How to Cite:

Correlation between optical coherence tomography angiography macular parameters with optical coherence tomography structural parameters in primary open angle glaucoma (a longitudinal descriptive study)

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***Abstract*---**Background: There is growing evidence indicating that glaucoma pathogenesis is attributed to vascular dysfunction. Aim: compare the macular circulation in normal individuals and glaucomatous patients in the superficial as well as the deep retinal plexuses, to determine and characterize macular circulation deficits in glaucoma along with correlating them with structural macular OCT parameters Methods: descriptive study included 100 eyes of 100 participants who were selected randomly from attendants of ophthalmology outpatient clinic in Beni-suef university hospital Participants were subjected to 24-2 SITA- standard automated VF test using SAP ,OCT ONH examination and OCTA (Macula) Results: IOP showed significant negative moderate to strong linear correlation with all the Macular Parameters in Glaucoma Participants. These correlations were highly significant; (p-values <0.001). All measurements of superficial and deep macular venues plexuses by studied macular OCTA was statistically significantly lower in glaucomatous as compared to non-glaucomatous participants; (p-values <0.001). Conclusion: There was a reduction in VD in particular that of superficial layer in POAG patients in macular region, according to OCTA measurements. Glaucomatous eyes have a significantly sparser superficial VD in the macula when compared to

healthy eyes, and these VD assessments are significantly accompanied by the severity of VF destruction and OCT structural affection.

***Keywords*---**Glaucoma, OCTA , macular circulation, superficial & deep retinal plexuses

Introduction

Glaucoma is considered one of the important leading causes of irreversible loss of vision globally [1]. The pathophysiological mechanism of glaucoma remains complex and incompletely cleared, yet [2].

Studying microcirculation of the eye in glaucoma is a challenge because of the incapability of clearly detect the microvasculature in within various retinal layers as well as the optic nerve head (ONH) in a direct manner.
The introduction of optical coherence tomography angiography (OCT-A) recently enables to enhance the understanding the role of blood flow of the eye as well as the microvascul ature of retina in glaucoma pathogenesis [3]. Also, specialized software (split-spectrum amplitude-decorrelation angiography - SSADA) can assess the microvasculature of the retina in a quantitative and a reproducible manner [4].

In principle, OCT-A can compare sequential B-scans obtained at the same site to determine alterations. As stationary structures are seen static in sequential B-scans, alterations determined via OCT-A are mainly due to RBCs motion in the perfused vasculature. Many algorithms including SSADA, OCT-A ratio analysis, and optical microangiography (OMAG) are currently used to compute blood flow assessment from the sequential B-scans [5].

SD-OCT segmentation algorithms allows for quantification of various layers in the macula individually that are in particular affected by glaucomatous destruction mainly macular RNFL (mRNFL), RGCs with inner plexiform layer (GCIPL) as well as GCC [6].

This study aimed to compare the macular circulation in normal individuals and glaucomatous patients in the superficial as well as the deep retinal plexuses, to determine and characterize macular circulation deficits in glaucoma along with correlating them with structural macular OCT parameters.

2. Patients and Methods

This was a descriptive study included 100 eyes of 100 participants who were selected randomly from attendants of ophthalmology outpatient clinic in Beni-suef university hospital at period between first of July 2018 to end of January 2021.

Participants were classified into 2 groups: Group A: fifty Glaucomatous patients and Group B: Non glaucomatous Individuals (50 participants)

Inclusion criteria: Patients with POAG and Age> 40 years.

Exclusion criteria: Eyes with coexisting retinal pathologies, Non-glaucomatous optic neuropathies, Other types of glaucoma as angle-closure, neovascular, uveitic, congenital or traumatic glaucoma, Visual acuity < 0.05, Myopia > -6 D, Hyperopia > +4 D or astigmatism > 4D, History of ocular surgery or trauma AND Media opacities that might affect the quality of the OCT image.

2.3 All participants were subjected to complete ophthalmological examination including: unaided and aided visual acuity by Landolt's C chart expressed by Decimal, and refractive error using autorefractometer, IOP assessment with a Goldmann applanation tonometer, anterior segment examination using slit-lamp biomicroscopy, gonioscopy fundus examination and ONH assessment using a 90D lens. 24-2 SITA- standard automated VF test using standard automated perimetry (SAP) (Humphrey Field Analyzer II; Carl Zeiss Meditec, Dublin, CA, USA) OCT ONH examination and OCTA (Macula) using AngioVue; Optovue, Inc., Fremont, CA, USA).

Patients selected randomly based upon the following Inclusion and Exclusion criteria

Non glaucomatous subjects were required to have normal-appeared optic discs, intact neuroretinal rims and RNFLs, IOP <21 mm Hg and normal VF test results, defined as a pattern standard deviation (PSD) within the 95%confidence limits and a GHT result within normal range. The healthy subjects didn't present with ocular disease except for simple refractive errors. If the 2 eyes of a normal or glaucomatous patient met the inclusion criteria, only a single eye from each patient was selected at random and included in the study.

The SAP VF were acquired using the Swedish Interactive Threshold Algorithm standard 24–2 strategies. Only reliable tests (<33% fixation losses, <10 % false-positives, and <10 % false-negatives); VF without rim and eyelid artifacts; and cases without evidence that the abnormal results were due to diseases other than glaucoma were included. Glaucoma was confirmed by the existence of > 2 repeatable abnormal SAP results, that were detected as follows: (1) the GHT was out of the normal limit or PSD was significant at a P < 5% level and (2) the existence of a cluster of > 3 nearby points in typical glaucomatous areas didn't cross the horizontal meridian, all of which were depressed on the pattern deviation plot at a P < 5 percent level and one of which was depressed at a P < 1 percent level on at > 2 consecutive plots. The severity of glaucoma was recorded as the MD value.

The OCT parameters included RNFL thickness and GCC thickness as well as OCTA parameters included macular VD were attained to be correlated with each other in all subjects.

The OCTA imaging system (AngioVue; Optovue, Inc., Fremont, CA, USA) used an 840-nm superluminescent diode and has an A-scan rate of 70,000 scans/sec. The split-spectrum amplitude decorrelation angiography algorithm discriminates

the movement of the RBCs in a flowing blood vessel to produce angiographic images of perfused vessels and optimize the image acquisition.

Each participant underwent imaging session that consisted of a 6.0 × 6.0-mm-diameter perifoveal scan centered at the fovea. Superficial capillary plexus VD in the macular region was imaged 3 μm below the ILM to 15 μm below the IPL and deep capillary plexus VD - 15 μm below the IPL - 70 μm below the IPL. VD was measured using the % area occupied by flowing blood vessels in the selected area using the intrinsic imaging system software (Optovue, Inc.).). For macular scans, the whole enface image VD was measured in the whole 6.0 × 6.0-mm image with various areas of the macula as within concentric circles with enlarging diameters of 1, 3 and 6 mm around the fovea corresponding to the foveal, parafoveal and perifoveal areas, respectively. Poor quality scans, defined as images with (1) a signal strength index < 45; (2) residual motion artifacts visible as an irregular vessel pattern or disc boundary on the en face angiogram; (3) RNFL segmentation errors; or (4) a local weak signal caused by medial opacities, were excluded. For the measurements of GCC and RNFL, the built-in Avanti glaucoma module enabled assessment of the optic nerve head and RNFL and provided GCC scans. The thickness of RNFL was detected along a 3.45-mm-diameter circle centered on the OD. The GCC scan was centered 1-mm temporal to the fovea and covered a 6-mm diameter circular area on the central macula. All participants underwent both OCT-A and SD-OCT imaging on the same day. Data were collected, coded and entered to Excel sheet.

Statistical methodology

Data were analyzed via using SPSS (Statistical Package for the Social Sciences) software; analysis was carried out via the use of suitable statistical tests; results was considered significant for p-values <0.05.

Ethical considerations through explanation of the study to participants, informed consent from participants and approval of the ethical committee were full filled.

Results

Table (1)
Age and IOP Distribution of the Studied Groups

		Studied Groups		
		Glaucoma patients N= 50	**Non glaucomatous Individuals N= 50**	***p-value***
Age	**Mean ±SD**	48.98 ±10.19	48.56 ±11.31	0.846
	Range (Mini – Max)	42.00 - 65.00	24.00 - 65.00	
IOP	**Mean ±SD**	18.04 ±3.25	14.28 ±1.92	**0.001 ***
	Range (Mini – Max)	13.00 - 25.00	12.00 - 18.00	

Participants' age was ranged from 24 to 65 years old with an average of (48.77 ±10.72) years old. The two groups were matched regarding their age with non-statistically significant difference (p-value= 0.847). Table (1)

IOP was significantly higher in Glaucoma patients as compared with Non - glaucomatous Individuals, (18.04 ±3.25 vs. 14.28 ±1.92) in glaucomatous and non-glaucomatous participants respectively; (p-value <0.001). Table (1)

Regarding participant's sex, Males represent 53% of all participants and females represent 47% of them. The two groups were matched regarding their sex with non-statistically significant difference

Table (2)
Evaluation of VF in studied glaucomatous and non-glaucomatous participants by Humphrey field analyzer (HFA)

		Glaucoma patients N= 50	**Non glaucomatous Individuals N= 50**	***p-value***
MD	**Mean ±SD**	-11.15 ±8.10	-0.47 ±0.83	**0.001 ***
	Range (Mini – Max)	(-31.73 - -1.06)	(-2.0 – 0.5)	
VFI%	**Mean ±SD**	76.34 ±17.92	98.08 ±1.02	**0.001 ***
	Range (Mini – Max)	21.00 - 94.00	96.00 - 99.00	

Mean deviation (MD) in glaucomatous participants was statistically significantly lower as compared with non- glaucomatous participants [range from (-31.73) to (-0.1.06) and from (-2.0) to (0.5) in glaucomatous and non-glaucomatous participants respectively], the mean MD between the two studied groups was statistically significant; (-11.15 ±8.10 vs. -0.47 ±0.83); (p-value<0.001). Table (2)
Visual field index (VFI) in glaucomatous participants was statistically significantly lower as compared with non- glaucomatous participants [range from (21) to (94) and from (98.08) to (99) in glaucomatous and non-glaucomatous participants respectively], the mean VFI between the two studied groups was statistically significant; (76.34 ±17.92 vs. 98.08 ±1.02); (p-value<0.001).

Sensitivity and specificity of HFA parameters in diagnosis of glaucoma disease:

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of Humphrey field analyzer (HFA) parameters in distinguish Glaucoma disease from the normal individuals. Table (3);

The results of (ROC) curve analysis showed diagnostic ability of the HFA, the best sensitivity/specificity balance was observed for the MD of HFA (100% Sensitivity and 76% Specificity at cut-off point ≤-6.65), p-value <0.05. The best sensitivity/specificity balance was observed for the VFI of HFA (100% Sensitivity

and 96% Specificity at cut-off point ≤93.5), p-value <0.05, so; the HFA (MD & VFI) parameters diagnosed the disease state at a statistically significant level with a 100% Sensitivity (true positive cases in MD & VFI) and 76% & 96% Specificity (true negative cases in MD & VFI respectively). Figure (1)

Table (3)
The results of ROC curve analysis of HFA parameters in diagnosis of glaucoma disease among studied population

	AUC	**SE[a]**	**95% CI**	**Sensitivity**	**Specificity**	**Cutoff value**	**p-value[b]**
MD	0.98	0.009	0.971 – 0.999	100%	76%	≤-6.65	<0.001
VFI	>0.999	0.000	0.999 – 1.000	100%	96%	≤93.5	<0.001

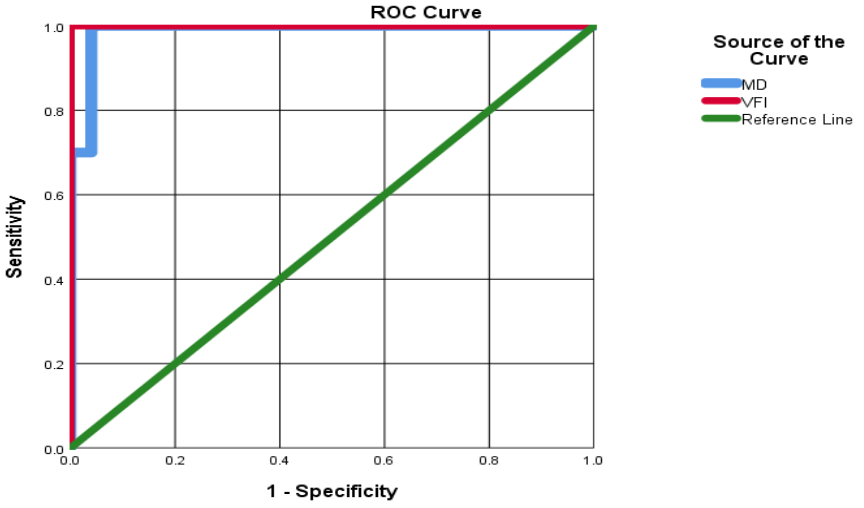

Figure (1): The ROC curve analysis of Humphrey field analyzer (HFA) parameters in diagnosis of glaucoma disease among studied population

Table (3)
Evaluation of the studied glaucomatous and non-glaucomatous participants by SD-OCT instruments

		Glaucoma patients N= 50	**Non glaucomatous Individuals N= 50**	***p-value***
Superior RNFL	**Mean ±SD**	68.28 ±15.10	105.06 ±5.82	**0.001 ***
	Range (Mini – Max)	45.00 - 98.00	98.00 - 116.00	

Inferior RNFL	**Mean ±SD**	66.56 ±14.54	109.20 ±7.48	**0.001 ***
	Range (Mini – Max)	43.00 - 103.00	94.00 - 119.00	
Average GCC	**Mean ±SD**	72.10 ±12.83	103.42 ±3.88	**0.001 ***
	Range (Mini – Max)	47.00 - 88.00	98.00 - 109.00	

Superior RNFL was statistically significantly lower in glaucomatous as compared with non- glaucomatous individuals (68.28 ±15.10 vs. 105.06 ±5.82); (p-value<0.001), Inferior RNFL was statistically significantly lower in glaucomatous as compared with non- glaucomatous individuals (66.56 ±14.54 vs. 109.20 ±7.48); (p-value<0.001), Average GCC was statistically significantly lower in glaucomatous as compared with non- glaucomatous individuals (72.10 ±12.83 vs. 103.42 ±3.88); (p-value<0.001). Table (3) and Figure (1)

Table (4)
SD-OCT parameters according to Glaucoma Severity among Studied glaucomatous and non-glaucomatous participants; (N=100)

		Glaucoma patients N= 50				
	Non-Glaucomatous Individuals N=50	**Mild N= 12**	**Moderate N=22**	**Advanced N=6**	**Severe N=10**	***p-value***
Superior RNFL						
Mean ±SD	105.06 ±5.82	82.16 ±5.20	78.00 ±15.72	61.00 ±15.22	61.80 ±5.82	**<0.001 ***
Range (Min – Max)	98.00 - 116.00	75.00 - 89.00	65.00 - 98.00	45.00 - 88.00	54.00 - 70.00	
Inferior RNFL						
Mean ±SD	109.20 ±7.480	80.33 ±4.03	81.00 ±17.06	56.45 ±10.33	63.60 ±8.36	**<0.001 ***
Range (Min – Max)	94.00 - 119.00	75.00 - 84.00	69.00 - 103.00	43.00 - 73.00	50.00 - 74.00	
Average GCC						
Mean ±SD	103.42 ±3.88	84.66 ±3.60	77.66 ±2.25	63.95 ±14.27	71.60 ±3.02	**<0.001 ***
Range (Min – Max)	98.00 - 109.00	78.00 - 88.00	75.00 - 80.00	47.00 - 85.00	69.00 - 76.00	

Results showed that patients with early (mild) disease had insignificantly higher average RNFL (Superior and Inferior RNFL) measurements when compared with patients with moderate and severe disease (p-value >0.05). Moreover, patients with moderate disease had significantly higher RNFL measurements when compared with patients with advanced and severe disease. In addition, normal controls had significantly higher RNFL measurements when compared with all degrees of glaucoma.

Results showed that patients with early disease (mild) had insignificantly higher average GCC thickness (Superior and Inferior GCC) measurements when compared with patients with moderate and severe disease (p-value >0.05). Moreover, patients with moderate disease had significantly higher GCC thickness measurements when compared with patients with severe disease. In addition, normal controls had significantly higher GCC measurements when compared with all degrees of glaucoma. Table (4)

Table (5)
Correlation between SD-OCT parameters with Evaluation of VF in studied glaucomatous and non-glaucomatous participants by HFA; (N=100)

OCT (SD-OCT) parameters		**Humphrey field analyzer (HFA) parameters**	
		MD	**VFI%**
Superior RNFL	**R**	0.659**	0.667**
	p-value	**<0.001***	**<0.001***
Inferior RNFL	**R**	0.653**	0.660**
	p-value	**<0.001***	**<0.001***
Average GCC	**R**	0.615**	0.661**
	P-value	**<0.001***	**<0.001***

According to Pearson correlation coefficient, there were moderate positive linear correlation between all the SD-OCT measured parameters (RNFL and GCC) and Humphrey field analyzer (HFA) measured parameters (MD and VFI%). Table (5)

Sensitivity and specificity of SD-OCT parameters [RNFL (superior and inferior) in diagnosis of glaucoma disease:

The results of (ROC) curve analysis in Figure (2) showed diagnostic ability of the SD-OCT, the best sensitivity/specificity balance was observed for the Superior RNFL of SD-OCT (100% Sensitivity and 96% Specificity at cut-off point ≤93.50), p-value <0.05. the best sensitivity/specificity balance was observed for the Superior RNFL of SD-OCT (100% Sensitivity and 96% Specificity at cut-off point ≤89.00), p-value <0.05. the best sensitivity/specific ity balance was observed for the Superior RNFL of SD-OCT (100% Sensitivity and 92% Specificity at cut-off point (≤86.00), p-value <0.05. So; the SD-OCT (RNFL & GCC) parameters diagnosed the disease state at a statistically significant level with a 100% Sensitivity (true positive cases in both RNFL & GCC) and 96%, 96%, & 92% Specificity (true negative cases in Superior RNFL Inferior RNFL & GCC respectively). Table (6)

Table (6)

The results of ROC curve analysis of SD-OCT parameters in diagnosis of glaucoma disease among studied population

	AUC	SE[a]	95% CI	Sensitivity	Specificity	Cutoff value	p-value[b]
Superior RNFL	0.996	0.004	0.988 – 1.000	100%	96%	≤93.50	<0.001
Inferior RNFL	0.990	0.008	0.974 – 1.000	100%	96%	≤89.00	<0.001
Average GCC	>0.999	<0.001	0.999 – 1.000	100%	92%	≤86.00	<0.001

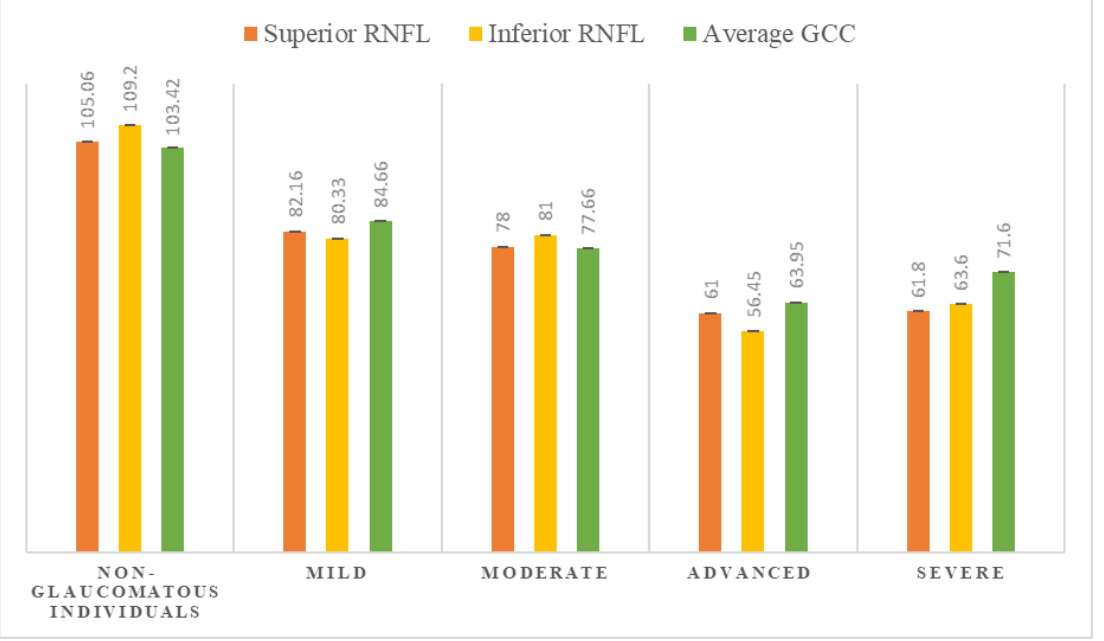

Figure (2): SD-OCTparameters according to Glaucoma Severity among Studied glaucomatous and non-glaucomatous participants.

All measurements of superficial macular venous plexuses by studied macular OCTA was statistically significantly lower in glaucomatous as compared to non-glaucomatous participants; (p-values <0.001). Table (7)

Table (7)
Superficial Macular Venous Plexuses by studied Macular OCTA glaucomatous and non-glaucomatous participants

		Glaucoma patients N= 50	Non glaucomatous Individuals N= 50	*p-value*
RFICI AL	**Whole Macula**	37.33 ±7.26	48.91 ±4.43	**<0.001***
	Superior Hemi	37.63 ±7.45	49.15 ±4.02	**<0.001***

	Inferior Hemi	37.00 ±7.04	48.64 ±5.12	**<0.001***
	Fovea	8.04 ±4.36	23.25 ±7.74	**<0.001***
	Para fovea	40.55 ±11.42	52.61 ±4.43	**<0.001***
	Superior Hemi Para Fovea	40.98 ±10.46	52.92 ±4.09	**<0.001***
	Inferior Hemi Para Fovea	40.16 ±12.52	52.28 ±5.12	**<0.001***
	Temporal Para Fovea	39.68 ±12.39	52.14 ±4.78	**<0.001***
	Superior Para Fovea	40.76 ±10.05	53.64 ±4.05	**<0.001***
	Nasal Para Fovea	40.36 ±12.98	51.52 ±4.19	**<0.001***
	Inferior Para Fovea	40.83 ±11.88	53.08 ±5.69	**<0.001***
	Peri Fovea	40.01 ±7.37	49.73 ±4.58	**<0.001***
	Superior Hemi Peri Fovea	39.87 ±7.512	49.66 ±4.80	**<0.001***
	Inferior Hemi Peri Fovea	40.22 ±7.37	50.27 ±4.15	**<0.001***
	Temporal Peri Fovea	38.01 ±6.81	46.07 ±4.82	**<0.001***
	Superior Peri Fovea	37.81 ±8.41	49.54 ±4.56	**<0.001***
	Nasal Peri Fovea	43.53 ±8.49	53.15 ±6.25	**<0.001***
	Inferior Peri Fovea	38.46 ±7.41	49.78 ±4.61	**<0.001***

All measurements of deep macular venues plexuses by studied macular OCTA was statistically significantly lower in glaucomatous as compared to non-glaucomatous participants; (p-values <0.001). Table (8)

Table (8)
Deep Macular Venous Plexuses by studied Macular OCTA in glaucomatous and non-glaucomatous participants

		Glaucoma patients N= 50	**Non glaucomatous Individuals N= 50**	***p-value***
DEEP PLEXUSES	**Whole Macula**	41.22 ±9.28	50.79 ±4.94	**<0.001***
	Superior Hemi	41.44 ±9.86	51.27 ±4.58775	**<0.001***
	Inferior Hemi	41.04 ±8.68	50.21 ±5.43	**<0.001***
	Fovea	21.50 ±8.89	38.10 ±7.54	**<0.001***
	Para Fovea	46.02 ±12.60	54.71 ±4.37	**<0.001***
	Superior Hemi Para	46.82 ±11.59	54.99 ±4.37	**<0.001***
	Inferior Hemi Para	45.22 ±13.72	54.39 ±4.62	**<0.001***
	Temporal Para	47.57 ±14.41	55.45 ±4.70	**<0.001***

	Superior Para	45.57 ±10.84	53.66 ±5.19	**<0.001***
	Nasal Para	46.88 ±13.37	56.06 ±3.87	**<0.001***
	Inferior Para	43.99 ±12.54	53.49 ±4.61	**<0.001***
	Peri	42.72 ±9.67	50.20 ±5.94	**<0.001***
	Superior Hemi Peri	42.67 ±10.76	50.80 ±5.33	**<0.001***
	Inferior Hemi Peri	42.78 ±8.61	49.55 ±6.73	**<0.001***
	Temporal Peri	45.22 ±9.53	53.38 ±5.18	**<0.001***
	Superior Peri	39.54 ±11.78	50.71 ±5.04	**<0.001***
	Nasal Peri	44.06 ±9.81	48.67 ±6.58	**0.007**
	Inferior Peri	40.00 ±8.17	51.31 ±6.24	**<0.001***

Sensitivity and specificity of studied macular OCTA parameters in diagnosis of glaucoma disease:

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of studied macular optical coherence tomography Angiography (OCT-A) parameters in distinguish Glaucoma disease from the normal individuals. Table (9)

The results of (ROC) curve analysis showed diagnostic ability of the OCT-A, the best sensitivity/specificity balance was observed for the Superficial Whole Macula plexuses of OCT-A (88% Sensitivity and 76% Specificity at cut-off point ≤42.65), p-value <0.05. The best sensitivity/specificity balance was observed for the Deep Whole Macula plexuses of OCT-A (90% Sensitivity and 60% Specificity at cut-off point ≤45.45), p-value <0.05.

So, the OCT-A parameters (superficial and deep all macular plexuses) parameters diagnosed the disease state at a statistically significant level with an 88% and 76% Sensitivity (true positive cases in superficial and deep all macular plexuses respectively) and 90% & 60% Specificity (true negative cases in superficial and deep all macular plexuses respectively).

Table (9)
The results of ROC curve analysis of macular OCTA parameters in diagnosis of glaucoma disease among studied population

	AUC	**SE[a]**	**95% CI**	**Sensitivity**	**Specificity**	**Cutoff value**	**p-value[b]**
Superficial	0.931	0.023	0.886 – 0.977	88%	76%	≤42.65	<0.001
Deep	0.825	0.041	0.745 – 0.905	90%	60%	≤45.45	<0.001

Correlation with traditional glaucoma diagnostic measurements in the glaucoma group, the superficial Whole Macula vascular Plexus had strong correlation with

the RNFL (Superior and Inferior) and GCC thickness and moderate correlation with the MD and VFI%. The deep Whole Macula vascular Plexus had moderate correlation with the RNFL (Superior and Inferior), GCC thickness, MD and VFI%. These correlations were highly significant; (p-values <0.001). Table (10)

Table (10)
Correlation Matrix of Macular Parameters in Glaucoma Participants

		Superficial Whole Macula	Deep whole macula
MD	**R**	0.604**	0.451**
	P-value	0.001*	0.001*
VFI%	**R**	0.590**	0.460**
	P-value	0.001*	0.001*
Superior RNFL	**R**	0.718**	0.647**
	P-value	0.001*	0.001*
Inferior RNFL	**R**	0.758**	0.676**
	P-value	0.001*	0.001*
Average GCC	**R**	0.748**	0.695**
	P-value	0.001*	0.001*

IOP showed significant negative moderate to strong linear correlation with all the Macular Parameters in Glaucoma Participants. These correlations were highly significant; (p-values <0.001). Table (11)

Table (11)
Correlation between Macular Parameters with the IOP in glaucoma subjects

		IOP
MD	**R**	-0.678**
	P-value	0.001*
VFI%	**R**	-0.718**
	P-value	0.001*
Superior RNFL	**R**	-0.563**
	P-value	0.001*
Inferior RNFL	**R**	-0.581**
	P-value	0.001*
Average GCC	**R**	-0.511**
	P-value	0.001*
Superficial Whole Macula	**R**	-0.555**
	P-value	0.001*
Deep whole macula	**R**	-0.422**
	P-value	0.001*

Discussion

The POAG is an optic neuropathy characterized by an open AC angle, high or sometimes average IOP and extensive RGCs & their axons degeneration resulting in characteristic excavation of the neuroretinal rim with corresponding VF defects

[7]. Since glaucoma destroys RGCs and nearly 1/3 of RGCs are located within the macula, macular perfusion is theoretically an important site to determine glaucoma and evaluate the glucoma severity. [8].

Structural OCT studies have proved that the macular GCC thickness in addition to other values of GCC thickness are decreased in glaucomatous eyes [9] and focal loss of macular GCC is an essential predictor of VF conversion and progression.

OCT-A has showed its significance in the field of glaucoma diagnosis and understanding the pathophysiology of such condition [10]. Assessments of the macular perfusion can detect reduced metabolic rate in dysfunction in RGCs prior their apoptosis and leads to thinning of GCC [5].

The aim of our study was to correlate strength of associations between OCT-A vessel density (VD) evaluation in the macula with standard structural OCT thickness measures in patients suffering POAG

Our study includes 100 eyes of 100 participants who divided into 2 groups: Group A: Glaucomatus patients (50 patients) and Group B: Non glaucomatous Individuals (50 participants)

Participants' age ranged from 24 - 65 ys with an average of (48.77 ±10.72) years old. Mean deviation (MD) in glaucomatous cases was statistically significantly less in comparison with non- glaucomatous participants range from (-0.1.06) to (-31.73) and from (0.5) to (-2.0) in glaucomatous and non-glaucomatous participants respectively,

Superior RNFL was statistically significantly lower in glaucomatous patients as compared with non- glaucomatous individuals (68.28 ±15.10 vs. 105.06 ±5.82); (p-value<0.001), Inferior RNFL was statistically significantly lower in glaucomatous as compared with non- glaucomatous individuals (66.56 ±14.54 vs. 109.20 ±7.48); (p-value<0.001), Average GCC was statistically significantly lower in glaucomatous as compared with non- glaucomatous individuals (72.10 ±12.83 vs. 103.42 ±3.88); (p-value<0.001).

All measurements of superficial and deep macular venoues plexuses by studied macular OCTA was statistically significantly lower in glaucomatous as compared to non-glaucomatous participants.

Chen et al [11] reported Humphery VF results in form of MD in glaucomatous eyes was less when compared to that in healthy eyes (-8.8 ± 6.2 Vs 0.1 ±1.3) (p-value<0.001) which was similar to our present study (-11.15 ±8.10 vs. -0.47 ±0.83); (p-value<0.001) .

According to chen et al [11] the superficial whole image VD (wiVD) in glaucomatous eyes was less when compared to healthy eyes in the macula (38.5% ± 2.2% vs. 43.2% ± 2.3%, $P < 0.001$) which were in favor to our results (37.33% ±7.26 % Vs 48.91 % ±4.43 % , $P < 0.001$).

Overall, the AUROC for comparing between glaucomatous and healthy eyes was highest for RNFL thickness (0.95) and GCC thickness (0.95), followed by superificial macular VD (0.94) while in our study it was (0.990, >0.999 and 0.931 respectively)

Also, the superficial macular VD and RNFL thickness revealed the highest sensitivity at 80 percent specificity (sensitivity: 0.92), and the GCC thickness showed the highest sensitivity at 90percent specificity (sensitivity: 0.89) while results in our study refer to Superficial Whole Macula plexuses (76 percent Specificity at cut-off point (COP) ≤42.65, p-value <0.05) and Deep Whole Macula plexuses 60 percent Specificity at COP ≤45.45, p-value <0.05).

As expected, both RNFL thickness and GCC thickness were significantly thinner in the glaucomatous eyes when compared to control eyes (P < 0.001 for all), including the average values, and the superior and inferior hemifield values as well as study had shown.

Chao and associates [12] reported that the superficial wiVD in glaucoma eyes was less when compared to control eyes in the macula (41.66 ± 5.18 vs. 48.97 ± 3.12, P < 0.01) which were comparable to our study results and the deep wiVD in glaucoma eyes less when compared to healthy eyes in the macula (46.46 ± 3.92 Vs 50.42 ± 8.11 , P <0.01) while our results were (41.22 ±9.28 Vs 50.79 ±4.94 ,P < 0.001)

Another study performed at 2020 by Köse and Tekeli [13] revealed that the VD in glaucoma eyes was significantly less when compared to the healthy group in both superficial (44.08%±5.46% vs 51.28%±2.85%, P<0.001) and deep (45.13%±8.55% vs 54.20%±5.44%, P<0.001) vascular plexus.

These results are in agreement with observational and prospective study made by Li et al [14] in which 218 eyes (116 participants) were classified into five groups: no glaucoma, early glaucomatous eyes, moderate glaucomatous eyes, advance glaucomatous eyes, severe glaucomatous eyes, they concluded that decreased VD in macula of glaucomatous eyed were determined and a statistically significant correlation with glaucoma stages (P<0.01). In addition, the results of retinal VD, decreased RNFL thickness and GCC thickness were statistically correlated to the stage of glaucoma as well.

Lommatzsch et al [15] revealed that macular VD was significantly decrease in both SL and DL in glaucoma eyes when compared to control eyes (p = SL < 0.0001; DL = 0.009). No significant difference in VD between the SL and the DL has been observed (p = 6.60 • 10-18). The marked reduction of VD in glaucoma eyes was observed in the inferior sector of the macula. Moderate - high correlation with IOP, MD, GCC, peripapillary RNFL thickness was documented.

Another study made by Yarmohammadi et al [16] to assess the association between VD measurements using OCTA and severity of VF loss in POAG exhibited that VD was more in normal eyes followed by glaucoma suspects, mild glaucoma, and moderate-severe glaucoma eyes for wiVD (55.5%, 51.3%, 48.3%, and 41.7%, respectively) (P < 0.001). The correlation between SAP MD with VD was stronger

(R2 ¼ 0.51) when compared to the correlation between SAP MD with RNFL (R2 ¼ 0.36) (P < 0.05) .

As regard the diagnostic abilities to differentiate glaucomatous eyes from healthy ones, our results are consistent with the findings of Yarmohammadi et al [16] that have revealed comparable diagnostic accuracies as regarding VD, RNFL thickness, and GCC thickness. Our results showed that alterations in macular superficial VD might be a reliable diagnostic parameter for the detection of glaucoma with similar sensitivities. Yarmohammadi and associates [16] also reported that reduced VD was significantly accompanied by the severity of VF destruction regardless the structural loss, and the vascular functional correlations were stronger in comparison with the standard structural (RNFL)-functional relationships. Moreover, the reduced VD was correlated at the corresponding side of the VF defects.

Another study made by Nesma [17] demonstrated that in glaucoma group; the VD was 21.18 ± 2.6 at the fovea, whereas it was 39.5 ± 4.71 at the parafoveal area. There was a statistically significant positive correlation between MVD (foveal and parafoveal (in particular at the superior quadrant) and the MD (R positive, P < 0.05). There was a statistically significant positive correlation between VD and the structural parameters.

The present study is in contrast with the study of Triolo et al. [18] who conducted their study on 40 controls, 40 cases with suspicious glaucoma, and 40 glaucomatous patients. they proved that Peripapillary RNFL, GCC, and macular RNFL thicknesses significantly reduced in the glaucomatous patients in comparison with control as well as glaucoma suspicious groups (P < 0.01). but macular VD wasn't statistically different in all groups (P > 0.05) and there was no statistically significant association between GCC thicknesses and macular VD (all P > 0.05) in previous groups.

The diagnostic accuracy of macular OCTA was studied by Rao et al [19] in comparison with peripapillary and disc OCTA. In sharp contrast to our results, they revealed that macular VD had poor diagnostic accuracy (AROC 0.69,). Our higher diagnostic accuracy was most likely because of a larger macular scan area of 6 × 6mm in comparison with the small scan area of 3 × 3 mm used by Rao et al.

Hou et al [20] reported decreased parafoveal VD while elevated foveal avascular zone in POAG eyes and this might be explained by the fact that some of the patients were suffering from hypertension and on medical therapy
We found that glaucoma affected the SVC to a marked extent than the DVC and those finding are comparable to findings that Takusagawa et al [21] had shown. According to their study localized capillary loss was determined in the SVC in glaucoma eyes without affection of DVC.

According to Takusagawa et al [21] among the overall macular VD parameters, the SVC VD had the best diagnostic accuracy as assessed by the AROC. The accuracy was even better when the worse hemisphere (inferior or superior) was

used, attaining an AROC of 0.983 and a sensitivity of 96.7 percent at a specificity of 95%.

It is not surprising that the SVC VD was markedly decreased in glaucoma eyes as it supplies the NFL, GCL, and part of the IPL, the anatomic layers most involved by glaucoma.The DCP was involved by less degree glaucoma, as it supplies the middle retinal layers that don't include the RGCs.

In the present study, we demonstrated that OCT-A VD , measured in the SVC and DVC of the retina in the macula, distinguishes between groups of glaucoma and healthy subjects. The macular VD showed a diagnostic accuracy the same as that of other known metrics including RNFL and GCC thickness to differentiate between glaucoma and healthy eyes.

our study also showed a potential correlation between VF severity with measurements of VD around the macula. The vessel dropout might exhibit a stepwise reduction during the early stage of glaucoma while reach a floor during the late stage of glaucoma. Another possible cause is that the current OCT-A device detects vessels according to the amplitude decorrelation of blood flow, and this method depends on blood flow over only a narrow range above a specific threshold of motion. By way of explanation , vessels with a flow less than the threshold of the device can't be visualized [22]. So, the correlated powers of the microvasculature might be limited in cases with advanced glaucoma with marked vessel drop-out.

Collectively, the results of our study suggest that measures of VD of the macula might help diagnosis of glaucoma and assess disease severity. Moreover, publications have shown that the mean VD is markedly correlated with age range & gender [23]. In healthy eyes, macular perfusion is reduced with increased age and is reduced more quickly in men than women [24]. Since there was no significant difference in age or gender between our study groups, there was no necessity for further adjustment in the current study. However, future studies should consider the variation in various study populations. Finally, we couldn't comment on the effectiveness of VD evaluation in assessing disease progression.

Conclusion

There was a reduction in VD particularly of superficial layer in POAG patients in macular region, according to OCT-A measurements. Glaucomatous eyes have a significantly sparser superficial VD in the macula when compared to healthy eyes, and these VD assessments are significantly accompanied by the severity of VF destruction. Measurements of macular superficial VD showed comparable diagnostic powers to other vascular or structural measurements for comparing glaucomatous and healthy eyes. Such finding offers new insights into the pathophysiology of glaucoma. Further studies that exclude the impacts of glaucoma medications are required to assess the relationship between vascular alterations and glaucomatous destruction

Limitations

The lack of patients with preperimetric glaucoma as a comparison group also limits the powers of our findings as we couldn't evaluate if decreased vascular density occurs before altered visual field or the reverse. We didn't assess this phenomenon, by the characteristics of the study. Further studies with more participants to assess if OCT-A has an adequate dynamic range to provide clinically relevant data across the full spectrum of glaucoma severity are warranted

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