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REVIEW

Corneal Biomechanics – an Emerging Ocular Property with a Significant Impact

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ABSTRACT

Corneal biomechanical properties reflect the capacity of the cornea to respond to applied mechanical forces. They are an increasingly important domain in ocular pathology, correlated to the diagnosis and evolution of eye diseases such as refractive errors, glaucoma or corneal ectasias. Refractive errors constitute a significant etiology of decreased vision worldwide, with a particular impact in children. Myopic eyes significantly differ from emmetropic eyes in terms of morphology and biomechanics, with differences being reported in both adults and children. In the latter, corneal hysteresis (CH) and the corneal resistance factor (CRF) are significantly lower in myopic individuals, and both biomechanical parameters correlate with the central corneal thickness and axial length.

Glaucoma is a progressive optic neuropathy that leads to thinning of the nerve fiber layer and specific visual field loss, in which intraocular pressure (IOP) is an important risk factor. There is an inverse correlation between IOP and CH – a low hysteresis is associated with a high IOP. Furthermore, CH is on average

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lower in primary open angle glaucoma (POAG) compared to ocular hypertension (OHT) for the same IOP. Significant correlations between CH and the thickness of the ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL), in both POAG and OHT, have been described. Keratoconus is the most frequent corneal ectasia, which leads to a progressive thinning and protruding of the cornea. Biomechanical parameters are severely affected in keratoconus – usually, both CH and CRF are lower compared to normal eyes.

The biomechanical behavior of the cornea modulates the evolution of several ocular pathologies. As research is ongoing, more data will enable us to apply this knowledge in diagnosing disease more efficiently and targeting the right treatment for the right patient, including refractive surgery.

Keywords: cornea, myopia, hyperopia, astigmatism, glaucoma, keratoconus, corneal hysteresis, corneal resistance factor.

INTRODUCTION

Corneal biomechanical properties reflect the capacity of the cornea to respond to applied mechanical forces (1). The cornea has a viscoelastic behavior – it does not instantly regain the initial form after applying an external force, and instead, a proportion of the energy is released as the cornea returns to the initial shape and dimension (2).

Among the corneal layers, the stroma and the Bowman's membrane have the most important contribution to the resistance and elasticity of the cornea, due to the large proportion of collagen fibers in their structure (3). Characteristics of collagen fibers, including density, spatial orientation, and degree of crosslinking, have a significant impact on the biomechanical behavior of the cornea (4).

Corneal biomechanics represent an increasingly important domain in ophthalmological pathology (5). Firstly, several preclinical studies support the idea that biomechanical properties of the anterior segment may be used with a reasonable degree of confidence in estimating the biomechanics of the whole globe (6). Secondly, biomechanical properties have been correlated to the diagnosis and evolution of ocular disease such as glaucoma or corneal ectasia (4).

Measuring corneal biomechanical parameters

The Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Inc., Buffalo, NY, USA) is a device using the principles of non-contact tonometry in measuring both intraocular pressure (IOP) and several biomechanical parameters. The ORA releases an air puff that leads to a deformation of the cornea, towards a concave shape (7). During this process, the cornea initially reaches a flat shape, which is noted as the first applanation (P1); it continues towards a concave shape and then returns to the convex normal shape, passing through the second applanation (P2). An infrared light electrooptic system detects the two moments (in which the plano cornea reflects the highest proportion of infrared light) (8). The device calculates the intraocular pressure based on the time it takes the cornea to reach the first applanation. The output of the device includes an IOP correlated with the Goldmann contact tonometry (IOPg) and a cornea-correlated IOP (IOPcc) (2).

The main biomechanical properties estimated by ORA, corneal hysteresis (CH) and corneal resistance factor (CRF), are both measured in mm Hg; CH equals the difference in pressure between the two applanations, and reflects the capacity of the cornea to absorb and release mechanical energy ($CH = P1 - P2$) (4), while CRF is equal to the same difference but P2 is multiplied with a constant calculated using P1, P2 and the central corneal thickness (CCT) ($CRF = P1 - k \times P2$). Thus, CH reflects the viscoelastic behavior of the cornea, while CRF is a more accurate indicator of corneal resistance and elasticity (8).

The Corneal Visualization Scheimpflug Technology device (CorVis ST, Oculus, Germany) is another tool that registers the corneal response to the application of an air puff. A Scheimpflug camera follows the cornea as it changes and regains its initial shape, and registers the IOP and central corneal thickness. While it does not record hysteresis (9), the CorVis ST records parameters such as the duration needed to reach the first applanation, the deformation amplitude and the radius of the corneal concavity resulted in the deformation (10). The Scheimpflug camera allows for a complex analysis of the corneal behavior, and the device displays both parameters that account for the whole eye response to the air puff, and parameters that do not compensate for this motion (5).

Corneal biomechanics in refractive errors

Refractive errors constitute a significant etiology of decreased vision worldwide, with a particular impact in children. Ocular development throughout childhood undergoes a process called emmetropization: at birth, the eye is hyperopic, and the refractive values gradually decrease until the age of five to seven years old, when usually children have a refractive error between 0 and +2.00 Spheric Diopters. Following this age group, the incidence of myopia follows an ascending trend, suggesting an abnormal continuation of emmetropization (11). Connections between the axial length growth and the general growth of the child have been discovered, such as a correlation between the height and the axial length growth of children (12).

The above-mentioned refractive error, myopia, is the most commonly emncountered ocular disease, the World Health Organization (WHO) reporting a prevalence of up to 24.4% in European populations (13). Moreover, WHO predicts that 52% of people will be myopic by the year 2050 (14).

Myopic eyes differ significantly from emmetropic eyes, both in terms of morphology and biomechanics, with differences being reported both in adults and children. In the latter, CH and CRF are significantly lower in myopes, and the two biomechanical parameters correlate with central corneal thickness and axial length, while CH in particular correlates with the spherical equivalent as well (15).

Data resulting from CorVis ST supports similar conclusions: rigidity is higher in myopic eyes (3.72-10.68%) than emmetropic eyes, depending on the degree of myopia (16).

An important domain to be studied is the potential of CH and CRF to help predict myopia progression. A recent meta-analysis confirms that both CH and CRF are higher in low to moderate myopia compared to high myopia (17). More data suggests that there is a correlation between myopia progression – represented by axial elongation – and the value of CH, measured at the initial examination and diagnosis of myopia in spectacle-wearing patients (18).

Central corneal thickness influences the interplay between corneal biomechanical parameters and myopia parameters: a study developing a regression model revealed that CH and CRF variation is rather dependent on the CCT than the spherical equivalent (19). This may be due to either the thinning and flattening effect that axial elongation has on the cornea (20) or the disturbance of collagen fibers in myopia which impacts biomechanical behavior (21).

Hyperopia and astigmatism have been also associated with variation in biomechanical parameters. Both CH and CRF are significantly higher in hyperopic eyes than in myopic ones. This difference is valid while taking into account degrees of refractive error: there are significant differences in CH between high hyperopia and emmetropia, and low, moderate and high myopia (22).

The waveform analysis of ORA output offers a series of additional information: the height and width of the P1 wave (corresponding to the first applanation) are different between myopes and hyperopes, revealing a slower corneal deformation in a hyperopic eye (23).

Lastly, the biomechanics of astigmatic eyes have been studied as well. Comparing keratoconus and high astigmatism (more than three cylinder Diopters) revealed significantly higher CH and CRF in the latter, with important correlations with the central corneal thickness (24). However, no differences in CH and CRF between patients with lower astigmatism (under 1.5 cylinder D) and higher astigmatism (over 1.5 cylinder D) have been detected (25).

Corneal biomechanics in keratoconus

Keratoconus is the most frequent corneal ectasia, usually bilateral but with an asymmetrical evolution. It leads to a progressive thinning and protruding of the cornea (26). In terms of histopathology, the main element of the disease is the thinning of the stromal layer, along with breaks in the Bowman membrane, a decrease of collagen fibrillary diameter and lamellae organization (27).

Biomechanical parameters are severely affected in keratoconus – usually, both CH and CRF are lower compared to normal eyes (28). Investigating these parameters has a supplementary role in the diagnosis of keratoconus (29).

Studies reveal a possible connection between keratoconus progression and the biomechanical properties of the keratoconic cornea. Parameters derived from the waveform analysis, provided by ORA, are significantly associated with keratoconus progression – mainly the p2 area and h2, which represent the area of the upper 75% of the second applanation peak and the height of the second applanation peak, respectively (30).

Similarly, certain CorVis ST parameters are affected along keratoconus progression, namely the stress-strain index and the integrated inverse radius – which signify a decrease in corneal stiffness as the disease progresses – and the first applanation stiffness parameter and the deflection amplitude ratio as well (31).

A primary treatment method in keratoconus is corneal collagen crosslinking, which is a method using UVA light and riboflavin in order to promote the formation of covalent bonds between and inside the corneal collagen fibrils (32). While an increase in corneal rigidity has been proposed as a mechanism, several studies reported no changes in biomechanics before and after the crosslinking procedure (33). Thus, it is believed that crosslinking acts upon the corneal ultrastructure, without a significant impact on the viscoelastic behavior of the cornea (34). On the other hand, studies have been focusing on data provided by ORA in order to identify new parameters with better sensitivity and specificity in diagnosing and following the evolution of keratoconus after undergoing crosslinking (35).

Corneal biomechanics in glaucoma

Glaucoma is a progressive optic neuropathy which leads to thinning of the nerve fiber layer and specific visual field loss, in which IOP is an important risk factor (9). Several studies have pointed out the connection between corneal biomechanical parameters, mainly the hysteresis, and the diagnosis and evolution of glaucoma. There is an inverse connection between IOP and CH – a low hysteresis is associated with a high IOP. Furthermore, CH is on average lower in primary open angle glaucoma (POAG) compared to ocular hypertension (OHT) for the same IOP (36, 37). Significant correlations between CH and the thickness of the ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL), both in POAG and OHT, have been described (38).

In terms of glaucoma evolution, a lower CH is correlated with visual field progression (39). Moreover, following POAG cases, which are bilateral but asymmetric in terms of progression, reveals that the more advanced eye has a lower CH, while not having a significantly higher IOP or lower CCT (40). Patients with high CH and CCT at diagnosis have a lower risk of glaucoma progression – a CH which is 1 mm Hg higher is associated with a 2.13 times higher risk of perimetric progression (41). One study has described different levels of correlation between CH and perimetric parameters, depending on the degree of glaucomatous damage (42).

It is important to note that CH is a dynamic property of the eye; thus, the effect of glaucoma treatment on corneal biomechanics has been studied. Topical treatment with prostaglandin analogues leads to an increase in CH, while beta-blockers have no effect (43). Moreover, a low CH measured before initiating treatment correlates to a higher impact of treatment in terms of IOP decrease (44). Other glaucoma treatments, including selective laser trabeculoplasty (45), trabeculectomy and Ahmed valve implantation (46), have been shown to increase CH.

Such correlations have been detected in other types of glaucoma as well. In normal tension glaucoma (NTG), low CH has a statistically significant correlation with a high cup-to-disk ratio and a low volume and surface of the neuroretinal rim, while in advanced NTG, CH and CRF are lower (47). Several studies have shown that CH was significantly lower in pseudoexfoliative glaucoma than POAG (48)(49), similarly in congenital glaucoma (50, 51). In primary angle closure glaucoma (PACG) several studies reported a lower CH, while others identified no correlations between corneal biomechanics and PACG evolution (9).

The mechanisms of corneal biomechanics – glaucoma physiopathology interaction is still a subject of study. Most likely, the biomechanical properties of the optic nerve head and surrounding tissue, including lamina cribrosa, modulate their response to intraocular pressure variations, and the progression of neuropathy. The biomechanical parameters of the cornea, including hysteresis, may act as biomarkers that reflect the biomechanics of the above-mentioned structures and their rigidity (52). ❑

CONCLUSIONS

The biomechanical behavior of the cornea modulates the evolution of several ocular pathologies, as previously detailed. As research is ongoing, more data will enable us to apply this knowledge in efficiently diagnosing disease and targeting treatments for the right patients, including refractive surgery (4).

There are several challenges in measuring corneal biomechanical parameters which relate to the biological behavior of the cornea, including the variability in collagen fiber distribution and density and in hydration, the nonlinear response to forces, and intersubject variation (53). Development in the available measuring devices and new devices based on principles such as Brillouin microscopy or elastography will provide useful data in managing diverse ocular pathologies (54). ❑

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