

A Prospective Longitudinal Study to Investigate Corneal Hysteresis as a Risk Factor for Predicting Development of Glaucoma

CAROLINA N. SUSANNA, ALBERTO DINIZ-FILHO, FÁBIO B. DAGA, BIANCA N. SUSANNA, FEILIN ZHU, NARA G. OGATA, AND FELIPE A. MEDEIROS

- **PURPOSE:** To investigate the role of corneal hysteresis (CH) as a risk factor for development of glaucoma.
- **DESIGN:** Prospective observational cohort study.
- **METHODS:** Two hundred and eighty-seven eyes of 199 patients suspected of having glaucoma were followed for an average of 3.9 ± 1.8 years. All eyes had normal visual fields at baseline. Development of glaucoma was defined as occurrence of 3 consecutive abnormal standard automated perimetry tests during follow-up, defined as pattern standard deviation (PSD) $< 5\%$, and/or Glaucoma Hemifield Test outside normal limits. Measurements of CH were acquired at baseline using the Ocular Response Analyzer (ORA). Univariable and multivariable Cox regression models were used to investigate baseline factors associated with development of visual field loss over time.
- **RESULTS:** Fifty-four (19%) eyes developed repeatable visual field defects during follow-up. Measurements of CH at baseline were significantly lower in patients who developed glaucoma vs those who did not (9.5 ± 1.5 mm Hg vs 10.2 ± 2.0 mm Hg; $P = .012$). Each 1-mm Hg lower CH was associated with an increase of 21% in the risk of developing glaucoma during follow-up (95% confidence interval [CI]: 1.04–1.41; $P = .013$). In a multivariable model adjusting for age, intraocular pressure, central corneal thickness, PSD, and treatment, CH was still predictive of development of glaucoma (hazard ratio = 1.20; 95% CI: 1.01–1.42; $P = .040$).
- **CONCLUSION:** Baseline lower CH measurements were significantly associated with increased risk of developing glaucomatous visual field defects over time. The prospective longitudinal design of this study supports a role of CH as a risk factor for developing glaucoma. (Am J Ophthalmol 2018; ■:■–■. © 2018 Elsevier Inc. All rights reserved.)

GLAUCOMA IS AN OPTIC NEUROPATHY CHARACTERIZED by progressive loss of retinal ganglion cells and their axons, potentially leading to irreversible loss of visual function.¹ Lowering of the intraocular pressure (IOP) has been shown to delay or prevent development of glaucomatous damage and its progression. However, as the disease frequently remains asymptomatic until relatively late stages, identification of subjects at high risk for developing glaucoma is important in order to allow early treatment and prevention of irreversible visual loss.

Besides IOP, other factors such as age, central corneal thickness (CCT), disc hemorrhages, and structural and functional measures of the status of the optic nerve have been identified as associated with risk of glaucoma development. More recent investigations have also shown that corneal hysteresis (CH), a measure of the viscoelastic property of the cornea, is associated with glaucoma progression.^{2–4} In a retrospective study, De Moraes and associates³ showed that lower CH measurements were predictive of faster velocity of glaucoma progression. In a prospective investigation, Medeiros and associates⁴ collected baseline CH measurements in patients with glaucoma and showed that those with lower CH measurements showed faster progression of visual field loss during subsequent follow-up. Although those studies have provided compelling evidence for the role of CH in predicting progression,^{2–4} they focused on patients who had already been diagnosed with glaucoma. It is possible that the factors predicting disease development may be different or carry a different weight than those predicting further progression in subjects who have already been diagnosed with the disease.

The purpose of the present study was to investigate the role of CH in predicting development of glaucoma in a cohort of patients suspected of having the disease followed over time.

METHODS

THIS WAS AN OBSERVATIONAL COHORT STUDY OF PARTICIPANTS from a prospective longitudinal study designed to evaluate visual function in glaucoma. This study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT00221897). Approval from the institutional review board at the University of

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From the Duke Eye Center and Department of Ophthalmology, Duke University, Durham, North Carolina (C.N.S., F.B.D., B.N.S., N.G.O., F.A.M.); and Department of Ophthalmology, University of California San Diego, La Jolla, California (C.N.S., A.D.-F., B.N.S., F.Z., F.A.M.).

Inquiries to Felipe A. Medeiros, Professor of Ophthalmology, Department of Ophthalmology – Duke University, 2351 Erwin Rd, Durham, NC 27705; e-mail: felipe.medeiros@duke.edu

California San Diego was obtained for this study, and it was conducted in adherence with the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants after the test procedures were explained.

At baseline and at each visit during follow-up, all participants underwent a comprehensive ophthalmologic examination including IOP measured using Goldmann applanation tonometry (GAT; Haag-Streit, Konig, Switzerland), gonioscopy, stereoscopic optic disc examination, and visual field testing. Patients also had CCT measurements obtained with ultrasound pachymetry (Pachette GDH 500; DGH Technology, Inc, Philadelphia, Pennsylvania, USA).

The study included glaucoma suspects (history of IOP greater than 21 mm Hg and/or suspicious appearance of the optic nerve, but normal and reliable visual field results at baseline) with open angles on gonioscopy. Subjects were followed every 6 months. Subjects were excluded if they presented any other ocular or systemic disease that could affect the optic nerve or the visual field. Standard automated perimetry (SAP) tests were performed using the Swedish Interactive Thresholding Algorithm (SITA) Standard 24-2 strategy on the Humphrey Field Analyzer II-i (Carl Zeiss Meditec, Inc, Dublin, California, USA). Visual fields with more than 33% fixation losses, or more than 15% false-positive errors, were excluded.

During follow-up, eyes were classified as developing glaucoma if they had repeatable (at least 3 consecutive) abnormal visual field test results. An abnormal visual field was defined as a pattern standard deviation (PSD) with $P < .05$ or a Glaucoma Hemifield Test result outside normal limits. Each participant was required to have a minimum of 5 SAP examinations during a minimum 2 years follow-up. Each patient was treated at the discretion of the attending ophthalmologist.

• **CORNEAL HYSTERESIS MEASUREMENTS:** Measurements of CH were acquired at the baseline visit using the Ocular Response Analyzer (ORA; Reichert Technologies, Inc, Depew, New York, USA). A trained technician obtained 3 measurements from each eye and the average of 3 measurements was calculated for analysis. The ORA determines corneal biomechanical properties using an applied force–displacement relationship. Details of its operation have been previously described.⁵ In summary, this device uses an air puff to deform the cornea into slight concavity and an optical sensor to measure the deflection of the cornea, which is timed to the pressure applied by the air puff. From these data, the pressures at which the cornea flattens inward and outward as the pressure rises and falls are derived. The difference between the 2 applanation pressures, measured in mm Hg, is coined CH, and is related to the viscoelastic property of the cornea. The device provides a waveform score to reflect the quality of measurements. Only measurements associated with a waveform

TABLE 1. Baseline Characteristics of Patients Who Developed Glaucoma and Those Who Did Not

	Developed Glaucoma (N = 54 Eyes, 46 Patients)	Did Not Develop Glaucoma (N = 233 Eyes, 153 Patients)	P Value
Age (y)	67.6 ± 13.1	63.4 ± 11.6	.043
Sex (% female)	58.5	58.9	.553
Race (%)			
White	56.1	71.5	
African American	34.2	19.0	.035
Other	9.7	9.5	
MD (dB)	−0.6 ± 1.3	0.1 ± 1.3	<.001
PSD (dB)	1.7 ± 0.2	1.5 ± 0.2	<.001
IOP (mm Hg)	17.0 ± 4.1	17.6 ± 4.1	.356
CH (mm Hg)	9.5 ± 1.5	10.2 ± 2.0	.012
CCT (μm)	550.6 ± 32.3	556.6 ± 40.7	.312
Treatment (% yes)	63.5	66.7	.754

CCT = central corneal thickness; CH = corneal hysteresis; dB = decibels; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation.

Values are presented as mean ± standard deviation, unless otherwise noted.

score greater than 4 were considered for inclusion in the study.

• **STATISTICAL ANALYSIS:** Cox proportional hazards models were used to obtain hazard ratios (HRs) and identify baseline factors that predicted which eyes developed glaucomatous visual field loss during the follow-up period.^{6–10} A frailty model was used to account for potential correlation between 2 eyes of the same individual. We reported HRs from univariable models, as well as adjusted HRs from the multivariable Cox proportional hazards models. Kaplan-Meier curves showing the cumulative probabilities of developing glaucoma over time were also provided.

All statistical analyses were performed using commercially available software Stata, version 14 (StataCorp LP, College Station, Texas, USA). The alpha level (type I error) was set at 0.05.

RESULTS

THE STUDY INCLUDED 287 EYES FROM 199 PATIENTS suspected of having glaucoma, as determined on the baseline visit, and subsequently followed for an average of 3.9 ± 1.8 years. Fifty-four of the 287 eyes (19%) developed repeatable visual field defects during follow-up. [Table 1](#) presents baseline demographic and clinical factors of the study sample. Mean age was 67.6 ± 13.1 years at baseline in patients who developed glaucoma and 63.4 ± 11.6 years

TABLE 2. Hazard Ratios With 95% Confidence Intervals for Risk Factors Associated With Development of Glaucoma

Characteristic	Univariable Model		Multivariable Model	
	HR (95% CI)	P Value	HR (95% CI)	P Value
CH (per 1 mm Hg lower)	1.21 (1.04–1.41)	.013	1.20 (1.01–1.42)	.040
Age (per 1 decade older)	1.50 (1.15–1.95)	.003	1.32 (0.99–1.76)	.053
Sex (male)	1.21 (0.70–2.07)	.497	–	–
Race (African American)	1.59 (0.88–2.84)	.121	–	–
IOP (per 1 mm Hg higher)	0.96 (0.90–1.03)	.311	0.99 (0.91–1.07)	.805
CCT (per 40 μ m thinner)	1.15 (0.87–1.51)	.323	0.83 (0.60–1.17)	.290
MD (per 1 dB lower)	1.35 (1.12–1.65)	.002	–	–
PSD (per 0.1 dB higher)	1.38 (1.21–1.56)	<.001	1.36 (1.19–1.54)	<.001
Treatment (yes)	0.93 (0.40–2.14)	.863	0.90 (0.50–1.64)	.734

CCT = central corneal thickness; CH = corneal hysteresis; CI = confidence interval; HR = hazard ratio; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation.

at baseline in those who did not ($P = .043$). There was no statistically significant difference in sex between the 2 groups. There was a greater percentage of African Americans in the group that developed glaucoma compared with the one that did not (34.2% vs 19.0%, respectively; $P = .035$). Patients who developed glaucoma had lower SAP mean deviation (MD) values compared with those who did not (-0.6 ± 1.3 dB vs 0.1 ± 1.3 dB; $P < .001$). PSD at baseline was significantly higher in patients who developed glaucoma vs those who did not (1.7 ± 0.2 dB vs 1.5 ± 0.2 dB; $P < .001$). CH measurements at baseline were significantly lower in patients who developed glaucoma vs those who did not (9.5 ± 1.5 mm Hg vs 10.2 ± 2.0 mm Hg; $P = .012$). There were no statistically significant differences in mean IOP and mean CCT at baseline between the 2 groups. Also there was no statistically significant difference in treatment (yes/no) between the 2 groups.

Table 2 presents HRs with 95% confidence interval (CI) for risk factors associated with development of glaucoma. Each 1-mm Hg lower CH was associated with an increase of 21% in the risk of developing glaucoma during follow-up (HR = 1.21; 95% CI: 1.04–1.41; $P = .013$). In a multivariable model adjusting for age, IOP, CCT, PSD, and treatment, CH was still predictive of development of glaucoma (HR = 1.20; 95% CI: 1.01–1.42; $P = .040$). The Figure shows cumulative probabilities of developing glaucoma in eyes with CH equal to or greater than average (10.2 mm Hg) and in eyes with CH less than average ($P = .001$).

DISCUSSION

IN THE CURRENT STUDY, EYES WITH LOWER BASELINE CH had a higher probability of developing glaucomatous visual field defects in a cohort of glaucoma suspects followed over time. Such a relationship was present even in the multivar-

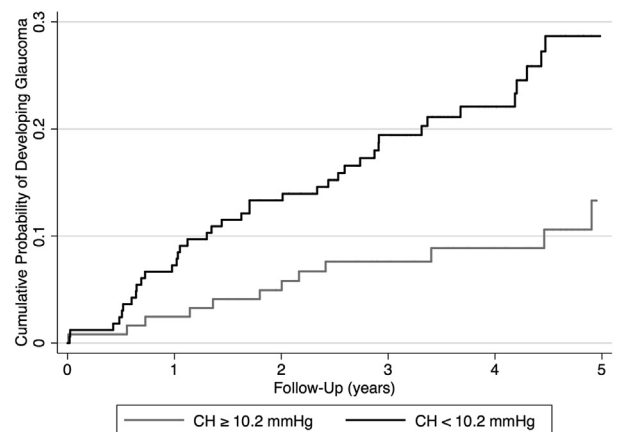


FIGURE. Cumulative probability of glaucoma development in suspect eyes with corneal hysteresis (CH) equal to or greater than 10.2 mm Hg, and in those with CH less than 10.2 mm Hg.

iable model adjusting for other factors known to potentially affect risk of glaucoma development. Other studies have already demonstrated low CH values to be associated with glaucoma progression in patients with established disease.^{2–4} However, to the best of our knowledge, this is the first prospective longitudinal study to evaluate the role of CH as a risk factor for the development of visual field loss in glaucoma suspects. Our findings suggest that evaluation of CH may add significant value to the assessment of risk of disease development in glaucoma suspects followed over time.

In the univariable model, each 1-mm Hg lower CH was associated with a 21% increase in the risk of developing glaucoma (HR = 1.21; 95% CI: 1.04–1.41; $P = .013$). This relationship was still present in the multivariable model adjusting for other factors known to affect glaucoma development, such as age, IOP, CCT, and PSD.¹¹ Each 1-mm Hg lower CH was associated with a 20%

higher risk of developing visual field defects (HR = 1.20; 95% CI: 1.01–1.42; $P = .040$). Previous cross-sectional studies have suggested the potential role of CH in glaucoma by showing that glaucomatous eyes tend to have lower CH values than healthy control eyes.^{2,12,13} Others have demonstrated that eyes with more severe damage tend to have lower CH values compared to the fellow eye in asymmetric disease.¹⁴ De Moraes and associates³ found a correlation between lower CH values and faster glaucomatous progression. Congdon and associates² investigated the relationship between CH levels and visual field progression and found a 20% risk of further functional loss for each 1-mm Hg lower CH, a percentage that is similar to the one found in our study. A prospective study by Medeiros and associates⁴ was able to demonstrate that CH was a statistically independent risk factor for glaucoma progression. Eyes with lower hysteresis had faster rates of visual field loss than those with higher hysteresis. However, these studies investigated the association between CH and visual field loss mostly in patients with already established glaucoma, whereas our results demonstrated CH as a baseline risk factor for disease development also in glaucoma suspects. Such assessment is important for development of predictive models assessing risk of glaucoma conversion.

It is still unclear why CH might be related to risk of glaucoma development and progression. In contrast to CCT, CH does not seem to exert a major effect on IOP estimation by Goldmann tonometry.^{5,15} Therefore, it seems unlikely that the predictive effect of CH would be related to artifacts associated with IOP measurement. It has been hypothesized that CH might be a surrogate biomarker to the biomechanical properties of tissues located posteriorly in the eye, such as lamina cribrosa and peripapillary sclera. According to this hypothesis, a low CH would increase the risk for glaucomatous damage, possibly by being associated with a reduced capacity of relevant posterior ocular structures in dampening IOP peaks or fluctuations.^{16–20} Supporting this hypothesis, a previous study has shown a significant correlation between CH and anterior lamina cribrosa displacement after reduction of IOP.²¹

The present study has limitations. There could be uncontrolled confounding by unmeasured factors, such as family history of glaucoma. In addition, we included only baseline values for the covariates included in the predictive models. It is possible that longitudinal information from these variables would show different predictive effect. However, our main goal was to assess the value of CH as a predictive factor during the initial evaluation of subjects suspected of glaucoma. Future studies should investigate the value of longitudinal measurements obtained from these variables. It should also be noted that high IOP has been clearly shown to be an important risk factor for glaucoma development and progression.^{11,22} In addition, IOP-lowering therapy has been shown to prevent or delay development of damage.^{22,23} However, in our multivariable analysis, we were not able to find IOP as a statistically significant risk factor for glaucoma development. This is most likely explained by the fact that our longitudinal study was observational, rather than interventional, and during follow-up subjects were treated at the discretion of the attending ophthalmologist. It is likely that subjects with higher IOP at baseline received more treatment, which decreased their chance of developing damage, artificially weakening the predictive value of baseline IOP measurements. Similarly, because the impact of CCT on risk of glaucoma development is now widely known,¹¹ it is likely that physicians may have treated more aggressively eyes of glaucoma suspects who had thin corneas, also artificially reducing the impact of CCT as a predictive factor in our study. As CH was only obtained as part of our research protocol, it is less likely that information about CH would have been used to guide treatment decisions. Therefore, the higher predictive value of CH compared to CCT in our study should be seen with caution. Future studies including randomization protocols controlling for treatment strategy should be performed to clarify the relative importance of these predictive factors.

In conclusion, lower CH measurements were significantly associated with increased risk of developing glaucoma. Future studies should attempt to incorporate CH measurements along with other known risk factors into models designed to improve risk assessment in glaucoma.

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