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# Longitudinal corneal tomographical changes in eyes of patients with unilateral and bilateral non-progressive keratoconus

Pinar Kosekahya[a,*], Mustafa Koc[a], Mehtap Caglayan[b], Hasan Kiziltoprak[a], Kemal Tekin[c], Cemile Ucgul Atilgan[a]

[a] Ulucanlar Eye Training and Research Hospital, Department of Ophthalmology, Ankara, Turkey
[b] Gazi Yasargil Training and Research Hospital, Department of Ophthalmology, Diyarbakir, Turkey
[c] Ercis State Hospital, Department of Ophthalmology, Van, Turkey

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ABSTRACT

*Aim:* To evaluate the tomographic indices changes in keratoconic eyes which were classified as unilateral and bilateral non-progressive keratoconus according to the definition of Global Consensus on keratoconus and ectatic disease.

*Methods:* Fifty non-progressive fellow eyes of 50 keratoconus patients who underwent corneal cross-linking treatment for the other progressive eyes (group 1), 50 eyes of 50 keratoconus patients who were followed up as bilateral non-progressive keratoconus (group 2), and 50 eyes of 50 control subjects (group 3) were included in this retrospective study. Topographic, topometric, and Belin–Ambrósio Enhanced Ectasia Display-III indices were recorded at baseline and after six months.

*Results:* Groups were similar in terms of age and gender. The changes in topographic parameters and topometric indices were similar among the three groups ($p > 0.05$ for all values). The maximum pachymetric progression index ($PPI_{max}$), maximum Ambrósio relational thickness ($ART_{max}$), and final D significantly increased at sixth-months in group 1 ($p < 0.001$, $p = 0.004$, and $p = 0.02$ respectively) but did not change in groups 2 and 3 ($p > 0.05$ for all values). $ART_{max}$, $PPI_{max}$, and final D value changes indicated a statistically significant difference among the groups using the one-way ANOVA test ($p = 0.03$, $p = 0.007$, and $p = 0.03$ respectively). The Bonferroni posttest revealed that these values increased at a higher rate in group 1 than in group 2 ($p = 0.03$, $p = 0.01$, and $p = 0.04$ respectively) and group 3 ($p = 0.04$, $p = 0.03$, and $p = 0.04$, respectively).

*Conclusions:* Fellow eyes of keratoconus patients who have underwent CXL for their progressive eyes may be more prone to progress than the patients who have no progression in both eyes. Screening unilateral non-progressive patients more closely than those with bilateral non-progressive patients and evaluating the changes in final D, $ART_{max}$, and $PPI_{max}$ values may be helpful in the follow up of non-progressive keratoconus.

## 1. Introduction

Keratoconus is the most common ectatic corneal disease which is characterized by stromal collagen matrix alterations that lead to stromal thinning and irregular protrusion of the cornea [1]. Although it is almost always bilateral, its presentation is asymmetric between two eyes [2]. Disease manifestation can vary from slightly irregular astigmatism to severe visual deterioration [3]. The non-surgical methods for visual recovery are spectacles and contact lenses, and the surgical methods consist of intracorneal ring segment implantation and lamellar and penetrating keratoplasty [4,5]. The only treatment modality halting the progression of keratoconus is corneal cross-linking (CXL).

A study analyzing the 10-year results of CXL for keratoconus defined CXL as an effective and safe method for treating progressive keratoconus [6]. Several short-term and long-term complications of CXL have been reported so far, including infection, haze, endothelial damage, and peripheral sterile infiltrates, among others [7]. CXL is not required for every keratoconic cornea. The common indication in the literature is the progression of keratoconus at a particular time. However, the progression parameters, cut-off values, and follow-up frequency are variable. If keratoconus patients can be classified into high risk or low risk for progression, the follow-up periods can be arranged closely or intermittently. In this way, progressive keratoconus may be diagnosed at early preclinical stages, and the loss of vision can be prevented through

* Corresponding author at: Ulucanlar Eye Training and Research Hospital, Ulucanlar Street, Number: 59, Ankara, 06240, Turkey.
*E-mail address:* drkosekahya2@gmail.com (P. Kosekahya).

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CXL [6].

The most common progression criterion in keratoconus is the maximum keratometry ($K_{max}$) value, but the reliability of $K_{max}$ is relatively low [7,8]. Therefore, more sensitive progression criteria are needed in keratoconus management. The hypothesis of the study was that enhanced ectasia display indices, which are highly sensitive in keratoconus diagnosis, could also be reliable parameters in the early diagnosis of progression before any topographic change [9]. To test this hypothesis, the changes in tomographic indices were evaluated in unilateral and bilateral non-progressive keratoconus according to the definition of Global Consensus on keratoconus and ectatic disease.

## 2. Materials and methods

This retrospective observational study was conducted in compliance with the institutional and government review board regulations. The study protocol was approved by the Local Ethics Committee, and the study was carried out in accordance with the Declaration of Helsinki. The medical records of patients who were followed-up for keratoconus at a tertiary care hospital were investigated. The diagnosis of clinical keratoconus was defined as the characteristic keratoconus signs in the anterior sagittal curvature maps, such as an asymmetric bowtie pattern with or without skewed axes, inferior or central steepening, and at least one biomicroscopic sign, such as a conical protrusion, Vogt's striae, Fleischer ring, or anterior stromal scar. Participants with a history of anterior segment surgery including CXL, ocular surface problems, topical eye drop usage, and corneal scarring were excluded.

The best spectacle corrected visual acuity (BSCVA) which was measured with a Snellen chart by a cornea specialist was noted and converted to Logarithm of the Minimum Angle of Resolution (logMAR) for statistical analysis. Tomographic measurements were performed after removing the rigid gas permeable contact lenses for at least three weeks and soft contact lenses for at least one week. A single expert examiner acquired the rotating Scheimpflug corneal tomography (Pentacam HR, Oculus Optikgeräte GmbH) measurements. Image acquisition involved a 1 s scan of 25 rotational Scheimpflug images. Acceptable maps had at least 10 mm of corneal coverage without any extrapolated data in the central 8 mm zone. When an artifact was observed, the Pentacam flagged the scan as unacceptable. Scans not meeting the acceptable criteria were repeated.

Two consecutive measurements of each participant with six months interval were evaluated retrospectively. Progression was defined as a consistent change in at least 2 of the following 3 parameters where the magnitude of the change is above the normal noise of the testing system: Progressive steepening of the anterior corneal surface, progressive steepening of the posterior corneal surface and progressive thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point [10]. If it is necessary to describe the parameters in detail, an increase of 1 D/year in $K_{max}$ and/or an increase of 0.04 mm/year in anterior best-fit-sphere elevation, pachymetric changes over the entire corneal thickness comparing the percentage thickness increase maps and/or a decrease of 10 μm/year in thinnest pachymetry, and an increase of approximately 15 μm/year in posterior elevation maps by keeping the best-fit-sphere reference constant [11,12]. First, the fellow eyes of keratoconus patients who underwent CXL treatment for their progressive eyes were evaluated for progression. Group 1 comprised 50 non-progressive fellow eyes of 50 keratoconus patients who underwent CXL treatment for their progressive eyes. Group 2 comprised 50 random eyes of 50 keratoconus patients who were followed up as bilateral non-progressive keratoconus. Group 3 served as the control group; 50 eyes of 50 control subjects were randomly selected from a database of age-matched candidates who were followed-up with myopia ($\leq$5.0 D), myopic astigmatism ($\leq$3.0 D), and normal enhanced ectasia display analysis in both eyes.

The topographic keratoconus classification (TKC) was evaluated for all keratoconic eyes and only moderate keratoconus patients were included to this study. TKC is adopted by the device software and labels the keratoconus as pre-stage, level 1, level 2, level 3, and level 4 by using only corneal front shape parameters. TKC scores of 0, 0–1, and 1 are considered as early keratoconus; TKC scores of 1–2, 2, and 2–3 are considered as moderate keratoconus; TKC scores of 3, 3–4, and 4 are considered as severe keratoconus.

The analyzed topographical parameters were flat keratometry ($K_1$) and steep keratometry ($K_2$) for the central 3.0 mm of the cornea, maximum keratometry ($K_{max}$), corneal astigmatism, and thinnest corneal thickness (thinnest CT) in the sagittal curvature map. The analyzed topometric indices in the topometric map were the index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), center keratoconus index (CKI), index of height asymmetry (IHA), and index of height decentration (IHD).

The Belin–Ambrósio Enhanced Ectasia Display (BAD)-III software evaluates the pachymetric progression and the anterior and posterior elevation values of the cornea. The anterior and posterior elevation values of the cornea were examined according to the best fit sphere (BFS) reference surface and to the enhanced BFS reference surface; the difference between these two was presented. Pachymetric progression refers to the percentage in corneal thickness along each meridian starting from the thinnest corneal point. The deviation of normality of the front elevation (Df), deviation of normality of the back elevation (Db), deviation of normality of pachymetric progression (Dp), deviation of normality of corneal thinnest point (Dt), deviation of normality of relational thickness (Da), and overall deviation of normality (final D) values; the maximum pachymetric progression index (PPI) values; and the Ambrósio relational thickness (ART) indices (maximum ART = thinnest corneal thickness/maximum PPI) were recorded as enhanced ectasia display indices.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Normality of data was analyzed with the Shapiro–Wilk test. Descriptive statistics were performed as mean ± standard deviation (SD). The chi-square test was used in the analysis of the categorical variables. Paired t-tests were performed to determine whether the difference between two measurements of the same eye was significant. Between-group comparisons of the three groups were performed using the one-way ANOVA test. When the overall ANOVA model was significant, the Bonferroni post-hoc test was conducted to determine the pairwise comparison of the means that were significantly different. A p value of less than 0.05 was considered statistically significant.

## 3. Results

Demographic characteristics of all participants were summarized in Table 1. The groups were similar in terms of age and gender ($p = 0.43$ and $p = 0.50$, respectively). According to the TKC, grade distribution was similar between group 1 and group 2 ($p = 0.76$). BSCVA did not change between the baseline and the sixth-month follow up in all groups ($p > 0.05$ for all values) and the changes in BSCVA were similar among the three groups ($p = 0.12$).

The changes in topographical and topometric indices between the baseline and the sixth-month follow-up in all groups are summarized in Table 2. $K_{max}$, astigmatism, and thinnest CT values did not show significant changes between the baseline and the sixth-month follow-up in all groups ($p > 0.05$ for all values). Anterior surface topometric indices did not change between the baseline and the sixth-month follow-up in all groups ($p > 0.05$ for all values). The changes in the topographical parameters and topometric indices were similar among the three groups ($p > 0.05$ for all values) (Table 3).

The changes in enhanced ectasia display indices in all groups are summarized in Table 4. $ART_{max}$, $PPI_{max}$, Dp, Dt, Da, and final D values significantly increased at the sixth-month follow-up compared with the

**Table 1**
Demographical characteristics of groups.

| Variable | Group 1 Mean ± SD n = 50 | Group 2 Mean ± SD n = 50 | Group 3 Mean ± SD n = 50 | p value |
|---|---|---|---|---|
| **Age (years)** | 31.44 ± 5.21 | 32.24 ± 8.59 | 29.67 ± 8.85 | 0.43* |
| **Gender (F/M)** | 35/15 | 31/19 | 36/14 | 0.50† |
| **TKC (grade 2/ grade 2-3/ grade 3)** | 32/5/13 | 27/7/16 | | 0.76† |
| **BSCVA (logMAR) Baseline/6th month follow-up/p value††** | 0.13/0.16/0.06 | 0.09/0.10/0.43 | 0.03/0.03/0.96 | 0.12* |

F: Female; M: Male; BSCVA: Best spectacle corrected distance visual acuity; logMAR: Logarithm of the Minimum Angle of Resolution; SD: Standard deviation; TKC: Topographic keratoconus classification; n: Number of eyes.
Boldface, significant values, $p < 0.05$.
* One-way anova test.
† Pearson Chi-square test.
†† Paired samples t-test.

baseline values in group 1 ($p < 0.001$, $p = 0.004$, $p = 0.001$, $p = 0.01$, $p = 0.001$, and $p = 0.02$ respectively). In group 2 and group 3, all enhanced ectasia display indices were similar between the baseline and the sixth-month follow-up ($p > 0.05$ for all values).

The changes in the $ART_{max}$, $PPI_{max}$, and final D values indicated a statistically significant difference among the groups through the one-way ANOVA test ($p = 0.03$, $p = 0.007$, and $p = 0.03$ respectively). The Bonferroni posttest revealed that $ART_{max}$, $PPI_{max}$, and final D values increased at a higher rate in group 1 than in group 2 ($p = 0.03$, $p = 0.01$, and $p = 0.04$, respectively) and group 3 ($p = 0.04$, $p = 0.03$, and $p = 0.04$ respectively) (Table 5).

## 4. Discussion

Keratoconus is a bilateral, asymmetrical corneal ectatic disease. It initially affects one eye, and the other eye becomes affected afterwards. The progression of keratoconus may vary among individuals and between the eyes of the same person [2]. Keratoconus progression screening has come into prominence after the identification of CXL as the only modality that can halt the progression of the disease [6]. Various parameters, such as corneal thickness, refraction error, and mean and maximum keratometry, were used for the detection of keratoconus progression in previous studies [9]. Despite various progression determinants in the literature, still there is no consistent or clear definition of ectasia progression [10]. $K_{max}$ is the most commonly used ectatic progression parameter and is also an indicator in the evaluation of CXL efficacy [13]. However, $K_{max}$ has many faults that deter it from being an ideal progression marker. It ignores the posterior corneal contribution, does not reflect the degree of the ectasia, and may not show correlation with ectatic progression [7,8]. Posterior corneal changes can occur without simultaneous anterior corneal changes. Changes in posterior corneal surface and enhanced ectasia display indices may be more precise progression indicators than anterior corneal parameters such as $K_{max}$. Recently, Ambrósio et al. have described the use of new ectasia display indices in the differential diagnosis of keratoconic and healthy corneas [14]. However, whether these parameters can be used in the determination of the progression remains unknown.

Asymmetry in keratoconus was examined in many studies with variable methods. Wittig-Silva published the sixth-month results of CXL and found an increase of 0.6 D in untreated eyes [13]. The reported progression rates in untreated eyes were 14% in O'Brart et al.'s [15], and 22% in Wollensak et al.'s study [16]. In the study of Coskunseven et al., the non-treated group exhibited progression of all corneal

**Table 2**
Topographic parameters and topometric indices at baseline and 6th months follow-up in all groups.

| Variable | Group 1 Baseline | 6th months follow-up | p value* | Group 2 Baseline | 6th months follow-up | p value* | Group 3 Baseline | 6th months follow-up | p value* |
|---|---|---|---|---|---|---|---|---|---|
| **$K_{max}$ (D)** Mean ± SD | 50.39 ± 5.74 | 50.22 ± 5.64 | 0.14 | 52.80 ± 5.24 | 52.72 ± 5.08 | 0.40 | 44.64 ± 1.76 | 44.70 ± 1.68 | 0.29 |
| **Astigmatism (D)** Mean ± SD | 2.70 ± 1.39 | 2.65 ± 1.38 | 0.52 | 3.24 ± 1.69 | 3.10 ± 1.58 | 0.27 | 1.83 ± 1.62 | 1.85 ± 1.63 | 0.53 |
| **Thinnest CT (μm)** Mean ± SD | 479.72 ± 43.93 | 475.74 ± 45.34 | 0.12 | 449.55 ± 50.58 | 450.68 ± 50.30 | 0.37 | 547.32 ± 30.53 | 544.60 ± 31.36 | 0.10 |
| **ISV** Mean ± SD | 52.42 ± 29.64 | 51.42 ± 26.99 | 0.36 | 63.22 ± 29.43 | 63.73 ± 29.35 | 0.36 | 22.32 ± 10.66 | 22.86 ± 10.60 | 0.80 |
| **IVA** Mean ± SD | 0.49 ± 0.31 | 0.49 ± 0.31 | 0.90 | 0.59 ± 0.35 | 0.63 ± 0.34 | 0.15 | 0.12 ± 0.06 | 0.13 ± 0.06 | 0.40 |
| **KI** Mean ± SD | 1.12 ± 0.09 | 1.12 ± 0.08 | 0.51 | 1.15 ± 0.10 | 1.16 ± 0.10 | 0.30 | 0.99 ± 0.14 | 1.02 ± 0.02 | 0.32 |
| **CKI** Mean ± SD | 1.03 ± 0.03 | 1.03 ± 0.03 | 0.90 | 1.04 ± 0.03 | 1.04 ± 0.03 | 1.00 | 1.00 ± 0.00 | 1.00 ± 0.00 | 0.29 |
| **IHA** Mean ± SD | 24.47 ± 19.89 | 25.98 ± 24.54 | 0.50 | 31.35 ± 26.35 | 32.86 ± 25.70 | 0.17 | 5.36 ± 5.55 | 6.65 ± 5.68 | 0.11 |
| **IHD** Mean ± SD | 0.06 ± 0.04 | 0.06 ± 0.05 | 0.39 | 0.07 ± 0.05 | 0.08 ± 0.05 | 0.60 | 0.01 ± 0.00 | 0.01 ± 0.00 | 0.98 |

$K_{max}$: Maximum keratometry, D: Diopters, SD: Standard deviation, CT: Corneal thickness, μm: micrometer, ISV:Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Center keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, Boldface, significant values, $p < 0.05$.
* Paired samples t-test.

**Table 3**
Enhanced ectasia display indices at baseline and 6th months follow-up in all groups.

| | Group 1 | | | Group 2 | | | Group 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Baseline | 6th months follow-up | p value* | Baseline | 6th months follow-up | p value* | Baseline | 6th months follow-up | p value* |
| **$ART_{max}$ (µm)** Mean ± SD | 223.38 ± 76.04 | 207.74 ± 73.47 | **< 0.001** | 176.68 ± 60.38 | 180.28 ± 61.61 | 0.30 | 443.15 ± 74.89 | 438.10 ± 77.90 | 0.20 |
| **$PPI_{max}$ (µm)** Mean ± SD | 2.37 ± 0.75 | 2.60 ± 1.11 | **0.004** | 2.74 ± 0.69 | 2.73 ± 0.74 | 0.77 | 1.26 ± 0.19 | 1.29 ± 0.20 | 0.31 |
| **Df** Mean ± SD | 5.40 ± 5.41 | 4.97 ± 4.54 | 0.23 | 7.31 ± 5.50 | 7.28 ± 5.48 | 0.89 | 0.50 ± 1.33 | 0.38 ± 1.31 | 0.26 |
| **Db** Mean ± SD | 5.38 ± 4.53 | 5.76 ± 11.59 | 0.23 | 5.96 ± 4.06 | 6.18 ± 4.23 | 0.17 | 0.11 ± 1.05 | −0.03 ± 1.07 | 0.06 |
| **Dp** Mean ± SD | 5.32 ± 3.74 | 5.35 ± 4.29 | **0.001** | 6.71 ± 2.94 | 6.76 ± 3.09 | 0.80 | 0.63 ± 1.15 | 1,74 ± 1.05 | 0.29 |
| **Dt** Mean ± SD | 2.01 ± 1.67 | 2.18 ± 1.82 | **0.01** | 3.32 ± 2.84 | 3.28 ± 2.89 | 0.46 | −0.16 ± 0.96 | −0.14 ± 0.86 | 0.73 |
| **Da** Mean ± SD | 2.42 ± 0.69 | 2.56 ± 0.67 | **0.001** | 2.83 ± 0.54 | 2.81 ± 0.56 | 0.38 | 0.41 ± 0.68 | 0.50 ± 0.70 | 0.20 |
| **D** Mean ± SD | 5.46 ± 3.29 | 5.96 ± 3.72 | **0.02** | 6.96 ± 2.86 | 6.93 ± 2.96 | 0.74 | 1.04 ± 0.72 | 1.07 ± 0.77 | 0.46 |

$ART_{max}$: Maximum Ambrósio relational thickness indice, $PPI_{max}$: Maximum pachymetric progression index, Df: Df: Deviation of normality of the front elevation, Db: deviation of normality of the back elevation, Dp: deviation of normality of pachymetric progression, Dt: deviation of normality of corneal thinnest point, Da: deviation of normality of relational thickness, D: overall deviation of normality, µm: micrometer, SD: Standard deviation, Boldface, significant values, $p < 0.05$.
* Paired samples t-test.

parameters under study [17]. So, the untreated eye of a keratoconus patient who had undergone CXL for the progressive eye would be a good sample for researching early progressive changes. Topographic and topometric indices did not show significant changes indicating progression in all keratoconus patients as the non-progressive keratoconic eyes were chosen for the study according to the definition of Global Consensus on keratoconus and ectatic diseases. Whereas bilateral non-progressive keratoconic eyes and control eyes also did not show increases in the enhanced ectasia display indices, the fellow non-progressive keratoconic eyes of patients who underwent CXL for their progressive eyes showed increases in Dp, Dt, Da, final D, $PPI_{max}$, and $ART_{max}$ values.

Topometric indices were investigated in a study for diagnosing subclinical and definite keratoconus, and the authors concluded that the predictive power of ISV and IVA indices in subclinical keratoconus detection was higher than that of other known variables, such as $K_{max}$ and/or $K_{mean}$ [18]. In another study evaluating topometric indices to detect progression, ISV and IHD were concluded to be sensitive and specific tools for the diagnosis and detection of the possible progression of keratoconus [19]. In this study, the changes in topometric indices were evaluated within and between groups and it has been found that topometric indices did not significantly change between the baseline and sixth-month follow-up in all groups, and also the changes in the mean indices did not differ among the three groups. Topometric indices are anterior surface-derived curvature indices similar to the $K_{max}$ value. Therefore, unsurprisingly, topometric indices remain the same when topographical indices are stable.

Recently, the combination of pachymetric indices and the enhanced elevation maps provided by the BADhas increased sensitivity and specificity in the screening of patients for ectasia. In their review, Belin and Ambrósio concluded that nine parameters of enhanced ectasia display could improve the ability of the refractive surgeon to screen patients for occult ectatic disease or to identify patients potentially at high risk for post laser-assisted in situkeratomileusis (LASIK) ectasia [20]. Villavicencio et al. investigated the validation of the third software of the enhanced ectasia display parameters both for refractive surgery screening and for studies evaluating CXL results [9]. They concluded that final D was the most useful parameter for both refractive screening and treatment protocols.

As far as the authors are aware, no study has yet investigated the role of enhanced ectasia display indices in the screening of keratoconus progression. In a recent study, the repeatability and reliability of enhanced ectasia display indices were investigated [21]. The reliability of all enhanced ectasia display indices was excellent in both keratoconic and normal eyes. $K_{max}$, topometric indices except for IHA, enhanced ectasia display indices except for Df and Db were repeatable in both normal and keratoconic eyes; however the repeatability indexes of all the parameters increased as the severity of keratoconus increased. To

**Table 4**
Changes in mean ± standard deviation values of topographical parameters and topometric indices in all groups.

| Variable | Group 1 Mean ± SD | Group 2 Mean ± SD | Group 3 Mean ± SD | F* | p value* |
|---|---|---|---|---|---|
| **$K_{max}$ (D)** | 0.16 ± 0.80 | 0.08 ± 0.67 | −0.06 ± 0.41 | 1.53 | 0.21 |
| **Astigmatism (D)** | 0.05 ± 0.57 | 0.13 ± 0.39 | −0.02 ± 0.23 | 1.50 | 0.22 |
| **Thinnest CT (µm)** | 3.98 ± 10.80 | 3.13 ± 8.46 | 2.71 ± 10.97 | 3.19 | 0.40 |
| **ISV** | 1.00 ± 7.76 | −0.51 ± 3.76 | −0.54 ± 2.06 | 1.37 | 0.25 |
| **IVA** | −0.00 ± 0.09 | −0.03 ± 0.14 | −0.01 ± 0.03 | 1.05 | 0.35 |
| **KI** | 0.00 ± 0.04 | −0.01 ± 0.01 | −0.02 ± 0.14 | 1.05 | 0.35 |
| **CKI** | 0.00 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 | 3.40 | 0.46 |
| **IHA** | −1.51 ± 26.68 | −1.52 ± 17.67 | −1.39 ± 3.74 | 0.24 | 0.78 |
| **IHD** | −0.00 ± 0.02 | −0.01 ± 0.03 | 0.00 ± 0.00 | 2.02 | 0.13 |

$K_{max}$: Maximum keratometry, D: Diopters, SD: Standard deviation, CT: Corneal thickness, µm: micrometer, ISV:Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Center keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, Boldface, significant values, $p < 0.05$.
* One-way anova test.

**Table 5**
Changes in mean ± standard deviation values of Belin-Ambrósio Enhanced Ectasia Display indices in all groups.

| Variable | Group 1 Mean ± SD | Group 2 Mean ± SD | Group 3 Mean ± SD | F* | p value* | p value† (Group 1 vs Group 2) | p value† (Group 1 vs Group 3) | p value† (Group 2 vs Group 3) |
|---|---|---|---|---|---|---|---|---|
| **$ART_{max}$ (μm)** | 15.64 ± 29.08 | −3.60 ± 23.25 | 5.04 ± 22.69 | 3.32 | **0.03** | **0.03** | **0.04** | 0.24 |
| **$PPI_{max}$ (μm)** | −0.22 ± 0.52 | 0.01 ± 0.38 | −0.02 ± 0.16 | 5.16 | **0.007** | **0.01** | **0.03** | 1.00 |
| **Df** | 0.42 ± 2.48 | 0.02 ± 1.48 | 0.11 ± 0.71 | 0.68 | 0.50 | | | |
| **Db** | −1.37 ± 8.07 | −0.22 ± 1.09 | 0.15 ± 0.54 | 1.30 | 0.27 | | | |
| **Dp** | −0.52 ± 1.08 | −0.05 ± 1.39 | −1.10 ± 1.02 | 0.74 | 0.47 | | | |
| **Dt** | −0.17 ± 0.49 | 0.04 ± 0.37 | −0.02 ± 0.47 | 2.78 | 0.67 | | | |
| **Da** | −0.13 ± 0.26 | 0.02 ± 0.20 | −0.09 ± 0.48 | 2.97 | 0.65 | | | |
| **D** | −0.48 ± 0.89 | 0.02 ± 0.55 | −0.03 ± 0.30 | 3.54 | **0.03** | **0.04** | **0.04** | 1.00 |

$ART_{max}$: Maximum Ambrósio relational thickness indice, $PPI_{max}$: Maximum pachymetric progression index, Df: Deviation of normality of the front elevation, Db: deviation of normality of the back elevation, Dp: deviation of normality of pachymetric progression, Dt: deviation of normality of corneal thinnest point, Da: deviation of normality of relational thickness, D: overall deviation of normality, μm: micrometer, SD: Standard deviation, Boldface, significant values, $p < 0.05$.
* One-way anova test.
† Bonferroni post-hoc test.

overcome this variability and due to the fact that different keratoconus stages might show different progression rates [22], only moderate keratoconus patients were included to this study and the TKC distribution of two keratoconus groups were also similar between groups. $ART_{max}$, $PPI_{max}$, Dp, Dt, Da, and final D value changes were larger in untreated fellow eyes of patients who underwent CXL for the other eyes compared to TKC-matched bilateral non-progressive keratoconic eyes. When the change values were compared with the repeatability indexes of the other study, the change amounts could not exceeded the repeatability indexes. It is the strength of the study that keratoconus groups were matched for TKC, so the differences between these groups would likely to be true changes rather than the noice of the measurement system. Despite this, the changes should be evaluated in various keratoconus stages with prospective long-standing studies before defining them as earlier progression determinants.

The most important limitation of this study is its retrospective design. Therefore, all measurements were not taken at the same time of day, and this variation could have affected the data. The measurements were evaluated at baseline and six months after the baseline visit. A long-term longitudinal follow-up may make the results more reliable and accurate. Although the repeatability and reliability of enhanced ectasia display were evaluated recently, there is no study yet evaluating the reproducibility of these indices. It would be better to know the reproducibility before describing the enhanced ectasia display indices as precise progression determinants in the follow-up of keratoconus.

In conclusion, the fellow eyes of keratoconus patients who have underwent CXL for their progressive eyes may be more prone to progress than the patients who have no progression in both eyes. Final D, $ART_{max}$, and $PPI_{max}$ may be precise criteria for detecting the progression of keratoconus before significant topographic changes. So, screening unilateral non-progressive patients more closely than those with bilateral non-progressive patients and evaluating the changes in final D, $ART_{max}$, and $PPI_{max}$ values may be helpful in the follow up of these patients. The use of enhanced ectasia display indices in the detection of progression, their validation, and cut-off values should be evaluated in future prospective studies with longer follow-up periods.

## Conflicts of interest

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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