AMERICAN ACADEMY OF OPHTHALMOLOGY®

Ophthalmic Technology Assessment

Corneal Hysteresis for the Diagnosis of Glaucoma and Assessment of Progression Risk

A Report by the American Academy of Ophthalmology

Arthur J. Sit, SM, MD,[1] Teresa C. Chen, MD,[2] Hana L. Takusagawa, MD,[3,4] Jullia A. Rosdahl, MD, PhD,[5] Ambika Hoguet, MD,[6] Vikas Chopra, MD,[7] Grace M. Richter, MD,[8,9] Yvonne Ou, MD,[10] Stephen J. Kim, MD,[11] Darrell WuDunn, MD, PhD[12]

Purpose: To review the current published literature on the utility of corneal hysteresis (CH) to assist the clinician in the diagnosis of glaucoma or in the assessment of risk for disease progression in existing glaucoma patients.

Methods: Searches of the peer-reviewed literature in the PubMed database were performed through July 2022. The abstracts of 423 identified articles were examined to exclude reviews and non-English articles. After inclusion and exclusion criteria were applied, 19 articles were selected, and the panel methodologist rated them for level of evidence. Eight articles were rated level I, and 5 articles were rated level II. The 6 articles rated level III were excluded.

Results: Corneal hysteresis is lower in patients with primary open-angle glaucoma, primary angle-closure glaucoma, pseudoexfoliative glaucoma, and pseudoexfoliation syndrome compared with normal subjects. Interpretation of low CH in patients with high intraocular pressure (IOP) or on topical hypotensive medications is complicated by the influence of these parameters on CH measurements. However, CH is also lower in treatment-naïve, normal-tension glaucoma patients compared with normal subjects who have a similar IOP. In addition, lower CH is associated with an increased risk of progression of glaucoma based on visual fields or structural markers in open-angle glaucoma patients, including those with apparently well-controlled IOP.

Conclusions: Corneal hysteresis is lower in glaucoma patients compared with normal subjects, and lower CH is associated with an increased risk of disease progression. However, a causal relationship remains to be demonstrated. Nevertheless, measurement of CH complements current structural and functional assessments in determining disease risk in glaucoma suspects and patients.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology 2023;130:433-442*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to systematically review the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment is to evaluate the current published literature on the utility of corneal hysteresis (CH) measurements in the diagnosis of glaucoma and in the assessment of risk for glaucoma progression.

Background

Reduction of intraocular pressure (IOP) is the only known effective treatment for glaucoma. However, despite treatment, many patients continue to progress and develop further vision loss.[1,2] Also, many individuals with elevated IOP do not develop glaucoma, and many glaucoma patients do not have elevated IOP.[3,4] This suggests that

https://doi.org/10.1016/j.ophtha.2022.11.009
ISSN 0161-6420/22

factors other than IOP are likely involved in glaucoma pathogenesis.

Biomechanical properties of the eye may be an important risk factor for glaucoma. Elevation of IOP results in distension of the eye wall with distortion of the lamina cribrosa,[5,6] potentially causing direct mechanical strain on optic nerve axons or impairment of optic nerve perfusion. Stretching and thinning of the lamina cribrosa also alter the translaminar pressure gradient and may impair retrograde transport of neurotrophic factors from the lateral geniculate nucleus to the retinal ganglion cells.[7] These changes may cause direct or indirect damage to optic nerve axons and retinal ganglion cells, resulting in glaucoma. Stiffer tissues in the eye would have greater ability to resist the distortion but would also lead to greater IOP variability for a given volume change, a possible risk factor for glaucoma development and progression.[8-10] However, the specific biomechanical properties that predispose eyes to develop glaucoma are incompletely understood.

Previous studies have used animal and cadaver models to assess ocular biomechanical properties and their relationship to glaucoma. Coudrillier et al[11] used posterior segments of human cadaver eyes mounted to an inflation system to measure scleral displacement as a function of inflation pressure. They compared 11 glaucomatous eyes with 22 eyes from donors who had no history of glaucoma. Glaucomatous eyes had stiffer peripapillary sclera, yet midposterior scleral stiffness was no different from normal controls. However, it was unclear if these differences represented a preexisting susceptibility to glaucoma or were compensatory changes due to glaucomatous optic neuropathy or elevated IOP. Possible glaucomatous changes in ocular biomechanics were also investigated by Downs et al,[12] who compared the stress-strain behavior of tissues from nonhuman primates that had experimental glaucoma with healthy controls by using a custom-built tissue tensometer. They reported that glaucomatous eyes had a significantly higher Young's modulus than normal eyes, indicating greater stiffness. However, increased stiffness was likely a compensatory change to elevated IOP from laser-induced damage of the trabecular meshwork because the animals did not have a preexisting risk of glaucoma or altered scleral properties. Whether or not abnormal tissue biomechanics contribute to glaucoma susceptibility is not fully understood.

The Ocular Response Analyzer ([ORA], Reichert) is a commercially available device that is Food and Drug Administration approved for the measurement of IOP and the biomechanical response of the cornea. No other Food and Drug Administration—-approved products to assess in vivo ocular biomechanical properties are commercially available at this time. The ORA produces a measurement of ocular biomechanical properties by assessing the response of the eye to an air jet to obtain an IOP measurement. With this device, the pressure in the air jet is ramped up and back down, causing indentation of the cornea. The air pressure corresponding to IOP occurs when light reflection off of the cornea reaches a maximum, indicating applanation of the cornea. With this technique, the IOP that is measured on the initial indentation is higher than the IOP during the rebound as the air-jet pressure is decreased. This difference in pressures (Fig 1) has been termed "CH" and is likely the result of tissue viscous damping, whereas a purely elastic cornea would have the same pressure on rebound. However, CH is likely to be influenced by both elasticity and viscosity. Viscosity reflects tissue damping and will determine the speed at which tissue deformation and recovery occurs. Elasticity will determine the magnitude of the deformation to a sustained force. The hysteresis will reflect both elasticity and viscosity, along with the magnitude and speed of the air-jet pulse. It thus represents an eye behavior influenced by ocular biomechanics and not a specific material property of the eye. Corneal hysteresis also demonstrates measurement stability, with little change due to circadian rhythms[13-16] and good intra-subject reproducibility.[17-20]

Although obtaining a CH measurement is straightforward, consensus on this measure's clinical significance is not intuitively obvious. The tissue viscosity will not affect the ultimate tissue deformation as a result of sustained IOP changes; instead, it will only damp the rate at which changes occur. Rapid short-duration changes in IOP will likely have less of an effect on tissue strain in eyes with high viscosity. For sustained IOP changes, tissue elasticity, or modulus, will determine the magnitude of deformation. However, even in a purely elastic tissue, the effect of IOP changes on the lamina cribrosa remains complex. Sigal et al[6,21] developed finite element models of the lamina cribrosa and sclera, and demonstrated that deformation of the lamina and scleral canal opening were dependent on a complex combination of factors, including tissue modulus, geometry, and tissue thickness. Further complicating understanding of CH measurements is the fact that ocular tissues are not uniform but that they demonstrate anisotropy (different properties when measured in different directions),[22-25] regional variations,[26-28] and strain stiffening (increase in elastic modulus with pressure and tissue distention).[25,28]

Ocular biomechanical properties also vary with age, axial length, and corneal thickness, adding further complexity to the interpretation of CH. The elastic modulus of ocular tissues, including both cornea and sclera, has been reported to increase with age.[29-31] In contrast, myopia has been associated with lower ocular-tissue elastic modulus[32] as well as decreased global ocular rigidity.[33,34] Although lower central corneal thickness (CCT) has been identified as a clear risk factor for the development of glaucoma in ocular hypertensive patients,[3,35] the effect on ocular biomechanics is unclear. A thicker normal cornea would be expected to require greater force to deform during applanation tonometry,[36] but the relationship between CCT and IOP measurement error is unclear.[37,38] Furthermore, tissue elastic modulus does not appear to be correlated with CCT in normal eyes,[39,40] although corneal thinning due to dehydration increases corneal stiffness.[41] Regardless, the effect of CCT as well as age and axial length should be considered in studies examining CH and glaucoma.

Ocular biomechanical changes have also been associated with glaucoma severity in previous studies. Midgett et al[42]

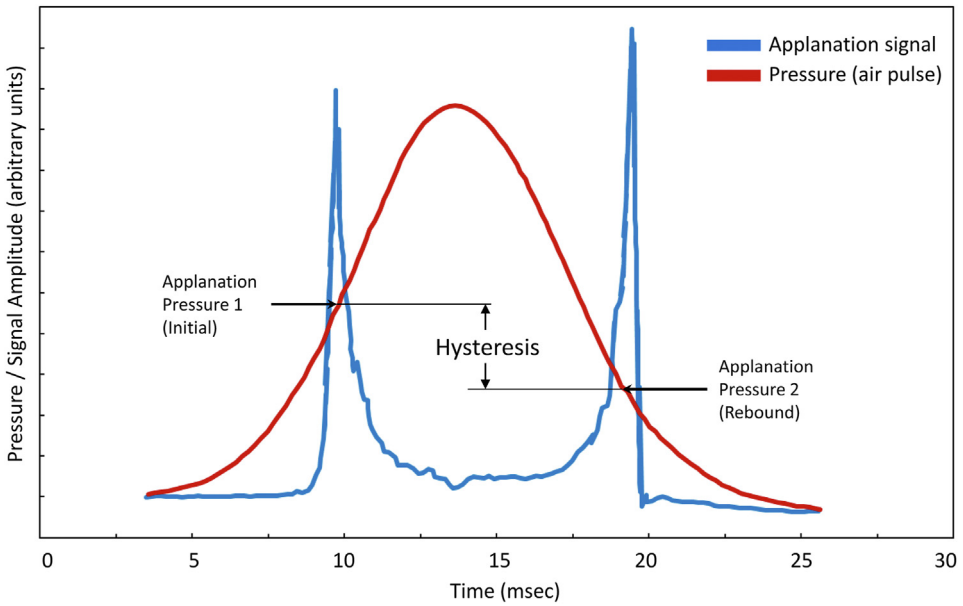

Figure 1. Ocular response analyzer pressure profile.

demonstrated that the ex vivo pressure-induced strain response of the lamina cribrosa was less in human cadaver eyes with more severe glaucoma compared with eyes that had milder glaucoma based on axon loss, and both were less than in normal eyes. This could be the result of tissue remodeling that increases stiffness, at least at the lamina cribrosa, as damage progresses. Alternatively, eyes with stiffer tissues may be more susceptible to severe disease.

Given the complexities of ocular biomechanics, representation of ocular tissue properties with a single number, such as CH, is difficult. However, the clinical utility of CH measurement has been the topic of numerous studies and is the focus of this assessment.

Question for Assessment

The purpose of this assessment is to address the following question: Is CH that is measured using the ORA able to assist the clinician in the diagnosis of glaucoma or in determining the risk of disease progression in patients with confirmed glaucoma?

Description of Evidence

Literature searches of the peer-reviewed literature in the PubMed database were performed through July 2022 using the search terms *corneal hysteresis* and *glaucoma*. The search identified 423 abstracts that were examined to exclude reviews and non-English articles. The remaining articles were reviewed in full text by the Glaucoma Panel to select only those that met the following inclusion criteria: (1) CH measured using the ORA was the technology focus of the study; (2) the study reported on the ability to differentiate between glaucoma patients and healthy subjects or on the ability to determine the risk of disease progression; (3) the study represented original research; and (4) the study subjects were adults, age 18 years or older.

Application of these criteria yielded 19 articles, and the panel methodologist (J.A.R.) assigned each study a level of evidence rating based on the rating scale developed by the Oxford Centre for Evidence-Based Medicine and adopted by the American Academy of Ophthalmology.[43] A level I rating was assigned to cross-sectional studies with consistently applied reference standards; a level II rating was assigned to nonconsecutive prospective studies and prospective studies without consistently applied reference standards; and a level III rating was assigned to case-control studies, case series, case reports, and poor-quality cohort and case-control studies. Eight articles were rated level I, and 5 articles were rated level II. A summary of the articles is included in Table 1. Six articles rated level III were excluded.

Published Results

Differences in Corneal Hysteresis between Normal and Glaucomatous Eyes

There were 8 articles comparing different populations of glaucoma patients, glaucoma suspects, and normal subjects (Table 2). Two additional articles reported on the relationship between CH and optic disc parameters associated with glaucoma in population-based studies but did not assess glaucoma patients. These 10 articles reported on studies performed in different locations worldwide, and several reported on multiple types of glaucoma. All of the studies were cross-sectional in design, with most reporting on glaucoma patients using topical ocular hypotensive medications at the time of CH measurements. This leads to potential confounding of results because the use of medical

Table 1. Summary of Included Studies

Authors	Year	Design	Industry Support	Evidence Level	Population Sample Size*							
					Normal	*OHT*	*POAG*	*PACG*	*PXS*	*PXG*	*NTG*	*NS*
Ayala[44]	2011	Case control	NR	II	30 (30)		30 (30)			30 (30)		
Cankaya et al[45]	2011	Cross-sectional	NR	II	102 (102)				64 (64)	78 (78)		
Congdon et al[46]	2006	Case series	NR	II			(131)†					(36)†
Estrela et al[47]	2020	Cohort	Yes	I			252 (126)					
Kaushik et al[48]	2012	Cross-sectional	No	I	71 (71)	38 (38)	36 (36)	59 (59)‡			18 (18)	
Medeiros et al[49]	2013	Cohort	Yes	I			114 (68)					
Narayanaswamy et al[50]	2011	Case control	No	I	150 (150)		162 (162)	131 (131)				
Pillunat et al[51]	2016	Cross-sectional	No	I	44 (44)	18 (18)	48 (48)				38 (38)	
Sun et al[52]	2009	Case series	No	II	40 (40)			40 (40)				
Susanna et al[53]	2019	Cohort	Yes	I			445 (327)					
Tejwani et al[54]	2016	Cross-sectional	No	I	59 (59)		83 (83)	57 (57)				
Yazgan et al[55]	2015	Case control	No	II	45 (45)				43 (43)	30 (30)		
Zhang et al[56]	2016	Cohort	Yes	I			186 (133)					

NS = not specified; NTG = normal-tension glaucoma; OHT = ocular hypertension; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliative glaucoma; PXS = pseudoexfoliation syndrome.
*Sample sizes are shown as number of eyes, with number of subjects in parentheses.
†Number of eyes not specified.
‡Includes primary angle-closure (PAC) patients without glaucoma.

glaucoma therapy may affect ocular biomechanics. In particular, prostaglandin analogs (PGAs) can upregulate matrix metalloproteinases and reduce collagen type I, III, and IV levels in the sclera.[57,58] Biomechanical changes in ex vivo corneas have also been reported with PGA use, resulting in a reduction of corneal stiffness.[59] Other studies examined treatment-naïve patients, but ocular biomechanical properties vary with IOP,[60] so comparison of CH in groups with different IOP levels may be difficult to interpret (Table 3). The studies included in this report were not uniform in design and have individual strengths and limitations.

Primary Open-Angle Glaucoma. Five articles described studies from various geographic and ethnic populations comparing primary open-angle glaucoma (POAG) patients with a healthy control group. Four of the 5 studies provided level 1 evidence (Table 1). In 4 of these studies, patients with POAG were found to have a lower CH compared with healthy controls, although 1 of the 4 found no difference after controlling for age and IOP, and the fifth found no difference.

In a cross-sectional study of Chinese patients in Singapore, Narayanaswamy et al[50] compared POAG patients, primary angle-closure glaucoma (PACG) patients, and healthy controls. They found that CH was lower in POAG patients (9.5 mmHg; 95% confidence interval [CI], 9.2−9.5 mmHg; n = 162) compared with healthy controls (10.4 mmHg; 95% CI, 10.1−10.6 mmHg;

Table 2. Mean Corneal Hysteresis by Study Population

Authors	Mean Corneal Hysteresis (mmHg)						
	Normal	*OHT*	*POAG*	*PACG*	*PXS*	*PXG*	*NTG*
Ayala[44]	9.8 ± 1.6		9.0 ± 1.9			**8.0 ± 1.5**	
Cankaya et al[45]	9.4 ± 1.4				**8.5 ± 1.5**	**6.9 ± 2.1**	
Kaushik et al[48]	9.5 ± 1.4	9.2 ± 1.9	**7.9 ± 2.8**	9.3 ± 1.5*			**8.0 ± 1.6**
Narayanaswamy et al[50]	10.4 (10.1−10.6)†		**9.5 (9.2−9.5)**†	**9.1 (8.7−9.4)**†			
Pillunat et al[51]	9.9 ± 1.4	**10.2 ± 1.5**	**8.9 ± 1.4**				**9.0 ± 1.4**
Sun et al[52]	10.6 ± 1.4			**6.8 ± 2.1**			
Tejwani et al[54]	9.6 (9.4−10.4)‡		**7.7 (7.3−8.2)**‡	**8.2 (7.7−8.6)**‡			
Yazgan et al[55]	10.3 ± 1.4				**8.2 ± 1.4**	**6.8 ± 1.7**	

Values are mean ± standard deviation unless indicated. Values in bold are significantly different from normal controls.
NTG = normal-tension glaucoma; OHT = ocular hypertension; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliative glaucoma; PXS = pseudoexfoliation syndrome.
*Includes PAC patients without glaucoma.
†Mean with 95% confidence interval (CI).
‡Median with 95% CI.

Table 3. Mean Intraocular Pressure (mmHg) by Study Population

Authors	Mean Intraocular Pressure (mmHg)							Statistical Significance Reported
	Normal	*OHT*	*POAG*	*PACG*	*PXS*	*PXG*	*NTG*	
Ayala[44]	15.4 ± 3.6		16.4 ± 4.6*			17.5 ± 5.6*		N
Cankaya et al[45]	15.9 ± 2.9				15.8 ± 3.0*	16.3 ± 4.1*		Y
Kaushik et al[48]	13.7 ± 2.4	**22.2 ± 3.5**	**23.6 ± 12.4**	16.2 ± 3.9†			14.6 ± 4.5	Y
Narayanaswamy et al[50]	14.4 ± 2.7		**14.9 ± 3.9***	**16.5 ± 4.4***				Y
Pillunat et al[51]	15.5 ± 3.2	22.3 ± 6.2*	14.7 ± 5.1*				13.2 ± 3.7*	N
Sun et al[52]	11.0 ± 3.4			**31.6 ± 10.5**				Y
Tejwani et al[54]	14 (13.0–15.0)‡		**15 (14.0–16.0)*,‡**	**16 (14.5–18.0)*,‡**				Y
Yazgan et al[55]	15.2 ± 3.2				13.4 ± 3.1	**15.7 ± 4.0***		Y

Values in bold are significantly different from normal controls.
NTG = normal-tension glaucoma; OHT = ocular hypertension; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliative glaucoma; PXS = pseudoexfoliation syndrome.
*Medically treated.
†Includes PAC patients without glaucoma.
‡Median with 95% CI.

n = 150; $P < 0.001$). However, after adjusting for the effect of IOP and age, which was lower in the healthy controls than in the POAG group, the difference in CH between the 2 groups did not reach statistical significance (CH 9.6 vs. 10.1 mmHg for POAG and controls, respectively; $P = 0.06$). However, patients on IOP-lowering medication were included, which may have affected measurements of CH as discussed earlier.

Pillunat et al[51] performed an observational cross-sectional study comparing patients with high-pressure and low-pressure glaucoma, ocular hypertensives, and normal age-matched controls in Dresden, Germany. Recognizing the potential confounding factors influencing measurements of ocular biomechanics, they adjusted CH for age, axial length, CCT, and IOP. Adjusted CH was found to be significantly lower in "high-pressure glaucoma" in their study (8.94 ± 1.41 mmHg; n = 48 eyes) than in age-matched controls (9.86 ± 1.42 mmHg; n = 44 eyes; $P = 0.005$). High-pressure glaucoma patients included in this study were treated, but the authors noted that the amount and class of pressure-lowering medications did not affect CH in that study.

In a cross-sectional study from Bangalore, India, Tejwani et al[54] compared CH with POAG, PACG, and healthy eyes. For the POAG cohort, 83 patients were included and compared with 59 age- and CCT-matched controls, with 1 eye from each patient randomly selected for the study. The median CH in the POAG cohort (7.7 mmHg; 95% CI, 7.3–8.2 mmHg) was found to be lower ($P < 0.0001$) than in healthy controls (9.6 mmHg; 95% CI, 9.4–10.4 mmHg). However, there were 2 potential important confounders that were not matched between the groups. First, the median Goldmann applanation tonometry (GAT) IOP in the POAG cohort (15 mmHg; 95% CI, 14.0–16.0 mmHg) was higher ($P = 0.002$) than in healthy controls (14 mmHg; 95% CI, 13.0–15.0 mmHg). Second, all POAG patients were on medical management, with most (80.0%) on a combination of a PGA and a β-blocker.

A cross-sectional study from Kaushik et al[48] circumvented the issue of medication treatment effects on CH by comparing treatment-naïve POAG patients, primary angle-closure (PAC) patients, normal-tension glaucoma (NTG) patients, and healthy controls in Chandigarh, India. In addition, patients with previous intraocular surgery or laser were excluded. Their study found that CH was significantly lower in POAG patients (7.9 ± 2.8 mmHg; n = 36) than in healthy controls (9.5 ± 1.4 mmHg; n = 71; $P = 0.034$). However, because the patients were treatment naïve, IOP was significantly higher in the POAG group (23.6 ± 12.4 mmHg) compared with the healthy controls (13.7 ± 2.4 mmHg), which likely influenced the results. In addition, IOP was noted to be significantly correlated with CH ($P < 0.001$) in this study.

In a retrospective cross-sectional study based in Stockholm, Sweden, Ayala[44] compared CH among pseudoexfoliative glaucoma patients, POAG patients, and healthy controls matched for age. In contrast to the other 4 studies, no significant difference was found in CH between POAG patients (9.0 ± 1.9 mmHg; n = 30) and normal subjects (9.8 ± 1.6 mmHg; n = 30; $P = 0.23$). However, IOP was also similar between the POAG group (16.4 ± 4.6 mmHg) and the healthy controls (15.4 ± 3.6 mmHg), and the POAG group was treated with topical glaucoma medications.

Primary Angle-Closure Glaucoma. Four articles reported on studies comparing CH between PACG patients and healthy controls. Three of the 4 studies provided level 1 evidence (Table 1). Three of these articles included multiple glaucoma subgroups and are described in the above section on POAG. The limitations and confounders surrounding different IOP levels between groups and potential effects of topical hypotensive medications on CH persist in comparisons of PACG patients and normal subjects. Three of the 4 included studies reported CH being lower in PACG patients than in healthy controls, whereas 1 study found no statistically significant difference.

In a prospective case series from Wenzhou, China, Sun et al[52] measured CH in 40 patients with newly diagnosed unilateral PACG and compared values with the unaffected contralateral eyes and with healthy control subjects. They reported that CH was significantly lower in affected eyes (6.83 ± 2.08 mmHg) compared with contralateral eyes (10.59 ± 1.38 mmHg) or healthy control subjects (10.55 ± 1.41 mmHg; $P < 0.001$). However, IOP was also significantly higher in affected eyes (31.55 ± 10.48 mmHg) compared with contralateral eyes (12.03 ± 4.17 mmHg) or healthy control subjects (11.01 ± 3.36 mmHg; $P < 0.001$). They also reported a significant correlation between IOP and CH ($r = -0.67$; $P < 0.001$) at baseline but not after IOP reduction by medication and trabeculectomy. Corneal hysteresis increased in PACG eyes after treatment (9.50 ± 1.66 mmHg) but was still lower than in contralateral eyes or healthy controls ($P = 0.001$).

Narayanaswamy et al[50] reported from their study of Singapore Chinese patients that CH was lower in patients with medically treated PACG (9.1 mmHg; 95% CI, 8.7−9.4 mmHg; n = 131) than in healthy controls (10.4 mmHg; 95% CI, 10.1−10.6 mmHg; n = 150; $P < 0.001$). After adjusting for the effect of IOP and age, a statistically significant difference in CH between PACG patients (9.4 mmHg; 95% CI, 9.1−9.7 mmHg) and healthy controls (CH 10.1 mmHg; 95% CI, 9.8−10.4; $P = 0.006$) persisted.

In their cross-sectional study from Bangalore, India, Tejwani et al[54] compared 57 PACG patients with 59 age- and CCT-matched controls. One eye from each patient was randomly selected for the study. The median CH in the PACG cohort (8.2 mmHg; 95% CI, 7.7−8.6 mmHg) was found to be lower ($P < 0.0001$) than in healthy controls (9.6 mmHg; 95% CI, 9.4−10.4 mmHg). However, median IOP in the PACG cohort (16 mmHg; 95% CI, 14.5−18.0 mmHg) was higher ($P = 0.002$) than in healthy controls (14 mmHg; 95% CI, 13.0−15.0 mmHg). Similar to the POAG cohort, all PACG patients were on medical management, with most (91.5%) being treated with a combination of PGA and β-blocker topical drops.

In contrast to the other 3 studies, Kaushik et al[48] did not find a difference between angle-closure patients and controls in their study from Chandigarh, India. However, their study grouped patients with PAC without glaucoma and PACG into a category that they termed "primary angle-closure disease" (PACD). No difference in CH between patients with PACD (9.3 ± 1.5 mmHg; n = 59) and normal subjects (9.5 ± 1.4 mmHg; n = 71) was detected.[48] Interestingly, the PACD patients were treatment naïve, and IOP was higher in the PACG group (16.2 ± 3.9 mmHg) compared with the healthy controls (13.7 ± 2.4 mmHg). A lack of difference in CH between the PACD and healthy control groups was found despite the difference in IOP and a correlation between CH and IOP in that study.

Pseudoexfoliative (Exfoliative) Glaucoma. Three articles reported on studies comparing CH in pseudoexfoliation syndrome or pseudoexfoliative glaucoma and healthy controls, and all 3 studies provided level II evidence (Table 1). All 3 studies found CH to be lower in pseudoexfoliative glaucoma compared with healthy controls. Pseudoexfoliation syndrome patients without evidence of glaucoma tended to have higher CH than pseudoexfoliative glaucoma patients but lower CH than healthy controls. As with studies on other types of glaucoma, the results are confounded by differing IOP levels between groups and the use of topical hypotensive medications.

In the cross-sectional study from Stockholm, Sweden, by Ayala,[44] CH was found to be lower in patients with pseudoexfoliative glaucoma (8.0 ± 1.5 mmHg; n = 30) than in healthy controls (9.8 ± 1.6 mmHg; n = 30; $P = 0.0001$) or POAG patients (9.0 ± 1.9 mmHg; $P = 0.042$). It is not clear if IOP was different in the pseudoexfoliative glaucoma group (17.5 ± 5.6 mmHg) compared with healthy controls (15.4 ± 3.6 mmHg) or POAG patients (16.4 ± 4.6 mmHg) because the statistical significance of these differences was not reported. The pseudoexfoliative glaucoma patients had received IOP-lowering therapy.

Cankaya et al[45] reported on a cross-sectional study from Ankara, Turkey, comparing CH in gender- and age-matched patients with pseudoexfoliative glaucoma, pseudoexfoliation syndrome, and healthy controls. They found that CH was lowest in the pseudoexfoliative glaucoma group (6.9 ± 2.1 mmHg; n = 78), higher in the pseudoexfoliation syndrome group (8.5 ± 1.5 mmHg; n = 64), and highest in the healthy controls (9.4 ± 1.4 mmHg; n = 102). The difference between each group was statistically significant ($P < 0.001$). No statistically significant difference in GAT IOP was found between the groups ($P \geq 0.1$). Glaucoma patients in this study were on medical therapy (including 27 of 78 who were on PGAs).

From a case-control study in Malatya, Turkey, Yazgan et al[55] reported on a comparison of patients with pseudoexfoliative glaucoma, pseudoexfoliation syndrome, and healthy controls. Corneal hysteresis was found to be highest in the control group (10.3 ± 1.5 mmHg; n = 45), followed by pseudoexfoliation syndrome (8.2 ± 1.4 mmHg; n = 43) and then pseudoexfoliative glaucoma (6.8 ± 1.7 mmHg; n = 30), with all comparisons statistically significant ($P < 0.001$). However, there were several potentially confounding factors that were not controlled. First, there was a statistically significant difference ($P < 0.05$ for all comparisons) in CCT among all of the groups, with the control group having the highest value (546.3 ± 28 μm), followed by pseudoexfoliation syndrome (525.5 ± 35 μm) and then pseudoexfoliation glaucoma (509 ± 36 μm). Second, all but 3 newly diagnosed patients in the pseudoexfoliative glaucoma group were on medical therapy, with 17 of the remaining 27 patients on a PGA as combination or monotherapy. Third, IOP was lower in the pseudoexfoliation syndrome group (13.4 ± 3.1 mmHg; $P < 0.001$) than in the control group (15.2 ± 3.2 mmHg) or the pseudoexfoliation glaucoma group (15.7 ± 4.0 mmHg). Central corneal thickness, topical PGA eye drops, and IOP have all been associated with alterations in CH, but the exact effects are incompletely understood.

Normal-Tension Glaucoma. Two of the included articles compared NTG patients with healthy controls, and both studies provided level I evidence (Table 1). This group of

patients is particularly interesting because untreated NTG patients can be IOP matched to healthy controls, potentially eliminating 2 key confounding parameters in the evaluation of CH between populations: IOP and topical hypotensive medications. Both studies found CH to be lower in NTG patients compared with normal subjects.

In the study by Pillunat et al[51] from Dresden, Germany, NTG patients were defined as open-angle glaucoma patients with a history of untreated IOP $\leq$ 21 mmHg, and these patients were compared with healthy controls. Corneal hysteresis adjusted for age, axial length, CCT, and IOP was significantly lower in NTG patients (8.99 $\pm$ 1.40 mmHg; n = 38 eyes) than in controls (9.86 $\pm$ 1.42 mmHg; n = 44 eyes; $P = 0.005$). There was no difference in adjusted CH between POAG and NTG patients ($P = 0.978$). However, both POAG and NTG patients were currently receiving medical treatment for their glaucoma, leaving open the possibility that topical medications may have altered ocular biomechanical properties.

In their cross-sectional study in Chandigarh, India, Kaushik et al[48] reported on a comparison of treatment-naïve NTG patients compared with healthy controls. They found that CH was lower in NTG patients (8.0 $\pm$ 1.6 mmHg; n = 18) compared with normal subjects (9.5 $\pm$ 1.4 mmHg; n = 71; $P = 0.030$). Intraocular pressure was similar in the NTG group (14.6 $\pm$ 4.5 mmHg) compared with the healthy controls (13.7 $\pm$ 2.4 mmHg), but no statistical comparison of these 2 groups' mean IOPs was provided.

Ocular Hypertension. Two of the included articles reported on untreated ocular hypertension (OHT) patients compared with healthy controls with conflicting results.

In the cross-sectional study from Pillunat et al,[51] patients with OHT (defined as IOP > 21 mmHg on at least 2 occasions) were compared with normal controls. Corneal hysteresis adjusted for age, axial length, CCT, and IOP was significantly higher in OHT patients (10.18 $\pm$ 1.53 mmHg; n = 18 eyes) than in controls (9.86 $\pm$ 1.42 mmHg; n = 44 eyes; $P = 0.003$).

In their cross-sectional study, Kaushik et al[48] defined OHT as IOP between 22 and 31 mmHg on at least 2 successive measurements spaced 2 weeks apart at approximately the same time of day, along with open angles and normal optic disc. They did not find a difference in CH between patients with OHT (9.2 $\pm$ 1.9 mmHg; n = 38) and normal subjects (9.5 $\pm$ 1.4 mmHg; n = 71; $P > 0.05$). However, IOP was higher in the OHT group (22.2 $\pm$ 3.5 mmHg) compared with the healthy control group (13.7 $\pm$ 2.4 mmHg; $P < 0.001$), potentially confounding the results.

Corneal Hysteresis and the Risk of Glaucoma Development or Progression

Five of the included articles investigated the association between CH and the risk of disease progression in patients with an existing glaucoma diagnosis. Four of the 5 studies provided level I evidence (Table 1). All 5 of the studies evaluated open-angle glaucoma patients. Four of the 5 studies determined glaucoma progression based on visual field changes using automated perimetry, whereas 1 study determined progression based on structural changes measured with OCT. All 5 articles reported an association between lower CH and an increased risk or rate of glaucoma progression.

In a prospective longitudinal cohort study of open-angle glaucoma patients in San Diego, California, Medeiros et al[49] investigated CH as a predictor for the rate of visual field progression. The study included 114 eyes from 68 patients followed at 6-month intervals with standard automated perimetry using the SITA Standard 24-2 algorithm performed at each visit. A linear mixed model was used to investigate the significance of potential predictors for visual field progression, including baseline CH, baseline age, race, baseline IOP-GAT, CCT, and axial length. Patients were followed for a mean of 4.0 $\pm$ 1.1 years (range, 2.0–6.5 years) and had a median of 7 (range, 5–12) visual field tests. Corneal hysteresis was found to be significantly associated with the rate of visual field progression in a univariate model, with each 1 mmHg lower CH being associated with a 0.25% per year faster rate of visual field index decline ($P < 0.001$). In the multivariable model, the rate of visual field progression was significantly associated with CH ($P < 0.001$) and IOP ($P = 0.001$) but not with baseline age, race, CCT, or axial length.

Zhang et al[56] reported on a prospective longitudinal cohort study, which was also from San Diego, California, and which investigated the relationship between CH and the rate of retinal nerve fiber layer (RNFL) loss as measured using spectral-domain OCT in open-angle glaucoma patients. Random-coefficient models with random intercepts and random slopes were used to evaluate the role of CH, CCT, IOP, and demographics on the rates of RNFL loss during follow-up. The study included 186 eyes of 133 patients, followed for an average of 3.8 $\pm$ 0.8 years, with a median of 9 (range, 4–18) spectral-domain OCT tests during follow-up. In univariate analysis, each 1 mmHg lower baseline CH was found to be associated with an additional 0.13 μm per year of RNFL loss ($P = 0.011$). In a multivariable model, lower CH and higher IOP were associated with a faster rate of RNFL loss, but older age, African American ancestry, and CCT were not.

Congdon et al[46] reported on a prospective case series from Baltimore, Maryland, investigating the association of CH and CCT with glaucoma progression in a population of POAG and POAG-suspect patients. The study included 230 subjects, 172 of whom were on topical hypotensive medications or had previously undergone laser or incisional surgery for glaucoma. Multivariable generalized estimating equation models were used to determine factors associated with visual field progression following the criteria of the Ocular Hypertension Treatment Study. These factors included lower CH (odds ratio, 0.81 per mmHg higher; $P = 0.03$), as well as older age and treatment for glaucoma but not CCT. However, when axial length was included in the model, CH was no longer significantly associated with progression (odds ratio, 0.83; $P = 0.09$), but axial length was significantly associated ($P = 0.009$).

In a longitudinal cohort study from Durham, North Carolina, Susanna et al[53] investigated the role of CH in disease progression in patients with well-controlled IOP,

which they defined as all measurements no higher than 18 mmHg. The study included 445 eyes of 334 patients, of which 179 were considered to have medically well-controlled IOP. Among the eyes with well-controlled IOP, 42 (23.5%) had visual field progression and 137 (76.5%) remained stable over the follow-up period (4.1 ± 0.9 years). Eyes that progressed were found to have lower baseline CH (8.6 ± 1.3 mmHg) than stable eyes (9.4 ± 1.6 mmHg; $P = 0.014$). In addition, eyes that progressed also had thinner CCT (515.1 ± 33.1 μm) compared with stable eyes (531.1 ± 42.4 μm; $P = 0.018$), but there was no significant difference in age, sex, race, baseline mean deviation, peak IOP, mean IOP, or IOP fluctuation (defined as the standard deviation of the mean IOP measurements during follow-up), number of IOP-lowering medications, laser procedures, or glaucoma surgeries at baseline. Multivariable models indicated that low CH was significantly associated with glaucoma progression, with a 1 standard deviation decrease (1.5 mmHg) being associated with a 65% increased risk of visual field loss.

In another longitudinal cohort study from Durham, North Carolina, Estrela et al[47] investigated the role of CH asymmetry in asymmetric rates of visual field progression. The group included 126 POAG patients, followed for a mean of 4.3 ± 0.8 years. Asymmetry in CH, rate of visual field change, CCT, IOP, and baseline mean deviation were calculated, and correlations between these variables were assessed. Only CH asymmetry was correlated with asymmetry of visual field rate of change. Although the strength of association was weak ($r = 0.22$; $P = 0.01$), a 1 mmHg increase in CH asymmetry was associated with an increase in asymmetry of visual field rate of change by 34%.

Conclusions

Corneal hysteresis is a novel clinical parameter representing a response of ocular tissue to transient compression and release by an air-puff tonometer. Although the interpretation of this measurement is complex and influenced by multiple factors, including elasticity and viscosity, CH appears to provide additional information that could be useful for the clinical assessment of glaucoma suspects and patients.

Corneal hysteresis is generally lower in glaucoma patients than in healthy subjects or OHT patients, and glaucoma patients with lower CH appear to be at greater risk of disease progression. However, interpretation of CH measurements in an individual patient is complicated by IOP effects as well as medical, laser, and surgical therapy, and other influencing parameters such as age, CCT, and axial length. Nevertheless, most evidence suggests that the CH measurement is a potential adjunct in identifying glaucoma patients and those who may be at increased risk for disease progression.

Future Research

Current published studies focus on demonstrating an association between lower CH and glaucoma, or the risk of glaucoma progression, which is helpful in diagnosis and risk stratification. There was variation in the mean values reported for different normal populations that require further investigation. However, the main issue for further research is that it is unclear if lower CH is causative of disease and should be a target of therapy. Instead, it is possible that lower CH is a response of the eye to elevated IOP or an incidental change in the properties of glaucomatous eyes. Unfortunately, testing causality surrounding CH and glaucoma is extremely difficult because of the effects of IOP-lowering treatments on this parameter. To overcome this impasse, future research should elucidate the specific tissue properties that contribute to CH. Modification of these tissue properties in glaucoma animal models can then help to clarify if low CH is a causative factor in glaucoma and glaucoma progression. If found to be true, alteration of ocular tissue properties to increase CH could become a new target for disease therapy independent of IOP reduction.

Footnotes and Disclosures

Originally received: September 27, 2022.
Final revision: November 3, 2022.
Accepted: November 8, 2022.
Available online: December 16, 2022. Manuscript no. OPHTHA-D-22-01722.

[1] Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota.

[2] Department of Ophthalmology, Harvard Medical School, Massachusetts Eye & Ear, Glaucoma Service, Boston, Massachusetts.

[3] VA Eugene Healthcare Center, Eugene, Oregon.

[4] Casey Eye Institute, Oregon Health & Sciences University, Portland, Oregon.

[5] Department of Ophthalmology, Duke University School of Medicine, Durham, North Carolina.

[6] Ophthalmic Consultants of Boston, Boston, Massachusetts.

[7] Doheny Eye Center UCLA, Pasadena, California.

[8] Department of Ophthalmology, Southern California Permanente Medical Group, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California.

[9] USC Roski Eye Institute Keck Medicine of University of Southern California Los Angeles, Los Angeles, California.

[10] Department of Ophthalmology, UCSF Medical Center, San Francisco, California.

[11] Department of Ophthalmology, Vanderbilt University School of Medicine, Nashville, Tennessee.

[12] University of Florida College of Medicine, Jacksonville, Department of Ophthalmology, Jacksonville, Florida.

Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): V.C.: Consulting fees − Alcon Laboratories.

G.M.R.: Funding − Carl Zeiss Meditec.

Y.O.: Funding − Astellas.

Funded without commercial support by the American Academy of Ophthalmology.

Prepared by the Ophthalmic Technology Assessment Committee Glaucoma Panel and approved by the American Academy of Ophthalmology's Board of Trustees September 10, 2022.

HUMAN SUBJECTS: No human subjects were included in this study. All of the cited research had appropriate humans subjects research approval from the respective institutions. The requirement for informed consent was waived because of the retrospective nature of the study. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Sit, Chen, Takusagawa, Rosdahl, Hoguet, Chopra, Richter, Ou, Kim, WuDunn

Analysis and interpretation: Sit, Chen, Takusagawa, Rosdahl, Hoguet, Chopra, Richter, Ou, Kim, WuDunn

Data collection: Sit, Chen, Takusagawa, Rosdahl, Hoguet, Chopra, Richter, Ou, Kim, WuDunn

Obtained funding: N/A; Study was performed as part of the authors' regular employment duties. No additional funding was provided.

Overall responsibility: Sit, Chen, Takusagawa, Rosdahl, Hoguet, Chopra, Richter, Ou, Kim, WuDunn

Abbreviations and Acronyms:
CCT = central corneal thickness; **CH** = corneal hysteresis; **CI** = confidence interval; **GAT** = Goldmann applanation tonometry; **IOP** = intraocular pressure; **NTG** = normal-tension glaucoma; **OHT** = ocular hypertension; **ORA** = Ocular Response Analyzer; **PAC** = primary angle-closure; **PACD** = primary angle-closure disease; **PACG** = primary angle-closure glaucoma; **PGA** = prostaglandin analog; **POAG** = primary open-angle glaucoma; **RNFL** = retinal nerve fiber layer.

Keywords:
corneal hysteresis, intraocular pressure, primary open-angle glaucoma, Ocular Response Analyzer, ocular biomechanics.

Correspondence:
Andre Ambrus, MLIS, American Academy of Ophthalmology, Quality and Data Science, P.O. Box 7424, San Francisco, CA 94120-7424. E-mail: aambrus@aao.org.

References

1. Malihi M, Moura Filho ER, Hodge DO, Sit AJ. Long-term trends in glaucoma-related blindness in Olmsted County, Minnesota. *Ophthalmology*. 2014;121:134−141.
2. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. *Am J Ophthalmol*. 2000;130:429−440.
3. Brandt JD, Beiser JA, Kass MA, Gordon MO. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). *Ophthalmology*. 2001;108:1779−1788.
4. Kim KE, Park KH. Update on the prevalence, etiology, diagnosis, and monitoring of normal-tension glaucoma. *Asia Pac J Ophthalmol (Phila)*. 2016;5:23−31.
5. Girard MJ, Suh JK, Bottlang M, et al. Biomechanical changes in the sclera of monkey eyes exposed to chronic iop elevations. *Invest Ophthalmol Vis Sci*. 2011;52:5656−5669.
6. Sigal IA, Yang H, Roberts MD, et al. IOP-induced lamina cribrosa deformation and scleral canal expansion: independent or related? *Invest Ophthalmol Vis Sci*. 2011;52:9023−9032.
7. Salinas-Navarro M, Alarcon-Martinez L, Valiente-Soriano FJ, et al. Ocular hypertension impairs optic nerve axonal transport leading to progressive retinal ganglion cell degeneration. *Exp Eye Res*. 2010;90:168−183.
8. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma*. 2000;9:134−142.
9. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. *Ophthalmology*. 2008;115:1123−1129, e1123.
10. Musch DC, Gillespie BW, Niziol LM, et al. Intraocular pressure control and long-term visual field loss in the collaborative initial glaucoma treatment study. *Ophthalmology*. 2011;118:1766−1773.
11. Coudrillier B, Tian J, Alexander S, et al. Biomechanics of the human posterior sclera: age- and glaucoma-related changes measured using inflation testing. *Invest Ophthalmol Vis Sci*. 2012;53:1714−1728.
12. Downs JC, Suh JK, Thomas KA, et al. Viscoelastic material properties of the peripapillary sclera in normal and early-glaucoma monkey eyes. *Invest Ophthalmol Vis Sci*. 2005;46:540−546.
13. Kida T, Liu JH, Weinreb RN. Effect of 24-hour corneal biomechanical changes on intraocular pressure measurement. *Invest Ophthalmol Vis Sci*. 2006;47:4422−4426.
14. Kida T, Liu JH, Weinreb RN. Effects of aging on corneal biomechanical properties and their impact on 24-hour measurement of intraocular pressure. *Am J Ophthalmol*. 2008;146:567−572.
15. Laiquzzaman M, Bhojwani R, Cunliffe I, Shah S. Diurnal variation of ocular hysteresis in normal subjects: relevance in clinical context. *Clin Exp Ophthalmol*. 2006;34:114−118.
16. Shen M, Wang J, Qu J, et al. Diurnal variation of ocular hysteresis, corneal thickness, and intraocular pressure. *Optom Vis Sci*. 2008;85:1185−1192.
17. Kopito R, Gaujoux T, Montard R, et al. Reproducibility of viscoelastic property and intraocular pressure measurements obtained with the ocular response analyzer. *Acta Ophthalmol*. 2011;89:e225−e230.
18. Kynigopoulos M, Schlote T, Kotecha A, et al. Repeatability of intraocular pressure and corneal biomechanical properties measurements by the ocular response analyser. *Klin Monbl Augenheilkd*. 2008;225:357−360.
19. Moreno-Montanes J, Maldonado MJ, Garcia N, et al. Reproducibility and clinical relevance of the ocular response analyzer in nonoperated eyes: corneal biomechanical and tonometric implications. *Invest Ophthalmol Vis Sci*. 2008;49:968−974.
20. Wasielica-Poslednik J, Berisha F, Aliyeva S, et al. Reproducibility of ocular response analyzer measurements and their correlation with central corneal thickness. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:1617−1622.
21. Sigal IA, Yang H, Roberts MD, et al. IOP-induced lamina cribrosa displacement and scleral canal expansion: an analysis of factor interactions using parameterized eye-specific models. *Invest Ophthalmol Vis Sci*. 2011;52:1896−1907.
22. Gogola A, Jan NJ, Lathrop KL, Sigal IA. Radial and circumferential collagen fibers are a feature of the peripapillary sclera of human, monkey, pig, cow, goat, and sheep. *Invest Ophthalmol Vis Sci*. 2018;59:4763−4774.

23. Roberts MD, Grau V, Grimm J, et al. Remodeling of the connective tissue microarchitecture of the lamina cribrosa in early experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2009;50:681−690.
24. Nguyen TM, Aubry JF, Fink M, et al. In vivo evidence of porcine cornea anisotropy using supersonic shear wave imaging. *Invest Ophthalmol Vis Sci*. 2014;55:7545−7552.
25. Grytz R, Fazio MA, Girard MJ, et al. Material properties of the posterior human sclera. *J Mech Behav Biomed Mater*. 2014;29:602−617.
26. Danford FL, Yan D, Dreier RA, et al. Differences in the region- and depth-dependent microstructural organization in normal versus glaucomatous human posterior sclerae. *Invest Ophthalmol Vis Sci*. 2013;54:7922−7932.
27. Pijanka JK, Coudrillier B, Ziegler K, et al. Quantitative mapping of collagen fiber orientation in non-glaucoma and glaucoma posterior human sclerae. *Invest Ophthalmol Vis Sci*. 2012;53:5258−5270.
28. Elsheikh A, Geraghty B, Alhasso D, et al. Regional variation in the biomechanical properties of the human sclera. *Exp Eye Res*. 2010;90:624−633.
29. Geraghty B, Jones SW, Rama P, et al. Age-related variations in the biomechanical properties of human sclera. *J Mech Behav Biomed Mater*. 2012;16:181−191.
30. Girard MJ, Suh JK, Bottlang M, et al. Scleral biomechanics in the aging monkey eye. *Invest Ophthalmol Vis Sci*. 2009;50:5226−5237.
31. Knox Cartwright NE, Tyrer JR, Marshall J. Age-related differences in the elasticity of the human cornea. *Invest Ophthalmol Vis Sci*. 2011;52:4324−4329.
32. Hon Y, Chen GZ, Lu SH, et al. High myopes have lower normalised corneal tangent moduli (less 'stiff' corneas) than low myopes. *Ophthalmic Physiol Opt*. 2017;37:42−50.
33. Dastiridou AI, Ginis H, Tsilimbaris M, et al. Ocular rigidity, ocular pulse amplitude, and pulsatile ocular blood flow: the effect of axial length. *Invest Ophthalmol Vis Sci*. 2013;54:2087−2092.
34. Pallikaris IG, Kymionis GD, Ginis HS, et al. Ocular rigidity in living human eyes. *Invest Ophthalmol Vis Sci*. 2005;46:409−414.
35. Gordon MO, Beiser JA, Brandt JD, et al. The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:714−720. discussion 829-730.
36. Whitacre MM, Stein R. Sources of error with use of goldmann-type tonometers. *Surv Ophthalmol*. 1993;38:1−30.
37. Feltgen N, Leifert D, Funk J. Correlation between central corneal thickness, applanation tonometry, and direct intracameral iop readings. *Br J Ophthalmol*. 2001;85:85−87.
38. McCafferty S, Levine J, Schwiegerling J, Enikov ET. Goldmann applanation tonometry error relative to true intracameral intraocular pressure in vitro and in vivo. *BMC Ophthalmol*. 2017;17:215.
39. Chen S, Jin Z, Zheng G, et al. Diurnal variation of corneal elasticity in healthy young human using air-puff optical coherence elastography. *J Biophotonics*. 2021;14(8):e202000440.
40. Sit AJ, Lin SC, Kazemi A, et al. In vivo noninvasive measurement of young's modulus of elasticity in human eyes: a feasibility study. *J Glaucoma*. 2017;26:967−973.
41. Singh M, Han Z, Li J, et al. Quantifying the effects of hydration on corneal stiffness with noncontact optical coherence elastography. *J Cataract Refract Surg*. 2018;44:1023−1031.
42. Midgett D, Liu B, Ling YTT, et al. The effects of glaucoma on the pressure-induced strain response of the human lamina cribrosa. *Invest Ophthalmol Vis Sci*. 2020;61:41.
43. Oxford centre for evidence-based medicine. Levels of evidence (March 2011). http://www.Cebm.Net/index.Aspx?O=1025. Accessed June 2, 2017, 2011; v. 2020.
44. Ayala M. Corneal hysteresis in normal subjects and in patients with primary open-angle glaucoma and pseudoexfoliation glaucoma. *Ophthalmic Res*. 2011;46:187−191.
45. Cankaya AB, Anayol A, Ozcelik D, et al. Ocular response analyzer to assess corneal biomechanical properties in exfoliation syndrome and exfoliative glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2012;250:255−260.
46. Congdon NG, Broman AT, Bandeen-Roche K, et al. Central corneal thickness and corneal hysteresis associated with glaucoma damage. *Am J Ophthalmol*. 2006;141:868−875.
47. Estrela T, Jammal AA, Mariottoni EB, et al. The relationship between asymmetries of corneal properties and rates of visual field progression in glaucoma patients. *J Glaucoma*. 2020;29:872−877.
48. Kaushik S, Pandav SS, Banger A, et al. Relationship between corneal biomechanical properties, central corneal thickness, and intraocular pressure across the spectrum of glaucoma. *Am J Ophthalmol*. 2012;153:840−849, e842.
49. Medeiros FA, Meira-Freitas D, Lisboa R, et al. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. *Ophthalmology*. 2013;120:1533−1540.
50. Narayanaswamy A, Su DH, Baskaran M, et al. Comparison of ocular response analyzer parameters in chinese subjects with primary angle-closure and primary open-angle glaucoma. *Arch Ophthalmol*. 2011;129:429−434.
51. Pillunat KR, Hermann C, Spoerl E, Pillunat LE. Analyzing biomechanical parameters of the cornea with glaucoma severity in open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:1345−1351.
52. Sun L, Shen M, Wang J, et al. Recovery of corneal hysteresis after reduction of intraocular pressure in chronic primary angle-closure glaucoma. *Am J Ophthalmol*. 2009;147:1061−1066, e1061-1062.
53. Susanna BN, Ogata NG, Jammal AA, et al. Corneal biomechanics and visual field progression in eyes with seemingly well-controlled intraocular pressure. *Ophthalmology*. 2019;126:1640−1646.
54. Tejwani S, Devi S, Dinakaran S, et al. Diagnostic efficacy of normalization of corneal deformation variables by the intraocular pressure in glaucomatous eyes. *Invest Ophthalmol Vis Sci*. 2016;57:1082−1086.
55. Yazgan S, Celik U, Alagoz N, Tas M. Corneal biomechanical comparison of pseudoexfoliation syndrome, pseudoexfoliative glaucoma and healthy subjects. *Curr Eye Res*. 2015;40:470−475.
56. Zhang C, Tatham AJ, Abe RY, et al. Corneal hysteresis and progressive retinal nerve fiber layer loss in glaucoma. *Am J Ophthalmol*. 2016;166:29−36.
57. Gaton DD, Sagara T, Lindsey JD, et al. Increased matrix metalloproteinases 1, 2, and 3 in the monkey uveoscleral outflow pathway after topical prostaglandin f(2 alpha)-isopropyl ester treatment. *Arch Ophthalmol*. 2001;119:1165−1170.
58. Sagara T, Gaton DD, Lindsey JD, et al. Topical prostaglandin f2alpha treatment reduces collagen types I, III, and IV in the monkey uveoscleral outflow pathway. *Arch Ophthalmol*. 1999;117:794−801.
59. Zheng X, Wang Y, Zhao Y, et al. Experimental evaluation of travoprost-induced changes in biomechanical behavior of ex-vivo rabbit corneas. *Curr Eye Res*. 2019;44:19−24.
60. Elsheikh A, Alhasso D, Rama P. Biomechanical properties of human and porcine corneas. *Exp Eye Res*. 2008;86:783−790.