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CROSS-LINKING WITH LASER EXCIMER IN KERATOCONUS - PROGNOSTIC FACTORS

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Abstract

Purpose: To evaluate which predictors contribute effectively towards the improvement of anatomic and functional results of keratoconus (KC) patients that underwent the Athens Protocol. Our goal is to match future treatment plans of eyes with identical characteristics to the ones who have been successfully treated.

Methods: In this retrospective clinical study, we used data regarding 77 eyes of 73 patients who underwent the Athens Protocol. Corrected distance visual acuity (CDVA) obtained by Snellen charts and converted to logMAR, mean (Km), steep (K2) and maximum (K_{max}) keratometry obtained by Pentacam or Orbscan, sphere, cylinder and spherical equivalent (SE), were evaluated preoperatively and at 6 months postoperatively.

Results: preoperative CDVA was 0.38 ± 0.19 logMAR and improved with statistically significance ($p<0.05$) to 0.28 ± 0.20 logMAR; preoperative mean K1 was 46.65 ± 3.68 D and reduced without statistically significantly ($p>0.05$) to 46.20 ± 3.01 D; preoperative K2 was 52.27 ± 7.65 D and K_{max} was 55.73 ± 4.84 D, and postoperatively both were statistically significantly ($p<0.05$) reduced to 49.72 ± 3.90 D and 52.61 ± 4.45 D, respectively. The mean sphere decreased from the preoperative value of -1.54 ± 2.82 D to -2.83 ± 2.55 D, the mean cylinder improved from the preoperative value of -2.87 ± 2.51 D to -2.08 ± 1.63 D and mean preoperative SE refraction worsened from the preoperative value of -2.93 ± 2.66 D to -3.84 ± 2.81 D. The analyses of potential predictors, such as thinnest pachymetry, CCT, Km, age at date of surgery or SE planned for surgery, did not show a statistically significant correlation with any of the different dependent variables, K_{max} and CDVA.

Conclusions: The observed changes in visual acuity, along with keratometric flattening and topographic regularization, suggested a postoperative improvement after the Athens Protocol procedure. However, the potential predictors did not show a statistically significant correlation with the outcomes, suggesting that other players take part in the response to cross-linking treatment of the cornea.

Keywords

CROSS-LINKING; LASER EXCIMER; KERATOCONUS; PROGNOSTIC FACTORS; ATHENS PROTOCOL

Resumo

O objetivo deste estudo foi avaliar quais os preditores que contribuem para a melhoria dos resultados anatómicos e funcionais no pós-operatório de pacientes com queratocone e que tenham sido submetidos ao Protocolo de Atenas. Desta forma, pretende-se que no futuro seja possível planear os tratamentos para os olhos com características semelhantes aos que foram previamente tratados e que obtiveram bons resultados cirúrgicos.

Foi feito um estudo clínico retrospetivo e os dados foram recolhidos de 77 olhos de 73 pacientes que foram submetidos ao Protocolo de Atenas. Acuidade visual corrigida (CDVA) avaliada segundo a tabela de Snellen, e posteriormente, convertida para logMAR, Km, K2 e K_{max} obtidos após a avaliação por Pentacam ou Orbscan, esfera, cilindro e equivalente esférico foram avaliados no pré-operatório e aos 6 meses de pós-operatório.

Houve melhoria da CDVA de 0.38 ± 0.19 logMAR para 0.28 ± 0.20 logMAR, com significância estatística ($p<0.05$); o K1 pré-operatório era 46.65 ± 3.68 D e reduziu, sem significância estatística ($p>0.05$), para 46.20 ± 3.01 D; o K2 pré-operatório era 52.27 ± 7.65 D e o K_{max} era 55.73 ± 4.84 D, no pós-operatório ambos reduziram com significância estatística ($p<0.05$) para 49.72 ± 3.90 D e 52.61 ± 4.45 D, respetivamente. O valor médio da esfera diminuiu do valor pré-operatório -1.54 ± 2.82 D para -2.83 ± 2.55 D, o valor médio do cilindro melhorou do valor pré-operatório -2.87 ± 2.51 D para -2.08 ± 1.63 D; o valor medio pré-operatório do SE era -2.93 ± 2.66 D e diminuiu para -3.84 ± 2.81 D no pós-operatório. A análise das diferentes variáveis independentes (espessura mínima, CCT, Km, idade na data da cirurgia ou equivalente esférico planeado para cirurgia) não mostrou significância estatística na correlação com os outcomes K_{max} e CDVA.

Foi possível concluir que o Protocolo de Atenas contribuiu para uma melhoria significativa da acuidade visual e diminuição da queratometria. Apesar disto, os fatores preditores não mostraram correlação estatística significativa com a melhoria dos outcomes, o que sugere o envolvimento de outras variáveis na resposta ao cross-linking.

Palavras-chave

CROSS-LINKING; LASER EXCIMER; QUERATOCONE; PROGNÓSTICO; PROTOCOLO DE ATENAS

Abbreviations

CDVA: corrected distance visual acuity

CCT: central corneal thickness

CHUC: centro hospitalar e universitário de Coimbra

CXL: cross-linking

D: dioptres

K1: flat keratometry

K2: steep keratometry

Km: mean keratometry

K_{max}: maximum keratometry

KC: keratoconus

logMAR: logarithm of the minimum angle of resolution

PRK: proliferative keratectomy

SD: standard deviations

SE: spherical equivalent

TG-CXL: topography-guided photorefractive keratectomy combined with corneal collagen cross-linking (Athens Protocol)

UCVA: uncorrected visual acuity

UV: ultraviolet

Introduction

Keratoconus is a non-inflammatory pathology that consists in a progressive thinning and ectasia of the cornea that induces impaired visual acuity primarily due to irregular astigmatism and myopia, and secondarily from corneal scarring. The classic histopathological features include breaks in Bowman's layer and thinning of the corneal stroma. The etiology remains unclear however seems to be a multifactorial disease caused by a combination of genetic and environmental factors, such as eye rubbing, atopy and UV radiation [1,2]. KC is usually diagnosed during adolescence, based in video topographical/ tomographic analysis, and tends to stabilize between the ages of 30 and 40. Since it affects mostly young people, this disease often has a direct impact on quality of life [3]. Treatment options in keratoconus include spectacle correction, contact lens adaptation, corneal collagen cross-linking (which can be augmented with laser refractive procedures), intrastromal corneal ring segments and corneal transplantation [3,4,13].

Corneal collagen cross-linking (CXL), with riboflavin (vitamin B2) and ultraviolet A (UVA) light is a minimally invasive surgical technique that aims to halt the progression of KC by increasing the biomechanical strength of the cornea through induction of the formation of new covalent bonds in the stromal matrix [4-6].

The Athens Protocol (consisting in CXL combined with topography-guided photorefractive keratectomy – PRK) intends to decrease the irregularity of the cornea, improve visual acuity and stabilize KC. This surgical technique (Fig. 1) consists of two steps described by Kanellopoulos [4,14,15]. The first step is the topography-guided (TG) transepithelial PRK technique, which uses customized excimer laser, guided by topographic images, in order to normalize the cornea by reducing irregular astigmatism, while treating part of the refractive error. The second step is collagen CXL with 0.1% riboflavin sodium phosphate ophthalmic solution applied topically, followed by emission of UVA light projected onto the surface of the cornea. In the postoperative period, topical ofloxacin and prednisolone are applied and protection with sunglasses is recommended [4, 7, 14].

According to different authors, this combined technique seems to be as safe as CXL alone. Additionally, it has showed better refractive, topographic and aberrometric outcomes than CXL alone [7,10,13].

Currently, there is little information about the prognostic factors of the Athens Protocol in the published literature. This information is essential to determine which patients effectively benefit from this surgery and to establish laser excimer guidelines for the procedure.

This study aims to discover which parameters are associated with a better clinical outcome: preoperative minimum corneal pachymetry, preoperative keratometry at the flat and steep axis, age at date of surgery, percent of spherical equivalent programmed for laser excimer ablation and agreement between the refractive astigmatism axis and the flat topographic axis (difference equal or less of 30 degrees).

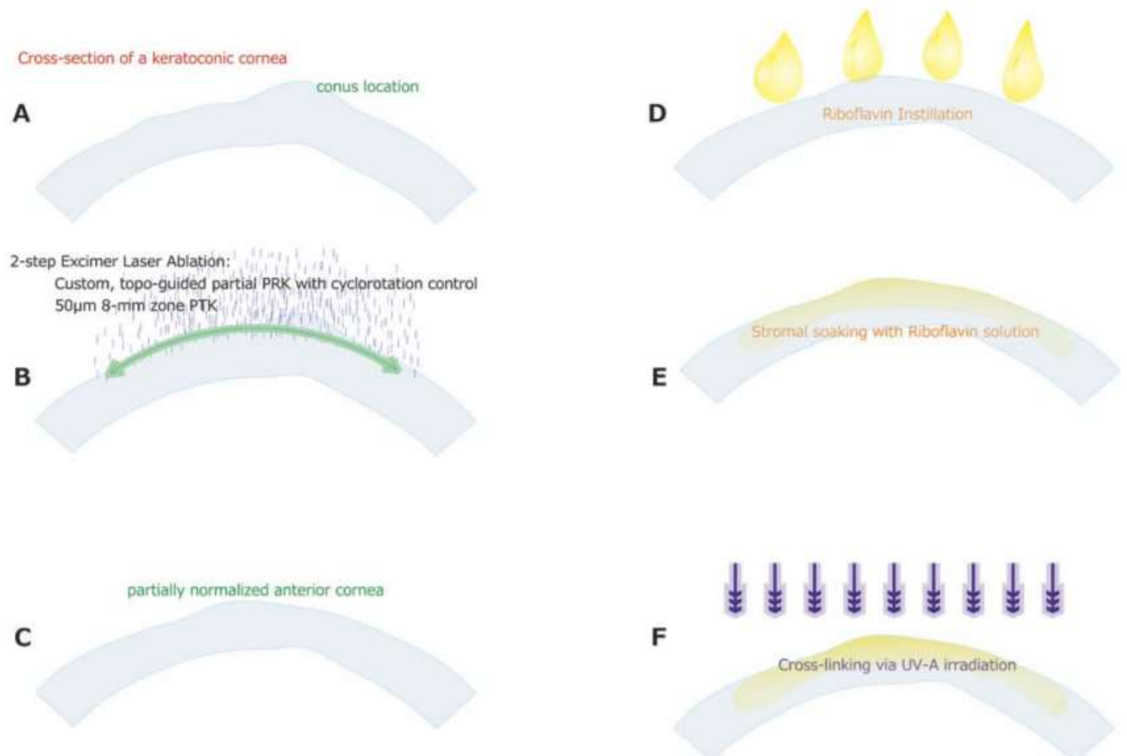

Figure 1 – Basic steps of the Athens Protocol procedure. (A) Import of TG data to the surgical platform, (B) a two-step excimer laser ablation comprising 50 µm deep, 7 mm optical zone diameter phototherapeutic keratectomy, custom TG-PRK, followed by (C) application of mytomicin C, (D) instillation of riboflavin, (E) stromal soaking for 10 minutes, and (F) UVA irradiance of 10 mW/cm2 applied for 10 minutes.

Adapted from: Kanellopoulos, A. J., & Asimellis, G. (2015). Novel Placido-derived Topography-guided Excimer Corneal Normalization With Cyclorotation Adjustment: Enhanced Athens Protocol for Keratoconus. Journal of Refractive Surgery, 31(11), 768–773.

Methods

Setting

This retrospective clinical study comprised patients with KC who underwent the Athens Protocol at the Ophthalmology Department, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal with a minimum follow-up of 6 months. Patients underwent the Athens Protocol in the presence of keratoconus with low visual acuity, not correctable by spectacles or contact lenses. The protocol currently used comprises 1) a PRK of 50µm debridement of the epithelium, 2) partial topography-guided excimer ablation (Fig.2) followed by 3) short duration corneal collagen CXL (Fig.3). The CXL consists of applying 0.1% riboflavin (10 min soak) followed by irradiation with UVA light (KXL I UVA system, 10 mW/cm², 10 min, total dose 6 J/cm²).

All patients provided written informed consent before surgery in accordance with the Declaration of Helsinki, and institutional review board approval was obtained from the Hospital Ethics Committee.

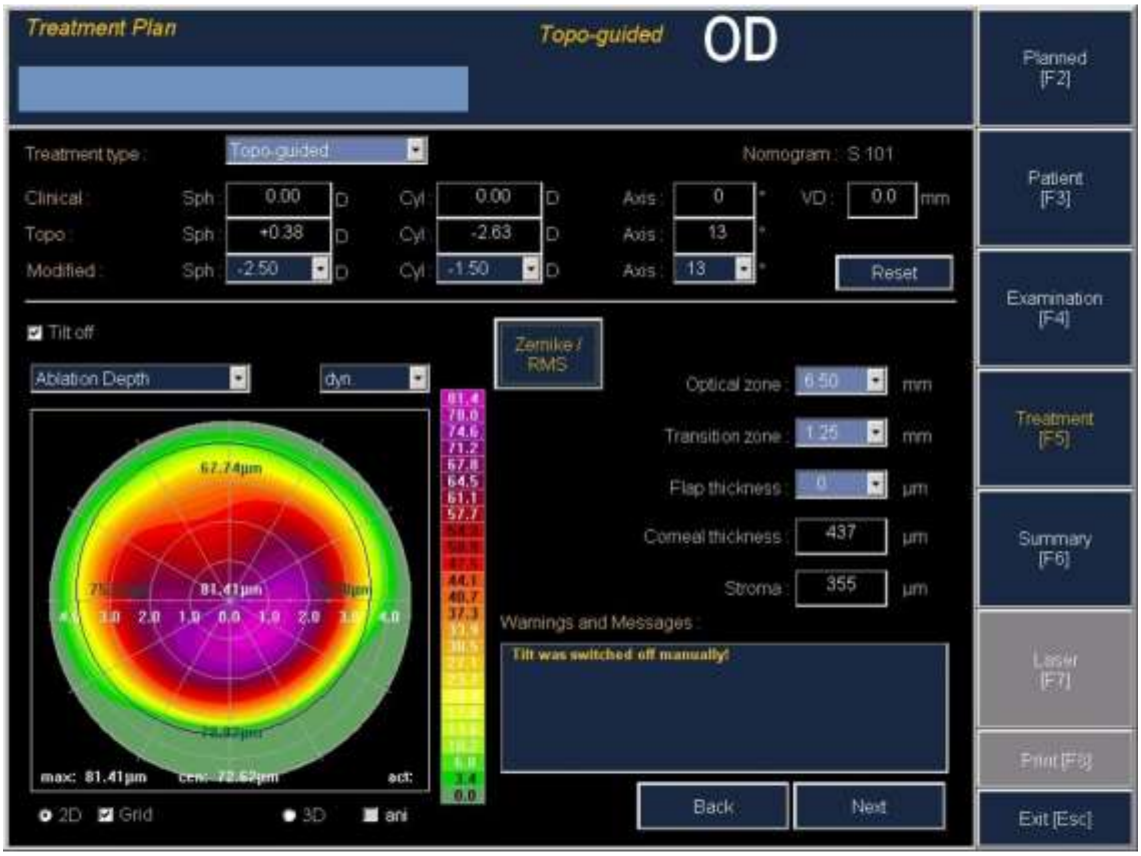

Figure 2 – Treatment plan of the topography-guided laser ablation.

Source: Ophthalmology Department of Centro Hospitalar e Universitário de Coimbra.

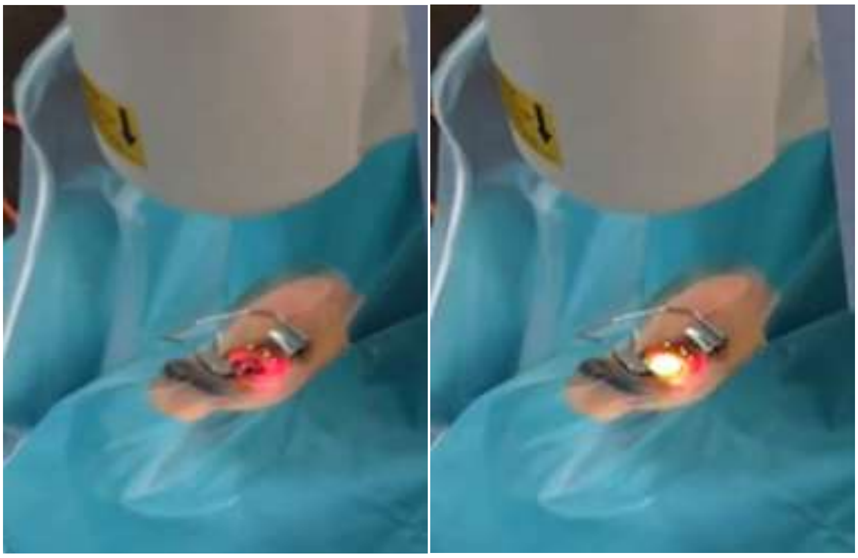

Figure 3 – Cross-linking procedure via *UVA irradiance of 10 mW/cm2 applied for 10 minutes.*

Source: Ophthalmology Department of Centro Hospitalar e Universitário de Coimbra.

Participants

Pre and postoperatively all patients had a complete ophthalmologic examination with an experienced ophthalmologist, which included determination of uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) with Snellen charts, refraction, fundoscopy, corneal pachymetry, keratometry readings and tomography (Pentacam High Resolution – Oculus Optikgeräte GmbH, Wetzlar, Germany; Orbscan II – Bausch & Lomb, Inc, Salt Lake City, Utah, USA).

The following information was collected from retrospective chart review: gender, age, date of birth, eye enrolled, UCVA and CDVA (transformed into the logarithm of the minimum angle of resolution, logMAR [11]), refractive sphere, cylinder, and calculation of the spherical equivalent. We evaluated the following tomographic parameters: the thinnest pachymetry and central cornea thickness (CCT), keratometry readings (flat keratometry (K1), steep keratometry (K2), mean keratometry (Km) and maximum keratometry (K_{max})), location of cone and the agreement between the refractive astigmatism axis and the flat topographic axis (difference equal or less of 30 degrees). Data regarding surgery was also collected: date of TG-CXL, planned spherical and cylinder correction, maximum ablation depth. Finally, in the postoperative period the UCVA, CDVA, sphere, cylinder, K1, K2 and K_{max} were recorded.

Data Analysis

The study of the population demographics, clinical, functional, refractive and topographic characteristics were summarized using traditional descriptive methods. Descriptive statistic was used to evaluate the changes between preoperative and postoperative clinical evaluation. For each outcome of interest linear regression analysis and paired t-test were performed to seek for possible correlations.

Data was entered and encoded in a Microsoft Excel® Office 365® spreadsheet, (Microsoft Corporation, Redmond, Washington, EUA). Descriptive and inferential statistics were performed using STATA®, version 16 (StataCorp LP, College Station, TX, EUA).

Experimental data was expressed as mean ± standard deviations. Means and percentages were used for the description of quantitative data, whose normality was verified using the Shapiro-Wilk test. Paired t-tests were used to compare treatment effects following TG-CXL; also, linear regression models were built to evaluate predictors of clinical outcomes. Statistical significance was defined by a two-tailed p-value lower than 0.05.

Results

We included 77 eyes of 73 patients (43 males and 30 females). There was a preponderance towards the male gender, consistent with the clinical experience in male-female incidence of KC reported in the literature [16]. The average age was 30,77 ± 9.30 years, ranging from 17 to 56 years. Surgery was performed in 39 right eyes (50,65%) and 38 left eyes (49,35%). Four patients had surgeries in both eyes. Concerning the location of the cone, 24 eyes had a central cone, 27 eyes had a paracentral cone and 3 eyes had a pericentral cone (i.e., when the apex is within the central 3 mm circle, between the 3 mm and 5 mm circles or out of the 5 mm circle, respectively) [17]. Minimum follow-up was 6 months for all patients.

Patients preoperative demographic, functional, refractive and topographic measures are summarized in Table I and are hereby enumerated: mean UVDA was 0.83 ± 0.35 logMAR, thinnest pachymetry was 465.94 ± 44.64 µm, mean CCT was 494.96 ± 45.76 µm and mean Km was 49.26 ± 4.85 D.

Preoperative demographic and topographic parameters	
Number of patients	73
Age (years) ± SD	30,77 ± 9.30(17-56)
Gender	
Male	43 (58,9%)
Female	30 (41,1%)
Eye	
Left	38 (49,35%)
Right	39 (50,65%)
Tomography device	
Pentacam	30 (39.47%)
Orbscan	46 (60.56%)
Cone location	
Central	24 (44.44%)
Paracentral	27 (50.00%)
Pericentral	3 (5.56%)
UCVA (logMAR)	0.83 ± 0.35
Thinnest pachymetry (µm)	465.94 ± 44.64
CCT (µm)	494.96 ± 45.76
Km (D)	49.26 ± 4.85

Table I – Preoperative demographic, functional, refractive and topographic parameters. Legend: SD – standard deviation; UCVA -uncorrected visual acuity; CCT – central corneal thickness; Km – medium keratometry; D – dioptres.

Preoperative CDVA was 0.38 ± 0.19 logMAR and improved with statistically significance ($p<0.05$) to 0.28 ± 0.20 logMAR. The mean sphere parameter was more negative (i.e., of higher magnitude) with a decrease of 1.29 ± 3.07 D from preoperative value of -1.54 ± 2.82 D to -2.83 ± 2.55 D, the mean cylinder showed an increase of 0.79 ± 2.76 D regarding the preoperative value of -2.87 ± 2.51 D to -2.08 ± 1.63 D, and mean preoperative SE refraction decreased from the preoperative value of -2.93 ± 2.66 D to -3.84 ± 2.81 D. All these modifications occurred up to 6 months after TG-CXL and all showed a statistically significant variation ($p<0.05$). Concerning corneal topography, preoperative mean K1 was 46.65 ± 3.68 D and at 6 months of follow-up reduced without statistically significant variation ($p>0.05$) to 46.20 ± 3.01 D. Preoperative mean K2 was 52.27 ± 7.65 D and mean K_{max} was 55.73 ± 4.84 D, and at 6 months of follow-up both were statistically significantly ($p<0.05$) reduced to 49.72 ± 3.90 D and 52.61 ± 4.45 D, respectively (Table II).

	Pre-operative (mean ± SD)	**Post-operative (mean ± SD)**	**Difference (mean ± SD)**	**p-value***
CDVA (logMAR)	0.38 ± 0.19	0.28 ± 0.20	-0.10 ± 0.22	< 0.001
Sphere (D)	-1.54 ± 2.82	-2.83 ± 2.55	-1.29 ± 3.07	0.001
Cylinder (D)	-2.87 ± 2.51	-2.08 ± 1.63	0.79 ± 2.76	0.026
SE (D)	-2.93 ± 2.66	-3.84 ± 2.81	-0.91 ± 0.40	0.025
K1 (D)	46.65 ± 3.68	46.20 ± 3.01	0.45 ± 2.07	0.087
K2 (D)	52.27 ± 7.65	49.72 ± 3.90	-2.55 ± 7.47	0.009
K_{max} (D)	55.73 ± 4.84	52.61 ± 4.45	-3.12 ± 3.65	< 0.001

Table II - Pre and postoperative results of functional, refractive and topographic parameters. Legend: SD – standard deviation; D – dioptres; CDVA – corrected distance visual acuity; SE – spherical equivalent; K1 – flat keratometry; K2 – steep keratometry; K_{max} – maximum keratometry.
** statistically significant at $p < 0.050$*

The analysis of the variance of K_{max} in function of different independent variables (Table III) did not show any statistically significant correlations between K_{max} and thinnest pachymetry, CCT, Km, age at date of surgery or SE planned for surgery. Furthermore, there was no statistically significant correlation between K_{max} and the preoperative location of the cone or the agreement between the refractive astigmatism axis and the flat topographic axis (difference equal or less of 30 degrees), p-values of 0.502 and 0.531, respectively.

K_{max}	β Coefficient	95% CI	p-value*
Thinnest pachymetry	0.007	[-0.017;0.031]	0.559
CCT	0.007	[-0.016;0.029]	0.553
Km	-0.165	[-0.347;0.017]	0.074
Age TG-CXL	-0.082	[-0.180;0.016]	0.099
Plan SE (%)	-0.050	[-1.131;1.031]	0.926

Table III – Summary of univariate linear regression analysis of potential predictors of Kmax reduction following the Athens Protocol. Legend: K_{max} – maximum keratometry; CI – confidence interval; CCT – central corneal thickness; Km– mean keratometry; Age TG-CXL – age at date of surgery; Plan SE – spherical equivalent planed for surgery.

**statistically significant at p<0.050*

The analysis of the variance of CDVA in function of different independent variables (Table IV) did not show any significant correlations between CDVA change and thinnest pachymetry, CCT, Km, age at date of surgery or SE planned for surgery. Also, there was no statistically significant correlation between the CDVA and the preoperative location of the cone or the agreement between the refractive astigmatism axis and the flat topographic axis (difference equal or less of 30 degrees), p-values of 0.446 and 0.539, respectively.

CDVA	β Coefficient	95% CI	p-value*
Thinnest pachymetry	0.001	[-0.000;0.002]	0.053
CCT	0.001	[-0.000;0.002]	0.126
Km	-0.003	[-0.017;0.011]	0.677
Age TG-CXL	0.001	[-0.005;0.007]	0.712
Plan SE (%)	-0.001	[-0.065;0.063]	0.970

Table IV – Summary of univariate linear regression analysis of potential predictors of CDVA improvement following the Athens Protocol. Legend: CDVA – corrected distance visual acuity; CI – confidence interval; CCT – central corneal thickness; Km – mean keratometry; Age CXL – age at date of surgery; Plan SE – spherical equivalent planed for surgery.

**statistically significant at p<0.050*

Discussion

KC is a condition that may lead to serious visual acuity decline. The Athens Protocol has showed that it is a safe and effective procedure for stabilizing keratoconus, yielding significant improvements in topographic measurements (Km and K_{max}), CDVA, and manifest cylinder. Also, in some studies, improvement of UCVA and a mild decrease in SE can be seen [6-8,10,13]. Critically, the accumulated evidence on the Athens Protocol shows a consistent improvement in best corrected visual acuity, at least until the third year of follow-up [18,23].

This study comprised a series of patients with KC who underwent TG-CXL surgery and observed changes in visual acuity, along with keratometric flattening and topometric improvement, suggesting a postoperative improvement after the Athens Protocol procedure, which is in agreement with the results reported in other studies [5-8,19,22,23].

However, because not all patients experience the same level of visual or topographic improvement, it is of upmost importance to evaluate which predictors effectively contribute towards the improvement of the visual acuity.

First, it was expected that age would affect the results (younger people were expected to present better postoperative results than older patients would). Young people cones are more central, and the Athens Protocol is best in correction of central corneas because the light is centered at the corneal apex, which also receives the highest amount of energy with current CXL devices. Central cones have also been associated with statistically significant improvements of CDVA, K_{max} and greater biomechanical stability [17]. However, this hypothesis was not confirmed. It may be due to the fact that our mean age was 30 years old and our sample lacks initial keratoconus cases, which appear earlier in life.

The average age of KC onset ranges between 9 and 28 years old and the literature suggests that these patients, despite being younger and having higher visual acuities, still suffer from impaired vision-related quality of life. Younger patients in progression are also more likely to still have corneas thick enough for TG-CXL eligibility, in comparison to older patients with thinner corneas where keratoplasty might be the only available treatment option [20-22].

Secondly, it was expected that preoperative thinner corneas would perform worst, since the excimer laser would have less tissue to correct the cornea surface, which was not verified in our sample. The epithelium in healthy eyes has a thinnest point around 0.33 mm temporally and 0.9 mm superiorly from the corneal vertex. However, keratoconic eyes have a lower epithelium thickness at the cone apex and increased thickness surrounding the cones [9]. Following the Athens Protocol, epithelial thickening is expected to increase at the preoperatively thinnest area, and Xiangjun *et al.* [8] demonstrated a reduction in epithelial thickness variation due to the thickening of the epithelium over the cone. The epithelial thickness variation decreases due to the reduced need for compensation for stromal bulging.

It was also demonstrated by Kanellopoulos, A. J. *et al.* [12, 23] that there is a short-term variability in corneal thickness distribution between the third and sixth months postoperatively, but the cornea appears to gradually thicken over a 3-year period. The sixth month was exactly the follow-up used in these cases, so it can be a limitation for this study. Padmanabhan *et al.* suggested that a flatter and broader cone may redistribute the biomechanical strain from forces and may represent an additional benefit to the patient [7]. Nevertheless, it is also necessary to have in consideration that the Athens Protocol procedure does involve some ablation over the already thin cone, which can be concerning, due to the cytotoxic effects of UVA light on corneal endothelial cells with pachymetries less than 350 µm [14]. This hypothesis can be avoided preoperatively by a three-dimensional mapping of the epithelial morphology and by limiting the ablation to no more than 50 µm [4, 5 ,9]. This was probably the reason why there was no correlation between preoperative corneal thickness and visual outcomes, as we did not remove more than 50 µm of tissue, which eliminates the advantage that thicker corneas could have.

Third, we expected that higher preoperative keratometry values would be associated with better results, due to the fact that there would be more space for improvement. This hypothesis was also not verified. Although TG-CXL attempts to regularize the cornea and flatten K2 with minimal effect on K1, it is possible to have different results at the early postoperative period, potentially because of the initial corneal remodelling effect of CXL [22]. In this study the follow-up period was of 6 months, which can be a limitation. According to the theorical model proposed by Sinha Roy and Dupps, a special variation of UVA intensity can result in greatest flattening effect [2]. This means that optimizing the UVA treatment profile may induce greater flattening with a significant improvement of visual acuity [10].

The preoperative percent of spherical equivalent that is programmed on the excimer laser was expected to be positively associated with better results (higher percentage, better results), but this hypothesis was also not confirmed. It is recommended to attempt at most 70% of the measured sphere when planning the TG-CXL [14]. A possible explanation is that correcting a higher percentage of preoperative refraction may also lead to more haze and inflammation, which may limit visual gains. In addition, it is likely that a higher percentage of correction is correlated with uncorrected visual acuity and not with corrected visual acuity, which was the outcome variable we selected.

Conclusion

In our sample, the observed changes in visual acuity, corneal tomography and refractive parameters show a postoperative improvement following the Athens Protocol procedure. We did not find any predictors of tomographic and visual improvement. Larger and longer studies are needed to determine whether we can reliably predict TG-CXL success from the preoperative evaluation.

Finally, it is also possible that there are other factors involved, probably at the biochemical level. Because KC is a multifactorial disease, it is likely that response to its treatment is also multifactorial. This way, the evaluation of anti-inflammatory cytokines, chemokines, trophic factors and the immunological profile of the ocular surface may lead to improved and personalized treatment strategies, that combine not only optical factors (addressed by the Athens Protocol) but also the ocular surface micro-environment.

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References

[1] Gordon-Shaag, A., Millodot, M., & Shneor, E. (2012). The Epidemiology and Etiology of Keratoconus. International Journal of Keratoconus and Ectatic Corneal Diseases, 1(1), 7–15.

[2] Roy, A. S., & Dupps, W. J. (2011). Patient-Specific Computational Modeling of Keratoconus Progression and Differential Responses to Collagen Cross-linking. Investigative Opthalmology & Visual Science, 52(12), 9174-9187.

[3] Fournié, P., Touboul, D., et al (2013). Kératocône. *Journal Français d'Ophtalmologie.* 618-626.

[4] Kanellopoulos, A. J., & Binder, P. S. (2011). Management of Corneal Ectasia After LASIK with Combined, Same-Day, Topography-Guided Partial Transepithelial PRK and Collagen Cross-Linking: The Athens Protocol. *Journal of Refractive Surgery*, *27*(5), 323–331.

[5] Nordström, M., Schiller, M., Fredriksson, A., & Behndig, A. (2016). Refractive improvements and safety with topography-guided corneal crosslinking for keratoconus: 1-year results. British Journal of Ophthalmology, 101(7), 920–925.

[6] Li J., Ji P., & Lin X. (2015). Efficacy of Corneal Collagen Cross-Linking for Treatment of Keratoconus: A Meta-Analysis of Randomized Controlled Trials. PLoS One, 10(5): e0127079.

[7] Padmanabhan, P., Radhakrishnan, A., Venkataraman, A., Gupta, N., & Srinivasan, B. (2014). Corneal changes following collagen cross linking and simultaneous topography guided photoablation with collagen cross linking for keratoconus. Indian Journal of Ophthalmology, 62(2), 229-235.

[8] Chen, X., Stojanovic, A., Wang, X., Liang, J., Hu, D., & Utheim, T. P. (2016). Epithelial Thickness Profile Change After Combined Topography-Guided Transepithelial Photorefractive Keratectomy and Corneal Cross-linking in Treatment of Keratoconus. Journal of Refractive Surgery, 32(9), 626–634.

[9] Reinstein, D. Z., Gobbe, M., Archer, T. J., Silverman, R. H., & Coleman, J. (2008). Epithelial Thickness in the Normal Cornea: Three-dimensional Display With Artemis Very High-frequency Digital Ultrasound. Journal of Refractive Surgery, 24(6), 571–581.

[10] Cassagne, M., Pierné, K., Galiacy, S. D., Asfaux-Marfaing, M.-P., Fournié, P., & Malecaze, F. (2017). Customized Topography-Guided Corneal Collagen Cross-linking for Keratoconus. Journal of Refractive Surgery, 33(5), 290–297.

[11] Camparini M, Cassinari P, Ferrigno L, et al. ETDRS-fast: implementing psychophysical adaptive methods to standardized visual acuity measurement with ETDRS charts. Invest Ophthalmol Vis Sci 2001;42:1226–31.

[12] Kanellopoulos, A. J., & Asimellis, G. (2014). Epithelial remodeling after partial topography-guided normalization and high-fluence short-duration crosslinking (Athens protocol): Results up to 1 year. Journal of Cataract & Refractive Surgery, 40(10), 1597–1602.

[13] Sakla, H., Altroudi, W., Muñoz, G., & Albarrán-Diego, C. (2014). Simultaneous topography-guided partial photorefractive keratectomy and corneal collagen crosslinking for keratoconus. Journal of Cataract & Refractive Surgery, 40(9), 1430–1438.

[14] Kanellopoulos, A. J. (2009). Comparison of Sequential vs Same-Day Simultaneous Collagen Cross-Linking and Topography-Guided PRK for Treatment of Keratoconus. Journal of Refractive Surgery, 25(9), 812-818.

[15] Kanellopoulos, A. J., & Asimellis, G. (2015). Novel Placido-derived Topography-guided Excimer Corneal Normalization With Cyclorotation Adjustment: Enhanced Athens Protocol for Keratoconus. Journal of Refractive Surgery, 31(11), 768–773.

[16] Kanellopoulos, A. J., & Asimellis, G. (2014). Corneal Refractive Power and Symmetry Changes Following Normalization of Ectasias Treated With Partial Topography-Guided PTK Combined With Higher-Fluence CXL (The Athens Protocol). Journal of Refractive Surgery, 30(5), 342–346.

[17] Shetty, R., Nuijts, R. M., Nicholson, M., Sargod, K., Jayadev, C., Veluri, H., & Roy, A. S. (2015). Cone Location–Dependent Outcomes After Combined Topography-Guided Photorefractive Keratectomy and Collagen Cross-linking. American Journal of Ophthalmology, 159(3), 419-425.

[18] Al-Tuwairqi, W. S., Osuagwu, U. L., Razzouk, H., & Ogbuehi, K. C. (2015). One-Year Clinical Outcomes of a Two-Step Surgical Management for Keratoconus—Topography-Guided Photorefractive Keratectomy/Cross-Linking After Intrastromal Corneal Ring Implantation. Eye & Contact Lens: Science & Clinical Practice, 41(6), 359–366.

[19] Stojanovic, A., Zhang, J., Chen, X., Nitter, T. A., Chen, S., & Wang, Q. (2010). Topography-Guided Transepithelial Surface Ablation Followed by Corneal Collagen Cross-Linking Performed in a Single Combined Procedure for the Treatment of Keratoconus and Pellucid Marginal Degeneration. Journal of Refractive Surgery, 26(2), 145–152.

[20] Labiris, G., Giarmoukakis, A., Sideroudi, H., Gkika, M., Fanariotis, M., & Kozobolis, V. (2012). Impact of Keratoconus, Cross-Linking and Cross-Linking Combined With Photorefractive Keratectomy on Self-Reported Quality of Life. Cornea, 31(7), 734–739.

[21] Labiris, G., Giarmoukakis, A., Sideroudi, H., & Kozobolis, V. (2013). Impact of Keratoconus, Cross-Linking and Cross-Linking Combined With Topography-guided Photorefractive Keratectomy on Self-Reported Quality of Life. Cornea, 32(9), 186-188.

[22] Sakla, H., Altroudi, W., Munoz, G., & Sakla, Y. (2016). Simultaneous Topography-Guided Photorefractive Keratectomy and Accelerated Corneal Collagen Cross-Linking for Keratoconus. Cornea, 35(7), 941–945.

[23] Kanellopoulos, A. J., & Asimellis, G. (2014). Keratoconus Management: Long-Term Stability of Topography-Guided Normalization Combined With High-Fluence CXL Stabilization (The Athens Protocol). Journal of Refractive Surgery, 30(2), 88–92.