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REVIEW

The importance of assessing corneal biomechanical properties in glaucoma patients care – a review

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Abstract

Purpose: to familiarize the public with the role of corneal biomechanics in glaucoma patient management.

Methods: Ocular Response Analyzer (ORA) is the only device that measures in vivo corneal biomechanics. Recent studies regarding "corneal biomechanics and glaucoma" were reviewed and the obtained data were compared in order to present a better understanding of the corneal biomechanical properties involvement in glaucoma care.

Results: According to the studies reviewed, in primary open angle glaucoma (POAG) the mean corneal hysteresis (CH) and the corneal resistance factor (CRF) were approximately 2 mmHg lower than in normal eyes. In ocular hypertension (OH), the mean CH was about 1mmHg higher than in POAG patients and 1mmHg lower than in the control group, while the mean CRF was about 2mmHg higher than in POAG and 1mmHg higher than in the control group. Regarding the normal tension glaucoma (NTG), there were studies that showed that the mean CH and CRF were approximately 1mmHg lower than in POAG and studies that showed similar values between the POAG and NTG groups. The mean CH did not differ much between POAG and angle closure glaucoma (ACG), being lower than in normal individuals, while CRF appeared to be higher in the ACG than in normal individuals. Concerning congenital glaucoma (CG), both CH and CRF were about 2mmHg lower than in normal eyes.

Conclusions: Corneal biomechanics influenced the IOP measurement and have been proven to be of a great significance in glaucoma patients regardless of the central corneal thickness (CCT). Lower values of CH and CRF could suggest an alteration in the corneal response associated to glaucoma.

Keywords: cornea, biomechanics, glaucoma, hysteresis, Ocular Response Analyzer

Introduction

In recent times a special interest in the study of corneal biomechanics has been granted [**1,2**]. The initial concern of corneal biomechanical profile was prior to refractive surgery [**1,3**]. Nowadays, as CCT is already known as an independent risk factor in glaucoma regardless of the IOP [**4-9**], more and more studies have shown the involvement of corneal biomechanics in the management of glaucoma patients [**1,2**]. However, regardless of the performed studies there are still some questions that need to be answered regarding the

implications of corneal biomechanics in glaucoma.

Methods

HYSTERESIS

Hysteresis is a parameter that characterizes deforming materials as a response to an applied force. It was first described for the magnetic materials, but the principals of hysteresis are applied in many departments [**3,10,11**]. In ophthalmology, corneal hysteresis is an indicator of the viscoelastic properties of the cornea [**1-3,12,10**].

VISCOELASTICITY

Viscoelasticity is a property of the materials that have simultaneous elastic and viscous characteristics when submitted to deformation [**1,3,5,11**]. These materials are capable of a degree of deformation when an external force is applied. Once the force is stopped, the deformation regresses and they come back, faster or slower, to their initial shape [**3,13,14**].

In medicine, an example of such a material is the cornea that acts as a viscoelastic system when an applanation force is tested to its surface. When the force is stopped it comes back to the initial shape, but loses some of the energy in the process [**1,13,14,15**]. This results in two different applanation pressures [**16,17**].

OCULAR RESPONSE ANALYZER

Ocular Response Analyzer (Reichert Ophthalmic Instruments, NY) is an instrument designed to improve the measurement of intraocular pressure (IOP) [**3,18-20**]. It is the only device that allows the evaluation of the biomechanical properties of the cornea in vivo [**3,15,21-23**].

ORA uses an air pulse that makes the cornea move inward and then outward as it comes back and an optical instrument that records the two applanation pressures [**1,17,18,24**]. The property known as viscoelasticity is the reason why the two-applanation pressures are different [**15**].

The ORA report provides four parameters: corneal compensated IOP (IOPcc), Goldmann-correlated IOP (IOPg), corneal hysteresis, and corneal resistance factor.

Corneal compensated IOP (IOPcc) is the first parameter given by the ORA report. It reveals an estimation of the IOP unaffected by the corneal biomechanics [**14,18,20**]. The device measures the basic IOP values and then attributes the data to a computer integrated algorithm that reevaluates the information taking into account the corneal properties [**23,25**].

Goldmann-correlated IOP (IOPg) brings a proximate value to the one given by the Goldmann applanotomometer [**20,23**]. It represents the average between the two pressures determined by the air pulse [**1,15**]. This concordance between Goldman applanation tonometry (GAT) and ORA's IOPg has been proven by various studies such as the one conducted by Ehrlich et al. [**26**].

Corneal hysteresis is probably the most important parameter measured by ORA. CH is an indicator of the viscoelastic properties of the cornea [**1,2,10,12**]. It reveals the cornea's ability to absorb and dissipate energy [**2,10**]. CH is calculated by the difference between the two pressures measured by ORA [**2,10,23**].

The last parameter is the corneal resistance factor, an indicator of the entire resistance of the cornea [**2,12**]. It is dependent on CH and can be calculated by the formula P1-(0,7P2) (pressure 1 = P1; pressure 2 = P2) [**27**].

Results

CLINICAL EVIDENCE

Cornea can be described by its thickness, curvature, topography, hysteresis, and resistance. The first three are structural properties and the last two are biomechanical [**2,4,5**].

CORNEAL BIOMECHANICS IN NORMAL EYES

The normal values of CH and CRF have been provided by various studies. Pillunat et al. conducted a prospective cross sectional study and showed that CH has variability according to age, axial length, CCH and IOP. The mean values for CH and CRF respectively were 10.49 ± 1.67mmHg for CH and 10.50 ± 1.44 mmHg for

CRF. After adjusting the data, both CH and CRF lowered [**28**].

Another study comparing African and Caucasian data revealed that the mean values for CH and CRF respectively were 10.8 ± 1.6 mmHg and 10.7 ± 1.5 mmHg in Caucasians. In Africans, the values were 9.2 ± 1.5 mmHg for mean CH and 9.8 ± 2.0 mmHg for mean CRF, a little lower than in Caucasians (Detry-Morel et al.) [**23**].

DEMOGRAPHICS

An important study performed by Foster et al. included 4184 participants and had the purpose of describing the distribution of the indices of corneal biomechanics in British population. It revealed that both CH and CRF were higher in women (10.2 mmHg vs. 10.4mmHg) than in men (9.79 mmHg vs. 10.02mmHg) and lowered with age in both genders with a rate of 0.31mmHg/ decade for CRF and 0.34mmHg/ decade for CH. Multiple regression analysis showed that CH and CRF are associated with age, height and sex [**27**].

CORNEAL BIOMECHANICS AND IOP

Corneal biomechanical properties are dependent on the corneal ability to deform when an extra ocular pressure is applied [**1,10,12,19,21,29,30**]. When the IOP is higher, the ability of the cornea to deform is lower [**23,29,31**]. ORA adjusts the IOP taking into consideration this aspect [**1,2,10,12,15,23**].

Studies such as the one conducted by Pensyl et al. showed the relationship between CH, CRF, and IOP. CH and IOPg are inversely correlated in both OH and POAG. It was demonstrated that a high IOP is correlated with a low CH and the other way around. In multivariate analyses, only CH and IOP had an independent association with glaucoma [**2**]. This proves that if ignoring the corneal biomechanics, the IOP in glaucoma patients is underestimated [**2,4,28,32**].

PRIMARY OPEN ANGLE GLAUCOMA

One of the most studied relationships of corneal biomechanical properties is to primary open angle glaucoma. A lower CH in glaucoma patients than in normal individuals was also demonstrated by Mangouritsas et al. (8,95 ± 10,97mmHg), Abitbol O et al. (8,77 ± 10,46mmHg) and Hirneiß at al. (7,73 ± 1,46mmHg) [**32-34**]. A way to integrate this information in glaucoma care needs to be found without disregarding the relationship between corneal biomechanics and CCT.

Due to the viscoelastic properties of the cornea, the values of the IOPcc and IOPg are different. This difference has been suggested by many authors, including Hirneiß et al., who included in their study patients with unilateral glaucoma and compared glaucomatous eyes to normal ones in the same individual. Their study revealed that in glaucomatous eyes the values for the IOPcc were higher than the IOPg and both IOP measurements were higher in the affected eye versus the unaffected one [**32**].

In the cross sectional study conducted by Pillunat et al., the adjusted values for CH and CRF were both lower in the POAG group than in normal individuals. In glaucomatous eyes, the mean CH was 8,54 ± 1,86 mmHg vs. 10,49 ± 1,67 mmHg in normal eyes. The values for CRF were 8,79 ± 2,56 mmHg in glaucomatous eyes vs. 10,50 ± 1,44 mmHg in normal eyes [**28**].

This proved that corneal properties were altered in glaucomatous eyes compared to normal eyes. Also, CH and CRF were factors that influenced the IOP measurements, being once again implicated in glaucoma care influencing the most basic measurement used in the follow up of glaucoma patients.

ANGLE CLOSURE GLAUCOMA (ACG)

The implication of corneal biomechanics in angle closure glaucoma is less significant because of the different mechanism of the disease. The studies are fewer, but it has been stated that CH does not differ between POAG (9,5mmHg with confidence interval (CI) 9,2-9,5mmHg) and ACG (9,1mmHg with CI 8,7-9,4mmHg), and that CH is lower in glaucoma patients than in normal individuals (10.4 mm Hg with CI 10.1 to 10.6 mm Hg) (study conducted by Narayanaswamy A et al. in Chinese individuals) [**35**].

In their study, Ang GS et al. highlighted that patients with ACG had a CH (9.3 ± 1.5mmHg) lower than normal individuals (9.5 ± 1.4 mmHg), and a CRF (9.9 ± 2.4mmHg) higher than normal individuals (9.2 ± 1.5 mmHg) [**36**].

OCULAR HYPERTENSION

Patients diagnosed with OH are susceptible to develop POAG and if other risk factors are

involved the probability rises. Probably the most crucial role of corneal biomechanical properties is played in ocular hypertension [**37**]. Corneal structural properties have already been proven as an important risk factor in these patients. Ocular hypertension treatment study revealed that in OH patients with low CCT, the risk of developing POAG was much higher than in patients with thick corneas [**7,38**].

A study, conducted by Pillunat et al. showed that CH adjusted by age, axial length, IOP and CCT was also higher in the OH group (9,70 ± 2,38mmHg) than in the POAG group (8,54 ± 1,86mmHg) and both were lower than in the control group (10,49 ± 1,67mmHg). CRF was also higher in the OH group (11,85 ± 2,60mmHg) vs. the POAG group (8,79 ± 2,56mmHg) and controls (10,50 ± 1,44mmHg) [**28**].

The relationship between CRF and OH is not as clear though, but according to Pillunat et al. and Shah S et al. CRF was higher in OH (12.0 ± 2.0 mmHg) than in POAG (10.6 ± 2.0mmHg) and NTG (9.1 ± 2.2mmHg) [**28,37**].

NORMAL TENSION GLAUCOMA

As well as in OH, corneal biomechanics play an important role in NTG. The studies showing the corneal biomechanics involvement in NTG are not as concluding as in POAG or OH.

Shah S et al. found that both CH and CRF were lower in NTG (9.0 ± 1.9 mmHg for CH and 9.1 ± 2.2mmHg for CRF) than in POAG (9.9 ± 2.1 mmHg for CH vs. 10.6 ± 2.0mmHg for CRF) and OH (10.2 ± 2.0 mmHg for CH and 12.0 ± 2.0 mmHg for CRF) [**37**].

Kaushik et al. observed that CH is lower in POAG (7.9 ± 2.8mmHg) and NTG (8.0 ± 1.6mmHg) than in normal individuals (9.5 ± 1.4mmHg). In this study, CRF was also lower in the NTG (7.8 ± 1.5mmHg) group than normal individuals (9.2 ± 1.5mmHg) and similar to the one found in the POAG group (7.9 ± 2.8 mmHg) [**39**].

On the other hand, Ang GS et al. designed a study in order to determine whether corneal biomechanical properties differ between POAG and NTG patients. They revealed that CH was lower in POAG patients in contrast to CRF; CH (9.6 ± 1.3 mm Hg in NTG vs. 9.0 ± 1.4 mm Hg in POAG) vs. CRF (9.9 ± 1.4 mmHg in NTG vs. 10.8 ± 1.7mmHg in POAG) [**36**].

CENTRAL CORNEAL THICKNESS AND CORNEAL BIOMECHANICS

It has already been stated that CCT is an independent risk factor for glaucoma progression (OHTS) [**8,40-43**]. CRF is more influenced by CCT than CH, but both have an interrelationship with the structural properties of the cornea [**41**].

Pensyl et al. presented an observational cross-sectional study that included 169 eyes divided in 3 subgroups by CCT in thin, intermediate, and thick corneas. It revealed that CH was lower in POAG than OH and it was the only factor that differentiated POAG and OH patients in each of the 3 subgroups [**40,44**]. This is a very important study because it demonstrated the value of CH in glaucoma if CH is an independent risk factor in glaucoma, regardless of the CCT.

A study proposed by Detry-Morel et al. demonstrated the relationship between corneal biomechanical properties and corneal thickness proving a positive correlation between CRF and CCT in Caucasians [**42,45**]. A correlation between CH and CCT in both POAG and OH groups was demonstrated by Pensyl et al. [**2,44**]. The relationship between CH and CCT was also proven by Mangouritsas et al., this time in glaucomatous and non-glaucomatous eyes [**33**].

This revealed that a thicker cornea was associated with a higher CH and CRF and a thinner cornea to a lower CH and CRF. Knowing that a low CCT is a risk factor in glaucoma, a low CH and CRF might also represent a risk factor in glaucoma patients.

CORNEAL BIOMECHANICS AND GLAUCOMA SEVERITY: VISUAL FIELD PARAMETERS, CH, AND CRF

Glaucoma patients need to be fully investigated and evaluated from their first visit. It is very important for the ophthalmologist to determine the risk factors for progression and to identify patients with advanced glaucoma in order to carefully monitor patients with higher risk and to preserve a good visual acuity as long as this is possible [**3,28**]. Nowadays CCT, CH and CRF play an important role in glaucoma care [**1,18,24,46**]. There are many studies that tend to prove the importance of corneal biomechanics in glaucoma patients and the most relevant is to

show their involvement in the disease progression.

Medeiros et al. directed a prospective longitudinal study with the purpose of evaluating CH as a risk factor for glaucoma progression. They proved that CH has a powerful influence on the visual field progression over time: the invariable model suggested that decreasing CH with 1mmHg is associated with 0.25% faster decline of the visual field index (VFI). In the multivariable model, eyes that associated high IOP and low CH showed an increased risk of fast progression [**47**]. Detry-Morel et al. also found a significantly positive correlation between CH, MD, and VFI in POAG African population [**33**].

Another study, presented by Mansouri et al. investigated the relationship between corneal biomechanics and glaucoma severity. In their study, CH was lower in worse eyes than in better eyes. They also found a weak positive correlation between CH, CRF, and mean deviation (MD) as well as pattern standard deviation (PSD) showing that in the eyes that have a lower MD and VFI both CH and CRF are lower [**4**].

De Moraes et al. conducted a study designed to evaluate the relationship between CH, CCT, and VF progression. Their study proved that progressing eyes had lower CH and lower CCT. In addition to this, they also demonstrated the correlation between CH and CCT [**48**].

OPTIC NERVE HEAD PARAMETERS AND ORA PARAMETERS

The study performed by Mansouri et al. presented a weak positive correlation between CH and CRF and retinal nerve fiber layer thickness measured by GDxECC. In a multivariable model, the correlation was no longer significant after adjusting CCT and axial length by age [**4**]. Further studies are needed to prove if this hypothesis is valid or not.

CONGENITAL GLAUCOMA (CG)

Studies have shown that corneal biomechanics are also modified in CG. Gatzioufas Z et al. designed a prospective observational study in order to investigate corneal biomechanics in children with congenital glaucoma. They showed that as well as in POAG, both CH (9.1 ± 1.6mmHg) and CRF (7.9 ± 1.1mmHg) are decreased in CG compared to normal eyes (11.4 ± 1.2 mmHg for CH and 10.4 ± 1.5 mmHg for CRF). CH and CRF were correlated positively with CCT and negatively with the corneal diameter. The relationship between corneal biomechanics and CCT was similar to the one found in adults, but in CG, the higher the corneal diameter the lower the CH was [**21,45,46,49**].

Kirwan C et al. found a lower CH in the majority of congenital glaucoma patients (approximately 6.3 mm Hg) included in their study compared to normal eyes (approximattly12.5 mm Hg) and found no correlation between age and CH [**50**].

Conclusions

Corneal properties have been proven as an important factor in the management of many ocular disorders. Their involvement in glaucoma is yet to be fully understood. CH and CRF are lower in CG, POAG, OH, and NTG than in normal individuals. CH is lower in POAG than in OH and NTG, while in CRF studies are not as clear. Probably one of the most important observations found is that CH is an independent risk factor in glaucoma, regardless of the CCT.

Disregarding their individual involvement in glaucoma, it has been shown that corneal biomechanics influence the IOP measurements. IOPcc measured by ORA appears to offer a more accurate IOP measurement than the other devices. Knowing that IOP is the only modifiable risk factor in glaucoma patients, it is very important to determine an accurate IOP measurement from the first visit in order to settle the target IOP for each of the patients.

The relationship between corneal biomechanics and glaucoma progression proved its role in glaucoma care once again. This role needs to be further investigated but the existing data is promising and even if we do not use them as a screening measurement, we should consider them when evaluating glaucoma patients.

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Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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