**Keratoconus: A biomechanical perspective**

**Abstract**

**Background & purpose:**

The relevance of corneal biomechanics and the importance of including it in the clinical assessment of corneal ectasias are being increasingly recognized. The connection between corneal ultrastructure, biomechanical properties and optical function is exemplified by a condition like keratoconus. Biomechanical instability is seen as the underlying basis for the secondary morphological changes in the cornea. Asymmetric biomechanical weakening is believed to drive progressive corneal steepening and thinning. Biomechanical strengthening is the principle of collagen crosslinking that has been shown to effectively arrest progression of the keratoconus. Corneal biomechanics has therefore ignited the interest of researchers and clinicians alike and has given us new insights into the cause and course of the disease.

This article is an overview of the extensive work published, predominantly in the last two decades, on the biomechanical aspect of keratoconus.

**Method:**

Published articles on corneal biomechanics in the specific context of keratoconus were reviewed, based on an electronic search using PubMed, Elsevier, Science Direct. The search terms used included “Corneal Biomechanics”, “Mechanical properties of the cornea”, “Corneal ultrastructure”, “Corneal Collagen” and “Keratoconus”. Articles pertaining to refractive surgery, keratoplasty, collagen crosslinking or intrastromal rings were excluded.

**Result:**

The electronic search revealed more than 500 articles, from which 80 were chosen for this article

**Conclusion:**

The structural and organizational pattern of the corneal stroma determine its mechanical properties and are responsible for the maintenance of the normal shape and function of the cornea. Changes in the ultrastructure are responsible for the biomechanical instability that leads to corneal ectasia. As non-invasive methods for evaluating corneal biomechanics in vivo evolve, our ability to diagnose subclinical keratoconus will improve, allowing identification of patients at risk to develop ectasia and to allow early treatment to arrest progression of the disease.

**Introduction**

The cornea has multiple functions: protecting the inner contents of the eye, remaining transparent to permit the entry of light and maintaining a shape that provides about two thirds of the refractive power of the eye1. There is evidence to suggest that these functions are interlinked and that there are intimate connections that exist between ultra-structural architecture, biomechanical behavior, geometric shape and optical function of the cornea2. Keratoconus is a classic example of a disease that bears out the importance of these connections when ultra-structural alterations are associated with biomechanical instability that lead to deformation of shape, resulting in optical distortions. The relevance of corneal biomechanics in keratoconus is being increasingly recognized – in understanding the pathogenesis and course of the disease, in early diagnosis and in leveraging its role for arresting its progression. This has resulted in a sizeable volume of published work in this field. This article attempts to collate and summarize the essence of those articles, and thus present keratoconus from a biomechanical perspective.

**Methods:**

A review was performed using electronic databases including PubMed, Elsevier, Science Direct. The search terms used included “Corneal biomechanics”, “Corneal Ultrastructure”, “Corneal Collagen” “Mechanical properties of the Cornea”, “Keratoconus”. Articles were screened for relevance and significance before being chosen for citation. Other references, cited by the authors of selected articles were also included, if found relevant. Laboratory, animal studies and human clinical studies were all included. Articles on corneal biomechanics related to collagen crosslinking, intrastromal rings, contact lenses and those related to refractive surgery or keratoplasty were excluded.

**Results & Discussion:**

The cornea is a multi-layered tissue, each layer being ultra-structurally and compositionally different and hence each layer possessing distinct mechanical properties. The term “mechanical properties” applies, in the broad sense of the term, to describe how a tissue responds to an applied force2. In the context of the cornea, it is usually used to describe the resistance to deformation and, as will be evident in the course of the review, refers to the viscoelastic properties of the cornea under specified conditions of stress.

**Ultrastructure of the normal cornea and its influence on corneal biomechanics:**

The mechanical properties of the cornea are dominated by the stroma, which constitutes over 90% of its thickness3. The stroma is primarily made of collagen fibrils organized into larger fibres or lamellae. The arrangement of corneal lamellae across the corneal stroma is not isotropic4.The anterior layers have a lamellar density that is about 50% greater than those in the deep layers5. They frequently branch and interweave, running at oblique angles relative to Bowman’s layer 6,7 in a construction that is thought to be important for the maintenance of normal corneal curvature8. Bow spring fibers that extend from Bowman’s layer and intertwine with deeper fibres have been described in the anterior stroma7,9. The posterior fibril layers are stacked like sheets of paper, mostly oriented orthogonally in a superior–inferior and temporal – nasal direction, possibly to withstand the forces of the extraocular muscles4,10. At the limbus, the collagen fibrils are more in number and appear to pursue a circumferential course4. Tangentially arranged collagen fibres co-localize with mature elastic fibres in an arrangement that is believed to maintain corneal shape and resist the increased circumferential tension at the limbus11. The region with the least concentration of collagen fibrils is found to be the transition zone between the central region (with orthogonal fibrils) and the limbal region (with circumferential fibrils) 12.

Collagen lamellae are embedded in a ground substance consisting of proteoglycans attached to glycosaminoglycans and bind to collagen fibrils at specific axial sites13. The anterior and posterior stromal layers show compositional differences in the proteoglycans, elastics, laminins etc 2.

The corneal stroma is thus an inhomogeneous tissue and correspondingly, its mechanical properties are heterogeneous as well. The collagen fibrils are the principal load bearing components that provide tensile strength and stiffness to the cornea. The lamella are ‘glued’ together by their interweaving anastomosis and by their molecular binding with proteoglycans2,7 . This interlamellar adhesion gives the cornea a cohesive stiffness to withstand shearing forces and is denoted by a shear modulus. Both the tensile strength and the cohesive shear modulus show depth-dependent variations, being significantly more in the anterior third of the cornea (where collagen lamellae are more interwoven), compared to the posterior two thirds2,7,14,15. Measurements of Youngs modulus (a measure of tangential stiffness) have also shown that the cornea is radially stronger in the centre and circumferentially stronger at the limbus16.

**Ultra structural and compositional changes in keratoconus and their biomechanical implications:**

Several structural and compositional changes have been documented in the keratoconic cornea. An increase in the activity of proteolytic enzymes along with a decrease in inhibitors of proteolytic enzymes causes collagenolysis, loss of keratocytes and reduced crosslinks 18,19,20, all of which could explain the corneal weakening and thinning in the keratoconic area of pathology 21. The collagen network in this area is described as being grossly unorganized 22,23, with a disruption of the preferential orthogonal arrangement, altered from 900 & 1800  to 600&1200 24, with evidence of lamellar slippage in the region of the cone23. The branching point density (BPD) of collagen fibres has been previously described as a metric for quantifying cell interconnectivity and was thought to be related to the elastic modulus7. A corresponding significant reduction in the volume of proteoglycans between collagen fibrils and a reduction in keratocytes 25 could contribute to a weakening of the interfibrillar adhesion and thus reduce the shear modulus.

In an insightful description of the likely cascade of events that lead to the observed shape changes in keratoconus, Roberts CJ and Dupps WJ 26 hypothesized that a focal reduction in elastic modulus of the stromal collagen initiates a cycle of biomechanical decompensation. The intraocular pressure acting on a cornea with a focal weakening, causes this area to stretch and thin out as it redistributes the stress in a compensatory fashion by increasing curvature. This results in further thinning, further modulation of stress distribution, setting up a cascading effect. The authors go on to explain how this cascade can be intercepted by therapeutic measures like implantation of intrastromal corneal ring segments which redistribute the stress more favorably or by collagen crosslinking which modifies the biomechanical properties of the corneal stroma.

Clinical studies have indeed confirmed that the cornea in keratoconus is softer than normal, although the sample size, enrollment criteria, devices used and parameters measured vary significantly among these studies.27-31 Likewise, simulations in finite element modelling have been able to represent a keratoconus phenotype by reducing the stiffness of the cornea. Carvalho et al32 used this approach to show that changes in local material properties of the cornea and intraocular pressure were intimately related to the pathogenesis of keratoconus. Gefen et al33 studied the effect of degraded global and local mechanical properties, tissue thinning and a combination of both on tissue displacement at the cone center. The authors showed that a combination of tissue thinning and degraded mechanical properties had the greatest effect and was probably involved in the pathogenesis of keratoconus.

The hypothesis of Roberts CJ and Dupps WJ26 at once explains not only the biomechanical roots of keratoconus but also how the sequence of events causes progression of the disease. A whole eye finite element model, using corneal tomographic data from clinical cases, demonstrated changes consistent with this hypothesis.34

Search for the possible cause for the focal biomechanical instability has invited several explanations. Meek et al23 proposed one or both of the following mechanisms: (a) a tissue degradation due to upregulation of proteases as demonstrated by Kenney et al35 and (b) slippage between collagen fibrils with no overall tissue loss.

Recognizing eye rubbing to be a major risk factor for Keratoconus, McMonnies CW36 proposed several ways by which biomechanical weakening could occur: (a) the indentation from eye rubbing and the associated surface forces, subjecting the collagen fibrils to shearing, compression and torsional forces, (b) the increased hydrostatic pressure from IOP spikes, especially when they occur frequently and/or chronically, (c) keratocyte loss due to corneal trauma and increased reactive oxygen species, which results in decreased fibrillogenesis and reduced proteoglycans, (d) impaired interlamellar adhesion allowing slippage of collagen fibrils and (e) decreased viscosity of the ground substance in response to the shear stress.

**Clinical measurement of Corneal Biomechanical properties:**

Measurement of corneal biomechanics is complicated by its very nature. The mechanical properties of the cornea are non-linear, viscoelastic and anisometric in nature, dependent on the complex, non-homogenous microstructure of the cornea40 and influenced by intraocular pressure of the eye and corneal geometry.41 Although laboratory methods like strip extensiometry and inflation technique have been used to study the material properties of cadaveric corneas, the challenge has been to develop non-destructive, non-invasive test tools which can be used in a clinical setting.40,42 That challenge was addressed by two clinical devices: the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments Inc. Buffalo, NY) and the Corvis – ST (Oculus, Wetzlar, Germany), which are currently available.

The Ocular Response Analyzer (ORA) utilizes a high speed air puff to quantify the dynamics of corneal deformation and recovery, which are then used to derive a corneal hysteresis factor (CH, a measure of corneal viscoelasticity) and a corneal resistance factor (CRF) that indicates the cornea’s overall elastic resistance.43 Although both parameters have been shown to be lower in keratoconus they have neither been found reliable in separating normal eyes from keratoconus or Forme fruste keratoconus44, nor have they reflected changes induced by collagen crosslinking.45 Newer waveform derived parameters are seen as being more sensitive,46 buttheir clinical applications await further evaluation.

The Corvis ST is a more recent, non-contact tonometer that employs a Scheimpflug camera to record and analyze dynamic changes as corneal deformation occurs in response to an air-puff. Numerous parameters are measured and have been studied, with no consensus, however, on any single parameter with sufficient discriminative power to detect keratoconus especially in its subclinical form.47

A major limitation of all the individual parameters from both devices, the ORA and the Corvis ST, is that they are vulnerable to the confounding effects of IOP, pachymetry and age.48

Using linear regression analysis and combining selected dynamic corneal response parameters from the Corvis ST with corneal horizontal thickness profile and the stiffness parameter (SPA1), the Corvis Biomechanical Index (CBI) was introduced to improve the predictive accuracy of the device.49

Later, using artificial intelligence to a combination of data derived from Scheimpflug-based tomography and Corvis-based biomechanical parameters, Ambrosio et al introduced the Tomographic and Biomechanical Index (TB1) which surpassed all other known parameters in its accuracy for detecting ectasia50

Atomic force microscopy57 and, more recently, acoustic radiation force elastic microscopy (ARFEM)52 have been used in cadaver corneas to measure elasticity at various points and found through-thickness and radial variations. These techniques, however, are not suited for in-vivo applications.

Optical coherence elastography (OCE) has been successfully used in vivo, but is not yet widely available.53 Recent studies using OCE on live keratoconus subjects, demonstrated for the first time direct evidence of a preferentially weakened anterior stroma that correlated with known microstructural changes.54

Brillouin microscopy is yet another imaging technique with potential clinical application to characterize the 3-D mechanical properties of the cornea.55,56 Ex-vivo models have demonstrated a mathematical relationship between the longitudinal modulus derived from the frequency shift measured by Brillouin microscopy and the shear modulus calculated from rheometry.57 Brillouin elasticity maps of keratoconus point to the development of diagnostic metrics based on spatially resolved biomechanical measurements.58 However their long acquisition time makes clinical translation difficult.

Phase decorrelation OCT (PhD-OCT), another non-invasive non-purturbatory OCT-based imaging device was recently described by Blackburn BJ et al.59 Pilot human studies demonstrate possible clinical feasibility and seem to indicate a potential role in being able to generate 3-D spatial properties of the cornea in vivo.

It is important to note that each device or test method is based on different principles, has its own method for measurement, and analyzes data with proprietary algorithms, which together make it impossible to make comparisons with each other. It must also be borne in mind that most of the in-vivo devices do not directly provide traditional intrinsic mechanical properties of the cornea, but rather, project their analyzed data in terms of parameters which, at best, are indicative of corneal response to the force applied under specific circumstances. The dependence of measured outputs of these devices on the conditions of the measurement, on the differences among the devices themselves, on the variables that influence corneal behavior (e. IOP, hydration, age), may explain the wide range of reported values.60-62

**Clinical application of Corneal Biomechanics in Keratoconus:**

The significant role of measuring corneal biomechanical properties in keratoconus is being increasingly recognized. Although advances in corneal tomography have remarkably increased the diagnostic accuracy of corneal ectasia 63,64, the detection of subclinical keratoconus remains a challenge. The hypothesis proposed by Roberts and Dupps26 strengthened by finite element computational models and confirmed by Brillouin microscopy65 suggests that a “biomechanical stage” of the disease precedes topographic and tomographic changes49. The combination of tomographic and biomechanical data was shown to perform better than either set of data alone in detecting subclinical ectasia66,67. Among all the analyzed parameters, the TB1 was found to have the highest discriminative accuracy in detecting subclinical keratoconus among eyes with normal topography in patients whose fellow eyes had frank ectasia50. The TB1 in this group of VAE-NT (very asymmetric ectasia with normal topography) eyes, showed an AUROC (area under receiver operating characteristic curve) of 0.985 and provided a sensitivity of 90.4% and a specificity of 96% when a cut off value of 0.29 was applied50. Several other studies have corroborated the efficiency of TB1 to be superior to other parameters 68-71. Additionally, Kataria et al68 also showed that among the parameters tested, the TB1 was least influenced by the confounding effect of IOP, keratometry and corneal thickness.

Against the backdrop of our current understanding of the disease, the classification and grading system for keratoconus has not found a universally accepted platform, as noted by the “Global consensus on keratoconus and ectatic corneal diseases”.72 Koh et al73 demonstrated significant correlations between tomographic and biomechanical indices, particularly with CBI beta, a linear transformation of CBI, suggesting that it could be an additional factor to be included in grading severity of keratoconus. Flockerzi et al74 further modified the CBI beta into a Corvis Biomechanical Factor (CBiF) to provide a measure for different stages of biomechanical destabilization and established a link between the ABCD keratoconus classification75 and corneal biomechanics by adding a grading parameter ‘E’ to augment the ABCD classification.

Another novel parameter was recently introduced by Eliasy etal76 called the Stress-Strain Index (SSI). It is based on an algorithm derived numerically using finite element models, which was subsequently validated on clinical datasets. The SSI was intended to estimate the whole stress-strain behavior of corneal tissue, and hence the elastic modulus at any stress or IOP level. As expected, this parameter showed no significant correlation with IOP or corneal thickness. The validation of this or other newer parameters to track progression of the disease is still awaited.

Roberts CJ and Dupps WJ26 proposed that the initial biomechanical modification in keratoconus was focal in nature rather than a uniform global softening. This explains why the ORA and Corvis ST, which analyze bulk corneal behavior, often show an overlap between normal and keratoconic eyes reducing the sensitivity of their parameters to detect corneas at risk for ectasia following refractive surgery.77,78 Also, these devices are not spatially sensitive and only study surface deformation but do not characterize the internal corneal biomechanical behavior.79 The ability to map the stress distribution within the cornea and to detect the spatial location of focal weakening would allow keratoconus to be diagnosed before shape changes deformed the optical surface of the cornea.

Recently a numerical approach using inverse finite element analysis of simulated models of keratoconic cornea was applied to determine the regional variation of SSI across the corneal surface. A single SSI value obtained from the Covis ST was translated into a map by adding geometric information and relying on the close correlation between collagen fibrillar distribution and material stiffness.80 Validation of the SSI maps in following up progression of KC is currently awaited.

The ability to detect and map spatial changes in biomechanical properties in the future will allow not only early detection of the incipient pre-tomographic stage of ectasia, but will also pave the way for customized collagen crosslinking that will arrest further deterioration of shape and hence optical distortion for the patient.

**Conclusion:**

The study of ocular biomechanics continues to evolve, giving us useful insights into corneal behavior in health and disease. Combining a deeper understanding of the mechanopathological contours of diseases like corneal ectasias with refinements in measurement of its tomographic details and biomechanical properties and exploiting the potential of computational modeling, our approach to management of such diseases promises to become more accurate, targeted and rational.

**References:**

1. Meek KM, Knupp C. Corneal structure and transparency. Prog Retin Eye Res. 2015 Nov;49:1-16.
2. Blackburn BJ, Jenkins MW, Rollins AM, Dupps WJ. A Review of Structural and Biomechanical Changes in the Cornea in Aging, Disease, and Photochemical Crosslinking. Front Bioeng Biotechnol. 2019 Mar 29;7:66.
3. Winkler M, Shoa G, Xie Y, Petsche SJ, Pinsky PM, Juhasz T, Brown DJ, Jester JV. Three-dimensional distribution of transverse collagen fibers in the anterior human corneal stroma. Invest Ophthalmol Vis Sci. 2013 Nov 5;54(12):7293-301
4. Meek KM. Corneal collagen-its role in maintaining corneal shape and transparency. Biophys Rev. 2009 Jul;1(2):83-93.
5. Bergmanson JP, Horne J, Doughty MJ, Garcia M, Gondo M. Assessment of the number of lamellae in the central region of the normal human corneal stroma at the resolution of the transmission electron microscope. Eye Contact Lens. 2005 Nov;31(6):281-7
6. Mikula E, Winkler M, Juhasz T, Brown DJ, Shoa G, Tran S, Kenney MC, Jester JV. Axial mechanical and structural characterization of keratoconus corneas. Exp Eye Res. 2018 Oct;175:14-19.
7. Winkler M, Chai D, Kriling S, Nien CJ, Brown DJ, Jester B, Juhasz T, Jester JV. Nonlinear optical macroscopic assessment of 3-D corneal collagen organization and axial biomechanics. Invest Ophthalmol Vis Sci. 2011 Nov 11;52(12):8818-27.
8. Müller LJ, Pels E, Vrensen GF. The specific architecture of the anterior stroma accounts for maintenance of corneal curvature. Br J Ophthalmol. 2001 Apr;85(4):437-43
9. Morishige N, Takagi Y, Chikama T, Takahara A, Nishida T. Three-dimensional analysis of collagen lamellae in the anterior stroma of the human cornea visualized by second harmonic generation imaging microscopy. Invest Ophthalmol Vis Sci. 2011 Feb 16;52(2):911-5.
10. Abass A, Hayes S, White N, Sorensen T, Meek KM. Transverse depth-dependent changes in corneal collagen lamellar orientation and distribution. J R Soc Interface. 2015 Mar 6;12(104):20140717.
11. Meek KM, Boote C. The use of X-ray scattering techniques to quantify the orientation and distribution of collagen in the corneal stroma. Prog Retin Eye Res. 2009 Sep;28(5):369-92.
12. Whitford C, Studer H, Boote C, Meek KM, Elsheikh A. Biomechanical model of the human cornea: considering shear stiffness and regional variation of collagen anisotropy and density. J Mech Behav Biomed Mater. 2015 Feb;42:76-87
13. Meek KM, Blamires T, Elliott GF, Gyi TJ, Nave C. The organisation of collagen fibrils in the human corneal stroma: a synchrotron X-ray diffraction study. Curr Eye Res. 1987 Jul;6(7):841-6
14. Smolek MK. Interlamellar cohesive strength in the vertical meridian of human eye bank corneas. Invest Ophthalmol Vis Sci. 1993 Sep;34(10):2962-69.
15. Petsche SJ, Chernyak D, Martiz J, Levenston ME, Pinsky PM. Depth-dependent transverse shear properties of the human corneal stroma. Invest Ophthalmol Vis Sci. 2012 Feb 21;53(2):873-80.
16. Hjortdal JO. Regional elastic performance of the human cornea. J Biomech. 1996 Jul;29(7):931-42.
17. Vellara HR, Patel DV. Biomechanical properties of the keratoconic cornea: a review. Clin Exp Optom. 2015 Jan;98(1):31-8
18. Shetty R, Sathyanarayanamoorthy A, Ramachandra RA, Arora V, Ghosh A, Srivatsa PR, Pahuja N, Nuijts RM, Sinha-Roy A, Mohan RR, Ghosh A. Attenuation of lysyl oxidase and collagen gene expression in keratoconus patient corneal epithelium corresponds to disease severity. Mol Vis. 2015 Jan 12;21:12-25.
19. Zhou L, Sawaguchi S, Twining SS, Sugar J, Feder RS, Yue BY. Expression of degradative enzymes and protease inhibitors in corneas with keratoconus. Invest Ophthalmol Vis Sci. 1998 Jun;39(7):1117-24
20. Kenney MC, Chwa M, Atilano SR, Tran A, Carballo M, Saghizadeh M, Vasiliou V, Adachi W, Brown DJ. Increased levels of catalase and cathepsin V/L2 but decreased TIMP-1 in keratoconus corneas: evidence that oxidative stress plays a role in this disorder. Invest Ophthalmol Vis Sci. 2005 Mar;46(3):823-32
21. Fullwood NJ, Tuft SJ, Malik NS, Meek KM, Ridgway AE, Harrison RJ. Synchrotron x-ray diffraction studies of keratoconus corneal stroma. Invest Ophthalmol Vis Sci. 1992 Apr;33(5):1734-41.
22. Akhtar S, Bron AJ, Salvi SM, Hawksworth NR, Tuft SJ, Meek KM. Ultrastructural analysis of collagen fibrils and proteoglycans in keratoconus. Acta Ophthalmol. 2008 Nov;86(7):764-72.
23. Meek KM, Tuft SJ, Huang Y, Gill PS, Hayes S, Newton RH, Bron AJ. Changes in collagen orientation and distribution in keratoconus corneas. Invest Ophthalmol Vis Sci. 2005 Jun;46(6):1948-956.
24. Daxer A, Fratzl P. Collagen fibril orientation in the human corneal stroma and its implication in keratoconus. Invest Ophthalmol Vis Sci. 1997 Jan;38(1):121-9.
25. Erie JC, Patel SV, McLaren JW, Nau CB, Hodge DO, Bourne WM. Keratocyte density in keratoconus. A confocal microscopy study(a). Am J Ophthalmol. 2002 Nov;134(5):689-95.
26. Roberts CJ, Dupps WJ Jr. Biomechanics of corneal ectasia and biomechanical treatments. J Cataract Refract Surg. 2014 Jun;40(6):991-98.
27. Yenerel NM, Kucumen RB, Gorgun E. Changes in corneal biomechanics in patients with keratoconus after penetrating keratoplasty. Cornea. 2010 Nov;29(11):1247-251.
28. Johnson RD, Nguyen MT, Lee N, Hamilton DR. Corneal biomechanical properties in normal, forme fruste keratoconus, and manifest keratoconus after statistical correction for potentially confounding factors. Cornea. 2011 May;30(5):516-23.
29. Viswanathan D, Kumar NL, Males JJ, Graham SL. Relationship of Structural Characteristics to Biomechanical Profile in Normal, Keratoconic, and Crosslinked Eyes. Cornea. 2015 Jul;34(7):791-96.
30. Ambrósio R Jr, Caiado AL, Guerra FP, Louzada R, Sinha RA, Luz A, Dupps WJ, Belin MW. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. J Refract Surg. 2011 Oct;27(10):753-58.
31. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. Invest Ophthalmol Vis Sci. 2010 Nov;51(11):5546-555.
32. Carvalho LA, Prado M, Cunha RH, et al. Keratoconus prediction using a finite element model of the cornea with local biomechanical properties. Arq Bras Oftalmol 2009:72:139–45.
33. Gefen A,Shalom R, Elad D, Mandel Y. Biomechanical analysis of the keratoconic Cornea. J Mech Behav Biomed Mater. 2009;2(3):224-36.
34. Sinha Roy A, Dupps WJ Jr. Patient-specific modeling of corneal refractive surgery outcomes and inverse estimation of elastic property changes. J Biomech Eng. 2011 Jan;133(1):011002.
35. Kenny MC\* Brown DJ, Rajeev B. The elusive causes of keratoconus: a working hypothesis. CLAO J. 2000;26: 10-13. Am J Ophthalmol. 2000 Aug;130(2):263. PMID: 11004321.
36. McMonnies CW. Mechanisms of rubbing-related corneal trauma in keratoconus. Cornea. 2009 Jul;28(6):607-15.
37. Sinha Roy A, Dupps WJ Jr. Patient-specific computational modeling of keratoconus progression and differential responses to collagen cross-linking. Invest Ophthalmol Vis Sci. 2011 Nov 25;52(12):9174-87.
38. Scarcelli G, Besner S, Pineda R, Yun SH. Biomechanical characterization of keratoconus corneas ex vivo with Brillouin microscopy. Invest Ophthalmol Vis Sci. 2014 Jul 1;55(7):4490-495.
39. Zhou D, Abass A, Eliasy A, Studer HP, Movchan A, Movchan N, Elsheikh A. Microstructure-based numerical simulation of the mechanical behaviour of ocular tissue. J R Soc Interface. 2019 May 31;16(154):20180685.
40. Chong J, Dupps WJ Jr. Corneal biomechanics: Measurement and structural correlations. Exp Eye Res. 2021 Apr;205:108508. doi: 10.1016/j.exer.2021.108508.
41. Roberts CJ. Concepts and misconceptions in corneal biomechanics. J Cataract Refract Surg. 2014 Jun;40(6):862-69
42. De Stefano VS, Dupps WJ Jr. Biomechanical Diagnostics of the Cornea. Int Ophthalmol Clin. 2017 Summer;57(3):75-86.
43. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg. 2005 Jan;31(1):156-62.
44. Fontes BM, Ambrósio R Jr, Jardim D, Velarde GC, Nosé W. Corneal biomechanical metrics and anterior segment parameters in mild keratoconus. Ophthalmology. 2010 Apr;117(4):673-79.
45. Goldich Y, Marcovich AL, Barkana Y, Mandel Y, Hirsh A, Morad Y, Avni I, Zadok D. Clinical and corneal biomechanical changes after collagen cross-linking with riboflavin and UV irradiation in patients with progressive keratoconus: results after 2 years of follow-up. Cornea. 2012 Jun;31(6):609-14.
46. Ambrósio R, Faria-Correia F, Ramos I, Valbon BF, Lopes B, Jardim D, Luz A. Enhanced screening for ectasia susceptibility among refractive candidates: the role of corneal tomography and biomechanics. Current Ophthalmology Reports. 2013 Mar 1;1(1):28-38.
47. Moshirfar M, Motlagh MN, Murri MS, Momeni-Moghaddam H, Ronquillo YC, Hoopes PC. Advances in biomechanical parameters for screening of refractive surgery candidates: a review of the literature, part III. Medical Hypothesis, Discovery and Innovation in Ophthalmology. 2019;8(3):219.
48. Vinciguerra R, Elsheikh A, Roberts CJ, Ambrósio R Jr, Kang DS, Lopes BT, Morenghi E, Azzolini C, Vinciguerra P. Influence of Pachymetry and Intraocular Pressure on Dynamic Corneal Response Parameters in Healthy Patients. J Refract Surg. 2016 Aug 1;32(8):550-56.
49. Vinciguerra R, Ambrósio R Jr, Elsheikh A, Roberts CJ, Lopes B, Morenghi E, Azzolini C, Vinciguerra P.Detection of Keratoconus With a New Biomechanical Index. J Refract Surg. 2016 Dec 1;32(12):803-10.
50. Ambrósio R Jr, Lopes BT, Faria-Correia F, Salomão MQ, Bühren J, Roberts CJ, Elsheikh A, Vinciguerra R, Vinciguerra P. Integration of Scheimpflug-Based Corneal Tomography and Biomechanical Assessments for Enhancing Ectasia Detection. J Refract Surg. 2017 Jul 1;33(7):434-43.
51. Last JA, Thomasy SM, Croasdale CR, Russell P, Murphy CJ. Compliance profile of the human cornea as measured by atomic force microscopy. Micron. 2012 Dec;43(12):1293-298.
52. Mikula E, Hollman K, Chai D, Jester JV, Juhasz T. Measurement of corneal elasticity with an acoustic radiation force elasticity microscope. Ultrasound Med Biol. 2014 Jul;40(7):1671-679.
53. De Stefano VS, Ford MR, Seven I, Dupps WJ Jr. Live human assessment of depth-dependent corneal displacements with swept-source optical coherence elastography. PLoS One. 2018 Dec 28;13(12):e0209480.
54. Morishige N, Wahlert AJ, Kenney MC, Brown DJ, Kawamoto K, Chikama T, Nishida T, Jester JV. Second-harmonic imaging microscopy of normal human and keratoconus cornea. Invest Ophthalmol Vis Sci. 2007 Mar;48(3):1087-94.
55. Scarcelli G, Kling S, Quijano E, Pineda R, Marcos S, Yun SH. Brillouin microscopy of collagen crosslinking: noncontact depth-dependent analysis of corneal elastic modulus. Invest Ophthalmol Vis Sci. 2013 Feb 19;54(2):1418-425.
56. Scarcelli G, Yun SH. Brillouin microscopy. In: Roberts CJ, Dupps WJ, Downs JC (Eds). Biomechanics of the eye. Kugler Publication, Amsterdam, Netherlands. Pp 159-68.
57. Scarcelli G, Besner S, Pineda R, Kalout P, Yun SH. In vivo biomechanical mapping of normal and keratoconus corneas. JAMA Ophthalmol. 2015 Apr;133(4):480-82.
58. Shao P, Eltony AM, Seiler TG, Tavakol B, Pineda R, Koller T, Seiler T, Yun SH. Spatially-resolved Brillouin spectroscopy reveals biomechanical abnormalities in mild to advanced keratoconus in vivo. Sci Rep. 2019 May 16;9(1):7467.
59. Blackburn BJ, Gu S, Ford MR, de Stefano V, Jenkins MW, Dupps WJ Jr, Rollins AM. Noninvasive Assessment of Corneal Crosslinking With Phase-Decorrelation Optical Coherence Tomography. Invest Ophthalmol Vis Sci. 2019 Jan 2;60(1):41-51.
60. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J Cataract Refract Surg. 2005 Jan;31(1):146-55.
61. Elsheikh A, Wang D, Pye D. Determination of the modulus of elasticity of the human cornea. J Refract Surg. 2007 Oct;23(8):808-18.
62. Nash IS, Greene PR, Foster CS. Comparison of mechanical properties of keratoconus and normal corneas. Exp Eye Res. 1982 Nov;35(5):413-24.
63. Ambrósio R Jr, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. J Cataract Refract Surg. 2006 Nov;32(11):1851-9.
64. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. Invest Ophthalmol Vis Sci. 2010 Nov;51(11):5546-55.
65. Scarcelli G, Besner S, Pineda R, Yun SH. Biomechanical characterization of keratoconus corneas ex vivo with Brillouin microscopy. Invest Ophthalmol Vis Sci. 2014 Jun 17;55(7):4490-5.
66. Zhang X, Ding L, Sun L, Huang Y, Han T, Qian Y, Zhou X. Prognostic Nomograms Predicting Risk of Keratoconus in Very Asymmetric Ectasia: Combined Corneal Tomographic and Biomechanical Assessments. Front Bioeng Biotechnol. 2022 Feb 17;10:839545. doi: 10.3389/fbioe.2022.839545.
67. Luz A, Lopes B, Hallahan KM, Valbon B, Ramos I, Faria-Correia F, Schor P, Dupps WJ Jr, Ambrósio R Jr. Enhanced Combined Tomography and Biomechanics Data for Distinguishing Forme Fruste Keratoconus. J Refract Surg. 2016 Jul 1;32(7):479-94.
68. Kataria P, Padmanabhan P, Gopalakrishnan A, Padmanaban V, Mahadik S, Ambrósio R Jr. Accuracy of Scheimpflug-derived corneal biomechanical and tomographic indices for detecting subclinical and mild keratectasia in a South Asian population. J Cataract Refract Surg. 2019 Mar;45(3):328-36.
69. Sedaghat MR, Momeni-Moghaddam H, Ambrósio R Jr, Roberts CJ, Yekta AA, Danesh Z, Reisdorf S, Khabazkhoob M, Heidari HR, Sadeghi J. Long-term Evaluation of Corneal Biomechanical Properties After Corneal Cross-linking for Keratoconus: A 4-Year Longitudinal Study. J Refract Surg. 2018 Dec 1;34(12):849-856.

70 Guo LL, Tian L, Cao K, Li YX, Li N, Yang WQ, Jie Y. Comparison of the morphological and biomechanical characteristics of keratoconus, forme fruste keratoconus, and normal corneas. Semin Ophthalmol. 2021 Nov 17;36(8):671-678. doi: 10.1080/08820538.2021.1896752.

71. Salomão MQ, Hofling-Lima AL, Gomes Esporcatte LP, Lopes B, Vinciguerra R, Vinciguerra P, Bühren J, Sena N Jr, Luz Hilgert GS, Ambrósio R Jr. The Role of Corneal Biomechanics for the Evaluation of Ectasia Patients. Int J Environ Res Public Health. 2020 Mar 23;17(6):2113. doi: 10.3390/ijerph17062113.

72. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, Malecaze F, Nishida K, Sangwan VS; Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. Global consensus on keratoconus and ectatic diseases. Cornea. 2015 Apr;34(4):359-69.

1. Koh S, Inoue R, Maeda N, Kabata D, Shintani A, Jhanji V, Klyce SD, Maruyama K, Nishida K. Long-term Chronological Changes in Very Asymmetric Keratoconus. Cornea. 2019 May;38(5):605-611.
2. Flockerzi E, Vinciguerra R, Belin MW, Vinciguerra P, Ambrósio R Jr, Seitz B. Combined biomechanical and tomographic keratoconus staging: Adding a biomechanical parameter to the ABCD keratoconus staging system. Acta Ophthalmol. 2021 Oct 16. doi: 10.1111/aos.15044.
3. Belin MW, Duncan J, Ambrósio R Jr, 4 Gomes JA. A New Tomographic Method of Staging/. Classifying Keratoconus: The ABCD Grading System. Int J. Kerat Ect Cor Dis 2015;4(3):85-93
4. Eliasy A, Chen KJ, Vinciguerra R, Lopes BT, Abass A, Vinciguerra P, Ambrósio Jr R, Roberts CJ, Elsheikh A. Determination of corneal biomechanical behavior in-vivo for healthy eyes using CorVis ST tonometry: stress-strain index. Front Bioeng Biotech. 2019;7:105.
5. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg. 2005 Jan;31(1):156-62.
6. 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 May;51(5):2403-410.
7. De Stefano VS, Ford MR, Seven I, Dupps WJ Jr. Depth-Dependent Corneal Biomechanical Properties in Normal and Keratoconic Subjects by Optical Coherence Elastography. Transl Vis Sci Technol. 2020 Jun 3;9(7):4.
8. Zhang H, Eliasy A, Lopes B, Abass A, Vinciguerra R, Vinciguerra P, Ambrósio R Jr, Roberts CJ, Elsheikh A. Stress-Strain Index Map: A New Way to Represent Corneal Material Stiffness. Front Bioeng Biotechnol. 2021 Mar 11;9:640434. doi: 10.3389/fbioe.2021.640434. PMID: 33777912; PMCID: PMC7991572.