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Original Article

A comparison study of Optical Coherence Tomography Angiography Peripapillary Vessel Density in Early Glaucomatous and Normal Nigerian Eyes.

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Abstract

Background: This study aimed to determine and compare the peripapillary vessel density (VD) in normal and early glaucomatous Nigerian eyes using Optical Coherence Tomography Angiography (OCTA), to provide evidence for the use of OCTA in enhancing the early diagnosis of glaucoma in Nigeria.

Methodology: This was a hospital-based cross-sectional comparative study of 90 early glaucomatous participants and 90 normal participants. Participants aged 40 and above, with open anterior chamber angles (Schaffer's) on gonioscopy, vertical cup disc ratio (VCDR)>0.4 and Central Visual Field (CVF) Mean deviation (MD) less than -6 dB, with glaucoma hemifield test (GHT) outside normal limits on a reliable 24-2 perimetry (Humphrey Field analyser II, Zeiss Humphrey Matrix 715) were recruited as early glaucomatous while aged matched control with vertical cup disc ratio <0.4, intact neuro-retinal rims, healthy OCT determined RNFL thickness and GCC, and a normal visual field test results were recruited as normal participants. The participants had a complete anterior and posterior segment examination. One eye of each participant had OCTA scans. The average peripapillary Vascular density in each optic nerve head (ONH) quadrant was determined using Angiovue OCTA (Optovue Inc., Fremont, CA, USA). The relevant data were analysed using the Statistical Package for Social Sciences (SPSS) version 26 with statistical significance set at $p<0.05$ and 95 % confidence interval.

Results: The mean peripapillary VD was significantly reduced in the early glaucomatous eyes (50.21 ± 4.54) compared to the normal (54.60 ± 2.50) eyes ($p <0.001$). The peripapillary VD in the optic nerve head quadrants followed a similar trend of being lower in the early glaucomatous eyes ($p<0.001$).

Conclusion: The reduced peripapillary VD in early glaucoma denoted a reduction in ONH perfusion in early glaucoma, and highlighted the usefulness of OCTA peripapillary VD in the early diagnosis of glaucoma in Nigerian eyes.

Keywords: Optical Coherence Tomography Angiography, Peripapillary Vessel Density, Early Glaucomatous Eyes.

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Quick Response Code:

Introduction

Glaucoma is a group of neurodegenerative diseases leading to irreversible loss of retinal ganglion cells, characteristic optic neuropathy, and typical visual field losses. [1,2] It is the leading cause of irreversible blindness globally and the second leading cause of blindness in Nigeria, with a prevalence of 0.7% in persons aged 40 and above. [3-5]

Although raised intraocular pressure (IOP) is the most widely accepted cause of retinal ganglion cell death and optic neuropathy in glaucoma, several studies have documented glaucoma progression despite adequate intraocular pressure control. Emerging evidence shows that impaired ONH perfusion contributes to the pathogenesis of glaucoma. [6-9] These findings support the vascular theory of glaucoma as a pressure-independent mechanism of glaucomatous optic nerve damage.

The optic nerve head (ONH) and retinal ganglion cells are richly perfused by the radial peripapillary capillaries (RPCs). [9-10] However, the quantitative in vivo assessment of this capillary network has been challenging.[11] The introduction of optical coherence tomography angiography (OCTA) now permits a non-invasive quantitative assessment of the RPC, which is reported as vascular density (VD). [12] OCTA compares sequential B-scans acquired at the same location to detect a vascular change. [13] It is based on the split-spectrum amplitude decorrelation algorithm (SSADA), which detects red blood cell (RBC) movement in vessels independently from the direction of movement and reports peripapillary VD as RPCs or VD.[13] In this algorithm, a vessel is seen as non-perfused if there is no RBC movement in the vessel at the time of acquisition of the image. [13] Vascular density is the perfused area expressed as a percentage of the total examined area or its predefined sectors within a retinal layer of interest. [1] Several studies have documented reduced RPC VD and blood flow at the ONH in glaucomatous eyes. [12-13] Researchers have also demonstrated a close relationship between the severity of glaucomatous damage on visual field analysis and reduced VD on OCTA. [14-15] Vascular density reduction has also been documented to occur before the typical visual field losses in glaucoma, whereas the typical visual field losses occurred after a significant reduction in RNFL thickness on OCT. [15-16] These findings present the possibility of using the peripapillary VD in the early diagnosis of glaucoma. Thus, a search for a reduction in RPC VD on OCTA promised to be of diagnostic value in the early diagnosis of glaucoma. These findings are already shifting the paradigm in glaucoma diagnosis by providing a possibly earlier diagnostic and monitoring tool for optimal glaucoma care. [15-16]

This study, therefore, is aimed at determining the usefulness of the OCTA in the early diagnosis of glaucoma by comparing the peripapillary VD in participants with early glaucoma to that of normal participants without glaucoma.

Methodology

This was a hospital-based cross-sectional comparative study of normal participants and those with early primary open-angle glaucoma at the glaucoma clinics of the Eye Foundation Hospital, Ikeja, Lagos.
The minimum sample size was calculated using the formula for single proportions: $n=z^2pq/d^2$ [17]
Where n is the desired sample size
z is the standard normal deviate, usually set at 1.96, corresponding to a 95% confidence interval.
p is the prevalence of primary open-angle glaucoma in African adults 40years and above in Southwest Nigeria. [18]
$q = 1.0 – p$
d = degree of accuracy
The glaucoma prevalence in adults aged 40 years and above in Southwest Nigeria was 6.2%.[18]
Thus, using 0.062 as prevalence (p) in the target population estimated to have a particular characteristic, the z statistic is 1.96, and the desired accuracy is set at 0.05
$n = (1.96)^2 (0.062) (0.938)/ (0.05)^2$

= 0.22341/0.0025
= 89.364
= 90
Ethical approval for the study was obtained from the Lagos State University Teaching Hospital Ethical Review Board (Ref No: LREC/06/10/1277, approved on 14th November 2019), and this study adhered to the Tenets of the Helsinki declaration.
Consecutive consenting normal participants and patients with early glaucoma were recruited for the study until the minimum sample size was accomplished. The eye with the lower MD (closer to -6) was selected if both eyes met the criteria in participants with early glaucoma. The eye with the lower VCDR was selected in the normal participants if both eyes met the criteria. This was aimed at eliminating selection bias. Normal (non-glaucomatous) eyes with normal appearing optic disc and normal visual fields were excluded if there was any significant reduction in OCT-determined RNFL and GCC. This was done to reduce the likelihood of selecting pre-perimetric glaucomatous eyes as normal.

Participants had a full ocular examination prior to central visual field assessment (Humphrey Field analyser II, Zeiss Humphrey Matrix 715), OCT and OCTA scans. The peripapillary VD in all quadrants was determined using Angiovue OCTA (Optovue Inc., Fremont, CA, USA). The average VD was also calculated.

Participants aged 40 years and above with a vertical cup disc ratio <0.4, intact neuro-retinal rims, healthy OCT determined RNFL thickness and GCC, and a normal visual field test result, defined as a pattern standard deviation (PSD) within the 95% confidence limits and a glaucoma hemifield test (GHT) result within normal limits, were recruited as normal.[17] While participants aged 40 and above, with open anterior chamber angles (Schaffer's) on gonioscopy, VCDR >0.4 and CVF Mean deviation (MD) less than -6 dB, with glaucoma hemifield test (GHT) outside normal limits on a reliable 24-2 perimetry (Humphrey Field analyser II, Zeiss Humphrey Matrix 715) were recruited as early glaucomatous. [19-20] Intraocular pressure was not considered in this definition. [21]

Participants with dense cataracts, previous ocular trauma, retinal pathologies, other types of glaucoma, advanced forms of glaucoma, unreliable CVF results, pre-perimetric glaucoma, and poor-quality scan (<6/10) were excluded.

The OCTA scan was centred around the ONH and covered a 4.5×4.5 mm^2 area. The peripapillary region was defined as a 750-µm width elliptical annular area extending from the optic disc margin and was divided into 8 sectors. The peripapillary VDs were measured in each sector (nasal-superior, nasal-inferior, inferotemporal, inferonasal, superotemporal, superonasal, tempoinferior, temposuperior; Figure 2) and summarised into superior, inferior, nasal, and temporal quadrants. The average of the VD of 4 quadrants (nasal, inferior, superior, temporal) was calculated.

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26. Frequencies and proportions were used to summarize the categorical variables, while mean, mode, and median were used for numerical variables. OCTA parameters from participants with early glaucoma were compared with parameters from normal participants and analyzed. The mean of the VD in each quadrant of the ONH and the average VD were compared using a Student's T-test. Participants were age-matched into age groups by age in decades of life. Using a student T-test, the mean peripapillary VD in the early glaucomatous eyes was compared to that of the eyes of normal participants within the same decade of life. An F-test was used to compare the mean peripapillary VD in participants within the same decade in each category of participants. A univariate and multivariate analysis was also done to ascertain the relationship between average peripapillary VD and other factors in both categories of participants. Statistical significance was set at P <0.05 and a confidence interval of 95%.

Results

A total of 180 eyes from 90 early glaucomatous participants and 90 normal eyes had OCTA peripapillary VD scanning. One eye was assessed per participant. The mean age of participants with early glaucoma (54.5 ± 10.1 years) was higher than that of the normal participants (49.9 ± 7.7years). This difference was statistically significant (p 0.002). The demographic profile, clinical, and ophthalmic characteristics of the participants are summarised in Table 1.

TABLE 1: Demographic and ophthalmic characteristics of the participants

PARAMETERS	EARLY GLAUCOMA	NORMALS	P VALUE
No of eyes	90	90	
Age (years)	54.5 ± 10.1	49.9 ± 7.7	0.002
Sex (M/F)	54/36	48/42	
VCDR	0.61	0.33	0.005
Hypertension	24	12	0.030
Diabetes mellitus	6	2	0.278
Hyperlipidaemia	9	6	0.591

There were no significant differences in sex, history of diabetes mellitus, and hyperlipidaemia between the two groups of participants. However, a significant proportion of the early glaucoma participants were hypertensive compared to the normal participants, as shown in Table 2.

Table 2: Peripapillary RNFL thickness and Vessel density among the participants

Peripapillary RNFLT (µm)	EARLY GLAUCOMA	NORMALS	P (95% CI) (2-tailed)
Inferior	118.97 ± 19.06	149.35 ± 19.06	0.000
Superior	118.04 ± 25.74	142.01 ± 18.05	0.000
Nasal	91.56 ± 17.34	105.68 ± 18.71	0.000
Temporal	62.56 ± 10.94	70.18 ± 9.94	0.000
Average	97.79 ± 17.33	116.56 ± 12.62	0.000
Peripapillary VD			
Inferior	50.39 ± 7.82%	56.11 ± 3.63%	0.000
Superior	50.38 ± 5.91%	55.53 ± 3.91%	0.000
Nasal	48.37 ± 5.67%	51.54 ± 3.68%	0.000
Temporal	51.28 ± 5.64%	55.26 ± 3.68%	0.000
Average	50.21 ± 4.54%	54.60 ± 2.50%	0.000
CVF* MD (dB)	-3.5	-0.4	0.001

***CVF-Central visual field**

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The Peripapillary RNFL thickness, OCTA peripapillary VD, and CVF MD were significantly decreased in the early glaucomatous eyes compared to the normal eyes, as shown in Table 3. Furthermore, peripapillary VD was noted to be significantly reduced in eye glaucomatous participant when compared to the normal participants within the same decade of life. Surprisingly, this reduction of peripapillary vessel density was more in the participants aged 60 and above compared to the younger ones across all participants, as depicted in Table 4.

Table 3: Comparison of average peripapillary vessel between the normal and early glaucomatous eyes matched by age groups (decades of life)

Age Groups	Mean VD Early Glaucomatous Eyes (%)	Mean VD Normal eyes (%)	T- Test	P-Value
40-49 years	52.2	54.7	3.4	0.002
50-59 years	49.3	55.5	6.2	0.000
60-69 years	49.1	52.2	2.8	0.008

Table 4: Comparison of average peripapillary vessel density across the age groups in the Normal participants (F-test)

Age group (mean peripapillary VD) (%)	Age group (years)	P value
40-49 (54.70)	50-59	0.151
	60-69	0.001
50-59 (55.48)	40-49	0.151
	60-69	0.000
60-69 (52.23)	40-49	0.001
	50-59	0.000

Table 5: Relationship between average peripapillary vessel density and other variables in the normal and early glaucomatous eyes

	NORMAL EYES				EARLY GLAUCOMATOUS EYES			
Variables	Beta coefficient	95% Confidence Interval	P-value	Correlation coefficient R	Beta coefficient	95% Confidence Interval	P-value	Correlation coefficient R
AGE	-0.092	-0.15 – (-.015)	0.072	0.251	-0.065	-0.23 – (-.051)	0.105	0.300
MALE SEX	-0.471	-1.40 – 0.71	0.590	0.079	-1.246	-3.63 – 0.20	0.050	0.186
FEMALE SEX	0.471	-0.71 – 1.40	0.516	0.069	1.246	-0.23 – 3.63	0.079	0.186
HYPERTENSION	0.183	-0.07 – 2.93	0.872	0.198	0.771	-2.06 – 2.27	0.325	0.010
DM	0.149	-1.01 – 6.07	0.160	0.149	-0.856	0.99 – 8.39	0.492	0.259
HYPERLIPIDEMIA	-0.380	-1.56 – 2.66	0.752	0.055	-0.437	-4.03 – 2.34	0.701	0.056
AV RNFL	0.035	-0.01 – 0.72	0.249	0.179	0.172	0.16 – 0. 23	0.000	0.752
VCDR	2.005	-4.36 – 8.57	0.623	0.069	1.90	-23.27 – (-5.53)	0.584	0.325
CVF MD	-0.047	-0.23 - 0.23	0.730	0.032	0.264	0.43 – 1.27	0.095	0.402

On univariate analysis, the average VD had a negative relationship with age, male sex, and history of hyperlipidemia in both categories of participants, while CVF MD had a negative relationship with average VD in the normal eyes only. However, on multivariate linear regression, average peripapillary VD had a significant relationship with only the peripapillary RNFL thickness in the early glaucomatous eyes (p 0.000, Beta 0.172, CI 0.16 – 0.23, R 0.752), and no variable in the normal eyes, as shown in Table 5 and Figure 1.

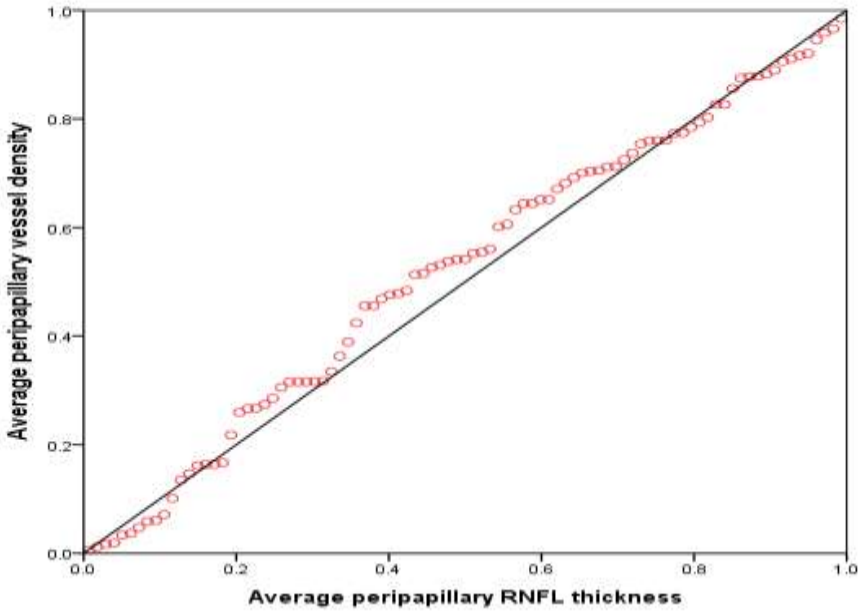

Figure 1: Correlation between average peripapillary Vessel Density and average peripapillary RNFL thickness in the early glaucomatous eyes on multiple regression analysis. (p 0.000, beta 0.749, CI. 156 - 0.230, r-square 0.562).

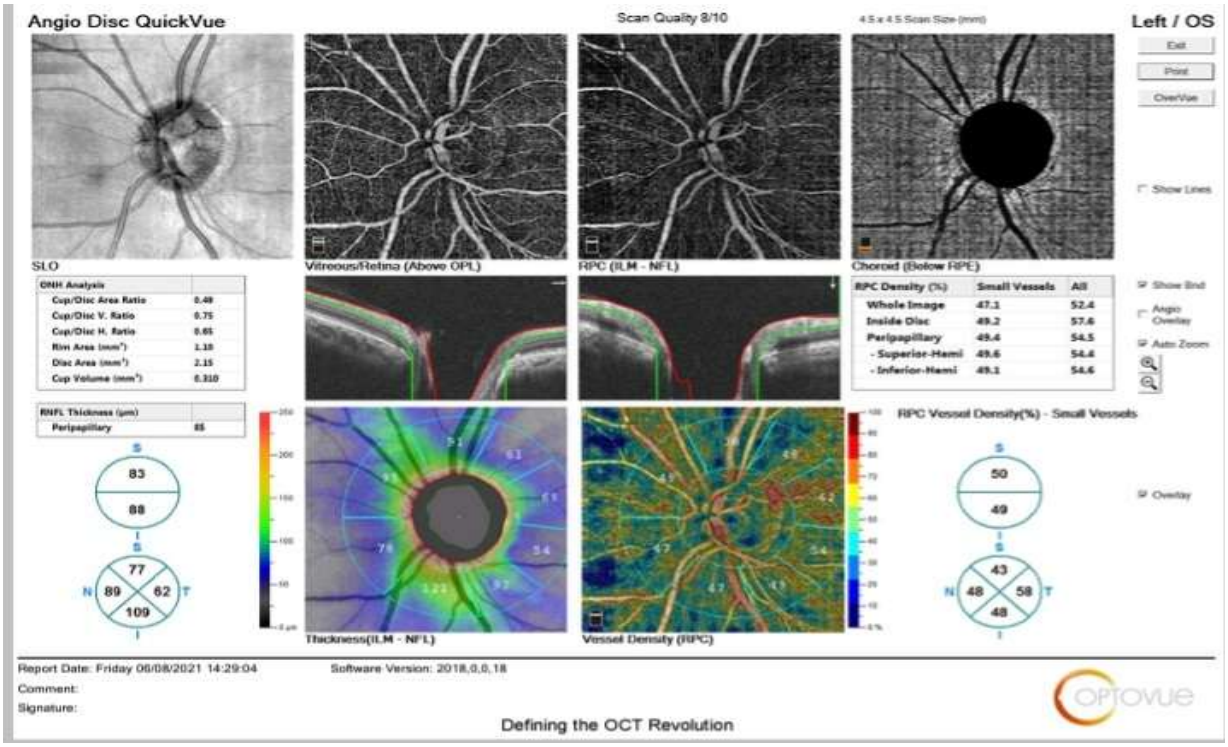

Figure 2: OCTA Vessel Density Scan of a 55-year-old male participant with early glaucoma (origin

Figure 2 shows a typical printout of an OCTA result.

Discussion

This study evaluated and compared the peripapillary VD between early glaucomatous Nigerian eyes and age-matched healthy controls using the OCTA. We noted a significant reduction in OCTA peripapillary VD in early glaucomatous eyes compared to the normal healthy eyes. In addition, we documented a peripapillary VD distribution which negates the ISNT peripapillary RNFL thickness in both categories of participants. This study also provided evidence on the effect of increasing age on the peripapillary VD in both early glaucomatous and normal Nigerian eyes. To the best of my knowledge, this is the first study to compare peripapillary vascular density between early glaucomatous and healthy normal Nigerian eyes using OCTA. These findings will definitely enrich the literature on glaucoma involving Nigerian eyes.

Normal Caucasian eyes had a higher (60.34±5.51) and similar (53.27±4.07) average peripapillary VD compared to the normal eyes (54.60 ± 2.50) in this study. [22-23] Rolle et al documented a higher peripapillary using a smaller en face scan and a different peripapillary disc definition in their OCTA software, while Köse HC *et al* used the same software as this study and documented a similar average peripapillary VD in normal Caucasian eyes. [22-23] It is striking that the average peripapillary VD in normal Caucasian and black African eyes are comparably similar despite being from two different human races.

The distribution of peripapillary VD in this study violated the ISNT RNFL thickness rule in both categories of participants (Table 2). This violation of the ISNT RNFL thickness rule has been previously documented in Caucasians by Dastiridou A *et al*. [24]. The temporal region in this study had a notably higher vascular supply compared to the pRNFL thickness, and this demonstrated that a higher vascular supply occurred to the papillomacular bundle compared to other RNFL bundles. This higher vascular supply may partly explain the resistance of the papillomacular bundle to glaucomatous damage and the resultant tunnel vision in advanced stages of glaucoma.

Our study showed a significant difference in the mean peripapillary VD between normal eyes and early glaucomatous eyes (Table 2). The normal eyes had a higher mean peripapillary VD compared to the early glaucomatous eyes in every ONH quadrant. The mean peripapillary VD in the early glaucomatous eyes in this study was reduced by 10.2%, 9.3%, 6.2%, and 7.2% in the inferior, superior, nasal, and temporal quadrants, respectively, compared to the normal eyes (Table 2). Rao *et al* and Akil *et al* documented similar reduction in the mean peripapillary VD in moderate/advanced POAG and early POAG, respectively. [25,15] These findings show that the peripapillary VD reduction occurs in early glaucoma, denoting established ONH vascular compromise in early glaucoma. Furthermore, this study found a lower average peripapillary VD in early glaucomatous participants when compared to their normal counterparts within the same decade of life (Table 3). In addition, average peripapillary VD was significantly reduced in participants within the seventh decade of life compared to those in the fifth and sixth decades of life in both categories of participants (Tables 4 and 5). These important findings validated the significant difference in average peripapillary VD between the early glaucomatous and normal eyes despite the initial difference in age between the two groups of participants. Contrarily, Rao *et al* found no effect of age on average peripapillary VD in normal eyes. This study, however, found no relationship between age and average peripapillary vessel density on multivariate analysis. [26]

The average pRNFL thickness was independently associated with the peripapillary VD on multivariate analysis in the early glaucomatous eyes (p 0.000, beta 0.172, 95 % CI 0.16 – 0. 23, R 0.752) in our study (Figure 1). This strong positive association had been suggested to indicate that blood supply (VD) increases proportionately with tissue thickness (pRNFL) to ensure adequate perfusion. Although a reduction in peripapillary VD had been documented to occur before a reduction in pRNFL, this interesting relationship is beyond the scope of this study, but can be investigated when we follow up on the participants for some years. [16, 27]

Hypertension has been suggested to have a protective effect in persons younger than 60 years by increasing ocular perfusion. [28] This would have resulted in a higher average peripapillary VD in our participants, as most were younger than 60 years. Contrary to this expectation, this study found no significant relationship between hypertension and average peripapillary VD in harmony with previous studies. [29,25,28] A longitudinal study will help explain the relationship between average peripapillary VD and hypertension.
There are different reports on the effect of the diabetes mellitus (DM) diagnosis, duration, and the presence of diabetic retinopathy on peripapillary vascular density. [29-30] Chuang *et al* reported a reduction in peripapillary VD with increasing duration of DM, while Rodriguez *et al* demonstrated a reduction in peripapillary VD in the early stages of DM in the absence of retinopathy. [29-30] Their findings suggested that ONH perfusion is reduced via microvascular damage and alteration of autoregulation in DM, regardless of the stage of the disease. [29-30] A negative relationship was noted between a history of DM and average peripapillary VD in the early glaucomatous, which suggested a reduction in VD in these participants. However, there was no significant relationship between average peripapillary VD and DM in both categories of participants. Other factors had no significant relationship with average peripapillary VD on multivariate analysis.

In this study, only one eye per participant had OCTA, and thus, there is no data for inter-eye variability. A study including both eyes in normal and early glaucomatous eyes will be able to provide this data. A larger prospective study in Nigeria involving the major ethnic nationalities will present more generalizable data for Nigerian eyes. A follow-up study on the early glaucoma patients will be paramount to document changes in VD as they progress towards moderate and advanced disease, and provide data for enhanced care.

Conclusion

This study showed significant reductions in average peripapillary vascular density in early Nigerian glaucomatous eyes compared with normal eyes, supporting the role of vascular compromise in early glaucomatous damage. The study also showed an independent relationship between peripapillary vascular density and peripapillary RNFL in early glaucomatous eyes. OCTA-derived peripapillary VD may thus serve as a valuable adjunct in early glaucoma screening and monitoring.

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