The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 2020-2025

Macular Area Perfusion in Normal and Glaucomatous Eyes Using Optical Coherence Tomography Angiography

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ABSTRACT

Background: The most common cause of blindness worldwide is glaucoma, a condition that progresses over time and has the potential to permanently impair eyesight. The only glaucoma-related anomaly for which therapy stops the disease from progressing is an increase in intraocular pressure (IOP).

Objective: The aim of the current work was to elucidate the differences of perfusion in macular area between normal and glaucomatous eyes, and determine the correlation between the macular area vessel density (VD) and glaucoma severity using optical Coherence tomography angiography (OCTA).

Patients and Methods: This Cross sectional prospective analytic study included 20 participants with 20 glaucomatous eyes and 20 normal eyes, attending at Outpatient Clinics, Department of Ophthalmology, Suez Canal University Hospital, Ismailia, Egypt. Cases were scheduled for OCTA examination.

Results The changes macular vessel density (MVD) had strongly positive correlation with ganglion cell layer (GCL) thickness and retinal nerve fiber layer (RNFL) thickness, had negative correlation with the severity of glaucoma, which meant the more severe the glaucoma was, the lower MVD was. Compared to traditional glaucoma staging system judged by visual field (VF), the changes MVD obtained by OCTA might be a new method to grade the stage of glaucoma. These findings theorize that the changes of MVD may be better facilitated for the observation and monitoring of glaucoma progression.

Conclusion: It could be concluded that macular vessel density (MVD) has strongly positive correlation with ganglion cell layer (GCL) thickness and RNFL thickness, has negative correlation with the severity of glaucoma, which mean that the more severe the glaucoma is, the lower (MVD), (RNFL) and (GCL) are.

Keywords: Macular Area Perfusion, Glaucomatous Eyes, Optical Coherence Tomography Angiography

INTRODUCTION

Glaucoma is the most common cause of blindness in the world and is a progressive condition that can result in irreversible visual loss [(1)]. The only glaucoma-related anomaly for which therapy stops the disease from progressing is an increase in intraocular pressure (IOP) [(2)].

A technique called optical coherence tomography angiography (OCTA) was created to examine the retinal and peripapillary microvasculature [(3)]. OCTA research showed alterations in the vascular density (VD) of the optic nerve head (ONH) [(4)], while a different study demonstrated a decline in peripapillary VD in glaucoma-affected eyes [(5)].

According to a study, the diagnostic value of peripapillary VD in eyes with primary open-angle and primary angle-closure glaucoma was equivalent to the thickness of the retinal nerve fiber layer [(6)]. Macular and optic nerve head vessel density (ONH-VD) measures, however, were revealed to have much lower diagnostic value than peripapillary VD readings [(7,8)].

Macular OCT measures that specifically target the macular ganglion cell complex (GCC) can increase the glaucoma diagnosis accuracy since the lamina cribrosa is made up of porous connective tissue. Studies have shown that the macula is home to a majority of retinal ganglion cells and that the macula is affected by early glaucomatous damage [(9, 10)].

The aim of the work was to elucidate the differences of perfusion in macular area between normal and glaucomatous eyes, and determine the correlation between the macular area vessel density (VD) and glaucoma severity using optical Coherence tomography angiography (OCTA).

PATIENTS AND METHODS

This Cross sectional prospective analytic study included 20 participants with 20 glaucomatous eyes and 20 normal eyes, attending at Outpatient Clinics, Department of Ophthalmology, Suez Canal University Hospital, Ismailia, Egypt. Cases were scheduled for OCTA examination.

Inclusion Criteria:

- Adult patients aged above 35 years old.
- Adult glaucomatous patients approved with visual field test, IOP measuring, Optic nerve head, and nerve fiber layer analysis.
- Nonglaucomatous adult patients.

Exclusion Criteria:

- Pre-existing ocular abnormalities.
- Previous ocular inflammations or trauma.
- Patients performed any previous ocular surgeries.
- Patients performed any anterior segment procedures during follow up.

Complete ophthalmic examinations were performed to all patients including the following:

- **History:** Personal Data: name, age, address, occupation and phone number, ocular history, and

Received: 09/09/2022
Accepted: 12/11/2022

systemic history.

- **Examination:**
  - Visual acuity: Uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) using Landolt chart.
  - Refraction: For the purpose of determination of the degree of refraction, cycloplegic refraction was measured with an auto refractometer (NIDEK AR-600).
  - **External eye examinations:** lids, orbit, lacrimal system and ocular motility.
  - **Slit-Lamp bio microscopic examination** (Topcon -Japan)**:** full examination of the anterior segment performed for cornea, sclera, anterior chamber, iris, pupil, and lens.
  - **Intra-ocular pressure measurement:** using Goldmann applanation tonometer (Keeler, UK).
- **Fundus examination:**
  - Indirect ophthalmoscope (TOPCON ID-5).
  - Volk's non-contact double aspheric biconvex lens (power: + 90).
- **Investigation:**

Optical coherence tomography angiography (OCTA): Macular area perfusion analysis were carried out by using optical coherence tomography angiography (OCTA) (DRI OCT Triton plus (Topcon Co2015, Tokyo, Japan)- Swept source with implemented SMART Track TM system [(11)].

Optical Coherence Tomography: (Dri OCT Triton plus Topcon Co 2015, Tokyo, Japan).
Macular thickness, choroidal thickness and the retinal nerve fiber layer measurements were performed using an optical coherence tomography.
OCT Triton plus Topcon used in this study. Optical coherence tomography (OCT) is a noncontact, noninvasive, in vivo, higher solution, cross-sectional imaging of the eye that measures backscattered light. In this study we used (Topcon Co 2015, Tokyo, Japan) OCT Triton plus, with Swept Source technology & 1050 nm wavelength.

Visual Field Test:

Visual field analysis was carried out by using (HUMPHREY FIELD ANALYZER (Carl Zeiss Meditec Inc. 2008, Dubin, CA, USA) –Model 745i) [(12)]**.**

***Ethical Consideration*:**

This study was ethically approved by Suez Canal University's Ethical Institutional Review Board. Written informed consent of all the participants was obtained after being informed of the research's goals. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical Analysis

Microsoft Excel software was used to code, input, and analyse historical data, basic clinical examinations, laboratory investigations, and outcome measurements. The Statistical Package for the Social Sciences (SPSS version 20.0) programme was then used to import the data and perform analysis. The following tests were performed to determine if differences were significant; difference and association of qualitative variable by Chi square test; quantitative continues group represent by mean ±SD; and according to the kind of data qualitative represent as number and percentage (X2). P values 0.05 were deemed significant when comparing differences across quantitative independent groups using the t-test, Pearson's correlation, or Spearman's correlation.

RESULTS

This study included 40 eyes (20 glaucomatous eyes and 20 normal eyes). This table shows that age was distributed as 38.3±12.36 and 42.40±3.97 years respectively with no significant difference between groups also groups were matched regard sex and side distribution **(Table 1).**

Table (1): Age and sex distribution between studied groups.

			Glaucomatous eyes Group	Normal eyes group	t	P
Age (years)			38.3±12.36	42.40±3.97	1.254	0.218
Sex	**Female**	**N**	14	14		
		%	70.0%	70.0%		
	Male	**N**	6	6	0.0	1.0
		%	30.0%	30.0%		
Side	**Right**	**N**	10	10		
		%	50.0%	50.0%		
	Left	**N**	10	10	0.0	1.0
		%	50.0%	50.0%		
Total		**N**	20	20		
		%	100.0%	100.0%		

This table shows that IOP was distributed as 14.70±1.89 and 15.45±2.16 respectively with no significant difference

between groups **(Table 2).**

Table (2): IOP distribution between studied groups.

	Glaucomatous eyes Group	Normal eyes group	t	P
IOP	14.70±1.89	15.45±2.16	1.166	0.251

This table shows that glaucomatous eyes group significantly associated with low VA **(Table 3)**.

Table (3): Visual acuity distribution between studied groups using log Mar.

			Group		X^2	P
			Glaucomatous eyes Group	Normal eyes group		
VA	**0.00**	**N**	1	9	36.40	0.00**
		%	5.0%	45.0%		
	0.20	**N**	0	7		
		%	0.0%	35.0%		
	0.30	**N**	0	4		
		%	0.0%	20.0%		
	0.70	**N**	11	0		
		%	55.0%	0.0%		
	1.00	**N**	6	0		
		%	30.0%	0.0%		
	1.1	**N**	2	0		
		%	10.0%	0.0%		
Total		**N**	20	20		
		%	100.0%	100.0%		

This table shows NFL thickness distribution between glaucomatous and normal eyes as (NFL sup 96.05±14.42 in glaucomatous, 123.65±2.20 in normal), (NFL inf 89.95±6.97 in glaucomatous, 120.85±3.55 in normal), (NFL nasal 77.75±9.20 in glaucomatous, 86.55±4.68 in normal) and (NFL temp 75.10±8.35 in glaucomatous, 87.45±4.11 in normal), so this proves that Glaucomatous eyes group was significantly lower regard NFL **(Table 4).**

Table (4): NFL distribution between studied groups

	Glaucomatous eyes Group	Normal eyes group	t	P
NFL sup	96.05±14.42	123.65±2.20	8.461	0.00**
NFL inf	89.95±6.97	120.85±3.55	17.644	0.00**
NFL nasal	77.75±9.20	86.55±4.68	3.810	0.00**
NFL temp	75.10±8.35	87.45±4.11	5.933	0.00**

This table shows GCL thickness distribution between glaucomatous and normal eyes as (GCL sup 72.0±2.79 in glaucomatous, 89.90±2.93 in normal), (GCL inf 72.50±2.41in glaucomatous, 86.90±3.69 in normal), (GCL nasal 69.60±2.03 in glaucomatous, 88.50±1.79 in normal) and (GCL temp 69.95±6.31 in glaucomatous, 87.10±3.0 in normal), so this proves that Glaucomatous eyes group was significantly lower regard GCL **(Table 5).**

Table (5): GCL distribution between studied groups.

	Glaucomatous eyes Group	Normal eyes group	t	P
GCL sup	72.0±2.79	89.90±2.93	19.761	0.00**
GCL inf	72.50±2.41	86.90±3.69	14.578	0.00**
GCL nasal	69.60±2.03	88.50±1.79	31.160	0.00**
GCL temp	69.95±6.31	87.10±3.0	10.970	0.00**

This table shows VD distribution between glaucomatous and normal eyes as (VD sup 44.38±3.98 in glaucomatous, 50.80±3.30 in normal), (VD inf 44.87±4.78in glaucomatous, 49.17±3.99 in normal), (VD nasal 43.43±5.36 in glaucomatous, 47.06±3.53 in normal) and (VD temp 40.57±6.21 in glaucomatous, 47.92±2.82 in normal), so this proves

that Glaucomatous eyes group was significantly lower regard VD **(Table 6).**

Table (6): VD distribution between studied groups.

	Glaucomatous eyes Group	Normal eyes group	t	P
VD sup	44.38±3.98	50.80±3.30	5.540	0.00**
VD inf	44.87±4.78	49.17±3.99	3.088	0.004*
VD nasal	43.43±5.36	47.06±3.53	2.523	0.016*
VD temp	40.57±6.21	47.92±2.82	4.820	0.00**

This table shows that VD in all aspect significantly positive correlated with NFL and GCL also superior and inferior significantly positive correlated with IOP **(Table 7).**

Table (7): correlation of IOP, NFL thickness and GCL thickness with VD.

		VD sup	VD inf	VD nasal	VD temp
IOP	**R**	.408**	.322*	.172	.234
	P	.009	.049	.288	.147
NFL sup	**R**	.624**	.442**	.552**	.561**
	P	.000	.004	.000	.000
NFL inf	**R**	.682**	.504**	.424**	.597**
	P	.000	.001	.006	.000
NFL nasal	**R**	.376*	.444**	.107	.217
	P	.017	.004	.511	.179
NFL temp	**R**	.423**	.451**	.500**	.679**
	P	.007	.002	.001	.000
GCL sup	**R**	.663**	.509**	.432**	.577**
	P	.000	.001	.005	.000
GCL inf	**R**	.668**	.379*	.347*	.620**
	P	.000	.016	.028	.000
GCL nasal	**R**	.647**	.451**	.321*	.605**
	P	.000	.003	.043	.000
GCL _temp	**R**	.652**	.505**	.329*	.459**
	P	.000	.001	.038	.003

DISCUSSION

The study included 40 eyes (20 right and 20 left eyes) of 20 participants, 14 female, 6 male. Participants were divided into two groups, normal eyes, glaucomatous eyes, each of them included 20 eyes.

The parameters which were evaluated in the current study included: Retinal nerve fiber layer (RNFL), Ganglion cell layer (GCL) and Vessel perfusion density (VD). We used OCTA to study parafoveal microvasculature changes in healthy and glaucomatous eyes in 4, and we used OCT to study parafoveal retinal nerve fiber layer and ganglion cell layer changes in healthy and glaucomatous eyes.

We found that there were highly statistically significant differences between normal and glaucomatous eyes regarding Retinal nerve fiber layer (RNFL), Ganglion cell layer (GCL) and Vessel perfusion density (VD). This study showed decreased macular vessel perfusion density (VD) in glaucomatous eyes relative to the eyes of normal subjects, that correlated with decreased RNFL and GCL.

This study results were consistent with **Chao *et al.*** [13] who analyzed early macular angiography among patients with glaucoma, ocular hypertension, and normal subjects .

Chao *et al.* [13] reported that decreased macular circulation in OAG and NTG eyes relative to the eyes of patients with OHT and normal subjects. In studies characterizing OAG via OCTA, decreased peripapillary microvascular network correlated with RNFL and VF defects as well as impaired macular VD was found.

Also **Chao *et al.*** [13] reported that the RNFL and GGC thicknesses were influenced by the vascular flow.

In this study, parafoveal VD was significantly lower in glaucoma subjects, VD sup. (44.38±3.98%, P=0.00), VD inf. (44.87±4.78%, P=0.004), VD nasal (43.43±5.36%, P=0.016), VD temp. (40.57±6.21%, P=0.00). Also parafoveal RNFL was significantly

lower in glaucoma subjects, RNFL sup. (96.5705±14.42%, P=0.00), RNFL inf. (89.95±6.97%, P=0.00), RNFL nasal. (77.75±9.20%, P=0.00), RNFL temp. (75.10±8.35%, P=0.00).

Also parafoveal GCL was significantly lower in glaucoma subjects, GCL sup. (72.0±2.79%, P=0.00), GCL inf. (72.50±2.03%, P=0.00), GCL nasal (69.60±2.03%, P=0.00), GCL temp. (69.95±6.31%, P=0.00).

This study results were consistent with **Onishi *et al.*** [14] who analyzed parafoveal and peripapillary perfusion in healthy, glaucoma suspect, normal-tension glaucoma, and primary open-angle glaucoma subjects.

Onishi *et al.* [14] reported that There were significant decreases in parafoveal superficial vessel density in primary open-angle (40.06±4.54%, P<0.001) and normal-tension glaucoma (42.82±5.16%, P=0.010) but not suspect eyes (45.72±4.37%, P=0.916) compared to healthy eyes (48.10±2.82%). Similarly, decreases were observed in parafoveal inner retinal thickness in primary open-angle (83.19±14.29 μm, P<0.001) and normal-tension glaucoma eyes (94.97±12.44 μm, P=0.035), but not suspect eyes (99.93±9.00 μm, P=0.648), compared to healthy controls (107.00±9.55 μm). Only primary open-angle glaucoma eyes displayed significant changes in peripapillary vessel density (37.63±7.19%) compared to healthy controls (49.12±2.80%, P<0.001). Further statistical adjustment for sex and age revealed a significant decrease in parafoveal vessel density in suspects relative to controls (P=0.039). Diagnostic accuracy of parafoveal vessel density was high with an area under the curve of 0.833±0.073 for normal-tension glaucoma and 0.946±0.049 for primary open-angle glaucoma.

This study results were consistent with **You *et al.*** [15] who analyzed macular vessel density measured with optical coherence tomography angiography and its associations in a large population-based study.

You *et al.* [15] reported that this large population-based study provided normative OCTA data of macular vessel density and demonstrated that a lower superficial retinal vessel density was significantly associated with lower SSI and male sex, while a lower deep layer retinal vessel density was significantly associated with lower SSI, longer AL, and higher level of creatinine. These associations must be considered when interpreting clinical quantitative OCTA data.

This study results were consistent with **Li *et al.*** [16] who analyzed comparisons of retinal vessel density and glaucomatous parameters in optical coherence tomography angiography.

Li *et al.* [16] reported that The changes of peripapillary vessel density (PVD) and macular vessel density (MVD) had strongly positive correlation with ganglion cell-inner plexiform layer (GCIPL) thickness and RNFL thickness, had negative correlation with the severity of glaucoma, which meant the more severe the glaucoma was, the lower PVD and MVD were. Compared to traditional glaucoma staging system judged by VF, the changes of PVD and MVD obtained by OCTA might be a new method to grade the stage of glaucoma. These findings theorize that the changes of PVD and MVD may be better facilitated for the observation and monitoring of glaucoma progression.

This study results were consistent with **Triolo *et al.*** [17] who analyzed macular and peripapillary vessel perfusion density (VD) in glaucoma suspects (GS) and glaucoma patients; to correlate ganglion cell–inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL) thicknesses with macular and peripapillary VD; and to evaluate the diagnostic accuracy of the structural and vascular parameters.

Triolo *et al.* [17] reported that Structural damage is evident both in the peripapillary and in macular areas. Vascular damage seems to be less prominent, as it was seen only for the glaucoma group and at the radial peripapillary plexus. Diagnostic abilities are excellent for structural variables, less so but still good for peripapillary VD, and poor for macular VD.

CONCLUSION

It could be concluded that macular vessel density (MVD) has strongly positive correlation with ganglion cell layer (GCL) thickness and RNFL thickness, has negative correlation with the severity of glaucoma, which mean that the more severe the glaucoma is, the lower (MVD), (RNFL) and (GCL) are.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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