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ABSTRACT

Purpose: To investigate the relationship between corneal hysteresis (CH) and progressive retinal nerve fiber layer (RNFL) loss in a cohort of patients with glaucoma followed prospectively over time.

Design: Prospective observational cohort study.

Methods: One-hundred and eighty-six eyes of 133 patients with glaucoma followed for an average of 3.8 ± 0.8 years, with a median of 9 visits during follow-up. The CH measurements were acquired using the Ocular Response Analyzer (Reichert Instruments, Depew, NY) and RNFL measurements were obtained at each follow up visit using spectral domain optical coherence tomography (SD-OCT). Random-coefficient models were used to investigate the relationship between baseline CH, central corneal thickness (CCT), average intraocular pressure (IOP) and rates of RNFL loss during follow up, while adjusting for potentially confounding factors.

Results: Average baseline RNFL thickness was 76.4 ± 18.1 μm and average baseline CH 9.2 ± 1.8 mmHg. CH had a significant effect on rates of RNFL progression. In the univariable model, including only CH as a predictive factor along with time and their interaction, each 1 mmHg lower CH was associated with a 0.13 μm/year faster rate of RNFL decline (P=0.011). A similar relationship between low CH and faster rates of RNFL loss was found using a multivariable model accounting for age, race, average IOP and CCT (P=0.015).

Conclusions: Lower CH was significantly associated with faster rates of RNFL loss over time. The prospective longitudinal design of this study provides further evidence that CH is an important factor to be considered in the assessment of the risk of progression in patients with glaucoma.

Corneal Hysteresis and Progressive Retinal Nerve Fiber Layer Loss in Glaucoma

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INTRODUCTION

Biomechanical properties of the cornea, such as thin central corneal thickness (CCT) and low corneal hysteresis (CH), have been identified as risk factors for primary open-angle glaucoma (POAG).[1] This suggests that they might be important biological markers of glaucoma susceptibility. Although measurement of CCT has become an integral component of examination of patients with glaucoma and suspected glaucoma in clinical practice, recent research has suggested that CH may be a stronger indicator of glaucoma progression.[2,3]

CH is a measure of the viscoelastic damping properties of the cornea, which can be estimated by analyzing the ability of the cornea to resist deformation induced by a pulse of air. CH may be evaluated in vivo using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments Inc., Depew, New York, USA), a device that delivers a metered air pulse to the cornea, while monitoring resulting changes in corneal curvature using a detector system.[4] The ability of the cornea to resist deformation is thought to reflect, at least in part, the constitution of its extracellular matrix; it has been suggested that the biomechanical properties of the cornea might correlate to biomechanical properties of posterior ocular tissues, such as the lamina cribrosa and peripapillary sclera.[5] An eye with a low CH could potentially have a lamina cribrosa that is less able to dampen pressure changes, and this might increase susceptibility to IOP-related strain and glaucomatous damage.[6] In support of this concept, eyes with higher CH have been reported to have greater deformation of the optic nerve surface during transient elevations of IOP.[5]

CH has been found to be lower in glaucomatous compared to normal eyes[1,7-9] and patients with lower CH have been found to be at higher risk of progressive visual field loss.[2,3,8] In a prospective longitudinal study, Medeiros and colleagues showed eyes with lower CH to have faster rates of visual field loss than those with higher CH; CH accounted for three times as much of progression as CCT in this study.[3] However, although previous longitudinal studies have examined the relationship between CH and functional measurements of glaucomatous damage, to our knowledge there have not been any reports on the relationship between CH and progressive structural changes to the optic nerve.

Due to the observation that optic nerve head and retinal nerve fiber layer (RNFL) changes often occur prior to detectable visual field changes, objective assessment of structural changes may provide a more sensitive method for measuring glaucoma progression, particularly in early disease.[10,11] Progressive glaucomatous structural changes can be detected by examination of optic disc stereophotographs however imaging devices such as optical coherence tomography (OCT) provide a more objective means to detect progression and allow calculation of rates of change over time. Although average RNFL thickness measurements have been extensively investigated in previous studies evaluating rates of glaucoma progression,[11] it is not known whether biomechanical properties of the cornea might be related to rates of change in these structural measures.

The purpose of this study was to investigate the relationship between CH and progressive RNFL loss in a cohort of glaucomatous eyes followed over time. To our knowledge, this is the first prospective longitudinal study to examine the relationship between CH and structural changes evaluated using an imaging instrument.

METHODS

This was an observational cohort study of participants from a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma [Diagnostic Innovations in Glaucoma Study (DIGS), clinical trial.gov identifier: NCT00221897, National Eye Institute] conducted at the Hamilton Glaucoma Center, University of California, San Diego (UCSD). Participants in the DIGS were longitudinally evaluated according to a pre-established protocol that included regular follow-up visits in which patients underwent clinical examination and several other imaging and functional tests. Written informed consent was obtained from all participants and the institutional review board (IRB #140276). The UCSD Human Subjects Committee approved all protocols, and the methods described adhered to the tenets of the Declaration of Helsinki. Subjects were followed at 6-month intervals.

At each visit during follow-up, subjects underwent a comprehensive ophthalmologic examination, including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, IOP measured using Goldmann applanation tonometry (GAT; Haag-Streit, Konig, Switzerland), gonioscopy, dilated fundoscopic examination, stereoscopic optic disc photography, standard automated perimetry (SAP) and retinal nerve fiber layer assessment with SD-OCT (software version 5.4.7.0 Heidelberg Engineering, Dossenheim, Germany). All patients also had CCT measurements obtained by a trained technician using ultrasound pachymetry (Pachette GDH 500, DGH Technology, Inc., Philadelphia, PA). Only subjects with open angles on gonioscopy were included. Subjects were excluded if they presented best-corrected visual acuity <20/40, spherical refraction outside ± 5.0 diopters or cylinder correction outside 3.0 diopters, or any other ocular or systemic disease that could affect the optic nerve or the visual field.

The study included 186 eyes from 133 patients diagnosed with glaucoma, as determined on the baseline visit. Eyes were classified as glaucomatous if they had repeatable (at least 3 consecutive) abnormal visual field test results on the baseline visits or a glaucomatous-appearing optic disc based on masked stereophotograph assessment. An abnormal visual field was defined as a pattern standard deviation outside of the 95% normal confidence limits (PSD) or a Glaucoma Hemifield Test (GHT) result outside normal limits. Signs of glaucomatous damage to the optic nerve were considered diffuse or localized neuroretinal rim loss, excavation, and retinal nerve fiber layer defects. Each participant was required to have a minimum of 4 SD-OCT examinations during a

minimum 2 years follow-up. Each patient was treated at the discretion of the attending ophthalmologist.

STANDARD AUTOMATED PERIMETRY:

SAP visual field tests were performed using the 24-2 Swedish interactive threshold algorithm on the Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc., Dublin, CA, USA). All visual fields were evaluated by the UCSD Visual Field Assessment Center.[12] Visual fields with more than 33% fixation losses or false-negative errors, or more than 15% false-positive errors, were excluded.

SD-OCT RETINAL NERVE FIBER LAYER ASSESSMENT:

Spectralis SD-OCT was used to obtain average circumpapillary RNFL thickness measurements from a 3.45-mm circle centered on the optic disc. The circle scan consisted of 1536 A-scan points. Details of the operation of the Spectralis SD-OCT have been described previously.[13,14] All SD-OCT images were reviewed by the UCSD Imaging Data Evaluation and Analysis Center to ensure the scan was centered, that the signal strength was more than 15 dB, and that there were no artifacts. Scans that were inverted or clipped or those that showed coexistent retinal pathologic abnormalities were excluded. The RNFL segmentation algorithm also was checked for errors.

CORNEAL HYSTERESIS MEASUREMENTS:

CH measurements were acquired at the baseline visit using the ORA. A trained technician obtained three measurements from each eye and the average of three 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.[4] During an ORA measurement, a precisely metered air pulse is delivered to the eye, causing the cornea to move inward, past a first applanation and move into a slight concavity. Milliseconds after the first applanation, the air pump generating the air pulse is shut down and the pressure applied to the eye decreases in an inverse-time, symmetrical fashion. As the pressure decreases, the cornea passes through a second applanated state while returning from concavity to its normal convex curvature. The two applanations take place within approximately 20 milliseconds (ms), a time sufficiently short to ensure that ocular pulse effect, or eye position, do not change during the measurement process. An electro-optical collimation detector system monitors the corneal curvature in the central 3.0 mm diameter throughout the 20 ms measurement period, based on the reflection of light from the cornea. When the cornea is flat (applanated), the reflection of light is maximal, generating a peak. A filtered version of the detector signal defines two precise applanation times corresponding to two well-defined peaks produced by inward and outward applanation events. Two corresponding pressures of an internal air supply plenum are determined from the applanation times derived from the detector applanation peaks. These 2 pressures are defined as the intersection of a vertical line drawn through the peaks of the applanation curve with the plenum pressure curve. The two applanation-pressures are different

primarily because of the biomechanical properties of the cornea. The difference between the two applanation-pressures is the CH, measured in mmHg, and is related to the viscous damping property of the cornea. The device provides a waveform score to reflect the quality of measurements. Only measurements associated with a waveform score greater than 4 were considered for inclusion. Baseline OCT and SAP tests were chosen as those closest to the baseline CH measurement date.

STATISTICAL ANALYSIS:

The evaluation of the effect of CH measurements on rates of change in RNFL thickness was performed using linear mixed models with random intercepts and random slopes.[15-17] In linear mixed models, the average evolution of the outcome variable (RNFL 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 RNFL loss over time, while also accommodating correlations between both eyes of the same individual.[15,18] 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. Several different predictors were investigated in this study, including baseline age, race, baseline CH, average GAT IOP, and CCT. We initially constructed univariable models containing only 1 putative predictor along with its interaction with time. Subsequently, more complex models containing multiple predictors and interactions were constructed to evaluate the effect of certain predictors while adjusting for potentially confounding factors. Similar models have been used previously to evaluate the role of CH as a risk factor for the rate of visual field progression in a cohort of patients with glaucoma followed prospectively over time.[3]

All statistical analyses were performed with commercially available software (STATA, version 13; Stata Corp LP, College Station, TX). The alpha level (type I error) was set at 0.05.

RESULTS

The study included 186 eyes of 133 patients with glaucoma followed for an average of 3.8 ± 0.8 years (range: 2.0 to 5.2 years). Included eyes had a median of 9 (range: 4 to 18) SD-OCT tests during follow-up. Table 1 shows baseline clinical and demographic information for eyes included in the study. Baseline CH was 9.2 ± 1.8 mmHg. Figure 1 shows distribution of corneal hysteresis values at baseline for all 186 eyes included in the study during follow-up.

Table 2 shows the effect of each putative predictive factor on the rates of RNFL loss over time according to the univariable models. Baseline CH had a significant effect on rates of RNFL progression over time (P=0.011) (Table 2).

That is, lower values of CH were associated with faster loss of RNFL thickness. Each 1-mmHg lower CH was associated with an additional RNFL loss of 0.13 μm/year. Average GAT IOP also was significantly associated with rates of RNFL change over time, with each 1 mmHg higher average GAT IOP associated with a 0.06 μm/year faster rate of RNFL loss. Being of African American ancestry was also associated with faster rates of RNFL loss in the univariable analysis, however age and CCT were not.

Table 3 shows the results of the multivariable model investigating the effect of baseline CH on rates of RNFL change over time, adjusting for age, race, average GAT IOP and CCT. Accounting for confounding variables, lower CH was still associated with a faster rate of RNFL loss during follow up (P=0.015). Each 1 mmHg lower CH was associated with a 0.13 μm per year faster rate of RNFL loss. Figure 2 (Top) shows the relationship between predicted slopes of change in RNFL thickness and baseline CH. Higher average GAT IOP was also associated with a faster rate of RNFL loss (P=0.010) (Figure 2, Bottom and Table 3). Older age and being of African American ancestry were not significantly associated with rate of RNFL loss over time in the multivariable model. There was also no significant relationship between CCT and rate of RNFL loss over time (P=0.681).

Figure 3 is an example of an eye included in the study that had low measured corneal hysteresis at baseline. This eye showed a significant rate of RNFL loss over time.

DISCUSSION

The current study showed lower baseline CH to be significantly associated with faster rates of RNFL loss in a cohort of patients with glaucoma followed over time. The relationship was present even in a multivariable model adjusting for other factors known to potentially affect rates of glaucoma progression. To our knowledge, this is the first prospective longitudinal study to evaluate the relationship between CH and changes in RNFL thickness. The results suggest that evaluation of CH adds valuable information to the assessment of the risk of glaucoma progression. The multivariable model showed each 1 mmHg lower CH to be associated with 0.13 μm per year faster rates of RNFL loss.

Interestingly, CCT was not significantly associated with rate of RNFL loss in this particular cohort, which was unexpected given the strong evidence of the importance of CCT from previous studies. Although longer follow up or inclusion of greater number of patients may have revealed an association between CCT and rate of RNFL loss, the finding suggests that baseline CH may be of greater value than baseline CCT in determining glaucoma progression. We have previously found glaucomatous eyes with lower CH to have significantly faster rates of visual field loss over time compared to eyes with higher CH and the effect of IOP on rates of progression to depend on CH.[3] Although thin CCT was also associated with faster rates of progression, it accounted for less of the variation in slopes of change in visual field than CH.

Biomechanical studies in non-human primates with experimental glaucoma have shown that IOP elevation results in displacement of the lamina cribrosa and expansion of the scleral canal.[19-21] These changes are thought to contribute to glaucomatous retinal ganglion cell loss in as a result of mechanical pressure on retinal ganglion cell axons passing through the lamina pores.[19,22,23] Hysteresis is a physical property related to the ability of connective tissues to dampen pressure changes. As the cornea and sclera are contiguous parts of the corneo-scleral envelope, formed from continuous extracellular matrix,[24] deformability of the cornea and sclera are likely to be closely related. Thus, measures of CH could be indicative of susceptibility of the optic nerve head to IOP-induced biomechanical changes. High CH has been found in a clinical study of human eyes to be associated with greater posterior displacement of the optic nerve head on acute IOP elevation.[5] In contrast, low CH as been associated with increased risk of glaucoma progression.[2] A possible explanation for these observations is that the optic nerve head of eyes with high CH may be more able to compensate for raised IOP. In contrast, the lamina and peripapillary sclera of eyes with lower CH would be less able to dampen IOP changes, potentially exposing retinal ganglion cells to greater mechanical strain with IOP elevation.

Several investigators have found an association between CH and optic nerve head morphology changes. Prata and colleagues recently investigated the association between corneal biomechanics and optic nerve head morphology in newly diagnosed glaucoma patients. Eyes with lower CH were found to have larger cup-to-disc ratio and deeper cup, independently of IOP.[25] Cross-sectional studies have also shown that patients with glaucoma have lower CH values than healthy subjects,[8,26,27] and patients with bilateral asymmetric disease have lower CH in the eye with more severe damage.[28] Lower CH has also been associated with glaucoma progression in longitudinal studies[2] however to our knowledge there has been only one previous prospective study examining the relationship between CH and progressive glaucomatous changes.[3] Medeiros and colleagues recently showed that eyes with lower CH at baseline subsequently experienced faster rates of visual field loss than those with higher CH. This suggested that CH might be an important factor to consider in the assessment of the risk of progression in patients with glaucoma.[3] However, it also is important to examine the relationship between CH and structural changes as progressive structural damage may be seen in the absence of detectable changes in the visual field in some patients.[29-31]

Although we have demonstrated a significant relationship between CH and rates of RNFL loss, the study has some limitations. While average IOP during follow up was examined, each patient was treated at the discretion of the attending ophthalmologist and it is possible that different management strategies could have influenced progression rate. Also, as SD-OCT is a relatively new technology, the follow up period for this study was relatively short; however, it was sufficient to test the study hypothesis, as we were able to demonstrate a significant relationship between CH and RNFL loss over time. Baseline CH was chosen to facilitate comparisons with other studies evaluating baseline risk factors for glaucoma progression. Although it is possible that CH might vary

during follow up, the long-term reproducibility of CH and any potential effect on progression has not been investigated. Furthermore, as all subjects in our study had the same number of CH measurements at baseline there is therefore little reason to suspect that variability of CH would have contributed significantly to the study findings.

It is also important to acknowledge the effect of disease severity on rates of change in RNFL. Due to the floor in structural measurements, eyes with advanced glaucoma are unlikely to show fast rates of change in RNFL thickness. The present study included patients with an average MD of only -5.3 ± 5.8 and therefore results may be different in other cohorts. However, measurement of CH is likely to be a useful indictor of risk of progression in all patients, as we have previously shown lower CH to also be associated with faster rates of visual field loss.

In conclusion, this study demonstrates that lower levels of CH at baseline are significantly associated with faster rates of progressive RNFL loss detected by SD-OCT. The prospective longitudinal design of this study supports a role for CH as a risk factor for progression in glaucoma.

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FIGURE LEGENDS

Figure 1. Distribution of corneal hysteresis values at baseline for all 186 eyes included in the study of the relationship between corneal hysteresis and retinal nerve fiber layer loss during follow-up.

Figure 2. Scatterplot showing the relationship between rate of change in retinal nerve fiber layer (RNFL) thickness and baseline corneal hysteresis (Top) and average intraocular pressure (IOP) (Bottom) during follow up.

Figure 3. Example of a patient included in the study with low corneal hysteresis (7.9 mmHg) and thick central corneal thickness (575 µm) who experienced significant loss of retinal nerve fiber layer (RNFL) thickness over time (Top). Average intraocular pressure was 17 mmHg. Serial standard automated perimetry (Bottom left row) and SD-OCT RNFL thickness measurements (Bottom right row) are shown.

Table 1. Baseline demographic and clinical characteristics of glaucomatous eyes included in the study of the relationship between corneal hysteresis and retinal nerve fiber layer loss.*

	Glaucomatous eyes (n = 186 eyes, 133 subjects)
Age (years)	68.3 ± 10.0
Gender, number (%)	
Female	65 (49%)
Ancestry, number (%)	
European	74 (56%)
African	47 (35%)
Other	12 (9%)
RNFL thickness (μm)	76.4 ± 18.1
Baseline PSD (dB)	5.3 ± 3.7
Baseline mean deviation (dB)	-5.3 ± 5.8
Baseline VFI (%)	86.7 ± 17.1
Baseline CH (mmHg)	9.2 ± 1.8
Follow-up (years)	3.8 ± 0.8
Average GAT IOP (mmHg)	13.8 ± 3.7
CCT (μm)	533 ± 42

RNFL = retinal nerve fiber layer; PSD = pattern standard deviation; VFI = visual field index; CH = corneal hysteresis; GAT = Goldmann applanation tonometry; IOP = intraocular pressure; CCT = central corneal thickness.
*Values are given in mean ± standard deviation.

Table 2. Results of univariable models assessing the effect of each putative predictive factor on retinal nerve fiber layer measurements at baseline and over time in glaucomatous eyes.*

Parameter	Effect on Baseline (Intercept)		Effect on Change Over Time	
	β_1 (SE)	P	β_2 (SE)	P
Baseline age (per year older)	-0.42 (0.13)	0.001	0.004 (0.01)	0.655
Race (African American)	8.04 (2.59)	0.002	-0.44 (0.14)	0.002
Baseline CH (per mmHg lower)	0.92 (0.71)	0.197	-0.13 (0.05)	0.011
Average GAT IOP (per mmHg higher)	1.38 (0.33)	<0.001	-0.06 (0.03)	0.017
CCT (per 100 μm thinner)	3.91 (3.08)	0.206	0.07 (0.22)	0.735

CH = corneal hysteresis; GAT = Goldmann applanation tonometry; IOP = intraocular pressure; CCT = central corneal thickness; SE = standard error.

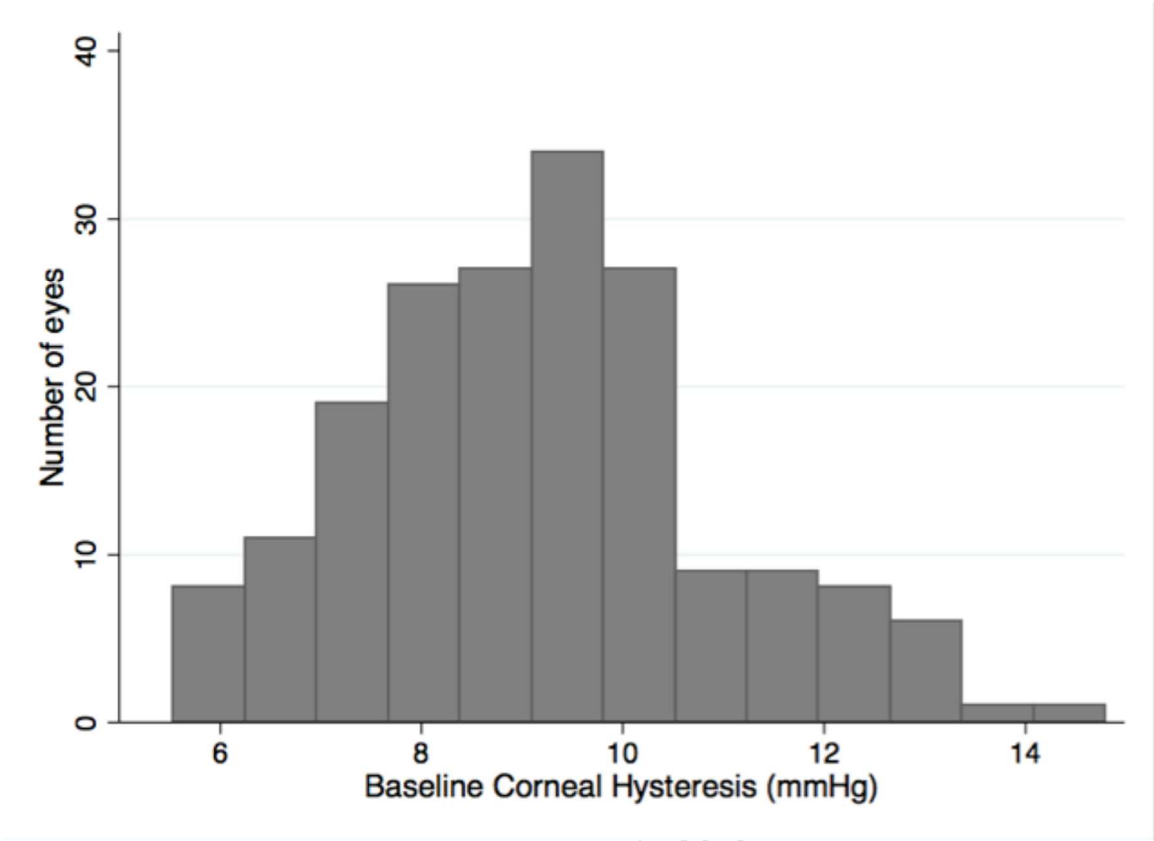
*The coefficient β_1 corresponds to the effect of each predictive factor on the baseline CH measurements. Negative values correspond to lower CH measurements at baseline. Coefficient β_2 corresponds to the effect on change over time. Negative values correspond to faster RNFL decline over time. Refer to the equation presented in "Materials and Methods." Variables were centered at their mean values.

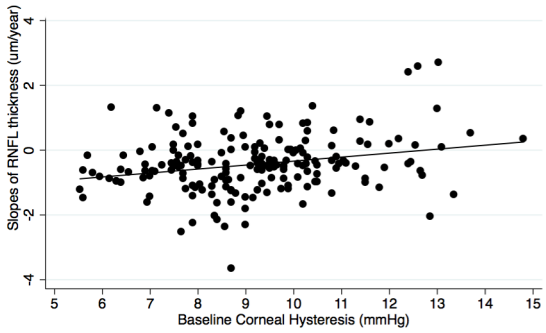
Table 3. Results of the multivariable linear mixed effects model investigating the effect of corneal hysteresis on retinal nerve fiber layer measurements decline over time, adjusting for potentially confounding factors in severe glaucoma eyes*.

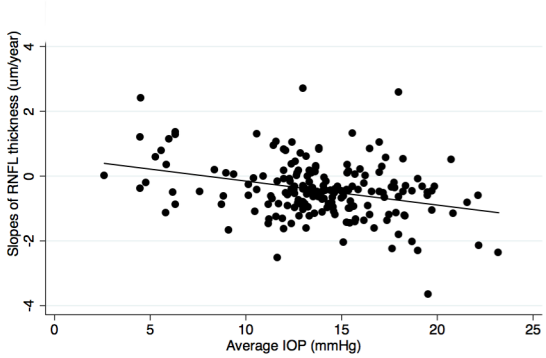
Parameter	β (SE)	P
Intercept (μm)	73.85 (1.56)	<0.001
Time (μm/year)	-0.46 (0.11)	<0.001
Baseline age (per year older)	-0.31 (0.12)	0.014
Baseline age × time	0.01 (0.01)	0.302
Race (African American)	5.46 (2.56)	0.033
Race × time	0.05 (0.18)	0.770
Baseline CH (per mmHg lower)	0.58 (0.76)	0.440
Baseline CH × time	-0.13 (0.05)	0.015
Average GAT IOP (per mmHg higher)	1.26 (0.35)	<0.001
Average GAT IOP × time	-0.06 (0.02)	0.010
CCT (per 100 μm thinner)	-0.14 (3.32)	0.966
CCT × time	-0.09 (0.23)	0.681

CH = corneal hysteresis; GAT = Goldmann applanation tonometry; IOP = intraocular pressure; CCT = central corneal thickness; SE = standard error.

*The interaction terms with time correspond to the effect of the predictive factor on rate of RNFL change over time. Negative values correspond to faster rate of RNFL decline over time. Variables were centered at their mean values.







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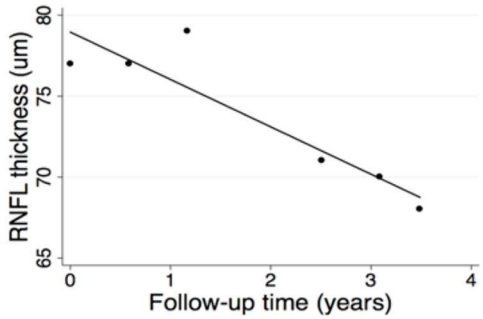
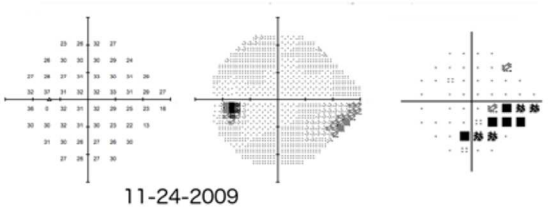


Baseline CH = 7.9 mmHg

CCT = 575 um

Slope = -2.34 um/year

B



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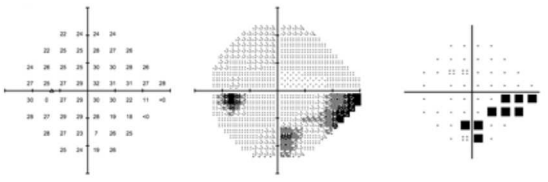

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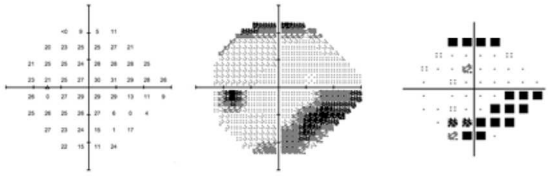

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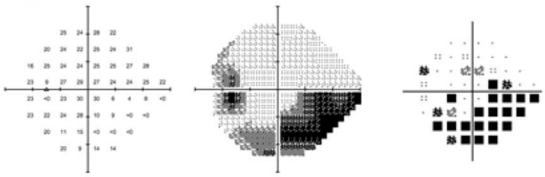

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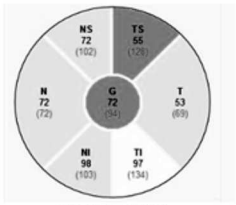

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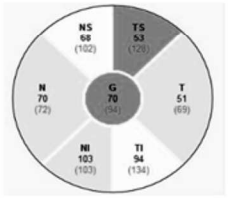

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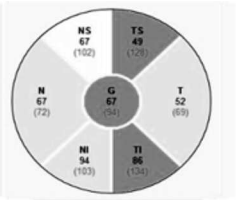

10-18-2012