In Vivo Biomechanical Changes Associated With Keratoconus Progression

Prema Padmanabhan, Bernardo T. Lopes, Ashkan Eliasy, Ahmed Abass, and Ahmed Elsheikh

Department of Cornea and Refractive Surgery, Sankara Nethralaya, Chennai, India; School of Engineering, University of Liverpool, Liverpool, UK; Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil; Department of Production Engineering and Mechanical Design, Faculty of Engineering, Port Said University, Port Fuad, Egypt; Beijing Advanced Innovation Center for Biomedical Engineering, Beihang University, Beijing, China; Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology, London, UK

ABSTRACT

Purpose: To assess the biomechanical deterioration arising from keratoconus progression in-vivo.

Methods: The preoperative examinations of 32 progressive KC cases that were submitted to corneal cross-linking were evaluated. The examinations included the corneal tomography using the Pentacam HR and biomechanical parameters assessed by the Corvis ST (Oculus, Wetzlar, Germany). The results were recorded at two time points, the latter of which was at the last visit before the CXL procedure. Keratoconus progression was characterised by a significant change in the ABCD system.

Results: At the last follow-up visit (41.4 ± 40.9 months) all morphological parameters of the ABCD grading system showed significant deterioration (p < 0.001). The comparative analyses revealed a significant reduction in corneal stiffness expressed by a significant reduction in the stress-strain index (SSI: −0.10 ± 0.06, p < 0.001), the Stiffness parameter A1 (SP-A1: −6.1 ± 12.0 mmHg/mm, p = 0.011), by a significant increase in the integrated Inverse Radius (IIR: 0.95 ± 1.04 mm−1, p < 0.001) and in the deflection amplitude (DA) ratio (0.23 ± 0.58, p = 0.034). A barely significant increase in the DA also pointed towards corneal stiffness reduction. (0.04 ± 0.13 mm, p = 0.056).

Conclusions: It has been demonstrated in-vivo that corneal biomechanical deterioration occurs with keratoconus progression. The larger changes observed in the SSI and the IIR when compared to the remaining biomechanical parameters suggests that these parameters could be suitable to assess the corneal stiffness reduction in keratoconus natural progression.

Introduction

Keratoconus is a progressive corneal ectatic disease that affects young individuals with onset in the second decade of life. It is a common condition; nonetheless, its prevalence varies in different regions of the globe. In the Netherlands, keratoconus prevalence is 1:345 (265 per 100,000), in 20-year-old Australians its prevalence increases to 1:84 (1.2%) and in Saudi Arabia, it can be as high as 1:21 (4.7%).

It is a disease that carries a high morbidity potential due to its progressive nature especially in the younger ages, leading to corneal irregularities and loss of clear vision. The quality of life of these young patients is directly impacted by the disease with many suffering from depression and anxiety.

Corneal cross-linking (CXL) is effective to halt keratoconus progression. The sooner progression can be detected and CXL offered, the better the outcomes in terms of visual acuity, refraction, corneal shape, and, ultimately, a better quality of life. According to the pathophysiology of the disease, the biomechanical deterioration precedes and leads to corneal tissue bulging and thinning. Yet still, keratoconus detection and progression landmarks are based on corneal shape distortion rather than the underlying biomechanical loss.

Recently the stress-strain index (SSI) has been introduced as a means of obtaining an in vivo estimation of the corneal biomechanical status. In this study, the changes in SSI alone with corresponding changes in the biomechanical response (DCR) parameters, provided by the Corvis ST (Oculus, Wetzlar, Germany), were evaluated between two examinations in keratoconus patients with documented progression.

Methods

An anonymised database of patients diagnosed with keratoconus at the Sankara Nethralaya Eye Hospital (Chennai, India) between January 2015 and December 2019 was retrospectively reviewed. The local institutional review board ruled that approval was not required for this anonymised
record review study. Nonetheless, it was conducted according to the ethical standards set in the Declaration of Helsinki and its further revisions with all patients providing signed informed consent for the use of their de-identified clinical data for research.

According to the common practices of the Sankara Nethralaya Eye Hospital at all visits, patients underwent a complete ophthalmic examination including corrected distance visual acuity, slit-lamp biomicroscopy and fundoscopy exams in addition to the corneal tomographic exam with the Pentacam HR and biomechanical assessment with Corvis ST (Both, Oculus, Wetzlar, Germany).

Keratoconus progression was identified at the preoperative exams of cases that underwent CXL surgery. It has been established by the Global Consensus in Keratoconus and Ectatic Diseases that ectasia progression should be assessed by consistent steeping in the anterior or posterior corneal surfaces or cornea thinning that is above the noise level of the testing system. As all cases were examined with the same corneal tomographer, the Pentacam HR, the ABCD grading system was used to assess disease progression based on changes in the anterior radius of curvature (ARC), the posterior radius of curvature (PRC) and the minimum thickness that were higher than 95% CI of the repeatability in KC cases. Results of tomography and biomechanical exams carried out in the last visit before CXL and at the first time point before that, which fulfilled these progression criteria, were recorded. If both eyes had progressive keratoconus, the eye that first fulfilled the progression criteria was included. Exclusion criteria included bad quality tomographic exams and the presence of previous ocular surgeries or corneal diseases other than keratoconus.

The biomechanical parameters obtained from the Corvis ST included (1) Stress-Strain Index (SSI) described by Ellia et al. as a means of objectively estimating the corneal biomechanical stiffness in vivo, (2) the maximum corneal deformation (Deflection amplitude, DA) denoting the maximum apical displacement along the visual axis, (3) the first applanation stiffness parameter (SP-A1) calculated as the resultant pressure over corneal tissue divided by the first applanation amplitude, and had shown good separation between KC and healthy corneas as well as significant deterioration with KC progression. (4) the integrated inverse radius (IIR), a measure of the inverse corneal radius over time between the first and second applanation events, (5) the deflection amplitude ratio (DA Ratio), or the ratio between the apical deformation and the average deformation in nasal and temporal directions 2 mm away from the corneal apex. Both IIR and DA Ratio have been shown to be relatively independent of IOP while being correlated with corneal thickness and age – attesting to their suitability to evaluate in-vivo corneal biomechanics. In addition to these parameters, the biomechanically-corrected intraocular pressure, bIOP, as provided by the Corvis ST, was recorded at each examination to consider its possible effects on the biomechanical parameters of the Corvis ST.

Statistical analyses were accomplished using R Core Team (2016, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Due to the absence of normal distribution in the evaluated variables, the non-parametric Wilcoxon signed-rank test was used to compare paired data of the first and last exams. Boxplots were used to assess the distribution of each variable at the first and last exams. Statistical significance was considered if \( p < 0.05 \).

### Results

Thirty-two patients fulfilled the inclusion criteria. One eye randomly selected of each of them was included in the study. The mean age at the last exam before the CXL procedure was 22.0 ± 7.7 years (10–43). The mean time between the two examinations was 16.6 ± 16.4 months (1.4–58.4). The right to left eye ratio was 1:1:1. A spectrum of disease stages was observed at the first examination with \( \text{KMax} = 54.41 \pm 4.34 \text{D} \) (44.5–64.4) and minimum thickness of 466.72 ± 28.48 \( \mu \text{m} \) (414–520).

According to the inclusion criteria, significant steepening (reduction in the mean central corneal radius of curvature) was observed between the first and the second examinations in the anterior (\( \Delta \text{ARC} = -0.40 \pm 0.28 \text{mm}, \text{range:} -1.14 \) to \(-0.11, \text{ } p < 0.001; \Delta \text{KMax}, 2.68 \pm 2.32 \text{D}, \text{range:} -0.5 \) to 10.5, \( p < 0.001 \)) and posterior surfaces (\( \Delta \text{PRC}, = -0.39 \pm 0.24 \text{mm}, \text{range:} -0.98 \) to \(-0.12, \text{ } p < 0.001 \)). A significant reduction in

### Table 1. Clinical characteristics.

| Variable | First exam | Second exam | Second - first exam | p-value |
|----------|------------|-------------|---------------------|---------|
| ARC (mm) | 6.86 \( \pm \) 0.45 | 5.96 \( \pm \) 0.72 | -0.40 \( \pm \) 0.28 | \( < 0.001 \) |
| PRC (mm) | 5.25 \( \pm \) 0.46 | 4.98 \( \pm \) 0.64 | -0.39 \( \pm \) 0.24 | \( p < 0.001 \) |
| Pachy Min (\( \mu \text{m} \)) | 466.7 \( \pm \) 28.5 | 441.7 \( \pm \) 52.0 | -0.25 \( \pm \) 0.15 | \( p < 0.001 \) |
| K Max (D) | 54.41 \( \pm \) 4.34 | 57.09 \( \pm \) 4.6 | -2.68 \( \pm \) 2.32 | \( p < 0.001 \) |
| Ele F Thinnest (\( \mu \text{m} \)) | 20.66 \( \pm \) 8.2 | 25.69 \( \pm \) 8.26 | 5.03 \( \pm \) 4.16 | \( p < 0.001 \) |
| Ele B Thinnest (\( \mu \text{m} \)) | 45.12 \( \pm \) 17.87 | 54.09 \( \pm \) 17.15 | 8.97 \( \pm \) 9.09 | \( < 0.001 \) |
| SSI | 0.82 \( \pm \) 0.14 | 0.75 \( \pm \) 0.12 | -0.10 \( \pm \) 0.06 | \( p < 0.001 \) |
| IIR \( (1/\text{mm}) \) | 10.23 \( \pm \) 1.86 | 11.17 \( \pm \) 1.85 | 0.95 \( \pm \) 1.04 | \( < 0.001 \) |
| SP-A1 \( (\text{mmHg/mm}) \) | 67.0 \( \pm \) 18.2 | 60.9 \( \pm \) 17.8 | -6.1 \( \pm \) 12.0 | \( p < 0.001 \) |
| DA (mm) | 1.1 \( \pm \) 0.11 | 1.14 \( \pm \) 0.13 | 0.04 \( \pm \) 0.13 | 0.056 |
| DA Ratio | 5.54 \( \pm \) 0.78 | 5.77 \( \pm \) 0.93 | 0.23 \( \pm \) 0.58 | 0.034 |
| bIOP (\( \text{mmHg} \)) | 15.62 \( \pm \) 1.24 | 15.56 \( \pm \) 1.24 | -0.05 \( \pm \) 1.21 | 0.731 |

ARC: anterior radius of curvature; PRC: posterior radius of curvature; Pachy Min: minimum corneal thickness; K Max: maximum anterior axial corneal curvature; Ele F Thinnest: anterior corneal elevation at the thinnest point; Ele B Thinnest: posterior corneal elevation at the thinnest point; SSI: stress-strain index; IIR: integrated inverse radius; SP-A1: stiffness parameter at the first applanation; DA: deflection amplitude; bIOP: biomechanically corrected intraocular pressure.
the corneal minimum thickness was also observed (−25.03 ± 17.45 μm, range: −85 to −7, p < 0.001).

The biomechanical parameters changed between the two time points towards tissue softening. There was a significant reduction in the SSI (−0.10 ± 0.06, range: −0.2 to 0.0, p < 0.001) and increase in IIR (0.95 ± 1.04 mm⁻¹, range: −2.34 ± 2.69, p < 0.001) – both indicating stiffness reduction. Corneal softening was also observed by barely significant increases in DA (0.04 ± 0.13 mm, range: −0.22 to 0.53, p = 0.056), significant increases in DA ratio (0.23 ± 0.58, range: −1.31 to 1.49, p = 0.034) and significant decreases in SP-A1 (−6.1 ± 12.0 mmHg/mm, range: −31.8 to 18.9, p = 0.011), although there were substantial overlaps between the two exam points in these three parameters. The measurements also included bIOP, which showed minimum non-significant alteration between the exams (−0.05 ± 1.21 mmHg, range: −2.0 to 2.3, p = 0.731). Table 1 and Figure 1 summarise these results.

**Discussion**

The progressive nature of KC is arguably its grimmest aspect. As visual acuity continuously deteriorates, the quality
of life is gradually affected.\(^7\) In a recent meta-analysis of KC natural progression conducted by Ferdi et al, younger age and steeper baseline KMax were the main variables associated with the disease progression.\(^2\) The authors suggested that patients aged below 17 years and with KMax steeper than 55 D undergo close follow-up with a lower threshold for CXL than other patient groups. This suggestion is in line with the pathophysiology of the disease, in which low biomechanical stiffness (experienced in young age and advanced disease stages) is an underlying cause of its natural progression.\(^8\) Despite this fact, previous attempts to classify disease severity and its progression often relied on morphologic and optic aspects of the disease without direct consideration of the biomechanical aspect.\(^9,10,11\) This study seeks to assess the biomechanics of the keratoconic cornea and present in vivo evidence of its deterioration with disease progression.

The in vivo assessment of corneal biomechanics has been successfully used to assess the effect of surgical procedures such as CXL, intracorneal rings and keratoplasty.\(^22,23\) It was also used to diagnose keratoconus in its mild forms, but not yet to assess disease progression. A recent advance in the in vivo biomechanical assessment is the SSI that was intended to estimate the material stiffness of individual corneas rather than their overall stiffness – and hence the SSI is expected to be independent of the cornea's geometric parameters including most notably the thickness and curvature.\(^14\) In addition to being the only in-vivo biomechanical index to have a direct link with the tangent modulus, the SSI has the advantage of being more closely related to the hyperelastic behaviour of the corneal material – it can be translated into a whole stress-strain plot and hence be also independent of the intraocular pressure (IOP).\(^28\) While the previous research on the SSI focused on its correlation with age, CCT and IOP,\(^14\) in this study its performance was assessed in progressive keratoconus cases following a predefined progression criteria where softening – or stiffness reduction – was expected.\(^29\) In the current study, and besides the significant reduction in SSI between the two examinations (\(-0.10 \pm 0.06, p < 0.001\)), the parameter was the index with the smallest overlap between the two sets of results.

Among the DCR parameters, IIR and DA Ratio have been shown to be suitable parameters to evaluate in vivo corneal biomechanics as they are relatively independent of intraocular pressure, while being correlated with corneal thickness and age.\(^19\) In the current study, both parameters showed significant increases (changes towards corneal softening) between the two exams, but the overlap between the examinations was lower in the IIR than in the DA Ratio.

Similar trends towards softening were observed with SP-A1 (\(-6.1 \pm 12.0, p = 0.011\)) and DA \((0.04 \pm 0.13, p = 0.056)\). The SP-A1 has been reported as the parameter with the greater separation between normal and KC groups with comparable intraocular pressure.\(^17\) It has also been shown that SP-A1 is a strong biomarker for corneal conditions, including KC.\(^30\) On the other hand, DA is a direct measure of corneal resistance to deformation – it is different from SP-A1 in that it is measured closer to the highest concavity zone, and therefore it is more influenced by IOP than the parameters that relate to the first applanation event, A1, such as SP-A1 and DA Ratio.\(^17\)

A new biomechanical parameter has recently been developed to assess the disease progression based on the Corneal Biomechanical Index (CBI) linear equation results.\(^31\) The new parameter, after a linear adjustment to match the PRC scale, was named corneal biomechanical factor (CBiF). The CBiF has been shown to be significantly correlated with all three ABC parameters. However, unlike the SSI, the CBiF, was not developed to represent a standard mechanical parameter. It is a linear combination of DCR parameters such as the IIR, DA Ratio, SP-A1 and A1 velocity with the shape parameter Ambrosio relational thickness through the horizontal meridian (ARTh). It is a promising parameter to evaluate disease progression and its use along with the SSI should be evaluated in future publications.

A limitation of the study is the Corvis ST only monitors the corneal deformation through the horizontal meridian making its biomechanical parameters to be less sensitive to small or eccentric cones. The localised nature of corneal softening that occurs in KC\(^13\) could at least partially explain the erratic behaviour of some parameters with larger overlaps between the two examinations. Future studies stratifying the different cone shapes and positions are also planned to elucidate which parameters would suit better each disease type. Another future perspective for this research is a prospective study to evaluate how sensitive the SSI is to small changes of biomechanics by evaluating KC patients with closely spaced examinations.

In summary, this study demonstrated the in vivo measured biomechanical deterioration with KC progression. While some parameters such as the SP-A1, the DA and the DA Ratio weren’t sensitive enough to consistently detect the biomechanical deterioration, the larger changes observed in SSI and IIR qualifies these two parameters to be suitable biomechanical biomarkers of the disease progression.

**Disclosure statement**

Prof Elsheikh is a consultant for Oculus, the remaining authors have nothing to disclose.

**Funding**

This work was partially funded by Horizon 2020 Framework Programme, European Project "Imcustomeye H2020-ICT-2017", Ref. 779960.

**Data availability statement**

The data that support the findings of this study are available from the corresponding author, BL, upon reasonable request.

**References**

1. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol. 1984;28(4):293–322. doi:10.1016/0039-6257(84)90094-8.

2. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42(4):297–319. doi:10.1016/s0039-6257(97)00119-7.
3. 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;15:169–172. doi:10.1016/j.ajo.2016.12.015.

4. Chan E, Chong EW, Lingham G, Stevenson LJ, Sanfilippo PG, Hewitt AW, Mackey DA, Yazar S. Prevalence of keratoconus based on Scheimpflug imaging: the Raine study. Ophthalmology. 2021;128(4):515–521. doi:10.1016/j.ophtha.2020.08.020.

5. Torres Netto EA, Al-Otaibi WM, Hafezi NL, Kling S, Al-Farhan HM, Randleman JB, Hafezi F. Prevalence of keratoconus in paediatric patients in Riyadh, Saudi Arabia. Br J Ophthalmol. 2018;102(10):1436–1441. doi:10.1136/bjo2017-311391.

6. Mas Tur V, MacGregor C, Jayaswal R, O’Dwyer D. Keratoconus natural progression: a systematic review and meta-analysis of 11,529 Eyes. Ophthalmology. 2019;126(7):707–715. doi:10.1016/j.ophtha.2019.02.029.

7. Yildiz M, Turhan SA, Yargi B, Ergun S, Ornek F, Toker EMKLAS: a new automatic scoring system for early and mild keratoconus detection. Transl Vis Sci Technol. 2020;9(2):30.

8. Nath S, Shen C, Koziarz A, Banfield L, Nowrouzi-Kia B, Fava F. Determination of corneal biomechanical behavior in-vivo for healthy eyes using corVis ST tonometry: stress-strain index. Front Physiol. 2019;10:704.

9. Gomes JA, Petropoulos IG, Belin MW, Azzolini C, Vinciguerra P. In-vivo elasticity of keratoconus without topographic or tomographic abnormalities. J Refract Surg. 2017;33(6):399–407. doi:10.1016/j.jrs.2017.0213-01.

10. Liu X, Bao F, Wang J, Liu X, Wang L, Abass A, Eliasy A. Development of a new biomechanical index. J Refract Surg. 2020;46(2):215–221. doi:10.1097/JRS.0000000000001989.

11. Keefe M. Cross-linking in children with keratoconus. J Cataract Refract Surg. 2017;43(2):221–227. doi:10.1016/j.jcrs.2016.12.023.

12. Lopes BT, Fujiwara TH, Batterbury M, Kaye SB. In vivo early corneal biomechanical changes after corneal cross-linking in patients with progressive keratoconus. J Refract Surg. 2017;33(12):840–846. doi:10.3928/1081597X-20170922-02.

13. Bhandal S, Sedaghat MR, Yasemi M, Maalhagh M. Intracorneal stromal ring can affect the biomechanics of ectatic cornea. J Ophthalmol. 2020;2020:4774037.

14. Pedrotti E, Caldarella G, Fasolo A, Bonacci E, Gennaro N, Gregorio A, Marchini G. Topographic and biomechanical changes after application of corneal cross-linking in recurrent keratoconus. Int J Environ Res Public Health. 2019;16:3872.

15. Mohammadpour M, Khoostinat N, Khorrami-Nejad M. Comparison of visual, tomographic, and biomechanical outcomes of 360 degrees intracorneal ring implantation with and without corneal cross-linking for progressive keratoconus: a 5-year follow-up. Cornea. 2021;40(3):303–310. doi:10.1097/ICO.0000000000002407.

16. Lopes BT, Bao F, Wang J, Liu X, Wang L, Abass A, Eliasy A, Elsheikh A. Review of in-vivo characterisation of corneal biomechanics. Med Novel Technol Dev. 2021;11:100073. doi:10.1016/j.medntd.2021.100073.

17. Belin MW, Meyer JJ, Duncan JK, Gelman R, Borgstrom M. Assessing progression of keratoconus and cross-linking efficacy: the Belin ABCD progression display, Int J Keratoconus Ectatic Corneal Dis. 2017;6(1):1–10. doi:10.5055/jp-journals-10025-1135.

18. Vinciguerra R, Ambrosio R Jr, Elsheikh A, Roberts CJ, Lopes BT, Morenghi E, Azzolini C, Vinciguerra P. Detection of keratoconus with a new biomechanical index. J Refract Surg. 2016;32(8):803–810. doi:10.3928/1081597X-20160629-01.

19. Flockerzi E, Vinciguerra R, Belin MW, Vinciguerra P, Ambrosio R Jr, Seitz B. Correlation of the corvis biomechanical factor with tomographic parameters in keratoconus. J Cataract Refract Surg. 2022;48(2):215–221. doi:10.1097/j.jcrs.0000000000001740.