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Original article

Assessment of Retinal Vessels Density and Blood Flow Density in Patients with Primary Open Angle Glaucoma Using Ocular Coherence Tomography Angiography

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Abstract

Background: Reducing IOP has been repeatedly shown to be an effective intervention across the glaucoma spectrum, regardless of subtype & disease stage. **This study aimed to** compare optic disc perfusion & radial peri-papillary capillary plexus density between the control group & primary open-angle glaucomatous patients using Ocular Coherence Tomography Angiography. **Methods:** This observational case-control research was carried out at the outpatient clinic of the Ophthalmology Department of Benha University Hospitals on 25 studied cases suffering from glaucoma (Group A). 25 healthy individuals of matched years old & gender were chosen as the control group (Group B) Scanned with OCT-A for optic disc perfusion and radial peri-papillary capillary plexus density and Superficial macular capillary plexuses density. **Results**: There was a highly statistically significant variation among 2 studied groups as regards the whole image density of the optic disc in which the mean inpatient group was (32,81) but in the control was (49.74) with P (<0.001), inside disc density the mean was(39.6.2) in patients and control was (50.63)with P (<0.001) and mean in peri-papillary density was (39.15) inpatients but (52.40) in control, Superficial macular capillary plexuses density which the mean in patients group was (32.49) but in control was (48.72) with P (<0.001). **Conclusion:** the data of this study suggest that quantitative OCTA can help diagnose glaucoma depending on the reduction of both RPC and Superficial macular vascular density. RPC and macular vessel density measured by OCTA have a relationship with the structural (thickness of both RNFL&GCL) & functional (visual field MD) parameters.

Keywords: Optical coherence tomography angiography; Vessel density; Glaucoma.

Introduction

The most important modifiable risk factor for glaucoma onset and progression is intraocular pressure. Reducing IOP has been repeatedly shown to be an effective intervention across the glaucoma spectrum, regardless of subtype & disease stage (1).

Regarding pathogenesis of the disease, it has long been believed that increased intraocular pressure exerts a mechanical force on peri-papillary nerve fibers, depressing fibers& leading to glaucomatous damage.

The potential role of microvasculature & blood flow in the pathophysiology of glaucoma, progressive optic neuropathy, has been extensively debated & researched (2).

Optical coherence tomography angiography is a noninvasive imaging method advanced to visualize vascular networks in the human retina and choroid (3), providing quantitative evaluation of microcirculation in the optic nerve head and peri-papillary region (4).

To distinguish areas of blood flow from areas of static tissue, OCTA employs low-coherence interferometry to measure variations in backscattered signal (5).

OCT-A is used in the detection of radial peri-papillary capillary plexus density. The radial peri-papillary capillary layer is a distinct capillary network located within the retinal nerve fiber layer, which supplies axons of retinal ganglion cells (6). Radial peri-papillary capillary lies among the internal limiting membrane & nerve fiber layer (7).

The purpose of this research is to compare optic disc perfusion & radial peri-papillary capillary plexus density in studied patients with POAG and normal using Ocular Coherence Tomography Angiography.

Patients and methods

This observational case-control study was carried out at the Ophthalmology outpatient clinic of the Department of Benha University Hospitals. Twenty-five studied cases suffering from POAG (Group A), and 25 healthy individuals of matched years old and gender were chosen as the control group (Group B).

In this study, we included patients with POAG (Group A) who are with Age: >eighteen, with refractive error is ≤ five Diopter Sphere & 2 Diopter Cylinder, previously diagnosed with primary open-angle glaucoma, IOP ≥ twenty-one mm Hg or ≤ 21mm Hg if under treatment, had optic neuropathy with Cup-disk ratio ≥ 0.5, had retinal nerve fiber layer defect & ganglion cell affection detected by Ocular Coherence Tomography & had visual field defect associated with glaucoma changes detected by visual field test.

While control group (Group B) included individuals who were > eighteen years old, had no previous history of Intraocular surgery except uncomplicated cataract surgery, had no family history of glaucoma, refractive error is ≤ 5Diopter sphere and 2 Diopter Cylinder, had normal optic nerve head, normal Intraocular pressure from 16 mm Hg to 21 mmHg and normal OC finding.

In both groups, we Excluded media opacity, any ocular disease except glaucoma and uncomplicated cataract, previous Intra ocular operation, and any

systemic disease affecting blood vessels such as diabetes mellitus and hypertension.

This research was carried out at the Ophthalmology outpatient clinic of Department of Banha University Hospitals from December 2021 to June 2022. This was on 25 studied cases suffering from glaucoma (Group A) and 25 healthy individuals.

All of the groups included had their histories discovered and investigated:

Visual acuity UAVA and BSCVA were measured by Snellen's chart, and IOP was measured by applanation tonometer (Goldmen Hass strick, German) Gonioscopy: using 4 mirror gonioscopy funds examination by fundus biomicroscopy using +90 lens (Volk).

The OCT-A device and scanning protocol:

(OPTVUE) was used for OCT-A imaging in both study groups. Scans were done with dilated pupils 3 images were collected for each eye: OCT-A six× six mm scan field centering fovea, OCT-A four and a half x four and a half mm scan field centring optic nerve, & OCT scan thickness of retinal nerve fiber layer. OCT-A scans needed an image quality of ≥ 5/10& OCT-A was used to scan radial peri-papillary capillary plexus& superficial capillary plexus of the macular region. They were separated into 5 sectors: central, nasal, temporal, superior, and inferior **(Figure, 1 and 2)**.

Approvals: written formed consent was obtained from all patients and healthy persons, & the confidentiality of information was ensured. The ethical committee, Banha University, at the same university provided an official written administrative permission letter. To ensure their cooperation, the title & objectives of the research were explained to them.

Statistical analysis

Data was fed into the computer & analyzed with IBM SPSS software package version twenty. The IBM Corporation, Armonk, New York Numbers & percentages were used to define qualitative data. The Kolmogorov-Smirnov test was used to confirm the distribution's normality. Range, mean, standard deviation, median, & interquartile range were used to define quantitative data. The significance of the findings was determined at a five percent level.

Research ethics committee: Ms.24.3.2020

Results

Comparison between mild, moderate, and severe cases according to total, Hemi-superior, and Hemi-inferior peri-papillary density and total, Hemi-superior, and Hemi-inferior macular density **Table 1, Figure 3**

We found the mean age in the patient group was 49.92 ± 12.86, while the mean age in the control group was 50.40 ± 12.86. There was an insignificant variation between the two studied groups regarding age **Figure 4A.**

Our study demonstrated that the mean IOP in the patient group was 22.34 ± 5.07 SD

and the mean IOP in the control group was 15.56 ± 2.72. There was high variation among the 2 studied groups as regards IOP **Figure 4B.**

And there was high variation among the 2 studied groups as regards total RNFL thickness as the mean in group (A) was (71.02) but in the group (B) was (111.9) with (P < 0.001), superior RNFL thickness mean in the group (A) was (72,78) but in the group (B) was (134.2) with (P < 0.001) and inferior RNFL thickness mean in the group (A) was (76,56) but in the group (B) was (141.5) with (P < 0.001) **Figure 4C.**

Our thesis demonstrated that there was a highly statistically significant variation among 2 studied groups as regards whole image density of the optic disc as the mean in the group (A) was (32,81) but in the group (B) was (49,74) with (P<0.001), inside disc density, had mean in the group (A) (39.62) but in the group (B) was (50.63) with (P < 0.001) .and peri-papillary density with mean in the group (A) was (38,67) but in the group (B) was (52,31) with (P<0.001) **Table 2.**

The results cleared that there was a highly statistically significant variation among the 2 studied groups as regards Superior –Hemi peri-papillary density as the mean in the group (A) was (38.87) but in the group (B) was (52.40) with (P < 0.001) and Inferior –Hemi peri-papillary density had mean in the group (A) (38.71) but in the group (B) was (52.01) with (P<0.001) **Table 3.**

We found there was high variation among the 2 studied groups as regards Nasal –Superior Peri-papillary density as the mean in the group (A) was (35.24) but in the group (B) was (49.01) with (P < 0.001) and Nasal –Inferior Peri-papillary density had mean in the group (A) (37.28) but in the group (B) was (47.82) with (P < 0.001) **Figure 4D.**

There was high variation among the two studied groups regarding Inferior-Nasal Peri-papillary density with the mean in the group (A) was (35.15) but in the group (B) was (50.79) with (P < 0.001) and Inferior-Temporal peri-papillary density mean in the group (A) was (37.97) but in the group (B) was (57.52) with (P < 0.001) **Figure 5A**

There was high variation among the 2 studied groups as regards Tempro–Inferior peri-papillary density with mean in the group (A) was (44.40) but in the group (B) was (52.41)with (P<0.001) and Tempro–Superior peri-papillary density had mean in the group (A) (45.45) but in the group (B) was (55.96) with (P < 0.001) **Figure 5B.**

We found there was high variation among the 2 studied groups as regards Superior-Temporal Peri-papillary density with mean in the group (A) was (41.48) but in the group (B) was (55.69) with (P<0.001) and Superior –Nasal Peri-papillary density had mean in the group (A) (34,91) but in the group (B) was (50,32) with (P<0.001) **Figure 5C.**

We illustrated that there was high difference between the two studied groups as regards Whole Image Macular density, with the mean in group (A) was (32.49) but

in group (B) was (48.72) with (P < 0.001) **Table 4.**

A highly statistically significant variation was found among 2 studied groups as regards Average GCL with mean in the group (A) was (72.14) but in the group (B) was (99.76) with (P < 0.001), Superior GCL had mean in the group (A) (71.36) but in the group (B) was (98.94) with (P < 0.001) and inferior GCL with mean in the group(A) was (72.60) but in the group (B) was (98,40) with (P < 0.001) **Table 4.**

We detected in our study in the patient's group that there was a highly positive significant correlation between peri-papillary density and RNFl thickness in total (R = 0.697), superior (R= 0.715), and inferior (R = 0.714) and ($p \leq 0.05$) **Table 5.**

We found in our research in the patients group that there was a weak positive significant correlation between Image macular density and GCL in total (R= 0.365), superior (R= 0.338) and inferior(R = 0.396) and ($p \leq 0.05$) **Table 5.**

Table 1: Comparison between the three studied subgroups according to different parameters

	Mild(n=10)	Moderate (n = 13)	Severe (n = 27)	F	p
Peripapillary density					
Mean ± SD.	43.64 ± 8.98	40.36 ± 7.89	36.75 ± 7.83	1.725	0.189
Median	44.9	43.5	36.4		
Superior –Hemi peripapillary density					
Mean ± SD.	42.32 ± 8.55	40.08 ± 7.94	37.49 ± 9.21	0.761	0.473
Median	43.10	42.25	37.10		
Inferior –Hemi peripapillary density					
Mean ± SD.	44.10± 9.79	40.45 ± 9.42	36.54 ± 8.49	1.817	0.174
Median	47.35	41.60	33.40		
Whole Image Macular density					
Mean ± SD.	43.15± 7.05	39.65 ± 7.20	37.82 ± 9.84	0.705	0.499
Median	42.55	41.0	33.90		
Superior–Hemi Macular density					
Mean ± SD.	42.79± 4.18	39.26 ± 8.11	37.39 ± 9.78	0.288	0.751
Median	41.30	40.10	36.20		
Inferior–Hemi Macular density					
Mean ± SD.	42.53± 5.49	39.62 ± 6.94	37.76 ± 10.41	0.080	0.923
Median	39.95	38.10	36.80		

Table 2: Comparing among 2 studied groups based on whole image density of optic disc, inside disc density and peripapillary density

	Patients (n = 50)	Control (n = 50)	t	P
Whole image density of optic disc				
Min. – Max.	22.60 – 47.40	45.0 – 55.0		
Mean ± SD.	32.81 ± 7.92	49.74 ± 2.34	10.308*	<0.001*
Median (IQR)	37.30 (33.20 – 44.50)	50.05 (47.90 – 51.50)		
Inside disc density				
Min. – Max.	27.80 – 61.0	39.20 – 57.90		
Mean ± SD.	39.62 ± 8.79	50.63 ± 4.31	4.341*	<0.001*
Median (IQR)	44.35 (39.20 – 51.70)	51.0 (48.80 – 53.40)		
Peripapillary density				
Min. – Max.	19.80 – 52.90	46.90 – 58.50		
Mean ± SD.	38.67 ± 8.20	52.31 ± 2.85	11.120*	<0.001*
Median (IQR)	39.15 (30.50 – 45.10)	52.40 (50.20 – 54.10)		

Table 3: Comparing among 2 studied groups based on hemi peripapillary density

	Patients (n = 50)	Control (n = 50)	t	p
Superior Hemi peripapillary density				
Min. – Max.	20.20 – 57.0	44.40 – 59.30		
Mean ± SD.	38.87 ± 8.73	52.40 ± 3.11	10.321*	<0.001*
Median (IQR)	38.65 (31.70 – 45)	52.35 (50.30 – 54.40)		
Inferior –Hemi peripapillary density				
Min. – Max.	16.70 – 57.70	43.0 – 57.80		
Mean ± SD.	38.71 ± 9.14	52.01 ± 3.12	9.740*	<0.001*
Median (IQR)	38.80 (31.0 – 47.10)	52.20 (50.0 – 54.30)		

IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, U: Mann Whitney test, p: p value comparison among studied groups,*: significant at $p \leq 0.05$

Table 4: Comparing among studied groups based on whole image macular density and GCL

	Patients (n = 50)	Control (n = 50)	U	p
Whole Image Macular density				
Min. – Max.	21.80 – 54.1	42.90 – 55.8	268.50*	<0.001*
Mean ± SD.	32.49 ± 3.69	48.72 ± 1.34		
Median (IQR)	38.65(33.10– 45.10)	50.65(49.50– 52.60)		
GCL			**t**	
Average GCL				
Min. – Max.	46.0 – 100.0	90.0 – 116.0	13.401*	<0.001*
Mean ± SD.	72.14 ± 12.89	99.76 ± 6.80		
Median (IQR)	72.0 (60.0 – 82.0)	100.0(94.0 – 105.0)		
Superior GCL				
Min. – Max.	44.0 – 94.0	88.0 – 112.0	13.801*	<0.001*
Mean ± SD.	71.36 ± 12.43	98.94 ± 6.73		
Median (IQR)	71.0 (63.0 – 79.0)	99.0 (92.0 – 103.0)		
Inferior GCL				
Min. – Max.	50.0 – 95.0	1.90 – 120.0	8.540*	<0.001*
Mean ± SD.	72.60 ± 14.61	98.40 ± 15.58		
Median (IQR)	68.50 (58.0 – 86.0)	100.50(93.0– 104.0)		

IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, U: Mann Whitney test, p: p value comparison among studied groups,*: significant at $p \leq 0.05$

Table 5: Relationship among peripapillary& RNFl in patients group and relationship among image macular density & GCL in patients group (n = 50)

peripapillary and. RNFL thickness	R	p
Total	0.697	<0.001*
Superior	0.715	<0.001*
Inferior	0.714	<0.001*
Image macular density vs. GCL	**R**	**p**
Total	0.365	0.009*
Superior	0.338	0.016*
Inferior	0.396	0.004*

r: Pearson coefficient, *: significant at $p \leq 0.05$

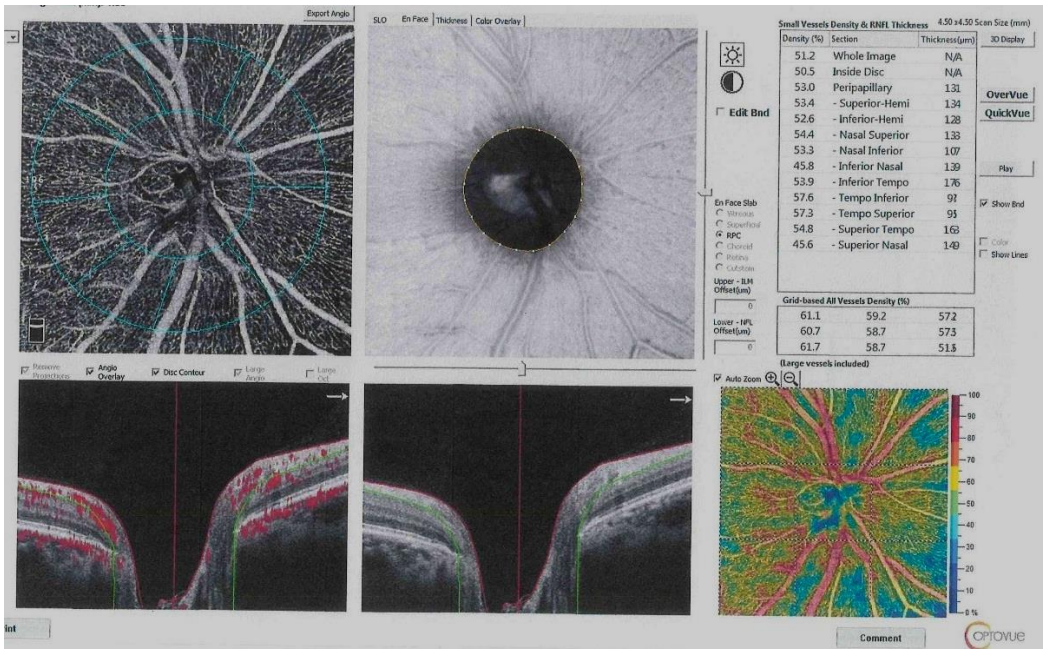

Figure 1: OCT –A in normal case show RPC equal (51.2%) in 4.5 x 4.5 scan size (mm) in right eye

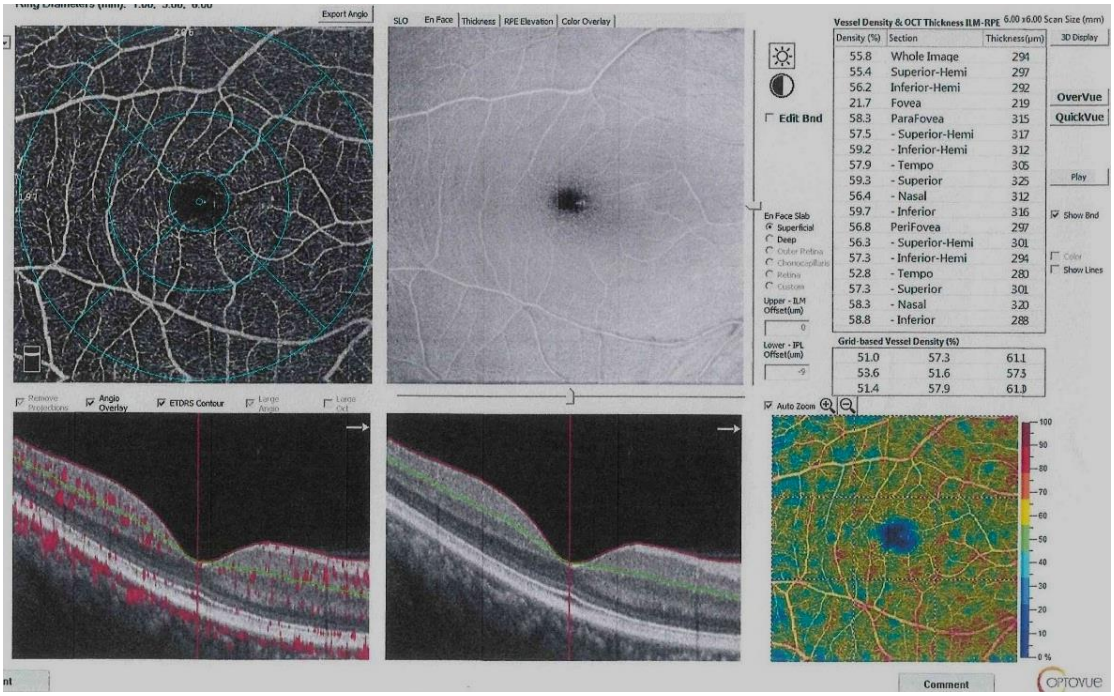

Figure 2: OCT –A in normal case show Superficial Macular VD equal (55.8%) in 6 x6 scan size (mm) in right eye

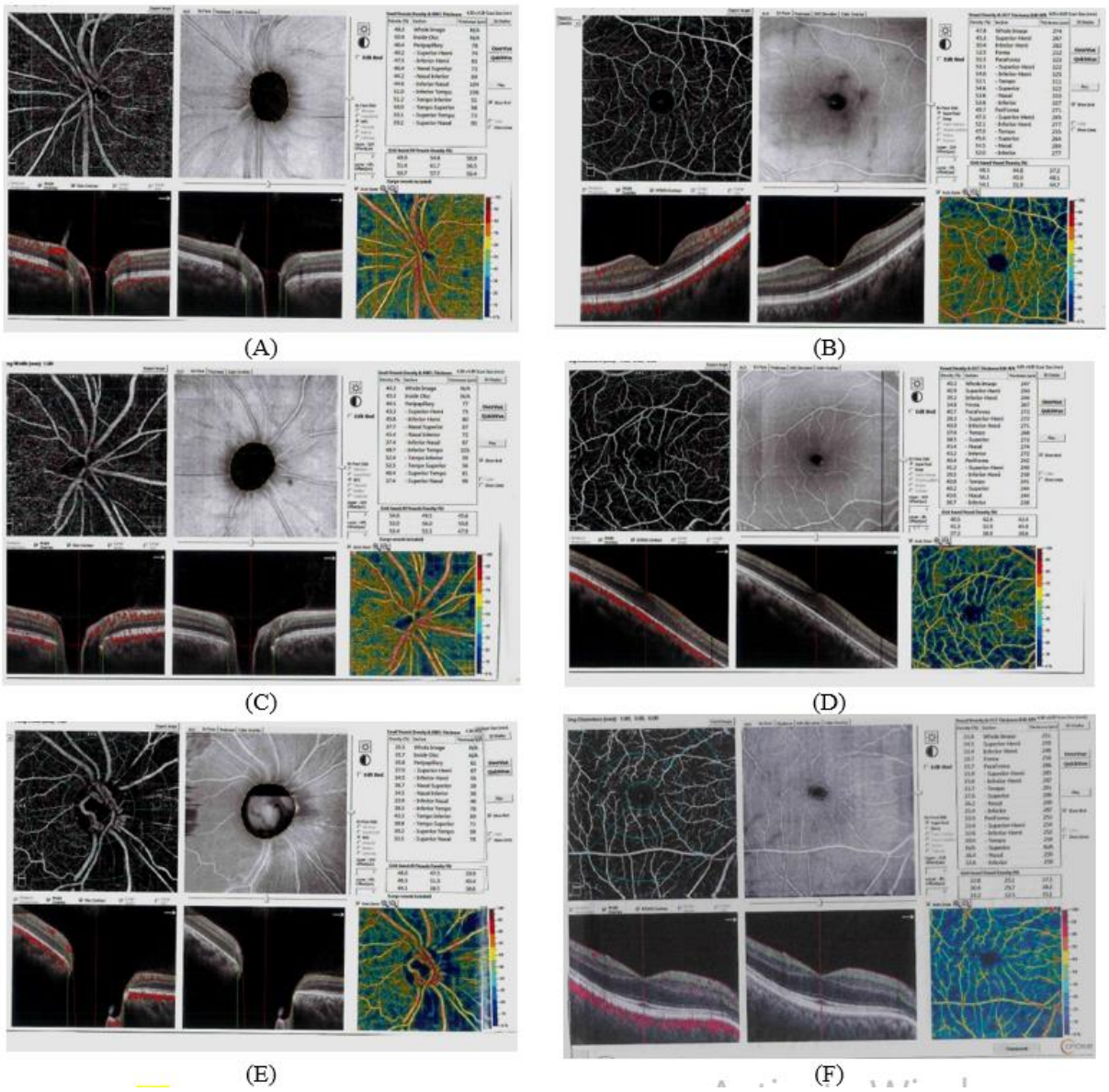

Figure 3: (A) OCT – A in mild case show RPC equal (48.3%) in 4.5 x 4.5 scan size (mm) in left eye (B) OCT – A in mild case show Superficial Macular VD equal (47.8%) in 6 x 6 scan size (mm) in left eye (C) OCT – A in moderate case show RPC equal (44.3%) in 4.5 x 4.5 scan size (mm) in right eye (D) OCT –A in moderate case show Superficial Macular VD equal (40.2%) in 6x6 scan size (mm) in right eye (E) OCT –A in severe case show RPC equal (35.5%) in 4.5 x 4.5 scan size (mm) in right eye (F) OCT –A in severe case show Superficial Macular VD equal (33.8%) in 6 x 6 scan size (mm) in right eye

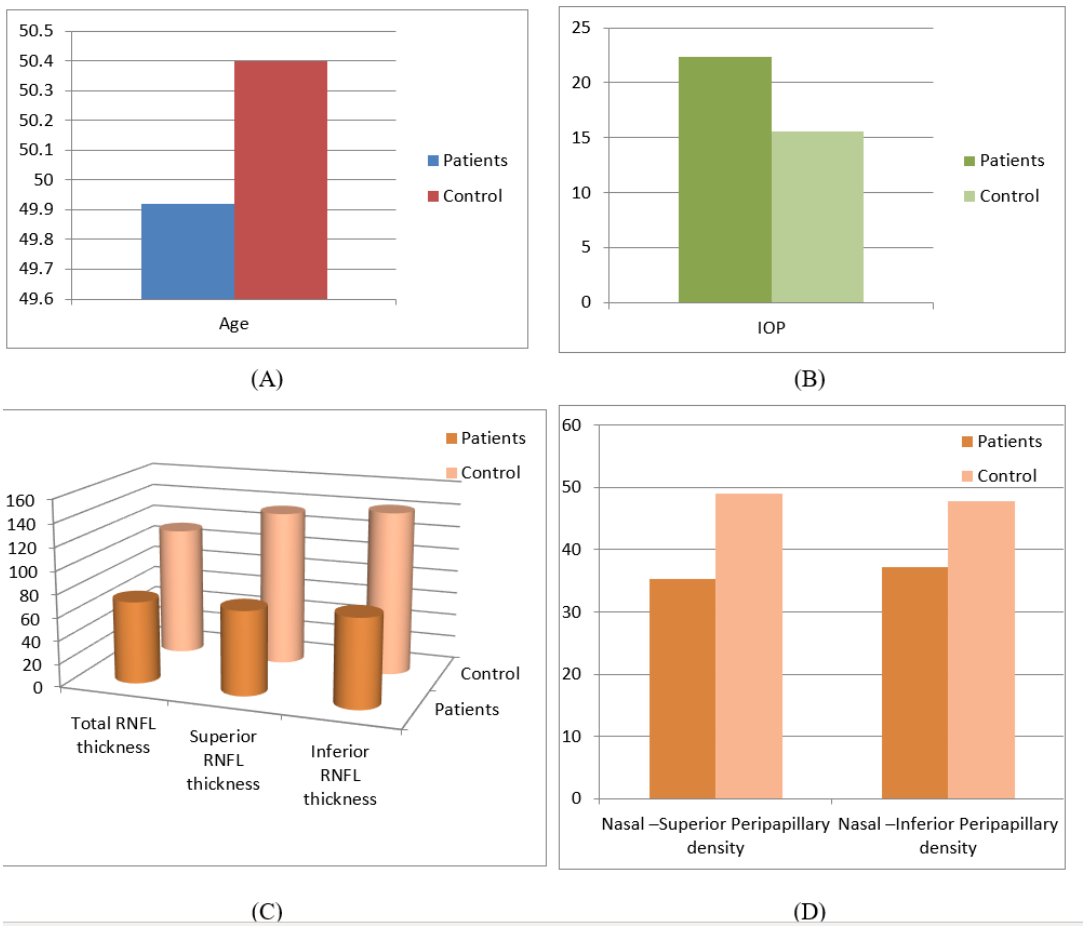

Figure 4: Comparing among 2 studied groups based on (A) age, (B) IOP(C) RNFL thickness, and (D) nasal.

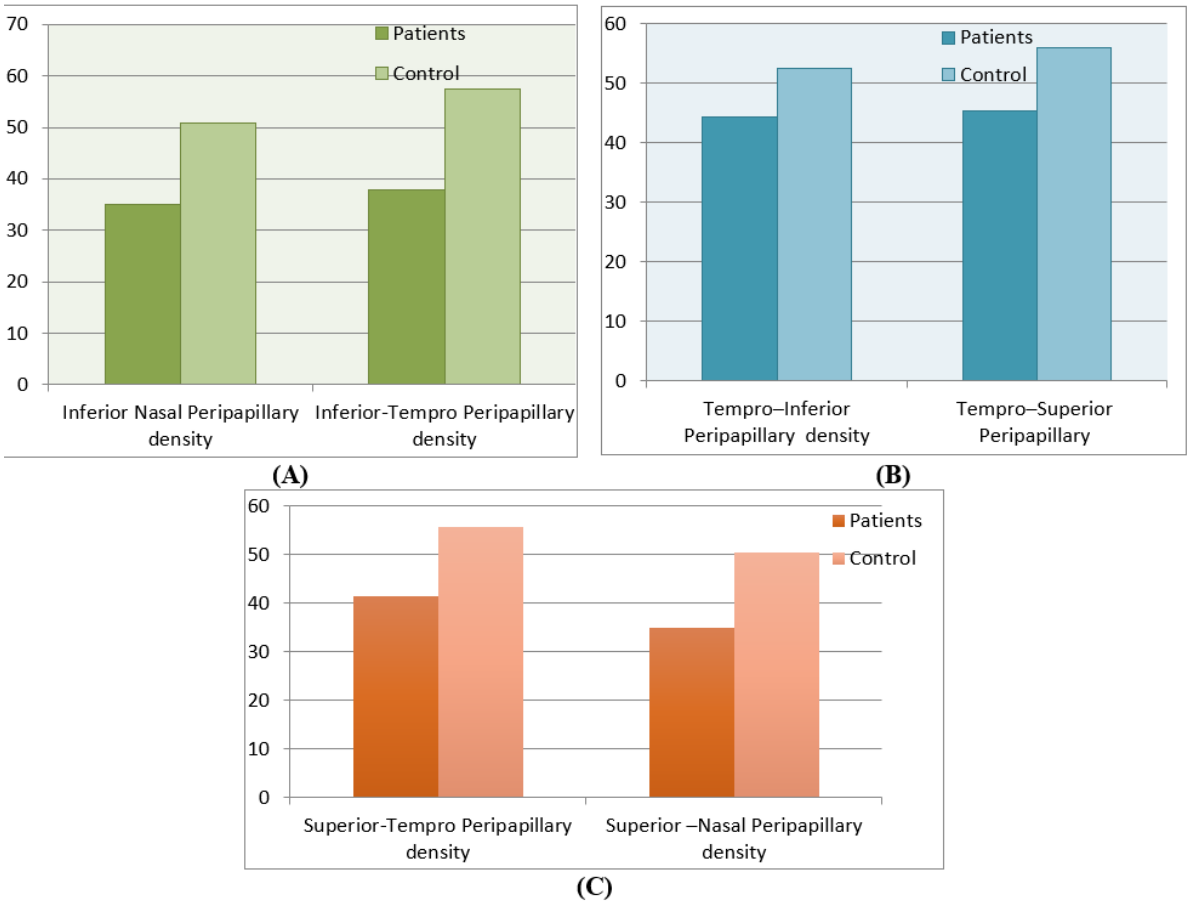

Figure 5: Comparing among 2 studied groups based on (A) inferior, (B) Tempro and (C) superior.

Discussion

Optical coherence tomography angiography is a noninvasive imaging method advanced to visualize vascular networks in the human retina and choroid (3), providing quantitative evaluation of microcirculation in optic nerve head 4 and peri-papillary region.

This research aimed to assess RPC & macular vascular density in patients with POAG with the detection of its correlation with a thickness of RNFL and GCC & visual field indices.

In this research, we demonstrated that the mean IOP in the patient group was 22.34 ± 5.07 and the mean IOP in the control group was 15.56 ± 2.72. There was high variation among the 2 studied groups as regards IOP.

In 2018 it was found that IOP measurements in glaucomatous patients were higher than normal ($p < 0.001$) (8).

Additionally, in the cross-sectional observational study (9) sixty-eight kHz Cirrus HD-OCT 5,000-based OMAG prototype system centered on the optic

nerve head was used to scan 1 eye from each subject. The OMAG dataset was used to generate micro-vascular images by identifying variations in the OCT signal among consecutive B-scans. The semi-automatic segmentation program was used to isolate the pre-laminar layer (9).

In this study, we illustrated that there was high variation among the two groups regarding total RNFL thickness, superior RNFL thickness, and inferior RNFL thickness.

In 2016, it was demonstrated that when comparing POAG & NTG eyes to normal eyes, the normal eyes had a more significant global average RNFL thickness & rim area and a lower average cup/disc ratio (P<0.001) (9).

In a recent study 2021, it was showed that regarding the evaluation of the structural parameters by OCT, there is a significant statistical variation in the average thickness of RNFL (P=0.0001) between the healthy control group B (103.85±0.6.2) and the glaucoma group A (81.34±0.11) (10).

In this present research, we proved significant variation among the two studied groups regarding the whole image density of the optic disc, the inside disc density, and the peri-papillary density.

A recent study 2021involved two hundred control subjects' eyes and 250 glaucomatous subjects' eyes separated into early, moderate, & developed glaucoma subgroups. All of them were evaluated for pre papillary & macular vascular densities using SS-OCTA (11).

All vessel density parameters in the glaucoma group were lower than in the control group (P < 0.05). In subgroup analysis, there was a trend toward reduced vessel density as glaucoma severity increased (P < 0.05).

In this research, we confirmed that there was a highly difference between the two studied groups as regards Superior –Hemi peri-papillary density and Inferior –Hemi peripapillary density.

As regards some authors (11) showed that vessel density parameters of the Hemi superior & Hemi inferior peri-papillary region in the glaucoma group were lower than the control group. They also concluded OCT-A plays an important role in early diagnosis & follow-up of PAOG. It contributes to the understanding of some aspects of the vascular role in glaucoma.

In this study, we cleared that there was high variation among the two studied groups as regards Nasal peri-papillary density, Inferior peri-papillary density, and superior peri-papillary density.

Furthermore, a study found that all vessel density & structural measurements in the glaucoma group were lower than in the control group (12).

When compared to glaucoma suspects & healthy eyes, years old adjusted mean vessel density in the OAG eyes, was lower, as suggested. Vessel density had diagnostic accuracy comparable to RNFLT

measurements in distinguishing between healthy & glaucoma eyes. These findings imply that OCTA measurements reflect tissue damage relevant to the pathophysiology of OAG (13).

In this research, we found significant variation among the two groups as regards Tempro–Inferior Peripapillary density and Tempro–Superior Peri-papillary density.

A study found that the highest variations in OCTA parameters among normal & glaucoma groups were shown in the inferior &superior temporal sectors of the peri-papillary area. This was expected given that these two industries are vulnerable to glaucomatous damage at an early stage (14).

Additionally, some authors showed a reduction in the infra-temporal & supra-temporal peri-papillary vessel density sectors of glaucoma and the RNFL thickness atrophy in the corresponding regions (15).

Also, a study found that when POAG-studied cases were compared to normal controls, the RPC was lower in inferior-temporal (P=0.002) &superior-temporal (P=0.008) sectors, with corresponding focal RNFL defects (16).

In this research, we showed significant variation between the two studied groups regarding Whole Image Macular density.

Some authors found that the Macular vascular density showed a significant difference between normal and glaucomatous eyes (P<0.001). Also, the macular vascular density was related to the degree of glaucoma severity (P<0.001) (17).

In our study, there was a highly positive significant correlation between peri-papillary density and RNFl thickness in the patients group and total, superior and inferior. Conversely, in our study, there was a weak positive significant correlation between Image macular density and. GCL and total, superior and inferior.

In this study, we illustrated that there was high variation among the two studied groups as regards average GCL, Superior GCL and Inferior GCL.

A study found that GCL thickness was measured also in all eyes with a significant difference between both normal and glaucomatous eyes (P<0.001) (17). Furthermore, it was concluded that OCTA can visualize & quantify RPC & macula vessel density, & it may be useful for measuring damage to retinal ganglion cells in open-angle glaucoma (17).

So in the recent study done in 2021, it showed a difference in average GCL thickness (P=0.0001) was detected between the healthy control group B (99.67±5.8) and the glaucoma group A (80.72±6.9). Also, They (10) concluded that quantitative evaluation of RPC & superficial macular capillary plexus VD is a promising tool for glaucoma decision-making. The VD of RPC & SCP in glaucoma-studied cases is lower when compared to healthy controls (10).

Conclusion

The data of this study suggest that quantitative OCTA can help in the diagnosis of glaucoma depending on the reduction of both RPC and macular vascular density. RPC & macular vessel density measured by OCTA have a relationship with the structural (thickness of both RNFL and GCL) & functional (visual field MD) parameters.

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