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ORIGINAL ARTICLE

Macular Microvascular Optical Coherence Tomography Angiographic Changes in Different Stages of Primary Open Angle Glaucoma

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Abstract

Background: ***Globally, primary open-angle glaucoma (POAG) is recognized as a cause of permanent blindness. A novel noninvasive technique called optical coherence tomography angiography (OCTA) can quickly and quantitatively analyze the vascular plexus of the retina and optic disc.***

Objective: ***To assess the alterations of macular microvasculature in different stages of POAG and correlate these alterations with retinal nerve fibre layer thickness visual field mean deviation.***

Subjects and Methods: ***A cross-sectional study was performed on 60 eyes, including 45 eyes of POAG cases and 15 eyes of normal controls. POAG individuals were classified into mild, moderate, and severe groups according to Hodapp, Parish, and Anderson classification. All subjects underwent Spectralis OCTA to assess macular microvasculature.***

Results: ***We found that the superficial and deep macular vessel density (MVD) was significantly reduced in cases with POAG compared to normal controls, which increased as glaucoma severity increased. The mean superficial MVD in the control group and POAG groups (mild, moderate and severe) was 52.8 ± 5.4, 47.6 ± 4.3, 40 ± 3.1 and 32.6 ± 2.9, respectively, while the mean deep MVD in the control group & POAG groups (mild, moderate and severe) was 57.5 ± 4.4, 51.5 ± 4.7, 45.3 ± 2.8 and 37.3 ± 3.2 respectively (p-value < 0.001).***

Conclusion: ***POAG patients had a lower MVD than normal controls. The MVD may be a supplementary diagnostic and monitoring tool for glaucoma progression.***

Keywords: OCT angiography; POAG; macular vessel density

1. Introduction

POAG stands for progressive optic neuropathy. The degeneration of retinal ganglionic cells and their axons causes structural damage in the optic nerve head (ONH) and inner retina, resulting in persistent visual field loss.[1]

Intraocular pressure, or IOP, is believed to play a significant role in its pathogenesis, particularly damage to the optic disc.[2]

POAG has a multifactorial etiology and no single mechanism fully explaining the vulnerability to glaucomatous damage.[3]

While the IOP has a significant role in the onset and course of glaucoma, glaucoma pathogenesis has also been linked to other risk factors, including ONH vascular insufficiency.[4]

Fluorescein angiography (FA) is one of the imaging methods utilized to estimate the microvasculature and perfusion of the retina. However, FA provides restricted access to the retinal microvasculature, and a contrast agent injection is needed.[5]

OCTA is a noninvasive method that does not involve an infusion of a contrast agent and can quantitatively evaluate and quantify vascularity in the optic disc and retina with motion contrast produced by erythrocytes and with no requirement of contrast agent injection.[6]

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Despite the high correlation between peripapillary microvasculature loss and impairment of visual field (VF), there is currently little data on the connection between impairment to the macular microvasculature and visual function. Nevertheless, conducting structural and efficient testing of the macula significantly improves the ability to diagnose and monitor glaucoma.[7]

The present study's objective was to ascertain the variations of retinal microvasculature in different stages of POAG using OCTA and to associate these changes with the changes of both peripapillary retinal nerve fibre layer (RNFL) thickness and VF mean deviation (MD).

2. Patients and methods

Study design: A cross-sectional observational study was carried out on 45 eyes with POAG who came to the Al Azhar University glaucoma subspecialty clinics and 15 age-matched normal participants' eyes who came to the ophthalmology outpatient clinics between November 2022 and July 2023. After being informed about the purpose of the research, each participant gave written informed consent.

Study population: Eyes with POAG were divided consistently with the Hodapp– Parrish–Anderson classification into mild, moderate, and severe glaucoma groups. Eyes were identified with POAG if they had glaucoma-related optic neuropathy and glaucoma-related VF defects. Standard healthy controls had an IOP 21 mmHg or less, within normal Humphrey Swedish interactive threshold algorism (SITA) 24-2 standard VF; normal ONH, an open angle on gonioscopy, and damaging history of any long-term eye or systemic diseases. The Participants were divided into four groups: Group 1: mild POAG (15 eyes) had a Mean Defect > - 6 decibels (dB). Group 2: Moderate POAG (15 eyes) had a Mean Defect - 6 dB > MD > - 12 dB. Group 3: severe POAG (15 eyes) had Mean Defect < -12 dB. Group 4: standard control (15 eyes).

Inclusion criteria: Participants must be above 18 years old, have POAG, and have a best corrected visual acuity (BCVA) of at least 6/60. They must also have a refractive error with a spherical equivalent (SE) within plus or minus five diopters (D) and a cylindrical refractive error within ± 3D.

Exclusion criteria: Secondary glaucoma, non-glaucomatous cause of optic neuropathy, patient with diseases affecting the VF, history of previous corneal disease or ocular trauma, patients with retinal diseases like diabetic retinopathy and high myopia, significant media opacity and previous eye operation other than uncomplicated cataract or glaucoma surgery.

Patient evaluation: All participants were evaluated in age, sex, medical history, surgical history, and ocular history. All cases underwent Comprehensive ophthalmic examination, including Slit Lamp examination for assessment of anterior segment and ONH, BCVA, Refraction using auto refractometer (Nidek AR-1000 autorefractor), Gonioscopy, Goldmann applanation tonometry was used to measure intraocular pressure, VF testing using ZEISS Humphrey Field Analyzer 3 (Carl et al., USA) using SITA standard algorithm and a 24-2 test pattern to evaluate VF defect, Spectralis OCTA (Heidelberg et al.) to measure RNFL thickness and to assess macular microvasculature.

OCTA image acquisition: All eyes underwent macular angiography using Heidelberg spectralis OCTA (Heidelberg et al., software version 6.15). A-scans can be obtained at a rate of 40,000 per second with the spectral OCT, a remarkable statistic. Specifically, the device possesses an axial resolution of 3.9 micrometres, a transverse resolution of 14 micrometres, as well as a scan depth of 1.9 millimetres. All OCTA images were attained by the 20°×20° scan angle (≈ 6 x 6 mm) positioned on the fovea that comprised 512 A-scans × 512 B-scans. Macular scans were accepted with a quality index of at least 25.

The Spectralis algorithm automatically segmented retinal layers to obtain OCTA images of the vascular plexus encompassing the superficial vascular complex (SVC) and the deep vascular complex (DVC) Figure 1. The software's ruler tool on the Heidelberg Spectralis OCTA device measured the avascular area.

All OCTA images were achieved with the same skilled examiner on the same device. In addition, each scan was assessed separately by two investigators for quality assessment purposes.

Figure 2. shows examples of the macula's microvasculature in POAG groups (mild, moderate, and severe) and normal eyes.

OCTA image processing: The vessel density of all complexes was detected by analyzing en-face OCTA pictures using the ImageJ program (National Institutes of Health, United States, Bethesda, Maryland). The vascular density was calculated as a ratio by dividing the total area occupied by blood vessels by the region under examination. After extracting the initial pictures from the viewing program, the images were subsequently uploaded into Image J to quantify the VD.

Statistical analysis: The Statistical Program for Social Science (SPSS) 24 was used to analyze the data after the collection and revision of data. The frequency and percentage of occurrence were used to express the qualitative data. Quantitative data were depicted as the mean plus or minus the standard deviation (SD) for data that was regularly distributed or as the median (interquartile range) for not commonly dispersed statistics. The

following tests were done: In the case of regularly distributed data, a one-way analysis of variance (ANOVA) test was used to compare more than two groups. When the groups were being compared (for abnormally distributed data), the Kruskal-Willi test was utilized. The Chi-square test was applied to equate non-parametric information. Pearson's correlation coefficient test was utilized to attempt to correlate the data. For multiple comparisons between various variables, the post hoc test was utilized.

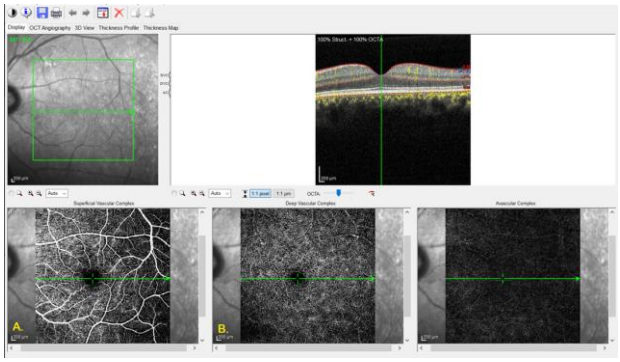

Figure 1. automated segmentation of macular vascular layers using OCTA show: A. The borders of the superficial vascular complex were defined by the internal limiting membrane, which extended 17 µm over the inner plexiform layer's bottom boundary. B. The deep vascular complex's boundaries extended up to the inferior border of the outer plexiform layer and the lower border of the inner plexiform layer, measuring 17 µm.

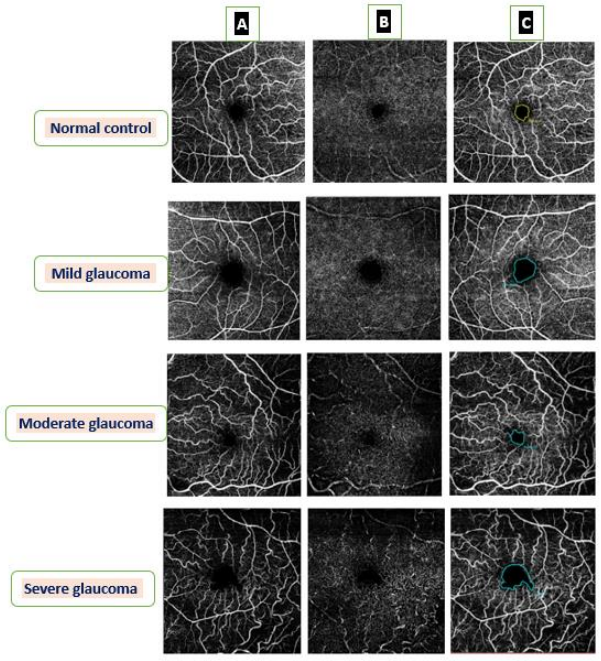

Figure 2. Representative cases of macular vascular scans created by optical coherence tomography from 6 × 6 mm angiograms: demonstrate microvasculature changes in groups of primary open angle glaucoma and normal control. A. The vessel density of the superficial vascular complex is shown in the first column. B. The vessel density of the deep vascular complex is shown in the second column. C. The size of the foveal avascular zone is shown in the third column.

3. Results

As regard age and gender, the difference between the control and POAG groups (mild, moderate, & severe) was not statistically significant. The mean ages of the POAG groups (mild, moderate as well as severe) & control group were 47.7 ± 14.7, 48.5 ± 10, 51.9 ± 10.1 and 50 ± 9.7 respectively. As regard sex in mild glaucoma, there were 5 males (33.3%) and 10 females (66.7%). In moderate glaucoma, there were 9 males (60%) and 6 females (40%). In severe glaucoma, there were 11 males (73.3%) and 4 females (26.7%). In normal control, there were eight males (53.3%) & seven females (46.7%) Table 1

Table 1. comparison between POAG groups & control group in terms of age and sex.

		Groups								P-value
		Mild glaucoma No.=15		Moderate glaucoma No.=15		Severe glaucoma No.=15		Control group No.=15		
AGE (YEARS)	Mean	47.7		48.5		51.9		50		0.753
	±SD	14.7		10.0		10.1		9.7		
SEX	Male	5	33.3%	9	60%	11	73.3%	8	53.3%	0.168
	Female	10	66.7%	6	40%	4	26.7%	7	46.7%	

*P more than 0.05 is considered insignificant

As regard BCVA and IOP, there was statistically significant difference between the study groups but no statistically significant difference between the research groups as regard refraction (p-value > 0.05) Table 2

Table 2. comparison between POAG groups & control group as regard best corrected visual acuity (BCVA), intraocular pressure (IOP) and refraction.

		GROUPS				P-VALUE
		Mild glaucoma No.=15	Moderate glaucoma No.=15	Severe glaucoma No.=15	Control group No.=15	
BCVA (IN DECIMAL)	Median	0.5	0.25	0.16	0.63	0.011*
	IQR	0.32 – 0.63	0.16 – 0.32	0.1 – 0.25	0.5 – 1.0	
IOP (MMHG)	Mean	17.9	20.2	22.4	14.6	<
	±SD	2.4	2.8	3.3	1.5	0.001*
REFRACTION (SE)	Median	-0.75	-1.0	1.25	- 0.75	0.775
	IQR	-1.25: 1.25	-1.25: 1.5	-1.5: 1.75	-1.5: 1.0	
	Post Hoc test by LSD (least significant difference)					
	P1	P2	P3	P4	P5	P6
BCVA	0.006	< 0.001	0.001	0.024	< 0.001	< 0.001
IOP (MMHG)	0.015	< 0.001	0.001	0.022	< 0.001	< 0.001

*SD, standard deviation; IQR, interquartile range; SE, spherical equivalent.

. *P less than or equal to 0.05 is considered significant.

*P1: mild versus moderate, P2: mild versus severe, P3: mild versus control, P4: moderate versus severe, P5: moderate versus control, P6:

severe versus control.

There were a highly statistically significant differences between the study groups as regard RNFL thickness and VF mean deviation (p-value < 0.05). The mean RNFL thickness in POAG groups (mild, moderate & severe) and control group was 81.7 ± 8.0, 67.1 ± 10.4, 45.7 ± 9.4 and 109.2 ± 14.9 respectively. The mean VF (MD) in POAG groups (mild, moderate and severe) and control group was -4.3 ± 1.3, -9.2 ± 2.0, -18.5 ± 6.0 and -1.15 ± 1.08 respectively . Table 3

Table 3. comparison between POAG groups & control group as regard peripapillary retinal nerve fiber layer thickness (pRNFLT) and visual field (VF) mean deviation (MD).

		GROUPS				P-VALUE
		Mild glaucoma No.=15	Moderate glaucoma No.=15	Severe glaucoma No.=15	Control group No.=15	
PRNFLT (µM)	Mean	81.7	67.1	45.7	109.2	< 0.001*
	±SD	8.0	10.4	9.4	14.9	
VF (MD)	Mean	-4.3	-9.2	-18.5	-1.15	< 0.001*
	±SD	1.3	2.0	6.0	1.08	
		Post Hoc test by LSD (least significant difference)				
	P1	P2	P3	P4	P5	P6
PRNFLT (µM)	0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
VF (MD)	< 0.001	< 0.001	0.01	< 0.001	< 0.001	< 0.001

*SD, standard deviation.

*P less than or equal to 0.05 is considered significant.

*P1: mild versus moderate, P2: mild versus severe, P3: mild versus control, P4: moderate versus severe, P5: moderate versus control, P6: severe versus control.

There were a statistically significant differences between the study groups as regard superficial and deep MVD. The mean superficial MVD in controls as well as mild, moderate & severe glaucoma groups was 52.8 ± 5.4, 47.6 ±4.3, 40 ± 3.1 and 32.6 ± 2.9 respectively (p-value < 0.001), while the mean deep MVD in controls as well as mild, moderate & severe glaucoma groups was 57.5 ± 4.4, 51.5 ± 4.7, 45.3 ± 2.8 and 37.3 ± 3.2 respectively (figure 3). In post hoc analysis, the superficial and deep MVD showed a statistically significant differences between mild against moderate, mild against Severe, moderate against Severe, mild against Control, moderate against Control & severe against control groups (p-value < 0.05) . Table 4

Table 4. comparison between POAG groups & control group as regard superficial macular vessel density (MVD), deep macular vessel density and foveal a vascular zone (FAZ).

		GROUPS				P-VALUE
		Mild glaucoma No. = 15	Moderate glaucoma No. = 15	Severe glaucoma No. = 15	Control No. = 15	
SUPERFICIAL MVD (%)	Mean	47.6	40.0	32.6	52.8	< 0.001*
	±SD	4.3	3.1	2.9	5.4	
DEEP MVD (%)	Mean	51.5	45.3	37.3	57.5	< 0.001*
	±SD	4.7	2.8	3.2	4.4	
FAZ SIZE (MM^2)	Mean	0.41	0.43	0.46	0.38	0.101
	±SD	0.08	0.08	0.08	0.1	
		Post Hoc test by LSD (least significant difference)				
	P1	P2	P3	P4	P5	P6
SUPERFICIAL MVD (%)	< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001
DEEP MVD (%)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
FAZ SIZE (MM^2)	0.542	0.103	0.416	0.310	0.158	0.016

*SD, standard deviation.

*P less than or equal to 0.05 is considered significant.

*P1: mild versus moderate, P2: mild versus severe, P3: mild versus control, P4: moderate versus severe, P5: moderate versus control, P6: severe versus control.

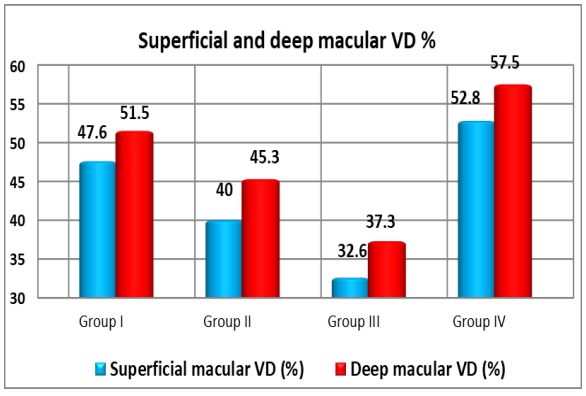

Figure 3. comparison between the study groups as regard superficial & deep macular vessel density (Group I represent mild glaucoma, Group II represents moderate glaucoma, Group III represents severe glaucoma, and Group IV represents the control group).

Table 5. shows the correlation of OCTA parameters with functional and structural parameters in glaucomatous eyes. A statistically significant positive association between MVD (superficial & deep) and VF and RNFL thickness in mild, moderate as well as severe glaucoma groups (P-value< 0

Table 5. Correlation between Macular vessel density (MVD) and retinal nerve fiber layer thickness (RNFLT) & visual field (VF) mean deviation (MD) in different stages of POAG.

		MILD POAG		MODERATE POAG		SEVERE POAG	
		Superficial MVD	Deep MVD	Superficial MVD	Deep MVD	Superficial MVD	Deep MVD
RNFLT (μM)	R=	0.52	0.56	0.53	0.79	0.57	0.86
	P-value	0.048*	0.032*	0.042*	< 0.001*	0.026*	< 0.001*
VF (MD)	R=	0.67	0.55	0.52	0.64	0.62	0.78
	P-value	0.006*	0.032*	0.046*	0.011*	0.015*	0.001*

*P ≤ 0.05 is considered significant

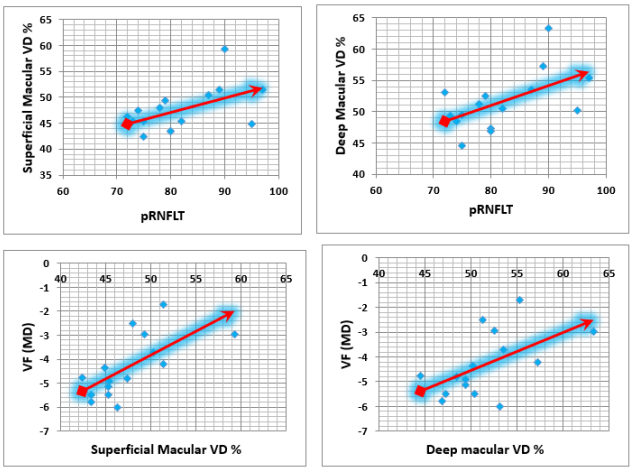

Figure 4. Correlations between superficial & deep macular vessel density & visual field (VF MD) and peripapillary retinal nerve fiber layer thickness (pRNFLT).

4. Discussion

POAG is a long-lasting condition where the cells and their axons in the retina's ganglion layer gradually deteriorate, resulting in injury of the inner retina and optic nerve head, causing permanent defects in the visual field.[8]

Several studies suggested that vascular factors significantly influenced the etiology and deterioration of optic neuropathy caused by glaucoma.[8]

Sensitive methods are used for follow-up of glaucoma to detect progression and avoid progression. OCT and OCTA facilitate the monitoring of glaucoma progression through several parameters.[9]

However, it is hard to anticipate the progression of this disease, particularly in severe stages of POAG, due to the presence of a "floor effect". Following this effect, no further structural alterations in RNFL thickness measurements using OCT may be observed, as it also causes a rise in the variability of VF measurements.[10]

In order to get a better knowledge of the underlying causes of glaucoma and investigate the potential role of vascular factors, we utilized OCTA to assess the microvasculature of the macula and the optic disc.[11]

In the present study, we observed that the RNFL thickness was significantly reduced in POAG cases compared to normal controls, and the thickness decreased as the severity of glaucoma increased in the glaucoma group.

This agrees with Dagdelen et al., who found the same previous results concerning the RNFLT decrease in glaucomatous eyes in comparison with normal ones.[12]

In this study, using OCTA, we detected a decrease in the macular VD of the SVC and DVC in glaucomatous eyes compared to normal eyes. We also found that the more severe the glaucoma, the lower the macular VD.

Previous studies had documented a notable decrease in metrics of macular blood flow, as assessed by various OCTA instruments, in glaucomatous eyes in comparison to normal eyes.[13]

Our findings agree with those of Lever M et al., who demonstrated that the macular vessel density of the superficial and deep vascular plexus decreased in the eyes affected by glaucoma instead of healthy eyes. The study revealed macular VD alterations amongst early to moderate glaucoma cases and healthy subjects.[14]

The findings of Lommatzsch et al. corroborate our findings; they found that, compared to normal eyes, glaucomatous eyes had lower VD of superficial and deep vascular plexus of the macula.[15]

This is in comparison to the research of Triolo et al., who did not find any variance in the macular VD among normal subjects, glaucoma suspects, and glaucoma patients. Significant discrepancies were observed in the structural characteristics rather than the vascular parameters.[16]

This is also in contrast with Takusagawa et al., who found that deep macular VD was minimally affected by glaucoma.[17]

As regards FAZ size, we found that it increased in patients with POAG compared to normal controls, but there was no statistical difference among glaucoma groups and standard control.

These outcomes agree with Huo Y et al., who found no significant alterations in the FAZ region among the controls and mild, moderate, and severe glaucoma groups.[18]

This is in contrast to Kwon et al., who found

that foveal avascular zone size increased significantly in the POAG group compared to normal subjects.[19]

Furthermore, we found a significant correlation between vascular density and structural and functional parameters. The decrease in superficial and deep MVD was associated with corresponding RNFL and VF (MD) thinning.

These results agree with Wu J et al., who detected that there was a positive correlation between macular VD & RNFL thickness and VF.[20]

These outcomes are also in line with Chen et al., who testified that there was a moderate positive association between MVD and VF (MD).[21]

4. Conclusion

The current study reported decreased VD in glaucomatous eyes compared to normal controls, and MVD was associated with functional and structural changes in glaucoma. Thus, vessel density may be a valuable tool for diagnosis as well as follow-up of glaucoma.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

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