Central Corneal Thickness and Corneal Hysteresis Associated With Glaucoma Damage

NATHAN G. CONGDON, MD, MPH, AIMEE T. BROMAN, MA, KAREN BANDEEN-ROCHE, PHD, DAVINDER GROVER, MPH, AND HARRY A. QUIGLEY, MD

• PURPOSE: We sought to measure the impact of central corneal thickness (CCT), a possible risk factor for glaucoma damage, and corneal hysteresis, a proposed measure of corneal resistance to deformation, on various indicators of glaucoma damage.

• DESIGN: Observational study.

• METHODS: Adult patients of the Wilmer Glaucoma Service underwent measurement of hysteresis on the Reichert Ocular Response Analyzer and measurement of CCT by ultrasonic pachymetry. Two glaucoma specialists (H.A.Q., N.G.C.) reviewed the chart to determine highest known intraocular pressure (IOP), target IOP, diagnosis, years with glaucoma, cup-to-disk ratio (CDR), mean defect (MD), pattern standard deviation (PSD), glaucoma hemifield test (GHT), and presence or absence of visual field progression.

• RESULTS: Among 230 subjects, the mean age was 65 ± 14 years, 127 (55%) were female, 161 (70%) were white, and 194 (85%) had a diagnosis of primary open-angle glaucoma (POAG) or suspected POAG. In multivariate generalized estimating equation models, lower corneal hysteresis value ($P = .03$), but not CCT, was associated with visual field progression. When axial length was included in the model, hysteresis was not a significant risk factor ($P = .09$). A thinner CCT ($P = .02$), but not hysteresis, was associated with a higher CDR at the most recent examination. Neither CCT nor hysteresis was associated with MD, PSD, or GHT "outside normal limits."

• CONCLUSIONS: Thinner CCT was associated with the state of glaucoma damage as indicated by CDR. Axial length and corneal hysteresis were associated with progressive field worsening. (Am J Ophthalmol 2006; 141:868–875. © 2006 by Elsevier Inc. All rights reserved.)

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From the Wilmer Eye Institute, Johns Hopkins University School of Medicine (N.G.C., A.T.B., D.G., H.A.Q.), and Johns Hopkins Bloomberg School of Public Health (K.B.-R.), Baltimore, Maryland.

Inquiries to Nathan G. Congdon, MD, Wilmer 120, 600 N Wolfe Street, Baltimore, MD 21287; e-mail: ncongdon@jhmi.edu

INTRAOCULAR PRESSURE (IOP) IS THE MOST SIGNIFICANT risk factor for glaucoma and remains at present the only parameter for which treatment has been demonstrated to decrease glaucoma incidence[1] and progression.[2–4] Increasing attention has focused on the impact of corneal parameters, particularly central corneal thickness (CCT), as a potential determinant of both measured IOP and glaucoma risk. Measured IOP has been demonstrated to vary with CCT in tonometry using the Goldmann tonometer,[5–8] the Tono-Pen XL,[7,9] the pneumotonometer,[10] and noncontact[5,11] tonometry (Ocular Response Analyzer [ORA], Reichert Ophthalmic Instruments, Depew, New York, USA). IOP is overestimated in eyes with thicker corneas and underestimated in thinner ones, in a relationship that has not been precisely specified and may or may not be linear in the range of typical IOP. Furthermore, thinner CCT may be a significant, independent risk factor for open-angle glaucoma among persons with ocular hypertension.[12] The relationship of CCT to glaucoma risk has been supported by some studies[13–15] but not by a clinical trial based on population-based recruitment.[2] Thus, it is unclear whether the impact of CCT as a risk factor for glaucoma is mediated largely through its role in determining measured IOP, or whether the thickness of the cornea is a surrogate for greater susceptibility of the eye to damage.

Additionally, CCT is of clinical interest due to the fact that an estimated 1.4 million persons are undergoing laser in situ keratomileusis (LASIK) procedures annually.[16] The corneal thinning from refractive surgery affects IOP measurement[17,18] and, possibly, glaucoma risk. The majority of persons undergoing LASIK are myopic and thus are at increased risk for glaucoma[19]; hence, there is a need to better understand the association between corneal anatomy and physiology on the one hand and measured IOP and glaucoma risk on the other.

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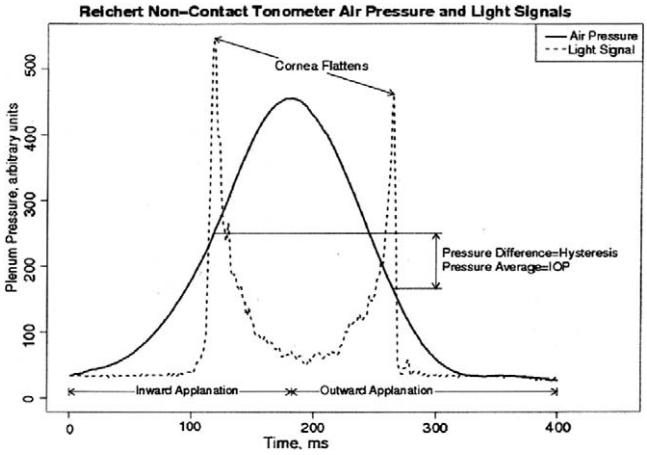

FIGURE. Corneal hysteresis as defined on the curve showing corneal applanation signal and air pressure over time.

Whereas CCT has been widely studied, it is likely that other factors, including corneal hydration,[20] connective tissue composition, and bio-elasticity, all determine to some extent the response of the corneoscleral shell to the force applied during the measurement of IOP. Epidemiologic studies further suggest that tonometry may demonstrate systematic bias in the measurement of IOP in certain racial groups when compared with manometrically measured values,[21] perhaps as a result of population differences in composition of the ocular coats.

The ORA determines IOP and corneal hysteresis during rapid motion of the cornea in response to the short-duration (20-ms) air impulse. The air impulse causes the cornea to move inward, through applanation, and into slight concavity. Milliseconds after applanation, the air pump shuts off and the cornea moves through a second applanation while returning from concavity to its normal convex curvature (Figure).

An electro-optical collimation detector system that monitors the corneal curvature in the central 3.0-mm diameter throughout the 20-ms measurement period establishes two applanation event times, corresponding to two well-defined peaks of the detector signal. The pressure values at the "inward" and "outward" applanation event times are averaged (P_{ave}), and then a regression of this average is performed vs Goldmann applanation tonometry, giving a slope "m" and an intercept "b." The inverse calculation is then carried out to calibrate the instrument to read a "Goldmann equivalent value," defined as (P_{ave} − b)/m. The Goldmann correlation is applied to the difference of the two applanation event time pressures to provide the corneal hysteresis in mm Hg. The measurement process is described in more detail elsewhere.[22]

The difference of the two applanation event pressures is determined by viscoelastic properties of the corneoscleral shell.[23] The rapid motion of the cornea during deformation creates velocity (rate)-dependent forces that oppose the forces (pressure) created by the air impulse. These opposition forces absorb energy from the air impulse, causing time delays (hence the term "hysteresis") in the occurrence of the applanation events. These time delays cause the inward and outward applanation event pressures to increase and decrease, respectively. Thus the difference in the pressures reflects a viscoelastic biomechanical property of the cornea.

The aim of this study was to measure and to compare corneal thickness and hysteresis as anatomic and physiologic parameters to the clinical features and history of progressive worsening among patients with glaucoma, ocular hypertension, or suspected glaucoma followed in a university glaucoma service.

METHODS

THIS RESEARCH WAS CARRIED OUT IN ACCORD WITH THE Declaration of Helsinki and after approval from the Institutional Review Board of the Johns Hopkins University School of Medicine. Subjects were over 18 years of age and were recruited sequentially among patients presenting to the Glaucoma Service of the Wilmer Eye Institute between December 1, 2003, and August 25, 2004. After obtaining informed consent, study personnel measured axial length and keratometry (IOL Master, Zeiss Meditec, Dublin, California). Visual acuity was measured with Snellen charts and current spectacle correction. Subjective refraction was performed if vision was worse than 20/40 in either eye. Demographic and clinical historical data were obtained, including date of birth, gender, self-identified race or ethnicity, time since diagnosis as an open-angle glaucoma suspect or patient, and glaucoma medications currently being used.

Next, IOP was measured with the Goldmann and ORA tonometers. On account of the known effect of tonometry in lowering IOP, each subject was assigned a random order for tonometer type and first eye measured. For Goldmann, three readings were taken in each eye; for ORA, two measurements were made in each eye. Topical anesthetic was placed in each eye before tonometry. Ultrasonic pachymetry (DGH Technology, Exton, Pennsylvania, USA) was then performed three times in each eye. All of these examinations were performed by a technician who is experienced in carrying out study protocols.

Charts for all study subjects were reviewed by one of two fellowship-trained glaucoma specialists (H.A.Q. or N.G.C.) to obtain the following information: baseline untreated IOP, target IOP, diagnosis, current or previous glaucoma treatment, duration of such treatment, cup-to-disk ratio (CDR) in each eye (based on photographs where available; otherwise based on the most recent CDR or disk description given in the chart), mean defect (MD), glaucoma hemifield test (GHT), and pattern standard deviation (PSD) on the most recent reliable visual field for each eye (or the most recent

field if no reliable fields were available), and presence or absence of visual field progression in each eye.

Progression of the field was defined as follows: among persons with three or more reliable fields over three or more years, or with five reliable fields in less than three years, progression was defined as having achieved the standard of "conversion" in the Ocular Hypertension Treatment Study (OHTS)[12] (if previously normal), or (if previously damaged as evidenced by an abnormal GHT or PSD) having worsened by 1 dB or greater per year in either MD or PSD,[24] without documented clinical evidence of cataract sufficient to explain the change. A "reliable" visual field was defined as having fixation losses of 33% or less,10% or fewer false positives, and 10% or fewer false negatives. When MD was greater than 4 dB, false negatives were no longer used as a reliability criterion.

It should be noted that all subjects underwent only a single study-specific visit and that the determination of visual field progression was made retrospectively on the basis of chart review.

For the purposes of this study, open-angle glaucoma was defined by the presence of a reliable visual field that was abnormal according to OHTS criteria[12] (that is, PSD abnormal at the 0.05 level or GHT outside normal limits at the $P = .01$ level, or both), with an optic nerve (photograph, heidelberg retinal tomograph (HRT) image, description, or CDR) thought to be consistent with the field damage by a fellowship-trained glaucoma specialist (H.A.Q. or N.G.C.).

Either one or both eyes of a subject could be eligible for the study. Eligibility requirements for an eye included no intraocular surgery within 90 days of examination and no finding on examination or by history of a condition other than glaucomatous optic neuropathy that would be expected to affect the visual field.

Thirty-four eyes were identified as having clinical suspicion of corneal edema on chart review. All analyses were carried out with and without these eyes. Analyses were also carried out including the entire data set, and then including only those persons (194 of 228, 85.1%) with a diagnosis of open-angle glaucoma or suspected open-angle glaucoma. Other diagnoses, including angle-closure glaucoma, suspected angle-closure glaucoma, and various secondary glaucomas, were based on the diagnosis recorded in the chart by the original examining physician.

Outcome measures for this study included CDR, "outside normal limits" on the GHT, progression of glaucoma, MD, and PSD. All outcome measures were collected for each eye separately. Associations were made between outcome measures and ocular characteristics in multiple linear or logistic regression models, adjusting for age, gender, and race. Ocular characteristics included corneal thickness, corneal hysteresis, axial length, glaucoma treatment, number of years of glaucoma diagnosis, and both current and untreated IOP. CDR, MD, and PSD were modeled as continuous variables, whereas GHT and progression were modeled as binary variables. Potential explanatory variables were observed in this model one at a time, and then all variables were placed in the model together. We did not use a stepwise model. We did not make any hypotheses about interactions and thus did not explore these in the models.

TABLE 1. Demographic and Diagnostic Characteristics of 230 Subjects Participating in a Study of Determinants of Glaucoma Damage and Progression

Category	n (%)
Race	
White	161 (70.0%)
Black	43 (18.7%)
Other	26 (11.3%)
Age (y)	
20–39	14 (6.1%)
40–59	48 (20.9%)
60–69	78 (33.9%)
70–79	58 (25.2%)
80–100	32 (13.9%)
Gender	
Female	127 (55.2%)
Male	103 (44.8%)
Diagnosis	
OAG/OAG suspect	194 (85.1%)
Other	34 (14.9%)
Glaucoma treatment*	
Yes	172 (74.8%)
No	58 (25.2%)

OAG = open-angle glaucoma.
*Current topical hypotensive therapy in either eye, or history of laser or incisional glaucoma surgery in either eye.

Whereas the distribution of CDR was close to normal, the distributions of MD and PSD were highly skewed. To address this issue, linear regression was performed and confidence intervals were obtained using the bootstrap method, sampling with replacement.

We used 1000 iterations of the bootstrap to estimate the parameter distribution; the sample size for each iteration was the same as the number of observations in the original sample. Confidence intervals were determined by rank: bootstrapped estimates were ranked, and the 2.5th percentile and 97.5th percentile were used for the confidence intervals. This bootstrap used generalized estimating equations, accounting for correlation between eyes of the same subject by treating each subject as a cluster.

In smoothed plots of age and untreated IOP vs CDR, there appeared to be a nonlinear relationship, which we attempted to estimate using spline terms in the regression model. For the binary outcomes, it appeared that this spline term continued to be significant but that the baseline IOP spline term did not, and thus it was removed. A spline regression allows the relationship between the

TABLE 2. Multiple Regression Model Results for Cup-to-Disk Ratio Among 230 Subjects Participating in a Study of Determinants of Glaucoma Damage and Progression

Category	Estimate	SE	*P* value
Age per year			
≤65 years	−0.001	0.0015	.50
>65 years	0.006	0.0018	.0004
Gender			
Female	0.002	0.025	.93
Race			
White	0.0	—	—
Black	0.070	0.034	.04
Other	0.035	0.036	.33
Goldmann IOP, per mm Hg	0.004	0.004	.32
Treatment	0.274	0.084	.001
IOP by treatment interaction	−0.005	0.004	.20
Corneal hysteresis, per mm Hg	−0.005	0.005	.36
Corneal thickness, per 100 μ	−0.068	0.029	.02
Time with glaucoma (per year)	0.005	0.001	<.001
Baseline IOP, per mm Hg			
IOP ≤ 25	−0.008	0.004	.02
IOP > 25	0.004	0.003	.12

IOP = intraocular pressure.

TABLE 3. Multiple Regression Model Results for Hemifield Test "Outside Normal Limits" Among 230 Subjects Participating in a Study of Determinants of Glaucoma Damage and Progression

Category	OR	LCL	UCL	*P* value
Age per year				
≤65 years	0.99	0.97	1.03	.72
>65 years	1.12	1.07	1.18	<.0001
Gender				
Female	0.95	0.57	1.57	.83
Race				
White	1.00	—	—	—
Black	2.03	1.04	3.94	.04
Other	2.27	0.90	5.71	.08
Goldmann IOP, per mm Hg	1.01	0.92	1.11	.78
Treatment	21.2	2.56	175.1	.005
IOP by treatment interaction	0.92	0.83	1.03	.12
Corneal hysteresis, per mm Hg	0.98	0.87	1.11	.80
Corneal thickness, per 100 μ	0.95	0.46	1.96	.89
Time with glaucoma, per year	1.03	1.00	1.06	.08
Baseline IOP, per mm Hg	0.99	0.95	1.03	.69

IOP = intraocular pressure; LCL = lower confidence limit; OR = odds ratio; UCL = upper confidence limit.

dependent and independent variable to change slope at a given cutpoint and for the regression lines to meet at that cutpoint. We add a spline term to the regression when there is reason to believe that the slope changes at that point. Age and IOP were treated as continuous variables in the models for MD, PSD, GHT, and field progression.

RESULTS

AMONG 230 PARTICIPANTS IN THE STUDY, 161 (70.0%) WERE white, 43 (18.7%) were black, and 26 (11.3%) were classified as "other" (mostly hispanic and asian) (Table 1). The mean age was 65 ± 14 years, 127 subjects (55.2%) were female, and 194 (85.1%) of 228 subjects for whom a diagnosis could be determined from the chart had primary open-angle glaucoma (POAG) (n = 131) or were suspected of having POAG (n = 63). A total of 172 subjects (74.8%) were currently receiving topical hypotensive therapy in either eye or had ever undergone laser or incisional surgery for glaucoma in either eye (Table 1).

Subjects had an average of 11.8 visual fields examined for this study (5.9 right eye fields and 5.9 left eye fields). A total of 34 subjects (14.8%) had progression of the visual field in either eye, whereas 37 subjects (16.1%) lacked sufficient field data to determine progression in either eye. Progression occurred in a least one eye of 17.8% of subjects with sufficient field data to make a determination.

The correlation coefficient for CCT and hysteresis among subjects in this database was $r = 0.27$ ($P < .0001$), whereas that between axial length and hysteresis was $r = -0.02$ (P = NS).

Based on the results of univariate analyses, we constructed multivariate generalized estimating equation models that treated each eligible eye of all subjects separately and adjusted for the correlation between eyes of a subject. The following potential determinants of glaucoma damage or progression were included in these models: age, gender, race, current Goldmann IOP, baseline untreated IOP, hysteresis (as measured by noncontact tonometry), CCT, years of treatment for glaucoma, and treatment (current topical or any past laser or incisional). We modeled separately the following outcome variables describing glaucoma damage or progression, using the above explanatory variables: CDR, MD, PSD, GHT, and presence or absence of progression on Humphrey Visual Field 24-2 testing. Age, gender, and race were utilized in all adjustments. In multivariate models, the following factors were predictive of higher CDR: increasing age past the age of 65, more years with glaucoma, treatment for glaucoma, and thinner CCT, but not corneal hysteresis. African-Americans was predictive of higher CDR in multivariate models (Table 2). Variables that were predictive of a GHT "outside normal limits" were older age and treatment for glaucoma. African-Americans (P = .04) was of borderline significance, but neither hysteresis nor CCT was significant (Table 3).

TABLE 4. Multiple Regression Model Results for Visual Field Progression Among 230 Subjects Participating in a Study of Determinants of Glaucoma Damage and Progression

Category	OR	LCL	UCL	*P* value
Age per year				
≤65 years	1.12	1.01	1.24	.03
>65 years	1.08	1.01	1.15	.02
Gender				
Female	0.75	0.33	1.73	.50
Race				
White	1.00	—	—	—
Black	1.32	0.51	3.43	.57
Other	0.63	0.07	5.82	.68
Goldmann IOP, per mm Hg	1.22	0.95	1.58	.12
Treatment	1874.6	3.16	10^6	.02
IOP by treatment interaction	0.79	0.61	1.03	.08
Corneal hysteresis, per mm Hg	0.81	0.66	0.98	.03
Corneal thickness, per 100 μ	1.65	0.66	0.98	.30
Time with glaucoma (y)	1.00	0.96	1.04	.98
Baseline IOP, per mm Hg	0.99	0.93	1.06	.79

IOP = intraocular pressure; LCL = lower confidence limit; OR = odds ratio; UCL = upper confidence limit.

Factors that were predictive of visual field progression were older age, treatment for glaucoma, and lower hysteresis (OR = 0.81, $P = .03$), but not CCT ($\beta = 1.3$, $P = .26$) (Table 4). When axial length was included in this model, the effect of hysteresis was less (odds ratio = 0.83, $P = .09$), whereas axial length was significant ($P = .009$).

Neither CCT nor hysteresis was significantly associated with MD or PSD in multivariate models, though African-Americans was associated with worse MD in both univariate and multivariate ($\beta = -3.07$, bootstrap 95% confidence interval = [−5.44, −0.87]) analyses (Tables 5 and 6).

These findings did not change when only persons with a diagnosis of POAG or suspected POAG (194 of 228, 85.1%) were included. When eyes with corneal edema (n = 34) on the basis of chart review were excluded, the association between CCT and the various clinical outcomes was generally strengthened, although inferences did not change and that between CCT and MD became of borderline significance ($\beta = 2.41$, $P = .07$).

We did not observe a statistically significant association between corneal hysteresis or CCT and treatment with any particular class of ocular hypotensive medications.

DISCUSSION

IN THE PRESENT STUDY, CCT AND CORNEAL HYSTERESIS are both independently associated with features of glaucoma damage but relate to different outcomes. It has been known for some 30 years that CCT affects IOP measurement using Goldmann applanation tonometry, but the frequency with which this is clinically relevant has only recently been appreciated.[25] Results from the OHTS[12] demonstrated that CCT is also an important and independent risk factor for progression to initial glaucoma damage among persons with ocular hypertension. There are several possible explanations of the association between CCT and glaucoma risk. First, because thinner corneas give lower measured IOP levels, these eyes may be subjected to less aggressive IOP-lowering therapy. Alternatively, thinner cornea may be a risk factor due to an association with the response of the corneoscleral shell and the ocular vasculature to IOP-induced stress. The results of the current study suggest that more elastic or distensible ocular tissues might be associated with glaucomatous progression.

The fact that all of our models adjusted for baseline IOP, current IOP, and treatment for glaucoma makes it somewhat less likely that the observed association between corneal characteristics and glaucoma damage is mediated solely through an effect on IOP. This is consistent with the hypothesis that corneal factors such as CCT and corneal hysteresis may constitute a pressure-independent risk factor for glaucoma, perhaps related to the composition of the eye wall itself.

In models that included axial length, this parameter was significantly associated with field progression. Inclusion of axial length led to a reduction in the significance of hysteresis in the model, perhaps suggesting that the two share similar risk features. This is consistent with evidence for a modest association between myopia and glaucoma risk[19,26] and with studies in which longer axial length or myopia was associated with higher IOP.[27] An association between axial lengths greater than 25 mm and higher IOP was also present in our subjects (data not shown). Axial length should be further studied as an indicator of glaucoma risk. There is evidence that the lamina cribrosa of long eyes is histologically thinner than in shorter eyes.[28] Furthermore, analysis of the likely physiologic behavior of the eye wall and optic nerve head is informative in describing the potential events that lead to nerve damage.[29]

After the publication of results from OHTS relating CCT and glaucoma risk, other studies have confirmed that a thinner CCT is a risk factor for glaucoma outcomes, including the cross-sectional presence of advanced glaucoma damage,[13] more short-wavelength automated perimetric defects among suspects with normal white-on-white perimetry,[14] development of initial field damage,[16] and further field progression in glaucoma patients.[30] However, two population-based studies, the Early Manifest Glaucoma Trial[2] and the Barbados Eye Study,[31] failed to find a significant association between CCT and glaucoma risk. In the case of the Early Manifest Glaucoma Trial, the study design was particularly strong, as the association was tested in a rigorous clinical trial design. Perhaps studies with clinic-based recruitment, such as OHTS and the others cited, tend to oversample for those

TABLE 5. Multiple Regression Model Results for Visual Field Mean Defect Among 230 Subjects Participating in a Study of Determinants of Glaucoma Damage and Progression

Category	Estimate	Z *P* value	Bootstrap LCL	Bootstrap UCL
Age per year				
≤65 years	0.021	.66	−0.08	0.12
>65 years	−0.23	.002	−0.40	−0.08
Gender				
Female	1.26	.11	−1.18	2.88
Race				
White	0.0	—	—	—
Black	−3.07	.007	−5.44	−0.87
Other	−2.06	.20	−5.20	1.12
Goldmann IOP, per mm Hg	−0.11	.25	−0.31	0.10
Treatment	−10.3	<.0001	−15.9	−4.62
IOP by treatment interaction	0.33	.006	0.07	0.60
Corneal hysteresis, per mm Hg	0.21	.41	−0.32	0.74
Corneal thickness, per 100 μ	1.30	.26	−1.04	3.76
Time with glaucoma (per year)	−0.10	.04	−0.19	0.005
Baseline IOP, per mm Hg				
IOP ≤ 25	−0.02	.83	−0.23	0.20
IOP > 25	−0.16	.14	−0.40	0.03

IOP = intraocular pressure; LCL = lower confidence limit; UCL = upper confidence limit.

TABLE 6. Multiple Regression Model Results for Visual Field Pattern Standard Deviation Among 230 Subjects Participating in a Study of Determinants of Glaucoma Damage and Progression

Category	Estimate	Z *P* value	Bootstrap LCL	Bootstrap UCL
Age per year				
≤65 years	0.03	.26	−0.02	0.07
>65 years	0.04	.16	−0.02	0.11
Gender				
Female	−0.41	.28	−1.26	0.37
Race				
White	0.0	—	—	—
Black	1.00	.07	−0.15	2.17
Other	0.81	.26	−0.60	2.27
Goldmann IOP, per mm Hg	0.04	.45	−0.06	0.13
Treatment	5.51	<.0001	3.07	8.14
IOP by treatment interaction	−0.16	.006	−0.28	−0.04
Corneal hysteresis, per mm Hg	−0.14	.11	−0.33	0.03
Corneal thickness, per 100 μ	−0.63	.25	−1.69	0.51
Time with glaucoma (per year)	0.02	.39	−0.03	0.06
Baseline IOP, per mm Hg				
IOP ≤ 25	−0.04	.52	−0.16	0.07
IOP > 25	−0.02	.53	−0.10	0.06

IOP = intraocular pressure; LCL = lower confidence limit; UCL = upper confidence limit.

with thick CCT compared with the population at large, favoring the detection of an association between CCT and glaucoma damage.

The current study suggests that the relationship between corneal features and glaucoma is more complex than simple anatomic thickness. Although it is not yet entirely

clear what corneal hysteresis measures, it does appear that this variable describes the response of the cornea to rapid deformation. In our data set, hysteresis was more closely associated with eyes that demonstrated progressive change than was the CCT. We are unaware of other studies that have focused on the risk associated with corneal deformability. The study of measurable indices of the compliance of the ocular coats are of particular importance if we believe that such measurements, made noninvasively at the front of the eye, may give information about responsiveness of the eye to mean IOP or changes in IOP. This should point our interest toward the behavior of the cornea and away from its thickness alone. For example, the tonometric measurement of cannulated, Asian eyes shows that their applanation IOP readings are lower than those of Europeans despite a similar distribution of CCT. Hence, eyes of the same CCT may differ in elastic responsiveness (in this case due to ethnically determined factors), giving rise to different tonometric values and potentially associated with different levels of glaucoma risk. It will be important to measure more detailed physiologic properties of the eye wall that are important in predicting glaucoma risk and clinical course.[32]

A number of other associations have been reported in the past with CCT. As has frequently been seen,[6,12,23] black race was associated with a thinner CCT in our study (20 μm thinner compared with whites, $P = .005$). We failed, however, to find a significant decline in CCT with increasing age ($P = .47$), as has been reported by other clinic-[33] and population-based[23,34] studies. An association between thicker CCT and more myopic refractive error, noted elsewhere,[35] was not present in our data set ($P = .13$). Whereas other reports have found a rapid decline in CCT soon after awakening,[36,37] our analyses failed to discover any association between time of day and CCT ($P = .14$), perhaps because the postawakening decline had already occurred before our patients presented to the clinic. One study reported an acute increase in CCT after the use of topical dorzolamide in subjects with Fuchs' dystrophy,[38] though this has not been reported in normal persons.[39,40] We failed to detect any association between CCT and use of specific classes of glaucoma medications. Finally, a rapid decline in CCT has also been reported (presumably due to corneal drying)[41] after administration of topical anesthetic; for this reason, the order of use of the tonometers was randomized in this study to avoid biased measurements.

This study has a number of limitations. The generalizability of clinic-based studies is limited to patients who resemble those who were included. This report describes a study group from an urban subspecialty practice in a tertiary care hospital, though persons from the full spectrum of socioeconomic status were included. The study was performed cross-sectionally, and thus only limited inferences may be drawn with regard to causality between corneal parameters and past progressive glaucoma damage. Finally, much of the clinical information utilized in our analyses was based on retrospective chart review. Protocols were not formally standardized for the measurement of some key outcomes, such as CDR. Despite these limitations, this study remains to our knowledge the first to report independent associations among corneal thickness, corneal deformability, and glaucoma damage.

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