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Intraocular Pressure Increases the Rate of Macular Vessel Density Loss in Glaucoma

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Abstract

Background/Aims: To evaluate the relationship over time between intraocular pressure (IOP) and the rate of macula whole image vessel density (wiVD) loss and whole image ganglion cell complex (wiGCC) thinning in glaucoma

Methods: From 62 patients in the Diagnostic Innovations in Glaucoma Study, 59 POAG and 27 glaucoma suspect eyes with mean follow-up of 3.2 years were followed. Optical coherence tomography angiography (OCT-A)-based vessel density and OCT-based structural thickness of the same 6×6-mm GCC scan slab were evaluated. Univariable and multivariable linear mixed models were performed for all eyes and also a subset of them in which peak IOP<18 mmHg to investigate the effect of IOP parameters on the rate of wiVD and wiGCC change.

Results: The mean baseline visual field mean deviation (95% CI) was −3.3 dB(−4.4,−2.1). Higher mean IOP (−0.07 %/year per 1mmHg(−0.14, −0.01), p=0.033), peak IOP(−0.07 %/year per 1mmHg (−0.13, −0.02), p=0.004), and IOP fluctuation(IOP standard deviation) (−0.17 %/year per 1mmHg(−0.32,0.02)),p=0.026) were associated with faster macular vessel density loss. Faster wiGCC thinning was associated with higher mean IOP (−0.05 μm/year per 1mmHg(−0.10,−0.01)),p=0.015), peak IOP (−0.05 μm/year per 1mmHg(−0.08, −0.02)),p=0.003), and IOP fluctuation (−0.12 μm/year per 1mmHg(−0.22,−0.01),p=0.032). In eyes

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d. **Author contribution**

Involved in design and conduct of study: GM and SM. Data collection: GM, TN, SM, EM, VM, JW, KD, and AK. Analysis and interpretation of data: GM, SM, and TN and RNW. Writing: GM, SM, and RNW. Critical revision: GM, TN, SM, EM, VM, JW, KD, and AK. Approval of the manuscript: GM, TN, SM, EM, VM, JW, KD, AK, and RNW. RNW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

STATEMENTS

Patient consent for publication: Consent obtained directly from patient(s).

Ethics approval: This study received the institutional review board (IRB #140276) approval of the University of California, San Diego and the methodology adhered to the tenets of the Declaration of Helsinki.

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with peak<18mmHg, faster wiVD progression was associated with higher mean IOP (p=0.042). Faster wiGCC progression was associated with higher mean IOP in these eyes (p=0.025).

Conclusion: IOP metrics were associated with faster rates of overall macular microvascular loss and also in the eyes with peak IOP<18mmHg. Future studies are needed to examine whether additional IOP lowering reduces the rate of microvascular loss in glaucoma patients.

Synopsis/Precis:

Peak IOP, mean IOP, and IOP fluctuation are associated with faster rates of microvascular loss in macula. Mean IOP is associated with faster rates of microvascular loss even in eyes with seemingly controlled IOP.

Keywords

Intraocular pressure; whole image vessel density; ganglion cell complex; macula

Introduction

Glaucoma, a leading cause of global blindness, is a progressive optic neuropathy characterized by loss of the retinal ganglion cell (RGC)-axonal complex, and subsequent visual field (VF) damage.[1]

Intraocular pressure (IOP) is the only modifiable risk factor for glaucoma. Lowering of the IOP, even in eyes with IOP in what is generally considered the normal range (10 to 21 mmHg), can reduce the rate of progression.[2] However, several patients still experience VF deterioration despite treatment.[3 4] Therefore, understanding how the level of IOP is associated with glaucoma progression can help clinicians to establish a target IOP and individualize glaucoma therapy.[4 5]

There is growing evidence that impaired vascular blood flow or changes in retinal microcirculation is associated with glaucoma.[6 7] Optical coherence tomography angiography (OCT-A) have enhanced our understanding of the potential role of the retinal microvasculature in the pathophysiology of glaucoma.[8] Studies using OCT-A have provided evidence of microvascular dropout, measured as a decrease of vessel density within the optic nerve head (ONH), the peripapillary retina, and the macula in POAG eyes.[8 9] Moreover, decreased vessel density has been associated with the severity of VF glaucoma.[10]

Macular ganglion cell complex (GCC) thinning also is detectable in glaucoma patients.[11] In POAG eyes, normalized macular vessel density decrease faster than GCC thinning in some patients.[11] GCC generally has better long-term reproducibility than vessel density, however, it is unclear which of these parameters is better for detecting progressive POAG changes.[11 12]

Although prior studies used VF as their outcome to show progression,[3 13] it has been suggested that OCTA may help in identifying eyes at risk of VF progression in patients with glaucoma.[14] Also, it has been reported previously that faster vessel density and GCC thinning loss during an initial follow-up period was associated with future 24–2 VF

progression.[15] Therefore, given the variability and fluctuation of VF to detect progression, structural changes may help to track the progression sooner with IOP modifications.[16 17]

There is limited evidence that higher IOP is associated with faster GCC thinning but not macular microvascular dropout.[11] Therefore, evaluating the relationship between IOP and both macular thickness and vascular parameters is of particular interest.

The purpose of the current study was to investigate the impact of IOP control on macular microvascular loss and GCC thinning rates in a seemingly well-controlled longitudinal studies of glaucoma patients.

Methods

This is a retrospective longitudinal observational study derived from Diagnostic Innovations Glaucoma Study (DIGS), clinical trial.gov identifier: NCT00221897, including demographics and OCT-A measurements. Informed consent was obtained from all study participants. The University of California Institutional Review Board (IRB # 140276) approved all protocols, and all methods adhered to tenets of the Declaration of Helsinki. All participants underwent annual comprehensive ophthalmologic evaluation, including best-corrected visual acuity, slit-lamp biomicroscopy, dilated fundus examination, and stereoscopic optic disc photography in both eyes.[18] Semi-annual evaluations included Goldmann applanation tonometry (GAT) measurement, standard automated perimetry (SAP), OCT, and OCT-A testing. OCT/OCTA scans have been captured post-dilation. [18]

The study included eyes diagnosed as glaucoma or glaucoma suspect with at least 2 years of follow-up with a minimum of 4 qualified OCT/OCT-A tests and 3 IOP measures with GAT in separate days over a minimum follow-up period of 6 months. Eyes were classified as glaucomatous if they had repeatable (≥2 consecutive) abnormal VF test results or evidence of glaucomatous optic neuropathy defined as excavation, the presence of focal thinning, notching of the neuroretinal rim, or localized or diffuse atrophy of the retinal nerve fiber layer based on masked grading of optic disc photographs by 2 graders or clinical examination by a glaucoma specialist.[19] Glaucoma suspects were defined as those having elevated IOP (≥22 mm Hg) or suspicious-appearing optic discs without the presence of repeatable glaucomatous VF damage. The 24–2 VF tests were considered reliable if they had fixation losses ≤15%, false negatives ≤ 33%, 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.[20]

Inclusion criteria included 1) older than 18 years of age, 2) open angles on gonioscopy, and 3) best-corrected visual acuity of 20/40 or better 4) qualified OCT-A or OCT imaging (Angiovue; Optovue Inc., Fremont, CA, software version 2018.1.0.43) 5) spherical refraction within ±5.0 diopters, cylinder correction within ±3.0 diopters, and 6) axial length less than 26.5 micrometers. [21]

Eyes were excluded if they have (1) a history of trauma or intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), (2) coexisting retinal disease, (3)

uveitis, and (4) nonglaucomatous optic neuropathy. Participants diagnosed with Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke were also excluded.[21] Participants who underwent glaucoma surgeries (i.e., trabeculectomy, tube shunt procedures) after the beginning of the study were excluded as well.[22]

OCT and OCT-A Imaging

Macula 6 × 6-mm scans centered on the fovea were acquired with the OCT-A AngioVue system. OCT-A-based vessel density and OCT-based GCC thickness measures were calculated from the same macula scan as follows. The split-spectrum amplitude-decorrelation angiography method was used to capture the dynamic motion of the red blood cells and provide a high-resolution 3-dimensional visualization of perfused retinal vasculature. Macula vessel density was calculated as the percent area occupied by flowing blood vessels in the selected region. The retinal layers of each scan were automatically segmented by the AngioVue software in order to visualize the superficial retinal capillary plexuses in a slab from the internal limiting membrane (ILM) to the inner plexiform layer (IPL) - 10 μm. For this study, whole en face image vessel density (wiVD) was derived from the entire 6 × 6-mm scan and perifoveal vessel density (pfVD) was measured in an annular centered on the fovea with an inner diameter of 1 mm and outer diameter of 6 mm.[23]

Image quality review was done on all scans according to the University of California, San Diego, Imaging Data Evaluation and Analysis Reading Center standard protocol. Trained graders reviewed scans and excluded poor-quality images, defined as images with (1) a signal strength index 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 macula scans was reviewed for accuracy and was adjusted manually if required.[24]

In this study, IOP parameters were investigated as follows: baseline IOP was the first measured IOP after enrollment in the study. Mean IOP was calculated as the average of all IOP measurements obtained during follow-up, and peak IOP was the highest single measurement during the entire follow-up. Fluctuation in IOP was defined as the standard deviation (SD) of inter-visit IOP measurements.[22]

Statistical Analysis:

For descriptive analyses, categorical variables were presented as count (%), and continuous variables were summarized using mean (95% confidence intervals). In addition to baseline variables, summaries of IOP parameters (mean, peak, and IOP fluctuation) were also presented.[22]

Eyes were then classified into other groups according to IOP control. Eyes were considered to have seemingly well-controlled IOP if all measurements recorded during follow-up were no higher than 18 mmHg. The cutoff of 18 mmHg to determine eyes with "seemingly well-controlled IOP" was motivated by the Advanced Glaucoma Intervention Study, which found that eyes with IOP consistently less than 18 mmHg in all visits did not show apparent progression as measured by the Advanced Glaucoma Intervention Study score.[25]

Linear mixed models were used to evaluate the effect of IOP parameters and baseline characteristics on the rates of change on wiGCC thickness and wiVD density loss over time for all eyes and eyes with peak IOP<18 mmHg while adjusting for potential correlations between both eyes from the same individual.[26] This model can account for the fact that different eyes may have different rates of wiVD density loss or wiGCC thinning over time, while allowing for correlation between two eyes of the same individual. Multivariable linear mixed models were adjusted for age, baseline mean deviation (MD), and any variable with a p-value less than 0.15. All statistical analyses were performed using the commercially available software Stata version 15 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05.[22]

Results

86 eyes (59 POAG and 27 glaucoma suspects) of 62 patients met the inclusion criteria. The demographic and baseline characteristics of the study eyes are summarized in Table 1. The mean (95% CI) baseline wiVD density was 44.3 (43.2, 45.4) %/year. The mean (95% CI) baseline wiGCC thickness was 83.2 (81.1, 85.4) μm/year. The mean (95% CI) follow-up period in this longitudinal study was 3.2 (3.1, 3.4) years. The overall number of OCT and OCT-A/OCT visits was 5.2(4.9, 5.4).

Age- and QI-adjusted rates of macular vessel density and GCC thickness loss are presented in Supplementary Table 1. Age- and QI-adjusted rates of both GCC thickness and macular vessel density change were significantly negative (all $P < 0.001$) in all eyes and eyes with peak IOP <18mmHg.

Table 2 presents the effect of IOP parameters on wiVD change in univariable and multivariable linear mixed models. In univariable analysis, higher peak IOP (β (95% CI) = −0.05 (−0.10, −0.00); P=0.035), and higher IOP fluctuation (β = −0.16 (−0.30, −0.01); P=0.037) were significantly associated with faster rates of wiVD loss over time, while higher mean IOP (β = 0.04 (−0.10, 0.02); P=0.187) was not associated with faster wiVD loss. Figure 1A and 1B show the scatter plots for the association between both IOP fluctuation and peak IOP, and wiVD loss in all eyes, separately. Supplementary Figure1 shows case example of the effect of different IOP metrics on macula vessel density and GCC changes. In the multivariable linear mixed model, higher mean IOP (β = −0.07 (−0.14, −0.01) per 1 mmHg higher; P=0.033), higher peak IOP (β = −0.07 (−0.13, −0.02) per 1 mmHg higher; P=0.004), and higher IOP fluctuation (β = 0.17 (−0.32, 0.02) per 1 mmHg higher; P=0.026) were associated with faster wiVD loss over time.

Table 3 also shows the effect of IOP parameters on wiGCC thinning in the univariable linear mixed model. In univariable analysis, higher mean IOP (β = −0.06 (−0.11, 0.01); P=0.007), and higher peak IOP (β = −0.05 (−0.09, −0.02); P=0.002) were significantly associated with a faster rate of GCC thinning. However, higher IOP fluctuation (β = −0.09 (−0.20, 0.02); P=0.105) was not associated with the faster rate of GCC thinning over time. Figure 1C and 1D show scatter plots of associations between peak IOP and mean IOP, and GCC thinning in all eyes, respectively.

In multivariable linear mixed model, higher mean IOP (β = −0.05 (−0.10, −0.01) per 1 mmHg; *P*=0.015), higher peak IOP (β = −0.05 (−0.08, −0.02); *P*=0.003), and higher IOP fluctuation (β = −0.12 (−0.22, −0.01); *P*=0.032) were associated with faster GCC thinning over time

Table 4 presents the effect of IOP parameters on wiVD loss in univariable linear mixed model in eyes with peak IOP<18 mmHg. In univariable analysis, higher mean IOP (β = −0.12 (−0.24, 0.01); *P*=0.038) was significantly associated with a faster rate of wiVD loss over time. However, higher peak IOP, and higher IOP fluctuation were not associated with faster wiVD loss over time (All *P*>0.05).

In multivariable mixed model analysis, higher mean IOP (β = −0.12 (−0.24, −0.00); *P*=0.042) was significantly associated with a faster rate of wiVD loss over time. However, higher peak IOP (β = −0.10 (−0.20, 0.01); *P*=0.079) tended to be associated with faster microvascular loss. Higher IOP fluctuation was not associated with the faster wiVD loss over time (*P*>0.05).

Supplementary table 2 presents the effect of IOP parameters on wiGCC thinning in the univariable linear mixed model in eyes with peak IOP<18 mmHg. In univariable analysis, none of the IOP metrics were associated with the faster rates of GCC thinning over time (All *P* >0.05).

In multivariable mixed model analysis, higher mean IOP (β = −0.06 (−0.11, −0.01) per 1 mmHg; *P*=0.025) was significantly associated with a greater rate of GCC thinning over time. However, higher peak IOP (β = −0.05 (−0.09, 0.00) per 1 mmHg; *P*=0.052) tended to be associated with faster GCC thinning. Higher IOP fluctuation was not associated with the faster GCC thinning over time (*P*>0.05).

Discussion

In this longitudinal study, higher IOP fluctuation, peak IOP, and mean IOP were associated in all eyes with faster macula microvascular loss. Additionally, mean IOP was associated with macular microvascular loss in eyes with peak IOP<18 mmHg.

Few studies have investigated the effect of acute IOP reduction on changes in vessel density. Previous study reported a significant increase in the peripapillary vessel density after trabeculectomy using OCT-A. The reversal of peripapillary vessel density after trabeculectomy was associated with higher preoperative IOP and greater IOP reduction. It is notable that in a recent study by Choi et al., vessel density loss was preceded by structural loss in monkeys. In this report, macular capillary vessel density of the superficial and deep vascular complex started to decrease at 40 mmHg. At higher IOP levels (50 mmHg), changes in retinal thickness were observed when vessel density decreased to 20% of baseline.[27]

In the current study, the increase in mean and peak IOP was associated with faster vessel density loss in all eyes. In contrast, some prior studies did not find any association between IOP metrics and microvascular loss. The discrepant results of the current study with earlier

ones may be related to the size of the scan area. A macular 6×6 scan was used in the present study, and it covers a larger area of the macula than in earlier studies ; the larger scan area provides more vessel density information than smaller scan areas.

We also observed that an increase in IOP fluctuation was associated with faster vessel density loss in all eyes. Previous studies reported equivocal results regarding the correlation between IOP fluctuation and glaucoma progression. The AGIS study found that long-term IOP fluctuation was a significant and independent predictor of VF worsening. A subsequent analysis showed that the effect of IOP fluctuation was greater in patients with low mean IOP (10–12 mmHg), whereas IOP fluctuation was not a significant predictor of VF progression in the high mean IOP group (mean IOP, >16 mm Hg). We did not observe any association between IOP fluctuation and vessel density loss in eyes with peak IOP<18mmHg. This can be due to several factors, including different ocular hypotensive medications, populations and study designs, as well as the lack of a standard definition of IOP fluctuation. IOP fluctuation can be more pronounced in lower IOP as the severity of glaucoma increases due to more aggressive therapy in the severe stage of glaucoma. Incorporation of another treatment (i.e., medication) to control the progression in advanced disease or eyes with fast progression can be another confounding factor which affects the relationship between IOP fluctuation and glaucoma progression. A majority of the subjects in the current study were in the early stage or were glaucoma suspects with higher IOP. These results are similar to results in the OHTS and EMGT studies, which also did not find any association between IOP fluctuation and VF progression.

In the present study, the increases in peak IOP, mean IOP, and IOP fluctuation during follow-up was associated with faster macular GCC thinning. Mean IOP also was associated with faster GCC thinning in eyes with peak IOP <18 mmHg and this, too, is consistent with previous studies.

To more closely replicate how clinicians monitor progression in practice, we also assessed the relationship between IOP and rates of structural change in eyes with peak IOP<18mmHg that were seemingly well-controlled. We investigated a cutoff of 18 mmHg based on the AGIS study. In the AGIS,[25] all eyes with IOP consistently lower than 18 mmHg during all visits and a mean IOP of 12.3 mmHg did not show apparent VF progression as measured by the AGIS score, a summary metric of VF damage that behaves similarly to mean deviation. In the current study, this cutoff did not translate to less microvascular change or GCC thinning. Each 1 mm Hg increase in mean IOP was correlated with 0.12 %/year faster macular microvascular loss in these seemingly well-controlled eyes. Jammal et al., also demonstrated that several eyes could show moderate and fast progression with peak IOP below 18 mmHg.[28]

Macular vulnerability in the fovea in response to ischemic change has been proposed as a mechanism involved in vascular change due to acute change in IOP.[29] [30] However, the current results show evidence for the chronic effect of IOP on macular microvascular progression. Changes in IOP itself, while contributing to mechanical stress at the ONH, may also have a role in POAG pathogenesis by altering ocular perfusion.[4] Previous studies showed that macular vessel density also has a correlation with RNFL thinning(r=0.69).[31] In

addition, eyes with lower baseline macular vessel density and ONH vessel density tended to have faster RNFL thinning than those with higher values.[32] Therefore, macular vessel density can possibly be a surrogate for ocular perfusion at the ONH level.

Mechanical stress is not the only reason for macular vascular changes. Several other factors can affect macular vascular changes. Inflammation, neurovascular degeneration, endothelial dysfunction, oxidative stress, and arteriosclerosis are other reasons that can affect macular vascular changes.[33–36] Topical medical therapies and surgical interventions such as trabeculectomy could also affect macular vascular changes. [33 34 37] Macular microvascular could be altered by systemic vascular conditions and cardiovascular risk profile. It has been shown that patients with low retinal vascular density presented indirect evidence of systemic vascular disease.[38] Indeed, they more often had previous peripheral artery disease, impaired renal function, and a history of high blood pressure and diabetes than did patients with intermediate or high vascular densities.[38 39]

Although we investigated the effect of self-reported diabetes, self-reported hypertension, and mean IOP on the macula vessel density changes, some unavailable factors also may characterize systemic vascular disorders, including HbA1c, 24h arterial tension, history of night dips, and intercurrent systemic vascular events. Topical glaucoma medications also may influence ocular blood flow[33 37]Therefore, we cannot exclude the possibility that the use of topical eye drops accounts for the observed vascular differences. Moreover, it is unclear whether systemic medications have an effect on macular vascular changes.[33] Although we adjusted our results for confounders, it is possible that some of these differences influenced our results.

This study has several limitations. OCT-A scans with poor quality were excluded. As compared to the current study, greater image quality variability can be expected in clinical practice.[40] Although it might have been helpful to evaluate macula and ONH OCTA images obtained at the same time, the sample size was insufficient to have both types of images at the same visit, particularly since ~30 % of the OCTA images were not qualified for the study because of artifacts.[40] Although the changes that have been seen over the follow-up can be affected by the reproducibility of macula OCTA, macular vessel densities have good reproducibility and repeatability in stable glaucoma eyes in a long-term follow-up.[12 41] Given a large number of therapeutic options and the frequent changes in the treatment scheme during a patient follow-up, it would be difficult to obtain reliable estimates of individual drug effects on rates of vessel density or GCC change.[28] Therefore, most of the time true IOP is not detected during office hours. With only 5 IOP measurements, future studies are needed to investigate the effect of IOP metrics. Some minor causes that may affect signal strength and vessel density measurement, such as mild cataract, were not considered in this study. While some patients (24%) were pseudophakic at baseline, only 2 eyes underwent cataract surgery during the course of study. The scans of these patients were reviewed to be sure that image quality was not affected by media opacity. Hence, the presence of media opacity did not likely have much influence on the results of the study. Although OCTA images were captured post-dilation, it previously was shown that dilation using topical 0.5% tropicamide and 2.5% phenylephrine resulted in a statistically significant but not clinically meaningful reduction in non-HD ONH scans.[42] Finally, not all POAG

patients are the same, and the effect of IOP depends on the characteristics of the patient, the baseline IOP, their stage of damage, and other as-yet-unknown factors.

To summarize, some IOP metrics were associated with macular microvascular loss and also GCC thinning, even in eyes with IOP<18mmHg at all visits. Longitudinal association of IOP with faster microvascular loss in seemingly well-controlled eyes can help clinicians better understand the influence of IOP on glaucoma progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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e. Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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key messages

○ What is already known on this topic

IOP is known to be associated with visual field progression. However, there is limited knowledge about the association between IOP and microvascular loss.

○ What this study adds

IOP metrics are associated with microvascular loss in macula even in eyes with peak IOP<18 mmHg.

○ How this study might affect research, practice or policy

This study can add to our knowledge about the pathophysiology of glaucoma and the chronic effect of IOP on microvascular loss. Given the variability of longitudinal visual fields, macular vascular changes may help to track the progression easier with IOP modifications.

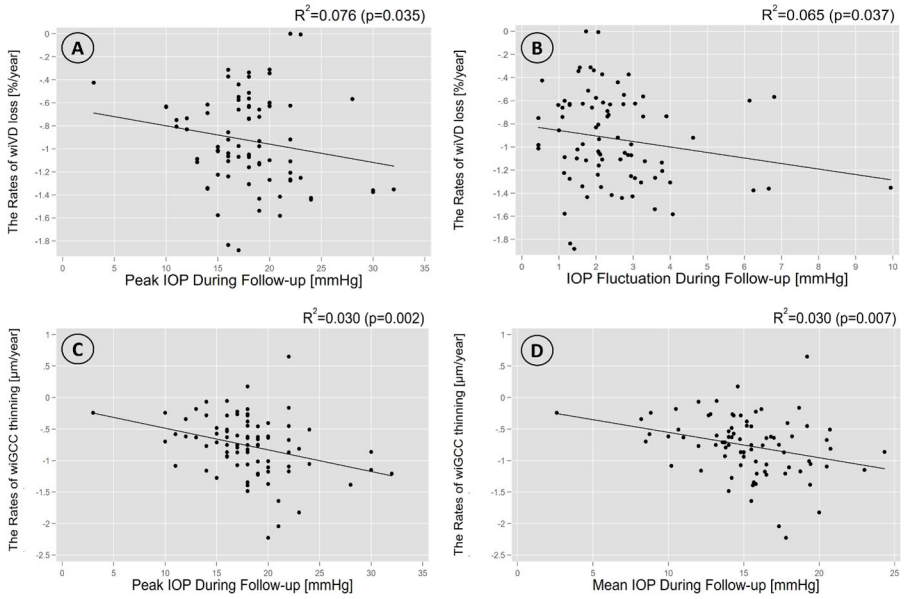

Figure1.

Scatter plot shows the association of significant intraocular pressure (IOP) metrics in univariable models with wiVD loss (peak IOP and IOP fluctuation) (Figure1A and 1B) and wiGCC thinning (peak IOP and mean IOP) (Figure1C and 1D) in all eyes. Abbreviations: wiGCC=whole image ganglion cell complex, wiVD=whole image vessel density.

Table 1.

Demographics and Baseline Characteristics of Included Eyes.

Characteristic	All Eyes (86 eyes of 62 patients)	Eyes with Peak IOP<18 mmHg (34 Eyes of 25 patients)
Baseline age	67.4 (64.3, 70.6)	68.9 (64.1, 73.6)
Gender (Female/ Male) n (%)	35 (65.5%)/27 (43.6%)	14 (56.0%)/11 (44.0%)
Race (African American/ Non-African American) n (%)	15 (24.2%)/47 (75.8%)	6 (24.0%)/19 (76.0%)
Self-reported hypertension,n (%)	39 (62.9%)	16 (64.0%)
Self-reported diabetes, n (%)	8 (12.9%)	2 (8%)
Axial length (mm)	24.4 (24.1, 24.7)	24.4 (24.0, 24.8)
CCT (per 100 μm)	5.4 (5.3, 5.5)	
Baseline IOP (mmHg)	15.4 (14.4, 16.4)	12.5 (11.3, 13.7)
Mean IOP during follow-up (mmHg)	15.2 (14.5, 16.0)	12.4 (11.4, 13.3)
Peak IOP during follow-up (mmHg)	18.1 (17.1, 19)	14.4 (13.4, 15.4)
IOP fluctutation during follow-up (mmHg)	2.5 (2.2, 2.8)	1.8 (1.5, 2.1)
Number of IOP meaurements during follow-up	5 (4.7, 5.3)	5 (4.5, 5.5)
Baseline VF MD (dB)	−3.3 (−4.4, −2.1)	−3.6 (−5.7, −1.4)
Baseline wiVD (%)	44.3 (43.2, 45.4)	42.9 (41.1, 44.7)
Baseline wiGCC (μm)	83.2 (81.1, 85.4)	81.1 (78.2, 84.1)
OCT/OCT-A follow-up visits (n)	5.2 (4.9, 5.4)	5 (4,7, 5.3)
Follow-up (years)	3.2 (3.1, 3.4)	3.1 (2.8, 3.4)

CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; OCT = optical coherence tomography; OCT-A = optical coherence tomography angiography; n = number, wiVD =whole image vessel density, wiGCC=whole image ganglion cell complex. Values are shown in mean (95% confidence interval), unless otherwise indicated.

Table 2.

Factors Contributing to the Rate of WiVD loss Thinning Over Time in all Eyes

Variables	Univariable Model		Multivariable Model (1)		Multivariable Model (2)		Multivariable Model (3)	
	β (95 % CI)	*P* value (Adjusted*)	β (95 % CI)	*P* value	β (95 % CI)	*P* value	β (95 % CI)	*P* value
Age (per 10 years)	−0.01 (−0.3, 0.1)	0.393	−0.02 (−0.20, 0.20)	0.859	0.01 (−0.20, 0.20)	0.950	0.10 (−0.20, 0.30)	0.619
Gender: Female	0.15 (−0.27, 0.57)	0.481 (0.170)						
Race: African American	0.08 (−0.38, 0.55)	0.724 (0.308)						
Self-reported hypertension	−0.18 (−0.59, 0.23)	0.393 (0.254)						
Self-reported diabetes	−0.01 (−0.60, 0.58)	0.975 (0.447)						
Axial length, per 1mm longer	0.14 (−0.04, 0.31)	0.120 **(0.053)**	0.05 (−0.14, 0.24)	0.609	0.03 (−0.16, 0.21)	0.772	0.06 (−0.12, 0.25)	0.504
CCT, per 100 pm thinner	0.34 (−0.10, 0.78)	0.133 (0.558)	0.52 (−0.00, 1.05)	0.050	0.60 (0.09, 1.11)	**0.022**	0.38 (−0.10, 0.85)	0.124
Baseline IOP, per 1 mmHg higher	−0.03 (−0.08, 0.01)	0.152 (0.111)						
Mean IOP during follow-up, per 1 mmHg higher	−0.04 (−0.10, 0.02)	0.187 (0.100)	−0.07 (−0.14, −0.01)	**0.033**				
Peak IOP during follow-up, per 1 mmHg higher	−0.05 (−0.10, −0.00)	**0.035 (0.017)**			−0.07 (−0.13, −0.02)	**0.004**		
IOP fluctuation during follow-up, per 1 mmHg higher	−0.16 (−0.30, −0.01)	**0.037 (0.025)**					−0.17 (−0.32, 0.02)	**0.026**
Baseline VF MD, per 1 dB worse	0.00 (−0.03, 0.04)	0.869 (0.981)	0.01 (−0.03, 0.06)	0.573	0.01 (−0.03, 0.06)	0.553	0.01 (−0.04, 0.05)	0.814
Scan Quality, per 1 higher	−0.12 (−0.30, 0.06)	0.194						
Follow-up period, per 1 year longer	−0.00 (−0.25, 0.25)	0.996 (0.806)						
No. of OCT follow-up visits	0.05 (−0.10, 0.20)	0.503 (0.384)						

CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; wiVD = whole image vessel density; wiGCC= whole image ganglion cell complex; OCT-A = optical coherence tomography angiography; VF =visual field. Values are shown in β coefficient (95% confidence interval). Statistically significant P values are shown in bold.

* = *P* value adjusted for age and scan quality.

Model 1 includes mean IOP while adjusted for age, baseline MD, axial length, and CCT.

Model 2 includes peak IOP while adjusted for age, baseline MD, axial length, and CCT.

Model 3 includes IOP fluctuation while adjusted for age, baseline MD, axial length, and CCT.

Table 3.

Factors Contributing to the Rate WiGCC Thinning Over Time in All Eyes

Variables	Univariable Model		Multivariable Model (1)		Multivariable Model (2)		Multivariable Model (3)	
	β (95 % CI)	*P* value (Adjusted*)	β (95 % CI)	*P* value	β (95 % CI)	*P* value	β (95 % CI)	*P* value
Age (per 10 years)	0.10 (−0.04, 0.24)	0.177	0.11 (−0.03, 0.24)	0.113	0.13 (−0.01, 0.26)	0.060	0.17 (0.03, 0.31)	**0.018**
Gender: Female	−0.13 (−0.47, 0.21)	0.463 (0.347)						
Race: African American	−0.11 (−0.48, 0.26)	0.560 (0.378)						
Self-reported hypertension	0.04 (−0.30, 0.38)	0.818 (0.726)						
Self-reported diabetes	−0.02 (−0.50, 0.46)	0.944 (0.964)						
Axial length, per 1mm longer	0.03 (−0.11, 0.17)	0.661 (0.291)						
CCT, per 100 pm thinner	0.11 (−0.26, 0.49)	0.557 (0.439)						
Baseline IOP, per 1 mmHg higher	−0.04 (−0.07, 0.00)	**0.043** (0.063)						
Mean IOP during follow-up, per 1 mmHg higher	−0.06 (−0.11, 0.01)	**0.007 (0.011)**	−0.05 (−0.10, −0.01)	**0.015**				
Peak IOP during follow-up, per 1 mmHg higher	−0.05 (−0.09, −0.02)	**0.002 (0.003)**			−0.05 (−0.08, −0.02)	**0.003**		
IOP fluctuation during follow-up, per 1 mmHg higher	−0.09 (−0.20, 0.02)	0.105 **(0.037)**					−0.12 (−0.22, −0.01)	**0.032**
Baseline VF MD, per 1 dB worse	−0.01 (−0.04, 0.02)	0.399 (0.337)	−0.01 (−0.04, 0.02)	0.408	−0.01 (−0.04, 0.01)	0.348	−0.02 (−0.05, 0.01)	0.223
Scan Quality, per 1 higher	−0.13 (−0.26, 0.01)	**0.069**	−0.10 (−0.24, −0.04)	0.156	−0.09 (−0.23, 0.04)	0.182	−0.10 (−0.24, 0.04)	0.175
Follow-up period, per 1 year longer	−0.00 (−0.21, 0.20)	0.969 (990)						
Number of OCT follow-up visits	−0.01 (−0.14, 0.12)	0.909 (0.844)						

CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; wiGCC= whole image ganglion cell complex; OCT= optical coherence tomography; VF =visual field. Values are shown in β coefficient (95% confidence interval). Statistically significant *P* values are shown in bold.

* = *P* value adjusted for age and scan quality.

Model 1 includes mean IOP while adjusted for age, baseline MD, and scan quality.

Model 2 includes peak IOP while adjusted for age, baseline MD, and scan quality.

Model 3 includes IOP fluctuation while adjusted for age, baseline MD, and scan quality.

Table 4.

Factors Contributing to the Rate of wiVD loss Over Time in Eyes with Peak IOP <18 mmHg

Variables	Univariable Model		Multivariable Model (1)		Multivariable Model (2)		Multivariable Model (3)	
	β (95 % CI)	*P* value (Adjusted*)	β (95 % CI)	*P* value	β (95 % CI)	*P* value	β (95 % CI)	*P* value
Age (per 10 years)	0.06 (−0.26, 0.37)	0.727	0.10 (−0.27, 0.38)	0.740	0.10 (−0.25, 0.39)	0.670	0.05 (−0.30, 0.39)	0.780
Gender: Female	0.24 (−0.35, 0.83)	0.432 (0.162)						
Race: African American	−0.20 (−0.83, 0.42)	0.527 (0.262)						
Self-reported hypertension	−0.24 (−0.87, 0.40)	0.466 (0.168)						
Self-reported diabetes	−0.22 (−0.95, 0.50)	0.545 (0.312)						
Axial length, per 1mm longer	−0.04 (−0.33, 0.25)	0.777 (0.710)						
CCT, per 100 pm thinner	0.42 (−0.22, 1.05)	0.199 (0.633)						
Baseline IOP, per 1 mmHg higher	−0.09 (−0.18, 0.00)	0.060 (0.070)						
Mean IOP during follow-up, per 1 mmHg higher	−0.12 (−0.24, 0.01)	0.038 (0.103)	−0.12 (−0.24, −0.00)	**0.042**				
Peak IOP during follow-up, per 1 mmHg higher	−0.10 (−0.21, 0.01)	0.075 (0.096)			−0.10 (−0.20, 0.01)	0.079		
IOP fluctuation during follow-up, per 1 mmHg higher	0.12 (−0.24, 0.49)	0.504 (0.783)					0.11 (−0.28, 0.49)	0.593
Baseline VF MD, per 1 dB worse	−0.00 (−0.06, 0.06)	0.946 (0.882)	−0.00 (−0.06, 0.06)	0.960	–0.00 (−0.06, 0.06)	0.908	–0.00 (−0.06, 0.06)	0.951
Scan Quality, per 1 higher	−0.12 (−0.41, 0.16)	0.401						
Follow-up period, per 1 year longer	0.15 (−0.22, 0.51)	0.432 (0.721)						
Number of OCT follow-up visits	−0.06 (−0.33, 0.20)	0.627 (0.919)						

CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; wiVD = whole image vessel density; OCT-A = optical coherence tomography angiography; VF =visual field. Values are shown in β coefficient (95% confidence interval). Statistically, significant *P* values are shown in bold.

*=*P* value adjusted for age and scan quality.

Model 1 includes mean IOP while adjusted for age and baseline MD.

Model 2 includes peak IOP while adjusted for age and baseline MD.

Model 3 includes IOP fluctuation while adjusted for age and baseline MD.