Corneal Biomechanics: A Paradigm shift in Studying Corneal Pathology
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Abstract
Biomechanics links corneal structure to its function. An area of intense research, corneal biomechanics can distinguish normal from ectatic corneas and has applications in various fields including cataract surgery, intraocular pressure measurement and glaucoma. It is also likely to serve as an important tool in the selection of suitable candidates for refractive surgery. This article reviews various methods of assessment of biomechanical properties of the cornea and its applications along with case examples to highlight the role it plays in clinical practice.

Keywords: biomechanics, ocular response analyzer, corvis ST, brillouin microscopy, finite element modelling

Introduction
The cornea possesses unique properties of mechanical stiffness, strength and toughness that enables it to withstand internal and external forces. Corneal biomechanics involves the study of deformation and equilibrium of corneal tissues with the application of these forces.1 Freidenwald was the first to describe the viscoelastic properties of the cornea in 1937, which were later elaborated by Nyquist and Woo.2,3 The cells, fibres and ground matrix of any tissue determine the mechanical properties.4 Biomechanics is the link between structure and function of the cornea and is now an area of intense focus in various fields of clinical ophthalmology. It will help us assess the pathological changes corneal tissue undergoes during different ocular and systemic conditions and predict the outcomes of therapeutic and refractive therapies.

Biomechanical Parameters
Till recently, corneal biomechanics could only be assessed in in vitro studies by measuring stress, strain and Young’s modulus in isolated corneas.1 In recent times, however new devices have been introduced which enable assessment of biomechanics in vivo in a clinical setting. Following are the commonly used biomechanical descriptors:5

| Term                  | Definition                                                                 |
|-----------------------|-----------------------------------------------------------------------------|
| Stress                | The force divided by the cross-sectional area of the applied stress          |
| Strain                | The magnitude of deformation in the direction of the applied stress          |
| Young’s Modulus       | The ratio of the stress and strain (the slope of the stress-strain curve) is called the Young’s modulus of the tissue. Higher the Young’s modulus, stiffer the tissue and hence lesser deformation and faster recovery. |
| Viscosity             | A time-dependent physical property that allows the cornea to deflect some input energy away from its elastic components and allows the cornea the possibility to reversibly or permanently change its elastic shape with time |
| Corneal hysteresis    | The portion of input energy dissipated during mechanical strain due to viscosity of the corneal tissue |

Evaluation of Corneal Biomechanics
The advent of tools to measure in vivo the biomechanics of cornea in different conditions has further advanced our knowledge of the structural and functional properties of cornea and its response to stress. The current commercially available devices include Ocular Response Analyzer, Corvis ST, Tonometry and Dynamic corneal imaging using Placido, Scheimpflug, or optical coherence tomography devices. There are more innovative tools for evaluation being used extensively in research but have not yet found their application in the clinics. These include Brillouin scattering spectroscopy, Surface wave elastometry, Supersonic shear imaging and electronic speckle pattern interferometry.

• Ocular Response Analyzer (ORA)
Ocular Response Analyzer (ORA) (Reichert Technologies, Depew, NY) analyses corneal response with a bidirectional applanation process induced by a customized air jet pressurizing the cornea which provides an indirect assessment of deformation in about 25 milliseconds (Figure 1).6 Corneal deformation is monitored by the infrared corneal reflex of an approximate diameter of 3 mm.

Measurements Produced by the ORA7 (Figure 2)
• IOPg: Goldmann Correlated IOP – Analogous to Goldmann Tonometry – Average of Applanation Pressure 1 (P1) and Pressure 2 (P2)
• IOPcc: Corneal Compensated IOP – Less affected by corneal thickness and properties – Empirically Determined Linear combination of P1 and P2
• CH: Corneal Hysteresis – Viscoelastic Response – Difference of P1 and P2; Normal value: 10.8 mm Hg +/- 1.5 mm Hg

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- CRF: Corneal Resistance Factor – Viscoelastic Response weighted for central corneal thickness – Empirically Determined Linear combination of P1 and P2. Normal value 11.0 mm Hg +/- 1.6 mm Hg.9
- CCT: Central corneal thickness

**Limitations of ORA:** Discrepancies from the expected results between CH and CRF have been observed. Only ORA waveform analysis is not adequate to analyze the cornea after cross-linking10,11 and biomechanical modeling is needed. Further exploration of the morphology of the ORA’s corneal signal (Bio-Corneagram Analysis), from which 38 new waveform-derived parameters have been developed, that might add to the robustness of this technique.

- **Oculus Corvis ST**
  Corvis ST (Oculus, Optikgerate, Germany) acquires Scheimpflug images of the cornea at 4300 frames per second with 8mm horizontal coverage while deforming it under a constant metered collimated air puff (Figure 3). Corneal deformation is influenced by IOP, thickness, and innate biomechanical properties.

**Measurements Produced by the Corvis ST (figure 4)**
- Time of applanation 1 (AT1): Time from the start until an air puff causes the corneal flattening (first applanation)
- Length of applanation 1 (AL1): Length of the flattened cornea in the first applanation
- Velocity of applanation 1 (AV1): Velocity of corneal deformation during the first applanation
- Deformation amplitude at the highest concavity (HCDA): Maximum deformation amplitude (from the start to the highest concavity) at the corneal apex
- Highest concavity time (HCT): Time to reach the maximum deformation amplitude
- Highest concavity peak distance (HCPD): Distance between the two-horizontal point where maximum deformation amplitude starts
- Highest concavity corneal radius (HCCR): Radius of curvature of the maximum deformation amplitude
- Time of applanation 2 (AT2): Time from the highest concavity until cornea restores its standard curvature
- Length of applanation 2 (AL2): Length of the flattened cornea in the second applanation
- Velocity of applanation 2 (AV2): Velocity of corneal deformation during the second applanation

**Limitations of Corvis ST:** Corvis ST records only 2-D cross-section images of the cornea. In disease (e.g. keratoconus) or treated (e.g. post-PRK) corneas, there may be lateral motion of the cornea, which may not be captured. IOP evaluation has been proven to be reliable and co-related well with ORA but comparison with Goldmann applanation tonometry (GAT) provides variable results.13 Also more standardized studies are required to confirm the results on corneas.
undergoing different kind of treatments.

- **Corneal Thickness Tests:** Tomography
  Tomography provides a complete view of the geometric structure of the cornea and allows an effective screening for ectatic diseases.\(^{14}\)

**Limitations:** A single tomography examination cannot determine when initial onset of injury occurred in the past, or if the changes will become progressive. Thus, misleading conclusions can be derived unless followed longitudinally to assess for further changes.

- **Tonometry**
  Goldmann applanation tonometry is influenced by corneal properties, including thickness, curvature, and Young’s Modulus.\(^{15}\) The Pascal dynamic contour tonometer is a novel device that measures IOP with a sensor integrated into the centre of the tip without applanation, thereby being less dependent on corneal properties. The differences between IOP measured by dynamic contour tonometry (DCT) and IOP measured by GAT are potential biomechanical identifiers.\(^{16}\)

- **Brillouin Scattering Spectroscopy**\(^{17-19}\)
  Noncontact method to measure in vivo corneal (and crystalline lens) biomechanical properties through the analysis of light scatter. The light interacting (photons) with natural acoustic photons in material lead to
Brillouin shift, which is related to elastic modulus. Photon is quantum of vibration of the crystalline lattice of the material. The photon may lose energy (Stokes process) or gain energy (anti-Stokes process) from this interaction and this change (gain or loss) corresponds with a shift in frequency in the Brillouin spectrum of the scattered light. This change is related to the elastic modulus (M') of the material, as shown in this equation ($\rho = \text{mass density}, \lambda = \text{wavelength}, \Omega = \text{frequency shift}, \text{and } n = \text{the refractive index}$):

$$M' = \frac{\rho \lambda^2 \Omega^2}{4n^2}$$

**Limitations:** The imaging system is sensitive to temperature, vibration and alignment. Although these factors are controlled in a laboratory setting, its transition into an accurate and reproducible commercially available clinical device is a hurdle that has yet to be overcome.

- **Finite element modelling**
  A mathematical technique to help better understand the biomechanical response of the cornea. Based on the principle of solid mechanics and soft tissues, it is useful in estimating the mechanical strain in the tissue. It facilitates improvement in outcomes of corneal surgery and helps identify the weak or degraded zones in corneal disease.\(^{20}\)

**Clinical Applications of Ocular Biomechanics**

Corneal Biomechanics is a new diagnostic modality that can potentially allow the early detection of pathological eyes and weaker corneas even at a subclinical stage.

1) **Refractive surgery**

- **Selection of the right procedure**
  There is a significant reduction of CH and CRF after different laser refractive treatments. Studies have shown a greater decrease in both CH and CRF in LASIK eyes when compared with photorefractive keratectomy.\(^{21}\) Thus patients with weaker biomechanics are more suitable for surface ablation with or without simultaneous crosslinking as compared to LASIK. Also, studies comparing SMILE and LASIK have found more reduction in biomechanics in patients that underwent LASIK, suggesting that the former may be more suitable for patients with pre-existing weaker biomechanics (Figure 5).

Case example 1 (Figure 8) demonstrates the role of corneal biomechanics in selection of the refractive procedure.

- **Robust screening of unsuitable patients**
  CH and CRF are significantly reduced after flap creation,
with a greater reduction in thicker flaps as compared to thinner flaps. Early assessment of biomechanical properties may enable exclusion of candidates who would otherwise show a normal topography but are at risk of developing ectasia. Case example 2 (Figure 9) demonstrates the role of corneal biomechanics in identifying the eligibility of a candidate for refractive surgery

2) Cataract
- Better prediction of outcomes of Cataract Surgery
Changes have been reported in corneal biomechanical parameters after cataract surgery. Corneal hysteresis was found to be reduced in the immediate postoperative period though it recovered to preoperative values in the long term. Also, Alia et al found MICS patients had more biomechanical stability 1 month post operative as compared to standard Coaxial phacoemulsification. In future, corneal biomechanics may play a role in planning the incision location in cataract surgery and help in achieving better refractive outcomes of cataract surgery

3) Keratoconus
- Early detection
Keratoconic eyes have been found to show a weaker stress versus strain response along with a more disorganized collagen network. CH and CRF measurements were reduced in KC eyes with greater decrease as KC severity increases. Parameters from Corvis ST like Highest Corneal Deflection Amplitude (HCDA) are worsened in patients with Keratoconus (Figure 6) and can be useful for the detection of such cases. Recently, Brillouin corneal

Case Example
Case 1: A 26-year-old female for refractive surgery opinion
Treatment Plan: Avoid Refractive Surgery

Case Example
Case 2: A 30-year-old male for opinion for refractive surgery
Treatment Plan: Surface Ablation

Figure 8: Suspicious corneal topography with poor corneal biomechanics

Figure 9: Suspicious Corneal Topography with strong corneal biomechanics
stiffness has been found to be increased significantly by both epi – on and epi – off modalities of CXL and showed that the mechanical loss in keratoconus is primarily concentrated in corneal protrusion.38,39

4) Intraocular Pressure Measurement
The ORA and Corvis ST allows IOP measurements, including Goldmann-correlated IOP (IOPg) and corneal compensated IOP (IOPcc) are less affected by corneal properties like CCT and CH. Correlation between Corvis ST and ORA is good but not so with GAT.33

5) Glaucma
Structural weakness has been noted in eyes with lower CH and/or thinner than normal CCT.31 These two parameters may be considered as independent risk factors of glaucoma.32

6) Keratoplasty
Highest Corneal Deformation Amplitude (HCDA) of patients, post Deep Anterior Lamellar Keratoplasty (DALK) was found to be close to the PK group.33 These results provide interesting information about corneal integrity after different kinds of corneal keratoplasties.

Conclusion
Corneal biomechanics is a new and rapidly evolving field that promises to change our understanding of many pathological processes in the eye. With the advent of tools for in vivo measurement, the translational value of this science has multiplied and has already found its way into the clinics. This article has highlighted various specialities in ophthalmology where corneal biomechanics has found applications. With further research, it is likely to lead to a customised ‘bespoke’ management of keratoconus targeting the biomechanically weaker areas in keratoconus and strengthening those specific areas. Increased interest among scientists and clinicians alike can push the discipline further and ultimately improve the quality of care provided to patients.

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