A Multivariate Analysis and Statistical Model for Predicting Visual Acuity and Keratometry One Year After Cross-linking for Keratoconus

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• PURPOSE: To investigate putative prognostic factors for predicting visual acuity and keratometry 1 year following corneal cross-linking (CXL) for treating keratoconus.
• DESIGN: Prospective cohort study.
• METHODS: This study included all consecutively treated keratoconus patients (102 eyes) in 1 academic treatment center, with minimal 1-year follow-up following CXL. Primary treatment outcomes were corrected distance visual acuity (logMAR CDVA) and maximum keratometry (K_{max}). Univariable analyses were performed to determine correlations between baseline parameters and follow-up measurements. Correlating factors ($P \leq .20$) were then entered into a multivariable linear regression analysis, and a model for predicting CDVA and K_{max} was created.
• RESULTS: Atopic constitution, positive family history, and smoking were not independent factors affecting CXL outcomes. Multivariable analysis identified cone eccentricity as a major factor for predicting K_{max} outcome (ß coefficient = 0.709, $P = .02$), whereas age, sex, and baseline keratometry were not independent contributors. Posttreatment visual acuity could be predicted based on pretreatment visual acuity (ß coefficient = −0.621, $P < .01$, $R^2 = 0.45$). Specifically, a low visual acuity predicts visual improvement. A prediction model for K_{max} did not accurately estimate treatment outcomes ($R^2 = 0.15$).
• CONCLUSIONS: Our results confirm the role of cone eccentricity with respect to the improvement of corneal curvature following CXL. Visual acuity outcome can be predicted accurately based on pretreatment visual acuity. Age, sex, and K_{max} are debated as independent factors for predicting the outcome of treating keratoconus with CXL. (Am J Ophthalmol 2014;157:519–525. © 2014 by Elsevier Inc. All rights reserved.)

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KERATOCONUS IS A PROGRESSIVE NONINFLAMMATORY disease, in which the cornea becomes thinner, inducing irregular astigmatism and reducing quality of vision.[1] Corneal cross-linking (CXL) is a relatively new treatment designed to increase the mechanical and biochemical strength of the stromal tissue by exposing the ectatic cornea to riboflavin and ultraviolet-A light.[2,3] When successful, CXL prevents the progression of keratoconus and can even cause the ectatic cornea to regress.[4] This stabilization of the keratoconus can prevent the future need for a corneal graft.[5] The clinical outcome following CXL with respect to visual acuity is generally positive, although loss of visual acuity can occur as a complication of the procedure.[6] In addition, CXL can affect the healthy endothelium, and treatment safety guidelines have been proposed to prevent this.[7,8] Importantly, the clinical benefits of CXL can vary among patients; indeed, nearly every clinician has encountered patients whose keratoconus proceeds seemingly unhampered despite CXL treatment. Therefore, the ability to reliably predict the outcome of performing CXL prior to the procedure will help clinicians manage their patients' expectations and minimize the exposure to potential side effects.

The etiology of keratoconus has been studied extensively, and factors associated with keratoconus include a positive family history,[9] an atopic constitution,[10] eye rubbing,[11] contact lens use,[12] and myriad syndromes such as Down,[13] chromosome 7,11 translocation,[14] and chromosome 13 ring abnormality.[15] However, whether these factors also play a role in the effectiveness and consequences of CXL treatment has not been established yet. Our understanding of the factors that are related with CXL treatment success is beginning to emerge. Achieving treatment success is based on a combination of clinical features, including postoperative visual acuity, improved keratometry, and the absence of adverse events. A systematic literature search to identify putative prognostic factors revealed that preoperative visual acuity, eccentricity of the cone, pretreatment maximum keratometry (K_{max}), age above 35 years, and sex are all predictors of CXL efficacy and safety.[16,17]

For example, Greenstein and associates reported that male subjects and patients with a central cone location seem to benefit more from CXL treatment in terms of K_{max} regression. However, whether a high K_{max} prior to treatment affects K_{max} regression is controversial.[18] Lamy

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and associates addressed post-CXL visual acuity outcomes and found that central cone location, visual acuity ≤20/25, and age ≤35 years predicted higher corrected distance visual acuity (CDVA) 1 year after treatment.[19] In addition, Spoerl and associates reported a negative association between smoking and keratoconus,[20] and Hafezi suggested that this might be explained by biomechanical changes that can occur in the cornea as a result of smoking.[21] Moreover, Altinors and associates reported that smoking can cause deterioration of the lipid layer in the precorneal tear film.[22] Therefore, smoking can affect the treatment outcome, particularly when CXL is performed in the presence of a corneal abrasion.

Here, we investigated the value of the aforementioned factors in predicting CXL treatment effectiveness in keratoconus patients. In addition, we assessed additional putative prognostic factors such as family history, atopic constitution, and smoking. By combining these factors, we attempted to create a prediction model that can assist clinicians in therapeutic decision making.

SUBJECTS AND METHODS

• **DATASET AND STUDY DESIGN:** The data were obtained from a cohort of patients with progressive keratoconus who received CXL treatment in our institution. We recruited all patients who were treated consecutively at the University Medical Center Utrecht from January 1, 2010 through December 31, 2010, followed by follow-up visit after 1 year. The inclusion criteria included a progression of K_{max} ≥ 1.0 diopter (D) within 6-12 months, and corneal thickness ≥400 μm (at the thinnest point). The exclusion criteria included corneal scarring, the concurrent presence of an infection, pregnancy, or lactation. The treatment effects were assessed at the 1-year follow-up visit. This study for predictor research was approved by the University Medical Center Utrecht Ethics Review Board, and the requirement for informed consent was waived. The treatment of the patient cohort was in accordance with the Declaration of Helsinki and local laws regarding research using human subjects.

• **SURGICAL PROCEDURE:** The surgical procedure was performed as described previously.[4,23] A 9-mm corneal abrasion was made using a blunt knife, after which a 0.1% solution of riboflavin (Peschke Meditrade GmbH, Waldshut-Tiengen, Germany) was applied every 3 minutes for 30 minutes. When corneal pachymetry was less than 400 μm, hypo-osmotic riboflavin was applied every 20 seconds for 5 minutes and repeated up to 2 times until adequate thickness (ie, ≥400 μm) was achieved. The cornea was exposed to an ultraviolet (UV) light source (UV-X; Peschke Meditrade GmbH, using a perpendicular emission plane) with a wavelength of 365 ± 10 nm for a total cumulative exposure time of 30 minutes. Riboflavin drops were instilled every 5 minutes during the UV irradiation. Following the treatment, a bandage lens (PureVision; Bausch + Lomb Nederland BV, Schiphol-Rijk, The Netherlands) was placed. Postoperative medication included nepafenac 0.1% drops (Nevanac; Alcon Nederland BV, Gorinchem, The Netherlands) 3 times a day (TID) for 1 week, moxifloxacin 0.5% drops (Vigamox; Alcon Nederland BV) TID for 1 month, and dextran/hypromellose drops (Duratears; Alcon Nederland BV) TID for 1 month. When the epithelium was healed the bandage contact lens was removed and fluorometholone 0.1% drops (FML Liquifilm; Allergan BV, Eindhoven, The Netherlands) were applied twice a day.

• **DATA COLLECTION:** Standardized preoperative assessment yielded a series of potential predictive factors. These measurements included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA, obtained using manifest refraction), corneal tomography (Pentacam HR type 70900; Oculus Optikgeräte GmbH, Wetzlar, Germany), endothelial cell count (SP-3000P; Topcon Corporation, Tokyo, Japan), and automated tonometry (CT-80; Topcon). These measurements were repeated postoperatively at 1, 3, 6, and 12 months. All patients were instructed to stop wearing their contact lenses 2 weeks before each evaluation.

Patients' histories were obtained using standardized forms and included their family history, atopic constitution, and smoking status. Family history for keratoconus was obtained to fourth-degree relatives (ie, nephews/nieces) and was defined as positive in the case of a first- or second-degree relative with keratoconus. An atopic constitution was defined as having asthma, hay fever, eczema, food allergies, and/or anti-allergy medication usage. Smoking status included current smoking status or smoking in the personal history, and the number of pack-years was noted. Any missing data in the medical files were obtained by consulting with the patients by phone or mail.

• **STATISTICAL ANALYSIS:** Visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR) of visual acuity. The following 2 primary outcomes were defined: (1) differences in visual acuity (logMAR CDVA) between baseline and 1-year follow-up visit; and (2) differences in keratometry (K_{max}) between baseline and 1-year follow-up visit. The paired-samples Student *t* test was used to analyze the differences between K_{max} and logMAR CDVA at baseline and 1 year after treatment. Missing measurements were excluded pairwise from the analysis.

Linearity of the baseline data and outcome measurements was determined visually in a histogram. Normality was tested based on skewness and kurtosis with a cut-off value of 3.29 ($P < .001$) and showed no deviations. The pretreatment measurements and potential prognostic factors (atopic constitution, family history, smoking habits, factors derived from a literature review, and preoperative measurements) were