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Rates of Circumpapillary Retinal Nerve Fiber Layer Thinning and Capillary Density Loss in Glaucomatous Eyes with Disc Hemorrhage

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Abstract

Purpose: To investigate longitudinal changes in rates of optic nerve head circumpapillary retinal nerve fiber layer (cpRNFL) thinning and vessel density loss in primary open angle glaucoma (POAG) with or without history of disc hemorrhage (DH).

Design: Observational cohort

Methods: In this longitudinal study, 34 eyes with DH and 134 eyes without DH that had at least 1.5 years of follow-up and three OCT and OCTA follow-up scans were enrolled. A linear mixed-effect model was used to compare the rates of cpRNFL thinning and vessel density loss between DH and non-DH eyes.

Results: Rates of whole image capillary density (wiCD) loss were faster in the DH group compared to non-DH group (mean difference (95% CI): -0.32 ($-0.59, -0.04$) %/year, $P=0.027$). Faster mean rates of vessel density loss were found in the inferotemporal, inferonasal, and nasal sectors in eyes with DH than without DH ($P<0.05$). There was no statistically significant difference in the global rate of cpRNFL thinning between the two groups ($P=0.679$). The mean rate of cpRNFL thinning was faster in the DH group compared to the non-DH group only in the inferotemporal sector (mean difference (95% CI): -1.01 ($-1.62, -0.40$) $\mu\text{m}/\text{year}$; $P=0.001$).

Conclusions: Mean rates of vessel density loss between DH and non-DH eyes were different not only in the affected area but also in the other regions. In contrast, a significant difference in

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Author contribution:

Concept and design: TN, SM, RCCD, RNW; Acquisition and reviewing of data: TN, SM, RCCD, WJH, NE, AK; Analysis or interpretation of data: TN, SM, RCCD, JAP, LMZ, RNW; Drafting of the manuscript: TN, SM, RCCD, ACC, RNW; Critical revision of the manuscript: All authors; Obtained funding: SM, LMZ, RNW; Supervision: SM, RNW

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cpRNFL thinning between the two groups was detected only in the inferotemporal sector. Disc hemorrhage is an independent predictor of faster vessel density loss in glaucoma suspects and POAG patients.

Keywords

optic disc hemorrhage; retinal nerve fiber layer; vessel density; glaucoma; progression

Introduction

Glaucoma is a progressive optic neuropathy characterized by loss of retinal ganglion cells and their axons, leading to distinctive patterns of visual field (VF) defects.^{1, 2} Disc hemorrhage (DH) is reported to be associated with the development³⁻⁵ and rapid progression of glaucoma in many previous studies.⁶⁻¹¹ Several hypotheses have been proposed to explain the pathophysiology of glaucomatous DHs, including vascular and mechanical theories.^{12, 13}

Optical coherence tomography angiography (OCTA) is a non-invasive technique of imaging optic nerve head (ONH) and retinal microvasculature that provides assessment of retinal microvascular changes in ocular diseases. Compared to retinal nerve fiber layer (RNFL) thickness, OCTA-derived ONH vessel density has been found to provide similar diagnostic accuracy for differentiating glaucomatous and healthy eyes.¹⁴ In addition, decreased circumpapillary (cp) vessel density has been found to be strongly associated with increasing severity of VF defects in the disease.^{15, 16}

Glaucomatous damage to the optic disc often may manifest earlier than a detectable VF defect.¹ Thus, monitoring structural changes such as vessel density loss may be a more sensitive method to detect early progression in glaucoma. This study evaluated longitudinal changes in rates of ONH RNFL thinning and vessel density loss in primary open angle glaucoma (POAG) patients with or without history of DH.

Methods

In this observational cohort study, subjects were enrolled from the Diagnostic Innovations Glaucoma Study (DIGS), a prospective longitudinal study designed to evaluate structural and functional changes in glaucoma. Participants were assessed longitudinally according to a pre-established protocol consisting of regular follow-up visits with clinical examination, imaging, and functional tests. All participants from the DIGS study who met the inclusion criteria described below were included in the present study. Informed consent was obtained from all study participants. The University of California, San Diego Human Subject Committee approved all protocols, and the methods described adhered to tenets of the Declaration of Helsinki.

Participants

All subjects underwent annual comprehensive ophthalmologic evaluation, including best-corrected visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic optic disc photography, ultrasound

pachymetry, and standard automated perimetry (SAP) in both eyes. Semi-annual evaluations included intraocular pressure (IOP) measurement, *OCTA imaging, and SAP testing*.

This study included eyes diagnosed as glaucoma or glaucoma suspect with or without history of DH with a minimum follow-up time of 1.5 years and a minimum of three follow-up OCTA scans. Glaucoma suspects included eyes with elevated IOP (≥ 22 mmHg) or glaucomatous-appearing optic discs without the presence of repeatable glaucomatous VF damage. Eyes were classified as glaucomatous if they had repeatable (at least 2 consecutive) abnormal VF test results with evidence of glaucomatous optic neuropathy – defined as excavation, the presence of focal thinning, notching of neuroretinal rim, or localized or diffuse atrophy of the RNFL on the basis of masked grading of optic disc photographs by 2 graders or clinical examination by a glaucoma specialist. An abnormal VF test was defined as a pattern standard deviation outside of the 95% normal confidence limits or a Glaucoma Hemifield Test result outside normal limits. Glaucoma disease severity was classified as early ($24-2$ VF MD > -6 dB), moderate (-6 dB $\leq 24-2$ VF MD > -12 dB), and advanced ($24-2$ VF MD ≤ -12 dB).

Inclusion criteria included (1) older than 18 years of age, (2) open angles on gonioscopy, (3) best-corrected visual acuity of 20/40 or better, and (4) at least 1.5 years of follow-up with a minimum of three follow-up OCT and OCTA scanning sessions.

Exclusion criteria included (1) history of trauma or intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), (2) coexisting retinal disease, (3) uveitis, or (4) non-glaucomatous optic neuropathy. Participants with the diagnosis of systemic diseases such as Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke were also excluded. Those with unreliable VFs or poor-quality OCTA and spectral domain optical coherence tomography (SDOCT) scans were also excluded from this report. Eyes with an axial length of 27 mm or more were also excluded from this study.

Stereophotography

All color stereophotographs were taken using a Nidek Stereo Camera Model 3-DX (Nidek Inc, Palo Alto, CA) after maximal pupil dilation. Evaluations of all photographs were performed using a simultaneous stereoscopic viewer (Asahi Pentax Stereo Viewer II; Pentax, Tokyo, Japan) with a standard fluorescent light bulb. Each grader (T.N. and R.D.) was masked to the subject's identity and other test results. Included photographs were judged to be of adequate quality or better. Discrepancies between the two graders were resolved by consensus or adjudication by a third experienced grader (S.M.). DHs were required to be located within one-half disc diameter from the optic disc border and not associated with optic disc edema, papillitis, diabetic retinopathy, central or branch retinal vein occlusion, or any other retinal disease.¹⁷ The location of DHs was categorized as hemispheric (superior, inferior, or both) and sectoral (nasal, temporal, inferior nasal, inferior temporal, superior nasal and superior temporal) corresponding to those on OCTA and OCT sectoral parameters.

OCT Angiography

Optic nerve head microvasculature was evaluated using the AngioVue OCT system (software version 5.6.3.0). This system has been described previously.¹⁸ Vessel density

was automatically calculated as the proportion of measured area occupied by flowing blood defined as pixels having decorrelation values acquired by the split-spectrum amplitude-decorrelation angiography algorithm above the threshold level. Vessel density in the cpRNFL was assessed within a 4.5×4.5 -mm field centered on the ONH. Vessel density within the cpRNFL was measured from the internal limiting membrane (ILM) to the cpRNFL posterior boundary using standard AngioVue software. Image quality review was done on all scans according to the University of California, San Diego, Imaging Data Evaluation and Analysis (IDEA) Reading Center standard protocol. Trained graders reviewed scans and excluded poor-quality images, defined as images with (1) a signal strength index (SSI) of less than 48, (2) poor clarity, (3) residual motion artifacts visible as irregular vessel pattern or disc boundary on the en face angiogram, (4) local weak signal, or (5) segmentation errors. The location of the disc margin in the ONH scans was reviewed for accuracy and was adjusted manually if required. ONH whole en face image capillary density (wiCD) and circumpapillary capillary density (cpCD) were obtained over the entire 4.5×4.5 mm scan. Regional measurements were also analyzed as described by Garway-Heath et al.¹⁹

OCT Measurements

The Spectralis SDOCT (Spectralis HRA+OCT, software version 5.4.7.0; Heidelberg Engineering, Inc.) was used for cpRNFL thickness measurements. Details of its operation have been discussed previously.²⁰ Spectralis uses a dual-beam SDOCT, a confocal laser-scanning ophthalmoscope with a wavelength of 870 nm, and an infrared reference image to obtain images of ocular microstructures. Spectralis incorporates a real-time eye-tracking system that couples a confocal laser-scanning ophthalmoscope and SDOCT scanners to adjust for eye movements and to ensure that the same location of the retina is scanned over time. The cpRNFL thickness was measured using a high-resolution RNFL circle scan, which consists of 1536 A-scan points from a 3.45mm circle centered on the optic disc. All images were processed and reviewed by the IDEA Reading Center. Images with non-centered scans, inaccurate segmentation of the RNFL, or quality scores of 15 dB or less were excluded from the analysis. The cpRNFL measurements evaluated in this study included the mean global index, temporal quadrant (316 – 45 degrees), superotemporal sector (46 – 90 degrees), superonasal sector (91 – 135 degrees), nasal quadrant (136 – 225 degrees), inferonasal sector (226 – 270 degrees) and inferotemporal sector (271 – 315 degrees).

Statistical analysis

All statistical analyses were performed with commercially available software (Stata version 15; StataCorp, College Station, Texas, USA). Statistical significance for tests was set at $P < 0.05$. Descriptive statistics were calculated as the mean and 95% confidence interval (CI). Categorical variables were compared using the chi-square test. Mixed-effects modeling was used to compare ocular parameters among groups. Models were fitted with ocular measurements as response variable and classification groups (DH history) as fixed effects. Measurements of bilateral eyes were nested within subjects to account for the fact that eyes from the same individual were more likely to have similar measurements.

Evaluation of the effect of DH on mean rates of change in cpRNFL and vessel density was performed using a linear mixed model with random intercepts and random slopes.^{21–23}

In this model, the average values of the outcome variables (vessel density and cpRNFL measurements) were explored using a linear function of time, and random intercepts and random slopes were introduced with patient- and eye-specific deviations from this average value. This model can account for the fact that different eyes may have different rates of vessel density loss and cpRNFL thinning over time, while allowing for correlation between two eyes of the same individual and between visits over time.^{21, 22} As structural decline may depend on disease severity, an unstructured covariance between random effects was assumed, allowing for correlation between intercepts and slopes of change.²⁴ Multivariable models were constructed including the following potential confounding factors: age, gender, mean IOP during follow-up, and baseline 24–2 mean deviation (MD). Factors contributing to the rate of vessel density loss were also explored using a linear mixed model. The effect of potential predictors – age, mean IOP during follow-up, and baseline 24–2 mean deviation (MD) or baseline global cpRNFL thickness as factors affecting glaucoma severity, and any other variable in which the P value was <0.1 in univariable analysis – on the rates of vessel density loss was examined.

Results

In this study, 34 eyes with DH and 134 eyes without DH that had at least 1.5 years of follow-up and three OCTA follow-up scans were enrolled. Initial DH occurrence was recorded with an average of 3.9 years prior to OCTA evaluation, and the most recent DH occurrence was an average of 1.9 years before the OCTA evaluation. Eyes with recent DH occurrence earlier than average (1.9 years) had mean (95% CI) wiCD loss of -0.77 ($-1.14, -0.39$) %/year, while those later than average had -1.14 ($-1.47, -0.80$) %/year, with mean difference of -0.37 ($-0.85, 0.10$) %/year, $P=0.119$. Eyes with recent DH occurrence earlier than the average had cpRNFL thinning of -0.52 ($-0.86, -0.19$) $\mu\text{m}/\text{year}$, and those later than average had -0.57 ($-1.03, -0.11$) $\mu\text{m}/\text{year}$, with mean difference of -0.04 ($-0.59, 0.50$) $\mu\text{m}/\text{year}$ ($P=0.868$). Demographics and baseline clinical characteristics between the DH and non-DH groups are presented in Table 1. Statistically significant differences were seen between two groups with respect to gender ($P=0.028$) and mean IOP during follow-up ($P=0.040$). There were no significant differences in age, race, hypertension, diabetes mellitus, mean ocular perfusion pressure (MOPP), axial length, central corneal thickness (CCT), baseline IOP, distribution of disease severity based on baseline 24–2 VF MD, number of follow-up years, and number of OCTA follow-up scans ($P>0.05$). Difference in diagnosis of glaucoma and glaucoma suspects ($P=0.304$), baseline 24–2 VF MD ($P=0.519$), baseline cpRNFL thickness ($P=0.874$), baseline wiCD ($P=0.657$), and baseline cpCD ($P=0.925$) also did not reach statistical difference between groups at baseline. Multiple DHs were seen in 41.2 % of DH patients. DHs were more common in the inferior hemiretina (73.5 %). The number of glaucoma medications before and after DH was also examined. Glaucoma medications (mean (95% CI)) remained unchanged in 23 eyes (2.0 (1.6, 2.4) to 1.8 (1.4, 2.2), $P=0.534$), and medications were escalated in 11 eyes after DH (1.6 (1.3, 2.0) to 3.0 (2.6, 3.4), $P<0.001$).

Table 2 summarizes the mean rates of CD loss in the DH and non-DH groups. Rates of wiCD were faster in the DH group compared to the non-DH group (mean difference (95% CI): -0.32 ($-0.59, -0.04$) %/year, $P=0.027$). Statistically significantly higher mean rates of

vessel density loss were found in the inferotemporal, (mean difference (95% CI): -0.86 ($-1.39, -0.33$) %/year, $P=0.002$), inferonasal (mean difference (95% CI): -0.70 ($-1.24, -0.15$) %/year, $P=0.012$), and nasal sectors (mean difference (95% CI): -0.46 ($-0.85, -0.06$) %/year, $P=0.023$). Similar results were found after adjusting for confounding factors. Differences in the rates of cpRNFL thickness change and CD change are represented in Figure 1.

Table 3 summarizes the mean rates of cpRNFL thinning in DH and non-DH group. No difference in the global rate of cpRNFL thinning between the DH and non-DH groups was found ($P=0.679$). A significantly higher mean rate of cpRNFL thinning in DH eyes compared to non-DH eyes was found only in inferotemporal sector (mean difference (95% CI): -1.01 ($-1.62, -0.40$) $\mu\text{m}/\text{year}$; $P=0.001$). Similar results were found after adjusting for confounding factors. In eyes with DH in inferior hemisphere ($n=20$), a faster capillary density loss was found in the superior hemisphere than in the inferior hemisphere (-1.08 ($-1.48, -0.67$) vs -0.54 ($-0.97, -0.12$) %/year, respectively, $P=0.077$). More prominent differences were found with cpRNFL between the inferior and superior hemispheres (-0.90 ($-1.29, -0.52$) $\mu\text{m}/\text{year}$ vs -0.29 ($-0.54, -0.42$) $\mu\text{m}/\text{year}$, respectively, $P=0.014$) in eyes with DH in the inferior hemisphere.

Table 4 summarizes the possible predictors of vessel density loss in follow-up evaluations. In model 1, baseline 24–2 VF MD was selected in addition to age, mean IOP, and history of DH, while baseline cpRNFL was replaced by 24–2 VF MD in model 2. In both multivariable models, factors including age and history of DH were found to be significantly associated with wiCD loss over time ($P<0.05$ for all).

Possible predictors of cpRNFL thinning in follow-up evaluations are summarized in Supplemental Table 3. Since no significant differences were seen in mean global cpRNFL change between DH eyes and non-DH eyes (Table 3), the factors contributing to inferotemporal cpRNFL thinning over time were examined. In model 1, baseline 24–2 VF MD was selected in addition to age, gender, axial length, mean IOP, and history of DH. In model 2, baseline wiCD was replaced by 24–2 VF MD. In both multivariable models, history of DH was found to be significantly associated with inferotemporal cpRNFL thinning over time ($P<0.05$ for both).

Discussion

DHs have been identified as a risk factor for the development and progression of glaucoma in prior studies.^{3–11} In this study, OCTA-derived measures of the rates of vessel density loss are significantly faster in DH eyes compared to non-DH eyes. Differences between the DH and non-DH groups were detected in the global rates of vessel density loss as well as in several sectoral rates of vessel density loss. While these findings support changes in optic disc microvasculature as being especially important in DH eyes, they also suggest that clinicians consider OCTA in addition to OCT imaging for monitoring glaucoma progression in patients with DH.

Several studies have explored the application of OCTA in DH eyes. Nitta et al. found a significant association between cpCD loss and DH occurrence in glaucoma patients.²⁵ Okamoto et al. reported a significant correlation between widening of the retinal nerve fiber layer defect and widening of the decreased superficial retinal microvasculature angle, as well as an association between DH and a subsequent decrease in the superficial retinal microvasculature in retinal nerve fiber layer defects.²⁶ In this study, we find DH to be an independent predictor of faster vessel density loss in glaucoma suspects and POAG patients. Our findings may help clinicians to better understand the role of OCTA in DH eyes as a tool in monitoring glaucoma progression in these high-risk patients.

While wiCD change rates are found in this study to be significantly different between DH and non-DH eyes, cpCD change rates are not. A possible explanation for these results is that wiCD evaluates a larger area, which may be advantageous in detecting vessel density change. The limited measurement area of cpCD may exclude areas of sparse vasculature that hold diagnostic value, as vascular dropout may also be seen in the areas beyond the limits of cpCD.²⁷ Another possible explanation for our finding is that in DH eyes the vessel density change happens diffusely which make these eyes susceptible to DH and subsequent localized cpRNFL loss. Prior studies also have shown that a history of migraine, low or high systolic blood pressure, and use of systemic β -blockers are IOP-independent parameters associated with DH.²⁸ The contribution of vascular mechanisms other than or in addition to IOP in the pathogenesis of DH may lead to failure of autoregulation and varying degrees of optic nerve ischemia, resulting in microinfarction of the optic nerve head and the occurrence of DH in glaucoma patients.²⁹

Liu et al. reported that when comparing DH and non-DH eyes, the rate of cpRNFL thinning was significantly higher in the quadrant of the DH, while the rate of global cpRNFL thinning was not statistically significant between the two groups.³⁰ This is consistent with our results, in which the inferotemporal sector of the cpRNFL shows a significantly faster rate of thinning in DH eyes compared to non-DH eyes, while the mean global cpRNFL thinning rate is not significantly different. One possible explanation for these findings is that cpRNFL thinning is topographically related to the DH location.³¹ In contrast, our analysis of OCTA measures suggests that vessel density may decrease not only in the affected sector but also in the other regions of the optic disc in DH eyes.

Akagi et al. explored how RNFL thinning rates changed after DH, and they found that RNFL thinning rates were significantly higher in quadrants with DH compared to quadrants without DH. Intensifying glaucoma treatment was found to slow progression of RNFL thinning globally as well as in both the DH and non-DH quadrants.³² We find significant cpCD loss in DH eyes. Therefore, it may be useful for clinicians to monitor for diffuse microvascular loss and sectoral RNFL thinning over time in these eyes, and to intensify treatment to prevent progression if detected.

This study has several limitations. First, the study duration is relatively short. Longer studies are needed to validate these results across the glaucoma continuum. Second, the frequency of optic disc photos may have been inadequate as they were obtained annually, while most DHs typically resolve within 6 months.³³ As such, it is possible that some DHs may have

been missed. Third, this is not a prospective observational study, and we did not collect data on baseline glaucoma treatment and changes in glaucoma treatment. Most of the patients were on glaucoma medication therapy and thus we could not evaluate the effect of the IOP intensive therapy on rate of CD change in DH eyes. Last, there is some evidence that topical glaucoma medications may affect ocular blood flow.^{34, 35} Therefore, we cannot exclude the possibility that the use of topical eye drops may have contributed to the observed vascular differences between the study groups.³⁴

In conclusion, this study demonstrates that differences in cpRNFL thinning rates between DH and non-DH eyes are detectable only in the inferotemporal sector (corresponding to the DH location), while differences in vessel density loss rates between DH and non-DH eyes are detected both globally and in several sectors. This study also finds DHs to be an independent predictor of faster vessel density loss in glaucoma suspects and POAG patients, supporting the use of OCTA in patients with a history of DH in order to better detect glaucomatous progression in this high-risk group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Weinreb RN, Leung CK, Crowston JG, et al. Primary open-angle glaucoma. *Nat Rev Dis Primers* 2016;2:16067. [PubMed: 27654570]
2. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA* 2014;311:1901–11. [PubMed: 24825645]
3. Budenz DL, Anderson DR, Feuer WJ, et al. Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. *Ophthalmology* 2006;113:2137–43. [PubMed: 16996592]
4. Kim HJ, Song YJ, Kim YK, Jeoung JW, Park KH. Development of visual field defect after first-detected optic disc hemorrhage in preperimetric open-angle glaucoma. *Jpn J Ophthalmol* 2017;61:307–313. [PubMed: 28357611]
5. Sawada A, Manabe Y, Yamamoto T, Nagata C. Long-term clinical course of normotensive preperimetric glaucoma. *Br J Ophthalmol* 2017;101:1649–1653. [PubMed: 28416494]
6. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48–56. [PubMed: 12523884]
7. Keltner JL, Johnson CA, Anderson DR, et al. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology* 2006;113:1603–12. [PubMed: 16949445]
8. De Moraes CG, Prata TS, Liebmann CA, Tello C, Ritch R, Liebmann JM. Spatially consistent, localized visual field loss before and after disc hemorrhage. *Invest Ophthalmol Vis Sci* 2009;50:4727–33. [PubMed: 19458330]

9. Medeiros FA, Alencar LM, Sample PA, Zangwill LM, Susanna R Jr., Weinreb RN. The relationship between intraocular pressure reduction and rates of progressive visual field loss in eyes with optic disc hemorrhage. *Ophthalmology* 2010;117:2061–6. [PubMed: 20541265]
10. Kim JM, Kyung H, Azarbod P, Lee JM, Caprioli J. Disc haemorrhage is associated with the fast component, but not the slow component, of visual field decay rate in glaucoma. *Br J Ophthalmol* 2014;98:1555–9. [PubMed: 24990873]
11. Chan TCW, Bala C, Siu A, Wan F, White A. Risk Factors for Rapid Glaucoma Disease Progression. *Am J Ophthalmol* 2017;180:151–157. [PubMed: 28624324]
12. Lee EJ, Han JC, Kee C. A novel hypothesis for the pathogenesis of glaucomatous disc hemorrhage. *Prog Retin Eye Res* 2017;60:20–43. [PubMed: 28864288]
13. Kim KE, Park KH. Optic disc hemorrhage in glaucoma: pathophysiology and prognostic significance. *Curr Opin Ophthalmol* 2017;28:105–112. [PubMed: 27820751]
14. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Optical coherence tomography angiography vessel density in healthy, glaucoma suspect, and glaucoma eyes. *Investigative ophthalmology & visual science* 2016;57:OCT451–OCT459. [PubMed: 27409505]
15. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Relationship between Optical Coherence Tomography Angiography Vessel Density and Severity of Visual Field Loss in Glaucoma. *Ophthalmology* 2016;123:2498–2508. [PubMed: 27726964]
16. Rao HL, Pradhan ZS, Weinreb RN, et al. Regional Comparisons of Optical Coherence Tomography Angiography Vessel Density in Primary Open-Angle Glaucoma. *Am J Ophthalmol* 2016;171:75–83. [PubMed: 27590118]
17. Jonas JB, Iester M. Disc hemorrhage and glaucoma. *Ophthalmology* 1995;102:365–6. [PubMed: 7891969]
18. Liu L, Jia Y, Takusagawa HL, et al. Optical Coherence Tomography Angiography of the Peripapillary Retina in Glaucoma. *JAMA Ophthalmol* 2015;133:1045–52. [PubMed: 26203793]
19. Garway-Heath DF, Holder GE, Fitzke FW, Hitchings RA. Relationship between electrophysiological, psychophysical, and anatomical measurements in glaucoma. *Invest Ophthalmol Vis Sci* 2002;43:2213–20. [PubMed: 12091419]
20. Leite MT, Rao HL, Weinreb RN, et al. Agreement among spectral-domain optical coherence tomography instruments for assessing retinal nerve fiber layer thickness. *Am J Ophthalmol* 2011;151:85–92 e1. [PubMed: 20970108]
21. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;38:963–74. [PubMed: 7168798]
22. Laird NM, Donnelly C, Ware JH. Longitudinal studies with continuous responses. *Stat Methods Med Res* 1992;1:225–47. [PubMed: 1341659]
23. Zhang X, Dastiridou A, Francis BA, et al. Baseline Fourier-Domain Optical Coherence Tomography Structural Risk Factors for Visual Field Progression in the Advanced Imaging for Glaucoma Study. *Am J Ophthalmol* 2016;172:94–103. [PubMed: 27651070]
24. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. *Ophthalmology* 2013;120:1533–40. [PubMed: 23642371]
25. Nitta K, Sugiyama K, Wajima R, Tachibana G, Yamada Y. Associations between changes in radial peripapillary capillaries and occurrence of disc hemorrhage in normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2019;257:1963–1970. [PubMed: 31209566]
26. Okamoto Y, Akagi T, Suda K, et al. Longitudinal changes in superficial microvasculature in glaucomatous retinal nerve fiber layer defects after disc hemorrhage. *Sci Rep* 2020;10:22058. [PubMed: 33328575]
27. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Optical Coherence Tomography Angiography Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes. *Invest Ophthalmol Vis Sci* 2016;57:OCT451–9. [PubMed: 27409505]
28. Furlanetto RL, De Moraes CG, Teng CC, et al. Risk factors for optic disc hemorrhage in the low-pressure glaucoma treatment study. *Am J Ophthalmol* 2014;157:945–52. [PubMed: 24513094]
29. Drance SM. Disc hemorrhages in the glaucomas. *Surv Ophthalmol* 1989;33:331–7. [PubMed: 2655138]

30. Liu X, Lau A, Hou H, et al. Progressive Thinning of Retinal Nerve Fiber Layer and Ganglion Cell-Inner Plexiform Layer in Glaucoma Eyes with Disc Hemorrhage. *Ophthalmol Glaucoma* 2021.
31. Suh MH, Park KH, Kim H, et al. Glaucoma progression after the first-detected optic disc hemorrhage by optical coherence tomography. *J Glaucoma* 2012;21:358–66. [PubMed: 21623225]
32. Akagi T, Zangwill LM, Saunders LJ, et al. Rates of Local Retinal Nerve Fiber Layer Thinning before and after Disc Hemorrhage in Glaucoma. *Ophthalmology* 2017;124:1403–1411. [PubMed: 28499748]
33. Kitazawa Y, Shirato S, Yamamoto T. Optic disc hemorrhage in low-tension glaucoma. *Ophthalmology* 1986;93:853–7. [PubMed: 3737131]
34. Mayama C, Araie M. Effects of antiglaucoma drugs on blood flow of optic nerve heads and related structures. *Jpn J Ophthalmol* 2013;57:133–49. [PubMed: 23321913]
35. Chihara E, Dimitrova G, Chihara T. Increase in the OCT angiographic peripapillary vessel density by ROCK inhibitor ripasudil instillation: a comparison with brimonidine. *Graefes Arch Clin Exp Ophthalmol* 2018;256:1257–1264. [PubMed: 29520478]

Synopsis:

In this prospective cohort study, glaucomatous eyes with disc hemorrhages (DH) exhibited faster vessel density loss than those without DH.

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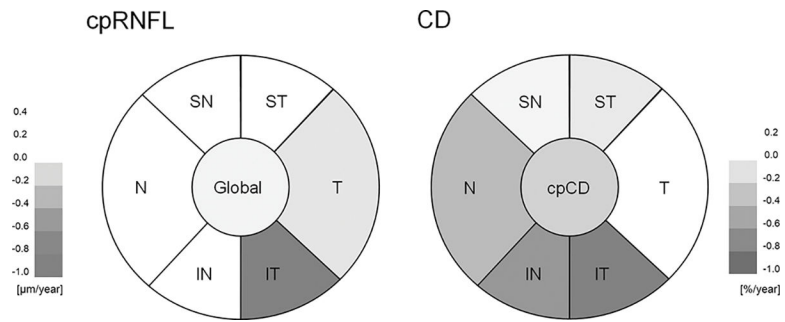


Figure 1.

Diagrams showing mean differences of cpRNFL thickness change rate (Left; $\mu\text{m}/\text{year}$) and CD change rate (Right; $\%/year$) between DH and Non-DH Eyes. cp = circumpapillary; CD = capillary density; IN = inferonasal; IT = inferotemporal; N = nasal; RNFL = retinal nerve fiber layer; SN = superonasal; ST = superotemporal; T = temporal; wi = whole image.

Table 1.

Demographics and Baseline Clinical Characteristics of DH and Non-DH Eyes

	DH group (32 subjects, 34 eyes)	Non-DH group (97 subjects, 134 eyes)	P value
Age (years)	71.0 (67.1, 75.0)	69.1 (67.0, 71.2)	0.383
Gender (Female/Male)	22/10	45/52	0.028
Race (African American/Non-African American)	5/27	25/72	0.239
Self-reported HTN, n (%)	20 (62.5%)	61 (62.9%)	0.969
Self-reported DM, n (%)	3 (9.4%)	15 (15.5%)	0.389
MOPP (mmHg)	50.5 (47.3, 53.6)	52.3 (50.9, 53.7)	0.280
Axial length (mm)	24.3 (23.9, 24.7)	24.4 (24.2, 24.6)	0.593
CCT (μm)	537.6 (520.0, 555.3)	536.5 (526.8, 546.2)	0.891
Baseline IOP (mmHg)	14.8 (13.3, 16.2)	15.3 (14.5, 16.2)	0.450
Mean IOP during follow-up (mmHg)	14.5 (13.5, 15.6)	15.7 (15.1, 16.3)	0.040
Diagnosis			
Glaucoma/Glaucoma suspect, Eye No.	25/9	86/48	0.304
Disease Severity by baseline 24–2 VF MD			0.892
Early glaucoma, Eye No. (%)	28 (82.4%)	109 (81.3%)	
Moderate and advanced glaucoma, Eye No. (%)	6 (17.6%)	25 (18.7%)	
Multiple DH, Eye No. (%)	14 (41.2%)		
DH Location, Eye No. (%)			
Inferior	20 (58.8%)		
Superior	9 (26.5%)		
Both hemispheres	5 (14.7%)		
DH Sectoral Location, Eye No. (%)			
Nasal	1 (2.9%)		
Temporal	0 (0.0%)		
Inferonasal	5 (14.7%)		
Inferotemporal	23 (67.7%)		
Superonasal	5 (14.7%)		
Superotemporal	8 (23.5%)		
Baseline 24–2 VF MD (dB)	–3.4 (–5.1, –1.8)	–2.9 (–3.5, –2.2)	0.519
Baseline 24–2 VF PSD (dB)	4.1 (2.8, 5.4)	4.3 (3.7, 4.9)	0.767
Baseline cpRNFL (μm)	76.3 (71.3, 81.2)	75.8 (73.0, 78.6)	0.874
Baseline wiCD (%)	43.1 (41.4, 44.8)	42.7 (41.9, 43.5)	0.657
Baseline cpCD (%)	44.2 (42.2, 46.3)	44.1 (43.2, 45.1)	0.925
Average SSI for OCTA	61.6 (60.3, 63.0)	62.6 (62, 63.2)	0.877
OCTA number of scans	4.9 (4.3, 5.4)	4.8 (4.6, 5.1)	0.898
Follow-up (years)	3.3 (3.1, 3.6)	3.4 (3.2, 3.5)	0.829
SDOCT number of scans	6.1 (5.9, 6.2)	6.3 (6.0, 6.5)	0.619
Average SQ for SDOCT	29.9 (29.4, 30.5)	29.3 (29.1, 29.6)	0.467

CCT = central corneal thickness; CD = capillary density; cp = circumpapillary; DH = disc hemorrhage; DM = diabetes mellitus; HTN = hypertension; IOP = intraocular pressure; MD = mean deviation; MOPP = mean ocular perfusion pressure; OCTA = optical coherence tomography

angiography; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer; SDOCT = spectral domain optical coherence tomography; SQ = scan quality; SSI = signal strength index; VF = visual field; wi = whole image. Values are shown in mean (95% confidence interval), unless otherwise indicated. Statistically significant P values are shown in bold.

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Table 2.

Comparison of Rates of CD Loss between DH and Non-DH Eyes

	DH Group Mean (95% CI)	Non-DH Group Mean (95% CI)	Difference Mean (95% CI)	P value (adjusted)
CD Change Rate (%/year)				
wiCD	-0.92 (-1.17, -0.67)	-0.60 (-0.73, -0.48)	-0.32 (-0.59, -0.04)	0.027 (0.050)
cpCD	-0.84 (-1.13, -0.56)	-0.53 (-0.67, -0.38)	-0.31 (-0.63, 0.00)	0.053 (0.104)
Nasal	-1.03 (-1.38, -0.68)	-0.58 (-0.75, -0.40)	-0.46 (-0.85, -0.06)	0.023 (0.013)
Temporal	-0.60 (-0.96, -0.24)	-0.63 (-0.82, -0.45)	0.04 (-0.37, 0.44)	0.862 (0.600)
Inferonasal	-1.02 (-1.51, -0.54)	-0.32 (-0.57, -0.08)	-0.70 (-1.24, -0.15)	0.012 (0.029)
Inferotemporal	-1.28 (-1.76, -0.81)	-0.43 (-0.67, -0.19)	-0.86 (-1.39, -0.33)	0.002 (0.007)
Superonasal	-0.42 (-0.85, 0.02)	-0.35 (-0.57, -0.12)	-0.07 (-0.56, 0.42)	0.781 (0.805)
Superotemporal	-0.82 (-1.35, -0.29)	-0.68 (-0.94, -0.41)	-0.14 (-0.74, 0.45)	0.639 (0.744)

CD = capillary density; cp = circumpapillary; DH = disc hemorrhage; IOP = intraocular pressure; M = male; wi = whole image. Values are shown in mean (95% confidence interval), unless otherwise indicated. Statistically significant P values are shown in bold.

* Adjusted to age, gender, baseline 24–2 visual field mean deviation, and mean IOP.

Table 3.

Comparison of Rates of cpRNFL Thinning between DH and Non-DH Eyes

	DH Group Mean (95% CI)	Non-DH Group Mean (95% CI)	Difference Mean (95% CI)	P value (adjusted)
cpRNFL Change Rate ($\mu\text{m}/\text{year}$)				
Mean Global	-0.53 (-0.79, -0.27)	-0.47 (-0.60, -0.34)	-0.06 (-0.36, 0.23)	0.679 (0.459)
Nasal	-0.13 (-0.52, 0.27)	-0.34 (-0.54, -0.14)	0.21 (-0.23, 0.65)	0.352 (0.748)
Temporal	-0.36 (-0.83, 0.12)	-0.22 (-0.46, 0.02)	-0.13 (-0.67, 0.40)	0.622 (0.511)
Inferonasal	-0.79 (-1.32, -0.26)	-0.82 (-1.09, -0.56)	0.04 (-0.56, 0.63)	0.907 (0.945)
Inferotemporal	-1.72 (-2.26, -1.17)	-0.71 (-0.98, -0.43)	-1.01 (-1.62, -0.40)	0.001 (0.002)
Superonasal	-0.26 (-0.77, 0.25)	-0.45 (-0.70, -0.19)	0.19 (-0.38, 0.76)	0.521 (0.879)
Superotemporal	-0.28 (-0.79, 0.24)	-0.65 (-0.91, -0.39)	0.37 (-0.21, 0.95)	0.209 (0.229)

cp = circumpapillary; DH = disc hemorrhage; RNFL = retinal nerve fiber layer. Values are shown in mean (95% confidence interval), unless otherwise indicated. Statistically significant P values are shown in bold.

* Adjusted to age, gender, baseline 24–2 visual field mean deviation, and mean IOP.

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Table 4.

Factors Contributing to the Rate of wiCD Loss Over Time in Study Participants by Univariable and Multivariable Mixed Model Analysis

Variables	Univariable Model		Multivariable Model 1		Multivariable Model 2	
	β , 95 % CI	P value	β , 95 % CI	P value		
Age, per 10 years older	-0.12 (-0.22, -0.02)	0.020	-0.12 (-0.22, -0.02)	0.017	-0.14 (-0.23, -0.04)	0.004
Gender: Female	-0.03 (-0.26, 0.20)	0.802				
Race:						
African American	0.08 (-0.18, 0.34)	0.554				
Self-reported diabetes	0.07 (-0.27, 0.40)	0.693				
Self-reported hypertension	-0.02 (-0.25, 0.21)	0.852				
MOPP, per 1 mmHg lower	0.00 (-0.02, 0.01)	0.964				
Axial length, per 1mm longer	-0.06 (-0.17, 0.05)	0.283				
CCT, per 100 μ m thinner	0.04 (-0.27, 0.35)	0.808				
Baseline IOP, per 1 mmHg higher	0.01 (-0.02, 0.04)	0.427				
Mean IOP, per 1 mmHg higher	0.00 (-0.04, 0.03)	0.864	-0.02 (-0.05, 0.02)	0.290	-0.02 (-0.05, 0.01)	0.182
History of disc hemorrhage	-0.32 (-0.59, -0.04)	0.027	-0.28 (-0.55, 0.00)	0.049	-0.27 (-0.51, -0.02)	0.036
History of inferior disc hemorrhage	-0.24 (-0.56, 0.07)	0.134				
Baseline 24-2 VF MD, per 1 dB worse	-0.02 (-0.05, 0.01)	0.114	-0.02 (-0.05, 0.00)	0.087		
Baseline cpRNFL, per 10 μ m thinner	-0.14 (-0.20, -0.07)	<0.001			-0.14 (-0.21, -0.08)	<0.001
Follow-up period, per 1 year longer	0.00 (-0.19, 0.19)	0.973				
OCTA number of scans	0.00 (-0.08, 0.07)	0.928				
Average SSI, per 1 higher	0.02 (-0.06, 0.10)	0.640				

CCT = central corneal thickness; CD = capillary density; cp = circumpapillary; IOP = intraocular pressure; MD = mean deviation; MOPP = mean ocular perfusion pressure; OCTA = optical coherence tomography angiography; RNFL = retinal nerve fiber layer; SQ = scan quality; SSI = signal strength index; VF = visual field; wi = whole image. Values are shown in β coefficient (95% confidence interval). Statistically significant P values are shown in bold.