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Relationship of Corneal Hysteresis and Anterior Lamina Cribrosa Displacement in Glaucoma

Brandon J. Wong[1,2], **Sasan Moghimi**[1], **Linda M. Zangwill**[1], **Mark Christopher**[1], **Akram Belghith**[1], **Eren Ekici**[1], **Christopher Bowd**[1], **Massimo A. Fazio**[3], **Christopher A. Girkin**[3], **Robert N. Weinreb**[1]

[1]Shiley Eye Institute, Hamilton Glaucoma Center, University of California San Diego, La Jolla, California, United States

[2]USC Roski Eye institute, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, California, United States

[3]Department of Ophthalmology and Vision Science, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama

Keywords

corneal hysteresis; lamina cribrosa; optical coherence tomography

Introduction

Glaucomatous optic neuropathy is a multifactorial disease characterized by progressive damage to the retinal ganglion cells, structural changes to the optic nerve, and concomitant visual field loss.[1] The neural damage observed in glaucoma is thought to be related to the complex interaction between intraocular pressure and the biomechanical properties of the optic nerve head (ONH) and surrounding tissues.[2, 3] Histopathologic studies have identified the lamina cribrosa as the primary site of axonal damage in glaucoma. Displacement or migration of the lamina has been reported both in acute intraocular pressure (IOP) elevation as well as chronic IOP elevation during the course of glaucoma progression [4–9] and has been proposed to be a marker of the overall mechanical stress exerted by the IOP surrounding connective tissue on the lamina cribrosa.[10] Assessment of the mechanical state of the ONH tissues is not readily available in a clinical setup; often, multiple scans at varying IOP are required to resolve the viscoelastic response of the ONH to IOP.

Corneal hysteresis (CH) is hypothesized to be a surrogate for the viscoelastic properties of the cornea and can be measured in-vivo by the commercially available Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments Inc, Depew, New York, USA). There is a

Corresponding Author: Robert N. Weinreb, 9415 Campus Point Drive, La Jolla, CA 92093-0946, rweinreb@ucsd.edu, (858) 534-6290.

growing literature regarding corneal hysteresis and its relationship to ONH changes. Prior studies have found that corneal hysteresis is associated with increased optic disc surface compliance as well as larger and deeper cups in patients with glaucoma.[11, 12] Lower corneal hysteresis has been associated with deeper anterior lamina depth and with anterior displacement of lamina cribrosa following surgical and medical IOP reduction.[13, 14] Corneal hysteresis has been shown to be lower in patients with glaucoma, and previous longitudinal studies have demonstrated lower corneal hysteresis as a risk factor for visual field progression and retinal nerve fiber layer (RNFL) progression in glaucoma.[15–21] Corneal hysteresis can affect the measurement of applanation tonometry and adjusting IOP measurements for corneal hysteresis improves the prediction of visual field progression in glaucoma.[22]

The exact mechanisms behind how lower corneal hysteresis may contribute to the development or progression of glaucoma remain unclear. Hypothetically, corneal hysteresis may serve as a surrogate biomarker of the viscoelastic properties of the lamina cribrosa, posterior sclera, and other ONH structures, and lower corneal hysteresis may indicate a decreased ability of the posterior tissues to compensate for IOP changes.[2, 10, 12, 19] The purpose of this study is to examine the relationship between baseline corneal hysteresis measurements and longitudinal changes to the anterior lamina cribrosa surface depth (ALCSD) as measured by spectral-domain optical coherence tomography (SD-OCT).

METHODS

This was a prospective observational case series using patients with glaucoma or suspected glaucoma from the patients enrolled in the UC San Diego Diagnostic Innovations in Glaucoma Study (DIGS, clinicaltrials.gov NCT00221897). The DIGS is an ongoing prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma. 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. Enrollment of participants in DIGS is based on the inclusion/exclusion criteria specified below. The UC San Diego Human Research Protection Program/Institutional Review Board approved all methodology and all methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Eligible participants had best-corrected visual acuity of 20/40 or better, spherical refraction within ±5.0 diopters, cylinder correction within ±3.0 diopters, and open angles on gonioscopy. All participants were older than 18 years of age. Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery). Patients with corneal or retinal pathologies (except mild dry age-related macular degeneration) were excluded from the study. Glaucoma patients in this study were defined as individuals who had reliable (fixation losses ≤20%, false negatives ≤ 33% and false positives≤ 15%) and repeatable abnormal Standard Automated Perimetry (SAP) tests using the 24-2 Swedish Interactive Threshold Algorithm (SITA) with either a Pattern Standard Deviation (PSD) outside the 95% normal limits or a Glaucoma Hemifield Test (GHT) result outside the 99% normal limit. Patients were defined as glaucoma suspects if they had

evidence of glaucomatous optic neuropathy without repeatable glaucomatous visual field defects.

A control group of 18 healthy eyes with a minimum of one year follow-up and 3 visits was used to estimate the longitudinal rate (and 95% confidence interval(CI)) of ALCSD displacement μm/year). Healthy eyes were required to have an IOP of 21 mmHg or less, normal-appearing optic discs, intact neuroretinal rims and RNFL, and normal visual field test results. This group was used as a reference for ALCSD displacement because testing was frequent over a time frame that should not show ALCSD change, rather just measurement variability.

At each visit during follow-up, subjects underwent a comprehensive ophthalmologic examination, including best-corrected visual acuity, slit-lamp biomicroscopy, IOP measured using Goldmann applanation tonometry (GAT; Haag-Streit, Konig, Switzerland), gonioscopy, dilated funduscopic examination, stereoscopic optic disc photography, standard automated perimetry, and retinal nerve fiber layer assessment with spectral-domain OCT (SD-OCT) (software version 5.4.7.0; Heidelberg Engineering, Dossenheim, Germany). All patients had central corneal thickness (CCT) measurements obtained by a trained technician using ultrasound pachymetry (Pachette GDH 500; DGH Technology, Inc, Philadelphia, Pennsylvania, USA). Each participant in the study was required to have at least five follow up visits with SD-OCT imaging during a minimum of 3 years of follow-up.

Measuring Corneal Hysteresis

Corneal hysteresis and corneal resistance factor (CRF) measurements were acquired at baseline using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments Inc, Depew, New York, USA). Subjects underwent testing with the ORA by a trained technician. Details of its operation have been described previously.[23] In brief, within a 20ms 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 two peaks produced by the applanation events. The CH is the difference between these two 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 5 were considered for analysis.

Spectral-domain Optical Coherence Tomography

The optic nerve head was examined using the Spectralis©SD-OCT (software version 5.2.0.3, Heidelberg Engineering GmbH) to obtain average circumpapillary RNFL thickness measurements from a 3.45-mm circle centered on the optic disc. All SD-OCT images were reviewed by the UCSD Imaging Data Evaluation and Analysis Center to ensure that the scan was centered, that the signal strength was more than 15 dB, and that there were no artifacts.

Measuring Anterior Lamina Cribrosa Depth and Choroidal Thickness

Scans were obtained using the enhanced depth imaging (EDI) optic nerve head-centered 48 radial scans. For each visit, the raw SD-OCT data were processed using the San Diego Automated Layer Segmentation Algorithm (SALSA), which has been previously described, to identify Bruch's membrane opening (BMO) and ALCS and the choroidal scleral interface.[24–26] ALCSD for each individual scan was calculated as the median depth of the lamina measured at a 61-point interval centered at the middle of the BMO reference plane (Figure 1A). The median ALCSD was calculated as the median of all 48 individual ALCSD values.

For choroidal measurements, SALSA was used to automatically segment the BM layer and choroidal-scleral interface using raw data from high resolution Spectralis RNFL circle scans consisting of 1536 A-scans centered on the optic disc with a 3.46 mm diameter. (Figure 1B) All automated scans were manually checked for segmentation errors and scans with poor segmentation were excluded from the study.

Visual Field Progression Analysis—Visual field (VF) progression was defined when there were ≥3 locations that showed a significant change (i.e., change greater than the test-retest variabilities) compared with 2 baseline examinations for at least 3 consecutive tests (i.e. "likely progression" reported in the GPA) during the study follow-up and when the changes also were observed at the latest follow-up visit.[27]

Statistical Analysis—Reproducibility of SD-OCT scans was assessed by calculating the intraclass correlation coefficient (ICC) for inter-visit ALCSD in 30 cases that had repeatable OCT exams within 1 week.

The rates of change of the ALCSD of individual eyes was calculated with a linear regression analysis between ALCSD and time. A significant anterior or posterior ALCS displacement was defined when the ALCSD slope was higher or lower than the 95% CI of the rate of ALCSD displacement in healthy eyes, respectively. In addition, the root mean squared error (RMSE) for each eye was calculated and was used as a surrogate for inter-visit variability of ALCS over time. Factors affecting variability of RMSE were examined using linear mixed models.

Linear mixed-modeling was also used to identify factors associated with the rates of change of ALCSD. First, the interactions between each putative factor and time (follow-up duration at each follow-up visit) were fitted in the univariable linear mixed-models as fixed effects using random intercepts and random slopes with eyes nested within subject to account for inter-eye correlation. This allows for different baseline ALCSD values and different rates of change of ALCSD for individual eyes. Baseline age, race, gender, baseline axial length, baseline CCT, baseline IOP, average IOP during follow-up, peak IOP during follow-up, IOP change during follow-up, standard automated perimetry mean deviation (SAP-MD), standard automated perimetry pattern standard deviation (SAP-PSD), and choroidal thickness (as time dependent covariate) were used as putative factors in the current study. Age and factors with borderline significant association ($P < 0.1$) in the univariable analysis were then used in the final multivariable model. To reduce collinearity, different models

were fitted with mean IOP, peak IOP, or IOP change during follow-up as putative factors in addition to other confounding variables.

Stratified linear mixed effects models were fitted for ALCSD to determine the effect of glaucoma severity and age on ALCSD displacement. Early glaucoma was defined as MD< −6dB and moderate to advanced glaucoma had MD >−6dB). Patients were divided into tertiles of age.

All statistical analyses were performed with commercially available software (STATA, version 15; Stata Corp LP, College Station, Texas, USA). The alpha level (type I error) was set at 0.05.

RESULTS

One hundred and forty-seven eyes from 96 patients met the inclusion criteria of minimum of 3 years of follow-up and a minimum 5 follow-up visits. In total, 2104 scans were examined of which 459 scans (21.8%) were excluded from the study. Of the excluded scans, 95/459 scans had poor identification of the BMO, 71/459 had poor visibility of the ALCS, and 293/459 had overall poor quality image quality. Table 1 shows the demographics and baseline characteristics of eyes included in this study.

In glaucoma or glaucoma suspect patients, the mean (95% CI) age at baseline was 68.3 (66.5-70.1) years, while the mean duration of follow up was 3.5 (3.5-3.6) years and mean number of follow up visits was 7.9 (7.4-8.4) visits. The mean baseline CH was 9.4 (95%CI: 9.1-9.7). Choroidal thickness thinned at a mean rate of −1.09 μm /year (95% CI: −1.75, −0.43) over follow-up.

Variability

The overall ICC for ALCSD was excellent for the qualified scans with SALSA segmentation method with 99.8% (95% CI = 99.5% to 99.9%). There was no significant ALCSD change in healthy control eyes (0.34 μm /year, p=0.917) over an average follow-up of 3.7 years. Upper and lower 95% CI of ALCSD displacement was 6.78 and −6.10 μm/year in this variability group, which were used for defining significant ALCSD displacement in glaucoma eyes.

Anterior lamina cribrosa surface depth change

108 glaucoma or glaucoma suspect eyes (73.4 %) showed no significant ALCS displacement over time. Seventeen eyes (11.5 %) showed a significant positive trend (i.e. posterior displacement of ALCS) whereas 22 eyes (15.0%) showed a significant negative trend (i.e. anterior displacement of ALCS). Guided Progression Analysis detected 9 eyes (6.1 %) with visual field progression during study follow-up. Eyes with posterior ALCS displacement progressed more frequently compared to eyes with anterior ALCS displacement or with stable ALCS (3 (17.6%), 1 (4.5%), and 5 (4.63%), respectively, P=0.108).

The RMSE analysis for all eyes showed no significant correlation between CH and inter-visit variability of the ALCSD over time (P=0.576). However older age was associated with lower RMSE of ALCSD over time (β= −0.10 (−0.22, 0.01), P=0.074).

Figure 2 demonstrates association of ALCSD displacement and CH over time. Using linear mixed modeling to examine factors affecting the rate of change of the ALCSD, univariate analysis showed that average IOP, peak IOP, IOP change, CCT, and choroidal thickness were significantly associated with rates of change of ALCSD (Table 2).

Table 3 shows the results of the multivariable model analysis investigating the effect of baseline CH on rates of change of ALCSD over time, adjusting for age, choroidal thinning, CCT, and average IOP (model 1), peak IOP (model 2) or IOP change during follow-up (model 3). In all models, choroidal thinning and CH were significantly associated with a faster rate of posterior placement of the ALCS during follow up (P=0.032 and P=0.037 in model 1, P=0.031 and P=0.033 in model 2, and P=0.034, and P=0.048 in model 3, respectively). Specifically, for every 1 mm Hg decrease in CH there was approximately a 0.66 μm/year posterior displacement of the anterior lamina cribrosa surface. When stratifying the eyes based on severity of glaucoma, a similar association between CH and ALCSD displacement (β= 1.09 (0.32, 1.86) μm/year for each 1 mm Hg lower CH, P=0.005) was observed in multivariable model when eyes with early glaucoma (MD<−6 dB) were included in the analysis. However, no link was found between CH and lamina cribrosa change in eyes with moderate to advanced (MD > −6 dB) glaucoma (β=−0.34 (−1.79, 1.11), P=0.648). In addition, age-stratified linear mixed model demonstrated that for every 1 mmHg decrease in CH, the ALCSD was displaced more posteriorly in eyes in the lower tertile age compared to higher tertile age (1.76 vs. 0.92 μm/year, P=0.189). No association was found between CRF and ALCSD displacement over time in univariable (P=0.225) and multivariable analysis (P=0.858) in our study group. Figure 3 shows the change in ALCSD and visual field over time in two patients with different corneal hysteresis measurements.

DISCUSSION

The current study shows that over time lower baseline CH is associated with posterior displacement of the anterior lamina cribrosa surface. The multivariable model shows that for every 1 mm Hg decrease in CH there was approximately a 0.66 μm/year posterior displacement of the anterior lamina cribrosa surface. Older age was associated with lower inter-visit displacements of ALCD. This provides the first evidence that variation in corneal hysteresis may modulate long-term remodeling of the load bearing connective tissues of the ONH.

Corneal hysteresis has been hypothesized to reflect the biomechanical characteristics of the optic nerve head complex. Wells and coworkers showed that CH was associated with increased deformation of the optic nerve using Heidelberg Retina Tomography II (HRT) after transient elevation of IOP.[12] Prata et al reported that in newly diagnosed glaucoma patients, lower corneal hysteresis was associated with deeper mean cup depth and a larger cup-to-disc ratio, independent of IOP and disc size.[11] They postulated that a reduced viscous damping of the cornea, represented by a low CH, may reflect an increased deformability of

the ONH complex. In addition to being associated with morphologic glaucomatous changes, lower corneal hysteresis has been shown to be a risk factor for both RNFL progression and HVF progression in cross-sectional and longitudinal studies.[17–19, 21] Lower CH has also been associated with the development of glaucoma in glaucoma suspects.[20]

Like corneal hysteresis, displacement of the anterior lamina cribrosa has also been associated with progression of glaucoma and may be an early marker of glaucomatous damage. Experimental animal models of glaucoma have shown that posterior displacement of the lamina cribrosa and changes to the optic nerve head as measured by confocal scanning laser ophthalmoscopy occur before a decrease in the RNFL thickness.[28] A prospective, longitudinal study showed that 82.6% of eyes with both ONH surface depression and RNFL thinning had the ONH depression detected before the RNFL thinning (median lag time of 16 months).[29] Lee et al showed in another longitudinal study using a fractional polynomial model that larger lamina cribrosa displacement was associated with faster rates of global RNFL thinning.[30] Wu et al found that a higher rate of change of the ALCD measured using the BMO was associated with a higher risk of visual field progression over a 5-year period.[31]

Few studies have examined the relationship between CH and the lamina. Fazio et al showed that after acute elevation of IOP in normal patients, lower CH was associated with greater posterior displacement of the ALCSD.[32] Lanzagorti-Aresti and co-workers examined the relationship between CH and lamina cribrosa displacement in patients with ocular hypertension and POAG after one week of medical therapy to lower IOP. They showed that lower CH was related to less anterior displacement of the lamina cribrosa (more posterior displacement) after one week of follow-up.[14] Bochmann and coworkers noted that CH was lower in patients with POAG with acquired pit of the optic nerve (APON), a localized defect in the lamina cribrosa, compared to POAG patients without APON.[33] However, these prior studies only investigated the effect of short term effect of IOP change on ALCS that reflective of the acute tissue response to IOP change. In contrast, longitudinal studies evaluate the long-term remodeling of the load bearing connective tissues in response to IOP, which may occur through entirely different mechanisms.

Our longitudinal results show that in glaucoma or suspected glaucoma eyes, lower corneal hysteresis is associated with posterior displacement of the ALCS over time in a multivariable model. It was observed that every 1 mm Hg decrease in CH leads to a 0.66 μm/year posterior displacement of the anterior lamina cribrosa surface.

Our findings are in contrast to that of Esfandiari and colleagues who showed there was no correlation between CH and ALCS displacement over time. In their study, they evaluated the short term (1-month) ALCS displacement in patients undergoing trabeculectomy and found no correlation between CH and ALCS displacement.[13] Our study differs in that we excluded patients with any glaucoma surgery which may have caused a significant change in IOP. Moreover, the duration of follow up in our study is much longer (average of 3.5 years) than in the earlier study. Further, we measured the lamina using 48 B-scans compared to only 6 B-scans in their study which may account for different measurements of the lamina depth. Despite the differences in methodology, these conflicting results serve to emphasize the

complexities of ONH biomechanics and the numerous factors that may influence ONH displacement.[3, 34] Sigal et al suggested that this deformation may be more dependent on scleral or lamina biomechanical properties rather than the direct influence of IOP on the ONH.[10]

We conducted a RMSE analysis to explore the possibility that corneal hysteresis may be related to the inter-visit variability of the ALCSD over time. No significant association was found between CH, gender, ethnicity, axial length, and IOP-related parameters (mean, peak, standard deviation, and range during follow-up) with RMSE analysis (P>0.05 for all). However, the amount of IOP reduction was associated with ALCSD change over time, similar to the findings of Lee et al.[35] In the present study, older age did show a trend in fewer inter-visit ALCSD variations over time. This may be explained by the fact that the magnitude of laminar deformation may be greater in younger, or more “compliant”, eyes compared to older, more “stiff’ eyes.[36] Ren et al showed in a cross-sectional study that the lamina was shallower in older eyes compared to younger eyes with same VF status and RNFL thickness.[3437] Lanzagorti-Aresti et al showed that younger age was associated with greater ALCS displacement in the short-term.[14] The present study also demonstrates greater displacement of the lamina in the lower tertile age of patients compared with the highest tertile age of patients. Given the degree of complexity in the interaction between the lamina, surrounding tissue, and IOP, it is not surprising that the lamina can respond in different ways to elevated IOP. The lamina cribrosa has been shown to move anteriorly (towards the vitreous) and posteriorly (away from the vitreous) in response to lowering IOP in glaucomatous eyes.[31, 38] The majority of glaucoma or suspected glaucoma eyes in our study (73.4.2%) showed stable or no significant ALCS displacement over time, while 11.5% showed posterior displacement of ALCS and 15% showed anterior displacement of the ALCS. Our results are different from those of Wu et al who reported 23.3% of eyes showed significant posterior ALCS displacement whereas 29.5% showed a significant anterior ALCS displacement of ALCSD. This may be due to differences in methods of measuring the ALCSD, demographic differences in study populations, as well different baseline IOP (15.4 mmHg in our study compared to 18.7 mm Hg in their study).

In contrast to CH, CRF is thought to reflect the overall resistance of the cornea[23]. While the relationship between CH and structural and functional progression of glaucoma has also been previously described,[17–19] the exact relationship between CRF and progression of glaucoma is unknown. Our results concur with those of De Moraes et al, who reported in their final multivariable analysis that only CH, and not CRF, was a statistically significant factor for glaucomatous visual field progression.[18] Nevertheless, after acute elevation of IOP, CRF has been shown to correlate with anterior lamina displacement in severe glaucoma.[39]

While it still remains unclear as to what intrinsic properties of the eye corneal hysteresis is actually measuring, our results support the hypothesis that low CH is a surrogate for lower ONH tissue biomechanics rigidity, which, over continued exposure to IOP, leads to a posterior displacement of the ALCS. This supports the supposition that lower corneal hysteresis predisposes an eye to developing structural or functional glaucoma progression as it serves as morphologic marker for posterior ALCS displacement.

This study had some limitations. First, the BMO was used as our reference plane to calculate ALCSD as the SALSA software automatically determines the end of BM. Johnstone et al. reported that the BMO migrates posteriorly with age, possibly as a result of age-related choroidal thinning, and a longitudinal study showed that using the anterior sclera as a reference could reduce the influence of choroidal thickness on lamina cribrosa depth measurements.[40, 41] Others have reported using the choroid-sclera interface or the anterior scleral canal opening as a reference to calculate the laminar depth, however measurement differences between different reference markers may be small and the clinical importance remains to be determined.[31, 42] Regardless, Belghith and coworkers showed in a longitudinal study that the location of BMO in glaucoma patients measured by the SALSA software was stable over a mean of 3.7 years.[43] Thus, the impact of any age-related changes within the choroid are likely to be small. Given the possibility that choroidal thickness could affect ALCSD measurements, we included choroidal thickness as measured by a circle scan around the ONH in our univariable and multivariable model and the results of the multivariable model were adjusted after fitting for changes in choroidal thickness. Second, we only measured the anterior lamina cribrosa surface depth as a marker of the lamina displacement. Other parameters of the lamina, such as lamina cribrosa thickness or lamina curvature, should be examined to obtain a more complete understanding of the lamina and its relationship to CH. Third, only 6% of our study group had VF progression, so our analysis regarding ALCSD displacement and its relationship to visual field progression may be affected by the small number of patients who actually progressed. Our follow-up period may not be sufficiently long enough to evaluate visual field deterioration and its correlation with ALCS changes. Finally, although this cohort had enough sample size to assess effect of CH in glaucoma patients, it might not be large enough to perform age, and/or disease severity stratification, and it is possible that younger age may significantly modify the effect of CH on ALCSD displacement.

In summary, the present study showed that lower corneal hysteresis is associated with posterior ALCS displacement over time. We propose that eyes with lower corneal hysteresis are at a higher risk of glaucoma progression. Studies with larger sample size and longer follow-up are needed to further characterize the effects of corneal hysteresis on the lamina cribrosa in glaucomatous eyes and its association with visual field progression.

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Synopsis:

This prospective and observational study demonstrates that lower corneal hysteresis is associated with posterior displacement of the anterior lamina cribrosa over time, and is a risk factor for glaucoma.

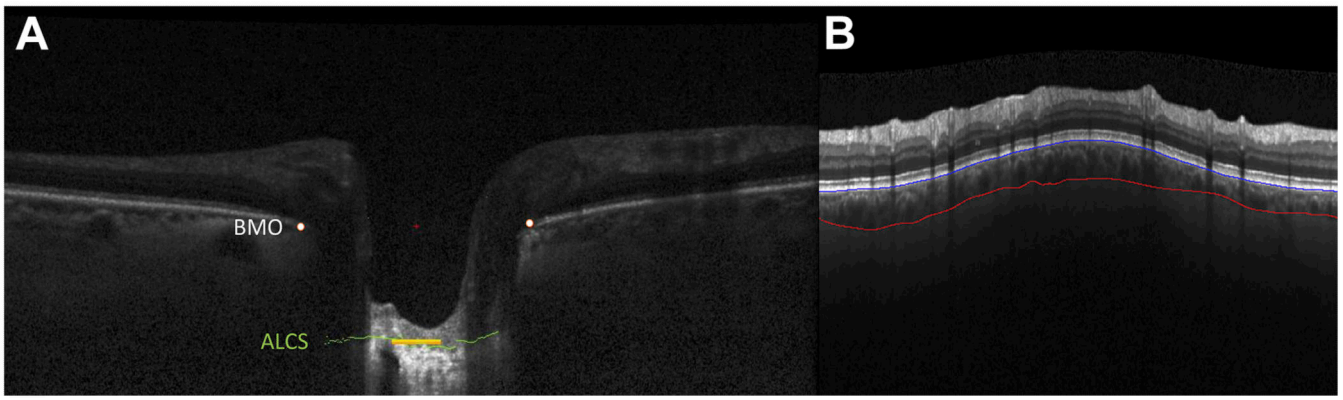

Figure 1.

A Measurement of the anterior lamina cribrosa surface depth (ALCSD). An optical coherence tomography B scan image of a glaucomatous eye after automated segmentation by the San Diego Automated Layer Segmentation Algorithm (SALSA) software. The Bruch's membrane opening (BMO) is identified (white dots) and a 61 point interval in the middle of the BMO is marked (middle red cross). The detectable anterior lamina cribrosa surface (ALCS) is segmented (green line). The individual ALCSD for the B scan is represented as the median depth of the 61 point interval of lamina points centered from the BMO plane, measured from the BMO plane (yellow line). B. Spectral-domain optical coherence tomography image with SALSA segmentation of the choroid, seen between the Bruch membrane (blue line) and the choroidal–scleral interface (red line).

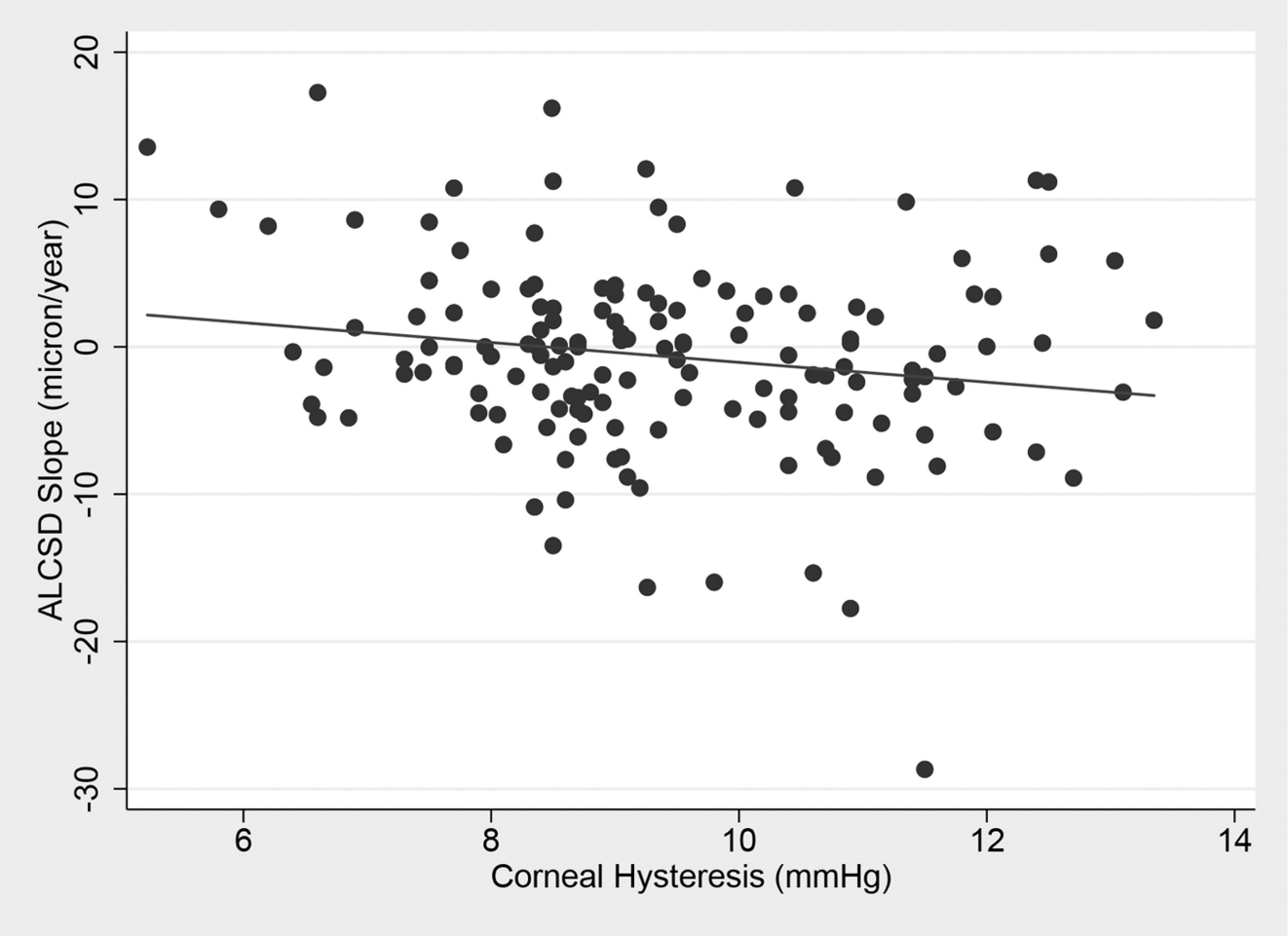

Figure 2.
Scatterplot showing association of corneal hysteresis with anterior lamina cribrosa surface depth (ALCSD) change over time.

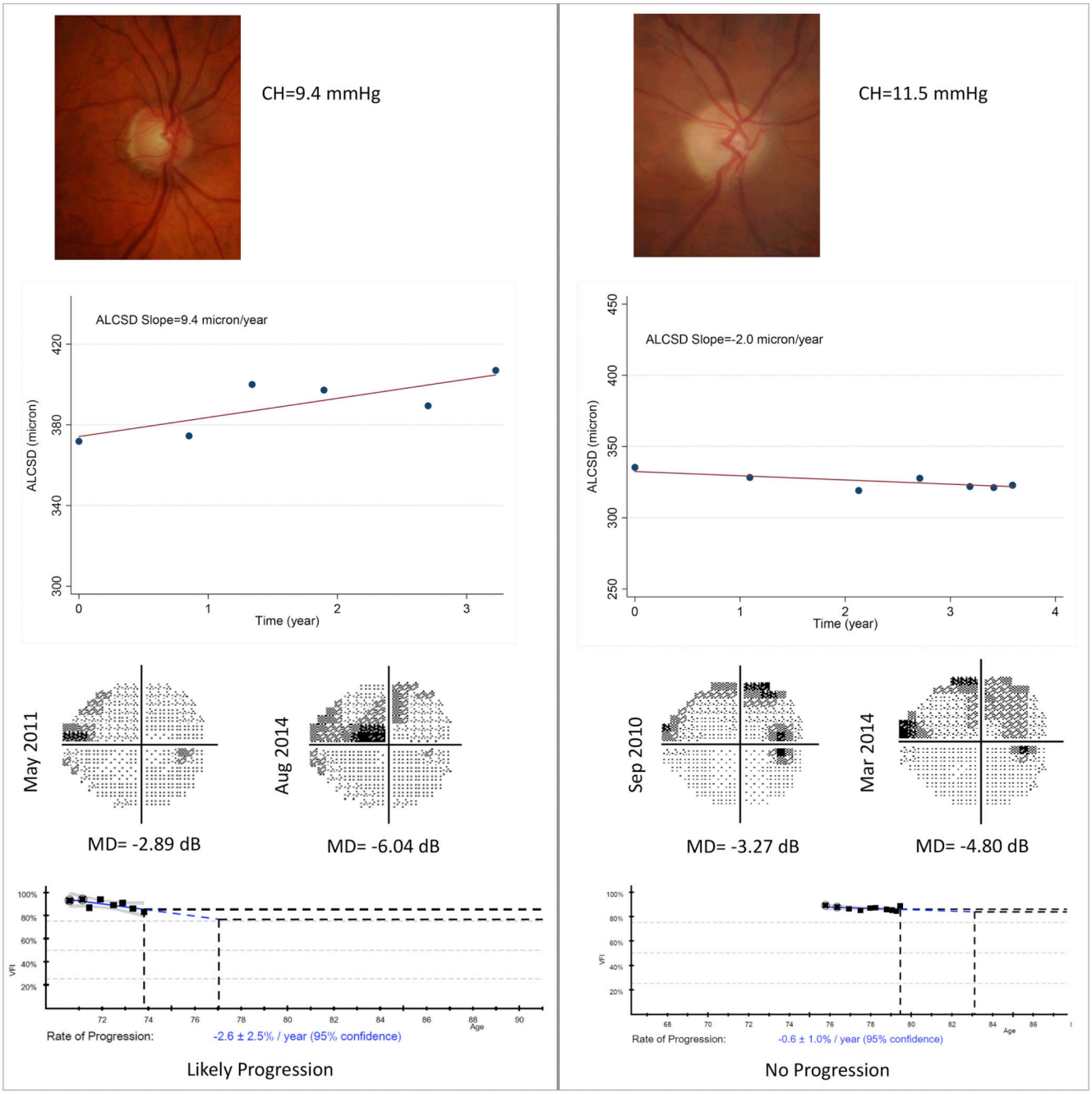

Figure 3-

Left-Example of a patient included in the study with low corneal hysteresis (9.3 mm Hg) who experienced significant posterior displacement of anterior lamina cribrosa surface depth (ALCSD) (Middle) and visual field deterioration over time (Bottom). **Right-** Example of a patient with high corneal hysteresis (12.1 mm Hg) with no significant ALCSD displacement (Middle). No visual field progression was found in this case using Glaucoma Progression Analysis (Bottom)

Table 1.

Demographics and Ocular Characteristics of Study Population

Parameter	Glaucoma (N=147 eyes, 96 subjects)
Age (years)	68.3 (66.5, 70.1)
Gender (Female:Male)	54:42
Glaucoma: Glaucoma suspect	96:51
Race: African American: Non-African American	27:69
Follow-up period (year)	3.5 (3.5, 3.6)
Number of visits	7.9 (7.4, 8.4)
Baseline IOP (mm Hg)	15.4 (14.7, 16.1)
Average IOP (mm Hg)	14.5 (13.9, 15.1)
Peak IOP (mm Hg)	18.2 (17.4, 18.9)
IOP change (mm Hg)	−1.0 (−1.6, −0.4)
CCT (μm)	547.1 (540.3, 553.9)
CH (mm Hg)	9.4 (9.1, 9.7)
CRF (mmHg)	9.1 (8.8, 9.4)
Axial length (mm)	24.1 (23.9, 24.3)
Baseline choroidal thickness (μm)	103.1 (93.5, 112.7)
Baseline SAP-MD (dB)	−3.1 (−4, −2.2)
Baseline SAP-PSD (dB)	4 (3.4, 4.6)
Baseline RNFL thickness (μm)	75.8 (73.4, 78.1)
Median Baseline ALCSD (μm)	449.2 (428.5, 469.9)
ALCSD Slope (μm/year)	−0.78 (−1.82, 0.26)

ALCSD: anterior lamina cribrosa surface depth; CI: confidence interval; CCT: central corneal thickness; CH: corneal hysteresis; CRF: corneal resistance factor; IOP: intraocular pressure; MD: mean deviation; PSD: pattern standard deviation; SAP: standard automated perimetry

Values are given as mean with 95% CI

Table 2.

Results of Univariable Analysis Evaluating the Effect of Each Predictive Factor on Anterior Lamina Cribrosa (ALCS) Displacement over Time (β) in Glaucoma eyes

Parameter	Effect on Change over Time (slope)	
	β (95% CI)	P
Age (per 10 year older)	−0.75 (−1.71, 0.21)	0.124
Gender (Female)	0.26 (−1.91, 2.43)	0.792
Race: African American	−0.12 (−2.44, 2.19)	0.916
Baseline IOP (per mm Hg higher)	0.18 (−0.06, 0.42)	0.142
Average IOP (per mm Hg higher)	0.34 (0.07, 0.61)	**0.013**
Peak IOP (per mm Hg higher)	0.29 (0.07, 0.51)	**0.009**
IOP change (per mm Hg higher)	0.36 (0.04, 0.68)	**0.029**
CCT (per 10 μm thinner)	−0.25 (−0.5, −0.01)	**0.042**
Choroidal Thickness (per 10 μm thinning)	−0.27 (−0.5, −0.03)	**0.025**
Baseline SAP-MD (per dB lower)	−0.10 (−0.29, 0.08)	0.283
Baseline SAP-PSD (per dB higher)	−0.19 (−0.49, 0.1)	0.196
CH (per 1 mm Hg lower)	0.63 (−0.1, 1.37)	0.093
CRF (per 1 mm Hg lower)	−0.33 (−0.86, 0.2)	0.225
Axial length (per 1 mm higher)	0.24 (−0.64, 1.12)	0.597

CCT: central corneal thickness; CH: corneal hysteresis; CI: confidence interval; CRF: corneal resistance factor; IOP: intraocular pressure; MD: mean deviation; SAP: standard automated perimetry

Coefficient β corresponds to the effect on change over time. Positive values correspond to posterior ALCS displacement over time while negative values correspond to anterior ALCS displacement over time

P<0.05 are shown as bold

Table 3.

Results of Multivariable Linear Mixed Effects Model Assessing the Effect of Corneal Hysteresis on Anterior Lamina Cribrosa Surface (ALCS) Displacement (adjusting for confounders)

Parameter	Effect on slope (model 1)		Effect on slope (model 2)		Effect on slope (model 3)	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Age (per 10 year older)	−0.22 (−1.52, 1.09)	0.747	−0.19 (−1.5, 1.11)	0.772	0.29 (−1.09, 1.67)	0.685
Average IOP (per mm Hg higher)	−0.12 (−0.44, 0.2)	0.468	-	-	-	-
Peak IOP (per mm Hg higher)	-	-	−0.08 (−0.31,0.15)	0.516	-	-
IOP change (per mm Hg higher)	-	-	-	-	0.35 (0.02, 0.69)	**0.037**
Baseline CCT (per 10 μm thinner)	−0.08 (−0.36, 0.19)	0.554	−0.07 (−0.33, 0.2)	0.616	−0.05 (−0.32, 0.23)	0.742
Choroidal Thickness (per 10 μm thinning)	−0.3 (−0.57, −0.03)	**0.032**	−0.29 (−0.56, −0.02)	**0.037**	−0.31 (−0.6, −0.02)	**0.034**
CH (per 1 mm Hg lower)	0.75 (0.07, 1.42)	**0.031**	0.73 (0.06, 1.39)	**0.033**	0.66 (0, 1.32)	**0.048**

P<0.05 are shown as bold

CCT: central corneal thickness; CH: corneal hysteresis; CI: confidence interval; IOP: intraocular pressure

Coefficient β corresponds to the effect on change over time. Positive values correspond to posterior ALCS displacement over time while negative values correspond to anterior ALCS displacement over time.