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Research Article

Corneal Densitometry Changes after a Unique Accelerated Epithelium-Off Corneal Collagen Crosslinking Protocol in Keratoconus

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Received: June 08, 2021; **Published:** July 30, 2021

Abstract

Background: Keratoconus is a progressive non-inflammatory, ectatic disease that affects the integrity of the collagen matrix within the corneal stroma. Corneal cross-linking (CXL) has been described as the only modality in halting the disease progression over the past decade.

Aim of the Work: To compare the change in corneal densitometry before and 6 months after CXL using our unique protocol.

Patients and Methods: A prospective observational study was conducted on 30 eyes of 30 patients with progressive keratoconus at Ain Shams University Hospitals and Maghrabi eye center.

Results: Within the anterior (120 um) stromal layer, the concentric zones (0 to 2 mm) and (2 to 6 mm) showed a significant elevation of mean densitometry 6 months post-surgery (P = 0.020) and (P = 0.023) respectively compared to the baseline, However the concentric zones (6 to 10 mm) and (10 to 12 mm) showed a non-significant elevation of mean densitometry 6 months post-surgery (P = 0.167) and (P = 0.234) respectively compared to the baseline.

Conclusion: There is a significant increase in corneal densitometry 6 months post-surgery of the anterior (120 um) stromal layer within the concentric zones (0 to 2 mm) and (2 to 6 mm).

Keywords: *Corneal Densitometry; Epithelium-Off Corneal Collagen Crosslinking*

Introduction

Keratoconus (KC) is a non-inflammatory bilateral progressive but asymmetrical disease. Described as corneal ectasia, thinning, gradual corneal protrusion and irregular astigmatism [1]. It usually starts during puberty with 75% of cases diagnosed before the age of 25 years [2].

Corneal cross-linking (CXL) has been described as the only modality in halting the disease progression over the past decade [3], by using Riboflavin eye drops and UVA light this creates bonds between corneal collagen fibers in the stroma [4]. Cross-linking has been shown to generate various effects in the cornea such as increased stiffness, changes in biomechanical and bioelastic behavior of corneal collagen tissue and different visual, refractive, topographic and abberometric changes [5]. There is a change in the corneal densitometry after epi-off corneal cross-linking. Variant protocols were conducted with variability in the riboflavin used and UV exposure time [6].

Aim of the Study

This study aimed at reporting the densitometer changes after the epi-off CXL protocol that has not been reported before.

Patients and Methods

This prospective observational study was conducted on included 30 Eyes of 30 patients with progressive keratoconus. An increase of 1 D or more in the steepest keratometry over a period of 12 months at Ain Shams University Hospitals and Maghrabi eye center, after the approval of the research ethics committee and according to Declaration of Helsinki.

The study included patients with progressive keratoconus (stages 1 - 3) with ages ranging from 20 to 40 years old. Patients with corneal thickness at the thinnest location less than 400 microns, corneal scaring or opacification, ocular surface diseases e.g. moderate to severe dry eye and systemic diseases e.g. Autoimmune diseases or diabetes mellitus were excluded from the study.

Complete ophthalmological examination was performed for all patients including Visual acuity assessment (Uncorrected and Best-corrected visual acuity), slit lamp examination and fundus examination through a dilated pupil.

Corneal imaging by the Pentacam Scheimpflug system (Oculus Inc., Wetzlar, Germany) was done.

Study interventions

The same surgeon (M.M.M.) performed all procedures using a specific protocol for epithelium off CXL: Sterilization of the patient then application of topical anesthesia and lid speculum. After application of 70% alcohol to the corneal surface, the epithelium was removed by a hockey stick followed by the application of Riboflavin (VibeX Rapid™) for 6 minutes at a rate of 1 drop/minute. UVA was delivered using the Avedro KXL machine (Avedro, Waltham, MA, USA) using the following parameters: 7.2 joules, 12 milli watt/minute, 10 minutes of continuous UV delivery:

- During UV delivery BSS was distilled every 2 minutes, after completion of UV delivery BCL applied.
- Patients received antibiotic eye drop e.g. Moxifloxacin (Vigamox, Alcon, USA) 4 times per day for 1 week, Non-steroidal anti-inflammatory e.g. Nepafenac, (Nevanac eye drop, Alcon, USA) 3 times per day for 1 week and lubricating drops, (Systane gel eye drop, Alcon, USA) 4 times per day for 1 month.

Follow up: Postoperative follow-up examinations performed on the first and fourth postoperative days for removal of the BCL, then on the third week, third and sixth month. Scheimpflug imaging was obtained at the sixth-month postoperative visit and densitometry was assessed.

Data was collected and statistically evaluated using SPSS software version 23.

Results

In this study 30 eyes of 30 patients suffering from progressive keratoconus who were treated with epi-off CXL were analyzed. The mean age of the 15 men and 15 women was 32.33 ± 6.38 (range 21 to 40 years).

All patients attended 1 and 4 days, 3 weeks, 3 and 6 month postoperative follow-up examination, no surgery-related complications were recorded, and epithelial closure was observed within 4 days in all patients.

There was no correlation between gender and preoperative corneal densitometry (Table 1).

Total (% of change)	Sex		Test value	P-value	Sig.
	Female	Male			
Mean ± SD	2.69 ± 9.44	3.84 ± 5.14	-0.413	0.682	NS

Table 1: *Correlation between gender and preoperative corneal densitometry.*

Regarding visual acuity, there was no significant change in mean UDVA and CDVA from preoperative to 6 months postoperatively respectively (P = 0.866, P = 0.916) (Table 2).

	UDVA (logMAR)	CDVA (logMAR)
	Mean ± SD	Mean ± SD
Pre-operative	1.09 ± 0.47	0.52 ± 0.3
6 months postoperative	1.07 ± 0.44	0.53 ± 0.42
Test value	-0.170	0.106
P-value	0.866 (NS)	0.916 (NS)

Table 2: *Comparison between "Preoperative UDVA and CDVA and "6 months postoperative UDVA and CDVA".*

Within the anterior (120 um) stromal layer, the concentric zones (0 to 2 mm) and (2 to 6 mm) showed a significant increase of mean densitometry 6 months post-surgery (P = 0.020) and (P = 0.023) respectively compared to the baseline, However the concentric zones (6 to 10 mm) and (10 to 12 mm) showed a non-significant change of mean densitometry 6 months post-surgery (P = 0.167) and (P = 0.234) respectively compared to the baseline (Table 3).

Anterior 120 um No. = 30		Pre	Post	% of change	Test value•	P-value	Sig.
		No. = 30					
0-2 mm	Mean ± SD	22.53 ± 1.20	23.37 ± 1.94	-	-2.456	0.020	S
	Range	20 - 24	21 - 29				
2 to 6 mm	Mean ± SD	20.10 ± 1.03	20.60 ± 1.40	-	-2.408	0.023	S
	Range	18 - 22	18 - 24				
6 to 10 mm	Mean ± SD	21.47 ± 5.45	21.87 ± 5.08	-	-1.418	0.167	NS
	Range	17 - 37	17 - 36				
10 to 12 mm	Mean ± SD	31.80 ± 6.84	32.77 ± 8.95	-	1.215	0.234	NS
	Range	17 - 44	18 - 50				
Total	Mean ± SD	22.87 ± 1.94	23.47 ± 2.34	3.26% ± 7.49	-1.989	0.056	NS
	Range	20 - 28	19 - 29				

Table 3: *Comparison between pre and postoperative densitometric values (Anterior 120 um).*

Within the central stromal layer, there was no significant change of mean densitometry 6 months post-surgery (P = 0.194) compared to the baseline (Table 4).

Central No. = 30		Pre	Post	% of change	Test value*	P-value	Sig.
		No. = 30					
0-2 mm	Mean ± SD	13.97 ± 1.03	14.20 ± 0.76	-	1.489	0.147	NS
	Range	12 - 16	13 - 15				
2 to 6 mm	Mean ± SD	12.60 ± 0.77	13.00 ± 1.68	-	1.278	0.211	NS
	Range	11 - 14	11 - 21				
6 to 10 mm	Mean ± SD	14.00 ± 3.35	14.30 ± 3.20	-	-1.663	0.107	NS
	Range	11 - 23	11 - 22				
10 to 12 mm	Mean ± SD	19.40 ± 3.53	19.63 ± 4.50	-	0.575	0.570	NS
	Range	14 - 27	12 - 28				
Total	Mean ± SD	14.13 ± 1.31	14.43 ± 1.50	2.36% ± 8.88	-1.329	0.194	NS
	Range	12 - 18	12 - 18				

Table 4: *Comparison between pre and postoperative densitometric values (central stromal layer).*

Within the posterior (60 um) stromal layer, there was no significant change of mean densitometry 6 months post-surgery (P = 0.564) compared to the baseline (Table 5).

Posterior 60 um No. = 30		Pre No. = 30	Post	% of change	Test value•	P-value	Sig.
0-2 mm	Mean ± SD	9.50 ± 0.82	9.77 ± 1.22	-	-1.072	0.293	NS
	Range	8 - 11	7 - 12				
2 to 6 mm	Mean ± SD	8.90 ± 0.88	9.17 ± 0.95	-	-1.393	0.174	NS
	Range	7 - 10	7 - 10				
6 to 10 mm	Mean ± SD	10.83 ± 2.32	11.17 ± 2.6	-	-1.720	0.096	NS
	Range	8 - 17	8 - 18				
10 to 12 mm	Mean ± SD	14.67 ± 3.37	15.03 ± 2.93	-	-1.302	0.203	NS
	Range	10 - 22	10 - 21				
Total	Mean ± SD	10.60 ± 1.04	10.73 ± 1.55	1.4% ± 11.92	-0.583	0.564	NS
	Range	9 - 13	8 - 14				

Table 5: *Comparison between pre and postoperative densitometric values (posterior 60 um).*

The anterior (120 um) showed the most percentage of change by (3.26% ± 7.49) (Table 6).

Total (% of change)	Groups		
	Anterior	Central	Posterior
Mean ± SD	3.26 ± 7.49	2.36 ± 8.88	1.4 ± 11.92

Table 6: *Comparison between the total percentage of change between anterior (120 um), central and posterior (60 um) stromal layer.*

Discussion

Pircher., *et al*. reported changes in densitometry after using the standard Dresden protocol for epi-off CXL using the (IROC Innocross AG) which delivers UVA as a Gaussian beam profile. There was a significant change in corneal densitometry between pre and postoperative in the anterior 120 um in 0 to 2 mm concentric zone [7].

Kim., *et al*. also reported after using the Dresden protocol for epi-off CXL, the highest densitometry measurements were observed in the anterior 120 mm of the cornea and inner (0 to 2 mm) zone. The anterior cornea and inner cornea continued to have the highest densitometry readings for 12 months after CXL [8].

Böhm., *et al*. used accelerated epi off CXL using a homogenous beam intensity, UVA delivery system (Avedro, Inc.), after removal of the central epithelium, they instilled riboflavin for 10 min followed by pulsed UVA delivered (1 sec. "on", 1 sec. "off") at 30 mW/cm^2 for 4 min with 8 min total UVA to deliver 7.2 J/cm^2. They reported that the anterior stromal layer showed a significant increase in mean densitometry, whereas the middle and posterior layers just showed a slight but nonsignificant increase in mean densitometry. Within the anterior (120 um) stromal layer, the two central concentric zones (0 to 2 mm and 2 to 6 mm) showed a significant elevation of mean densitometry 3 months post-surgery compared to the baseline [9].

In our study we used epi-off CXL technique and delivered 7.2J over 10 min at 12 mW/cm^2, using a homogenous UVA delivery system (KXL System, Avedro). Our study was unique in using total energy of 7.2 J delivered continuously over 10 min.

Regarding gender, we didn't find any correlation between gender and preoperative corneal densitometry, this is in agreement with Yin., *et al*. who reported that, there was no significant influence of gender on densitometry [10].

We found that within the anterior (120 um) stromal layer, the concentric zone (0 to 2 mm) showed a significant elevation of mean densitometry 6 months post-surgery (P = 0.020) compared to the baseline, and the concentric zone (2 to 6 mm) showed a significant elevation of mean densitometry 6 months post-surgery (P = 0.023) compared to the baseline, this is in agreement with previous studies, although different CXL protocols were used.

As per the central stromal and posterior (60 um) layers, we noticed a non-significant change between pre and postoperative corneal densitometry which was in agreement with the literature.

Comparing the change in the 3 layers, we noticed that the maximum change was in the anterior (120 um) layer followed by the central stromal layer and lastly the posterior (60 um).

Our study also reported a non-significant change in the (10 to 12 mm) zone of the anterior (120 um) stromal layer 6 months post-surgery (P = 0.234) compared to the baseline in this zone, only Böhm., *et al*. frankly reported on this zone and also found a non-significant increase in this zone although they used the accelerated CXL protocol.

Yin., *et al*. also reported that the densitometric values for the (10 to 12 mm) zone must be interpreted with caution, due to the normal variations in the white-to-white corneal diameter mean that some participants have corneas smaller than the 12 mm analysis limit, Portions of the limbus and sclera can therefore be included in the assessment of the outermost zone, resulting in higher backscatter values. Even small changes in the position of the limbus can have a significant effect on the (10 to 12 mm) densitometry results, though this does not occur in the more central annuli [10]. We didn't measure the corneal diameter in our study, this might affect the accuracy of our results.

Helaly and Osman reported changes in corneal densitometry after using the Dresden protocol for epi-off CXL. There was a statistically significant increase in the mean densitometry between baseline and 1 month postoperatively that was not measured in our study. The study also stated that the mean densitometry continued to decrease at 3, 6, and 12 months postoperatively, but it remained elevated compared to baseline values. But they did not mention the change in every concentric zones and corneal stromal layers [11].

They also reported that there was no clinically or statistically significant difference between lens densitometry preoperatively and postoperatively, this supports the fact that exposing the eye to UVA with an irradiance of 18 mW/cm^2 for 5 min has no harmful effects on the lens clarity [11].

Yin., *et al*. reported that in normal corneas the mean corneal densitometry over the entire 12-mm diameter area was (19.74 ± 3.83) GSU in the right eye and (19.55 ± 3.76) GSU in the left eye, however the mean densitometry of the anterior (120 um) stromal layer in our study was (22.87 ± 1.94) GSU of preoperative keratoconic corneas [10].

Also, the study found that there was no significant difference between the densitometry values of the central (0 to 2 mm) zone and the surrounding (2 to 6 mm) annulus, though values for the (6 to 10 mm) and the (10 to 12 mm) zones were significantly higher, which is in agreement of our results.

Regarding the stromal layers they found that the anterior layer displayed the highest degree of backscatter (25.81 ± 5.14) GSU, which was significantly higher than for both the central and the posterior layers, with the lowest backscatter occurring at the posterior 60 um.

Dong., *et al*. reported that there was difference between corneal densitometry in highly myopic (HM) eyes (axial length > 25 mm) and normal corneas [12].

When the cornea was divided into 3 layers, all layers found to have a lower light backscatter in the HM group than in the normal group [12]. We didn't measure the axial length in our study as there may be associated axial myopia with keratoconus.

Several limitations in our study are present, the first being the small sample size and short follow up period for only 6 months, the second is that we did not correlate the change in densitometry with the presence and depth of the demarcation line detected with OCT

which is considered as the hallmark for successful CXL. Also, we did not measure neither the corneal diameter nor the axial length which can affect densitometry results.

Another correlation that is beyond the scope of this study is that between the change in densitometry and corneal biomechanics which may be of value to determine whether densitometry also can be considered as a measure of successful CXL, future studies are needed to assess this issue.

Conclusion

There is a significant increase in corneal densitometry 6 months post-surgery of the anterior (120 um) stromal layer within the concentric zones (0 to 2 mm) and (2 to 6 mm).

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Volume 12 Issue 8 August 2021