**Evaluation of Corneal Biomechanical Behavior in-vivo for Healthy and Keratoconic Eyes Using the Stress-Strain Index**

**Short Running Head: In vivo corneal biomechanics of healthy and keratoconic eyes.**

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**Abstract:**

**Purpose:** To evaluate corneal material properties characteristics in healthy and keratoconic patients utilising the stress-strain index (SSI).

**Setting:** Vincieye Clinic in Milan, Italy, and Instituto de Olhos Renato Ambrósio in Rio de Janeiro, Brazil

**Design:** Retrospective observational cross-sectional study

**Methods:** Records of 1,221 patients were divided into 3 groups: healthy corneas (n=728), bilateral keratoconus (KC, n=388), and very asymmetric ectasia (VAE, n=105) when patients presented one eye with clinical ectasia and the fellow-eye with normal topography (VAE-NT). All patients were examined with Pentacam HR and Corvis ST (both, Oculus, Wetzlar, Germany). KC cases severity were stratified according to Pentacam’s topographic keratoconus classification. The SSI distribution across the different groups and its correlation with age, biomechanically corrected intraocular pressure (bIOP) and central corneal thickness (CCT) were assessed.

**Results:** There was a significant difference between healthy and each of the keratoconic groups (p<0.001) and a progressive reduction in SSI was observed across the groups. There was a significant correlation between SSI and age in all groups (p<0.010), but KC severe (p=0.361). No correlation between SSI and bIOP or CCT was observed in all KC subgroups and VAE-NT (p>0.050). Among healthy eyes, there was only a mild correlation between SSI and bIOP (R=0.12, p=0.002) and CCT (R=0.13, p=0.001).

**Conclusions:** This study estimates with a new method the in vivo corneal material properties in healthy and keratoconus patients. The SSI showed a progressive deterioration within the advance in disease stages, while being relatively independent of bIOP and CCT but positively correlated with age.

**Introduction**

It is ironic that more than a century and a half after the British physician, John Nottingham first described the “Conical Cornea”, Keratoconus continues to be defined and described in terms of the secondary effects of the disease rather than in terms of its underlying cause1.

Although the exact chronology of events that lead to the disease is still not entirely clear, it is widely believed that a biomechanical instability of corneal stroma represents the final common pathway for molecular, biochemical, genetic, and environmental factors that results in corneal ectasia and thinning 2,3.

While shape changes are more easily visualized in a clinical setting and more easily measured by a multitude of imaging devices, the more logical approach of measuring corneal biomechanics has been more elusive. The complexity of corneal biomechanical properties and the practical difficulties of being able to measure them non-invasively in vivo have been some of the challenges that clinicians have faced.

The Ocular Response Analyser (ORA, Reichert Ophthalmic Instruments, New York, USA) was the first commercial device that attempted to characterize the viscoelastic properties of the cornea but did not use classical terms that describe biomechanics 4,5. More recently the CorVis ST (Oculus, Wetzlar, Germany), also a non-contact tonometer that uses a high-speed Schiempflug camera to image corneal response to an air puff, has been used to analyse the deformation profile in real-time to derive multiple parameters collectively called the Dynamic Corneal response (DCR) parameters 6,7. A major challenge of in vivo corneal biomechanical measurement stems from the fact that the corneal deformation under an air puff pressure is strongly influenced by corneal geometry (thickness in particular) and the initial stress due to the intraocular pressure (IOP) 7.

The need to accurately measure IOP independent of the influence of corneal thickness and biomechanics led to the development of the biomechanically corrected IOP (bIOP) algorithm 8. Using a combination of numerical modelling and DCR parameters, the algorithm was validated in experimental and clinical settings 9,10. As the next logical step, a biomechanical parameter, independent of IOP and corneal thickness, was derived using numerical models that simulated a wide range of ocular topography, corneal thickness profiles, IOP, and material behaviour trends 11. The Stress-Strain Index (SSI), as it was named, was clinically validated in terms of its relative independence from IOP and corneal thickness and its correlation with age in a large dataset of normal patients and was found to agree with the results of ex-vivo inflation tests done on human cadaver corneas 12.

The present study aims to expand the analyses of SSI, evaluating its correlations with IOP and corneal thickness in healthy and keratoconic eyes and assessing its consonance with the currently used gradation of disease severity based on corneal shape characteristics as measured by corneal tomography 13.

**Methods**

This retrospective record review study analysed a secondary fully anonymised dataset composed of 1221 patients. In the primary data collection, the patients were enrolled at two clinics located in two continents: the Vincieye Clinic in Milan, Italy, Europe and Instituto de Olhos Renato Ambrósio in Rio de Janeiro, Brazil, South America. According to the University of Liverpool’s Policy on Research Ethics, ethical approval was ruled unnecessary for this study, which included only secondary fully anonymised data. Yet, the study followed the tenets of the Helsinki Declaration revised in 2013. Written informed consent was also provided by all participants for the use of their de-identified data in scientific research in the primary data collection.

*Participants*

The patients were initially divided into 3 groups: normal, very asymmetric ectasia (VAE), and keratoconus (KC). The normal group included 728 cases with normal corneas bilaterally, the VAE group 105 cases with frank keratoconus in one eye and normal topography in the other, and the KC group 388 cases with bilateral disease. One eye was included per patient. In normal and KC groups the inclusion was random, while in the VAE group eyes with normal topography were selected. The KC group was further subdivided into mild, moderate, and severe according to Pentacam’s Topographic Keratoconus Classification (TKC) in mild – grades ≤ 1; moderate – from grades 1-2 to 2-3; and advanced – grades ≥ 3.

All cases included in the analysed dataset had completed a comprehensive ophthalmic examination, including the Pentacam HR and Corvis ST (both: Oculus, Wetzlar, Germany) examinations with good quality score. Per standards of both clinics, soft contact lens wear was discontinued for a minimum period of 3 days before the examination and rigid contact lenses were discontinued for at least 3 weeks.

The inclusion criteria of the normal group were the presence of normal corneas on the general ocular examination in both eyes, including corrected distance visual acuity of 20/20 or better, normal slit-lamp biomicroscopy, and normal subjective topography and tomography examinations assessed by two experienced cornea specialists (RA and PV). Also, none of the patients were using topical medications other than artificial tears in both eyes or were subjected to any surgical procedure.

Patients clinically diagnosed with keratoconus, as defined by the binocular presence of topographic characteristics including skewed asymmetric bowtie or inferior steepening and at least one slit-lamp finding such as Vogt’s striae, Fleischer’s ring, apical thinning, Munson’s or Rizutti’s signs were included in the study. Patients with a history of previous ocular procedures, e.g., corneal collagen cross-linking or intracorneal ring segments implantation were excluded.

The VAE cases were defined by the presence of the aforementioned criteria of clinical diagnosis of ectasia in one eye with normal front surface curvature (topometric) map in the other. The normal topography eye of VAE cases (VAE-NT) was defined by the presence of objective criteria previously described by Ambrosio et al and included keratoconus percentage index (KISA%) score lower than 60 and a paracentral inferior–superior (I-S value) asymmetry value at 6 mm (3-mm radii) less than 1.45 14.

*Variables assessed*

The raw anonymised data (u12 files) were obtained from all cases. The Pentacam software version 1.20r118 and Corvis ST software version 1.6b1970 were used to process all u12 files. The patient’s age was recorded along with maximum anterior axial curvature (KMax), central corneal thickness (CCT), minimum thickness (Pachy Min), and anterior and posterior elevation concerning the best-fit-sphere (8mm diameter) at the thinnest point (AETP and PETP), total deviation of the Belin-Ambrosio display indices (BAD-D), stiffness parameter at the first applanation (SP-A1), biomechanically corrected intraocular pressure (bIOP), corneal biomechanical index (CBI), tomographic and biomechanical index (TBI) and the stress-strain index (SSI). The stress-strain index (SSI), as described by Eliasy et al 11, is an objective assessment of individual corneal material stiffness. It was developed using numerical simulation of Corvis ST exams and was experimentally and clinically validated.

*Statistical analysis*

Statistical analysis was accomplished using R Core Team (2016, R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). The Gaussian distribution of the main analysed variables (SSI, bIOP, CCT, and Age) was assessed using histograms and the Shapiro-Wilk and Kolmogorov-Smirnov normality tests. The differences in SSI among the five groups was assessed with Kruskal-Wallis test and pairwise comparisons were accomplished with post-hoc Dunn’s test. For correlation analysis, data transformation was conducted where non-normal distribution was observed. The SSI distribution was positively skewed in all groups. To achieve approximately normal distribution and p>0.05 on normality test, log-transformation was performed in Healthy and VAE-NT groups, while reciprocal transformation (-1/x) was implemented in all three KC subgroups (mild, moderate, and severe). The distribution of bIOP in the healthy group after square root transformation was approximately normal and p=0.05. The CCT distribution was negatively skewed in VAE-NT and KC severe groups. The following transformation was successfully applied to obtain normal approximate distribution and p>0.05.

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| --- | --- |
|  | Equation 1 |

The age was positively skewed in all subgroups. In the healthy subgroup, data transformations were not successful in reaching the approximately normal distribution. Log transformation was successful in VAE-NT, KC mild, and KC severe subgroups. Approximate normal distribution was obtained in KC severe subgroup using squared-root transformation.

The variable’s distributions can be observed in supplemental figures 1-4.

The relation between most of the variables was assessed using Pearson’s correlation. The correlation coefficient R was used to assess the degree to which a change in SSI was associated with a change in bIOP or CCT. As age did not show normal distribution, non-parametric spearman’s correlation coefficient (ρ) was used instead to assess its correlation with SSI. The correlations between SSI and two shape variables (CCT and KMax) in all KC cases were also evaluated with ρ. The correlation was considered negligible if R/ρ < 0.1 and weak if R/ρ < 0.4 and moderate if R/ρ is between 0.4 and 0.7 15. P values less than 0.05 were defined as statistically significant.

**Results**

The patient’s demographic characteristics are described in table 1.

Progressive deterioration in material stiffness can be observed by a decrease in SSI from Healthy to severe KC, figure 1. Between healthy and VAE-NT groups there was a mean reduction in SSI of 5% (p=0.173). There was significant SSI deterioration between VAE-NT and each of the three KC groups. Between VAE-NT and Mild, there was a 31% reduction in SSI (p<0.001). The mean reduction between VAE-NT and Moderate and Severe was 38.1% and 43.3%, respectively (p<0.001). The pairwise comparisons among the different KC groups showed a statistically significant difference in all pairs except Moderate and Severe (p=0.183). Despite the significant reduction in SSI values, the groups presented significant overlap.

SSI was moderately correlated with age in the Healthy group (ρ = 0.53, p<0.001) and significantly but weakly correlated in VAE-NT, KC mild, and KC moderate groups (R<0.3, p<0.010). The correlation between SSI and age was not significant in KC severe group (R=0.12, p=0.361). Figure 2.

The correlations between SSI and both bIOP and CCT are depicted in Figure 3. In the Healthy group, a weak correlation was observed between SSI and both bIOP (R=0.12, p=0.002) and CCT (R=0.13, p=0.001) respectively.

In VAE-NT group non-significant weak correlations were observed between SSI and bIOP (R=0.16, p=0.102) and CCT (R=0.18, p=0.064).

A considered negligible negative correlation was observed between SSI and bIOP in KC mild (R=-0.01, p=0.859) and moderate (R=-0.04, p=0.625). In KC severe the correlation between SSI and bIOP was weak and non-significant (R=-0.17, p=0.192). The correlation between SSI and CCT in all three KC groups was weak and non-significant (mild KC: R=0.13, p=0.098, moderate KC: R=0.15, p=0.071, and severe KC: R=0.17, p=0.186).

The correlations between corneal material properties and two important shape variables (KMax and Pachy Min) considering all KC cases were assessed. In this group SSI was moderately inverse correlated with KMax (ρ = -0.46, p<0.001) and weakly direct correlated with Pachy Min (ρ = 0.32, p<0.001). Figure 4.

**Discussion**

A focal reduction of elastic modulus is believed to trigger the cyclic cascade of events that lead to corneal thinning and bulging that characterize Keratoconus 3. Although the shape changes are subsequent effects of the underlying biomechanical instability, Keratoconus has been characterized, staged and its natural course tracked in terms of those secondary effects rather than in terms of the primary biomechanical cause 16. There have been two major challenges in attempting to detect and define keratoconus from a biomechanical perspective: first, to identify the appropriate unit of measure that will reflect a true biomechanical characteristic of the cornea and will not be significantly confounded by corneal geometry or intraocular pressure (IOP) and second, to be able to make reliable, consistent and non-invasive measurements in vivo.

Preliminary studies suggest that the recently introduced Stress-Strain Index (SSI) can potentially meet both requirements: the algorithm to derive the SSI curves can be integrated with the Corvis ST which provides dynamic parameters in varied phases of deformation in vivo and the tangent modulus could be directly derived from the SSI curves 11. It has been also observed that as a biomechanical parameter, SSI conforms with the physiological age-related corneal stiffening 11,12.

SSI also addresses two important confounding factors of in vivo corneal biomechanics measurement, namely, the influences of IOP and corneal thickness. The non-linear behaviour of corneal deformation under pressure means that it is not possible to describe corneal stiffness with a single value of tangent modulus as it increases with increasing IOP 3. An ideal corneal biomechanical parameter should be able to represent the tissue’s material stiffness under different IOP values. It should also be independent of corneal geometry, since geometry is also an important component of overall tissue stiffness, with the thickness being the most influential component 7. If two corneas possess the same material stiffness and one is thicker than the other it will, as a result, hold a higher overall stiffness. Therefore, a parameter that can describe corneal material properties should have little or no correlation with IOP or CCT.

Eliasy et al have observed that SSI was not significantly correlated with either bIOP or CCT in two different sets of healthy populations, while its correlation with age could demonstrate the physiological stiffening of ageing 11. A similar observation was made in the present study in a larger healthy dataset in which SSI was moderately correlated with age (ρ = 0.53, p<0.001). The correlations between SSI and both bIOP and CCT were weak. While the p-value revealed statistical significance (influenced by the large sample size), the correlation coefficients were low (R < 0.15) with high scattering and a low gradient of the trendline.

The present study extends the potential application of SSI to a wide spectrum of patients, encompassing normal and all grades of keratoconus including very asymmetric ectasia (VAE) eyes with mild forms of the disease. Age was weakly correlated with SSI in VAE-NT, KC mild, and KC moderate, and no significant correlation was observed in KC severe subgroup (p>0.05). As keratoconus progressively disrupts the gross organization of stromal lamellae 17 it is expected that the age-related stiffening pattern would not be observed in these populations, especially in the most advanced cases.

Regarding the correlations between SSI and bIOP and CCT, the results in all disease groups were similar to those observed in the healthy population. Only mild non-significant correlations were observed between SSI and bIOP and CCT (|R| < 0.2, p > 0.05) Here again, the relative independence of the SSI from the confounding effects of CCT and bIOP suggests that the SSI could be considered a robust indicator of material stiffness of the cornea in normal as well as in ectatic eyes.

This study also showed that with increasing grades of keratoconus (as determined by the Pentacam based TKC scale), the SSI showed a corresponding trend of decrease in magnitude. This trend, which was not unexpected, confirms that the material stiffness of the cornea decreases as the severity of the disease advances.

KC progression is also associated with characteristic corneal shape changes such as a reduction in corneal thickness and an increase in corneal curvature. When considering all KC cases combined there was a moderate inverse correlation between SSI and KMax (ρ = -0.46, p<0.001) and a weak direct correlation between SSI and Pachy Min (ρ = 0.32, p<0.001).These significant correlations corroborate the theory that material stiffness deterioration is responsible for corneal shape alterations.

The large standard deviation and overlap of values seen in both normal and keratoconic eyes as also among various grades of keratoconus, limits the suitability of the SSI as a single diagnostic parameter to grade the severity of the disease. Also, when considering all KC cases combined the spread of data resulting in weak and moderate correlation between SSI and Pachy Min and KMax, respectively limits the use of SSI as an universal indicator of KC progression. The arrangement of the stromal lamellae and the degree of fibril dispersion, which determine the elastic modulus, exhibit a considerable spatial variation between healthy and keratoconic eyes 17-19. This may explain the variation noticed among patients in our study as well, indicating that SSI is better suited for evaluating intra rather than inter-subject variations. Another source of this variation and overlap between the groups is the focal nature of the biomechanical deterioration in keratoconus disease and the fact that the SSI is an estimation of the overall corneal material properties. A study to translate a single SSI value into a map of its regional variation across the corneal surface is under way to tackle this limitation. Another limitation is the potential reduction in the examination’s reliability in patients with keratoconus given the challenges to acquiring well aligned and of good quality images in these cases. However, the observed trends, consistent with the biomechanical expectations, allow us to draw the study’s conclusions.

In summary, it has been observed in this study that SSI can be used as an indicator of material stiffness in normal and ectactic subjects. A few potential applications of this new index infrequently encountered clinical situations include the monitoring of changes in material stiffness that may occur with the natural progression of the disease or those that could be induced by treatments like collagen crosslinking. The criteria to define and track the progression of keratoconus are currently based on changes in corneal shape and deterioration in optical performance. The Belin ABCD platform, which combines both, would manifest only after these secondary changes have occurred 16. The BAD-D and TBI, both sensitive parameters to detect subclinical keratoconus, would still need subtle shape changes to register a progression of the disease 14,20. The SSI, on the other hand, has the potential to reflect early changes in the tangent modulus and thus be able to detect progression at its very biomechanical root. Currently, a longitudinal study is being carried out to explore this hypothesis.

**Value Statement**

**What was known**

* The stress-strain index (SSI) is an estimation of the corneal material properties that can be obtained in vivo.
* It has shown to be relatively independent of Intraocular pressure (IOP) and central corneal thickness (CCT) while being significantly correlated with subject’s age.

**What this paper adds**

* SSI can also estimate the overall corneal material properties in keratoconic (KC) eyes.
* SSI deteriorates with the disease progression
* Due to the keratoconus’ focal nature, no differences between healthy and very early cases were observed in SSI.

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**Figure Legends**

Supplemental Figure 1- SSI distribution before and after transformation in Healthy (A), VAE-NT (B), KC Mild (C), KC Moderate (D), KC Severe (E)

Supplemental Figure 2- bIOP distribution before and after transformation in Healthy (A), VAE-NT (B), KC Mild (C), KC Moderate (D), KC Severe (E)

Supplemental Figure 3- CCT distribution before and after transformation in Healthy (A), VAE-NT (B), KC Mild (C), KC Moderate (D), KC Severe (E)

Supplemental Figure 4- Age distribution before and after transformation in Healthy (A), VAE-NT (B), KC Mild (C), KC Moderate (D), KC Severe (E)

Figure 1- SSI distribution across the groups

\*non-significant difference in pairwise comparison.

SSI: Stress-strain index; VAE-NT: very asymmetric ectasia normal topography; KC keratoconus. Boxplot: Box drawn from the first to third quartile, central line representing the median and the whiskers representing the minimum to maximum values excluding outliers.

Figure 2- Correlation between SSI and age in Healthy (A), VAE-NT (B), KC Mild (C), KC Moderate (D), KC Severe (E)

SSI: Stress-strain index; VAE-NT: very asymmetric ectasia normal topography; KC keratoconus.

Figure 3- Correlation between SSI and bIOP and CCT in Healthy (A), VAE-NT (B), KC Mild (C), KC Moderate (D), KC Severe (E)

SSI: Stress-strain index; VAE-NT: very asymmetric ectasia normal topography; KC keratoconus.

Figure 4- Correlation between SSI and Kmax (A) and Pachy Min (B) among KC eyes.

SSI: Stress-strain index; KMax: Maximum anterior curvature; Pachy Min: Minimum Corneal Thickness; KC: keratoconus.

**Table Legends**

Table 1- Patients’ demographic and clinical characteristics

Kmax: Maximum curvature in anterior topography; Pachy Apex: corneal thickness at the apex; Pachy min: minimum corneal thickness; EleBBFS8mmThinnest: Back elevation at the thinnest point; EleFBFS8mmThinnest: Front elevation at the thinnest point; BADD: total deviation of the Belin-Ambrosio display; IntegratedRadius: Integrated inverse concave radius; SPA1: stiffness parameter at the first applanation; bIOP: biomechanically corrected intraocular pressure; CBI: Corneal biomechanical index; TBI; tomographic and biomechanical index; SSI: stress-strain index.