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ORIGINAL ARTICLE

Long-term Follow-up of Pachymetric and Topographic Alterations after Corneal Collagen Cross-Linking for Keratoconus

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ABSTRACT

Purpose: To determine the long-term alterations of corneal thickness, along with topographic outcomes, after corneal collagen cross-linking treatment (CXL) for keratoconus.

Materials and methods: In this retrospective case series, 46 patients (52 eyes), 32 males and 14 females, with progressive keratoconus were included. All eyes underwent CXL in accordance with the standard protocol (Dresden) for the treatment of their ectatic corneal disorder between January 2006 and June 2007. Pachymetric and topographic outcomes were evaluated preoperatively and at 1, 3, 6, 12, 24 and 36 months postoperatively.

Results: Mean follow-up was 28.08 ± 8.39 months (range, from 12 to 36 months). A statistically significant decline in corneal pachymetric values (at the thinnest location) when compared with preoperative values (467.65 ± 41.08 μm) was demonstrated at 1 (437.63 ± 50.57 μm), 3 (439.08 ± 52.27 μm), 6 (449.37 ± 52.73 μm), 12 (449.63 ± 83.53 μm) and 24 (459.97 ± 47.32 μm) months after CXL ($p < 0.05$, for all mentioned time intervals). Return to preoperative pachymetric values (469.52 ± 40.52 μm) was revealed 36 months post-CXL ($p > 0.05$). With respect to topographic (flat and steep keratometric values, keratoconus index), no statistically significant differences between preoperative and all postoperative intervals were found ($p > 0.05$, for all values for all time intervals).

Conclusion: Corneal pachymetric values reduce significantly up to 24 months after CXL treatment, while a return to preoperative values was revealed 36 months after the procedure. No significant changes' concerning topographic outcomes was demonstrated after CXL, indicating stability of these parameters.

Keywords: Keratoconus, Corneal cross-linking, Corneal pachymetry, Corneal topography, Keratoconus index.

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INTRODUCTION

Keratoconus is a frequent, noninflammatory disease, characterized by corneal thinning and steepening overtime; the incidence in the general population is estimated to be 1/2000.[1] Progressive corneal thinning, leads to irregular astigmatism, myopia and subsequent decrease in visual acuity. Keratoconus usually begins at puberty and tends to progress in approximately 20% of patients to such a degree that management is required in order to improve and preserve visual function.[1,2]

The interventions proposed to improve visual function, such as rigid contact lenses, spectacles, intracorneal rings, can only correct refractive errors (they do not interfere with the pathophysiology of the disease), while progression of keratoconus may still continue.[3] Penetrating or lamellar keratoplasty is used as the only therapeutic approach, on the condition that contact lenses become intolerant, the cornea becomes extremely thin and in presence of corneal scaring (hydrops).[4]

Collagen cross-linking (CXL) is a relatively new minimally invasive surgical technique, which strengthens the corneal tissue by increasing the number of intrafibrillar and interfibrillar covalent bonds, thus increasing corneal rigidity, inhibiting this way the progression of keratoconus.[5-7] Besides the induced covalent bonds, CXL also procures a series of corneal tissue alterations which have been described by *in vivo* corneal confocal microscopy studies;[8-10] these extensive structural changes have been linked with corneal topographic and pachymetric modifications.

The mentioned micro and macrostructural corneal alterations after CXL treatment are not yet completely defined, while they are crucial for understanding CXLs therapeutic mechanisms. The aim of the current study is to evaluate corneal alterations concerning pachymetric and topographic outcomes over a period of 3 years after CXL treatment.

MATERIALS AND METHODS

Patient Population

Fifty two eyes of 46 patients (32 males and 14 females) that underwent CXL with rivoflavin and UV-A for keratoconus between January 2006 and June 2007 were included in this study. Mean patient's age was 27.31 ± 5.61 years, ranging from 19 to 35 years. Mean follow-up was 28.08 ± 8.39 months (range, from 12 to 36 months). All patients were informed of risks and benefits prior to CXL and they gave their written

informed consent in accordance with the Declaration of Helsinki for human research. Study approval was obtained from the Aristotle University of Thessaloniki, Faculty of Medicine.

Inclusion criteria were progressive keratoconus (keratoconus was described as progressive when there was in the cone apex keratometry of 0.75D diopters (D) or alteration of 0.75D in the spherical equivalent refraction in a period of at least 6 months), no other corneal or anterior segment pathological signs, no pregnancy or lactation and no any ocular or systemic disease that could affect the epithelial healing. Exclusion criteria were presence of corneal hydrops, history of herpetic keratitis, severe eye dryness, concurrent corneal infections, endothelial cell count less than 1000 cell per mm², any previous ocular surgery, autoimmune diseases, pregnancy and breastfeeding.

Examinations

All examinations were performed preoperatively and at 1, 3, 6, 12, 24 and 36 months after CXL treatment. The clinical diagnosis of keratoconus was based on corneal topography data (Wavelight Alegro Oculizer, Nyremberg, Germany). Corneal pachymetry (CT) at the thinnest location was evaluated with the use of pentacam Scheimpflug (Wavelight Allegro Oculizer, Nyremberg, Germany). Topographic outcomes [K1 (flat keratometry), K2 (steep keratometry), KI (keratoconus index)] were retrieved from the Allegro Oculyzer program (Oculink software, Nyremberg, Germany). Keratoconus index represents a ratio between the peripheral corneal thickness over the thinnest corneal thickness (PCT/TCT ratio), which offers an index of the severity of keratoconus (as keratoconus index increases, the severity of keratoconus increases as well).

Surgical Technique

The procedure was performed under sterile conditions. Preoperative local anesthesia was achieved using proxymetacainhydrochloride 0.5% [Alcaine, Alcon laboratories (Australia), Pty Ltd] eye drops. Corneal epithelium was mechanically removed in the central 8 mm using a mechanical rotating brush. Commercially available rivoflavin solution 0.1% (Medio-Haus medizinprodykte GmbH, Neudorf, Germany) was instilled every 3 minutes for approximately 30 minutes prior to UV-A application. Ultraviolet-A irradiation was performed using a commercially available UVA system at a preset 370 nm wavelength (UV-X ; Pesche Meditrade GmbH, Zyrich, Switzerland). Before irradiation, an intended 3.0 mW/cm^2 (5.4 J/cm^2 total surface dose after 30 minutes UV-A exposure) of surface irradiance was calibrated using a UV light meter at a working distance of 5 cm. During treatment, riboflavin 0.1% solution was applied every 5 minutes to maintain corneal stromal saturation. After CXL, a soft therapeutic contact lens was placed in all eyes, until full reepithelization of the cornea. The postoperative regimen included: Artificial tears four times daily for a month, antibiotic drops ofloxacin 0.3% and fluoromethanole 0.1% four times daily for 1 and 2 weeks respectively.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 (SPSS, Inc.) software package. The paired t-test was used to check the significance of the difference between two dependent groups for every continuous variable (CT, KI, K1, K2). The level of statistical significance was considered when p-value was lower than 0.05.

RESULTS

Pachymetric Outcomes

Mean corneal pachymetry, at the thinnest point, reduced significantly from preoperative 467.65 ± 41.08 µm to 437.63 ± 50.57 µm, 439.09 ± 52.27 µm, 449.38 ± 52.73 µm, 449.64 ± 83.53 µm and 459.98 ± 47.32 µm at 1, 3, 6, 12 and 24 month post-CXL treatment respectively ($p < 0.05$, at all mentioned postoperative intervals) (Fig. 1). Mean percentage of pachymetric difference (preoperative-postoperative) was 6.85, 6.50, 4.06, 4.00 and 1.66% at 1, 3, 6, 12 and 24 month post-CXL treatment respectively. Corneal pachymetry returned to preoperative values, demonstrating no statistical significant difference ($p > 0.05$) when compared to preoperative values, 36 months after CXL treatment (469.53 ± 40.52 µm).

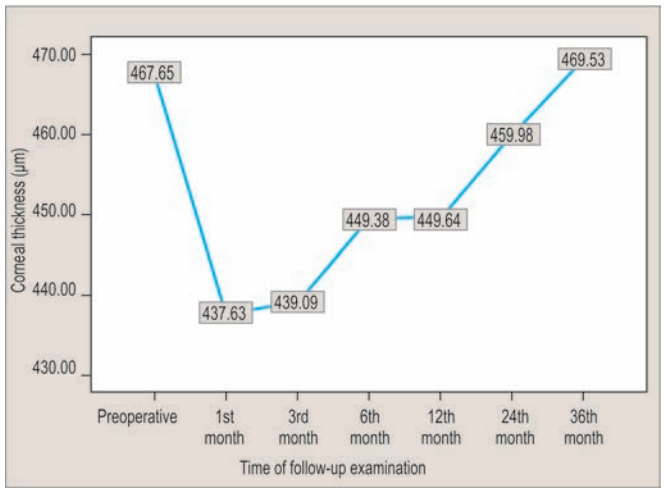

Fig. 1: Mean corneal pachymetric readings (at the thinnest location) preoperatively and at 1, 3, 6, 12, 24 and 36 months after corneal cross-linking treatment

Topographic Outcomes

The results of topography concerning the indices of the flattest and the steepest meridian keratometry and keratoconus index are shown on Table 1. There was no statistically significant difference for these parameters between the preoperative and postoperative values at all intervals ($p > 0.05$).

DISCUSSION

Collagen cross-linking with riboflavin and UVA is a new method of treatment for corneal ectatic disorders, aiming at delaying or stopping the progression of keratoconus and reducing the need of corneal transplantations.[11,12] CXL increases the biomechanical strength of the cornea by inducing bonds between the collagen fibers;[13-15] it has been described that in many cases CXL improves patient's visual acuity and topographic characteristics (corneal flattening).[12,16-18]

Even though, the efficacy of CXL is well-established,[19-20] a lot of aspects related to the changes of the corneal tissue after the procedure have to be elucidated. In respect with corneal pachymetry, as shown in the present study, there seems to be a significant decline at the thinnest point up to 24 months after CXL. These results come in agreement with the study by Arbelaez et al,[19] in which a significant decrease in thinnest point corneal pachymetry was found for all patients up to 6 months after CXL, with an accumulative 5% reduction at the 3rd postoperative interval; pachymetric values returned to preoperative levels 1 year after CXL in this study, while in our study, this was documented at 36 months. Furthermore, the results reported by Vinciguerra et al,[21] who found that corneal pachymetry at the thinnest point to be significantly reduced up to 1 year after CXL; the same study also documented a return in preoperative pachymetric values 24 months after surgery. In our study, a tendency of returning to preoperative pachymetric values was evident at 24 months post-CXL (even though significantly reduced pachymetry was documented at 24 months, an increase of mean pachymetry of 10 µm was evident when comparing the values at 12 and 24 post-CXL months), while at 36 months pachymetry returned to preoperative values.

Corneal pachymetry reduction may be attributed to the corneal structural alterations induced by CXL treatment. Corneal stromal keratocyte nuclei apoptosis which is evident immediately after the procedure up to 300 µm in depth, may cause corneal thinning; keratocytes occupy intra-stromal volume and their apoptosis in a 75% corneal thickness causes decrease in stromal volume. Furthermore, keratocytes are responsible for the collagen turnover (stromal metabolism) and thereby their dramatic decrease also diminishes the production of new collagen.

Concerning the other examined parameters in the present study (K1, K2, KI) no statistically significant postoperative differences were found. Our results are in agreement with those reported by Kymionis et al, where K readings did not change after CXL treatment in a follow-up of 1 year.[20] However, other studies showed statistically significant changes of topographic readings after CXL treatment.[19,21,22] Vinciguerra et al found statistically significant reduction in postoperative keratometric readings as well as significant reduction in total corneal aberrations in their patient group.[22] In another study Vinciguerra et al which involved 28 eyes demonstrated a statistically significant reduction in K1, K2 and Abr values supporting this way the revealed improvement in postoperative visual acuity. A recent study by Koller et al, concluded that statistically significant corneal flattening occurs more commonly in corneas with preoperative maximum K readings of more than 54D;[23] in our patient population mean preoperative steep K did not exceed 50D, therefore, the stability in K readings throughout the 36 months follow-up maybe explained.

CONCLUSION

CXL treatment seems to induce some corneal macrostructural alterations, since it reduces statistically significant corneal pachymetric values up to 24 months after treatment. A return to preoperative pachymetric values is revealed 36 months after CXL. Steep and flat keratometric values along with keratoconus index seem to remain unchanged during the entire follow-up period signifying corneal stability after CXL treatment.

Table 1: Three years follow-up examination of corneal topographic readings [flattest, steepest meridian of keratometry (K1, K2), keratoconus index (KI)] after CXL treatment [expressed as, average ± standard deviation (range)]

	K1 diopters	*K2 diopters*	*KI PCT/TCT**
Preoperative	45,37 ± 4,10 (38, 3-57, 7)	49,29 ± 4,82 (39, 6-62, 5)	1,23 ± 0,14 (1, 0-1, 5)
1 post-CXL month	45,22 ± 4,48 (37,3-56,8)	49,27 ± 4,99 (40,0-61,8)	1,24 ± 0,14 (1, 0-1, 5)
3 post-CXL months	45,57 ± 4,03 (38,8-54,1)	49,23 ± 4,36 (41, 5-59, 2)	1,25 ± 0,14 (0, 9-1, 5)
6 post-CXL months	45,60 ± 4,27 (37,6-56,5)	49,59 ± 4,84 (41, 2-62, 8)	1,23 ± 0,14 (0.9-1, 5)
12 post-CXL months	44,63 ± 3,92 (37,8-55,8)	48,37 ± 4,22 (40,4-60,9)	1,20 ± 0,13 (1, 0-1, 5)
24 post-CXL months	45,32 ± 4,02 (39,1-56,1)	49,19 ± 4,59 (40, 3-61, 3)	1,22 ± 0,13 (1, 0-1, 5)
36 post-CXL months	43,98 ± 2,18 (41,5-49,3)	48,52 ± 3,15 (43, 2-52, 4)	1,17 ± 0,09 (1, 0-1, 4)

*PCT/TCT: Keratoconus index is the peripheral corneal thickness/thinnest corneal thickness

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