**Biomechanical Evaluation of Topographically and Tomographically Normal Fellow Eyes of Keratoconus Patients**

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**ABSTRACT**

***Purpose:***

To determine the effectiveness of parameters and indices based on biomechanical measures at discriminating keratoconus suspects with topographically and tomographically normal corneas, from normal control corneas.

***Methods:***

47 keratoconus suspect eyes, comprised of the normal fellow eyes of patients with diagnosed keratoconus in the other eye, were included in the study. Eyes were imaged using Pentacam HR and Corvis ST. Fellow eyes were then categorized as topographically/tomographically normal fellow eyes (TNF) and topographically/tomographically borderline fellow eyes (TBF). The ability of each of the Corvis Biomechanical Index (CBI), Tomographic and Biomechanical Index (TBI), Stiffness Parameter at Applanation 1 (SP-A1), and Stress-Strain Index (SSI) at discriminating between normal controls and keratoconus suspects was assessed.

***Results:***

The TBI had the best discriminative ability with the greatest area under the receiver operating characteristic curve (AUROC) of 0.946 for normal controls versus TBF eyes, and 0.824 for normal controls versus TNF eyes. Compared to the TBI AUROC curves, SP-A1 and CBI had AUROC curves of 0.833 (*p*=0.09) and 0.822 (*p*=0.01) for normal controls versus TBF eyes, respectively, and AUROC curves of 0.822 (*p*=0.96) and 0.550 (*p*=0.0002) for normal controls versus TNF eyes, respectively. TBI had the best positive predictive value for TNF and TBF eyes, followed by CBI and SP-A1.

***Conclusions:***

The TBI, and the purely biomechanical parameter SP-A1, were of moderate utility in distinguishing between normal and keratoconus suspect eyes. In the absence of topographic/tomographic evidence of keratectasia, an independently abnormal biomechanical parameter does not strongly suggest an increased risk of ectasia.

**INTRODUCTION**

Keratoconus is a non-inflammatory condition characterized by progressive thinning and protrusion of the cornea, resulting in visual impairment.1,2 The advent of refractive surgery has necessitated the detection of early keratoconus, and the identification of corneas with underlying biomechanical abnormalities leading to increased susceptibility for the development of ectasia, since undergoing the procedure in undiagnosed eyes can result in iatrogenic ectasia.3,4 The current understanding and general consensus about keratoconus is that it is a bilateral disease.5 While unilateral ectasia can occur, the seemingly normal fellow eyes of patients with a diagnosis of keratoconus in one eye only, represent a set of eyes that traditional testing has likely failed to diagnose.

Conventional imaging methods for detecting keratectasia include corneal topographic assessment by means of Placido disk devices, as well as Scheimpflug tomography, which may reveal relatively late sequelae of the disease. In contrast, corneal biomechanical weakness is believed to be the first manifestation of the disease, with thinning and increase in curvature as a consequence of primary focal weakening due to local disruption of the lamellar structure.6–8 As such, instruments that assess corneal biomechanics have been developed, the latest of which being the Corvis ST (Oculus Optikgeräte GmbH; Wetzlar, Germany).

The Corvis ST is a system that integrates an air puff with an ultra-high-speed Scheimpflug camera, and measures central corneal thickness, true intraocular pressure independent of corneal thickness and biomechanical properties, as well several corneal biomechanical deformation parameters. It generates, along with the Pentacam HR (Oculus Optikgeräte GmbH; Wetzlar, Germany), several indices that integrate corneal biomechanical data from the Corvis ST with tomographic data from the Pentacam HR. Among these measures and indices are the Corvis Biomechanical Index (CBI), the Tomographic and Biomechanical Index (TBI), and the Stiffness Parameter at Applanation 1 (SP-A1), which have all been shown to be effective at discriminating eyes with keratoconus from normal eyes.9–12 However, they have shown variable success in the discrimination between normal eyes and keratoconus suspect eyes, depending on the criteria used to define suspect eyes.10,13–19 More recently, the Corvis ST introduced the Stress-Strain Index (SSI), a parameter intended to estimate corneal material stiffness, rather than overall corneal stiffness, as measured by the SP-A1. As keratoconus is known to lead to corneal biomechanical deterioration, the SSI is expected to decrease with disease progression.20 The aim of this study is to determine the effectiveness of objective parameters and indices based on biomechanical measures, at discriminating keratoconus suspects with topographically and tomographically normal corneas, from completely normal control corneas, using a relatively large sample size.

**PATIENTS AND METHODS**

This prospective observational study was conducted at the Cornea and Refractive Surgery Division of the Ophthalmology department at the American University of Beirut Medical Center in Beirut, Lebanon. As such, the participants were almost exclusively Lebanese. Approval was obtained from the Institutional Review Board (IRB ID: BIO-2018-0080), and the study adhered to the tenets of the declaration of Helsinki. All enrolled participants provided written informed consent after receiving a full explanation of the nature, intent, and possible consequences of the study.

All patients had previously undergone imaging with the Galilei dual Scheimpflug-Placido system (Ziemer Group AG, Switzerland), as part of their routine follow up for keratoconus, or as part of their pre-refractive surgery assessment. A chart review was conducted to identify patients who were categorized as having keratoconus in one eye, with no clear topographic or tomographic abnormality in the fellow eye. These patients were then re-called for repeat imaging with the Galilei, and imaging with the Pentacam HR and Corvis ST.

Inclusion criteria were a diagnosis of keratoconus, or keratectasia, in one eye, with the fellow eye displaying no clinically, topographically or tomographically discernable abnormality that can diagnose the disease. A diagnosis of keratoconus was made based on the presence of at least one clinical sign on slit-lamp examination, such as Vogt’s striae and Fleischer rings, as well as both objective and subjective analyses of the tomographic maps, as previously described by the authors.21 The objective measure was based on a Cone Location and Magnitude Index (CLMI-X) of more than 25%, which has 100% sensitivity and 99.5% specificity for the diagnosis of keratoconus.22 The subjective interpretation of the maps relied on anterior corneal curvature asymmetry and posterior surface abnormality. The former included major criteria such as skewed radial axis > 20 degrees, I-S value > 2.38 diopters (D) and Keratoconus Prediction Index (KPI) > 30%. Minor criteria consisted of inferior steepening of at least 1 D, an asymmetric bowtie pattern without a skewed radial axis, an I-S value of more than 1.4 D but less than 2.3 D, and 18.5% < KPI < 30%.23Posterior surface abnormality consisted of having a highest posterior elevation point of >18 microns in the 3-mm central zone, or >22.5 microns in the 5 mm central zone**.**24The subjective diagnosis of keratoconus was based on at least 2 major anterior corneal curvature asymmetry criteria, 1 major criterion with posterior surface abnormality, or 2 minor criteria along with posterior surface abnormality.

Fellow eyes were deemed ‘normal’ and were defined as keratoconus suspect eyes when they did not qualify for a diagnosis of keratoconus, and additionally fulfilled the following objective criteria: central mean keratometry < 47.20D, Keratoconus Percentage Index (KISA) < 60%, Cone Location and Magnitude Index (CLMI-X) < 25%,22 Keratoconus Probability (Kprob) < 22.55%, KPI < 18.55%, as well as a Belin/Ambrósio Enhanced Ectasia Deviation index (BAD-D) of less than 2.69.25 Exclusion criteria were the presence of keratectasia bilaterally, a history of corneal or ocular surgery, such as corneal collagen cross-linking or intrastromal ring insertion, as well as other ocular pathologies such as retinal disease.

Of the 57 patients re-called for imaging, 10 were excluded due to the finding of at least one abnormality among the objective inclusion criteria for keratoconus suspect eyes. The 47 remaining fellow eyes were then subdivided based on their BAD-D index, KPI, and Kprob. The group of topographically/tomographically normal fellow eyes (TNF) had a BAD-D of less than 1.65, KPI of less than 5%,23,26 and Kprob of less than 11.60%.23,26 The group of topographically/tomographically borderline fellow eyes (TNF) either had a BAD-D between 1.65 and 2.69, a KPI between 5% and 18.55%,23,26 or a Kprob between 11.60% and 25.55%,23,26 or a combination of these borderline values. Classification was also attempted based on the Percentage Probability of Keratoconus (PPK), with cut-offs of 25.0% and 45.0%23 for the TNF and TBF groups, respectively, as well as the Index of Surface Variance (ISV), with cut-offs of 37.0 and 41.023 for the TNF and TBF groups, respectively. However, all fellow eyes in both TNF and TBF groups had a PPK of less than 25% (range = 0.20% to 11.92%) and an ISV of less than 37 (range = 8 to 28).

100 eyes of 100 patients with bilaterally normal corneas constituted the normal control group. These patients were identified on presentation for refractive surgery. They had no clinical, topographic, or tomographic evidence of keratectasia in either eye, in addition to no family history of keratoconus. All normal controls underwent refractive surgery and had no evidence of ectasia at least 1 year following the procedure. The choice between left and right eyes for each control patient was random. All enrolled patients underwent a complete ophthalmic examination, as well as imaging with Pentacam HR and Corvis ST. Imaging was repeated if it was of inadequate quality. Only image acquisitions with acceptable quality, marked by “OK” on Pentacam HR and Corvis ST, were used. Rigid contact lens wear was discontinued for at least 4 weeks, and soft contact lens wear was discontinued for at least 2 weeks, prior to imaging.

The Corvis Biomechanical Index (CBI), Tomographic and Biomechanical Index (TBI), and Stiffness Parameter at Applanation 1 (SP-A1) were extracted from the output data of the Pentacam HR and Corvis ST, in addition to the Stress-Strain Index (SSI), which was derived based on the algorithm by Eliasy *et al*.20 The SSI was developed as an estimate of the in vivo material stiffness of the cornea,20 and can potentially detect biomechanical deterioration with keratoconus progression in individual patients, or improvements in biomechanics following corneal collagen cross-linking. Although not intended as a tool to differentiate between normal and keratoconic, or keratoconus suspect corneas, its ability to serve this function was assessed in this study.

All data were analyzed using the Statistical Package for Social Sciences (SPSS) software (version 24.0, IBM SPSS, inc., Chicago, IL), and MedCalc statistical software (version 19.2.0, MedCal, Ostend, Belgium). The area under the receiver operator characteristic (AUROC) curve was determined for the parameters of interest, namely the CBI, TBI, SP-A1 and SSI. The optimal cut-off value of each, along with their sensitivities and specificities was also determined. A comparison of the AUROC curves of the different parameters was done using DeLong’s method.27 A *p*-value of less than 0.05 was considered to be statistically significant.

**RESULTS**

A total of 34% of the group of fellow eyes were females, while 44% of the normal controls were males. Mean age of the group of fellow eyes was 31.04 years, whereas the mean age of the normal control group was 28.55 years (*p*=0.11). Of the 47 fellow eyes included, 24 eyes were classified as TNF, and 23 eyes were classified as TBF. Table 1 shows the average values of the classification parameters for the TNF and TBF groups.

Figure 1 shows the distributions of the CBI, TBI, SP-A1 and SSI for the different groups. The greatest degree of overlap between normal controls and the three study groups was seen with the SSI, while the TBI showed the least overlap, followed by the SP-A1. ROC curve analysis was conducted for each parameter (Table 2 and Figure 2).

For distinguishing between normal control eyes and all fellow eyes, between normal control eyes and TNF eyes, and between normal control eyes and TBF eyes, the TBI had the greatest AUROC curve, followed closely by SP-A1, and then the CBI. The AUROC curve of the TBI was statistically significantly different than that of the CBI in each comparison, and was not statistically significantly different than the AUROC curve of the SP-A1 in any comparison (Table 3).

In all comparisons, the AUROC curve of the SSI, which was not developed as a diagnostic tool, was not significantly different from 0.5, indicating that it did not adequately distinguish between normal and keratoconus suspect eyes. In addition, the AUROC curve of the CBI was not significantly different than 0.5 for distinguishing between normal control and TNF eyes (Table 2).

Predictably, the discriminative power of each of the CBI, TBI and SP-A1 was less in the TNF group than the TBF group, as evidenced by smaller AUROC curves, sensitivities, and specificities (Table 2), but with a significant difference in AUROC curves between the two groups, for only the CBI and TBI (Table 3). However, the optimal cut-off value for each parameter was similar for both groups, but with different sensitivities and specificities.

The TBI had the greatest positive predictive value for both TNF and TBF eyes, followed by the CBI, and SP-A1. Additionally, the TBI had the best negative predictive value for both TNF and TBF eyes, followed by the CBI for TBF eyes and the SP-A1 for TNF eyes (Table 2).

**DISCUSSION**

Given the uncommon finding of keratectasia in one eye with a topographically and tomographically normal fellow eye, this study included a relatively large sample of keratoconus suspects. The results of our study demonstrate that corneal biomechanical parameters, particularly the TBI and SP-A1, can be useful in distinguishing between normal corneas and keratoconus suspects. However, their diagnostic utility is reduced with suspect eyes that fulfill stricter criteria that define a normal cornea.

The TBI demonstrated the best discriminative ability in all three comparisons of normal controls versus all fellow eyes, normal controls versus Topographically/Tomographically Normal Fellow (TNF) eyes, and normal controls versus Topographically/Tomographically Borderline Fellow (TBF) eyes. This is in agreement with the results of other studies10,13–16,18,19 showing the superiority of the TBI’s discriminatory power over other biomechanical measures and indices. These studies have reported AUROC curves for the TBI ranging from 0.732 to 0.985,10,13–16,18,19 as well as a variety of cut-off values, with different sensitivities and specificities. The original study detailing the development of the TBI by Ambrósio et al., found that an optimized cut-off of 0.29 had a sensitivity of 90.4% and a specificity of 96.0%, for distinguishing the topographically normal eyes of patients with asymmetric ectasia, from normal control eyes.10 However, other studies with stricter criteria of topographically and tomographically normal fellow eyes in patients with asymmetric ectasia, demonstrated lower sensitivities and specificities.13,14,16 Similar to our TNF group, Koc *et al.* classified eyes as “subclinical keratoconus”16 if they were the fellow eyes of patients with frank keratoconus, and had no suspicious topographic, topometric, or tomographic findings, in addition to fulfilling several objective criteria, including a normal BAD-D. ﻿Under these conditions, the AUROC curve of the TBI was 0.790, with an optimal cut-off of 0.29, and a sensitivity and specificity of 67.0% and 86.0%, respectively.16 This lower discriminatory ability with stricter criteria was also demonstrated in our study, which included a greater number of patients, with an optimal TBI cut-off of 0.27 for TNF eyes, and a sensitivity and specificity of 54.2% and 96.0%, respectively. While the cut-off of 0.27 for TBF eyes was identical to that of TNF eyes, the sensitivity of 91.3% was much higher, with a very similar specificity of 95.0%. Such a lower diagnostic power is to be expected, since the TBI incorporates multiple topographic and tomographic parameters, some of which are borderline in the TBF group, but normal in the TNF group.

Of the parameters assessed in our study, the SP-A1 displayed the next best discriminative ability, following the TBI. The SP-A1 has been shown to be significantly different between normal corneas, and those with keratoconus,9,11with smaller values indicating a more abnormal result. However, to the best of our knowledge, only one study, by Kataria *et al.*, has assessed the discriminatory power of the SP-A1 between normal control corneas and seemingly normal corneas of patients with very asymmetric ectasia. The result of their analysis of normal control corneas versus topographically normal fellow corneas showed an AUROC curve of 0.762, with a cut-off of 93.74, sensitivity of 66.0% and specificity of 83.0%, while the analysis of normal control corneas versus topographically and tomographically normal fellow corneas showed an AUROC curve of 0.655, with a cut-off of 93.61, sensitivity of 48.0% and specificity of 83.0%.13 This is similar to our cut-offs of 91.99 for TBF eyes, and 92.34 for TNF eyes, however with greater AUROC curves of 0.833 and 0.822, respectively. Interestingly, the diagnostic power of the SP-A1 did not differ significantly between the TNF and TBF groups. This suggests that even very normal suspect eyes can have underlying biomechanical weakness, and more severe disease manifests as morphologic changes in topography and tomography. However, given the low positive predictive value of the SP-A1 (Table 2), an abnormal SP-A1 should not independently be interpreted as a marker of increased susceptibility for ectasia. In addition to differences in topographic and tomographic selection criteria, differences in the age of included patients may also explain the variation in the results of different studies. This is due to the fact that corneal stiffness increases with age,28 and thus impacts corneal biomechanical parameters and indices.

Stricter criteria for a normal keratoconus suspect cornea also resulted in a diminished discriminative ability of the CBI. Several studies have been conducted to assess the ability of the CBI to distinguish normal control corneas from apparently normal corneas of patients with asymmetric ectasia, and have generated a range of results, with cut-off values ranging from 0.01 to 0.515.10,13–15,17,19 Studies with more rigid criteria for patient selection have reported lower AUROC curves ranging from 0.615 to 0.704,13,14,16 with lower sensitivities and specificities than those that employed less rigid criteria, which had AUROC curves ranging from 0.660 to 0.822.10,13–15,17,19 Similarly, our results showed AUROC curves of 0.822 and 0.550 in the TBF and TNF groups, respectively. The CBI was initially developed to differentiate between normal corneas, and those with keratoconus, rather than keratoconus suspect eyes. For that purpose, Vinciguerra *et al.* found that a cut-off of 0.5 had a sensitivity of 94.1% and specificity of 100%.9 It was then tested on the topographically normal eyes of patients with very asymmetric ectasia, and was found to have an AUROC curve of 0.822, with an optimal cut-off of 0.07, sensitivity of 68.1% and specificity of 82.3%.10 With our more rigid criteria of topographically and tomographically normal TNF corneas, the optimal CBI cut-off had a sensitivity of 29.2%, which was lower than that of the SP-A1 and TBI, with almost the same specificity. Interestingly, although the SP-A1 is integrated into the CBI, our study showed that the discriminative power of the CBI was not superior to that of the SP-A1. Similarly, Kataria *et al.* did not demonstrate the superiority of the CBI over the SP-A1, reporting similar AUROC curves of 0.655 and 0.678 for the SP-A1 and CBI, respectively, with comparable sensitivities and specificities, for the discrimination between normal and subclinical keratoconus corneas with normal tomographies.13 This could be explained by the way in which the CBI has been formulated, using logistic regression. The incorporation of a tomographic parameter, Ambrósio’s Relational Thickness to the horizontal profile (ARTh), to the CBI increases its ability to discriminate between normal corneas and keratoconic corneas, which is what the CBI was initially developed to do. However, this may serve to decrease the discriminative power of the CBI in keratoconus suspect corneas with normal tomography, and dilute the power of other integrated parameters, such as the SP-A1, as more weight may have been allocated to ARTh than other biomechanical parameters in the initial development of the index. This also explains the gap in the performance of the CBI and SP-A1 in the TNF group, but not the TBF group, which is topographically and tomographically more abnormal, but not necessarily biomechanically weaker. Additionally, such a finding highlights our limited understanding of corneal biomechanics, since we would expect more abnormal corneas to be biomechanically weaker.

The SSI was developed as a measure of in vivo corneal biomechanical behavior, in particular the material stiffness of the cornea, independent of corneal thickness and intraocular pressure.20 It was suggested that it may possibly increase the sensitivities and specificities of the CBI and TBI. In addition, an increase in SSI following corneal collagen cross-linking has been demonstrated,29 indicating success of the procedure. The material stiffness of corneal tissue has been shown to vary considerably, even for people of the same age.30 Therefore, a single SSI value for a particular eye cannot be taken as an indicator of disease status, unless the SSI is very high (more than 1.5) or very low (less than 0.5).20 As such, the SSI was not intended as a diagnostic marker to differentiate between normal and ectatic corneas, and our study demonstrated that it does not serve this function. However, the SSI could be useful in indicating keratoconus progression for individual patients, in which case values are expected to decrease.

The rationale behind the use of corneal biomechanical properties for the detection of corneas at risk for the development of ectasia is that a biomechanical abnormality is believed to precede morphologic changes. It has been shown that this abnormality is initially focal in nature,6 and is proposed to lead to a cycle of corneal biomechanical decompensation, resulting in corneal thinning, and increased curvature.7 However, while there is a general consensus that keratoconus is a bilateral disease,5 ectasia due to other factors, such as a pure mechanical insult that leads to ectasia without an underlying susceptibility, may be unilateral in nature. As such, perhaps some of the eyes labeled as keratoconus suspects in our study, are in fact normal corneas, and this is a limitation of our study. This limitation, if true, restricts the diagnostic abilities of the parameters and indices studied, and would result in an underestimation of their AUROC curves, sensitivities and specificities.

The TBI, as well as the purely biomechanically derived SP-A1, were of moderate utility in distinguishing between normal eyes and keratoconus suspect eyes deemed normal based on strict tomographic criteria. While useful, in the absence of topographic and/or tomographic evidence of keratectasia, an independently abnormal biomechanical parameter does not strongly suggest a significantly increased risk of ectasia. In the near future, improvement in corneal biomechanical assessment, such as the detection of very early focal abnormalities, might ultimately improve the detection of corneas at risk for developing ectasia.

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**FIGURE CAPTIONS**

**Figure 1.** Box-and-dot plots showing the distribution of the **A.** CBI, **B.** TBI, **C.** SP-A1, and **D.** SSI for the groups of normal controls, TNF eyes, TBF eyes, and all fellow eyes (all keratoconus suspect eyes). CBI=Corvis Biomechanical Index; TBI=Tomographic and Biomechanical Index; SP-A1=Stiffness Parameter at Applanation 1; TBF=Topographically/Tomographically Borderline Fellow; TNF=Topographically/Tomographically Normal Fellow.

**Figure 2**. Receiver Operating Characteristic Curves of the CBI, TBI, SP-A1, and SSI for comparisons of **A.** Normal controls versus all fellow eyes (all keratoconus suspect eyes), **B.** Normal controls versus TNF eyes, and **C.** Normal controls versus TBF eyes. CBI=Corvis Biomechanical Index; TBI=Tomographic and Biomechanical Index; SP-A1=Stiffness Parameter at Applanation 1; TBF=Topographically/Tomographically Borderline Fellow; TNF=Topographically/Tomographically Normal Fellow.