Original Article

Optical Coherence Tomography Angiography Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes

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Abstract

Purpose: To evaluate and compare optical coherence tomography angiography (OCTA) retinal vasculature measurements in healthy, glaucoma suspect (GS), and glaucoma patients.

Methods: One hundred fourteen eyes with good quality OCTA pictures were included from 38 healthy, 38 GS, 38 and primary open-angle glaucoma (POAG) participants. The information on retinal vasculature was summarized as a vessel density map and as vessel density (%), which is the fraction of the flowing vessel area over the total area examined. The superior, inferior, nasal, and temporal quadrants, as well as whole vessel density (wVD) and peripapillary vessel density (ppVD) data taken from the retinal nerve fiber layer, were studied. Global indices of the visual field were correlated with vessel density measurement.

Results: Mean vessel density was significantly lower in POAG eyes compared with GSs and healthy eyes (wVD) 45.34% ± 6.64%, 50.06% ± 1.97% and 53.06% ± 2.12%, respectively ($P < 0.001$), and ppVD 47.42% ± 7.73%, 47.42% ± 7.73% and 56.074% ± 2.71%, respectively ($P < 0.001$). A linear relationship between vessel density (wVD and ppVD) and global indices of the visual field (mean deviation [MD] and pattern standard deviation [PSD]) shows a significant ($P < 0.001$) relation. R^2 is 0.35, 0.36, 0.36, and 0.33 for MD and wVD, PSD and wVD, PSD and ppVD, and MD and ppVD, respectively.

Conclusions: For distinguishing between healthy and glaucoma eyes, OCTA vessel density demonstrated near similar diagnostic accuracy to visual field tests. These findings imply that OCTA measurements reflect damage to tissues important in the pathogenesis of POAG.

Keywords: Glaucoma, Optical coherence tomography angiography, Vessel density, Visual field

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Introduction

Glaucoma is a progressive optic neuropathy characterized by structural and functional visual defects. While functional damage can be assessed by visual field testing, structural damage can be detected by thinning the retinal ganglion cell layer and retinal nerve fiber layer (RNFL) using optical coherence tomography (OCT).[1] Glaucoma is one of the leading causes of irreversible blindness. The incidence of glaucoma is increasing day by day, therefore, early detection of glaucoma and improved glaucoma diagnosis are critical.

The early detection of glaucoma is challenging. There have been numerous reports of disagreement between structural and functional evaluations, as in the Ocular Hypertension Treatment Study[2] and European Glaucoma Prevention Study[3] and both structural and functional assessments need to be considered.[4]

There are two main hypotheses, which are considered to be the pathogenesis of glaucoma. It has long been believed that higher intraocular pressure (IOP) causes mechanical force to be applied to the peripapillary nerve fibers, depressing the fibers and causing glaucomatous changes (mechanical

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hypothesis).[5] On the other hand, the vascular hypothesis states that perfusion is disturbed by excessive IOP. A growing body of data indicates that vascular dysfunction plays a role in the pathogenesis of glaucoma.[6,7]

To visualize vascular changes, the most commonly used angiographic techniques in clinical practice are fluorescein angiography (FA) or indocyanine green angiography (ICGA). Fluorescein is typically used to visualize the retinal vasculature, while ICGA is used to see the choroidal vasculature. While useful, they require intravenous dye injection, which is time-consuming and can have adverse side effects.[8,9]

To develop a no injection, dye-free method for visualizing ocular vasculature, many functional extensions of OCT have been explored. These techniques aim to contrast blood vessels from static tissue by assessing the change in the OCT signal caused by flowing blood cells. These intrinsic contrasts can be broadly classified as Doppler shift and speckle variance/decorrelation.[10] With optical coherence tomography angiography (OCTA), it is now possible to assess the blood flow at the optic nerve head (ONH) noninvasively and quantitatively. In 2012, Jia *et al.*[11] were the first to describe a measurement of reduced vessel density in glaucomatous eyes by OCTA.

This study utilizes OCTA algorithms to generate segmented retinal images (3–12 mm²) across four zones: superficial retinal plexus, deep retinal plexus, outer retina, and choriocapillaris, including the optic disc.[12] ONH blood flow is supplied by the central retinal artery for superficial layers and the posterior ciliary artery for deeper layers.[11] Unlike FA, OCTA offers high-resolution images of papillary and peripapillary microvasculature. The focus is on comparing retinal vasculature measurements in healthy, glaucoma suspect (GS), and glaucoma patients, emphasizing radial peripapillary capillaries in the RNFL.[13]

Vessel density measurement stands out as a promising diagnostic tool for glaucoma. Reduced vessel density serves as an effective indicator for both diagnosis and follow-up, offering valuable insights into the progression of glaucomatous damage. In addition, the early detection potential of vessel density underscores its significance in identifying glaucoma at its nascent stages, facilitating timely interventions to prevent irreversible vision loss. This research aims to succinctly explore the empirical evidence supporting the utility of vessel density in enhancing glaucoma assessment strategies.

Methods

The study employed a cross-sectional, prospective research design and utilized a quantitative research approach. The research was conducted in the outpatient department of Himalaya Eye Hospital with the study population consisting of patients visiting the hospital. The sample selection was based on the convenience sampling technique, and the sample size for the study was determined to be 114 eyes, comprising 38 glaucomatous eyes, 38 GS eyes, and 38 normal eyes.

Inclusion criteria for the study involved age requirements and willingness to participate. Different criteria were specified for healthy subjects, glaucomatous subjects, and GS subjects. Exclusion criteria included a history of intraocular surgery, retinal pathologies, uveitis, ocular trauma, and unreliable visual field or poor-quality OCTA images. Furthermore, individuals with diagnoses such as Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke were ineligible for participation were excluded. Conversely, participants with systemic hypertension and diabetes mellitus were included, except in cases, where they had been diagnosed with diabetic or hypertensive retinopathy.

Healthy individuals were identified as those with IOP below 21 mmHg and no history of elevated IOP; optic disc, neuroretinal rim, and RNFL appearing normal; and at least two reliably normal visual fields, characterized by a pattern standard deviation (PSD) within the 95% confidence limits and a glaucoma hemifield test (GHT) results within normal limits. Eyes were categorized as having glaucoma if they exhibited consistent glaucomatous visual field damage, defined as a GHT result outside normal limits and PSD outside the 95% normal limits. GSs were individuals with glaucomatous optic neuropathy or suspicious-looking optic discs, as determined through stereophotograph review by two experienced graders or individuals with ocular hypertension (IOP >21 mmHg) lacking evidence of consistent glaucomatous visual field damage. The diagnostic classification for each participant was based on the worst eye diagnosis.

Various tools were used for data collection, including distance and near visual acuity charts, retinoscope, tonometer, slit-lamp biomicroscope, 90 diopter lens, gonioscope, Humphrey visual field analyzer, and OCT. The validity and reliability of the study tools were ensured using instruments that are routinely employed in clinical settings as gold standards for diagnosing and managing diseases.

The data collection process involved subject selection and history, assessment of visual acuity, refraction, slit-lamp biomicroscopy, fundus examination, IOP measurement, gonioscopy evaluation, visual field evaluation, and OCTA.

During the OCTA, vessel density in the peripapillary RNFL of the ONH was analyzed for four different sectors as well as whole vessel density (wVD) and peripapillary vessel density (ppVD). The ONH scan was a 4.5 mm × 4.5 mm cube centered on the ONH using SD-OCT RTVue-100. According to the suggested threshold for satisfactory image quality on the AngioVue system, scans with an SQ score of 6 or higher are considered acceptable.[14] Scans meeting or exceeding this score were included in our analysis.

Ethical considerations were taken into account, with the project receiving approval from the institutional review board at Pokhara University and following the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Statistical analysis

The study involved assessing numerical data for normality using the Shapiro–Wilk test and utilizing descriptive statistics such as mean and standard deviation (SD) for normally distributed variables. Group comparisons were conducted using age-adjusted analysis of variance (ANOVA), followed by the Tukey–Kramer HSD *post hoc* test for further analysis. The statistical analysis of the data was performed using SPSS® (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The significance level was set at $P < 0.05$ to indicate statistical significance.

Results

A total of 114 eyes of 57 subjects were enrolled in the study, 25 were male and 32 were female. Among them, 9 (47.37%) were male and 10 (52.63%) were female in the primary open-angle glaucoma (POAG) group. In the GS group and normal control group, 8 (42.10%) were male and 11 (57.89%) were female [Table 1]. The mean ± SD best-corrected visual acuity was 0.11 ± 0.13 for POAG, 0.35 ± 0.71 for the GS, and 0.179 ± 0.53 for the normal control group.

IOP measurements revealed significant differences: 17.97 ± 4.9 mmHg for POAG, 14.79 ± 2.76 mmHg for GS, and 15.29 ± 2.4 mmHg for normal individuals. Significant differences were found between POAG and GS ($P < 0.001$) and between POAG and the normal control group ($P = 0.02$). However, IOP between GS and the normal control group was not statistically significant ($P = 0.78$). Central corneal thickness (CCT) measurements also showed significant differences: 498.55 ± 35.08 μm for POAG, 519.50 ± 25.92 μm for GS, and 529.5 ± 18.49 μm for the normal control group. Statistically significant differences were observed between POAG and GS ($P = 0.03$) and between POAG and the normal control group ($P < 0.001$). However, CCT between GS and the normal control group was not statistically significant ($P = 0.25$). The cup–disc ratio measurements exhibited significant differences: 0.71 ± 0.07 for POAG, 0.62 ± 0.62 for GS, and 0.24 ± 0.76 for the healthy control group. Statistically significant differences were found between POAG and GS ($P = 0.03$), POAG and the normal control group ($P < 0.001$), and GS and the normal control group ($P < 0.001$) [Table 2].

Table 1: Age- and gender-wise distribution (*n*=19)

	POAG	GS	Normal
Age			
Mean±SD	57.89±9.267	55.37±11.98	56±9.918
Range	40–80	40–80	40–80
Sex, *n* (%)			
Male	9 (47.37)	8 (42.10)	8 (42.10)
Female	10 (52.63)	11 (57.89)	11 (57.89)

POAG: Primary open-angle glaucoma, GS: Glaucoma suspect, SD: Standard deviation

The mean deviation (MD) measurement done by the Humphrey visual field analyzer was −12.39 ± 7.43 dB in the POAG group, −2.64 ± 1.50 dB in the GS, and −1.92 ± 1.13 dB in the normal control group. The MD was consistently higher in the POAG group than GS and control groups. The mean value of PSD measurement done by the Humphrey visual field analyzer was 7.87 ± 3.11 dB in the POAG group, 2.76 ± 1.45 dB in GS, and 2.37 ± 0.67 dB in the normal control group. The PSD was consistently higher in the POAG group than GS and normal control groups. The mean value of visual field index (VFI) measurement done by Humphrey visual field analyzer was 69.39% ± 23% in the POAG group, 96.13% ± 3.63% in GS, and 95.76% ± 8.29% in the normal control group. The VFI was consistently lower in the POAG group than GS and control groups [Table 2].

In our study, we performed one-way ANOVA tests to compare various vessel density measurements among three groups. In the superior quadrant, vessel density was 47.08 ± 10.73% in POAG, 53.39% ± 3.57% in GS, and 56.16% ± 3.42% in healthy individuals. The mean difference in superior vessel density between POAG and GS was 6.31% ($P < 0.001$), and between POAG and healthy individuals, it was 9.07% ($P < 0.001$). However, the difference in vessel density between GS and healthy individuals was 2.76% ($P = 0.186$) [Table 3].

Vessel density in the inferior quadrant was lower in POAG (45.96%) than in GS (54.74%) and healthy individuals (56.71%). Similar trends were observed in the nasal and temporal quadrants. Significant differences were found between POAG and GS and POAG and healthy individuals, but not between GS and healthy individuals.

wVD was lower in POAG (45.342%) compared to GS (50.068%) and healthy individuals (53.061%). Significant differences existed between POAG and GS, POAG and healthy individuals, and between GS and healthy individuals. ppVD showed a similar trend, with significant differences between POAG and GS and POAG and healthy individuals, but not between GS and healthy individuals. ONH vessel density does not adhere to the ISNT rule (inferior ≥ superior ≥ nasal ≥ temporal), as shown in Figure 1.

Linear regression analysis demonstrated significant associations between OCTA wVD and MD measurement of visual field ($P < 0.001$, $R^2 = 0.35$) as well as between wVD and PSD measurement of visual field ($P < 0.001$, $R^2 = 0.36$). Similarly, significant associations were found between OCTA ppVD and MD ($P < 0.001$, $R^2 = 0.32$) and between ppVD and PSD ($P < 0.001$, $R^2 = 0.36$). These associations suggest the clinical relevance of OCTA-derived vessel density measurements in glaucoma evaluation [Figures 2-5].

Discussion

The main finding of the current study about OCT angiography is the reduction of vessel density on optic discs in most of the sectors in glaucoma eyes as compared to GS and the[15] normal control group. Optic disc, wVD, and ppVD were also reduced

Table 2: Comparison of variables among study groups

	POAG	GS	Normal	*P*		
				POAG versus GS	POAG versus normal	GS versus normal
IOP	17.97±4.9	14.79±2.76	15.29±2.4	<0.001	0.02	0.78
CCT	498.55±35.08	519.50±25.92	529.50±18.49	0.03	<0.001	0.25
CD ratio	0.71±0.07	0.62±0.76	0.24±0.72	<0.001	<0.001	<0.001
VF						
MD	−12.39±7.43	−2.64±1.50	−1.29±1.14	<0.001	<0.001	<0.001
PSD	7.89±3.11	2.76±1.45	2.37±0.67	<0.001	<0.001	0.67

P: One-way analysis of variance. POAG: Primary open-angle glaucoma, GS: Glaucoma suspect, IOP: Intraocular pressure, CCT: Central corneal thickness, CD: Cup disc, VF: Visual field, MD: Mean deviation, PSD: Pattern standard deviation

Table 3: Comparison of vessel density among study groups

Variable	POAG	GS	Normal	*P*		
				POAG versus GS	POAG versus normal	GS versus normal
VD superior (%)	47.08±10.73	53.39±3.57	56.16±3.42	<0.001	<0.001	0.186
VD inferior (%)	45.96±12.32	54.74±3.70	56.71±2.90	<0.001	<0.001	0.498
VD nasal (%)	45.11±7.91	50.76±4.13	55.68±3.0	<0.001	<0.001	<0.001
VD temporal (%)	51.11±6.33	54.32±4.30	56.37±2.64	0.01	<0.001	0.14
wVD (%)	45.34±6.64	50.06±1.97	53.06±2.12	<0.001	<0.001	0.007
ppVD (%)	47.42±7.73	52.62±2.41	56.07±2.71	<0.001	<0.001	0.09

P: Tukey-Kramer HSD *post hoc* test. POAG: Primary open-angle glaucoma, GS: Glaucoma suspect, VD: Vessel density, wVD: Whole vessel density, ppVD: Peripapillary vessel density, HSD: Highly standard deviation

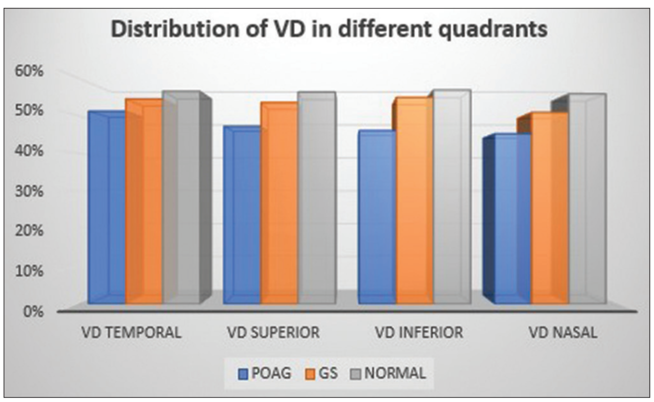

Figure 1: The bar graph illustrates the distribution of vessel density across various quadrants of the optic nerve head, deviating from the conventional ISNT rule (inferior ≥ superior ≥ nasal ≥ temporal)

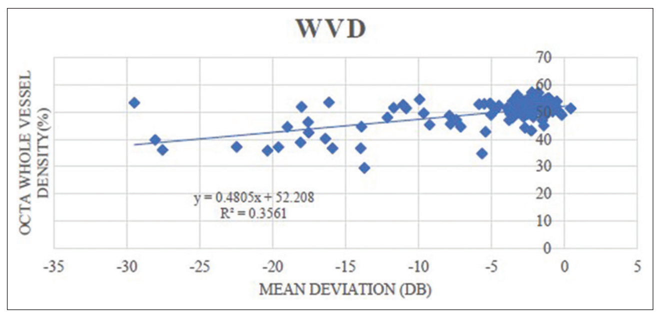

Figure 2: Linear regression analysis revealed a significant association (<0.001) between optical coherence tomography angiography whole vessel density and mean deviation measurement of visual field (R^2 = 0.35)

in the glaucoma group and GS group as compared to a normal control group. The relationship between vascular density and VF PSD ($P < 0.001$) points to a connection between the severity of glaucoma and decreased disc perfusion. In this investigation, we also discovered a relationship between vessel density and VF MD ($P < 0.001$). In the current study, subjects above 40 years of age were included by considering the increased risk of glaucoma more than that age. However, Yarmohammadi *et al.* included more than 18 years of age.[16]

Lommatzschi *et al.* also included those who were more than 18 years. A significant difference in IOP was found between the 31 POAG group with GS and the normal control group. However, due to the autoregulation of blood flow, it has been shown that mild IOP rise has no substantial impact on retinal microcirculation.[17] Glaucoma patients exhibited reduced IOPs as compared to the GS and normal control group ($P < 0.001$ and $P = 0.042$, respectively). Recently, it was discovered that a thin CCT was a predictor of glaucoma progression. IOP measurements have long been known to be impacted by CCT, with thinner corneas causing an underestimation of IOP.[18] CCT measurement was found to be significant between the POAG group, GS group, and normal control group. A significant percentage of the increased risk of glaucoma appears to be explained by CCT.[19] Narrower central corneas were noticed on the POAG group as compared to the glaucoma suspicion group ($P = 0.040$).[16] POAG is a progressive optic neuropathy characterized by tissue loss in the neuroretinal rim of the optic disc and an increase in the size of the optic cup.

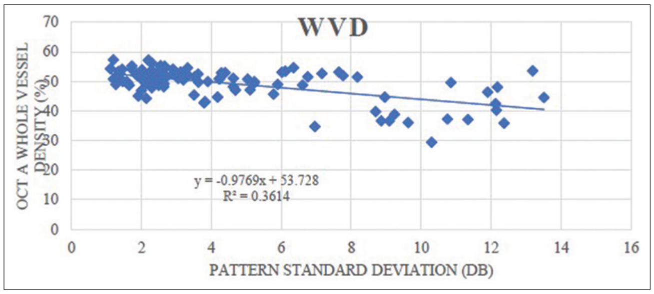

Figure 3: Linear regression analysis revealed a significant association (<0.001) between optical coherence tomography angiography whole vessel density and pattern standard deviation measurement of visual field ($R^2 = 0.36$)

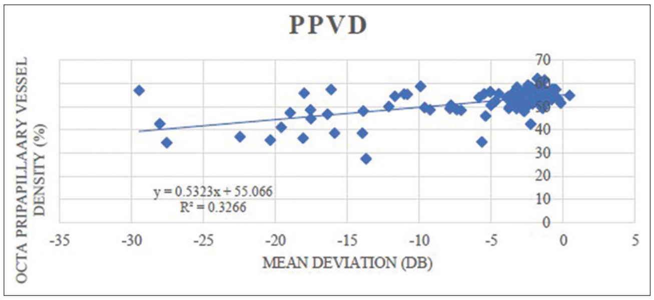

Figure 4: Linear regression analysis revealed a significant association (<0.001) between optical coherence tomography angiography peripapillary vessel density and mean deviation measurement of visual field ($R^2 = 0.32$)

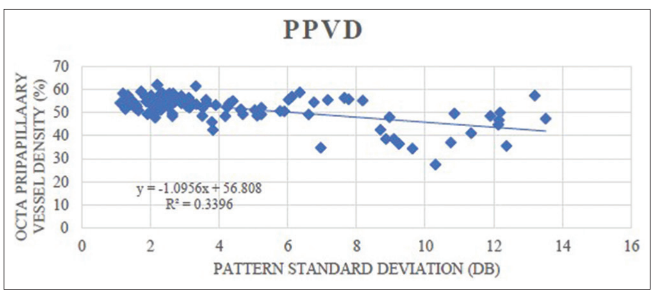

Figure 5: Linear regression analysis revealed a significant association (<0.001) between optical coherence tomography angiography peripapillary vessel density pattern standard deviation measurement of visual field ($R^2 = 0.36$)

Before the development of visual field impairment, cupping is an early symptom that has been seen in people with glaucoma and ocular hypertension.[20] Statistically significant result was found between all three groups in cup–disc ratio. Similar findings were obtained by Lommatzschi *et al.* between the glaucoma group and the normal control age-matched group. [15] Clinically, glaucoma damages the nerve head mostly in the temporal superior and temporal inferior sectors, and severe illness causes nasal displacement of central vessels.[21] As a result, we expected the lowest vessel density in the temporal sector. However, as compared to the other sectors, our OCTA data demonstrate lower vessel density in the nasal and inferior ONH quadrants.

In this study, when quadrantal analysis of vessel density was performed nasal and temporal sectoral vessel densities show significant differences between POAG, GS, and normal control group. Vessel density in the superior quadrant was found to be reduces in POAG as compared to GS and normal control group. Durmuş Ece and Sarıcaoğlu *et al.* found no significant difference in vessel density values among glaucoma groups but were significantly lower in both POAG and pseudoexfoliation syndrome compared to the control group.[22]

The 4.5 mm × 4.5 mm scan field, centered on the optic disc, is used to calculate wVD. wVD shows 55.5% in healthy control subjects, 51.3% in GS, and 48.3 in glaucoma patients and it shows statistically significant (<0.001) in a study done by Yarmohamaddi *et al.*[23] Similar kind of results were obtained in our study. Lommatzsch *et al.* found out that whole vessel density was reduced in glaucoma patients as compared to the normal control group ($P < 0.001$).[15] In a study done by Mangouritsas *et al*., wVD was 45.9% ± 3.5% and 50.1% ± 3.9% of preperimetric glaucoma eyes and fellow eyes, and the mean difference shows statistically significant.[24]

The optic disc boundary forms a 0.75 mm-wide elliptical annulus where ppVD is assessed. ppVD was found to be reduces on a study done by Mangouritsas *et al.*[24] Yarmohamaddi *et al.* found mean ppVD values were significantly lower in moderate-to-severe glaucoma eyes (49.6% ± 6.9%), followed by mild glaucoma (57.5% ± 4.4%), GSs (61.0% ± 4.7%), and healthy eyes (62.8% ± 3.9%) ($P < 0.001$).[23]

Structural and functional assessment is always important in glaucoma evaluation and management. Vessel density parameter and VF parameter comparison add its value. Statistical significant ($P = 0.003$) was obtained in PSD and MD between glaucoma and normal individuals in a study done by Mangouritsas *et al.*[24] We also found out statistically significant difference between all three groups in PSD and MD. A global statistic known as the VFI uses a single integer to reflect the whole visual field. It is calculated by estimating the age-corrected defect depth at the test spots that have been indicated in pattern deviation probability maps as significantly depressed. In our current study, VFI was found to be reduced in glaucoma as compared to GS and the normal control group and was found statistically significant ($P < 0.001$). We expected a substantial association with MD in visual field evaluation because early descriptions revealed a significant link between wVD and ppVD and the severity of visual field damage independent of structural loss.[21] Our findings revealed just a moderate association ($R^2 = 0.35$). However, a significant P value (<0.001) was obtained. Similar findings were obtained for the association between PSD and wVD/ppVD. A study done by Yarmohammadi *et al.*[16] found statistical differences in MD and PSD between glaucoma, GS, and normal control group ($P < 0.001$).

Our study has limitations; it is unclear whether the decreased vessel density is the result of glaucomatous ONH damage or the cause of it. According to Holló,[25] measures of peripapillary angioflow density can detect decreased peripapillary perfusion in early glaucoma before the development of severe RNFL destruction and visual field degeneration. During the OCTA scanning, no blood pressure measures were taken in our study. A link between blood pressure and ONH blood flow is attainable. Previous research, however, found no significant link between blood pressure and ONH VD.[24]

We were unable to analyze intraobserver variability since the OCT images were obtained by a single operator but only one measurement was taken.

In our glaucoma group, the majority of the patients were using several ocular antihypertensive eye drops. With our small sample size, we cannot evaluate their individual effects on disc perfusion, and we cannot completely rule out the idea that the glaucoma drops are to blame for the lower disc perfusion.

The RNFL's retinal ganglion cells are primarily concentrated in the macula, and several studies[26] have established a strong association between ganglion cell-inner plexiform layer thickness and glaucoma. The current study did not examine the vessel density in the macula.

We measured optic disc perfusion *in vivo* using OCT angiography based on the SSADA algorithm. Our research shows that lower vascular density at the ONH in glaucomatous eyes can be measured using spectral domain OCTA and that these findings are connected to both functional and structural glaucomatous changes.

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Conflicts of interest

There are no conflicts of interest.

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