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Multilayer Macula Vessel Density and Visual Field Progression in Glaucoma

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Abstract

Purpose: To evaluate the association of macular superficial vessel density (SVD) and projection-resolved deep vessel density (DVD) with past visual field (VF) progression in primary open angle glaucoma patients.

Design: Retrospective cohort

Materials and Methods: In this longitudinal study, 208 eyes of 147 glaucoma patients from the Diagnostics Innovations in Glaucoma Study were included. Eligible participants were required to have at least five 24-2 VF tests over a minimum follow-up period of 3 years prior to macular optical coherence tomography angiography (OCTA) imaging. Visual field progression was defined based on both event-based pointwise linear regression (PLR) and trend-based methods. The association of macular SVD and DVD with the probability and rate of past VF progression was evaluated using linear mixed effects model.

Results: Fifty-two (25%) eyes had VF progression based on the PLR based criterion at the end of a mean (±SD) follow-up duration of 6.9 (±1.2) years. In the event-based multivariable analysis, lower baseline SVD was associated with a higher likelihood of past VF progression (OR per 1% lower = 1.28, 95% CI: 1.02, 1.59). Similarly, in the trend-based multivariable analysis, lower macular SVD was associated with a faster past rate of mean deviation decline (coefficient = −0.03 dB/year; 95% CI: −0.04, −0.01). Event-based and trend-based analyses found no significant associations for macular DVD with the likelihood/rate of past VF progression (P>0.05).

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Author contribution:

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

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Conclusions: Lower macular SVD, and not DVD, was associated with a higher probability of past VF progression. Macular OCTA imaging shows promise for identifying eyes at risk of VF progression in glaucoma patients.

Table of Contents Statement:

Lower macular superficial vessel density but not deep vessel density is associated with past glaucomatous visual field progression.

Keywords

optical coherence tomography angiography; macula; visual field progression; glaucoma

Introduction

Glaucoma is a progressive optic neuropathy resulting from damage to the retinal ganglion cells with characteristic morphologic changes of the optic nerve head (ONH).[1, 2] Glaucomatous structural damage will eventually lead to retinal nerve fiber loss and visual field (VF) defects that may considerably impact a patient's quality of life.[3, 4] It has been shown that higher intraocular pressure (IOP),[4-10] older age,[4-6, 8] decreased ocular perfusion pressure,[4, 8, 11] presence of optic disc hemorrhage,[4, 10, 12-14] thinner central corneas,[4-6, 8, 9] focal lamina cribrosa defect[4, 15] and β-zone peripapillary atrophy[4, 16, 17] are risk factors associated with VF progression.

While not having a clear role as either a causal factor or an epiphenomenon in the pathophysiology of glaucoma development and progression, the alteration and impairment of ocular circulation in glaucoma has been well documented.[18-22] Color doppler imaging has showed alterations of ocular circulation in glaucoma. Plange and colleagues found that glaucoma patients with asymmetric VF loss exhibit asymmetric flow velocities of the central retinal artery and the ophthalmic artery with reduced flow velocity in the eye with more severe glaucomatous damage compared to the contralateral eye.[23] Others demonstrated an association between ocular vascular metrics with VF progression in eyes with glaucoma.[24-27] In addition, a recent study showed that laser speckle flowgraphy parameters that have been proposed to represent ocular blood flow might help clinicians to predict the severity of VF defect and VF progression in glaucoma patients.[28] Recently, the advent of optical coherence tomography angiography (OCTA) technology has provided a unique opportunity for direct quantitative evaluation of retinal microvasculature at the ONH and macula in a non-invasive manner.[29, 30] Numerous studies have demonstrated the value of OCTA for the diagnosis of glaucoma, and also to assess the utility of its measured microvascular parameters in the assessment of glaucoma progression.[31-36]

OCTA microvascular assessments have been shown previously to discriminate between healthy, glaucoma suspect, and glaucoma patients.[31, 37-40] OCTA was also been shown to detect microvascular attenuation in the perimetrically intact fellow eyes of glaucoma patients[41] and perimetrically intact hemiretinea of glaucomatous eye with hemifield VF defect.[42] Moreover, some recent studies in glaucoma patients suggest correlations between localized VF defects and OCTA microvascular measurements that may be superior to those

of OCT measures. Wong and colleagues[43] found that focal microvascular measurements show significant associations with VF total deviation in a larger proportion of 24-2 VF test grid locations (at 34 VF test locations [66.7% of 24-2 VF]) compared to focal retinal nerve fiber layer (RNFL) thickness (16 VF test locations [31.4% of 24-2 VF]). Moreover, the same study showed that central 10° structure-function relationship reaches to an apparent plateau for RNFL thickness but not for microvascular measurements that suggests a wider dynamic range of association with visual function for focal microvasculature compared to focal RNFL thickness in glaucoma patients. In addition, Kamalipour et al. reported regional structure-function correlations between OCTA measurements and VF indices in all regions of early glaucoma eyes with some regions showing better structure-function association for OCTA measurements compared to RNFL thickness.[40] However, there have been discrepant reports of OCTA measured microvascular dropout at different macular layers in glaucoma eyes. While some studies claimed that glaucomatous microvascular attenuation is detectable at both superficial and deep macular layers,[44-46] other findings suggested the preferential involvement of superficial macular microvasculature in glaucoma.[47, 48]

The utility of OCTA measurements for glaucoma risk-assessment and progression also has been investigated.[33, 49] OCTA measured retinal[33] and choroidal[49] microvascular dropout at the ONH area are associated with faster rates of RNFL thinning. However, the association of OCTA microvascular dropout with the probability and rates of VF progression has been largely unaddressed. The purpose of this study was to evaluate the association of OCTA measured multilayer macular vessel density with the probability and rate of past VF progression and to assess the potential utility of these measurements in the risk-assessment of VF progression in glaucoma patients.

Methods

This was a retrospective, observational cohort study including primary open angle glaucoma patients enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS) who underwent serial 24-2 VF tests and macula OCTA imaging at the end of the follow up. All the methods adhered to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. The institutional review boards at the University of California, San Diego, approved the methods. The study protocols were explained to all participants and written informed consent was obtained.

DIGS protocol and eligibility criteria have been described in detail previously.[50] In brief, all participants underwent a comprehensive ophthalmological examination, including assessment of best corrected visual acuity (BCVA), slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, ultrasound pachymetry, dilated fundus examination, simultaneous stereophotography of the optic disc and visual field testing (Humphrey Field Analyzer; 24-2 Swedish interactive threshold algorithm standard; Carl Zeiss Meditec, Jena, Germany). All participants also completed Spectral-domain OCT (SD-OCT) [Avanti; Optovue, Inc.], and OCTA (Angiovue; Optovue, Inc., Fremont, CA, USA) imaging of the macula.

Systemic measurements included systolic and diastolic blood pressure and pulse rate measured at the height of the heart with an Omron Automatic blood pressure instrument (model BP791IT; Omron Healthcare, Inc., Lake Forest, IL). Mean arterial pressure was calculated as 1/3 systolic blood pressure + 2/3 diastolic blood pressure.

Overall inclusion criteria at study entry were age of more than 18 years, open angles on gonioscopy, and BCVA ≥ 20/40. Participants included in this study were required to have at least five 24-2 VF tests over a minimum of 3 years of follow up. In addition, each participant was required to have a good quality macula OCTA image within 6-months of the last VF test. Participants with a history of intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), axial length of 27 mm or more, coexisting retinal pathologies, non-glaucomatous optic neuropathy, uveitis, or ocular trauma were excluded from the study. Participants were also excluded if they had a diagnosis of Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke. Participants with systemic hypertension and diabetes mellitus were included unless they were diagnosed with diabetic or hypertensive retinopathy.

Glaucoma eyes were defined as those having repeatable (on at least two consecutive tests) and reliable glaucomatous VF damage defined as a glaucoma hemifield test (GHT) result outside normal limits or a pattern standard deviation (PSD) outside 95% normal limits.[32, 41]

Visual Field Testing

Visual field tests were performed using Swedish Interactive Threshold Algorithm (SITA) standard 24-2 threshold test (Humphrey Field Analyzer 750 II-I, Carl Zeiss Meditec, Inc., Dublin, CA, USA). The quality of visual field tests was reviewed by the Visual Field Assessment Center (VisFACT) staff at UCSD. Only reliable tests (≤ 33% fixation losses and false negative errors, and ≤ 33% false positive errors) were included in the analysis. Visual fields with the following artifacts were also excluded: evidence of rim and eyelid artifacts, inattention or fatigue effects, or visual field damage caused by a disease other than glaucoma. Both trend-based and event-based criteria of VF progression were used to identify factors that are associated with increased probability and/or rate of VF progression. In the trend-based analysis, the rate of VF progression was defined as the slope of 24-2 mean deviation (MD) over time. For the event-based analysis, pointwise linear regression (PLR) of threshold sensitivities over time was carried out.[51, 52] The definition of VF progression required a rate of threshold sensitivity change of −1 dB/year with a P value < 0.01 detected at 3 or more locations.[51, 53-56] Past VF progression was determined using VF tests that occurred prior to and including the visit within 6-months of OCTA image capture.

OCT Angiography and Spectral-Domain OCT

OCTA and Spectral-domain OCT imaging of the macula were performed by the AngioVue imaging system (Optovue, Inc., Fremont, CA, USA, Version 2017,1,0,151). Using this platform, OCTA and Spectral-domain OCT images are obtained from the same volumetric scans allowing precise automated registration of OCTA and OCT images and providing quantified metrics for the analysis of different layers of interest.

For this report, we analyzed vessel density at the superficial and deep macular slabs obtained from 6×6-mm^2 OCTA images comprised of 304×304 A-scans centered on the fovea. Angiovue split-spectrum amplitude-decorrelation angiography was used to capture the dynamic motion of the red blood cells and provide a high-resolution 3-dimensional visualization of perfused retinal microvasculature. Vessel density was calculated as the percent area occupied by flowing blood vessels in the selected region. The retinal layers of each scan were segmented automatically by the AngioVue software to visualize the superficial retinal capillary and deep retinal capillary plexuses, as follows. Superficial vessel density was calculated in a macular slab extending from the internal limiting membrane (ILM) to 10 μm offset below the inner plexiform layer (IPL). Deep vessel density was calculated in a macular slab extending from 10 μm offset below the IPL to 10 μm offset above the outer plexiform layer (OPL).

For this study, superficial vessel density (SVD) and deep vessel density (DVD) were derived from the entire area of 6×6-mm^2 images. Similarly, hemifield measurements were obtained using the entire corresponding hemifield in each image. The macula cube ganglion cell complex (GCC) thickness was calculated using the same volumetric scans as those of OCTA images. GCC thickness of the whole image as well as the corresponding hemifield measurements were included in the analyses.

Only good-quality images were included in the analysis. Image quality review was completed on all OCTA and OCT images processed with standard AngioVue software (version 2017.1.0.151) according to a standard protocol established by the Imaging Data Evaluation and Analysis (IDEA) Reading Center. Expert reviewers evaluated all of the images and excluded those with poor quality, defined as images with any of the following: 1) low scan quality with quality index (QI) of less than 4, (2) poor clarity, (3) residual motion artifacts visible as irregular vessel pattern or disc boundary on the en-face angiogram, (4) image cropping or local weak signal resulting from vitreous opacity, (5) signal devoid area as a result of blink, (6) poor centration on the fovea and (7) the presence of segmentation errors that could not be corrected.[57]

Statistical Analysis

Continuous and categorical data are presented as mean (95% confidence interval [CI]) and counts (%). Linear mixed effects model with random intercept to adjust for inter-eye correlations was used to compare characteristics between eyes with and those without past event-based VF progression. Univariable and multivariable mixed effects logistic regression models are used to determine the association between different characteristics and the likelihood of a PLR VF progression event at the end of the follow up. Diagnostic accuracy of macula SVD, DVD (age, and signal strength index [SSI] adjusted) and GCC thickness (age adjusted) to differentiate eyes with from those without prior event-based VF progression was evaluated using receiver operating characteristic (ROC) curves. To evaluate the association of macular OCTA parameters with past rates of VF MD change, linear mixed effects model with random intercepts and random slopes was used to account for the fact that different eyes can have different rates of VF progression over time, while adjusting for correlations between both eyes of the same individual.[58-60] Interaction terms between

time and the putative predictors were included in the model to explore whether there is a significant effect of the predictor on changes of the outcome variable over time. Univariable models were constructed using only one predictor along with its interaction with time. To evaluate the association of macular vessel density parameters with the prior rate of VF change while adjusting for potentially confounding factors, clinically independent variables that were associated with the rate of change in VF MD at P < 0.10 in the univariable analysis were included in the multivariable analysis, along with other predictors consistently reported as having a significant association with glaucoma progression.[61-63] OCTA SSI was forced in the final multivariable models of macular OCTA parameters to adjust for the variability of vessel density measurements as a result of differences in the OCTA signal. Because measurements of macular SVD and GCC thickness were correlated, each of these variables were included in separate multivariable models to avoid collinearity. Statistical analysis was performed using Stata software version 15.1 (StataCorp, College Station, TX). P-value < 0.05 was considered as statistically significant.

Results

A total of 208 eyes of 147 glaucoma patients were included in this retrospective cohort study. Fifty-two (25%) eyes showed VF progression at the end of the follow-up. Demographic and ocular characteristics including gender, race, baseline age, axial length, average IOP during follow up, IOP at last follow up visit, baseline 24-2 MD, baseline 24-2 PSD, and baseline RNFL thickness were similar between eyes with and those without VF progression ($P > 0.05$ for all pairs). Eyes without VF progression had a similar average follow-up duration (6.9 years) compared to those with VF progression (7.1 years) [$P = 0.267$]. At the end of the VF follow-up, eyes with VF progression had worse 24-2 MD ($P < 0.001$) and higher 24-2 PSD ($P < 0.001$) compared to eyes without VF progression. Macular SVD, DVD, and GCC thickness were significantly lower in eyes with VF progression compared to those without VF progression (37.1% versus 40.5% for SVD [$P < 0.001$], 41.7% versus 44.6% for DVD [$P = 0.004$], and 76.7 μm versus 79.8 μm for GCC thickness [$P = 0.030$], respectively) [Table 1].

In the univariable analysis, macular SVD (OR = 1.24 per 1% lower, 95% CI: 1.04, 1.47) was significantly associated with an increased likelihood of event-based VF progression while such an association was not observed for macular DVD ($P = 0.251$) after adjustment for signal strength index (SSI). No statistically significant association was observed for other demographic and ocular characteristics, including age at the last visit, gender, race, axial length, central corneal thickness (CCT), history of diabetes, history of hypertension, mean arterial pressure, IOP at the last visit, mean IOP during follow up, baseline 24-2 MD, and 24-2 PSD, macular GCC thickness, and follow up duration ($P > 0.05$ for all associations). In the multivariable analysis, SVD, and GCC thickness were included in two separate models. Macular SVD remained significantly associated with an increased likelihood of event-based VF progression after adjustment for age, race, mean arterial pressure, mean IOP during follow up, baseline 24-2 MD, and signal strength index (OR = 1.28 per 1% lower, 95% CI: 1.02, 1.59). No statistically significant association with the likelihood of event-based VF progression was observed for macular GCC thickness ($P = 0.159$) (Table 2). Figure 1 illustrates the classification accuracy for SVD, DVD (age and SSI adjusted) [A] (AUROC =

0.62 [95% CI: 0.53, 0.71] and 0.54 [95% CI: 0.44, 0.64], respectively), and GCC thickness (age-adjusted) [B] (AUROC = 0.58 [95% CI: 0.48, 0.67]) in detecting event-based past VF progression.

Table 3 shows the results of the trend-based analysis using univariable and multivariable linear mixed effects models to evaluate the association of patient and ocular characteristics with the rate of VF progression. In the univariable analysis, baseline age (−0.09 dB/year per 10 years older; 95% CI: −0.14, −0.04), axial length (0.09 dB/year per 1 mm longer; 95% CI: 0.04, 0.15), SVD (SSI adjusted) (−0.02 dB/year per 1% lower; 95% CI: −0.03, −0.01), and GCC thickness (−0.01 dB/year per 1μm thinner; 95% CI: −0.01, 00.00) were significantly associated with the rate of VF progression. No statistically significant association between macular DVD and the rate of VF progression was observed after adjustment for SSI (P = 0.211). Two separate multivariable models were implemented, including SVD, and GCC thickness one at a time. In the SVD model, axial length (0.11 dB/year per 1 mm longer; 95% CI: 0.05, 0.17), mean IOP during follow up (−0.02 dB/year per 1 mmHg higher; 95% CI: −0.04, −0.01), and SVD (−0.03 dB/year per 1% lower; 95% CI: −0.04, −0.01) were significantly associated with the rate of VF progression. Baseline age (−0.08 dB/year per 10 years older; 95% CI: −0.14, −0.02), and axial length (0.09 dB/year per 1 mm longer; 95% CI: 0.02, 0.15) were significantly associated with the rate of VF progression in the GCC model while mean IOP during follow up (P = 0.052) and GCC thickness (P = 0.067) were close to the significance threshold. Separate analyses were done including PSD at the end of follow-up as a surrogate measure of disease severity in the multivariable models. The results revealed a statistically significant association for macular SVD with the rate of VF progression (−0.02 dB/year per 1% lower; P = 0.006), but not for macular GCC thickness (P = 0.637) [Supplemental Table 1].

Separate analyses revealed statistically significant associations between hemifield SVD and the rate of the corresponding hemifield VF progression in both hemifields and also between inferior hemifield GCC thickness and the rate of VF progression in the superior hemifield after adjustment for other demographic and ocular characteristics (P < 0.05 for all associations) [Supplemental Tables 1 and 2]. Notably, no statistically significant associations between DVD and the rate of VF progression were observed at the hemifield level (P > 0.05 for all associations) [Supplemental Tables 2 and 3].

Figure 2 shows a representative example of an eye with glaucomatous damage to the inferonasal side of the VF at the beginning of the follow up (initial 24-2 MD = −1.6 dB) and progression in an arcuate fashion extending to the inferotemporal side at the end of the study follow up (last 24-2 MD = −7.82 dB) [A]. Optical coherence tomography angiography images of the same patient at the end of the VF follow-up show a noticeable dropout in the superotemporal side of the macular microvasculature at the superficial layer (B1 and B2), while such a dropout is less pronounced on the en-face angiogram of the deep layer (C1, and C2).

Discussion

The results of the present study show the utility of macular OCTA imaging to serve as an indicator past VF progression based on a cohort of primary open angle glaucoma patients with approximately seven years of follow-up. Glaucomatous VF progression was associated with microvascular attenuation in the superficial, but not the deep macular layer. Whether VF progression is defined using trend-based or event-based methods did not affect the association between the location of microvascular dropout and the likelihood of VF progression. These observations support the preferential involvement of superficial macular microvasculature in the process of glaucomatous VF progression. These findings suggest the potential value of OCTA-derived macular measurements in the risk assessment of glaucoma patients to identify those patients at high risk of progression.

Specifically, we found that lower macular SVD is associated with an increase in the rate and the probability of past VF progression. Similar associations were observed irrespective of the method used to define VF progression. Participants of this study were included from a wide range of glaucoma severity that ranged from the mild perimetric stage up to the advanced disease. In addition, there were no statistically significant differences in the baseline demographic and ocular characteristics including age, gender, race, axial length, CCT and glaucoma severity between those with and without VF progression.

Most previous studies on the utility of macular microvascular imaging in glaucoma have been cross-sectional. Their results show measurable dropout in the superficial macular layer and suggest this parameter to be able to discriminate between healthy, glaucoma suspect and glaucoma patients.[38, 41, 42, 44-48] Also, macular SVD was shown to be correlated with other structural (including RNFL thickness,[44] Bruch's membrane opening-minimum rim width[44] and GCC thickness[46]) and functional measurements[38] known to be affected in glaucoma. Although progressive change in macular SVD has been documented with a mean of 2.6 years of follow-up of healthy, glaucoma suspect and glaucoma patients,[35] currently available studies on the usefulness of SVD in the evaluation of glaucoma progression are limited. A recent DIGS report showed that lower baseline macular SVD was associated with faster rates of retinal nerve fiber layer progression in mild to moderate glaucoma patients on an average follow-up duration of two years.[33] The current study also showed that lower SVD was associated with faster VF progression, albeit VF progression was evaluated retrospectively. The association between the rate of VF progression and macular GCC thickness was borderline but not significant. Although some studies found associations between ganglion cell-inner plexiform layer thickness and glaucoma progression, global GCC thickness was shown not to be associated with VF progression in a previous study.[64] However, the same study revealed that focal GCC thinning is associated with VF progression and might be a better surrogate for identifying glaucomatous eyes that are at risk of VF progression.[64] The findings of the present study show that macular SVD, and not GCC thickness, is associated with prior VF progression even after controlling for current disease severity. This suggests that macular SVD shows promise as a surrogate measure for the assessment of eyes at risk of glaucomatous VF progression. As there are a limited number of cases in different disease stages in this longitudinal cohort, future studies are

needed to confirm that long term measurements of macular SVD in glaucoma patients enhance the efficacy of prognostic models of glaucoma progression.

In the present study, macular DVD was not associated with the likelihood or rate of VF progression. This finding adds to the existing evidence showing that glaucoma preferentially affects perfusion in the superficial layers of the macular compared with the deeper plexuses.[47, 48] Jeon and associates studied 104 glaucoma patients over an average follow-up of around nine years and found that macular DVD, and not SVD, was associated with prior VF progression.[65] However, several possible reasons may account for the observed differences. First, the authors of that study used a different OCTA instrument (DRI OCT Triton; Topcon) with a different macular segmentation protocol. Inconsistent determination of boundaries of macular layers might have influenced the observed outcome. Second, the authors did not use a systematic algorithm that would adjust for projection artifacts, the aberrant influence of SVD on the deeper layers. Last and most importantly, it was not clear from the study protocol if the timing of OCTA image acquisition was consistent for all study participants and when exactly it occurred during the study follow-up. Most previous studies showing macular DVD attenuation in glaucoma patients did not consider the potential influence of projection artifacts on DVD measurements.[44-46] Takusagawa and associates demonstrated that the implementation of the projection-resolved algorithm in OCTA images' analysis removes the correlation between DVD and glaucoma severity.[48] This finding was later confirmed in a recent study showing that only the superficial, and not the deep, microvascular attenuation in the macula demonstrates diagnostic efficacy to discriminate between glaucoma and healthy eyes.[47]

In clinical practice, patients with faster rates of VF progression should be more intensively treated compared to those with a slower rate of functional decline. This is particularly important when considering the relationship between prior rates of VF deterioration and the trajectory of future VF progression. Moreover, glaucoma patients who have progressed faster in the past are more likely to show a faster rate of progression in the future if no apparent modifying interventions are made.[66] In this regard, Bengtsson and colleagues conducted a longitudinal study of VF progression in glaucoma patients with a mean follow-up duration of 8 years. They showed that final global indices of VF in an entire sequence of 10 or more VF tests can be estimated using the information on rate of VF progression obtained in the first half of the study follow-up in ~70% of the patients.[67] Considering the association of lower macular SVD with faster prior rates of VF progression found in this study, macular SVD has the potential to be a useful indicator for the risk assessment of future VF progression in glaucoma patients. This should be particularly relevant to settings where limited historical data is available on disease progression.

Our study is not without limitations. Visual field testing is variable so that longer follow-up duration is needed to detect progression compared to OCT. Since OCTA is a relatively new imaging technology, we did not have sufficient follow-up duration to assess the effect of baseline macular OCTA parameters on future VF progression. The influence of OCTA parameters on subsequent rates of VF progression will be of great interest once enough follow-up data is available. Second, the sample size included in this study was relatively small. Third, it was shown that artifacts with a potential influence on OCTA parameters are

frequent.[57] To avoid this influence, all images were carefully reviewed by expert reviewers according to previously published robust systematic criteria[57] before the measurements were included in the analysis. Fourth, while the acquired measurements of SVD by OCTA are reliable,[68] analysis of DVD is more prone to projection artifacts, which may not be completely removed by projection artifacts removal algorithm.[47] Thus, although minimal, the measured DVD might still possess greater variability than that of SVD. Finally, different definitions of VF progression are not necessarily in agreement in terms of follow-up outcomes.[69] To minimize the dependence of the observed associations on the methods of defining VF progression, both event-based and trend-based methods were used separately in the analysis, and the agreement of the results was verified.

In conclusion, the results of this retrospective cohort study indicate that lower macular superficial vessel density, and not deeper macular vessel density, is associated with a higher probability of past VF progression. These data are particularly important as glaucoma patients who have progressed faster in the past are more likely to show a faster rate of progression in the future in the absence of additional IOP lowering.[66] Therefore, macular OCTA imaging in glaucoma patients shows promise in identifying eyes at a higher risk of VF progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

Alireza Kamalipour, MD, MPH, is a post-doctoral research fellow at UCSD, department of Ophthalmology. He received his medical degree from Shiraz University of Medical Sciences and was a former silver medal recipient at the 42nd. International Physics Olympiad (IPhO). His current research focuses on glaucoma and applications of novel imaging techniques and artificial intelligence. His career goals include training in ophthalmology in an academic setting with a long-term plan of becoming a successful clinician-scientist.

Abbreviations and Acronyms:

AUROC	area under the receiver operating characteristic curve
BCVA	best corrected visual acuity
BP	blood pressure
CCT	central corneal thickness
CI	confidence interval
D	diopter
DIGS	Diagnostic Innovations in Glaucoma Study
DVD	deep vessel density
GCC	ganglion cell complex
GHT	glaucoma hemifield test
IDEA	Imaging Data Evaluation and Analysis
ILM	internal limiting membrane
IOP	intraocular pressure
IPL	inner plexiform layer
MD	mean deviation
OCTA	optical coherence tomography angiography
ONH	optic nerve head
OPL	outer plexiform layer
PLR	pointwise linear regression
PSD	pattern standard deviation
QI	quality index
RNFL	retinal nerve fiber layer
SD-OCT	spectral-domain OCT
SITA	Swedish Interactive Threshold Algorithm
SSI	signal strength index
SVD	superficial vessel density
VD	vessel density
VF	visual field

VisFACT Visual Field Assessment Center

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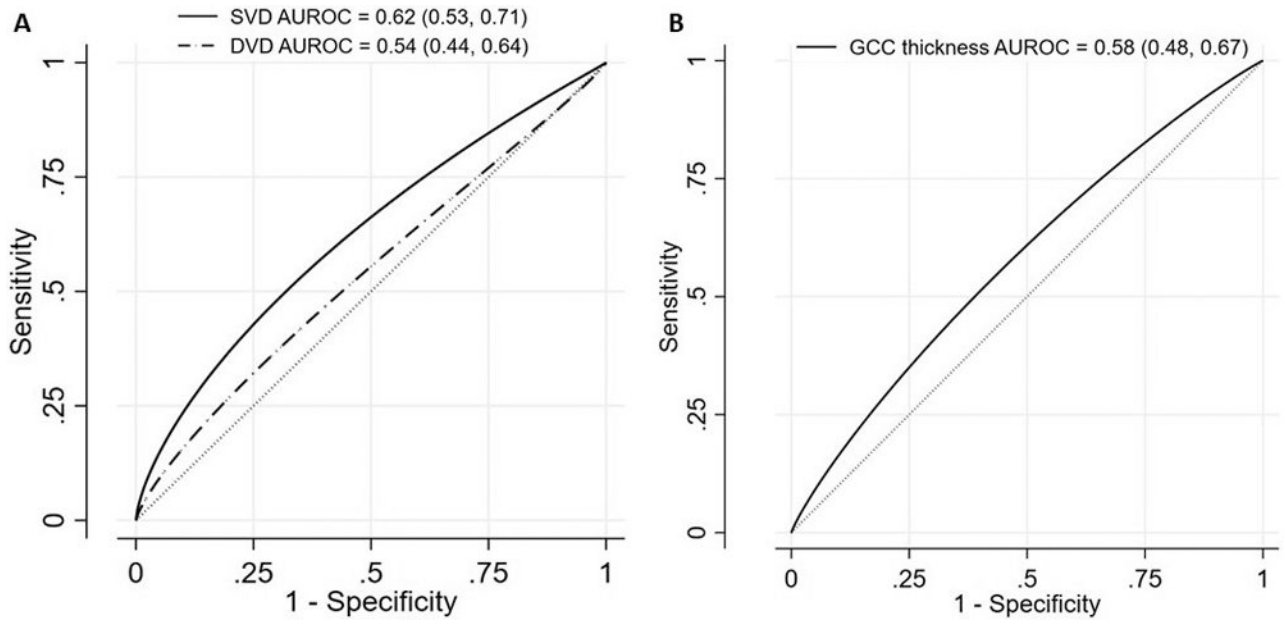

Figure 1.

Classification performance of superficial vessel density (SVD) and deep vessel density (DVD) [A], and ganglion cell complex (GCC) thickness (B) in the discrimination of eyes with and without visual field progression defined by pointwise linear regression event-based criterion. The classification accuracy is represented as the area under the receiver operating characteristic curve (AUROC) [95% CI].

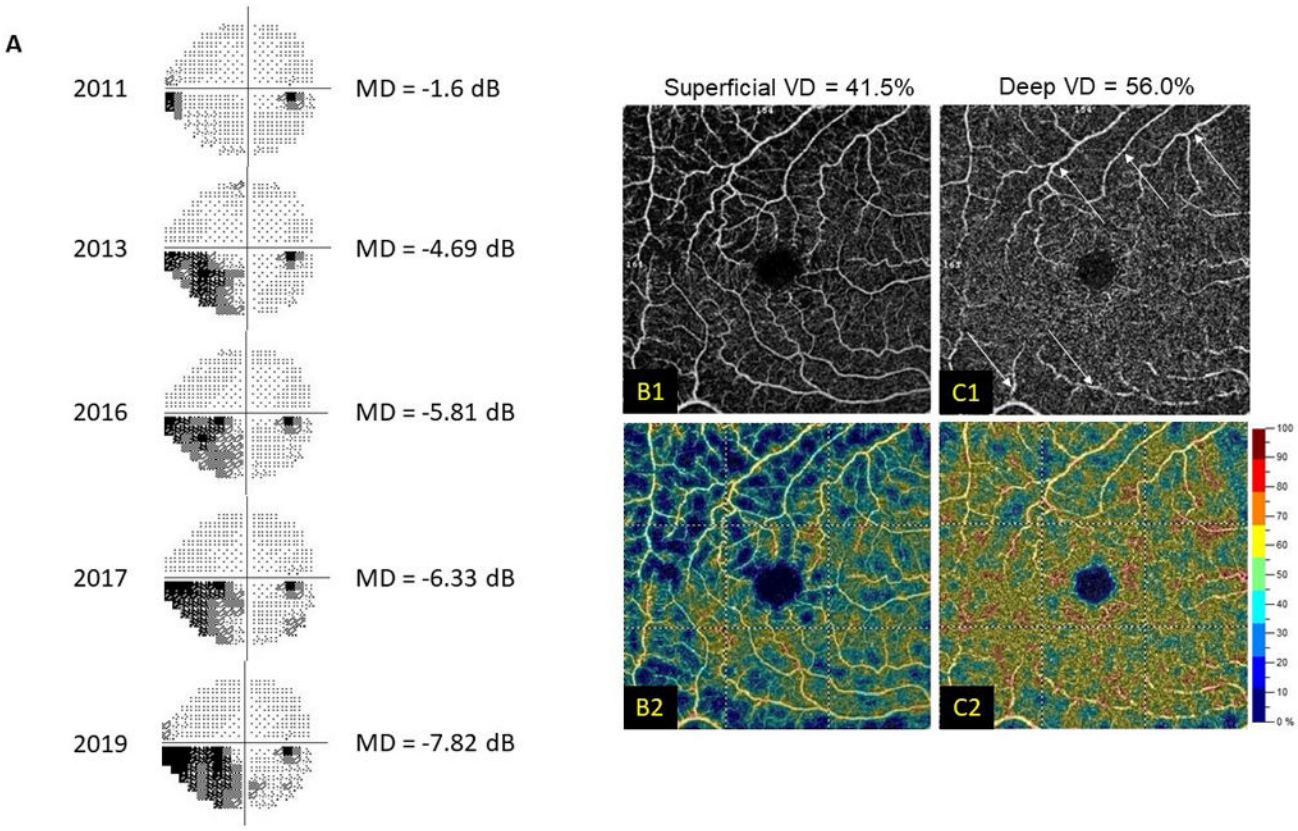

Figure 2.

"A" shows series of 24-2 visual field tests and their corresponding mean deviation (MD) values for one of the study participants with visual field progression (based on pointwise linear regression criterion) from 2011 to 2019. "B", and "C" shows en-face Optical Coherence Tomography Angiography (OCTA) images of the same participant at the end of the study follow-up. "B1" and "C1" show the actual enface OCTA images segmented at the superficial and the deep vascular layers, respectively. The respective vessel density (VD) measurements are shown on the top of each image. "B2" and "C2" show the corresponding color-coded heatmaps of the same en-face OCTA images. Note that, some degrees of residual projection artifacts are still visible in the deep vascular layer (as demarcated by arrows in "C1") even after the implementation of the projection-resolved algorithm.

Table 1.

Characteristics of the study population (147 patients, 208 eyes)

Variables	Non progressors	Progressors	*P*-value*
Patient level characteristics	121 (82.3%)	26 (17.7 %)	
Gender			
Female	56 (46.3%)	14 (53.8%)	0.522
Male	65 (53.7%)	12 (46.2%)	
Race	48/108	16/36	
African American	37 (30.6%)	8 (30.8%)	> 0.99
Non-African American	84 (69.4%)	18 (69.2%)	
History of diabetes			
Negative	96 (79.3%)	21 (80.8%)	> 0.99
Positive	25 (20.7%)	5 (19.2%)	
History of hypertension			
Negative	40 (33.1%)	13 (50.0%)	0.118
Positive	81 (66.9%)	13 (50.0%)	
Systolic BP (mmHg)	129.3 (125.7, 132.9)	129.4 (120.9, 137.9)	0.990
Diastolic BP (mmHg)	78.7 (76.5, 81.0)	76.2 (71.1, 81.2)	0.329
Mean arterial BP (mmHg)	95.3 (92.8, 97.7)	94.2 (88.9, 99.6)	0.724
Eye level characteristics	156 (75.0%)	52 (25.0%)	
Baseline age (years)	66.8 (65.2, 68.4)	70.1 (67.7, 72.5)	0.136
Age at the last visit (years)	73.8 (72.1, 75.4)	77.2 (74.7, 79.7)	0.128
Axial length (mm)	24.2 (24.0, 24.3)	23.9 (23.6, 24.2)	0.076
CCT (μm)	532.3 (522.5, 542.2)	536.3 (514.9, 557.8)	0.437
Mean IOP during follow-up (mmHg)	14.03 (13.40, 14.66)	14.04 (13.07, 15.00)	0.735
IOP at the last visit (mmHg)	14.31 (13.42, 15.20)	14.47 (12.92, 16.02)	0.782
VF Measurements			
Baseline MD (dB)	−4.25 (−5.17, −3.34)	−5.00 (−6.45, −3.55)	0.401
Baseline PSD (dB)	4.78 (4.18, 5.38)	5.76 (4.68, 6.84)	0.090
Last MD (dB)	−4.85 (−5.76, −3.95)	−10.47 (−12.11, −8.83)	**< 0.001**
Last PSD (dB)	5.13 (4.55, 5.71)	8.72 (7.86, 9.58)	**< 0.001**
Baseline RNFL thickness (μm)	75.6 (73.2, 78.1)	72.5 (67.9, 77.1)	0.124
SVD (%)	40.5 (39.6, 41.3)	37.1 (35.8, 38.5)	**< 0.001**
DVD (%)	44.6 (43.6, 45.6)	41.7 (40.0, 43.4)	**0.004**
GCC thickness (μm)	79.8 (78.0, 81.6)	76.7 (74.0, 79.3)	**0.030**
Signal strength index (%)	60.5 (59.3, 61.6)	57.2 (55.4, 59.1)	**0.006**
Follow up duration (years)	6.9 (6.7, 7.1)	7.1 (6.7, 7.4)	0.267

VF: visual field, BP: blood pressure, CCT: central corneal thickness, IOP: intraocular pressure, MD: mean deviation, PSD: pattern standard deviation, SVD: superficial vascular density, DVD: deep vascular density, GCC: ganglion cell complex.

* Linear mixed effects model was used to compare the characteristics between the groups. *P*-value < 0.05 was considered as statistically significant and is shown in bold.

Table 2.

Patient and ocular characteristics associated with increased likelihood of event-based visual field progression

Variables	Univariable Model		Multivariable Model SVD		Multivariable Model GCC thickness	
	Odds ratio (95 % CI)	*P*-value*	Odds ratio (95 % CI)	*P*-value*	Odds ratio (95 % CI)	*P*-value*
Age at last VF test, per 10 years older	1.80 (0.98, 3.32)	0.059	1.25 (0.59, 2.65)	0.567	1.79 (0.93, 3.47)	0.082
Gender: female/male	1.20 (0.41, 3.49)	0.742				
Race: African American/ Non-African American	1.10 (0.34, 3.53)	0.872	2.05 (0.43, 9.67)	0.365	1.44 (0.40, 5.20)	0.578
Axial length, per 1mm longer	0.61 (0.33, 1.11)	0.104				
CCT, per 10μm thicker	1.06 (0.89, 1.26)	0.535				
History of diabetes	1.20 (0.32, 4.45)	0.787				
History of hypertension	0.60 (0.20, 1.80)	0.360				
Mean arterial BP, per 1 mmHg higher	0.99 (0.95, 1.03)	0.565	0.98 (0.93, 1.03)	0.452		
IOP at the time of last visit, per 1 mmHg higher	1.02 (0.92, 1.13)	0.696				
Mean IOP, per 1 mmHg higher	0.99 (0.86, 1.15)	0.934	1.07 (0.87, 1.31)	0.528	1.02 (0.85, 1.21)	0.855
Baseline MD, per 1 dB worse	1.04 (0.95, 1.13)	0.397	0.93 (0.80, 1.07)	0.310	1.00 (0.88, 1.12)	0.944
Baseline PSD, per 1 dB higher	1.11 (0.97, 1.27)	0.114				
SVD‡, per 1% lower	1.24 (1.04, 1.47)	**0.016**	1.28 (1.02, 1.59)	**0.030**		
DVD‡, per 1% lower	1.08 (0.95, 1.24)	0.251				
GCC thickness, per 1μm thinner	1.06 (1.00, 1.12)	0.065			1.05 (0.98, 1.12)	0.159
Follow up duration, per 1 year longer	1.23 (0.77, 1.97)	0.388				

VF: visual field, CCT: central corneal thickness, BP: blood pressure, IOP: intraocular pressure, MD: mean deviation, PSD: pattern standard deviation, SVD: superficial vascular density, DVD: deep vascular density, GCC: ganglion cell complex.

*Linear mixed effects model was used to evaluate the associations of different characteristics with the likelihood of Event-based VF progression. *P*-value < 0.05 was considered as statistically significant and is shown in bold.

‡vessel density values were adjusted for signal strength index.

Table 3.

Patient and ocular characteristics associated with faster rate of visual field progression

Variables	Univariable Model		Multivariable Model SVD		Multivariable Model GCC	
	Coefficient (95 % CI)	*P*-value*	Coefficient (95 % CI)	*P*-value*	Coefficient (95 % CI)	*P*-value*
Age at first VF test, per 10 years older	−0.09 (−0.14, −0.04)	**0.001**	−0.02 (−0.09, 0.04)	0.446	−0.08 (−0.14, −0.02)	**0.011**
Gender: female/male	0.01 (−0.10, 0.12)	0.909				
Race: African American/ Non-African American	0.03 (−0.09, 0.15)	0.645	0.01 (−0.11, 0.13)	0.913	0.04 (−0.08, 0.16)	0.531
Axial length, per 1mm longer	0.09 (0.04, 0.15)	**0.001**	0.11 (0.05, 0.17)	< **0.001**	0.09 (0.02, 0.15)	**0.008**
CCT, per 10μm thicker	0.00 (−0.02, 0.01)	0.884				
History of diabetes	0.01 (−0.12, 0.15)	0.851				
History of hypertension	−0.02 (−0.13, 0.10)	0.796				
Mean arterial BP, per 10 mmHg higher	0.01 (−0.03, 0.05)	0.697	0.02 (−0.03, 0.06)	0.414		
Mean IOP, per 1 mmHg higher	−0.01 (−0.03, 0.00)	0.101	−0.02 (−0.04, −0.01)	**0.005**	−0.02 (−0.04, 0.00)	0.052
Baseline MD, per 1 dB worse	0.00 (−0.01, 0.01)	0.741	0.01 (−0.01, 0.02)	0.395	0.00 (−0.02, 0.01)	0.662
Baseline PSD, per 1 dB higher	0.00 (−0.02, 0.01)	0.772				
SVD‡, per 1% lower	−0.02 (−0.03, 0.00)	**0.017**	−0.03 (−0.04, −0.01)	**0.002**		
DVD‡, per 1% lower	−0.01 (−0.02, 0.00)	0.211				
GCC thickness, per 1μm thinner	−0.01 (−0.01, 0.00)	**0.012**			−0.01 (−0.01, 0.00)	0.067
Follow up duration, per 1 year longer	0.00 (−0.05, 0.05)	0.898				

VF: visual field, CCT: central corneal thickness, BP: blood pressure, IOP: intraocular pressure, MD: mean deviation, PSD: pattern standard deviation, SVD: superficial vascular density, DVD: deep vascular density, GCC: ganglion cell complex.

*Linear mixed effects model was used to evaluate the associations of different characteristics with the rate of VF progression. *P*-value < 0.05 was considered as statistically significant and is shown in bold.

‡vessel density values were adjusted for signal strength index.