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A Prospective Longitudinal Study to Investigate Corneal Hysteresis as a Risk Factor of Central Visual Field Progression in Glaucoma

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Abstract

Purpose—To evaluate the role of corneal hysteresis (CH) as a risk factor of central visual field (VF) progression in a cohort of glaucoma suspect and glaucoma patients

Design—Prospective cohort study.

Methods—Two hundred forty-eight eyes of 143 subjects who were followed for an average of 4.8 years with a minimum of 5 visits with 10-2 and 24-2 VF tests were included. Univariable and multivariable linear mixed effects models were used to identify characteristics associated with the

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Author contribution:

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rate of change over time in 10-2 and 24-2 mean deviation (MD). Mixed effects logistic regression was used to evaluate characteristics associated with an increased likelihood of event-based 10-2 VF progression based on clustered pointwise linear regression (PLR) criterion.

Results—The CH was significantly associated with 10-2 and 24-2 VF progression in the univariable trend-based analysis. In multivariable trend-based analyses, lower CH was associated with a faster rate of decline in 10-2 MD (0.07 dB/year per 1 mmHg, $P<0.001$) but not with 24-2 MD ($P=0.490$). In multivariable event-based analysis, lower CH was associated with an increased likelihood of 10-2 VF progression (OR=1.35 per 1mmHg lower, $P=0.025$). Similar results were found in eyes with early glaucomatous damage at the baseline (baseline 24-2 MD ≥−6dB).

Conclusion—Lower CH was associated with a statistically significant, but relatively small, increased risk of central VF progression on the 10-2 test grid. Given the substantial influence of central VF impairment on the quality of life, clinicians should consider using CH to assess the risk of progression in primary open angle glaucoma patients including those with early disease.

Keywords

corneal hysteresis; glaucoma; visual field; progression; 10-2; 24-2

Introduction

Glaucoma is characterized by progressive retinal ganglion cell loss and commensurate visual field (VF) loss.[1, 2] Assessing the possibility and rate of disease progression is of particular importance given the irreversible nature of glaucomatous damage and the potential for lifetime functional impairment. The probability and rate of disease progression varies among different individuals.[3–5] Identification of baseline risk factors of disease progression allows clinicians to individualize therapy to reduce the likelihood of disease worsening. Higher intraocular pressure (IOP),[6–12] older age,[6–8, 10] decreased ocular perfusion pressure,[6, 10, 13] presence of optic disc hemorrhage,[6, 12, 14–16] thinner central corneas,[6–8, 10, 11] lower corneal hysteresis (CH),[17–19] focal lamina cribrosa defect,[6, 20] and β-zone peripapillary atrophy[6, 21, 22] all have been reported to be associated with glaucomatous VF progression.

Glaucomatous VF impairment affects quality of life and negatively impacts completion of everyday tasks including reading, driving, walking and taking medications in addition to putting them at increased risk of psychiatric comorbidities including depression.[23–26] Glaucoma patients with similar severity of visual field damage based on the magnitudes of global VF indices may have different areas of VF damage, with some locations affecting vision related quality of life more than others.[25] Central VF metrics have provided a stronger association with the quality of life measures compared to those of global VF.[26] This is particularly important considering the accumulating body of evidence regarding the presence of central VF impairment in the early stages of glaucoma.[27]

Corneal biomechanical characteristics have been reported to affect the susceptibility of glaucoma suspects to develop a subsequent VF defect[19, 28] and it also influences the risk of progression in those with established VF damage.[17, 29] Corneal hysteresis is a biomechanical feature that defined by the viscous dampening of the anterior chamber

when an air-puff of varying pressure is applied to the anterior surface of the cornea, and it is hypothesized to reflect corneal extracellular matrix constituents.[18] Considering the corneoscleral envelope as a closely linked unit, CH may provide indirect information of the structural constituents of the posterior pole related to glaucomatous damage including lamina cribrosa and peripapillary sclera.[18] Previous studies have shown that lower CH is a significant predictor of faster retinal nerve fiber layer[29] and global VF progression.[17] However, no study has yet evaluated CH as a predictor of central VF progression in glaucoma patients. The purpose of the current study was to investigate baseline CH as a risk factor of central VF progression in a prospective cohort of glaucoma suspect and glaucoma patients.

Methods

Participants

In this observational cohort study, participants were included from a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma (Diagnostic Innovations in Glaucoma Study [DIGS] and African Descent and Glaucoma Evaluation Study [ADAGES]). Participants in these cohorts were longitudinally evaluated according to a pre-established protocol that included regular follow-up visits in which patients underwent a clinical examination and several imaging and functional tests. All participants from the DIGS and ADAGES study who met the inclusion criteria described below were enrolled in the current study. Written informed consent was obtained from all participants. The University of California, San Diego Human Subjects Committee approved all protocols, and the methods described adhered to the tenets of the Declaration of Helsinki. ADAGES and DIGS were designed with similar testing protocols and details of the procedures in DIGS and ADAGES have been previously published.[30–32]

Subjects underwent annual comprehensive ophthalmologic examinations, including a review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, IOP measurement, dilated funduscopic examination, stereoscopic optic disc photography, and standard automated perimetry using Swedish Interactive Threshold Standard Algorithm (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, California, USA). Semiannual examinations included standard automated perimetry (10-2 VF and 24-2 VF) and IOP measurement. Only subjects with open angles on gonioscopy at baseline were included. Subjects were excluded if they had a baseline best-corrected visual acuity <20/40, axial length of more than 26.5 mm, baseline 24-2 mean deviation (MD) of worse than −20 dB, or any ocular or systemic disease that could affect the optic nerve or VF.

The study included eyes diagnosed as glaucoma or glaucoma suspect with baseline CH measurements and a minimum follow-up time of 2.5 years with a minimum of five 10-2 and 24-2 VF tests. Eyes were classified as glaucomatous if they had repeatable (≥2 consecutive) abnormal VF test results or evidence of glaucomatous optic neuropathy defined as excavation, the presence of focal thinning, notching of the neuroretinal rim, or localized or diffuse atrophy of the retinal nerve fiber layer based on masked grading of optic disc photographs by 2 graders or clinical examination by a glaucoma specialist. An abnormal VF test was defined as a pattern standard deviation (PSD) outside of the 95% normal confidence

limits or a Glaucoma Hemifield Test (GHT) result outside normal limits. Glaucoma suspects were defined as those having elevated IOP (≥22 mm Hg) or suspicious-appearing optic discs without the presence of repeatable glaucomatous VF damage.

Standard Automated Perimetry

The 10-2 and 24-2 VF tests were considered unreliable and excluded if there was >33% fixation losses, >33% false-positive errors, or >33% false-negative errors. Experienced graders at the University of California, San Diego Visual Field Assessment Center (VisFACT) reviewed the results, excluding tests with eyelid or rim artifacts, fatigue or learning effects, inappropriate fixation, or evidence that the VF results were caused by a disease other than glaucoma (e.g., homonymous hemianopia) or inattention. Patients with glaucoma were stratified into 2 groups based on the severity of their VF damage. Patients with baseline 24-2 MD > −6.0 dB were classified as mild glaucoma, and patients with baseline 24-2 MD ≤ −6.0 were classified as moderate to severe glaucoma.[33]

10-2 regions proposed by Hood and associates[27] were divided into 5 zones: the superior nasal (zone 1), superior temporal (zone 2), superior temporal band (zone 3), inferior temporal (zone 4), and inferior nasal (zone 5). For calculation of the mean sensitivity in each zone, threshold sensitivity values in decibels (dB) were used. The zonal mean sensitivity measurements were calculated as the average threshold sensitivity values of all points tested in that region.

Central visual field Progression

Different trend-based and event-based analyses were used to characterize progression in the 10-2 VF tests are described below.

Best linear unbiased prediction (trend-based): Estimates of rates of change for individual eyes in different zones were obtained by best linear unbiased prediction (BLUP). Ordinary least square estimates can be imprecise in eyes with just a few measurements available over time or with large intraindividual variability.[34] Individual ordinary least square estimates (i.e., individual regression lines) also do not take into account the information provided by the whole population, whereas BLUPs are shrinkage estimates that take into account the results obtained by evaluating the whole sample of eyes, giving less weight to estimates obtained from eyes with few measurement occasions or large intraindividual variability (i.e., more “noise”).[35] In eyes with a large number of measurements over time, BLUP and ordinary least square estimates give similar results. BLUPs have been used to estimate individual rates of structural change measured by different instruments in glaucoma and to measure the rate of cognitive change in longitudinal models.[36, 37]

Clustered pointwise linear regression (event-based): Regression of VF parameters over time has been used to identify VF deterioration and to estimate the magnitude of VF loss. Regression of individual locations or of clusters provided more information about the location of VF loss than regression of global indices.[38, 39] A VF test point was flagged as worsening if it showed a significant negative slope faster than −1 dB/year, with a

significance level of $P < 0.01$.[40, 41] Per De Moraes and colleagues,[42] a progression event in 10-2 VF was defined when ≥ 3 test points located in the same latent class analysis (LCA) derived 10-2 VF sector progressed faster than −1.0 dB/year at $P < .01$ over the follow-up period.

Corneal Hysteresis Measurements

Corneal hysteresis measurements were acquired at the baseline visit using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments 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.[43] In brief, within a 20-ms time frame, a metered air pulse is delivered to the eye, causing the cornea to move inward in a concave fashion (past a first applanation point), and then the cornea returns (past a second applanation point) to its initial position. An electro-optical collimation detector system monitors the corneal curvature in the central 3.0-mm diameter during the measurement period and defines 2 peaks produced by the applanation events. The CH is the difference between these 2 applanation pressures measured in millimeters of mercury. CH thus relates to the viscous dampening ability of the cornea. The device provides a waveform score to reflect the quality of measurements. Three measurements were obtained for each eye in each visit, and the average of the qualified measurements with a waveform score greater than 4 were considered for analysis. Baseline VF tests were chosen as those closest to the baseline CH measurement date.

Statistical Analysis

Continuous and categorical data were presented as mean (95% confidence interval [CI]) and count (%). Statistically significant differences in characteristics between glaucoma suspect and glaucoma patients were determined by 2-sample t tests for continuous variables and the Fisher exact test for categorical variables. Eye characteristics were compared using linear mixed effects models with random intercepts to account for within-subject variability. In the trend-based analysis, VF trajectories were estimated using linear mixed effects models with random eye-within-patient intercepts and independent random slopes-within-eye. The details on the use of these models for evaluation of rates of change in glaucoma and to model longitudinal processes have been published.[5, 44, 45] In linear mixed models, the average evolution of the outcome variable (visual field measurements) is described using a linear function of time, and random intercepts and random slopes introduce subject- and eye-specific deviations from this average evolution. The model can account for the fact that different eyes can have different rates of visual field loss over time, while also accommodating correlations between both eyes of the same individual.[45, 46] Interaction terms between time and putative predictors (e.g., CH) can be included in the model to test whether there is a significant effect of the putative predictor on changes of the outcome variable over time. Multivariable models were fit after including all variables with P value ≤ 0.10 in univariable analysis. In addition to age, demographic characteristics, and follow-up duration, all models were adjusted for both mean IOP during follow-up[47, 48] and positive history of disc hemorrhage[16, 49, 50] because of their reported associations with glaucomatous VF progression. In the event-based analysis, univariable and multivariable mixed effects

logistic regression models were used to identify characteristics associated with an increased likelihood of 10-2 VF progression defined by the clustered pointwise linear regression (PLR) criterion. Linear mixed-effect models with random intercepts and random slopes were used to compare the rates of 10-2 MD loss and age adjusted zonal rates of mean sensitivity loss between two group of eyes divided based on baseline CH (CH ≥ 10 mmHg and CH < 10 mmHg).[17] All statistical analyses were performed with commercially available software (STATA, version 17.0; Stata Corp LP, College Station, Texas, USA). The alpha level (type I error) was set at 0.05.

Results

A total of 248 eyes (71 glaucoma suspect, 177 glaucoma) of 143 patients were included in this prospective cohort study. The cohort included 72 females (50.3%) and 99 non-African descent (69.2%) participants. The mean (95% confidence interval [CI]) baseline age at the study entry was 68.4 (67.1, 69.7) years and the average follow up duration of eyes were 4.8 (4.7, 4.9) years and the average number of visits was 7.8 (7.5, 8.1). A total of 76.6% of study participants were already on ocular hypotensive eye drops at the study entry. Specifically, 63.3% of participants were using prostaglandin analogues at the beginning of the follow up. Glaucoma eyes had lower baseline IOP, lower mean IOP during follow-up, worse baseline 24-2 and 10-2 MDs, and higher baseline 24-2 and 10-2 PSDs (all *P*-values < 0.05) than glaucoma suspect eyes. Other characteristics including axial length, central corneal thickness, CH, positive history of disc hemorrhage, follow-up duration and number of test visits were similar between glaucoma suspect and glaucoma eyes (all *P*-values > 0.05) [Table 1]. Figure 1 shows the distribution of baseline CH measurements for all 248 eyes included in the study during follow-up.

Table 2 shows the results of univariable and multivariable trend-based analysis of the characteristics associated with rate of change in 10-2 VF MD over time. In the univariable analysis, male gender, higher baseline 10-2 PSD, worse baseline 24-2 MD, higher baseline 24-2 PSD, and lower baseline CH were associated with faster rate of 10-2 VF progression (all *P*-values < 0.05). Results of the multivariable analysis showed that lower mean IOP during follow-up (β = −0.02 dB/year per 1 mmHg higher, $P = 0.043$), worse baseline 24-2 MD (β = −0.02 dB/year per 1 dB worse, $P = 0.004$), and lower baseline CH (β = −0.07 dB/year per 1 mmHg lower, $P < 0.001$) were significantly associated with faster rate of 10-2 VF progression.

Table 3 shows the results of univariable and multivariable mixed effects logistic regression model analysis of the characteristics associated with an increased likelihood of event-based 10-2 VF progression at the end of study follow-up. Twenty-eight eyes (11.3%) showed 10-2 VF progression defined by clustered PLR criterion. Worse baseline 24-2 MD, higher baseline 24-2 PSD, and lower baseline CH were the only significantly associated characteristics with an increased likelihood of 10-2 VF progression (all *P*-values < 0.05). After adjusting for confounders, worse baseline 24-2 MD (OR = 1.09 per 1 dB worse, $P = 0.045$), and lower baseline CH (OR = 1.35 per 1 mmHg lower, $P = 0.025$) remained significantly associated with an increased likelihood of 10-2 VF progression.

Table 4 shows factors associated with the rate of 24-2 VF MD change over time. In the univariable analysis, higher baseline age, and lower baseline CH, and lower follow-up duration were associated with faster rate of 24-2 VF progression (all *P*-values < 0.05). In the multivariable model including baseline age, gender, race, mean IOP during follow-up and follow-up duration as possible confounders, the association of baseline CH with the rate of 24-2 VF progression was not significant ($P = 0.490$).

Supplemental Tables 1 (trend-based analysis) and 2 (event-based analysis) demonstrate the results of separate univariable and multivariable models including the subgroup of eyes with early glaucoma at the baseline (24-2 MD ≥ −6 dB). After adjusting for other covariates in the multivariable models, lower CH was associated with a faster rate of 10-2 VF progression ($\beta = -0.05$ dB/year per 1 mmHg lower, $P = 0.004$) in the trend-based analysis and an increased likelihood of 10-2 event-based VF progression (OR = 1.37 per 1 mmHg lower, $P = 0.021$).

Figure 2 compares the age-adjusted rates of change in different zones of 10-2 VF test grid between the subgroup of eyes with baseline CH < 10 mmHg (147, 59.3%) to those with baseline CH ≥ 10 mmHg (101, 40.7%). The cut-off of 10 mmHg was chosen for illustrative purposes based on a previous publication.[17] As demonstrated, eyes with baseline CH < 10 mmHg had faster VF progression in the superior temporal (difference: −0.18 dB/year, $P = 0.002$), and the superior nasal zones (difference: −0.28 dB/year, $P = 0.001$) than eyes with CH ≥ 10 mm Hg. The difference in the rates of change between CH groups did not reach statistical significance in the superior temporal band (difference: −0.07 dB/year, $P = 0.189$), the inferior nasal (difference: −0.11 dB/year, $P = 0.154$), and the inferior temporal (difference: −0.11 dB/year, $P = 0.053$) zones. Overall, eyes with baseline CH < 10 mmHg had faster rate of change in 10-2 MD compared to those with baseline CH ≥ 10 mmHg (difference: −0.15 dB/year, $P = 0.008$).

Discussion

This prospective study demonstrated that lower baseline CH is associated with faster global (24-2) and central (10-2) VF progression in a cohort of glaucoma suspect and glaucoma patients over an average follow-up duration of 4.8 years. Moreover, we found that lower CH increases the likelihood of central VF progression defined by clustered PLR criteria on the 10-2 test grid. The observed associations were derived from multivariable models after adjusting for demographic and other possible risk factors of glaucoma progression. These results show that CH is a significant predictor of glaucomatous central and peripheral VF progression. Given the substantial influence of central VF impairment on the performance and quality of life, our findings suggest that CH should be considered in the risk assessment of disease progression in clinical practice.

Prior studies have found lower CH to be associated with an increased rate of functional[17] and structural[29] deterioration in glaucoma patients. In this study, the event-based multivariable analysis showed that one mmHg lower CH corresponds to a 35% increase in the odds of central VF progression after adjusting for other covariates. Central vision is particularly important in daily functioning, and impairments in this area are strongly

associated with lower self-reported quality of life in glaucoma patients.[23–26] There is an accumulating body of evidence that glaucomatous damage can affect the central VF area even at the early stages of the disease.[27] Therefore, we performed a subanalysis including early glaucoma patients (baseline 24-2 VF MD ≥ −6 dB). The results revealed similar associations between lower CH and increased likelihood of central VF progression.

Other investigators have evaluated the prognostic value of corneal biomechanical properties in forecasting glaucoma progression at earlier stages. Susanna et al.,[19] in a prospective longitudinal study, followed glaucoma suspect patients without apparent VF defects at the baseline for an average of 3.9 years and found that lower baseline CH is a significant predictor (hazard ratio = 1.20) of the development of VF defect at the end of follow-up. In a recent longitudinal study, Qassim and collaborators[28] followed eyes with suspicious appearing optic discs but without apparent VF defects at baseline; they found that eyes with higher corneal stiffness at baseline are at increased risk of future VF progression and demonstrate a faster rate of structural decline in the retinal nerve fiber layer and macular measurements.

In the trend-based analysis, lower CH was found to be a statistically significant predictor of faster central VF progression. Consistent associations were obtained after a sub-analysis, including the early glaucoma patients (baseline 24-2 VF MD ≥ −6 dB). Each one mmHg lower CH led to a 0.07 dB/year faster rate of decline in 10-2 VF MD. Such an association was found after adjusting for demographic and other potential factors associated with a faster rate of central VF progression, including mean IOP during study follow-up and positive history of disc hemorrhage. According to our findings, the effect of a lower CH on the rate of VF change (both globally and in the central vision) may appear small when considered a separate risk factor of glaucoma progression. In a previous study, Medeiros and colleagues[17] found that each 1 mmHg lower CH corresponds to a 0.16% faster rate of decline in the 24-2 VF index, which is in line with our findings in terms of the magnitude of effect. Many prior studies have tried to investigate risk factors that are predictive of glaucoma progression and, as a result, several other demographic and clinical characteristics have been identified.[7, 8, 51, 52] Not a single baseline factor has been shown to be accurately predictive, and most of the reported associations have been weak in terms of the magnitude of effect.[7, 8, 51, 52] As is the case with most chronic diseases of aging, glaucoma progression is multifactorial with complex genetic and environmental interactions in most cases, one might not expect to find the cause in a single predictive parameter. Differences in inclusion criteria, characteristics of the study population, and definitions of the study outcomes may contribute to the relatively weak and probably inconsistent associations.[52] It must be acknowledged that CH alone is one of the risk factors in the global risk assessment of glaucoma, and it may not necessarily be a major determinant. Nonetheless, when it comes to clinical decision-making, a holistic approach including many individualized risk factors should be undertaken. According to the ample available evidence on the prognostic significance of corneal biomechanical properties for subsequent glaucoma progression at different stages of the disease, clinicians should consider taking these characteristics into account as a part of this approach to risk stratify the patients.

Previous studies have shown that central VF damage in glaucoma usually tends to follow a pattern of earlier and more profound involvement of superior zones and a “central island” of relative preservation which includes the superior temporal band and a great proportion of the inferior zones on the 10-2 test grid.[27, 42, 53–55] The higher propensity of superior 10-2 zones to glaucomatous VF damage is consistent with reports of Hood and colleagues[27] and Hood[53] suggesting that the inferior macular region is more susceptible to glaucomatous damage than the superior macular region. They coined the term “macular vulnerability zone” to describe the 50% of inferotemporal arcuate retinal nerve fiber layer fibers that are more susceptible to glaucomatous damage. In the present study, we found statistically significant faster rates of central VF progression in the superior 10-2 zones of eyes with lower CH. Whether lower CH is a risk factor that accelerates central VF progression globally or it differently influences the rates of central VF progression in other zones is a topic for future studies.

The exact underlying mechanisms of how corneal biomechanical properties might influence the susceptibility of the optic nerve head to glaucomatous damage are still unclear. Hysteresis has been introduced as a parameter that reflects the viscoelastic biophysical properties of tissue in dampening pressure fluctuations.[17] Since cornea and sclera are arranged in a contiguous configuration collectively forming the corneoscleral envelope, and they are formed from the continuous extracellular matrix, deformability and stretching of these structures appear to be closely linked. Hence, CH may indicate a surrogate biomarker reflecting the physical properties of lamina cribrosa and peripapillary sclera.[17] In favor of this hypothesis, prior studies have shown an association between CH and anterior displacement of lamina cribrosa after IOP reduction[56] and posterior displacement of the lamina after IOP increase.[57] Lower CH is reported to be linked to a reduction in the ability of posterior ocular structures to dampen fluctuations and peaks of IOP.[56, 58–61] Accordingly, a prior study has found that CH and IOP have an interactive role in increasing the risk of glaucoma progression.[17] Another possible implication of CH in glaucoma patients is the potential underestimation of transcorneal pressure gradient measured by Goldmann applanation tonometry. As a result, patients with lower CH might have, in fact, been exposed to higher levels of IOP than those perceived by their clinicians, leading to a higher probability of disease progression.[62, 63] For further support, a recent study has found that approximately one-quarter of eyes with apparently well-controlled IOP show evidence of VF progression over time, with low CH being a major risk factor.[18]

It must be acknowledged that the majority of study participants were already under ocular hypotensive treatment at the study onset. Specifically, approximately two thirds of the patients were receiving prostaglandin analogues at the beginning of the follow up. Previous studies have demonstrated that different topical ocular hypotensive agents may affect corneal properties and induce alterations of CH.[64–67] Prostaglandin analogues, in particular, seem to induce extracellular matrix alteration resulting from increased matrix metalloproteinase activity that may lead to an increase in CH.[67–72] Considering that patients with worse disease severity were more likely to have been receiving antiglaucoma eye drops compared to those with better prognosis at the time of baseline CH measurement may have created a potential bias that needs to be addressed for interpretation of the results of the present study and those of previously mentioned investigations.[17, 18, 28, 29] However, the association between baseline CH and subsequent rate of central VF progression in the present study

remained similar after adjusting for receiving any kinds of ocular hypotensive agents or prostaglandin analogues (data not shown).

There are several limitations of the present study. First, baseline CH measurements were used as predictors of central VF progression. Even though such an assessment facilitates comparing the findings with those of similar studies evaluating the association of baseline characteristics with the risk of glaucoma progression, the potential influence of alterations in corneal biomechanical properties over time on the rate of disease progression cannot be ignored. Future studies are needed to assess whether including longitudinal variability of these measurements into more complex statistical models provides added prognostic significance. Nevertheless, the observations of the present study are sufficient to suggest the role of CH as a potential risk factor of central VF progression. In addition, study participants were treated at the discretion of their attending ophthalmologists. It is possible that more intense treatment of those with previously known risk factors of disease progression, like thinner central corneas, affected the association of some of the baseline characteristics with subsequent disease progression. However, the sparse use of CH in current clinical practice as a determinant of treatment modulation lowers the probability of such an influence. And last, glaucoma eyes had lower IOP because of existing treatment. Information on the washout IOP's was not available.

In conclusion, the present study demonstrates that lower baseline CH is associated with a statistically significant, but relatively small, increased risk of central VF progression in patients with primary open angle glaucoma including those with early disease. Given the importance of central vision, clinicians should consider evaluating CH when estimating the risk of glaucoma progression in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

ADAGES	African Descent and Glaucoma Evaluation Study
BLUP	best linear unbiased prediction
CH	corneal hysteresis
DIGS	Diagnostic Innovations in Glaucoma Study
GHT	glaucoma hemifield test

IOP	intraocular pressure
MD	mean deviation
LCA	latent class analysis
ORA	ocular response analyzer
PSD	pattern standard deviation
PLR	pointwise linear regression
VF	visual field
VisFACT	Visual Field Assessment Center

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Table of Contents Statement

Lower baseline corneal hysteresis was associated with a statistically significant, but relatively small, increased risk of central 10° visual field progression in a prospective cohort of glaucoma suspect and glaucoma patients.

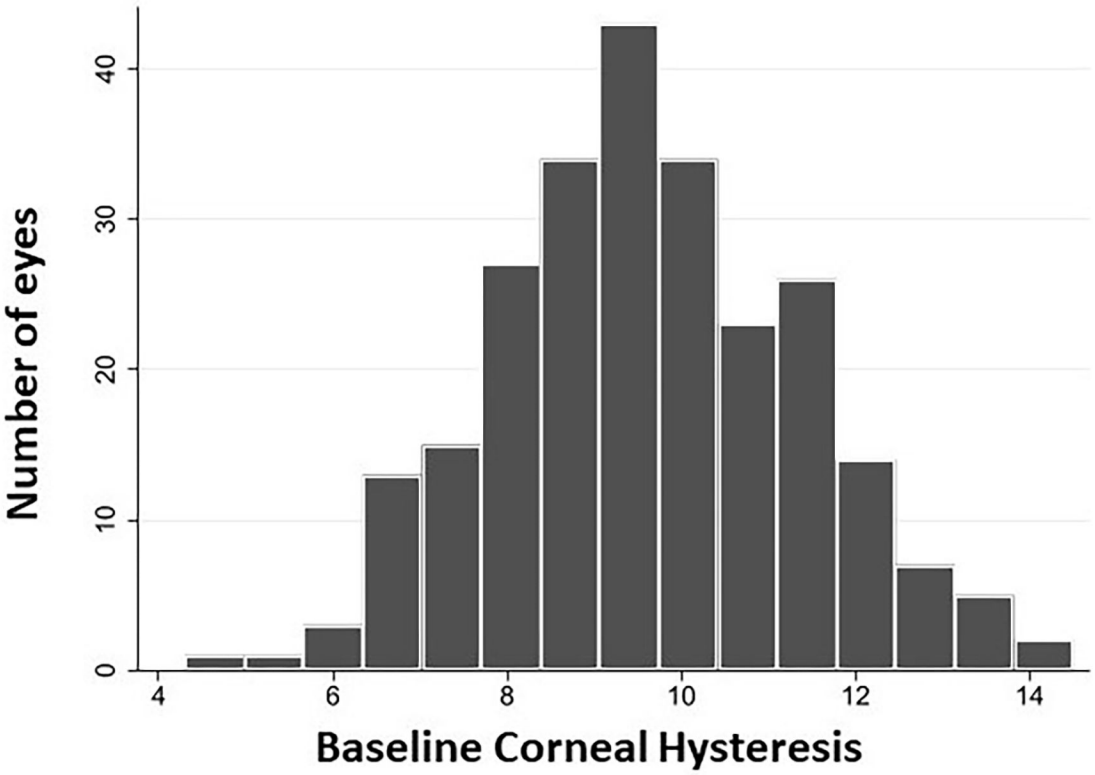

Figure 1.

Distribution of baseline corneal hysteresis measurements for all 248 eyes included in the study of the relationship between corneal hysteresis and central visual field loss during follow-up.

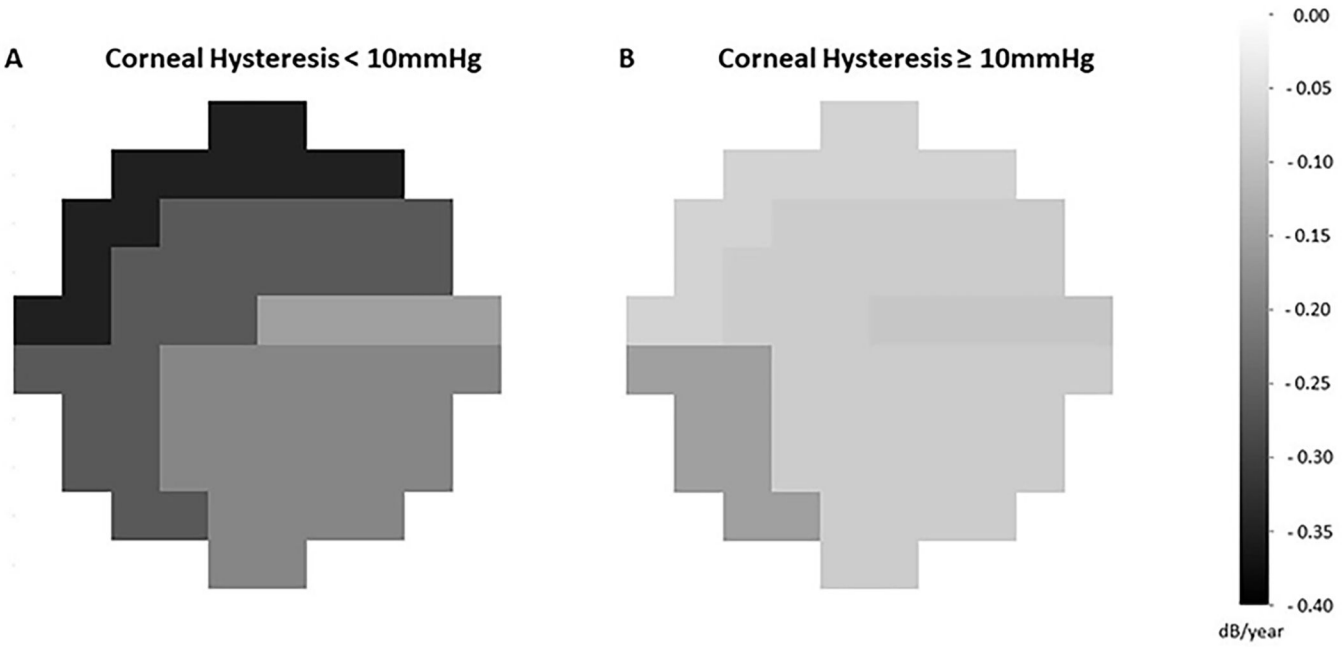

Figure 2.

Zonal rates of change (dB/year) in 10-2 test grid are compared between eyes with baseline corneal hysteresis < 10 mmHg (A, 147 eyes) and those with baseline corneal hysteresis ≥ 10 mmHg (B, 101 eyes). Darker areas correspond to faster rate of visual field progression.

Table 1.

Demographics and Baseline Characteristics of the Study Population

Characteristics	Overall	By Diagnosis		
		Glaucoma Suspect	Glaucoma	*P*-value
At the patient level	143	40 (28.0)	103 (72.0)	
Gender				
Male (%)	71 (49.7)	19 (47.5)	52 (50.5)	0.853
Female (%)	72 (50.3)	21 (52.5)	51 (49.5)	
Race				
Non-African American (%)	99 (69.2)	27 (67.5)	72 (69.9)	0.841
African American (%)	44 (30.8)	13 (32.5)	31 (30.1)	
Self-reported DM (%)	23 (16.1)	6 (15.0)	17 (16.5)	> 0.99
Self-reported HTN (%)	89 (62.2)	24 (60.0)	65 (63.1)	0.848
Systolic blood pressure (mmHg)	130.2 (126.9, 133.4)	131.9 (125.0, 138.8)	129.5 (125.9, 133.1)	0.511
Diastolic blood pressure (mmHg)	76.6 (74.7, 78.5)	78.6 (74.8, 82.4)	75.8 (73.6, 78.1)	0.207
At the eye level	248	71 (28.6)	177 (71.4)	
Baseline age (years)	68.4 (67.1, 69.7)	64.9 (62.4, 67.5)	69.8 (68.3, 71.2)	0.119
Axial length (mm)	24.09 (23.97, 24.21)	24.23 (23.98, 24.48)	24.03 (23.89, 24.17)	0.362
CCT (μm)	543.3 (537.2, 549.4)	561.0 (549.7, 572.2)	537.0 (529.9, 544.1)	0.213
Baseline IOP (mmHg)	14.6 (14.1, 15.1)	16.0 (15.2, 16.9)	13.9 (13.3, 14.5)	**0.012**
Mean IOP during follow-up (mmHg)	14.7 (14.2, 15.2)	16.4 (15.5, 17.3)	14.0 (13.5, 14.5)	< **0.001**
CH (mmHg)	9.62 (9.40, 9.84)	10.12 (9.70, 10.54)	9.42 (9.17, 9.67)	0.291
History of DH (%)	32 (12.9)	7 (9.9)	25 (14.1)	0.317
Glaucoma severity				
Suspect	71 (28.6)			
Mild	135 (54.4)			
Moderate	22 (8.9)			
Advanced	20 (8.1)			
Baseline 24-2 MD (dB)	−3.31 (−3.85, −2.78)	−0.40 (−0.74, −0.05)	−4.48 (−5.15, −3.82)	< **0.001**
Baseline 24-2 PSD (dB)	4.28 (3.83, 4.72)	1.74 (1.61, 1.87)	5.29 (4.74, 5.85)	< **0.001**
Baseline 10-2 MD (dB)	−2.87 (−3.44, −2.29)	−0.50 (−0.81, −0.18)	−3.82 (−4.57, −3.06)	< **0.001**
Baseline 10-2 PSD (dB)	3.59 (3.08, 4.10)	1.29 (1.22, 1.36)	4.51 (3.84, 5.18)	< **0.001**
10-2 Follow-up (years)	4.8 (4.7, 4.9)	5.0 (4.9, 5.2)	4.7 (4.6, 4.9)	0.079
Visits of 10-2 Visual Field	7.8 (7.5, 8.1)	7.4 (7.0, 7.9)	8.0 (7.6, 8.3)	0.842

F = female; M = male; DM = diabetes mellitus; HTN = hypertension; CCT = central corneal thickness; IOP = intraocular pressure; CH = corneal hysteresis; DH = disc hemorrhage; MD = mean deviation; PSD = pattern standard deviation.

Values are shown in mean (95% confidence interval), unless otherwise indicated.

Table 2.

Characteristics Associated with the Rate of 10-2 MD Change Over Time by Univariable and Multivariable Linear Mixed Effects Model Analysis

Variables	Univariable Model		Multivariable Model	
	β (95 % CI)	*p* value	β (95 % CI)	*p* value
Age, per 10 years older	−0.05 (−0.11, 0.01)	0.102	−0.02 (−0.09, 0.05)	0.561
Gender: F/M	0.13 (0.00, 0.26)	**0.049**	0.04 (−0.10, 0.18)	0.586
Race:				
African American/ Non-African American	−0.01 (−0.15, 0.13)	0.889	−0.02 (−0.17, 0.12)	0.762
Axial length, per 1mm longer	0.01 (−0.06, 0.07)	0.790	–	–
CCT, per 10 μm thinner	0.00 (−0.02, 0.01)	0.844	–	–
Self-reported diabetes	−0.07 (−0.25, 0.11)	0.433	–	–
Self-reported hypertension	0.06 (−0.08, 0.19)	0.412	–	–
Baseline systolic blood pressure, per 10 mmHg higher	0.00 (−0.04, 0.03)	0.827	–	–
Baseline diastolic blood pressure, per 10 mmHg higher	0.00 (−0.05, 0.05)	0.992	–	–
Baseline IOP, per 1 mmHg higher	0.00 (−0.02, 0.01)	0.612	–	–
Mean IOP during follow up, per 1 mmHg higher	−0.01 (−0.03, 0.01)	0.277	−0.02 (−0.04, 0.00)	**0.043**
History of disc hemorrhage	−0.11 (−0.25, 0.02)	0.096	−0.12 (−0.25, 0.02)	0.093
Baseline MD 10-2, per 1 dB worse	−0.01 (−0.02, 0.00)	0.111	–	–
Baseline PSD 10-2, per 1 dB higher	−0.01 (−0.02, 0.00)	**0.036**	–	–
Baseline MD 24-2, per 1 dB worse	−0.02 (−0.03, −0.01)	**0.002**	−0.02 (−0.03, −0.01)	**0.004**
Baseline PSD 24-2, per 1 dB higher	−0.02 (−0.03, 0.00)	**0.007**	–	–
CH, per 1 mmHg lower	−0.07 (−0.11, −0.04)	< **0.001**	−0.07 (−0.11, −0.03)	< **0.001**
Follow up duration, per 1 year longer	0.04 (−0.04, 0.11)	0.363	0.02 (−0.06, 0.10)	0.628

MD = mean deviation; F = female; M = male; CCT = central corneal thickness; IOP = intraocular pressure; PSD = pattern standard deviation; CH = corneal hysteresis.

Values are shown in β coefficient (95% confidence interval), unless otherwise indicated. Age, Race, mean IOP and clinically independent variables with a *p* value of less than 0.10 in the univariable analysis were included in the multivariable model. Statistically significant *p* values are shown in bold. Negative values correspond to faster MD decline over time.

Table 3.

Characteristics Associated with the Likelihood of Event-Based 10-2 VF Progression Defined by Clustered Pointwise Linear Regression (PLR) Criteria of Mean Sensitivity using Univariable and Multivariable Mixed Effects Logistic Regression Analysis

Variables	Univariable Model		Multivariable Model	
	Odds ratio (95 % CI)	*p* value	Odds ratio (95 % CI)	*p* value
Age, per 10 years older	0.98 (0.65, 1.48)	0.937	0.87 (0.60, 1.27)	0.472
Gender: F/M	0.57 (0.23, 1.43)	0.232	0.67 (0.21, 2.08)	0.486
Race:				
African American/ Non-African American	1.11 (0.41, 2.99)	0.844	1.31 (0.45, 3.82)	0.616
Axial length, per 1mm longer	0.93 (0.68, 1.27)	0.633	–	–
CCT, per 10 μm thinner	0.99 (0.89, 1.11)	0.882	–	–
Self-reported diabetes	1.49 (0.48, 4.65)	0.490	–	–
Self-reported hypertension	0.51 (0.21, 1.27)	0.150	–	–
Baseline systolic blood pressure, per 10 mmHg higher	0.97 (0.79, 1.19)	0.772	–	–
Baseline diastolic blood pressure, per 10 mmHg higher	1.03 (0.71, 1.49)	0.870	–	–
Baseline IOP, per 1 mmHg higher	0.97 (0.88, 1.08)	0.636	–	–
Mean IOP during follow up, per 1 mmHg higher	1.02 (0.90, 1.15)	0.805	1.05 (0.92, 1.21)	0.444
History of disc hemorrhage	2.60 (0.99, 6.82)	0.052	2.23 (0.66, 7.46)	0.194
Baseline MD 10-2, per 1 dB worse	1.04 (0.97, 1.12)	0.242	–	–
Baseline PSD 10-2, per 1 dB higher	1.08 (0.99, 1.18)	0.101	–	–
Baseline MD 24-2, per 1 dB worse	1.08 (1.01, 1.16)	**0.024**	1.09 (1.00, 1.18)	**0.045**
Baseline PSD 24-2, per 1 dB higher	1.10 (1.00, 1.20)	**0.041**	–	–
CH, per 1 mmHg lower	1.35 (1.09, 1.67)	**0.006**	1.35 (1.04, 1.75)	**0.025**
Follow up duration, per 1 year longer	1.14 (0.73, 1.78)	0.564	1.18 (0.75, 1.85)	0.475

MD = mean deviation; F = female; M = male; CCT = central corneal thickness; IOP = intraocular pressure; PSD = pattern standard deviation; CH = corneal hysteresis.

Values are shown in β coefficient (95% confidence interval), unless otherwise indicated. Age, Race, mean IOP and clinically independent variables with a *p* value of less than 0.10 in the univariable analysis were included in the multivariable model. Statistically significant *p* values are shown in bold.

Table 4.

Characteristics Associated with the Rate of 24-2 MD Change Over Time by Univariable and Multivariable Linear Mixed Effects Model Analysis

Variables	Univariable Model		Multivariable Model	
	β (95 % CI)	*p* value	β (95 % CI)	*p* value
Age, per 10 years older	−0.08 (−0.14, 0.00)	**0.021**	−0.07 (−0.14, 0.00)	0.060
Gender: F/M	0.11 (−0.03, 0.25)	0.120	0.11 (−0.04, 0.26)	0.167
Race:				
African American/ Non-African American	−0.05 (−0.21, 0.10)	0.487	−0.08 (−0.23, 0.08)	0.332
Axial length, per 1mm longer	0.04 (−0.03, 0.11)	0.248	–	–
CCT, per 10 μm thinner	−0.01 (−0.03, 0.01)	0.284	–	–
Self-reported diabetes	−0.14 (−0.33, 0.05)	0.151	–	–
Self-reported hypertension	0.05 (−0.09, 0.20)	0.487	–	–
Baseline systolic blood pressure, per 1 mmHg higher	−0.02 (−0.06, 0.02)	0.280	–	–
Baseline diastolic blood pressure, per 1 mmHg higher	0.01 (−0.05, 0.06)	0.819	–	–
Baseline IOP, per 1 mmHg higher	−0.01 (−0.02, 0.01)	0.505	–	–
Mean IOP during follow up, per 1 mmHg higher	−0.01 (−0.03, 0.01)	0.499	−0.01 (−0.03, 0.01)	0.271
History of disc hemorrhage	−0.04 (−0.20, 0.12)	0.603	–	–
CH, per 1 mmHg lower	−0.04 (−0.07, 0.00)	**0.044**	−0.01 (−0.06, 0.03)	0.490
Follow up duration, per 1 year longer	0.04 (−0.05, 0.14)	0.383	0.04 (−0.06, 0.14)	0.439

MD = mean deviation; F = female; M = male; CCT = central corneal thickness; IOP = intraocular pressure; PSD = pattern standard deviation; CH = corneal hysteresis.

Values are shown in β coefficient (95% confidence interval), unless otherwise indicated. Race and clinically independent variables with a *p* value of less than 0.10 in the univariable analysis were included in the multivariable model. Statistically significant *p* values are shown in bold. Negative values correspond to faster MD decline over time.