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Changes in retinal vessel and retinal layer thickness after cross-linking in keratoconus via swept-source OCT angiography

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Abstract

Purpose To analyze the postoperative foveal avascular zone (FAZ) area, superficial capillary plexus (SCP), deep capillary plexus (DCP) vascular densities (VD), and retinal layers after cross-linking (CXL) for keratoconus treatment.

Methods Twenty-seven eyes with cross-linking treatment for keratoconus were included in the study. Foveal avascular zone (FAZ) area, SCP VD, DCP VD, and retinal layers were evaluated by using optical coherence tomography angiography (OCTA). OCTA measurements were made at preoperative, first week, and first and sixth months after the surgery. In addition, corneal topography measurements were also made.

Results Although there was a decrease in corneal thickness in the follow-up of the patients, there was no significant difference in axial length and anterior chamber depth. There was no significant difference in full retinal thickness in the foveal and parafoveal areas. While there was a significant increase in retinal nerve fiber layer (RNFL) thickness in the foveal area ($p=0.032$, $p=0.015$, $p=0.017$; preoperative values compared to first week, first month, and sixth month respectively), there was a decrease in ganglion cell layer (GCL) thickness in the parafoveal area in the postoperative sixth month ($p=0.028$). There was no difference in FAZ measurements. In the parafoveal area, a decrease was observed in SCP VD in the sixth-month control ($p=0.019$). There was a significant increase in DCP VD in the foveal area ($p=0.008$, $p=0.043$, $p=0.040$). The preoperative mean CDVA (corrected distance visual acuity) was 0.37 ± 0.16 logMAR and postoperative sixth month mean CDVA was 0.39 ± 0.15. There was no significant difference in visual acuity ($p=0.71$).

Conclusion Keratoconus patients successfully treated with CXL had significant changes in retinal layers and vessel density in the superficial and deep retinal plexus.

Keywords Cross-linking · Deep retinal plexus · Keratoconus · Optical coherence tomography angiography · Superficial retinal plexus · Vessel density

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Key Messages:

- Continuous UVA light exposure during CXL treatment raises concerns over potential phototoxicity damage to the retina.
- After CXL, no significant difference was detected in full retinal thickness in the foveal and parafoveal areas and in the FAZ area.
- A significant increase in Retinal Nerve Fiber Layer (RNFL) thickness in the foveal area and a decrease in Ganglion Cell Layer (GCL) thickness in the parafoveal area were detected
- A decrease was observed in SCP VD in the parafoveal area and an increase in DCP VDin the foveal area.

Introduction

Keratoconus is a degenerative, noninflammatory disease of the cornea, with onset generally at puberty. It is progressive in 20% of cases and can be treated by lamellar or penetrating keratoplasty. Its incidence in the general population is reported to be 1/2000 [1].

The corneal collagen cross-linking (CXL) procedure with the use of riboflavin and ultraviolet A (UVA) radiation provides an effective solution for stabilizing corneal ectatic disorders such as keratoconus, pellucid marginal degeneration, and iatrogenic keratectasia after corneal refractive surgery [2–8]. Wide-ranging research over the past 2 decades has shown the benefits of CXL on improving corneal strength, increasing the resistance of corneal, and improving corneal topography and aberrations, mainly by flattening the anterior corneal curvature and reducing irregular astigmatism and higher-order aberrations [9–17].

There are few publications in the literature regarding functional and structural retinal changes after the CXL procedure, and no studies have referred to retinal microvascular changes via optical coherence tomography angiography (OCTA). The purpose of our study is to evaluate the retinal microvascular changes after UVA exposure during CXL (with the wavelength, irradiance, and irradiation time suggested by the Dresden protocol). OCTA measurements were used to investigate the retinal microvascular changes; optical coherence tomography (OCT) measurements were used to assess the retinal structure, optical biometry, and corneal topography for corneal and anterior segment structural changes.

Methods

Twenty-seven eyes of 20 patients with cross-linking treatment for keratoconus were included in the study. The study was conducted in compliance with the ethical standards set out in the Declaration of Helsinki and was approved by the local ethics committee of the Akdeniz University Hospital (Approval Number KAEK—486). Adult, mentally healthy patients with keratoconus, who would be considered candidates for the CXL procedure, were included. Exclusion criteria were previous corneal or intraocular surgery, ocular trauma, corneal scars, herpes keratitis, cataract, acute or chronic uveitis, maculopathy, retinopathy, glaucoma, eyelid abnormalities, collagen vascular/autoimmune diseases, acute or chronic infectious diseases, and neoplasia.

All patients were scheduled for CXL with the Dresden protocol. Preoperatively, all patients underwent an ophthalmic evaluation that included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), slit-lamp examination of the anterior segment and the dilated fundus, OCT for measurement of the macular thickness (MT), and OCTA (DRI OCT Triton; Topcon), corneal densitometry (CD) analysis with Pentacam Scheimpflug imaging (Pentacam HR, Oculus Incorporation, Wetzlar, Germany). All measurements were repeated at the first week and first and sixth months postoperatively and postoperative values compared with the preoperative values.

Corneal topography analysis

Four Pentacam (Pentacam HR, Oculus Incorporation, Wetzlar, Germany) measurements were taken from each patient preoperatively and postoperatively during the first week, the first month, and sixth months, without the use of any topical drops, using the standard automated method. All corneal topography measurements used in this study had an "OK" rating of quality.

Visual acuity

Visual acuity was evaluated using a Snellen chart at a 6-m testing distance with the ambient room lighting remaining

constant and habitual. Progressive cases were defined as those having a decrease of at least 2 lines of CDVA (corrected distance visual acuity) in 6 months. After the CXL treatment, the visual acuity was considered to have stabilized if there was a 1-line gain or loss of CDVA and to have improved if there was a 2-line gain of CDVA.

Optical coherence tomography

MT was assessed with Topcon (DRI OCT Triton; Topcon). Measurement of the macula was obtained using the ETDRS protocol, and MT values (central zone and parafoveal 3 mm zone) were analyzed. Only measurements with good centering, signal strength higher than 30, and correct segmentation were included.

Optical coherence tomography angiography

All participants underwent OCTA using a swept-source OCT (DRI OCT Triton; Topcon) with a wavelength of 1050 nm, an acquisition speed of 100,000 A-scans per second, and an axial and transversal resolution of 7 and 20 mm in tissue, respectively. We used a 33-mm volumetric scan centered at the fovea, each consisting of 320 A-scans per B-scan for a total of 320 B-scans, to obtain OCTA images. Slabs of superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina (OR) and choriocapillaris (CC) were automated and segmented by the built-in software (IMAGEnet6, v1.23.15008, Basic License 10). SCP en face view; the inner border was segmented 3 μm (micrometer) below the ILM and the outer border was 15 μm below the inner plexiform layer, for DCP inner border 15 μm below the inner plexiform layer and an outer border 70 μm below the inner plexiform layer. The image of the choriocapillaris en face was segmented as the inner border was Bruch's membrane and its outer border was 10 μm below Bruch's membrane. The superficial capillary plexus VD measurement was calculated automatically, and the deep capillary plexus and choriocapillaris VD measurements were calculated by the device after manually entering the internal and external limit values. FAZ areas were measured manually by two retinal specialists from 3 × 3 OCTA images and the average value was used.

Corneal cross-linking procedure

The procedure was performed according to the Dresden protocol. After administration of pilocarpine and application of topical anesthesia, the central 9 mm of corneal epithelium, soaked for 30 s with 20% alcohol solution, was removed manually. Riboflavin 0.1% solution (10 mg riboflavin 59-phosphate in 10 mL 20% dextran T-500) was instilled onto the cornea every 2 to 3 min for 30 min before irradiation, until riboflavin saturated the corneal stroma. During the course of the 30-min exposure to 370 nm UVA with an irradiance of 3 mW/cm^2, riboflavin was instilled onto the corneal surface at 5-min intervals. All procedures were performed without any intraoperative or postoperative complications.

Statistical analysis

Mean, standard deviation, median, minimum, and maximum values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov Smirnov test. Wilcoxon signed-ranks tests were used in the analysis of dependent quantitative data, the chi-square test was used in the analysis of qualitative independent data, and

Table 1 Changes of corneal topography measurements with keratoconus 6 months postoperatively

	Preoperative	First week	First month	Sixth month
AXL (mm)	23.7 ± 1.2	23.7 ± 1.1 $p = 0.712$	23.7 ± 1.1 $p = 0.473$	23.6 ± 1.1 $p = 0.306$
ACD (mm)	3.7 ± 0.3	3.8 ± 0.3 $p = 0.503$	3.8 ± 0.2 $p = 0.26$	3.8 ± 0.3 $p = 0.358$
K1 (diopters)	47.3 ± 3.7	47.5 ± 3.8 $p = 0.449$	47.6 ± 4.0 $p = 0.082$	47.2 ± 3.8 $p = 0.190$
K2 (diopters)	52.3 ± 3.9	52.9 ± 3.9 $p = \mathbf{0.014}$*	53.0 ± 4.1 $p = \mathbf{0.001}$*	52.3 ± 4.0 $p = 0.804$
CCT (μm)	464.5 ± 40.3	470.0 ± 38.4 $p = 0.428$	450.5 ± 39.4 $p = \mathbf{0.000}$*	452.1 ± 42.0 $p = \mathbf{0.004}$*
CV (mm^3)	58.4 ± 3.6	58.6 ± 3.8 $p = 0.654$	58.0 ± 3.8 $p = 0.122$	58.3 ± 3.5 $p = 0.702$

Postoperative measurement compared with preoperative values

AXL axial length, *ACD* anterior chamber diameter, *CCT* central corneal thickness, *CV* corneal volume

*$p < 0.05$

Table 2 Changes of the retinal thickness of the eyes with keratoconus 6 months postoperatively

	Preoperative	First week	First month	Sixth month
Total retina thickness (μm)				
Center	237.9 ± 33.4	234.6 ± 66.7 $p = 0.836$	256.2 ± 69.4 $p = 0.282$	258.0 ± 81.1 $p = 0.300$
Parafovea	282.5 ± 43.9	273.6 ± 61.3 $p = 0.551$	284.4 ± 60.7 $p = 0.909$	284.2 ± 65.3 $p = 0.909$
RNFL thickness (μm)				
Center	11.7 ± 5.1	19.0 ± 11.9 $p = \mathbf{0.032}$*	23.2 ± 17.3 $p = \mathbf{0.015}$*	24.3 ± 19.1 $p = \mathbf{0.017}$*
Parafovea	25.5 ± 4.1	28.2 ± 10.3 $p = 0.243$	31.3 ± 17.1 $p = 0.149$	31.4 ± 19.5 $p = 0.189$
GCL thickness (μm)				
Center	44.8 ± 15.4	45.9 ± 22.8 $p = 0.883$	49.6 ± 26.1 $p = 0.417$	47.4 ± 26.0 $p = 0.662$
Parafovea	72.0 ± 27.1	68.0 ± 27.1 $p = 0.141$	64.9 ± 24.8 $p = 0.180$	60.8 ± 27.6 $p = \mathbf{0.028}$*
Choroidal thickness (μm)				
Center	362.3 ± 89.2	374.5 ± 87.8 $p = 0.286$	377.7 ± 98.1 $p = 0.334$	383.8 ± 94.8 $p = 0.393$
Parafovea	347. ± 80.8	359.2 ± 92.8 $p = 0.361$	374.6 ± 97.1 $p = 0.084$	377.8 ± 94.6 $p = 0.164$

RNFL retina nerve fiber layer, *GCL* ganglion cell layer

*$p < 0.05$

the Fischer test was used when the chi-square test conditions were not met. SPSS Statistics version 27.0 (IBM Corp., Chicago, IL, USA) was used for the analysis. For the manual measurements, the kappa coefficient was used to evaluate the agreement between two independent retina specialists. A *p*-value less than 0.05 is considered statistically significant.

Results

Twenty-seven eyes of 16 male and 9 female patients with keratoconus were included in the study. The corneal topography data is presented in Table 1, the MT data is presented in Table 2, and vascular density measurements in OCTA are presented in Table 3.

Corneal topography analysis

A decrease in CCT was observed after the CXL operation in our study. There was no significant difference in axial length, anterior chamber depth, and corneal volume (Table 1).

Table 3 Changes of the vessel density in the superficial retinal capillary plexus, deep retinal capillary plexus, and choriocapillaris of eyes with keratoconus 6 months postoperatively

	Preoperative	First week	First month	Sixth month
SCP VD (%)				
Center	33.2 ± 11.4	35.1 ± 11.3 $p = 0.190$	35.6 ± 10.9 $p = 0.751$	36.0 ± 10.6 $p = 0.690$
Parafovea	49.1 ± 4.9	48.6 ± 3.7 $p = 0.273$	47.6 ± 3.1 $p = 0.138$	46.3 ± 3.0 $p = \mathbf{0.019}$*
DCP VD (%)				
Center	40.1 ± 11.4	47.9 ± 13.9 $p = \mathbf{0.008}$*	46.7 ± 11.6 $p = \mathbf{0.043}$*	47.4 ± 10.1 $p = \mathbf{0.040}$*
Parafovea	49.5 ± 3.9	47.4 ± 4.1 $p = 0.059$	48.1 ± 4.7 $p = 0.368$	48.9 ± 2.7 $p = 0.570$
OR VD (%)				
Center	43.8 ± 9.7	41.9 ± 7.1 $p = 0.285$	44.2 ± 11.6 $p = 0.766$	47.4 ± 8.4 $p = 0.083$
Parafovea	52.2 ± 3.6	52.7 ± 2.2 $p = 0.546$	53.7 ± 2.3 $p = 0.147$	53.0 ± 2.9 $p = 0.456$
CC VD (%)				
Center	48.0 ± 4.5	46.8 ± 3.6 $p = 0.058$	46.9 ± 3.7 $p = 0.259$	47.4 ± 4.1 $p = 0.340$
Parafovea	49.3 ± 3.1	49.1 ± 2.5 $p = 0.721$	49.7 ± 1.6 $p = 0.608$	49.3 ± 2.2 $p = 0.977$
SCP FAZ (μm^2)	238.2 ± 57.1	235.7 ± 67.4 $p = 0.846$	231.4 ± 65.9 $p = 0.815$	222.5 ± 84.9 $p = 0.615$
DCP FAZ (μm^2)	212.4 ± 84.3	219.5 ± 95.9 $p = 0.793$	212.1 ± 71.8 $p = 0.919$	226.7 ± 69.89 $p = 0.695$

VD vessel density, *SCP* superficial retinal capillary plexus, *DCP* deep retinal capillary plexus, *OR* other retina, *CC* choriocapillaris, *SCP FAZ* superficial FAZ area, *DCP FAZ* deep FAZ area

*$p < 0.05$

Optical coherence tomography analysis

Total retinal thickness in the center zone measurements is summarized in Table 2. There was no significant difference in full retinal thickness in the foveal and parafoveal areas.

While there was a significant increase in retinal nerve fiber layer (RNFL) thickness in the foveal area ($p=0.032$, $p=0.015$, $p=0.017$; p values of the first-week, first-month, and sixth-month measurements respectively). There was a significant decrease in ganglion cell layer (GCL) thickness in the parafoveal area in the sixth month ($p=0.028$).

Optical coherence tomography angiography analysis

In our study, there was no difference in SCP FAZ area, DCP FAZ area, SCP, OR, and CC VD measurements. However center zone of DCP VD was significantly increased after CXL ($p=0.008$, $p=0.043$, $p=0.040$; p values of the first week, first month, and sixth month respectively) (Table 3).

Visual acuity results

Four eyes lost more than 2 lines and four eyes gained 2 lines or more in the CDVA. CDVA was stable in 19 eyes after the procedure. The preoperative mean CDVA (logMAR) was 0.37 ± 0.16 and the postoperative sixth-month mean CDVA (logMAR) was 0.39 ± 0.15. There was no significant difference in visual acuity ($p=0.71$).

Discussion

Corneal collagen CXL is the only treatment that affects the progression of keratoconus and is effective in the stabilization of moderate corneal ectasia, in decreasing maximum keratometry, and in improving CDVA [4, 18–20]. In an attempt to strengthen the corneal stroma, the eye is exposed to a direct source of UVA light, a process that creates UVA–riboflavin-induced cross-links on the cornea. It is unknown whether the UVA light, which the patient is exposed to during the procedure, passes through ocular structures and causes phototoxicity damage to the retina [21]. Though in vitro studies have shown that the shielding effect of riboflavin limits radiant transmission on inner ocular structures, few in vivo studies have been performed to assess the morphological changes to the retina after UVA–riboflavin CXL, and some studies were found in the literature on functional damage to the retinal tissue [22, 23].

To the best of our knowledge, this is the first study in the literature that examined the effect of CXL operation with the Dresden protocol on the retinal vascular changes using optical coherence tomography angiography. In this study, 27 eyes were evaluated to determine the structural and microvascular changes before and after exposure to UVA during the CXL procedure. The effect of UVA radiation after CXL on the retinal structure was also investigated using OCT scans of the macula. Based on officially accepted guidelines regarding direct UV damage, as well as outcomes of experimental studies on animal models, it was suggested that UVA irradiance and dose used during the CXL procedure (3 mW/cm^2, 5.4 J/cm^2) are below the damage threshold for the retina, taking into consideration the saturation of corneal stroma with riboflavin and the UVA absorption from the lens [24]. The damage thresholds, however, were set based on structural changes/damages and not changes in retinal function [25]. Lazaridis et al.'s [26] results showed a significant decrease in the retinal response at 2 weeks after CXL and normalization of these responses at 6 weeks. After CXL, their results showed a statistically insignificant increase in central MT, a statistically insignificant increase in MT at the 1-mm zone, and a significant decrease in the parafoveal and perifoveal thickness. The significant decrease in the parafoveal and perifoveal thickness may be associated with retinal phototoxicity [26]. In this study, there was no significant difference in full retinal thickness in the foveal and parafoveal areas. While there was a significant increase in RNFL thickness in the foveal area ($p=0.032$, $p=0.015$, $p=0.017$; respectively) and a decrease in GCL thickness in the parafoveal area in the sixth month ($p=0.028$). The hypothesis here is that this increase in RNFL and MT could be explained by a mild and self-limiting inflammatory reaction to the procedure and to UV light exposure. This reaction was evident 7 days after the procedure. Further studies are needed to prove or disprove this hypothesis. There were no changes in the fundus examination with indirect ophthalmoscopy or biomicroscopy. The superficial corneal changes seen in the patients regressed to levels that do not affect the quality of the shooting as of the 1st week. The fact that corneal changes did not affect the results can be explained by the consistency of the measurement results after the postoperative 1st week, although the corneal findings improved over time in the follow-up.

There were significant changes in VD, especially in the parafoveal area, a significant decrease in SCP VD at the sixth month ($p=0.019$), and a significant increase in DCP VD in the foveal area ($p=0.008$, $p=0.043$, $p=0.040$ respectively). Hasmani et al. [27] found a positive correlation between vascular density and retinal thickness in the fovea. In our study, OCTA showed an increase in DCP VD due to increased retinal thickness from the first week in line with their study. No changes were detected in the FAZ area.

A limitation of our study is the number of patients included. Nevertheless, our sample size was sufficient for a

reliable statistical analysis. In total, both eyes of 7 patients were included in the study. Of the remaining 13 eyes (that are not included in the study), 4 had a history of cross-linking from the other eye in an external center and 2 eyes had previously undergone penetrating keratoplasty surgery. The remaining 7 eyes were not included in the study, considering that they would not yield a statistically significant result due to the low number. The insufficient number of control group data can be considered one of the limitations of our study.

Larger studies with data are needed to further address possible phototoxicity and microvascular changes of the retina and the safety of corneal CXL for keratoconus patients.

Conclusion

Continuous UVA light exposure during CXL treatment raises concerns over potential phototoxicity damage to the retina. This is the first study in the literature in which the vascularity of the macula has been analyzed after exposure to UVA light from the corneal CXL procedure by OCTA. Although no UV-related vascular changes were detected in the images taken with fluorescein angiography in previous studies in the literature, we showed that UV-related retinal microvascular changes can be seen with OCTA in our study. Further studies are needed to evaluate the effect of UVA on the retina during CXL with accelerated protocols and the effect of UVA on the retina when applying a combination of corneal refractive procedures with CXL. We showed morphological and microvascular changes in our study. In the 6-month follow-up, there was no change in the parameters that could show the functional results (such as visual acuity), which correlated with the microvascular changes. We want to bring the longer-term functional results of the patients we follow up in the future to the literature.

In conclusion, keratoconus patients were successfully treated with CXL; however, significant changes occur in the retinal layers and vessel density in the superficial and deep retinal plexus.

Declarations

Ethical approval This study was approved by the Ethics Committee of the Akdeniz University Medical Faculty (Approval Number KAEK-486). 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 to participate and publish Informed consent for publication of their clinical details and/or clinical images was obtained from all individual participants included in the study. A copy of the consent form is available for review by the Editor of this journal.

Conflict of interest The authors declare no competing interests.

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