



Influence of Crosslinking on Astigmatism Vector in Keratoconus: A Vector Analysis

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ABSTRACT

Introduction: Corneal cross linking (CXL) is an appropriate method to treat progressive keratoconus in order to stop progression. Generally, the change in the maximum corneal power (Kmax), corneal thickness, and total astigmatism are assessed for progression analysis. The aim of this study is to answer the question of whether corneal astigmatism is suitable for quantifying keratoconus progression or demonstrating stability. To improve accuracy, we analyze astigmatism as a vector parameter in CXL follow-up.

Methods: We performed a retrospective observational study analyzing a total of 74 eyes diagnosed with progressive keratoconus that received CXL treatment and had a follow-up period of at least 12 months, and in some cases, up to 5 years. In the Scheimpflug imaging

examination (Pentacam[®]), the focus was on the change of Kmax in diopter (D), astigmatism of the corneal front, and its vector parameter.

Results: Preoperatively, we observed an increase in Kmax difference (KmaxD) (median +1.9 D ± standard deviation, SD 2.2) and astigmatism vector difference (AVD) (median +0.7 D ± SD 1.6) with a positive correlation, which establishes a treatment indication. The follow-up showed a stabilization of KmaxD and AVD after 12 months (median KmaxD −0.7 D, AVD −0.4), and over the periods of 3 and 5 years, a further stabilization of the curvature parameters with a lower number of cases.

Conclusions: Compared with an analysis of an absolute value only, the vector analysis of astigmatism allows a much more precise description of astigmatism in order to verify the effectiveness of CXL. Both astigmatism vector and Kmax preoperatively increased and stabilized postoperatively. Astigmatism presumably has a significant effect on the quality of vision and should therefore also be used as an additional stability factor beside Kmax.

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Keywords: Keratoconus; Crosslinking (CXL); Astigmatism vector analysis; Postoperative follow up; Progression

Key Summary Points

Why carry out this study?

Crosslinking (CXL) is performed to reduce progression in patients with keratoconus, and maximum corneal power (K max) should be stable in the postoperative follow-up.

Astigmatism has an impact on visual acuity and contact lens fit, especially in patients with keratoconus. Is astigmatism suitable for quantifying keratoconus progression or for demonstrating stability, and how should it be calculated?

What was learned from this study?

Astigmatism does not change as much as Kmax preoperatively and remains stable postoperatively.

Precise vector analysis of corneal astigmatism after cross linking helps to detect stability after cross linking in patients with keratoconus, but not as a standalone parameter.

INTRODUCTION

The main complaints of patients with keratoconus are distorted vision and increased sensitivity to glare, initially at night, as refractive errors such as myopia and increasing astigmatism have a greater impact when the pupil is dilated. Although keratoconus (KC) can occur at any age, it mainly affects adolescents and young adults. If untreated, the disease often progresses into the third to fourth decade of life and then stops [1].

An appropriate method to stop progression is crosslinking (CXL) [2–4]. Since the often young patients are in the middle of life and rely on vision that is as clear as possible, considering how CXL affects the refractive power of the cornea is crucial. Rapid short-term treatment is particularly necessary in children, as the rate of progression is significantly higher in young people, and delayed treatment has a negative impact on future visual acuity [5]. To detect the success of the treatment, the change in the

maximum corneal power (Kmax) or the central corneal radii of the front and back surfaces is usually considered [6, 7]. Pure myopia can often be corrected with glasses, while changes in astigmatism are much more complex and make correction with glasses and even contact lenses more difficult. Astigmatism is often reported only by the absolute value [5, 8]. In addition to analyzing the Pentacam® data, several of the working groups use objective refraction to determine astigmatism or detect corneal aberration [9]. After CXL, a flattening of the corneal anterior surface with a reduction in the Kmax value is often observed. The pure astigmatism value also frequently decreases. However, these approaches ignore the impact of the axis [10, 11]. In addition, changing axis positions with the same astigmatism value has an influence on visual acuity and contact lens fit.

Few studies have analyzed astigmatism vector changes after CXL therapy [12–14]. Previous research used the Alpins method to assess surgically induced astigmatism (SIA) [12, 13]. This allows for a more accurate evaluation of astigmatism changes.

In the present study, the more precise vector analysis of astigmatism and its change by CXL is investigated. Our study aims to determine whether postoperative astigmatism remains stable and to what extent we can predict astigmatism changes over time. We hypothesize that our method will provide superior results compared with previous approaches.

In this context, the question of whether astigmatism is suitable for quantifying keratoconus progression or for demonstrating stability is addressed [15].

METHODS

Study Design

In this retrospective observational case study, pre- and post-operative visual, refractive, and topometric data were analyzed from patients who received CXL treatment at the Department of Ophthalmology at the University Medical Center Mainz. The study included a total of 74

eyes from 60 patients, diagnosed with progressive KC from 2009 to 2018. The follow-up period was a minimum of 12 months and a maximum of 6 years (Fig. 1). The number of cases decreased as the observation time increased. A main cohort with a sample size of 74 cases and a follow-up period of 12 months was formed, as well as four subcohorts with a reduced number of cases and follow-up periods of 3 (U3) and 5 years (U5). In addition, for a subgroup, the preoperative course in a period of 12 months (U_pre) before CXL was examined (Fig. 1). It was not necessary to obtain an ethics vote as this was a retrospective data analysis of patients' reports between 2013 and 2019. The data collection began in 2019. All the data were analyzed pseudonymously, and the principles of the Declaration of Helsinki were respected. If only health data are evaluated retrospectively that are routinely collected at the clinic/department (neither additional study-related surveys nor study-related examinations are carried out), so-called "third parties" are not given access to the data, and the data are passed on and published exclusively in anonymous form; neither consultation with the ethics committee nor informed consent from the patients is

necessary. This procedure is regulated in Rhineland-Palatinate by the State Hospital Act (§ 36 and § 37). Landesärztekammer Rheinland-Pfalz.

Inclusion Criteria

This analysis initially included every patient diagnosed with progressive KC at the Department of Ophthalmology at the University Medical Center Mainz who underwent CXL treatment and had a follow-up period of at least 12 months. Diagnosis of KC was determined by both clinical presentation and indices of corneal tomographic measurements. Typical clinical signs of KC were defined, such as irregular astigmatism, which can hardly be corrected by spectacles; Vogt's Striae; Fleischer ring; Munson sign; corneal scarring; and thinning [16]. Indices of corneal topography were obtained by using the Scheimpflug technique-based camera Pentacam® (OCULUS, Wetzlar, Germany). Progress of disease was described by meeting at least one of the following criteria between two measurements within 6–12 months: decrease in objective or subjective visual acuity, increase of

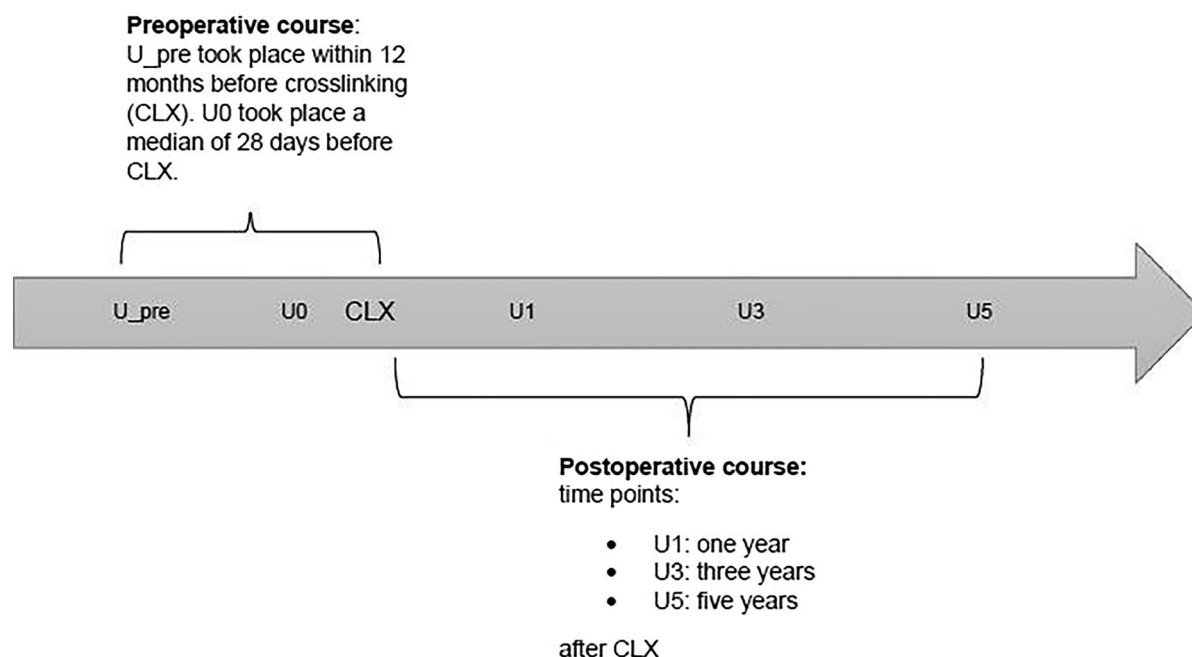


Fig. 1 Timeline of the study

astigmatism by ≥ 1 D (diopter) and increase in Kmax by ≥ 1 D [17, 18].

Exclusion Criteria

Excluded from this study were patients who had had any kind of corneal surgery before, i.e., CXL, laser treatments, and keratoplasty, who were diagnosed with degenerative corneal disease other than keratoconus, i.e., pellucid marginal degeneration, keratoglobus, or posterior keratoconus.

Preoperative Evaluation

All patients were examined continuously through the whole study. As baseline (U0), we used the last preoperative visit that took place within 1 month before CXL treatment. The examination consisted of anamnesis, best corrected visual acuity (LogMar_BCVA) measurement, slit-lamp survey, corneal tomography by Pentacam®, and measurement of endothelial cell number (Endozz). Patients were asked if they had experienced decrease of visual acuity or other symptoms of clinical KC such as sensing “halos”, double vision, or glare. Visual acuity was measured in decimal by auto refractometer AR-360A (NIDEK CO., LTD., Tokyo, Japan) and converted to logMAR (logarithm of the minimum angle of resolution). During slit lamp examination, we checked for signs of Vogt’s striae, Fleischer’s ring, Munson sign, scarring, and corneal thinning.

Corneal topographic data were obtained by analyzing three different topographic maps, recorded by the Pentacam®: the refractive power map (anterior surface), the true net power map, and the total corneal refractive power map. The focus in all three maps was on mean keratometry (Km) and astigmatism (Asti). Additionally, the maximum corneal power (Kmax) was evaluated in the data of the refractive power map of the anterior surface. As Pentacam® measurements can be difficult owing to the irregularity of the corneal surface, and there is therefore a higher measurement variability, the measurements

were repeated several times until the quality specification indicated “OK.” These values were then used in the calculation.

KC was graded by automatic identification system of the Pentacam® software (OCULUS, Wetzlar, Germany), which is based on the Amsler–Krumeich classification and the Belin ABCD Grading System [19].

To ensure corneal thickness ≥ 400 μm at the thinnest point preoperatively, pachymetry values were analyzed before UV radiation.

Endothelial cell number measurement was performed by using the Specular Microscope SP-3000P (TOPCON CORPORATION, Tokyo, Japan). All patients were advised to maintain abstention from wearing contact lenses 4 days before examination.

Surgical Procedure

CXL epithelium-off procedure was performed under topical anesthesia with tetracaine eye-drops followed by antisepsis of the conjunctiva with 1% PVP-iodine solution. A central zone of the corneal epithelium with a diameter of 9 mm was removed. Riboflavin (0,1% eye drops, Mediocross M, Avedro, USA) was instilled every 2 min for 30 min, followed by applying irradiation (UV-A, 365 nm, 3 mW/cm²) for 30 min. At the end of the surgery, the conjunctival sac was rinsed with 0.9% sodium chloride solution, followed by a rinse with 1% povidone (PVP)-iodine solution. Subsequently, ofloxacin eye ointment and a bandage was applied. Throughout the whole procedure, several pachymetric measurements ensured a minimum of ≥ 400 μm of corneal thickness.

Postoperative Tracing and Evaluation

All patients were examined daily by slit-lamp survey after CXL treatment until epithelial closure. A detailed control examination took place 12 months (U1) after the surgery. All procedures from the preoperative evaluation were repeated and compared with the preoperative baseline data. A smaller subgroup was

also examined 3 (U3) and 5 years (U5) after the surgery.

Statistical Analysis

Microsoft® Excel for Windows version 2306 was used for documentation and data collection. Descriptive and exploratory data analysis was performed using SPSS (version 27.0; SPSS for Windows, IBM, Armonk, NY).

Descriptive Statistics

First, the patients were pseudonymized and groups were formed by length of follow up.

In the main cohort, the age at the time of surgery, the gender and the treated eye were recorded. The topographic data from the Pentacam® was then descriptively evaluated. The following values were analyzed from the topographic map of the front surface: the degree of keratoconus (TKC), the mean keratometry value (Km), the maximum corneal power (Kmax), the value for the thinnest part of the cornea (Pachy_min), and the value for the minimum sagittal curvature radius (RSagMin). Finally, the data for visual acuity (LogMar_BCVA) and the endothelial cell count (Endozz) were descriptively evaluated in the postoperative course.

To test whether there was an association between changes in the Kmax values and the strength of astigmatism in the preoperative course, the Spearman rank correlation coefficient was calculated. For this calculation, the absolute value of the difference between the Kmax values and the absolute value of the vector difference in the astigmatism strength at the two examination times were used.

Exploratory Statistics

The Wilcoxon signed rank sum test was used as a significance test for comparing a continuous outcome between two independent groups in the exploratory statistics. A *p*-value below 0.05 was considered to be statistically significant.

Astigmatism

For the evaluation of different aspects of astigmatism, the astigmatism values of the anterior corneal surface (F_Asti) and the angle of the corresponding steep axis were used to detect possible axis rotation.

RESULTS

The results for the different examination periods are presented separately.

In total, 74 eyes of 60 patients were analyzed, with 82% from male patients and 18% from female patients. In 14 cases, both eyes of a patient were treated.

The average age at the time of surgery was 26 ± 13 years for men and 21 ± 22 years for women. CXL treatment was performed with central abrasion in all cases.

Preoperative Data

Indication for CXL treatment was based on the observed differences (KC progress) between two time points, U_pre and U0. U0 was a median of 1 month prior to treatment. The time of U0 is used as reference for all follow-up periods (Fig. 1).

The refractive power parameters of the cornea changed significantly (*p*-values of < 0.001 throughout) during the preoperative course (Table 1). If a progression was detected, cross linking was planned.

Visual acuity and endothelial cell density remained stable (Table 1).

Astigmatism Vector Analysis

The output for the vector difference between the two examination times shows that 60 out of 74 cases were localized in the innermost ring segment, with a difference of 0–2 D in magnitude and a median increase of 0.7. The centroid of the vector difference was $-0.32/74^\circ$ (Fig. 2 and Table 2).

Table 1 Descriptive statistics of the preoperatively collected data for the degree of keratoconus (TKC), the mean keratometry value (F_Km) [D], the maximum keratometry value (F_Kmax) [D], the thinnest part of thecornea (Pachy_min) [μm], the minimum sagittal radius of curvature (RSagMin) [mm], the visual acuity (logMAR_BCVA), and the endothelial cell count (Endozz)

	<i>n</i>	Mean	Median	SD	Min.	Max.	
TKC_pre	74	2.4	2.0	0.8	0.0	4.0	
TKC_U0	74	2.6	2.5	0.7	1.0	4.0	
F_Km_pre	74	47.1	46.2	3.9	41.5	58.7	
F_Km_U0	74	48.1	47.5	4.4	41.5	61.3	
F_Kmax_pre	74	55.4	55.8	5.9	45.4	75.8	
F_Kmax_U0	74	57.6	57.3	6.2	46.5	75.5	
Pachy_min_pre	74	466.6	461.0	39.6	377.0	558.0	
Pachy_min_U0	74	460.4	456.0	38.8	378.0	548.0	
RSagMin_pre	74	6.1	6.1	0.6	4.5	7.4	
RSagMin_U0	74	5.9	5.9	0.6	4.5	7.3	
LogMAR_BCVA_pre	68	0.4	0.4	0.3	0.0	1.3	
LogMAR_BCVA_U0	48	0.5	0.4	0.3	0.0	1.0	
Endozz_pre	60	2826	2868	336.7	2093	3600	
Endozz_U0	55	2856	2876	344.7	1978	3600	
	TKC_ Pre—TKC_ U0	F_Km_ Pre-F_Km_ U0	F_Kmax_ Pre—F_ Kmax_U0	Pachy_min_ Pre— Pachy_min_ U0	RSagMin_ Pre—RSag- Min_U0	LogMAR_ BCVA_ pre—Log- MAR_ BCVA_U0	Endozz_pre- Endozz_U0
Wilcoxon test (<i>p</i> -value)	<0.001	<0.001	<0.001	<0.001	<0.001	0.910	0.568

The mean value calculated for the number of data (*N*), the median and the standard deviation (SD), the minimum (Min.) and the maximum (Max.) in the preoperative course are shown

For comparison, the absolute value of central corneal astigmatism changes in median was -0.1 D (Table 3).

Spearman's rank correlation coefficient analysis was performed to detect correlation between the amount of the difference in Kmax and the amount of the absolute value of the vector difference of the group (Fig. 3).

The calculation resulted in a value of 0.206 and thus revealed a slight positive correlation.

The *p*-value of 0.078 exceeded the significance level of 0.01, and thus the coefficient correlation is not significant.

Year Follow-Up (U0 versus U1)

Table 4 summarizes the results of the descriptive and exploratory statistics of the 1-year follow-up. These show stable findings for the investigated parameters and a decrease in Kmax with a

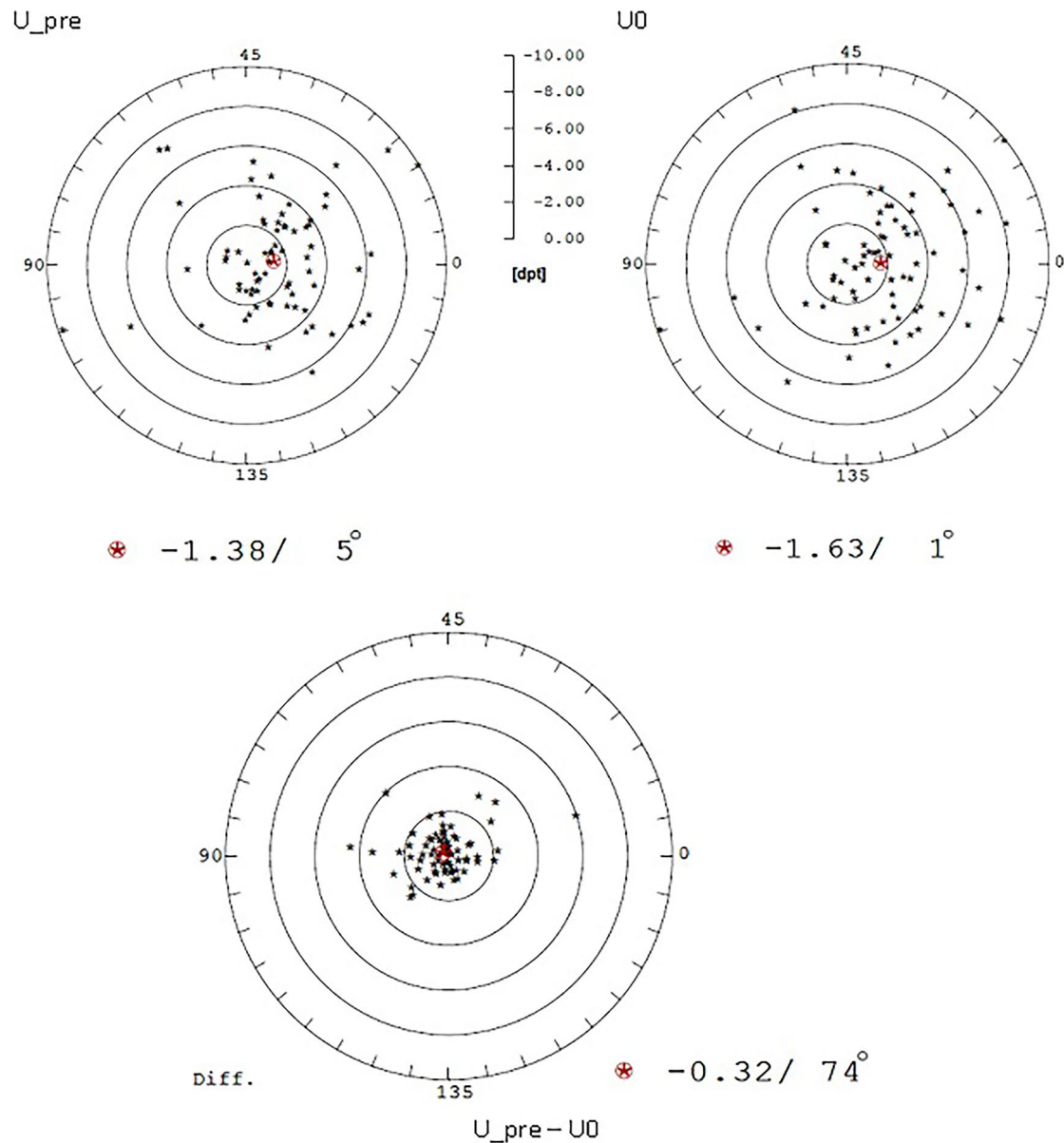


Fig. 2 Graphical vector analysis of the astigmatic data of the anterior surface at the time U_pre, U0, and vectorial difference in the preoperative course with the values: power

in diopters and the corresponding steep axis in degrees. The vector mean (centroid) is marked in red

corresponding increase in the minimum sagittal radius of curvature (RSagMin), which corresponds to postoperative stabilization after CXL. The median of Kmax decreases in median by -0.7 D.

Astigmatism Vector Analysis

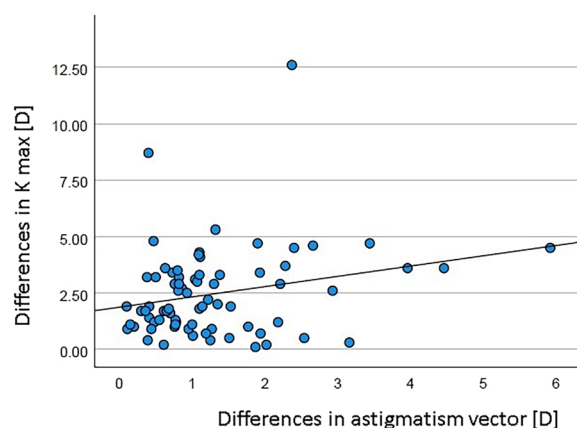
Figure 4 shows the graphical output of astigmatism vector analysis at the corresponding examination times and their difference. The median decrease was -0.4 . The centroid of the vector difference was $-0.25/97^\circ$. The output for the vector difference shows that most cases (60 out of

Table 2 Comparison of the change of the absolute value of the vector of central corneal astigmatism at the different visits, in diopter

	U0–U–1	U0–U1	U0–U3	U0–U5
Mean	0.6	–0.4	–0.5	–0.3
Median	0.7	–0.4	–0.5	–0.5
Standard deviation	1.6	1.6	2.1	2.6
Minimum	–3.2	–6.0	–9.7	–6.0
Maximum	5.9	2.7	2.1	4.2

Table 3 Comparison of the change of the absolute value of central corneal astigmatism at the different visits, in diopter

	U0–U–1	U0–U1	U0–U3	U0–U5
Mean	+0.39	–0.13	–0.36	–0.19
Median	–0.10	–0.10	–0.20	–0.05
Standard deviation	± 1.16	± 1.21	± 1.65	± 1.50
Minimum	–2.90	–5.80	–7.90	–5.70
Maximum	+5.80	+2.60	+2.10	+2.10

**Fig. 3** Scatter plot showing the difference in Kmax and astigmatism vector between U0 and U_pre

74) were in the innermost ring segment with an absolute value of 0–2 D, and around half of the cases (38 out of 74) were in the 0–1 D range.

For comparison, the absolute value of central corneal astigmatism changed by a median of –0.1 D, the same amount as preoperatively (Table 3).

The calculation of the Spearman correlation coefficient between the absolute value of the vector difference of the astigmatism and the magnitude of the difference in the Kmax values between the examination times U0 and U1 resulted in a value of 0.406, which shows a significant correlation between the two parameters (p value < 0.001). Compared with the preoperative time point U0 and the postoperative time point U1, there is a positive correlation between the changes in Kmax and the strength of the vector difference. A high change in Kmax correlated with a high change in the magnitude of the vector difference of astigmatism (Fig. 5).

Follow-Up at 3 and 5 Years

The following evaluation includes 33 eyes of 27 patients after 3 years and 22 eyes of 19 patients after 5 years.

The parameters TKC, Kmax, Km, R Sagmin, pachymetry, LogMar_BCVA, and endothelial cell count remained stable at both examination times and are therefore no longer shown in detail.

Astigmatism Vector Analysis

The median of the vector difference showed a decrease of 0.5 D between U0 and U3 (Table 2). Most cases were between 0 and 2 D, with 48% (16 of 33 cases) in the 0–1 D interval.

The graphical output of astigmatism vector analysis at the corresponding examination times is shown in Fig. 6. In this cohort as well, most cases in the vector difference output were in the innermost ring segment, with an absolute value of 0–2 D. The centroid of the vector difference was –0.59/93° (Fig. 6).

The median of the absolute value of the vector difference in the 5-year follow up was 0.5 D (Table 2).

Table 4 Descriptive statistics of the data collected at time points U0 and U1 for the degree of keratoconus (TKC), the mean keratometry value (F_Km) [D], the maximum keratometry value (F_Kmax) [D], the thinnest part of the cornea (Pachy_min) [μm], the minimum sagittal radius of curvature (RSagMin) [mm], the visual acuity (logMAR_BCVA), and the endothelial cell count (Endozz)

	<i>N</i>	Mean	Median	SD	Min.	Max.	
TKC_U0	74	2.6	2.5	0.7	1.0	4.0	
TKC_U1	74	2.5	2.5	0.8	0.0	4.0	
F_Km_U0	74	48.1	47.5	4.4	41.5	61.3	
F_Km_U1	74	47.7	47.2	4.3	40.7	60.6	
F_Kmax_U0	74	57.6	57.3	6.2	46.5	75.5	
F_Kmax_U1	74	57.0	56.3	6.6	46.8	81.5	
Pachy_min_U0	74	460.4	456.0	38.8	378.0	548.0	
Pachy_min_U1	74	452.9	449.5	41.1	367.0	559.0	
RSagMin_U0	74	5.9	5.9	0.6	4.5	7.3	
RSagMin_U1	74	6.0	6.0	0.7	4.1	7.2	
BCVA_logMAR_U0	48	0.5	0.4	0.3	0.0	1.0	
BCVA_logMAR_U1	58	0.5	0.4	0.3	0.0	1.3	
Endozz_U0	55	2856	2876	344.7	1978	3600	
Endozz_U1	59	2746	2772	360.9	1387	3481	
	TKC_U0 — TKC_U1	F_Km — F_Km_U1	F_Kmax — F_Kmax_U1	Pachy_min_U0 — Pachy_min_U1	RSagMin_U0 — RSagMin_U1	BCVA_logMAR_U0 — BCVA_logMAR_U1	Endozz_U0 — Endozz_U1
Wilcoxon test (<i>p</i> -Wert)	0.33	< 0.001	< 0.001	0.004	< 0.001	0.325	0.670

The mean value calculated for the number of data (*N*), the median, and the standard deviation (SD); the minimum (Min.) and the maximum (Max.) are shown

The absolute value of central corneal astigmatism changed by a median of 0.2 D after 3 years and by 0.05 D after 5 years (Table 3).

DISCUSSION

Keratoconus is a not-so-rare disease that restricts the vision of even young adults. Current findings from the Gutenberg Health Study indicate that the prevalence of keratoconus in

predominantly white populations is 1:200; this is around ten times higher than previously assumed [20].

Although the Krumeich classification, which, along with Amsler, has long been considered the established standard method for keratoconus classification, explicitly lists astigmatism as a criterion [21], astigmatism is investigated in detail in surprisingly few cases in current studies on CXL in keratoconus. Although many studies mention an increase in astigmatism of ≥ 1 D as an inclusion criterion [3, 22, 23], none of these

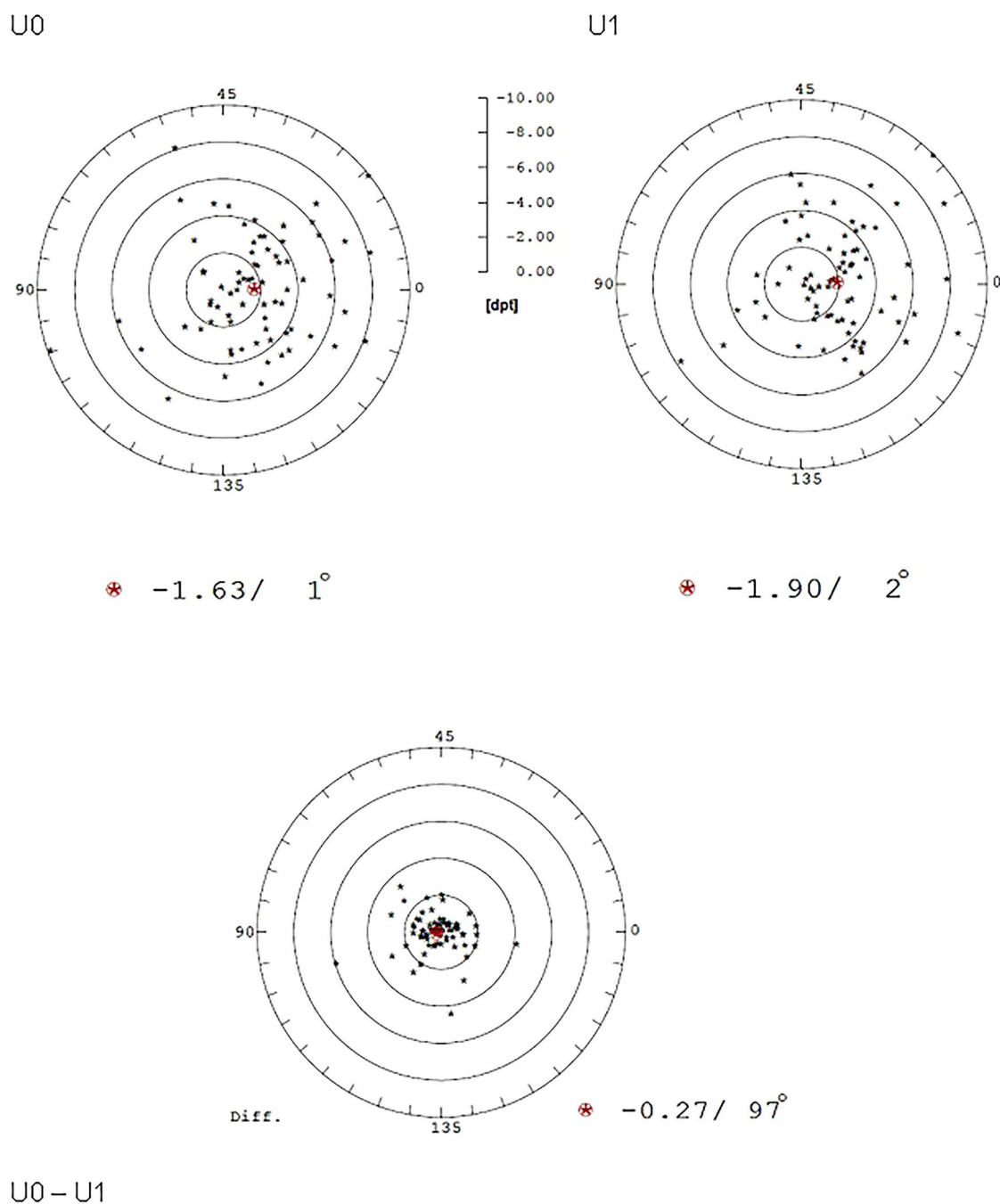


Fig. 4 Graphical vector analysis of the astigmatic data of the anterior surface at time points U0 and U1 and vectorial difference for the group with central abrasion with the val-

ues: power in diopters and the corresponding steep axis in degrees. The vector mean (centroid) is marked in red

studies considered astigmatism as a vector. Meta-analyses and systematic reviews on CXL in keratoconus, such as those by Greenstein et al. and

Sarma et al., also primarily examine keratometry values, such as Kmax [24, 25].

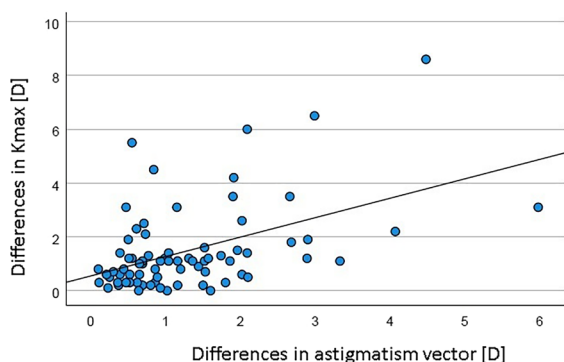


Fig. 5 Scatter plot showing the difference in Kmax and astigmatism vector between U1 and U0

Astigmatism in particular, as a refractive aberration of the cornea, leads to distorted vision and is associated with a high level of suffering for many patients with keratoconus owing to frequent changes in spectacle prescription combined with unsatisfactory correction results [16].

Since astigmatism is therefore of great relevance to the patient, this leads us back to the aims of the present study, in which we consider that astigmatism is often described mathematically incorrectly. Only a description of a two-dimensional vector is adequate, and it allows for investigation of how it develops before and after CXL. As described in more detail in the methods section, we started from the hypothesis that the vector of astigmatism, as well as the Kmax, would not increase after CXL.

It is certainly useful to calculate the total astigmatism in view of the patient's visual acuity. This would also include back surface data. In this study, however, we focused on the parameters of the front surface, since anterior surface data are more frequently used in the postoperative follow-up. The front surface parameter Kmax is used most frequently to assess both progression and stability [26, 27].

In the postoperative course of CXL, it is important to measure not only the visual acuity but also the possible flattening of the corneal curvature, as well as the possible reduction or stability of Kmax and astigmatism on the front surface. This would enable better long-term care

of patients with contact lenses and thus a better visual outcome.

Studies investigating the variability of astigmatism in normal and keratoconus eyes have shown that measurement errors increase with higher astigmatism and irregularity [28, 29]. In addition, a study from the Wagner et al. working group showed that the measurement variability of the absolute value of the vector difference was in the range of 0.3 D in a group of all different eyes after cataract surgery, including keratoconic eyes [30].

We are aware that measuring astigmatism and other corneal parameters is difficult and that measurement fluctuations increase with the irregularity of the cornea. To reduce possible incorrect measurements, the measurements were repeated until the quality of the measurement was classified as “OK.”

How can Our Results be Classified?

Considering now the much more precise vector analysis, we detect a clear difference between the preoperative and the postoperative follow-up data. Preoperatively, the median of the vector increased by +0.7 D, with a range of up to +5.9 D. Postoperatively, the astigmatism stabilized, and even a decrease in the absolute value of astigmatism to −0.4 D was observed after 1 year. This value remained stable over the follow-up periods of 3 and 5 years (Table 2).

Compared with the Alpins method used in some studies [13], we used a mathematically equivalent approach with a different layout to calculate the absolute value of the astigmatism vector. The measurement results and errors are comparable. As we assume that the effects of CXL are not yet complete even after 12 months, the results after 3 and 5 years were also analyzed in this study and showed a stability of astigmatism vector (Table 2).

If only the absolute value of astigmatism in diopters is considered, pre- and post-operative differences could hardly be detected (Table 3). If the astigmatism is analyzed in more detail using a vector analysis, clearer differences can

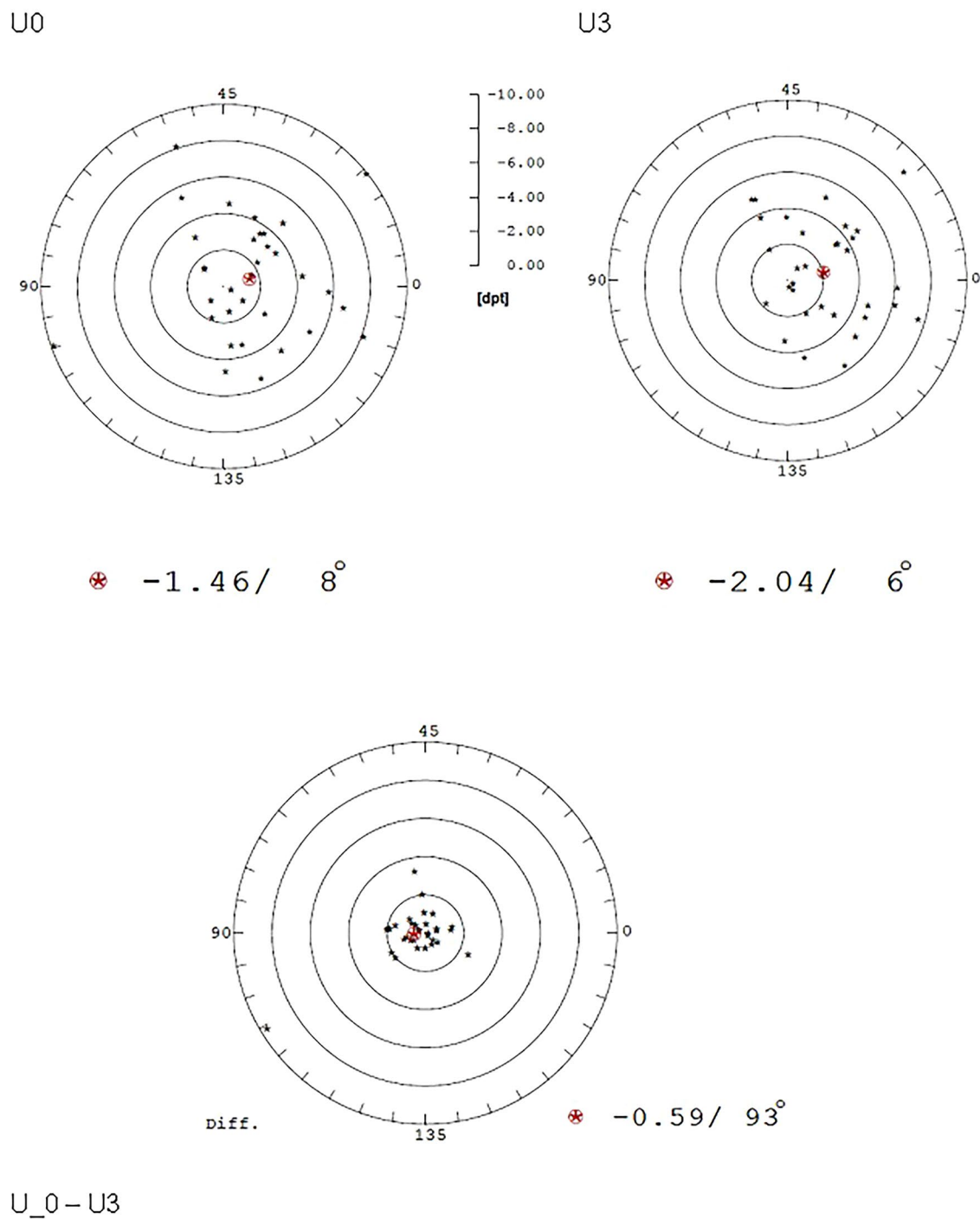


Fig. 6 Graphical vector analysis of the astigmatic data of the anterior surface at time points U0 and U3 and vectorial difference for the group with the values; power in diop-

ters and the corresponding steep axis in degrees. The vector mean (centroid) is marked in red

be worked out and thus enable a more precise analysis of the astigmatism.

We were able to show that, in the preoperative course, the astigmatism increased clearly less than the Kmax and the central radii of the anterior surface, but both increased significantly and had a positive correlation. After 1 year postoperatively, the Kmax stabilized to an median decrease of -0.4 D, as well as the astigmatism vector.

The question remains whether astigmatism is suitable as a progression predictor. The variability of the measurements in the Pentacam® for astigmatism analysis increases with the height of astigmatism as well as with the irregularity; therefore, the change in the vector certainly serves as an additional parameter for assessing progression and stability, but cannot be detected with sufficient accuracy as the standalone parameter.

The changes in KMax, particularly in the preoperative course, are higher and can therefore be better used as a stability criteria. Nevertheless, astigmatism as a progression parameter is a decisive value, as the quality of vision is associated with changes or stability of the astigmatism vector.

If astigmatism is slightly altered or relatively stable, it is assumed that the quality of vision also remains more stable than with higher variations. However, this should be investigated again in a follow-up study.

The following limitations should be considered.

Measurement fluctuations increase with the irregularity of the cornea. This should be kept to a minimum by repeating the measurements.

It certainly is useful to include the back surface parameters. A ray-tracing analysis would be even more accurate in the next study to determine the total astigmatism. However, this study focused on the anterior surface of the cornea, which is especially relevant for the postoperative contact lens fit and therefore for the visual outcome.

In our opinion, the change in subjective refraction, which is considered a progression criterion in some studies, is not a sufficiently reliable criterion, as spectacle refraction becomes more difficult or even impossible with advanced

disease. Therefore, this parameter was not prioritized.

A control group of untreated patients with keratoconus progression was not added for ethical reasons, as treatment should never be avoided in advanced disease.

CONCLUSIONS

CXL leads to postoperative stabilization of the cornea. This applies to both Kmax and astigmatism vector. Compared with an analysis of an absolute value only, the vector analysis of astigmatism allows a much more precise description of astigmatism, both pre- and post-operatively, to verify the effectiveness of CXL treatment. The differences in the astigmatism vector are smaller than the differences in KMax, which is currently used as a parameter for follow-up. Therefore, the astigmatism vector represents an additional important parameter for assessing the course of the cornea, but should not be used as a standalone parameter.

Astigmatism presumably has a significant effect on the quality of vision and should therefore also be used as a stability factor, particularly postoperatively. Smaller changes in astigmatism probably also indicate a more stable vision quality. This should be investigated in further studies, for example by correlating the astigmatism vector to the other progression criteria.

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Declarations

Conflicts of Interest. Anne J Winter, Daniel Wollschlaeger, and Paul-Rolf Preussner declare that they have no competing interests regarding this work. Susanne Marx-Gross declares that she has no competing interests regarding this work; outside the submitted work, she reports grants from Bayer AG.

Ethical Approval. It was not necessary to obtain an ethics vote as this was a retrospective data analysis of patients' reports between 2013 and 2019. The data collection began in 2019. All the data were analyzed pseudonymously, and the principles of the Declaration of Helsinki were respected. If only health data are evaluated retrospectively that are routinely collected at the clinic/department (neither additional study-related surveys nor study-related examinations are carried out), so-called "third parties" are not given access to the data, and the data are passed on and published exclusively in anonymous form; neither consultation with the ethics committee nor informed consent from the patients is necessary. This procedure is

regulated in Rhineland-Palatinate by the State Hospital Act (§ 36 and § 37). Landesärztekammer Rheinland-Pfalz.

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