 0.001	− 0.792	− 0.264
Regression adding baseline middle-layer density						
Constant	19.831	4.736		< 0.001	10.258	29.403
Accelerated/conventional CXL	0.769	0.792	0.117	0.337	− 0.832	2.369
Female/male	− 0.286	0.944	− 0.042	0.763	− 2.194	1.622
Age (year)	0.015	0.075	0.026	0.840	− 0.136	0.167
OD/OS	− 0.998	0.931	− 0.149	0.290	− 2.879	0.883
Baseline thickness of middle layer	− 1.161	0.226	− 0.689	< 0.001	− 1.618	− 0.704
Regression adding baseline posterior layer density						
Constant	14.198	4.413		0.003	5.278	23.117
Accelerated/conventional CXL	1.318	0.852	0.200	0.130	− 0.404	3.041
Female/male	− 0.089	1.005	− 0.013	0.930	− 2.120	1.943
Age (year)	− 0.025	0.078	− 0.043	0.750	− 0.184	0.133
OD/OS	− 0.368	0.959	− 0.055	0.703	− 2.306	1.570
Baseline thickness of posterior layer	− 1.032	0.241	− 0.593	< 0.001	− 1.519	− 0.545

Similarly, our study showed a significant rise in anterior corneal layer density in both conventional and accelerated methods; however, middle-layer density was increased only in accelerated technique. These findings could be explained by the fact that during the CXL procedures, the central 8 mm of the cornea receives the most irradiation due to its perpendicular angle to the beam of radiation. Additionally, there are relatively higher concentrations of riboflavin in central zones especially in the anterior layers of cornea.

Comparing the two study groups, we found that in group A (accelerated CXL), the observed changes in density over the 6–10 mm zone and the posterior layer of the cornea were more substantial than the changes in group C (conventional). We speculated that this observation might be related to the amount of exposure to these regions of the cornea to UV-A radiation, which was specifically more intense in the accelerated method of CXL. However, there has been no study that comparatively examined regional exposure of the cornea to UV-A or the regional concentrations of the riboflavin between the accelerated and the conventional techniques of CXL.

The findings of the current study once more signified the use of corneal densitometry in comparative assessment of two acceptable techniques for corneal CXL. Tomita et al. [19] showed that both accelerated and conventional methods of corneal CXL improved vision in patients with KCN. Similar to the study by Pahuja et al. [8], we demonstrated that the

accelerated method of CXL possessed more extensive and deeper effects than the conventional technique by affecting deeper layers and more peripheral zones of the cornea.

This study is limited since its primary outcome is purely based on the results obtained from corneal densitometry. Recent evidence by Pahuja et al. cautions about the low repeatability of corneal densitometry when gauging the refractive and visual effects of cornea after CXL [8]. Hence, availability of supporting clinical data (visual or refractive outcomes) in this study was crucial to making any conclusion based on relevant changes in the corneal stromal density associated with different methods of corneal CXL protocols. Regardless, additional studies with longer follow-up periods and concomitant evaluation of corneal topography are necessary to expand these findings to clinical outcome after corneal CXL. Additionally, the rationale of measuring corneal densitometry 6 months after the CXL procedure and the importance of repeated measurements over time (1, 3, 6 months) has been based on the fact that the corneal densitometry changes in the postoperative period due to stromal extracellular matrix remodeling and cellular population density changes. Therefore, the findings discussed in this study with regard to corneal density should be interpreted with discretion and ideally reproduced with a larger sample and observed on different follow-up periods.

We conclude that both methods of CXL are effective in increasing density over the central regions of the cornea in patients with KCN. However, the accelerated technique of CXL has shown a higher penetration as it effectively increases density over the posterior layers and more peripheral regions of the cornea. Although the duration of UV-A radiation is shorter, the excess level of the energy delivery basically eliminates this theoretical advantage with accelerated technique. Despite increasing density over the peripheral regions of the cornea, the accelerated method of CXL is not associated with superior clinical outcome. As this study is limited by using corneal density as its sole outcome variable, assessment of therapeutic response to available methods of CXL requires studies with longer follow-up duration and evaluation of both topographic and clinical information.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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