Corneal hysteresis and its relevance to glaucoma

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Purpose of review
Glaucoma is a leading cause of irreversible blindness worldwide. It is estimated that roughly 60.5 million people had glaucoma in 2010 and that this number is increasing. Many patients continue to lose vision despite apparent disease control according to traditional risk factors. The purpose of this review is to discuss the recent findings with regard to corneal hysteresis, a variable that is thought to be associated with the risk and progression of glaucoma.

Recent findings
Low corneal hysteresis is associated with optic nerve and visual field damage in glaucoma and the risk of structural and functional glaucoma progression. In addition, hysteresis may enhance intraocular pressure (IOP) interpretation: low corneal hysteresis is associated with a larger magnitude of IOP reduction following various glaucoma therapies. Corneal hysteresis is dynamic and may increase in eyes after IOP-lowering interventions are implemented.

Summary
It is widely accepted that central corneal thickness is a predictive factor for the risk of glaucoma progression. Recent evidence shows that corneal hysteresis also provides valuable information for several aspects of glaucoma management. In fact, corneal hysteresis may be more strongly associated with glaucoma presence, risk of progression, and effectiveness of glaucoma treatments than central corneal thickness.

Keywords
biomechanics, corneal hysteresis, glaucoma

INTRODUCTION
The cornea can be defined by its physical dimensions, such as its thickness, or physical behavior, for example, biomechanics. Initially, the biomechanical properties of the cornea were of interest primarily to refractive surgeons trying to understand keratoconus or risk factors for post-laser-assisted in-situ keratomileusis ectasia. Early work on this topic sought to identify Young’s modulus of the cornea in a variety of models. The development and commercialization of the corneal hysteresis measurement, however, made possible by the Reichert ocular response analyzer (ORA), accelerated research and clinical experience in this arena for the field of glaucoma [1,2].

The ORA is based on noncontact tonometer technology, which uses an air jet to apply force to the cornea and an electrooptical system to determine applanation [3]. This machine was initially developed to provide a Goldmann applanation tonometry (GAT)-like intraocular pressure (IOP) measurement without anesthesia or ocular contact; however, after David Luce, PhD, discovered that additional corneal information was also present in the measurement signal, a more advanced ORA was launched in 2005 (D. Luce, personal communication).

The Corvis ST, produced by Oculus (Wetzlar, Germany), has also been developed for biomechanical assessment of the eye. It uses an air jet tonometer to measure pressure and a high-speed Scheimpflug camera to simultaneously monitor corneal movement. It can calculate various parameters; however, there is limited published literature and the device is not yet approved by the Food and Drug Administration for measuring biomechanical properties.

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**The Cornea is Viscoelastic**

The cornea, like most biological materials, is ‘viscoelastic’, meaning that it contains characteristics of both elastic and viscous materials. A viscoelastic system can be illustrated by an automotive suspension strut. When a load is applied to the strut, the response is dependent on both the elastic properties of the component of the coil spring and the viscosity of the oil in the shock absorber.

Viscoelastic materials and systems are often characterized by hysteresis. Hysteresis is not actually an intrinsic or constant property, but a measurement characterizing how a material or system responds to the loading and unloading of an applied force [4,5].

Corneal hysteresis reflects the ability of corneal tissue to absorb and dissipate energy during a bidirectional applanation process (where energy is lost as heat during the rapid loading/unloading of the cornea).

**Operation of the Ocular Response Analyzer**

As the cornea moves inward and outward in response to the increasing and decreasing velocity of the air jet, its deformation is tracked by an electro-optical system. The inward and outward applanation events are identified by the peak amplitude of the reflected light hitting the photodetector.

Pressure values are recorded at the inward (P1) and outward (P2) applanation states. P1 and P2 are a function of the actual IOP, the static resistance of the cornea, and the dynamic (viscous) resistance of the cornea. The average of P1 and P2 provides a Goldmann-correlated IOP value referred to as IOPg. The difference between P1 and P2 is termed corneal hysteresis, given in mmHg (Fig. 1).

**Corneal Hysteresis: A New Ocular Parameter**

The corneal hysteresis measurement is repeatable in individual eyes [6] and strongly correlated in right and left eyes of the same patient [7]. Corneal hysteresis, however, differs from person to person. It is not strongly correlated with other common metrics such as corneal radius, astigmatism, spherical equivalence (SE), axial length, and IOP measured by GAT. Corneal hysteresis and central corneal thickness (CCT) are moderately correlated in normal corneas ($r = 0.43$ [8], $r = 0.42$ [9], $r = 0.74$ [10]) and weakly to moderately correlated in corneas with disorder ($r = 0.20$ [11], $r = 0.43$ [10], $r = 0.44$ [12], $r = 0.45$ [9], $r = 0.51$ [13]). Corneal hysteresis is lower than normal in patients with corneal disorders, such as Fuchs’ keratoconus, and glaucoma [14].

**Corneal Biomechanics and the Measurement of Intraocular Pressure**

The IOPg measurement provided by the ORA is intended to estimate GAT. In studies involving more than 200 patients with glaucoma, both Broman et al. [11] and Ehrlich et al. [15] demonstrated that GAT and ORA IOPg show good agreement, with Ehrlich...
et al. finding a mean GAT–IOPg difference of 0.1 mmHg (±0.3). Lam et al. [16] showed that IOPg had a mean difference of 0.33 compared with GAT in a study of 125 normal Chinese eyes.

**CORNEAL HYSTERESIS IN NORMAL EYES**

Shah et al. [9] reported an average corneal hysteresis of 10.7 in 207 normal eyes (average age = 62.1 years) and Carbonaro et al. [17] reported a mean corneal hysteresis of 10.24 in a large twin study. Other studies have reported similar measurements. Several investigations have also shown that, in normal eyes, corneal hysteresis does not vary significantly throughout the day [7,18–20].

**CORNEAL HYSTERESIS AND STRUCTURAL MARKERS OF GLAUCOMA**

Various investigators have found associations between corneal hysteresis and optic nerve head (ONH) morphology. In a prospective study of untreated patients with primary open-angle glaucoma (POAG), Prata et al. [21] showed that low corneal hysteresis was associated with greater mean cup depth \( r = -0.34, P = 0.03 \) and a larger cup-to-disc ratio \( r = 0.41, P = 0.01 \), independent of IOP and disc size. Low CCT was only associated with mean cup depth \( r = 0.35, P = 0.02 \). Khawaja et al. [22*] analyzed data from 5134 participants in the European Prospective Investigation of Cancer–Norfolk Eye Study and found that corneal hysteresis was positively associated with Heidelberg retina tomograph (HRT) rim area \( P < 0.001 \) and negatively associated with HRT linear cup-to-disc ratio \( P < 0.001 \), after adjustment for IOPg and other possible confounders. Corneal hysteresis was also positively associated with GDx variable cornea compensation retinal nerve fiber layer (RNFL) average thickness \( P = 0.006 \). Finally, Bochmann et al. [23] showed that patients with acquired pit of the optic nerve had significantly lower corneal hysteresis than patients without such structural changes of the optic disc. These findings may be due to the pressure-independent mechanisms involved in the pathogenesis of optic nerve changes in glaucoma or they may indicate that corneal hysteresis is somehow associated with the accumulation of IOP-related optic nerve damage.

Corneal hysteresis is also associated with ONH deformation after acute IOP reduction in patients with POAG. Prata et al. [24] found that low corneal hysteresis was associated with a greater change in cup area \( r^2 = 0.17, P < 0.01 \), after controlling for baseline IOP and magnitude of IOP change. This did not hold in a multivariable model incorporating all significant factors. Wells et al. [25] showed that low corneal hysteresis was correlated with greater mean cup depth increase \( \beta = 0.032 \). Eyes with higher corneal hysteresis experienced more ONH deformation with IOP elevation, a process that may allow the eye to dissipate mechanical forces and better protect the retinal nerve fibers than an eye with lower corneal hysteresis. Baseline CCT was not associated with ONH parameters in either study.

In general, there has been very limited evidence for a relationship between structural optic nerve damage and corneal hysteresis. Mansouri et al. [26] conducted a cross-sectional study of 299 glaucomatous eyes. After adjusting for CCT, age, and axial length, corneal hysteresis was not associated with RNFL thickness measured by either polarimetry or spectral-domain optical coherence tomography. Vu et al. [27*] conducted a retrospective study of 131 patients with glaucoma. In a univariable model, corneal hysteresis varied as a function of mean deviation and spectral-domain optical coherence tomography RNFL thickness \( \beta = 0.2, P = 0.001 \); after multivariable analysis, however, the relationship between corneal hysteresis and RNFL did not hold. Finally, Carbonaro et al. [28*] conducted a study in 1754 population-based (normal) study participants from the TwinsUK cohort and did not find an association between either corneal hysteresis or CCT and quantitative measures of optic disc cupping (optic disc area, cup area, and vertical cup-to-disc ratio).

**LOW CORNEAL HYSTERESIS IS ASSOCIATED WITH VARIOUS TYPES OF GLAUCOMA**

Several studies have compared the biochemical characteristics of eyes with and without glaucoma. It has been repeatedly shown that patients with glaucoma have significantly lower corneal hysteresis and CCT than individuals with normal eyes [23,29].

**Primary open-angle glaucoma**

Corneal hysteresis is significantly lower in POAG eyes than normal eyes [10,30]. With analysis of variance, Sullivan-Mee et al. [31] demonstrated that corneal hysteresis was significantly lower in POAG patients than ocular hypertension, glaucoma suspect, and normal patients. In a multivariable model, corneal hysteresis continued to discriminate between the POAG and the normal group, whereas CCT did not do so.

Castro et al. [32] examined corneal hysteresis in POAG patients with and without diabetes mellitus. Patients with diabetes presented significantly higher
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corneal hysteresis values than patients without dia-
tes (\(P = 0.04\); CCT did not differ between the
roups (\(P = 0.21\)).

Asymmetric primary open-angle glaucoma
Anand et al. [33] found that corneal hysteresis was
significantly lower in the worse eye of POAG patients
with visual field asymmetry (\(P < 0.001\)), independent
of its effect on IOP measurement. No difference was
seen in CCT or GAT values. On the contrary, Hirneiss
et al. [34] did not find a significant difference in
corneal hysteresis between eyes of patients with uni-
elateral POAG, after correcting for IOP.

Primary angle-closure glaucoma
Narayanaswamy et al. [35] compared corneal hys-
teresis and IOPg in 443 Chinese patients with primary
angle-closure glaucoma (PACG), POAG, or normal
eyes in a prospective observational study. After
adjusting for age, sex, and GAT–IOP, corneal hys-
teresis was significantly lower only in eyes with
PACG in comparison with normal eyes (9.4 vs.
10.1 mmHg; \(P = 0.006\)). Corneal hysteresis did not
differ between eyes with PACG and POAG.

Normal tension glaucoma and ocular
hypertension
Multiple investigators have shown that corneal hys-
teresis was significantly lower in patients with nor-
mal tension glaucoma (NTG) compared with normal
patients [30,36,37]. Of these, both Grise-Dulac et al.
[36] and Morita et al. [37] did not find a significant
difference in CCT between the two groups. Ang et al.
[38] showed that mean corneal hysteresis was higher
in eyes with NTG than eyes with POAG, albeit it was a
small but significant difference.

Pseudoexfoliative glaucoma
In a prospective case series of 73 eyes, Ozkok et al.
[39\*] showed that corneal hysteresis was signifi-
cantly lower in patients with pseudoexfoliative glau-
coma (PEXG) (8.8 ± 1.4 mmHg) than in patients
with POAG (9.9 ± 1.2 mmHg; \(P = 0.0007\)); CCT did
not differ between groups (\(P = 0.66\)). Ayala [40] re-
trospectively determined that corneal hysteresis was
lower in patients with PEXG in comparison with
POAG (\(P = 0.042\)) and normal patients (\(P = 0.0001\)).

Congenital glaucoma
Both Kirwan et al. [41] and Gatzioufas et al. [13\*]
found that patients with congenital glaucoma had
significantly lower corneal hysteresis than normal
eyes.

CORNEAL HYSTERESIS AND GLAUCOMA
PROGRESSION
In the first publication to investigate the potential
utility of the corneal hysteresis measurement in
glaucoma, Congdon et al. [42] determined that
low corneal hysteresis, but not CCT, was associated
with progressive visual field loss in 230 patients with
5 years of visual field follow-up history.

Medeiros et al. [43\*\*] conducted a prospective
cohort study to determine if baseline corneal hys-
teresis was predictive of rate of visual field index
(VFI) decline in glaucomatous patients. The study
included 68 patients (114 eyes) with glaucoma,
followed for an average of 4.0 years. Linear mixed
models showed that corneal hysteresis and baseline
IOP, but not CCT, influenced the rate of visual field
progression. In a univariable model, each 1 mmHg
decrease in baseline corneal hysteresis was associ-
ated with a 0.25%/year faster rate of VFI decline over
time (\(P < 0.001\)). A multivariable model examined
the interaction between and combined effect of
baseline corneal hysteresis and baseline IOP on rate
of progression. In individuals with low-baseline
corneal hysteresis, baseline IOP had a significantly
larger influence on rate of visual field loss. The
fastest rate of decline was expected in individuals
with low corneal hysteresis and high IOP. The multi-
variable model also showed that CCT was associ-
ated with rate of visual field loss; corneal hysteresis,
however, explained three times as much of the
variation in slopes of VFI change than CCT (17.4 vs.
5.2\%, respectively).

De Moraes et al. [44] also demonstrated in a
retrospective cohort study that low corneal hyste-
resis is associated with faster rates of glaucoma
progression. In 153 patients, followed for an average
of 5.3 years, the mean rate of VFI change was
−0.34 dB/year. Individuals who met a preestab-
lished definition of progression had lower corneal
hysteresis (7.5 ± 1.4 vs. 9.0 ± 1.8 mmHg, \(P < 0.01\))
and lower CCT (525.0 vs. 542.3 \(\mu\)m, \(P = 0.04\)) com-
pared with individuals who did not. After multi-
ivariate analysis, corneal hysteresis (OR = 1.55 per
mmHg lower, \(P < 0.01\)) remained a statistically sig-
nificant predictor of VFI change. The authors con-
cluded that although both corneal biomechanical
(corneal hysteresis) and physical (CCT) properties
are correlated with glaucoma progression, corneal
hysteresis may be more strongly associated.

Finally, Chee et al. [45\*] demonstrated that
corneal hysteresis (but not CCT or IOP) was associated
with overall structural glaucomatous progression
seen on a retrospective study of serial fundus photographs analyzed using flicker chronoscopy. This finding indicated that corneal hysteresis is directly associated with progressive glaucomatous optic neuropathy.

**CORNEAL HYSTERESIS AND INTRAOCULAR PRESSURE REDUCTION THERAPY: INTRAOCULAR PRESSURE REDUCTION LEADS TO AN INCREASE IN CORNEAL HYSTERESIS**

Studies have shown an inverse relationship between corneal hysteresis and IOP [38,46]. As IOP decreases, corneal hysteresis increases, and vice versa. Tsikripis et al. [47*] showed in a 3-year study of 108 eyes with POAG that IOP values significantly decreased and corneal hysteresis constantly and significantly increased after local prostaglandin analogue (PGA) treatment.

Sun et al. [46] showed the same result at 2 weeks in 40 unilateral patients with PACG who underwent IOP reduction medically, followed by trabeculectomy. Corneal hysteresis in the treated eye still remained lower than that of the fellow, healthy eye.

In a prospective comparative case series by Pakravan et al. [48*], corneal hysteresis was assessed before and 3 months after surgery in 23 eyes undergoing trabeculectomy, 23 eyes undergoing phacotrabeculectomy, 17 eyes undergoing Ahmed glaucoma value implantation, and 26 nonglaucomatous eyes undergoing phacoemulsification. Corneal hysteresis significantly increased after 3 months following the glaucoma surgeries \((P < 0.001)\). Postoperative corneal hysteresis increase in glaucomatous eyes was more significant when IOP was reduced by >10 mmHg.

**BASELINE CORNEAL HYSTERESIS IS ASSOCIATED WITH MAGNITUDE OF INTRAOCULAR PRESSURE REDUCTION FOLLOWING THERAPY**

Agarwal et al. [49] conducted a retrospective study with 109 eyes of 57 patients with POAG to examine factors associated with the magnitude of IOP reduction following PGA therapy. Low-baseline corneal hysteresis (but not baseline CCT) was associated with greater IOP reduction. Patients in the lowest quartile of corneal hysteresis (mean 7.0 mmHg) experienced 29.0% IOP reduction whereas those in the highest corneal hysteresis quartile (mean 11.9 mmHg) experienced 7.6% IOP reduction \((P = 0.006)\). A multivariate analysis controlling for baseline IOP demonstrated that baseline corneal hysteresis independently predicted the magnitude of IOP reduction from PGA therapy \((\beta = 3.5, P = 0.01)\).

In addition, Hirneiss et al. [50*] showed that low corneal hysteresis was associated with greater IOP reduction following selective laser trabeculoplasty (SLT). Sixty-eight patients with open angle glaucoma uncontrolled with topical medication were enrolled. In linear regression analysis, both corneal hysteresis and corneal resistance factor together with the baseline IOP improved the modeling power for the IOP lowering effect of SLT \((R^2 = 0.64, \text{ respectively})\). CCT did not improve the predictive power of baseline IOP \((P = 0.67)\). This finding suggests that greater IOP lowering in eyes with low corneal hysteresis cannot be explained by medication absorption, but instead must be related to either measurement artifact or truly greater pressure lowering in eyes with lower corneal hysteresis. The data thus far are consistent with the possibility that in eyes with high corneal hysteresis, IOP reduction may appear modest following therapy, perhaps because of high corneal hysteresis levels bias toward elevated IOP readings from GAT.

**CORNEAL HYSTERESIS AND DEMOGRAPHICS**

Hastline et al. [51] retrospectively evaluated 270 patients with glaucoma and found that African-Americans have lower CCT (529.3 μm) and corneal hysteresis (8.7 mmHg) compared with Hispanics (544.7 μm, \(P = 0.008\); 9.4 mmHg, \(P = 0.007\)) and Whites (549.9 μm, \(P < 0.001\); 9.8 mmHg, \(P < 0.001\)).

Detry-Morel et al. [52] also found that corneal hysteresis was lower in African normal and POAG patients in comparison to their White counterparts \((P < 0.001)\). African patients with POAG were younger than White patients with POAG, and low corneal hysteresis may be a contributing factor.

On the contrary, Leite et al. [53] did not find a difference in corneal hysteresis between African-American and White patients after adjusting for CCT, age, axial length, and corneal curvature. A significant relationship was found between corneal hysteresis and CCT, and investigators concluded that the increased susceptibility to disease among Blacks may be explained in part by differences in CCT. David et al. [54*] showed that corneal hysteresis did not significantly differ by sex in normal eyes.

**CONCLUSION**

Corneal biomechanics can influence the accuracy of GAT and other tonometers. Although valuable in estimating glaucoma risk, CCT is a suboptimal surrogate for the mechanical bending characteristics of the cornea. Correction of IOP based on a CCT
formula is mathematically imperfect [55]; using biomechanical properties, such as corneal hysteresis, to adjust IOP may be less biased by corneal thickness and better associated with glaucoma status.

Biomechanical properties provide valuable information about the risk of glaucoma development and progression and may predict the effectiveness of various glaucoma therapies for individual patients. Although CCT continues to be a valuable tool, clinicians should also consider incorporating hysteresis measurements into practice. In several studies comparing the two variables, corneal hysteresis was more strongly related to progression than CCT. Corneal hysteresis has been the subject of considerable research recently, and with further investigation, its clinical implications for the diagnosis and management of glaucoma will become clearer.

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Conflicts of interest

M.D. has no conflicts of interest. D.A.T. is an employee with Reichert Inc. N.M.R. is associated as a Consultant with Reichert and Glaukos, a Consultant and Speaker with Allergan, Inc., Alcon Laboratories, Iridex, Merge Healthcare, and Carl Zeiss Meditec, and a Speaker with Merck Pharmaceuticals.

REFERENCES AND RECOMMENDED READING

A comprehensive list of references and recommended readings can be found in the original document. This is beyond the scope of this summary.
Corneal hysteresis and its relevance to glaucoma

Deol et al.

This study suggested that the biomechanical properties of the eye may differentiate between pseudexfoliative glaucoma and POAG.
This study shows that low corneal hysteresis is more strongly associated with the rate of glaucoma progression than CCT, the current standard for estimation of glaucoma risk and progression. Individuals with low corneal hysteresis and high IOP are at the highest risk for rapid visual field loss.
Corneal hysteresis is directly associated with glaucomatous optic neuropathy, not just with visual field loss.
This study corroborates previous studies that show an inverse relationship between corneal hysteresis and baseline IOP, as corneal hysteresis increases after IOP reduction through prostaglandin therapy.
This study shows that corneal hysteresis will increase after various combinations of glaucoma therapy, displaying the inverse relationship between corneal hysteresis and IOP.
This study shows that in patients with low-baseline corneal hysteresis, there will be a greater reduction in IOP following SLT. Baseline corneal hysteresis may thus be a good predictor for the effectiveness of various IOP reduction therapies.