Original Article

Superiority of Baseline Biomechanical Properties over Corneal Tomography in Predicting Keratoconus Progression

⬤ Mehmet Akif Erol, ⬤ Eray Atalay, ⬤ Onur Özalp, ⬤ Abdullah Divarcı, ⬤ Nilgün Yıldırım

Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey

Abstract

Objectives: To determine corneal biomechanical and tomographic factors associated with keratoconus (KC) progression.

Materials and Methods: This study included 111 eyes of 111 KC patients who were followed-up for at least 1 year. Progression was defined as the presence of progressive change between the first two consecutive baseline visits in any single parameter (A, B, or C) ≥95% confidence interval or two parameters ≥80% confidence interval for the KC population evaluated by the Belin ABCD progression display. The eye with better initial tomographic findings was chosen as the study eye. Analyzed Pentacam parameters were maximum keratometry (Kmax), minimum pachymetry (Kmin), central corneal thickness, thinnest corneal thickness, 90° vertical anterior and posterior coma data in Zernike analysis, and Belin Ambrosio Enhanced Ectasia Display Final D value. Corneal hysteresis (CH) and corneal resistance factor (CRF) were analyzed together with the waveform parameters obtained with Ocular Response Analyzer (ORA). Factors related to KC progression were evaluated using t-tests and logistic regression tests. Statistical significance was accepted as p<0.05.

Results: There were 44 (mean age: 27.1±8.5 years, female: 25) and 67 (mean age: 31.1±9.1 years, female: 36) patients in the progressive and non-progressive groups, respectively. Although Pentacam parameters along with CH and CRF were similar between the two groups, ORA waveform parameter derived from the second applanation signal p2area was statistically significantly lower in the progressive group (p=0.02). Each 100-unit decrease in p2area increased the likelihood of keratoconus progression by approximately 30% in the logistic regression analysis (β=0.707, p=0.001, model r2=0.27).

Conclusion: Parameters derived from the second applanation signal of ORA may be superior to conventional ORA parameters and corneal tomography in predicting KC progression.

Keywords: Keratoconus, progression, ORA, biomechanics, tomography, topography

Introduction

Keratoconus (KC) is a progressive ectatic disease with unknown pathogenesis, characterized by thinning and cone-like steepening of the cornea. The general prevalence of KC is 1/2,000, but recent studies using more advanced tomographic/topographic methods have reported rates of 1.5% to 3.6%.[1,2,3] KC often begins in adolescence and usually shows asymmetric involvement.[4,5,6] Although onset seems to occur in the second decade of life, a Netherlands-based study found that patients with KC were diagnosed at a later age (mean age: 28.3 years).[7] Delayed diagnosis and difficulty in the early detection of progression affect the treatment approach algorithm in progressive KC.

Corneal cross-linking (CXL) therapy was developed to prevent progression of KC and also significantly reduces the need for keratoplasty.[8,9] The decision to perform CXL is based on monitoring of progression in KC patients over 18 years of age,

whereas for pediatric patients the general approach is to perform CXL when the initial diagnosis is made because progression occurs in up to 88% in this group.[10,11]

Although many different parameters are used to detect KC progression, there is no consensus on the definition of progression. Based on the ABCD KC staging system developed by Belin et al.[12], the Belin ABCD progression display was added to the Pentacam software in 2017, bringing a more systematic new approach to KC progression. This program presents the anterior (A) and posterior (B) radius of curvature in the 3-mm zone centered on the thinnest point of the cornea, the thinnest corneal thickness (TCT) (C), and best corrected visual acuity (D) values within the 80% and 95% confidence intervals of measurement variability in normal and KC eyes. Measurements beyond these variability confidence intervals are interpreted as indicating progression.

This study was conducted to examine the association between progression and baseline tomographic and biomechanical characteristics in KC patients with progression according to Belin ABCD analysis.

Materials and Methods

This retrospective study included 111 KC patients who were followed up in the corneal unit of the ophthalmology department of Eskişehir Osmangazi University Hospital between 2015 and 2019 and had at least 1 year of follow-up and 3 separate Scheimpflug corneal tomography (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany) measurements at intervals of at least 3 months and Ocular Response Analyzer (ORA, Reichert Inc., Depew, NY, USA) measurement at baseline. The study was conducted in accordance with the requirements of the Declaration of Helsinki after obtaining approval from the Eskişehir Osmangazi University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (12.05.2020/07).

KC was diagnosed in the presence of slit-lamp findings such as Fleischer ring, Vogt striae, and apical scar; keratometry values (K1/K2) >48 diopters (D); and corneal tomographic findings consistent with KC such as maximum keratometry (Kmax) >49 D, axial distortion, inferior steepening, irregular astigmatism, abnormal posterior elevation, and abnormal corneal thickness distribution.[1] Patients with history of ocular surgery including CXL, penetrating keratoplasty, deep anterior lamellar keratoplasty, and cataract surgery, patients with corneal scarring and ocular surface problems, patients under 18 years of age, and patients with no potential for progression due to stage 4 (end-stage) KC according to topographic KC classification (TKC) were excluded.

Pentacam measurements performed at the patient's first two consecutive visits at an interval of 3±1 months were evaluated separately on the Belin ABCD KC progression display. Progression was defined as any one of the parameters A,

B, and C on this screen exceeding the ≥95% confidence interval for the KC patient population (solid red line) or any two of the parameters exceeding the ≥80% confidence interval for the KC patient population (dotted red line). We did not evaluate criterion D, visual acuity, because studies have shown it is not a valuable finding in terms of progression.[11,13] One eye of each patient was included in the study. Patients with progression in either eye were evaluated on a case basis as progression. In patients with unilateral progression, the progressive eye was included in the analysis; for patients with bilateral progression or no progression, the eye with better baseline values was included. As is routine practice in our clinic, Pentacam and ORA readings were performed at least 1 hour after removing contact lenses.

Pentacam parameters analyzed in relation to progression were Kmax, TCT, central corneal thickness (CCT), 90° vertical anterior and posterior coma, and Belin Ambrosio Enhanced Ectasia Display Final D value (BAD D). ORA parameters analyzed were corneal hysteresis (CH), corneal resistance factor (CRF) and applanation waveform parameters (p1area, p2area, uslope1, uslope2, dslope1, dslope2, w1, w2, h1, h2) (Table 1).

Statistical Analysis

IBM SPSS version 22.0 (IBM Corp, Armonk, NY, USA) was used for statistical analyses. Independent groups t-test and univariate and multivariate logistic regression analysis were used to evaluate factors associated with KC progression. Variables that showed significance in univariate logistic regression (p<0.05) and did not show multicollinearity were included in the multivariate model. Paired samples t-test was used to compare initial and final examinations within groups. A p value <0.05 was considered statistically significant.

Results

The mean age of the 111 patients included in the study was 29.4±9.0 years, 50 (45%) were male, and the frequency of progression within the mean follow-up period of 26.4±12.0 months was 39.6% (n=44). The male to female ratio in the progression and non-progression groups was 25/19 and 36/31, respectively, and the difference was not statistically

Table 1. Ocular Response Analyzer waveform parameter descriptions	
Parameter	**Definitions**
p1area/p2area	Area of the upper 75% of the peak of applanation waves 1 and 2
uslope1/uslope2	Upward slope in the upper 75% of applanation waves 1 and 2
dslope1/dslope2	Downward slope in the upper 75% of applanation waves 1 and 2
w1/w2	Width of applanation waves 1 and 2 at 25% elevation
h1/h2	Height of applanation waves 1 and 2 from 25% elevation to peak

significant (p=0.75). The progression group was younger than the non-progression group (mean age 27.1±8.5 and 31.1±9.1, respectively, p=0.02). The mean follow-up time was longer in the progression group (29.5±10.9 and 24.4±11.7 months, respectively, p=0.03). During follow-up, there was a statistically significant increase in Kmax and mean keratometry (Kmean) values (p<0.05) and marginally significant decreases in CCT and TCT in the progression group (Figure 1). These four parameters were stable in the non-progression group during follow-up (Figure 1).

The TKC stages at initial examination of patients in the progression and non-progression groups are shown in Table 2. According to TKC staging, 63.6% (28/44) of patients with progression and 58.2% (39/67) of those without progression were stage 2 or 3. The ABC criteria indicating progression in patients in the progression group were, in order of frequency, B (84%), A (77%), and C (64%) (Figure 2).

The two groups had similar initial mean values for Kmax, Kmean, TCT, CCT, 90 vertical anterior and posterior coma, final BAD D, minimum/maximum/mean Ambrosio-related thickness (ART Min/Max/Avg, respectively) (p>0.05 for all; Table 3). Although the mean initial CRF and CH values were also similar in both groups (p>0.05), the p2area, uslope2, dslope1, h1, and h2 values obtained from the waveform were significantly lower in the progression group compared to the non-progression group (p=0.026, 0.036, 0.021, 0.034, and 0.029, respectively; Table 3).

In the univariate logistic regression analysis examining tomographic and biomechanical factors associated with KC progression with correction for age, sex, Kmax, and follow-up time, none of the initial Pentacam variables were associated with progression (Table 4). However, progression was associated with the ORA parameters h2 (for each 10-unit increase, odds ratio [OR]: 1.06, 95% CI: 1.01-1.11, p=0.03) and p2area (for each 100-unit increase, OR: 1.08, 95% CI: 1.01-1.15, p=0.02; Table 4) derived from the second applanation wave. In the same analysis, age (for each year increase, OR: 1.07, p=0.01) and follow-up period (for each year increase, OR: 1.60, p=0.03; Table 4) were also associated with progression. In the multivariate model, age, follow-up time, and p2area were found to be independent determinants of progression (Table 4). Superimposition of the ORA applanation curves of patients with and without progression showed that patients with progression had a relatively earlier applanation in the first applanation and

later recovery in the second applanation, and lower height in both the first and second applanation curves compared to patients without progression (Figure 3).

Discussion

In this study, progression defined according to parameters A, B, and C on the Belin ABCD progression display was observed in 39.6% (n=44) of the patients. In patients with progression, we observed that Kmax and Kmean increased by 1.0 D and 0.5 D, respectively, and CCT and TCT decreased by approximately 5 µm during follow-up (Figure 1). The parameter most effective in determining progression was posterior surface radius of curvature (criterion B, 84%), followed by anterior surface radius of curvature (criterion A, 77%) and thinnest pachymetry value (criterion C, 64%) (Figure 2). KC progression was associated with younger age (for each additional year, OR: 1.08, p=0.006), longer follow-up time (for each additional year, OR: 1.78, p=0.01), and lower p2area on initial ORA measurement (for each 100-unit increase, OR: 1.07, p=0.01) (Table 3).

According to the 2015 global consensus report on KC and ectatic diseases created by Delphi panel, progression was defined as meeting at least two of three criteria (steepening of the anterior corneal surface, steepening of the posterior corneal surface, and corneal thinning and/or an increase in the rate of thickness change from the peripheral cornea to the thinnest point), but it was not clearly stated what amount of change in these parameters should be considered progression.[11] Many topographic/tomographic parameters are used in routine progression monitoring. The most important of these, Kmax, represents only the anterior surface of the cornea but does not provide information about the posterior surface, may vary in patients using hard gas-permeable contact lenses, and has been reported to remain unchanged or even decrease in progression, resulting in controversy regarding its use in the follow-up of progression and CXL effectiveness.[14,15,16,17] This idea is supported by our finding that the radius of curvature of the posterior corneal surface (criterion B) was a more frequent sign of progression than the anterior surface radius of curvature radius (criterion A) (84% and 77%, respectively, Figure 2). In a meta-analysis examining changes in other parameters used in progression monitoring during the natural course of KC, it was reported that best corrected visual acuity and sphere/cylinder values did not show statistically significant changes during the follow-up period and thus its use in follow-up would not provide meaningful results.[18]

The Belin ABCD progression display offers a different perspective on progression based on changes in the ABCD staging system developed by Belin et al.[12] Unlike the Amsler-Krumeich classification, it also takes into account the posterior corneal surface, evaluates not the entire cornea but the central cone where the main changes are seen (3-mm area centered on the thinnest point of the cornea), presents separate ratings on

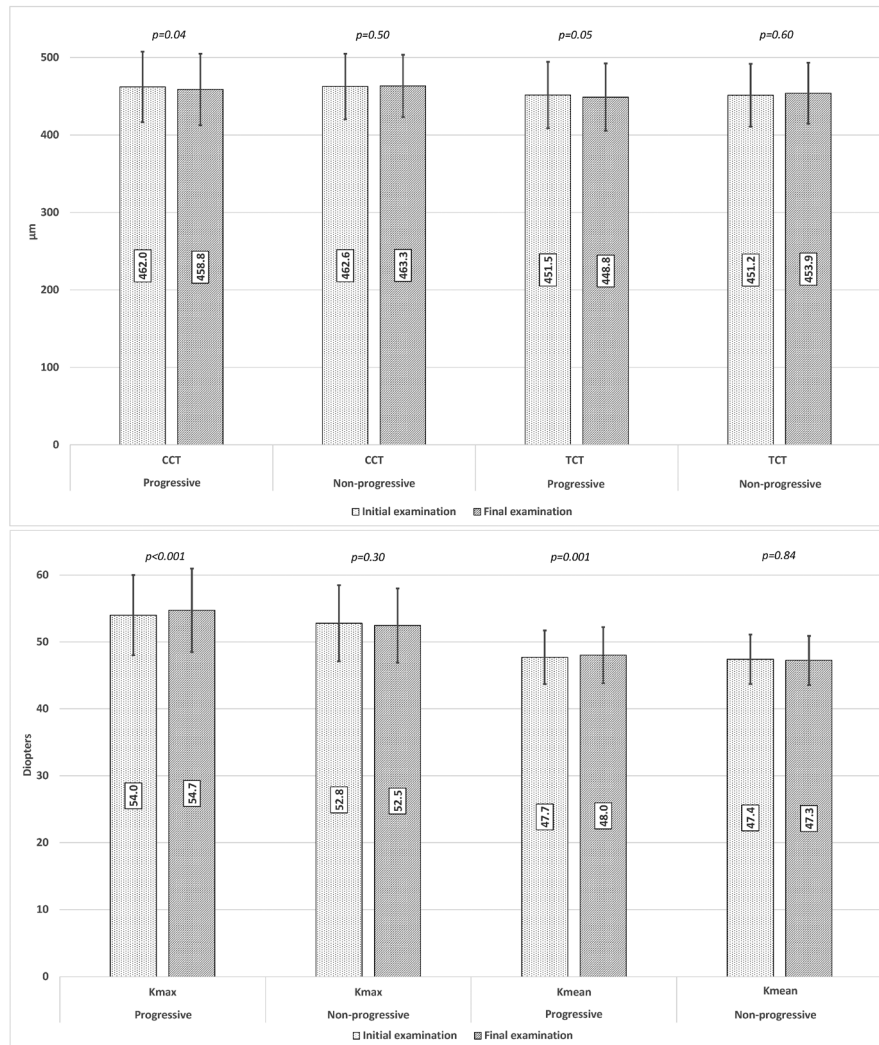| Table 2. Tomographic keratoconus stages according to progression status					
	TKC stage, n (%)				
	0	1	2	3	p value
No progression	13 (19.4%)	15 (22.4%)	28 (41.8%)	11 (16.4%)	0.10
Progression	2 (4.5%)	14 (31.8%)	17 (38.6%)	11 (25.0%)	

Figure 1. Analyses of corneal thickness and keratometry values according to progression status

CCT: Central corneal thickness, TCT: Thinnest corneal thickness, Kmax: Maximum keratometry value, Kmean: Mean keratometry value
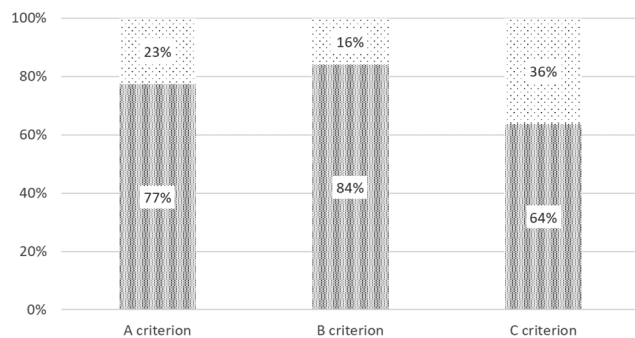

Figure 2. Frequency of A, B, and C parameters exceeding the ≥95% confidence interval for one criterion or ≥80% in any two criteria simultaneously on the Belin ABCD progression display according to the first two visits (shaded area, proportion of cases)

the basis of 4 parameters, and is consistent with the criteria proposed in the global consensus report.[15,16,17] Kösekahya et al.[19] compared the Belin ABCD progression display with traditional criteria (Kmax, CCT, and anterior/posterior elevation changes) in the detection of progression and showed that the Belin ABCD progression display could provide an acceptable level of differentiation.

In the literature, parameters reported to have predictive value in KC progression include young age,[20,21,22,23] low TCT,[24] high Kmean,[24] high anterior Kmax[18,23] and posterior Kmax,[25] high central posterior[24] or anterior[20] elevation, index of surface variance (ISV),[26] high index of height decentration (IHD),[26] and vertical coma.[25] The fact that none of the initial corneal tomography parameters had predictive value for progression in this study whereas some initial biomechanical parameters showed
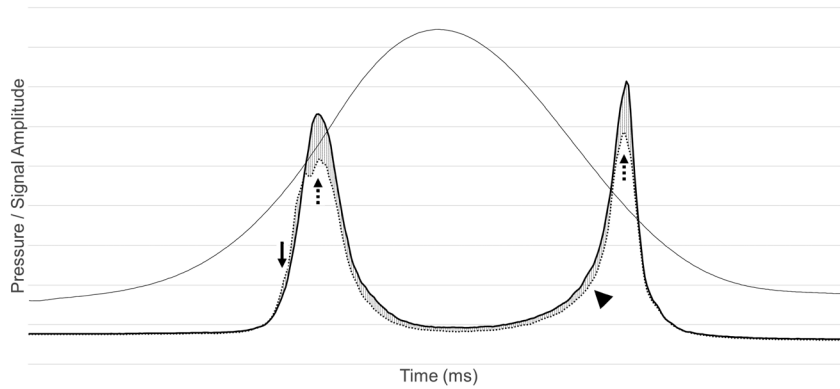
Figure 3. Superimposition of the ORA applanation curves of patients with and without progression shows that patients with progression (dotted line) had a relatively earlier applanation (solid arrow) in the first applanation and later recovery (arrowhead) in the second applanation. In addition, the height of the first and second applanation curves were lower in patients with progression (dotted arrows) than those without progression

Table 3. Tomographic and biomechanical parameter values and significance levels according to progression status

Parameter	No progression Mean ± SD	Progression Mean ± SD	p value
Kmax	52.8±5.7	54.0±6.0	0.29
Kmean	47.4±3.7	47.7±4.0	0.70
CCT	462.6±42.4	462.0±45.4	0.94
TCT	451.3±40.5	451.5±42.8	0.97
Anterior vertical 90° coma	-1.38±1.04	-1.67±0.90	0.14
Posterior vertical 90° coma	0.36±0.28	0.44±0.22	0.12
Final BAD D	7.1±3.7	7.5±3.6	0.51
ART Min	388±189	402±236	0.74
ART Max	194±81	179±61	0.30
ART Avg	276±109	263±94	0.53
IOPg	10.5±3.5	9.7±3.2	0.28
IOPcc	14.7±3.1	14.3±2.4	0.51
CRF	6.5±1.6	6.1±1.8	0.22
CH	7.6±1.2	7.4±1.3	0.34
p1area	3166±1198	2753±1047	0.07
p2area	2424±984	2026±762	0.02
uslope1	46.8±18.7	40.4±16.2	0.07
uslope2	57.2±31.6	44.8±26.1	**0.04**
dslope1	28.5±9.9	24.1±9.1	**0.02**
dslope2	29.0±13.1	24.7±13.8	0.10
w1	20.4±3.7	21.1±4.3	0.38
w2	18.6±5.3	19.9±5.7	0.24
h1	337±103	294±100	**0.03**
h2	306±108	261±95	**0.03**

Kmax: Maximum keratometry value, Kmean: Mean keratometry value, CCT: Central corneal thickness, TCT: Thinnest corneal thickness, Final BAD D: Belin Ambrosio Enhanced Ectasia Display Final D, ART Min/Max/Avg: Minimum/maximum/average Ambrosio relational thickness, CRF: Corneal resistance factor, CH: Corneal hysteresis

Table 4. Univariate and multivariate model analysis and significance levels of parameters in the study

Variable	Univariate model[‡] OR (95% CI)	p value	Multivariate model OR (95% CI)	p value
Age (1 year)*	1.07 (1.02-1.13)	**0.01**	1.08 (1.02-1.14)	**0.006**
Sex (male)	0.79 (0.34-1.82)	0.58		
Follow-up period (1 year)[†]	1.60 (1.04-2.47)	**0.03**	1.78 (1.14-2.75)	**0.01**
Kmax (1 D)[†]	1.03 (0.96-1.10)	0.46		
TCT (10 μm)[†]	1.007 (0.99-1.02)	0.30		
BAD D (1 unit)[†]	0.90 (0.69-1.17)	0.41		
ART Max (10 units)[†]	1.00 (0.99-1.01)	0.85		
CRF (1 unit)*	1.15 (0.85-1.54)	0.36		
CH (1 unit)*	1.17 (0.80-1.69)	0.42		
p1area (100 units)*	1.05 (0.99-1.10)	0.08		
p2area (100 units)*	1.08 (1.01-1.15)	**0.02**	1.07 (1.01-1.13)	**0.01**
uslope1 (10 units)*	1.14 (0.88-1.46)	0.32		
uslope2 (10 units)*	1.15 (0.98-1.35)	0.08		
dslope1 (10 units)*	1.52 (0.95-2.46)	0.08		
dslope2 (10 units)*	1.30 (0.92-1.84)	0.14		
w1 (10 units)[†]	1.06 (0.35-3.17)	0.92		
w2 (10 units)[†]	1.44 (0.65-3.18)	0.37		
h1 (10 units)*	1.05 (1.00-1.10)	0.08		
h2 (10 units)*	1.06 (1.01-1.11)	**0.03**		

*Decrease, [†]Increase, [‡]Univariate models were corrected for age, sex, Kmax, and follow-up time. OR: Odds ratio, CI: Confidence interval, Kmax: Maximum keratometry value, TCT: Thinnest corneal thickness, BAD D: Belin Ambrosio Enhanced Ectasia Display Final D, ART Max: Maximum Ambrosio relational thickness, CRF: Corneal resistance factor, CH: Corneal hysteresis

significant differences between the groups supports the argument that the primary derangement in KC is biomechanical and that tomographic changes follow biomechanical disruption.[27,28,29] Age is a confirmed surrogate for corneal biomechanics[30] and was a significant predictive of progression in previous studies as well as our own, which strengthens the likelihood that biomechanical changes in KC are more important in the early stage.

The non-significance of CRF and CH, the basic ORA parameters, in our study while some waveform parameters showed significance requires explanation. CRF and CH are calculated based on the pressure difference between the first and second applanations, and CRF is calculated using a coefficient that emphasizes the first applanation. Although these two parameters are lower in eyes with KC, it has been reported that they have low diagnostic sensitivity and specificity and their ranges may overlap in normal and KC eyes.[31] Although the importance of the ORA waveform parameters is still not clearly understood, various assumptions have been put forward.[32] p1area and p2area are proportional to the time required for the cornea to transition from its natural convex shape to concave and back again; w1 and w2 (applanation width) are proportional to the transition speed of the cornea between convex and concave forms, h1 and h2 (applanation height) are proportional to the amount of light reflected from the corneal surface to the detector during applanation, and lower values for these parameters are suggested to be associated with a weaker corneal structure.[33,34,35] In parallel with the findings of our study, the presence of other studies demonstrating that waveform parameters have greater diagnostic value than pressure-based parameters (CRF and CH) in eyes with early-stage KC suggests that these parameters may be better biomechanical indicators.[36,37] In another study evaluating biomechanical changes with ORA before and after CXL, p2area, which is the most valuable predictive parameter in progression, was reported to be the parameter that best demonstrates biomechanical changes after CXL, but there was no significant change in CRF and CH values.[38] In a study by Küçümen et al.[39] examining changes in CRF and CH after CXL, no statistically significant change was observed in CH in the early or late postoperative period, while the change in CRF showed early significance that disappeared in the late postoperative period.

In our study, when ORA curves were averaged for all eyes with and without progression, we observed that corneas showing progression flattened earlier, started to recover later, and had significantly lower wave height for both applanations. Earlier applanation of a biomechanically weaker cornea is a finding that can be explained biologically. On the other hand, the air puff continues for a short while after the first applanation and the cornea becomes concave, and the transition back to the cornea's normal state seems to be prolonged in progressive eyes. This may also be due to the relationship between the maximum concave radius of curvature, which is also a parameter of Corvis ST, and biomechanical strength. This radius is more resistant to deformation and has higher values in biomechanically stiff eyes.[31] In other words, a weak cornea forms a deeper concavity when subjected to the air puff and thus takes longer to normalize, while a stronger cornea forms a shallower concavity and has a shorter normalization.

Study Limitations

One of the limitations of this study may be the exclusion of Belin ABCD progression criterion D (visual acuity) from our evaluation. However, although progression has been associated with a decrease in visual acuity in many articles in the literature, the widespread view in recent years is that uncorrected and best corrected visual acuity are not significant criteria for demonstrating progression.[11,18] Evaluating progression according to a change based on a single initial visit would increase variability and thus the false positivity rate; therefore, it has been stipulated that change based on two consecutive initial visits must be seen to be called progression. Since patients under the age of 18 were excluded from this study, our findings may not be valid for pediatric cases. Although the progression group had longer follow-up, statistical correction was made for the follow-up period in our analysis of predictive factors. Some patients included in the study used hard gas permeable or soft contact lenses. Although corneal contact lenses vary according to fitting choice, they may cause changes in the curvature of the anterior and posterior surfaces due to the mechanical effect and the hypoxia they cause, and even if the contact lenses are removed, the stabilization process may take several weeks.[40,41] Because it is not possible to wait this long in practice, measurements were obtained from our patients at least 1 hour after lens removal, as per routine practice in our clinic. The extent to which the ORA device performs a true biomechanical assessment is controversial, as the pressure and waveform-based parameters obtained with the ORA are seriously affected by the geometric properties of the cornea (e.g., thickness) and by intraocular pressure. In addition, the ORA has variable air puff pressure and utilizes an infrared camera that can provide low-resolution data, which are shortcomings compared to the Corvis ST.[31] For this reason, conducting similar studies with new generation devices such as Corvis ST and Brillouin spectroscopy, which provide advanced biomechanical evaluation, will better elucidate the extent to which biomechanical properties are associated with progression.

Conclusion

In conclusion, this study demonstrates that younger age and biomechanical properties may be indicators of future progression and that tomographic parameters follow biomechanical changes. This study is the first report showing that the biomechanical parameters obtained with the ORA device may be important in predicting the progression of KC.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee with the decision no. 07 dated 12.05.2020.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.A., M.A.E., Design: E.A., M.A.E., N.Y., Data Collection or Processing: M.A.E., O.Ö., A.D., Analysis or Interpretation: E.A., M.A.E., N.Y., Literature Search: E.A., M.A.E., N.Y., A.D., Writing: E.A., M.A.E., O.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42:297-319.
2. Shehadeh MM, Diakonis VF, Jalil SA, Younis R, Qadoumi J, Al-Labadi L. Prevalence of Keratoconus Among a Palestinian Tertiary Student Population. Open Ophthalmol J. 2015;9:172-176.
3. Hashemi H, Heydarian S, Yekta A, Ostadimoghaddam H, Aghamirsalim M, Derakhshan A, Khabazkhoob M. High prevalence and familial aggregation of keratoconus in an Iranian rural population: a population-based study. Ophthalmic Physiol Opt. 2018;38:447-455.
4. Jonas JB, Nangia V, Matin A, Kulkarni M, Bhojwani K. Prevalence and associations of keratoconus in rural maharashtra in central India: the central India eye and medical study. Am J Ophthalmol. 2009;148:760-765.
5. McGhee CN, Kim BZ, Wilson PJ. Contemporary Treatment Paradigms in Keratoconus. Cornea. 2015;34(Suppl 10):S16-23.
6. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol. 1986;101:267-273.
7. Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM, Wisse RP. Age-specific Incidence and Prevalence of Keratoconus: A Nationwide Registration Study. Am J Ophthalmol. 2017;175:169-172.
8. Sandvik GF, Thorsrud A, Raen M, Ostern AE, Saethre M, Drolsum L. Does Corneal Collagen Cross-linking Reduce the Need for Keratoplasties in Patients With Keratoconus? Cornea. 2015;34:991-995.
9. Godefrooij DA, Gans R, Imhof SM, Wisse RP. Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of cross-linking. Acta Ophthalmol. 2016;94:675-678.
10. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric [corrected] corneal collagen cross-linking in children and adolescents. J Refract Surg. 2012;28:753-758.
11. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrosio R, Jr., Guell JL, Malecaze F, Nishida K, Sangwan VS, Group of Panelists for the Global Delphi Panel of K, Ectatic D. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34:359-369.
12. Belin MW, Meyer JJ, Duncan JK, Gelman R, Borgstrom M, Ambrósio JR. Assessing Progression of Keratoconus and Cross-linking Efficacy: The Belin ABCD Progression Display. Int J Kerat Ect Cor Dis. 2017;6:1-10.
13. Zadnik K, Barr JT, Edrington TB, Everett DF, Jameson M, McMahon TT, Shin JA, Sterling JL, Wagner H, Gordon MO. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Invest Ophthalmol Vis Sci. 1998;39:2537-2546.
14. Duncan JK, Belin MW, Borgstrom M. Assessing progression of keratoconus: novel tomographic determinants. Eye Vis (Lond). 2016;3:6.
15. Mahmoud AM, Nunez MX, Blanco C, Koch DD, Wang L, Weikert MP, Frueh BE, Tappeiner C, Twa MD, Roberts CJ. Expanding the cone location and magnitude index to include corneal thickness and posterior surface information for the detection of keratoconus. Am J Ophthalmol. 2013;156:1102-1111.
16. de Sanctis U, Loiacono C, Richiardi L, Turco D, Mutani B, Grignolo FM. Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus. Ophthalmology. 2008;115:1534-1539.
17. Tomidokoro A, Oshika T, Amano S, Higaki S, Maeda N, Miyata K. Changes in anterior and posterior corneal curvatures in keratoconus. Ophthalmology. 2000;107:1328-1332.
18. Ferdi AC, Nguyen V, Gore DM, Allan BD, Rozema JJ, Watson SL. Keratoconus Natural Progression: A Systematic Review and Meta-analysis of 11 529 Eyes. Ophthalmology. 2019;126:935-945.
19. Kosekahya P, Caglayan M, Koc M, Kiziltoprak H, Tekin K, Atilgan CU. Longitudinal Evaluation of the Progression of Keratoconus Using a Novel Progression Display. Eye Contact Lens. 2019;45:324-330.
20. Choi JA, Kim MS. Progression of keratoconus by longitudinal assessment with corneal topography. Invest Ophthalmol Vis Sci. 2012;53:927-935.
21. Ahn SJ, Kim MK, Wee WR. Topographic progression of keratoconus in the Korean population. Korean J Ophthalmol. 2013;27:162-166.
22. Wagner H, Barr JT, Zadnik K. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: methods and findings to date. Cont Lens Anterior Eye. 2007;30:223-232.
23. Kato N, Negishi K, Sakai C, Tsubota K. Baseline factors predicting the need for corneal crosslinking in patients with keratoconus. PLoS One. 2020;15:e0231439.
24. Hamilton A, Wong S, Carley F, Chaudhry N, Biswas S. Tomographic indices as possible risk factors for progression in pediatric keratoconus. J AAPOS. 2016;20:523-526.
25. Tellouck J, Touboul D, Santhiago MR, Tellouck L, Paya C, Smadja D. Evolution Profiles of Different Corneal Parameters in Progressive Keratoconus. Cornea. 2016;35:807-813.
26. Kanellopoulos A, Moustou V, Asimellis G. Evaluation of visual acuity, pachymetry and anterior-surface irregularity in keratoconus and crosslinking intervention follow-up in 737 cases. J Kerat Ect Cor Dis. 2013;2:95-103.
27. Roberts C. Symposium on Corneal Cross-Linking: Current Status and Future Perspectives. ESCRS/EuCornea. Viyana; 2018.
28. Piñero DP, Alio JL, Barraquer RI, Michael R, Jiménez R. Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated study. Invest Ophthalmol Vis Sci. 2010;51:1948-1955.
29. Roberts CJ, Dupps WJ Jr. Biomechanics of corneal ectasia and biomechanical treatments. J Cataract Refract Surg. 2014;40:991-998.
30. Wisse RPL, Simons RWP, van der Vossen MJB, Muijzer MB, Soeters N, Nuijts RMMA, Godefrooij DA. Clinical Evaluation and Validation of the Dutch Crosslinking for Keratoconus Score. JAMA Ophthalmol. 2019;137:610-616.
31. E Esporcatte LPG, Salomão MQ, Lopes BT, Vinciguerra P, Vinciguerra R, Roberts C, Elsheikh A, Dawson DG, Ambrósio R Jr. Biomechanical diagnostics of the cornea. Eye Vis (Lond). 2020;7:9.
32. Kotecha A. What biomechanical properties of the cornea are relevant for the clinician? Surv Ophthalmol. 2007;52(Suppl 2):109-114.
33. Schweitzer C, Roberts CJ, Mahmoud AM, Colin J, Maurice-Tison S, Kerautret J. Screening of forme fruste keratoconus with the ocular response analyzer. Invest Ophthalmol Vis Sci. 2010;51:2403-2410.
34. Roberts CJ. Concepts and misconceptions in corneal biomechanics. J Cataract Refract Surg. 2014;40:862-869.
35. Mikielewicz M, Kotliar K, Barraquer RI, Michael R. Air-pulse corneal applanation signal curve parameters for the characterisation of keratoconus. Br J Ophthalmol. 2011;95:793-798.
36. Galletti JD, Ruiseñor Vázquez PR, Fuentes Bonthoux F, Pförtner T, Galletti JG. Multivariate Analysis of the Ocular Response Analyzer's Corneal Deformation Response Curve for Early Keratoconus Detection. J Ophthalmol. 2015;2015:496382.
37. Ventura BV, Machado AP, Ambrósio R Jr, Ribeiro G, Araújo LN, Luz A, Lyra JM. Analysis of waveform-derived ORA parameters in early forms of keratoconus and normal corneas. J Refract Surg. 2013;29:637-643.

38. Spoerl E, Terai N, Scholz F, Raiskup F, Pillunat LE. Detection of biomechanical changes after corneal cross-linking using Ocular Response Analyzer software. J Refract Surg. 2011;27:452-457.

39. Küçümen RB, Şahan B, Yıldırım CA, Çiftçi F. Evaluation of Corneal Biomechanical Changes After Collagen Crosslinking in Patients with Progressive Keratoconus by Ocular Response Analyzer. Turk J Ophthalmol. 2018;48:160-165.

40. Soeters N, Visser ES, Imhof SM, Tahzib NG. Scleral lens influence on corneal curvature and pachymetry in keratoconus patients. Cont Lens Anterior Eye. 2015;38:294-297.

41. Tsai PS, Dowidar A, Naseri A, McLeod SD. Predicting time to refractive stability after discontinuation of rigid contact lens wear before refractive surgery. J Cataract Refract Surg. 2004;30:2290-2294.