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Association between Rates of Retinal Nerve Fiber Layer Thinning after Intraocular Pressure–Lowering Procedures and Disc Hemorrhage

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Abstract

Purpose: To compare the rates of retinal nerve fiber layer (RNFL) thinning after intraocular pressure (IOP) lowering procedures in eyes with or without disc hemorrhage (DH) history.

Design: Observational cohort study.

Methods: A total of 166 primary open angle glaucoma (POAG) eyes and glaucoma suspect eyes (37 eyes with DH history (DH group) and 129 eyes without DH (non-DH group)) were included from the African Decent and Glaucoma Evaluation Study (ADAGES) and the Diagnostic Innovations in Glaucoma Study (DIGS). Subjects underwent stereoscopic optic disc photography annually and spectral-domain optical coherence tomography (OCT) RNFL thickness

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measurements every 6 months. The rates of RNFL thinning were compared in eyes with and without DH using univariate and multivariable linear mixed effects models.

Main Outcome Measures: The rates of RNFL thinning

Results: The mean follow-up of DH group and non-DH group was 4.6 years and 4.2 years, respectively. DH group had more procedures (2.4 vs. 1.9, $P=0.080$) before follow-up, and more medications (1.8 vs. 1.4, $P=0.052$) and lower mean IOP (12.69 mmHg vs. 14.41 mmHg, $P=0.012$) during follow-up compared to non-DH group. When mean IOP was adjusted as a covariate in the model, the RNFL thinning rate in the DH group was 2-fold faster than in the non-DH group ($-0.61 \mu\text{m}/\text{year}$ vs. $-0.33 \mu\text{m}/\text{year}$, $P=0.025$). Higher mean IOP during follow-up was associated with a faster rate of RNFL thinning after procedures.

Conclusions: POAG or glaucoma suspect eyes with a history of DH should be carefully followed after IOP-lowering procedures. Additional IOP-lowering may be needed to slow structural progression of the DH eyes to the same rate as the non-DH eyes.

Precis

This study evaluated the effect of disc hemorrhage (DH) history on retinal nerve fiber layer (RNFL) thinning after intraocular pressure (IOP) lowering procedures. With IOP adjustment, DH eyes showed faster RNFL thinning than non-DH eyes.

Disc hemorrhage (DH) can precede the development,¹ as well as functional and structural progression, of glaucoma.¹⁻⁹ The history of a past DH, even many years prior, predicts faster structural progression.¹⁰ Clinicians often consider DH as an indication for additional intraocular pressure (IOP) lowering therapy.^{2, 11-13} In fact, as many as 31% of the glaucoma eyes in which a DH is observed soon undergo surgery to lower IOP.¹³ However, the benefit of reducing IOP to slow progression in eyes with DH has not been completely elucidated. Some have reported that IOP-lowering treatment might reduce DH occurrence^{4, 14, 15}, post-DH vision field (VF) progression¹³ and structural progression¹². In contrast, IOP-lowering did not preserve VF in eyes with DH as long as eyes without DH in the Collaborative Normal Tension Glaucoma Study.¹⁶ Moreover, it is still unknown if IOP lowering procedures like trabeculectomy and laser trabeculoplasty, which are often indicated for eyes with risk of progression, have similar efficiency on eyes with and without DH history.

In order to study whether a DH history affects the benefit of IOP-lowering procedures on RNFL thinning, we compared the rates of RNFL thinning after IOP lowering procedures in eyes with and without DH history.

Methods

Participants

Participants were recruited from the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES) which are conducted at the Hamilton Glaucoma Center at the University of California, San Diego (UCSD) and ADAGES is a multicenter study conducted at UCSD, the University of Alabama at Birmingham, and Columbia University (previously at the New York Eye and Ear Infirmary).

The protocols of the two studies are identical, and the methodological details have been described previously.¹⁷ The studies received institutional review board approval at each of the 3 sites. The methodology adhered to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. Informed consent was obtained from all participants.

Inclusion criteria for DIGS and ADAGES were a best-corrected visual acuity of 20/40 or better, a spherical refraction within ± 5.0 diopters (D), cylinder correction within ± 3.0 D, and open angles on gonioscopy at study entry. Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract or glaucoma surgery). Eyes with secondary causes of elevated IOP, other intraocular diseases, or other diseases affecting VF or who were using medications known to affect VF sensitivity also were excluded.

Participants of DIGS/ADAGES were evaluated every 6 months. At each annual follow-up visit, subjects underwent complete ophthalmologic examination including slit-lamp biomicroscopy, IOP measurement, dilated stereoscopic fundus examination, and stereophotography of the optic nerve head. VF test and spectral domain optical coherence tomography (SD-OCT) imaging were completed every 6 months.

The study included patients with POAG and suspected glaucoma. Eyes were classified as POAG if they had reliable ($\geq 33\%$ fixation losses and false negative results and $\leq 15\%$ false positive results) and repeatable abnormal Standard Automated Perimetry tests with the Humphrey 24-2 Swedish Interactive Threshold Algorithm (SITA) (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) with Pattern Standard Deviation (PSD) outside the 95% normal limits and a Glaucoma Hemifield Test (GHT) results outside normal limits. Eyes were classified as glaucoma suspects if they had a history of elevated IOP (>21 mmHg), suspicious or glaucomatous appearance of the optic nerve but normal and reliable VF results at baseline, or both. All included eyes had at least one of the following IOP lowering procedures, argon laser trabeculoplasty (ALT), selective laser trabeculoplasty (SLT), and trabeculectomy. SD-OCT follow-up started within 2 years after the last procedure. The first OCT imaging session after the last procedure was considered as the baseline OCT. All included eyes had at least 3 high-quality OCT examinations. Based on stereoscopic optic disc photographs review, included eyes were divided into 2 groups: those without DH history (non-DH group) and those with DH history before the last procedure (DH group).

Stereoscopic optic disc photography

Patients had stereoscopic optic disc photographs repeated every 12 months during follow-up. The images were reviewed with a stereoscopic viewer (Screen-VU stereoscope; PS Manufacturing, Portland, OR) by 2 or more experienced graders masked to the subjects' identity and to other test results. The methodology used to grade optic disc photographs at the UCSD Optic Disc Reading Center has been provided elsewhere.¹⁷ Only photographs of adequate quality were included. Discrepancies between the 2 graders were resolved by consensus or adjudication by a third experienced grader. For this study, DHs were defined as located within $1/2$ disc diameter from the optic disc border or within the RNFL as a splinter or flame-shaped hemorrhage and not associated with optic disc edema, papillitis, diabetic

retinopathy, central or branch retinal vein occlusion, or any other retinal disease.¹⁸ The location of the DH was classified into 4 90-degree sectors (superior, inferior, temporal, and nasal) using the same criteria as SD-OCT RNFL thickness measurement.¹²

Spectral-Domain Optical Coherence Tomography Measurement

The RNFL thickness was measured with the high resolution Spectralis SD-OCT parapapillary circle scan (software version 5.4.7.0). Details of the procedure have been described previously.¹⁹ Spectralis incorporates a real-time eye tracking system that couples confocal laser scanning ophthalmoscopy and SD-OCT scanners to adjust for eye movements and to ensure that the same location of the retina is scanned over time. A total of 1536 A-scan points were acquired from a 12-degree circle centered on the optic disc. The RNFL thickness measurements were estimated in 4 sectors separated into 90-degree intervals (superior, inferior, temporal, and nasal) using the same sectors as DH on photographs.¹² All images were processed and reviewed by the Imaging Data Evaluation and Analysis (IDEA) Reading Center in the University of California, San Diego. Images with non-centered scans, inaccurate segmentation of the RNFL that could not be manually corrected, or signal strength of 15 dB or less were excluded from the analysis.

Statistical Analysis

Values were presented as mean (95% confidence interval, CI) for continuous variables. Categorical variables were compared using the chi-square test. Linear mixed effects modeling was used to estimate the rates of change of global and local RNFL thickness in each group to account for repeated measurements over time and correlations between the 2 eyes of an individual.¹⁹ In brief, models were fit with RNFL thickness measurements as response variable with time, group and a time group interaction as fixed effects, and random intercept and slope for each eye nested within each patient. Then the models included mean IOP during OCT follow-up as a co-variable to adjust for the effect of IOP on the rate of RNFL thinning. Two-way interactions between time and the various putative variables were used to determine whether these variables were significantly associated with the rate of RNFL thinning over time. The multivariable models were evaluated with other potentially confounding variables that could affect rates of RNFL thinning- race, mean IOP during OCT follow-up, baseline age, baseline VF mean deviation (MD), and central corneal thickness (CCT), to evaluate relationships between RNFL thickness measurements over time after IOP lowering procedures and the presence of DH history. The variable, time, was calculated as time in years from the first OCT examination.

Statistical analyses were performed using statistical software Stata 14.2 (StataCorp LLC, College Station, TX) and R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). *P* values less than 0.05 were considered statistically significant.

Results

Of the 166 included eyes (136 subjects), 37 (22%) eyes (32 subjects) had DH history before the last IOP lowering procedure. Baseline demographics and ophthalmic characteristics of the DH group (n=37 eyes) and the non-DH group (n=129 eyes) are summarized in Table 1.

The mean (95% CI) number of detected DHs in eyes in the DH group was 2.5 (2.0, 3.1). The recurrence rate of DH was 64.9%. Among the eyes with DH recurrence, 2 (8.3%) had DH after the last procedure, and all other DH recurrence happened before the last procedure. The most common location of DH was inferior sector (73.0%), followed by superior (27.0%), temporal (18.9%), and nasal (2.7%). At baseline, there was no significant difference between the non-DH and DH groups in terms of age, gender, diagnosis category (POAG or glaucoma suspect), axial length, CCT, VF MD, VF PSD, global RNFL thickness, interval between last procedure and OCT follow-up, and procedure category (with or without trabeculectomy) (all $P > 0.1$). However, the DH group had a higher proportion of Caucasians, lower baseline IOP and mean IOP during follow-up, more procedures and more glaucoma medications. The mean follow-up duration (4.6 years vs. 4.2 years) and OCT visit number (9.2 vs. 8.3) were similar between the DH group and non-DH group (all $P > 0.1$).

Table 2 summarizes mean rates of global and quadrant RNFL thinning in DH and non-DH eyes after IOP-lowering procedures, and shows the comparison of rates using the univariate mixed effect model and the model adjusted for mean IOP during OCT follow-up. In the DH group, data of DH quadrant derived from the inferior quadrant of 27 eyes that had DH presence in the inferior quadrant; and data of quadrant without DH derived from superior quadrant of 27 eyes that no DH was detected in this quadrant during the whole study. These data were compared with data derived from corresponding quadrants (inferior and superior) of 129 non-DH eyes, respectively. The DH group had approximately 2-fold faster rates of global, DH quadrant, and quadrant without DH RNFL thinning compared to the non-DH group, but the differences were not statistically significant until mean IOP during OCT follow-up was included in the multivariable model ($P < 0.05$). Both DH quadrant and quadrant without DH of DH eyes had significant faster rates of RNFL thinning ($P < 0.05$) compared to that of corresponding quadrants in the non-DH eyes after including mean IOP as a covariate in the model.

Potential factors, which could be associated with the baseline RNFL thickness or the rate of RNFL thinning during follow-up, are summarized in Table 3. Mean IOP during follow-up and baseline MD were significantly associated with RNFL thinning over time ($P < 0.05$). Specifically, each 1 mmHg higher mean IOP during follow-up was associated with a 0.05 $\mu\text{m}/\text{year}$ faster rate of RNFL thinning ($P = 0.007$).

Table 4 presents the fixed effects from the fitted multivariable mixed effects model, showing the effects of DH history and other potentially important factors on post-procedure rate of RNFL thinning (global, DH quadrant, and quadrant without DH) over time. In multivariable analysis, the rates of RNFL loss in global and DH quadrant (inferior quadrant) of the DH group were still significantly faster compared to the non-DH group. Specifically, DH eyes had a 0.36 $\mu\text{m}/\text{year}$ faster rate of global RNFL thinning compared to non-DH eyes ($P = 0.025$); and DH quadrant of DH eyes showed 0.57 $\mu\text{m}/\text{year}$ faster RNFL thinning compared to the corresponding quadrant of non-DH eyes ($P = 0.030$). In addition to DH history, mean IOP during follow-up was also associated with the rate of RNFL loss ($P = 0.015$ for global, and $P = 0.030$ for DH quadrant, respectively). Baseline MD, although associated with baseline RNFL thickness measurements, was not significantly associated with the rates of RNFL loss.

Discussion

The current study investigated the effect of IOP lowering procedures on RNFL thinning in POAG and glaucoma suspect eyes with and without DH history. Eyes with DH history showed faster rates of RNFL thinning compared to non-DH eyes. Lower mean IOP after procedures was significantly associated with slower rates of RNFL thinning. This suggests that eyes with DH history may need additional IOP lowering compared with eyes without DH history to achieve similar structure progression rate.

Current management guidelines from the American Academy of Ophthalmology Preferred Practice Pattern recommend lowering the IOP toward a target level at which the clinician believes that the rate of disease progression will be slowed sufficiently to avoid functional impairment from the disease.²⁰ The occurrence of DH is often interpreted as a marker for insufficient IOP lowering treatment, and more intense treatment is suggested in eyes with hemorrhages to prevent progression.^{2, 10, 11, 13} Therefore, when rates of glaucoma progression between eyes with and without DH are compared, the need of additional treatment of DH eyes should be considered.^{7, 21} It has been reported that, after DH, the mean rate of RNFL thinning was significantly reduced by treatment intensification, but was unchanged if treatment was not intensified.¹² In the current study, the RNFL thinning rate of DH group was faster than non-DH group despite IOP-lowering in both groups, but did not reach statistical significance until mean IOP during follow-up was accounted for in the model. The DH group had a lower mean IOP during follow-up compared to non-DH group and lower mean IOP during follow-up was significantly associated with a slower rate of RNFL thinning.

An earlier study indicated that treatment intensification, which brought the mean IOP from 16.0 mmHg before DH to 14.6 mmHg after DH, could slow the worsening of RNFL thinning.¹² Another study indicated that each 1 mmHg of IOP reduction was associated with a difference of 0.31%/year in the rate of visual field index change pre- and post-hemorrhage, and a 35% reduction in mean IOP would be necessary to bring VF loss slopes close to zero (the mean IOP after DH was 14.1 ± 5.1 mmHg).¹³ In the current study, after IOP lowering procedures, the mean IOP during follow-up in the DH group was 12.7 mmHg which was 12% lower than the non-DH group, and the DH group had a similar RNFL thinning rate ($-0.61 \mu\text{m}/\text{year}$) as the non-DH group. This rate is slower than the reported rate of RNFL thinning ($-0.82 \mu\text{m}/\text{year}$) that has been reported to avoid detectable VF damage in a 2.2-year time frame,¹⁹ and similar with the mean age-related RNFL thinning rate ($-0.52 \mu\text{m}/\text{year}$) of normal eyes,²² although this age-related RNFL thinning was not detectable in most normal eyes (72.7%) in a 3-5 year time frame.²³ It was suggested in the earlier study that additional IOP lowering could protect eyes with DH from acceleration of glaucoma progression,^{12, 13} which is consistent with the current study.

However, it is controversial that whether the efficacy of IOP-lowering treatment on slowing glaucoma progression in eyes with DH and without DH is the same. The Early Manifest Glaucoma Trial⁹ did not demonstrate any interaction between treatment group and DH with regard to time to VF progression, suggesting that the effect of treatment in prolonging time to VF progression was similar in eyes with and without DH, although the mean IOP during

follow-up or the degree of IOP reduction was not reported. However, the secondary analysis¹⁶ of the collaborative Normal-Tension Glaucoma Study, with a relatively small sample size (12 eyes untreated and 11 eyes treated), reported that a 30% lowering of IOP did not slow VF progression in normal-tension glaucoma eyes with DH but readily slowed down progression of eyes without DH. It was not investigated whether further intensification of treatment affected subsequent glaucoma progression. In the current study, although eyes in the DH group obtained similar rates of RNFL thinning compared with the non-DH group in the univariate analysis, the mean IOP through follow-up of the DH group (12.69 mmHg) was significantly lower than the non-DH group (14.41 mmHg), likely because of having had more procedures prior to the OCT follow-up and more medications during follow-up. These intensified treatment is believed based on careful follow-up after each intervention. After the mean IOP was included in the model, alone or with other confounding factors, the DH group showed significantly a faster rate of RNFL thinning compared with non-DH eyes. This suggested that lower target IOP is needed to protect glaucoma eyes with DH history against progression compared to non-DH eyes. However, given each 1 mmHg higher mean IOP during follow-up was found only associated with a 0.05 $\mu\text{m}/\text{year}$ faster rate of RNFL thinning which is similar with previous report,¹⁰ a large reduction of IOP that could be clinically beneficial may not be achievable for all patients who has DH history. It is important to consider the benefit/risk ratio of further interventions in the long run. Many more factors like disease stage, patient's life expectance, potential side effects or complications, and economic burdens should be taken into account.¹³ Another possible reason for the small rate difference corresponding to each 1 mmHg IOP change is that, the IOP during follow-up (mean (95% CI), DH eyes 12.7 (11.5, 13.8); non-DH eyes 14.4 (13.7, 15.1)) was low enough that IOP related variation of RNFL thinning rate is limited. Moreover, it has been reported that the additional loss of RNFL caused by higher IOP could be different in progressing eyes and nonprogressing eyes. In nonprogressing eyes, each 1 mmHg higher IOP was associated with only 0.04 $\mu\text{m}/\text{year}$ additional RNFL loss, while in progressing eyes, the association could be 0.20 $\mu\text{m}/\text{year}$.²⁴ Therefore, further study is needed to investigate the association of IOP with RNFL thinning in DH eyes with different progression status.

To support our finding, Medeiros et al¹³ found that, although substantial IOP reduction was significantly associated with differences in rates of progressive VF loss, more than 60% of the variability in rates of VF progression change could not be explained by reduction in IOP. The fact that DHs are frequently observed at relatively lower IOPs suggests the contribution of IOP-independent mechanisms.^{25, 26} IOP-independent factors may contribute to the likelihood of glaucoma progression. Further studies are needed to identify the appropriate target IOP for treatment of eyes with DH to obtain the maximum benefit /risk ratio, and to understand the non-IOP factors in disease mechanisms, for guiding glaucoma management of individual patients.

There are several limitations to our study. DH was detected solely by stereoscopic optic disc photography reviewing in this study. Some DHs might have been missed during follow-up as photographs were recorded annually, while DH has been reported to be observable for only 2 to 6 months.²⁷ However, it has been found that the total number of DH was not significantly associated with the rate of RNFL thinning in DH eyes ($P= 0.768$) (data not

shown), which is consistent with previous reports.^{10, 28} Moreover, if there was misclassification bias and eyes with DHs were included in the non-DH group, the difference in rates between the DH and non-DH eyes would likely be underestimated. Second, the sample sizes for evaluation of DH quadrant (27 eyes) and quadrant without DH (27 eyes) were relatively small. There is evidence that the rates of RNFL thinning of the four quadrants in glaucoma eyes could be quite different, and inferior and superior quadrant are susceptible to glaucomatous damage.¹⁹ The inferior quadrant in the current study had the highest incidence of DH (72.97%). Conversely, in the DH group, there were 27 eyes that had no DH detected in the superior quadrant which was defined as the quadrant without DH to compare with the corresponding superior quadrant of non-DH eyes. Several potential confounding factors that could affect rates of RNFL thinning had been included in the multivariable models to evaluate their effects. However, there might be unidentified factors like social status, educational level, et al, that we cannot exclude their potential contribution to the differences in glaucoma progression between the two groups. Although as a multicenter study, most of the participants (74.3%) of the current study were enrolled at one site. Because of the limited sample size of the other two sites, we cannot comment on any potential geographical effect. However, the demographics and baseline confounders were included in the models to take this into account. Last, most of the participants of the study had multiple glaucoma procedures before OCT follow-up. About 20% of them were enrolled in DIGS/ADAGES after their first procedure, and had no pre-procedure IOP documented. Therefore, the total IOP lowering of procedures was unavailable.

In summary, the RNFL thinned faster in POAG and glaucoma suspect eyes with DH than in non-DH eyes at the same mean IOP after IOP lowering procedures. A history of DH in such eyes should prompt vigilant follow-up as a lower IOP may be needed to reduce the rate of RNFL thinning to the same as observed in non-DH eyes.

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Abbreviations and Acronyms:

DIGS	Diagnostic Innovations in Glaucoma Study
ADAGES	African Descent and Glaucoma Evaluation Study
UCSD	University of California, San Diego
CCT	central corneal thickness
SD	spectral-domain
OCT	optical coherence tomography
D	diopter

DH	disc hemorrhage
IOP	intraocular pressure
MD	mean deviation
RNFL	retinal nerve fiber layer
SITA	Swedish interactive thresholding algorithm

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Table 1.

Demographics and Baseline Ophthalmic Characteristics of DH and Non-DH Group

	DH group	Non-DH group	P value
By Subject (No.)	32	104	
Gender (M/F, No.)	12/20	50/54	0.291
Race, No. (%)			0.038
Caucasian	28 (87.5%)	71 (68.3%)	
African American	2 (6.2%)	26 (25.0%)	
Asian	2 (6.2%)	7 (6.7%)	
By Eye (No.)	37	129	
Follow-up (years)	4.6 (3.9, 5.2)	4.2 (3.9, 4.5)	0.339
Visits of OCT	9.2 (7.5, 10.9)	8.3 (7.6, 9.1)	0.390
Diagnosis (POAG/glaucoma suspect), No.	31/6	103/26	0.587
Age (years)	69.5 (66.6, 72.4)	69.5 (67.7, 71.4)	0.999
Axial length (mm)	24.2 (23.7, 24.6)	24.3 (24.0, 24.5)	0.741
CCT (μm)	549.7 (536.9, 562.5)	544.4 (537.6, 551.2)	0.487
Baseline IOP (mmHg)	13.3 (12.1, 14.5)	14.8 (13.9, 15.6)	0.089
Mean IOP during follow-up (mmHg)	12.7 (11.5, 13.8)	14.4 (13.7, 15.1)	0.012
Glaucoma medication during OCT follow-up, No.	1.8 (1.5, 2.1)	1.4 (1.2, 1.6)	0.052
Total DH No.	2.5 (2.0, 3.1)	N/A	
Multiple DH, Eye No. (%)	24 (64.9%)	N/A	
DH Location		N/A	
Inferior, Eye No. (%)	27 (73.0%)		
Superior, Eye No. (%)	10 (27.0%)		
Nasal, Eye No. (%)	1 (2.7%)		
Temporal, Eye No. (%)	7 (18.9%)		
Number of procedures	2.4 (1.9, 2.8)	1.9 (1.7, 2.1)	0.080
Procedure category (Eyes with/without trabeculectomy)	15/22	50/79	0.845
Interval between last procedure and first OCT follow-up (months)	8.7 (6.2, 11.2)	9.0 (7.6, 10.3)	0.846
Baseline MD (dB)	-4.5 (-6.3, -2.7)	-4.8 (-5.7, -3.9)	0.726
Baseline PSD (dB)	6.3 (4.9, 7.6)	5.3 (4.6, 5.9)	0.156
Baseline global RNFLT (μm)	73.8 (69.3, 78.2)	71.0 (68.4, 73.7)	0.343

DH = eyes with disc hemorrhage history; Non-DH = eyes without disc hemorrhage history; M=male; F=female; OCT = optical coherence tomography; POAG = primary open angle glaucoma; CCT=central corneal thickness; IOP=intraocular pressure; MD=mean deviation; PSD=pattern standard deviation; BP=blood pressure; RNFLT= retinal nerve fiber layer thickness.

Values are shown in mean (95% confident interval), unless otherwise indicated. Statistically significant P value is shown in bold. The first OCT exam after the last IOP lowering procedure was considered as the baseline.

Table 2.

Rates of Retinal Nerve Fiber Layer Thinning in the DH and Non-DH Eyes

	DH group	Non-DH group	<i>P Value</i>	
	Mean (95% CI)	Mean (95% CI)	Univariate	IOP Adjusted*
Retinal Nerve Fiber Layer Thickness Change Rate (µm/year)				
No. of Eye	37	129		
Global	-0.61 (-0.90, -0.32)	-0.33 (-0.50, -0.16)	0.111	0.025
DH Quadrant Retinal Nerve Fiber Layer Thickness Change Rate (µm/year)				
No. of Eye	27	129		
Inferior	-1.11 (-1.60, -0.62)	-0.66 (-0.89, -0.43)	0.103	0.040
Quadrant without DH Retinal Nerve Fiber Layer Thickness Change Rate (µm/year)				
No. of Eye	27	129		
Superior	-0.71 (-1.12, -0.30)	-0.28 (-0.50, -0.05)	0.067	0.029

DH group= eyes with disc hemorrhage history; Non-DH group= eyes without disc hemorrhage history; CI= confidence interval; IOP=intraocular pressure.

Statistically significant P value is shown in bold.

* Mean IOP during OCT follow-up was included in the mixed effects models. Data of DH quadrant derived from the inferior quadrant of 27 eyes of DH group that had DH presence in the inferior quadrant; and data of quadrant without DH derived from superior quadrant of 27 eyes of DH group that no DH was detected in this quadrant during the whole study.

Table 3.

Results of Univariable Models Assessing the Effect of Each Putative Predictive Factor on Baseline Retinal Nerve Fiber Layer Thickness and the Rate of RNFL Thinning Over Time

Variables	Effect on Baseline RNFL thickness		Effect on Rate of RNFL Thinning Over Time	
	Coefficients	P Value	Coefficients	P Value
Age at baseline, per year older	−0.18 (−0.46, 0.10)	0.204	0.002 (−0.01, 0.02)	0.773
Race, AA	−4.15 (−10.09, 1.79)	0.171	−0.08 (−0.41, 0.24)	0.616
Gender, male	2.38 (−2.93, 7.70)	0.380	0.01 (−0.29, 0.31)	0.954
Mean IOP, per 1mmHg higher	0.87 (0.29, 1.45)	0.003	−0.05 (−0.09, −0.01)	0.007
Baseline MD, per 1 dB better	1.60 (1.22, 1.99)	<.0001	−0.04 (−0.07, −0.01)	0.020
CCT, per 100 µm thicker	2.40 (−3.30, 8.11)	0.409	0.19 (−0.19, 0.56)	0.334
AL, per 1 mm longer	0.37 (−1.98, 2.73)	0.755	−0.04 (−0.15, 0.06)	0.417
DH history, yes	2.63 (−3.06, 8.31)	0.366	−0.28 (−0.62, 0.06)	0.106

AA= African American; IOP=intraocular pressure; MD= mean deviation; CCT= central corneal thickness; AL= axial length.

Values are shown in mean (95% confident interval). Statistically significant P value is shown in bold.

Table 4.

Results of the Multivariable Mixed Effects Model Investigating Longitudinal Change in Retinal Nerve Fiber Layer Thickness

Variables	Global		Inferior (DH Quadrant of DH group)		Superior (Quadrant without DH of DH group)	
	Coefficients	P Value	Coefficients	P Value	Coefficients	P Value
Intercept	74.60 (36.67, 112.53)	<.0001	91.09 (18.86, 163.31)	0.013	93.44 (38.82, 148.06)	0.001
Time, year	−0.52 (−3.05, 2.02)	0.690	−2.36 (−6.31, 1.58)	0.241	−0.56 (−4.19, 3.06)	0.761
DH history, yes	3.20 (−1.30, 7.70)	0.164	−7.19 (−14.75, 0.37)	0.062	10.96 (2.72, 19.20)	0.009
DH history, × time	−0.36 (−0.67, −0.04)	0.025	−0.57 (−1.09, −0.06)	0.030	−0.48 (−0.96, 0.01)	0.055
Race, AA	−4.81 (−10.01, 0.39)	0.070	−8.05 (−18.01, 1.91)	0.113	−5.42 (−12.35, 1.50)	0.125
Race × time	0.04 (−0.27, 0.35)	0.800	0.09 (−0.35, 0.52)	0.698	−0.11 (−0.54, 0.32)	0.622
Mean IOP, per 1mmHg higher	0.11 (−0.47, 0.70)	0.703	0.67 (−0.36, 1.70)	0.204	−0.12 (−1.15, 0.92)	0.826
Mean IOP × time	−0.06 (−0.10, −0.01)	0.015	−0.07 (−0.14, −0.01)	0.030	−0.07 (−0.15, 0.002)	0.057
Age at baseline, per 1 year older	−0.02 (−0.27, 0.22)	0.839	0.03 (−0.42, 0.48)	0.899	0.03 (−0.29, 0.35)	0.863
Age at baseline × time	−0.001 (−0.02, 0.01)	0.845	−0.005 (−0.03, 0.02)	0.710	0.01 (−0.02, 0.03)	0.605
Baseline MD, per 1 dB better	1.53 (1.09, 1.97)	<.0001	2.85 (1.98, 3.73)	<.0001	1.78 (1.04, 2.51)	<.0001
Baseline MD × time	−0.01 (−0.04, 0.02)	0.406	−0.03 (−0.07, 0.02)	0.252	−0.007 (−0.05, 0.04)	0.771
CCT, per 100 µm thicker	1.35 (−3.01, 5.71)	0.544	0.41 (−7.42, 8.24)	0.918	0.67 (−6.51, 7.86)	0.855
CCT × time	0.19 (−0.16, 0.54)	0.289	0.53 (−0.04, 1.10)	0.067	−0.19 (−0.32, 0.70)	0.463

DH group= eyes with disc hemorrhage history; Non-DM group= eyes without disc hemorrhage history; AA= African American; IOP=intraocular pressure; MD= mean deviation; CCT= central corneal thickness.

Values are shown in mean (95% confident interval). Statistically significant P value is shown in bold.