Introduction

Glaucoma is a progressive optic neuropathy characterized by the degeneration of retinal ganglion cells and their axons, resulting in a characteristic appearance of the optic disc and visual field loss (1). According to WHO, glaucoma is the second leading cause of blindness after cataract worldwide(2). Although the pathogenic mechanisms leading to retinal ganglion cell death are not yet fully known, intraocular pressure induced mechanical injury is a major causative factor, which is evidenced by the increase in the risk of incident glaucoma and its progression with higher intraocular pressure. (3,4) On the contrary, many epidemiological studies have revealed that IOP reduction alone cannot prevent the progression of visual field loss in all patients. (5–7).It has also been suggested that reduced optic nerve head perfusion also plays a part in the pathogenesis of glaucoma.(8,9) Even though it believed that the reduced blood flow seen in glaucoma is secondary to retinal ganglion cell death and thus a reduced need for perfusion (10,11) , while others are of the view that the reduced blood flow is the primary event that eventually leads to the characteristic structural and functional changes of glaucoma(10) . However, the lack of measurement tools has held back the development of a clinical investigation for optic disc perfusion. At present, there are 2 groups of complementary investigations used for the diagnosis and follow-up of glaucoma patients: structural (where OCT has a considerable role) and functional (visual field) optic nerve head measurements, both of which has its own strengths and limitations. Earlier studies have measured optic nerve head (ONH) blood flow using a variety of techniques and have shown reduction in ONH perfusion in patients with glaucoma. OCT Angiography (OCT-A) demonstrated the ability to quantify retinal and disc blood flow rapidly and accurately.(12–14) It is a non-invasive technique that does not require the injection of any exogenous dye or contrast agent and provides near automatic quantification of the optic disc perfusion. OCT-A provides reproducible quantitative assessment of the microvasculature in the optic nerve head, peripapillary retina, and macula. Recent studies(15–18) show that OCT-A is promising investigational tool useful in diagnosis, staging and monitoring of glaucoma which may help to clarify the role of microcirculation and optic nerve head blood flow in the pathogenesis of Glaucoma.The radial peripapillary capillary plexus is known to play a crucial role in glaucoma. These capillaries are seen in exquisite details in OCT-A, while poorly viewed on traditional fluorescein and indocyanine Green Angiography, which is a distinct advantage of OCT-A over traditional imaging modalities.

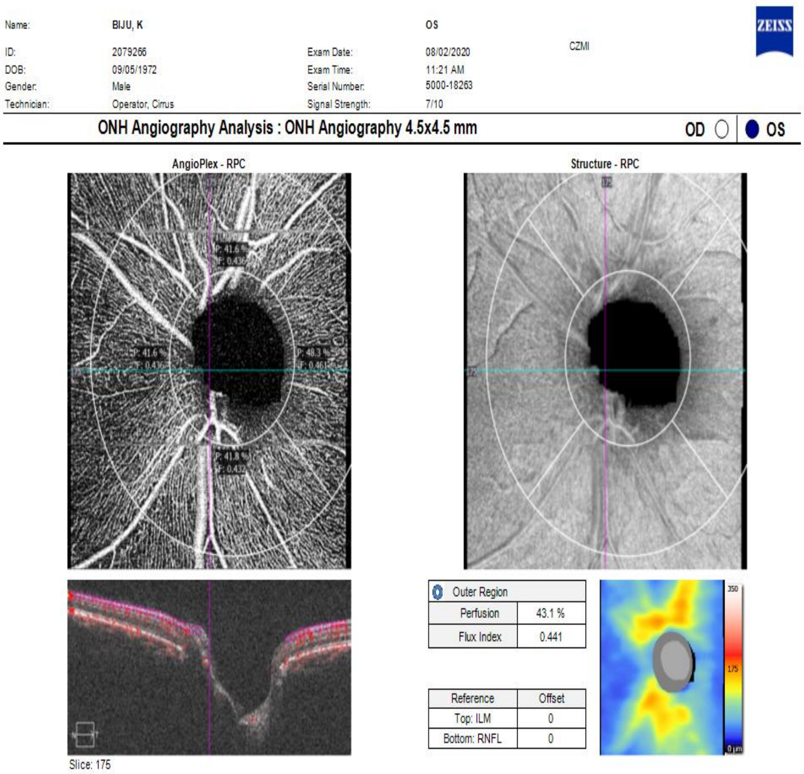
The purpose of this study was to look for the correlation of peripapillary capillary perfusion parameters measured by OCT-A with structural and functional changes in mild, moderate and severe primary open angle glaucoma patients.

Materials and Methods

This was an observational, Cross-sectional study conducted in tertiary eye care center to compare the peripapillary perfusion parameters measured by SD-OCT Angioplex in normal, mild, moderate and severe primary open angle glaucoma patients. This study was conducted as per guidelines of Declaration of Helsinki. The research proposal was approved by the research committee and the ethical review board of the institute. All the Mild, Moderate and Severe POAG patients and age matched normal patients between 40-70 years of age fulfilling the inclusion criteria and willing to participate were recruited to participate in the study, after taking the Informed consent. After satisfying the study criteria, a total of 100 eyes of 72 patients were enrolled in the study. Data was collected over a period of 18 months from February 1st 2019 to October 31st 2020 and standardised statistical methods were performed by the software STATA 11.0 with p value, 0.05 being considered as statistically significant. Patients were divided into four groups viz., normal, mild POAG, moderate POAG and severe POAG. Mild, moderate and severe POAG patients were grouped on the basis of Hoddap-Anderson-Parrish(17) scale as measured by visual field mean deviation scores on Humphreys Field Analysis Perimetry. 1) Mild POAG: visual field mean deviation > -6.0 dB 2) Moderate POAG: visual field mean deviation between -6.0 and -12.0dB. 3) Severe POAG: visual field mean deviation ≤ -12.0dB. Eyes with best-corrected visual acuity less than 20/40(6/12), history of intraocular surgery except uncomplicated cataract extraction with posterior chamber intraocular lens implantation, media opacities that interfere with OCT and OCT-A, secondary causes of glaucoma, non-glaucomatous optic neuropathies, vascular or non-vascular retinopathies and other ocular or systemic disease known to impair visual field, non-reliable visual fields were excluded from study.

All of them underwent best corrected visual acuity evaluation by using Snellen's chart, detailed and comprehensive anterior segment examination by slit lamp biomicroscopy, stereoscopic evaluation of optic disc with 90D lens, intraocular pressure measured using standard Goldmann applanation tonometer three times in quick succession in each eye and mean of three readings was recorded, and gonioscopy by four mirror gonioscopic lens. The anterior chamber was graded according to Shaffer's grading system with consideration to visibility of structures. Central corneal thickness was measured in all patients using SONOMED (Pac Scan 300P) pachymeter. Every patient included in the study underwent visual field evaluation, under standard condition, with full refractive correction on achromatic automated perimetry (Carl Zeiss Meditech) Humphrey Field Analyzer 750 i-series software version 2.0 using SITA 24-2 strategy. The visual fields were considered satisfactory when false negative and false positive errors did not exceed 33% and fixation errors did not exceed 20%. Optical Coherence Tomography analysis of the retinal nerve fibre layer thickness using CIRRUS HD-OCT (devic model 5000). All OCT scans were taken by an experienced operator and after full dilatation. The software version used at the time of this study had signal strength of the image >6 to 10 to set high accuracy image. The OCT parameters studied were Average RNFL thickness, and four quadrant RNFL thickness; ONH topography as cup area, cup volume, rim area, disc area and cup-disc area ratio. Optical Coherence Tomography Angiography analysis by OCT-A ANGIOPLEX of the optic nerve head vasculature, papillary vasculature was done. After dilating the pupils (with 1% tropicamide and 2.5% phenylephrine), participants were seated in front of the OCT scanner, and their heads were stabilized with the aid of both a supporting chin rest and a forehead rest. Participants were directed to focus their gaze on the internal fixation target, and a real-time en face view was used by the operator to visualize the imaging area on the fundus. A 4.5 mm X 4.5 mm scans with a resolution of 320 X 320 were obtained at a speed of 68,000 A scan/s, with an axial resolution of 5μm, using a FastTrack eye tracking system to minimize artifacts, centered on the optic nerve head using AngioPlex™ CIRRUS™ HD-OCT device (model 5000, Carl Zeiss Meditec, Inc., Dublin, USA). A fully-automated retinal layer segmentation algorithm and peripapillary segmentation algorithm was applied to select a superficial slab that included the RNFL and Internal Limiting Membrane (ILM) layer for calculation of peripapillary vessel density and Flux Index. The Vessel Perfusion Density is defined as the total area of perfused vasculature per unit area in a region of interest (ROI). It is calculated by averaging the binary vessel image within the desired ROI. The Flux Index is defined as the total weighted area of perfused vasculature per unit area in an ROI. The weight is the flow intensity corresponding to each pixel. Essentially, the flux index is calculated by averaging the intensity of all vessel pixels divided by total vessel pixels within the ROI. The ROI was a circular band-shaped pattern centered on the ONH (inner disc margin, outer circle outlining the outer border of peripapillary region) on the peripapillary OCT-A scan. The Vessel Density and Flux Index were calculated in 4 quadrants (Superior, Nasal, Inferior and Temporal) and averaged accordingly using preinstalled algorithm by AngioPlex™ CIRRUS™ HD-OCT.

CIRRUS OCT ANGIOPLEX – ONH angiography printout



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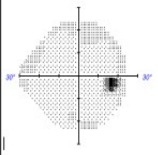
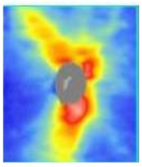
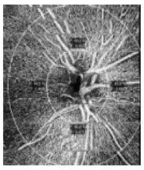
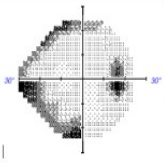
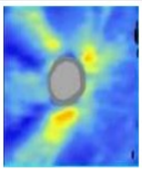
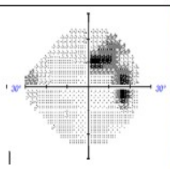
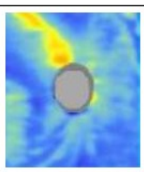
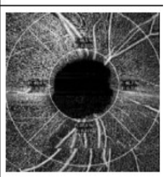
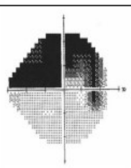
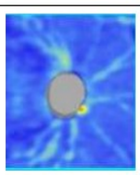
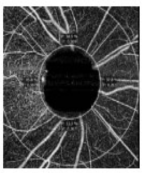
NORMAL			
MILD POAG			
MODERATE POAG			
SEVERE POAG			

Results

The baseline information, including demographics for the two groups, are described in Table1.

Table 1

	Normal	**Mild**	**Moderate**	**Severe**	**P-value**
Age	51.12(4.9)	57.92(4.8)	58.68(4.6)	62.56(4.4)	**<0.001**†
CCT, µm Mean(SD)	538.76(18.3)	520.64(33.3)	524.64(48.0)	541.80(28.9)	0.077 †
IOP, mmHg Mean(SD)	13.36(2.0)	23.76(2.0)	25.76(3.6)	29.76(5.1)	**<0.001** †
MD Mean(SD)	1.52(0.9)	-3.99(1.0)	-8.62(1.9)	-15.13(2.1)	**0.0001 @**
PSD Mean(SD)	1.76(0.2)	4.20(2.5)	7.79(3.8)	10.49(2.7)	**0.0001 @**

The mean age in normal group was 51.2 years, mild POAG was 57.92 years, moderate POAG was 58.68 years and severe POAG was 62.56 years. The percentage of males in the study was 41% and females were 59%. The comparison of baseline characteristics among each of the three group of study population shows that the difference in the mean age amongst the three groups was statistically significant (p value< 0.001). The central corneal thickness was not statistically significant (p value 0.077) and the intraocular pressure however showed statistically significant as expected (p value <0.001). The mean deviation (MD) and pattern standard deviation (PSD) among the four groups were also statistically significant (p value 0.0001).

The average RNFL thickness in mild, moderate and severe POAG groups was significantly thinner than in normal (p values <0.001). The average RNFL thickness in moderate POAG group showed significantly thinner values as compared to that of mild POAG group (p value 0.006). The average RNFL thickness in severe POAG group also showed significantly thinner values as compared to that of mild and moderate POAG groups (p values< 0.001 and 0.005 respectively) as shown in table 2.

Table 2

Average RNFL thickness	**Mean (SD)**	**Min - Max**	**P-value***	**Pairwise comparison (p value)**		
				Normal	**Mild**	**Moderate**
Normal	94.28(11.7)	77 to 117	**<0.001**	**-**	**-**	**-**
Mild POAG	80.36(13.0)	61 to 105		**<0.001**	-	-
Moderate POAG	69.52(12.9)	54 to 94		**<0.001**	**0.006**	-
Severe POAG	58.44(6.5)	47 to 72		**<0.001**	**<0.001**	**0.005**

Comparison of mean vessel density in the four quadrants and average vessel density among the normal, mild POAG, moderate POAG and severe POAG groups is shown in table 3 .The decrease in mean vessel density in the superior, inferior, nasal and temporal quadrants across the stages of severity of POAG was statistically significant (p values < 0.001) . The average vessel density also showed the same stepwise decrease across the stages of severity of POAG and the difference between the groups were statistically significant.(p value < 0.001)Temporal vessel density was found to be the highest of all quadrants in all the groups.

Table3

Vessel density	Normal	Mild POAG	Moderate POAG	Severe POAG	P-value*
Superior	44.35	41.87	39.44	37.08	**<0.001**
Inferior	44.37	42.21	39.98	37.91	**<0.001**
Nasal	45.91	43.93	42.05	40.10	**<0.001**
Temporal	48.52	48.08	45.91	43.70	**<0.001**
Average	45.83	44.02	41.84	39.69	**<0.001**

Comparison of mean FLUX INDEX in the four quadrants and average flux index among the normal, mild POAG, moderate POAG and severe POAG groups shown in table4. The mean quadrant wise flux index in superior, inferior, nasal and temporal quadrants was found to be decreasing in the order of normal > mild POAG > moderate POAG > severe POAG, and the reduction across stages of severity was statistically significant (p value < 0.001). The average flux index also showed the step wise reduction in flux index and the reduction among the groups were statistically significant (p value < 0.001).

Table4

FLUX INDEX	**Normal**	**Mild POAG**	**Moderate POAG**	**Severe POAG**	**P-value***
Superior	0.42	0.35	0.33	0.30	**<0.001**
Inferior	0.42	0.35	0.33	0.29	**<0.001**
Nasal	0.42	0.35	0.34	0.30	**<0.001**
Temporal	0.42	0.35	0.33	0.29	**<0.001**
Average	0.43	0.36	0.33	0.30	**<0.001**

Correlation of average vessel density with MD and PSD in all the four groups showed, average vessel density showed significant positive correlation with MD in mild POAG, moderate POAG and severe POAG groups; i.e., as the vessel density decreases across the severity of POAG the MD also decreases (i.e., as vessel density decreases the MD becomes more negative). The average vessel density showed significant negative correlation with PSD in mild POAG, moderate POAG and severe POAG groups; i.e., as the vessel density decreases across the severity of POAG the PSD increasesas seen in table 5

Table5

Average vessel density	MD		PSD	
	Correlation (rho)	P-value*	Correlation (rho)	P-value*
Normal	0.49	**0.014**	-0.14	0.511
Mild	0.41	**0.040**	-0.60	**0.002**
Moderate	0.40	**0.046**	-0.55	**0.005**
Severe	0.64	**0.001**	-0.64	**0.001**

Similarly the average flux index showed significant positive correlation with MD in mild POAG, moderate POAG and severe POAG groups; i.e., as the flux index decreases across the severity of POAG the MD also decreases (i.e., as flux index decreases the MD becomes more negative). PSD showed significant negative correlation with average flux index in mild, moderate and severe POAG groups as shown in table 6.

Table6

Average flux index	MD		PSD	
	Correlation (rho)	P-value*	Correlation (rho)	P-value*
Normal	0.54	**0.006**	-0.11	0.585
Mild	0.45	**0.024**	-0.56	**0.003**
Moderate	0.42	**0.037**	-0.58	**0.002**
Severe	0.75	**<0.001**	-0.76	**<0.001**

Measuring the structural correlation showed that average analysis of RNFL thickness showed statistically significant positive correlation with the average vessel density and average flux index in normal, mild, moderate and severe POAG groups. Also, the mean RNFL thickness in the four quadrants showed statistically significant positive correlation with mean vessel density and mean flux index in the four quadrants in control and severity stages of POAG groups as shown in table7a and 7b

Table 7 a

OCT	**DIAGNOSIS**				**Vessel density**
	Normal	**Mild**	**Moderate**	**Severe**	
Superior RNFL	0.79**(<0.001)**	0.81(**<0.001**)	0.58(**0.003**)	0.81(**<0.001**)	Superior
Inferior RNFL	0.69(**0.0001**)	**0.87(<0.001)**	**0.68(0.0002)**	0.86(**<0.001**)	Inferior
Nasal RNFL	0.81(<**0.001**)	**0.88(<0.001)**	0.53(**0.006**)	0.87(**<0.001**)	Nasal
Temporal RNFL	0.68(**0.0002**)	0.80(**<0.001**)	0.66(**0.0003**)	0.91(**<0.001**)	Temporal
Average RNFL	0.87(**<0.001**)	0.93**(<0.001)**	**0.84(<0.001)**	**0.94(<0.001)**	Average

Table7b

OCT	**DIAGNOSIS**				**Flux Index**
	Normal	**Mild**	**Moderate**	**Severe**	
Superior RNFL	0.72(**<0.001**)	**0.76(<0.001)**	**0.79(<0.001)**	**0.64(0.001)**	Superior
Inferior RNFL	**0.78(<0.001)**	**0.79(<0.001)**	**0.85(<0.001)**	**0.82(<0.001)**	Inferior
Nasal RNFL	**0.72(0.0001)**	**0.85(<0.001)**	**0.66(0.0003)**	0.81(**<0.001**)	Nasal
Temporal RNFL	0.83(**<0.001**)	0.86(**<0.001**)	0.54(**0.006**)	0.63(**0.001**)	Temporal
Average RNFL	**0.93(<0.001)**	**0.92(<0.001)**	**0.92(<0.001)**	**0.94(<0.001)**	Average

Discussion

Glaucoma is a multifactorial optic neuropathy characterized by a slowly progressive neurodegeneration of retinal ganglion cells and their axons characterized by a specific pattern of optic nerve head and visualfield damage(19). Monitoring for progression is a crucial part of the management of glaucoma patients as current management of POAG.

In accordance with the vascular theory of pathogenesis of glaucoma, a vascular dysregulation, leading to changes in the retinal microcirculation, is responsible for the derangement of perfusion to the optic nerve head and peri-papillary retina. (20–28) But, there is also the concept that retinal ganglion cell loss is the precursor to reduction in vessel caliber and density in the retinal microcirculation, because of the reduced metabolic demand leading to vasoconstriction, which is in agreement with the observation of retinal arterial narrowing in patients with non-glaucomatous optic atrophy. (29-31)

Several studies have been conducted to analyze the retinal vascular bed, using various non-invasive and invasive techniques. The earlier studies tried using fluorescein angiography to study optic nerve head blood flow.(32,33) But fluorescein angiography cannot be used on a regular basis to monitor patients for glaucoma because it is invasive and has its own side effects. Moreover, there are also problems in accurate quantification of the deficit. LASER Doppler flowmetry and LASER speckle flowmetry are non-invasive techniques that have also been used to measure optic nerve head blood supply and they have demonstrated that there is significant reduction in the blood flow at the ONH in glaucomatous eyes. (28,34)

The distinct advantage of OCT-A over traditional imaging modalities is the radial peripapillary capillaries are seen in details in OCTA, while poorly viewed on traditional fluorescein and indocyanine green angiography.

In our study 100 eyes of 72 patients were studied which included 25 each in Mild, Moderate, Severe POAG groups and 25 in Normal group. In our study the difference in the mean age amongst the four groups was statistically significant (p = <0.001) and, we found that the patients belonging to the POAG group were in general, slightly older (age ranging from 48 to 70 years). This is in agreement with several previous studies, which have found glaucoma to occur in a slightly older population. (35 36) The Intraocular pressure (IOP) was measured at the time of evaluation of the patient and was compared between the four groups was statistically significant as expected (p = <0.001)

We found out a statistically significant difference in the average RNFL thickness parameters among normal eyes and severity stages of POAG (p<0.001).All the RNFL parameters were statistically significant between normal eyes and eyes in the various stages of POAG, on post hoc (Bonferroni) analysis (P<0.001). Pairwise analysis of mean RNFL thickness in each quadrant also demonstrated statistically significant differences between control and severity of glaucoma stages. Whereas, the reduction in the RNFL thickness seen in the POAG group was consistent with RNFL loss following the ISNT rule, with inferior quadrant being more thinned than the superior quadrant . Contemporary literature also showed statistically significant difference between the RNFL thickness of normal eyes and eyes in the various stages of POAG.(37) Previous studies have revealed that Stratus OCTgenerated RNFL thickness is reliable for discriminating eyes with early glaucoma from normal eyes (38-44). Chen et al.(43) also showed that average RNFL was the reliable parameter for differentiating early glaucoma from normal eyes.

We compared the perfusion parameters from the four groups; normal, mild POAG, moderate POAG and severe POAG groups, to look for any significant differences, by performing paired analysis between the groups, for each of the specific areas of interest. Previously, various researchers have tried to analyse the perfusion parameters between the severity of POAG patients (45,46,47). All these studies have used OCT angiography images of various area measurements, But, one fact was evident, is that there was a definite trend or pattern in the distribution of the vessel densities in the different populations, i.e., the perfusion parameters were highest in the normal, and reduced in order of Normal > Mild POAG > Moderate POAG > Severe POAG group

We compared the ONH average vessel density between all the groups; measurements in the descending order of average vessel density were, Normal> Mild POAG > Moderate POAG > Severe POAG (in that order) and the difference was statistically significant between all four groups (p<0.001). This was in agreement with the previous similar studies. (15,53,45,47,48). In Bonferroni pair wise comparison, the average disc vessel density was seen to be statistically significantly lower in eyes with mild, moderate and severe glaucoma compared to normal eyes (normal vs. mild p<0.046, normal vs. moderate p<0.001 and normal vs. severe p<0.001). Pairwise analysis of mean vessel density at each quadrant demonstrated statistically significant differences between each stage of POAG and control, except between mild POAG and control at the temporal sector. This was in also in agreement with the similar studies done previously (45). In quadrant wise analysis among all the four groups, it showed that the measurements were in descending order Normal > Mild POAG > Moderate POAG > Severe POAG and the difference was statistically significant between all the four groups ($p<0.001$).

The superior and inferior quadrants exhibited the greatest reduction in vessel density between normal and mild POAG groups, corroborating their early involvement in POAG.(11,47,48,49,50) In addition, these two quadrants continued to exhibit decrease in vessel density throughout progressive stage of disease to the greatest degree among all peripapillary quadrants. Another compelling observation in our study was that the temporal peripapillary vessel density was the highest of all quadrants in all the groups and also revealed a smaller decrease across POAG stage relative to other quadrants . This may be described by its unique anatomic location. The temporal peripapillary sector carries axons that supply the maculopapillary and macular regions, which often develop visual field scotomas late in the disease course.(49–52)

Average Flux Index when compared among the four groups were in the descending order of Normal > Mild POAG > Moderate POAG > Severe POAG and the difference was statistically significant between all four groups(p Mild POAG > Moderate POAG > Severe POAG (in that order) and the difference was statistically significant between all four groups (p<0.001)

In Bonferroni pair wise comparison of average disc flux index and mean flux index in quadrant with the normal group (normal vs. mild: p<0.001, normal vs, moderate:p<0.0001, normal vs severe:p<0.0001).) we found that the flux index was statistically significantly lower in the glaucoma eyes. This was in agreement with the study by Wang et al(53) . Hence, altered flow index values were found to be good indicators of eyes with POAG. A quadrant wise analysis for mean flux index was done and this was compared among all the four groups. It showed that the measurements were in descending order as Normal > Mild POAG > Moderate POAG > Severe POAG (in that order) and the difference was statistically significant between all four groups (p<0.001).

In our study among four groups; vessel density showed statistically significant positive correlation to MD in mild, moderate and severe POAG groups i.e., as the vessel density decreased the MD also decreased (the more negative the value becomes). This suggests that reduced OCT-A vessel density is associated with more severe glaucoma. Moreover, the PSD showed statistically significant negative correlation with vessel density across the severity of POAG; i.e., as the vessel density decreased the PSD increased. This was also in agreement with other previous studies. (15,16,53,45,47,48). Wang et al(53) reported that optic disc OCT-A vessel density correlated with both MD and PSD, but it was more strongly related with MD. However, it is worth mentioning that these studies measured vessel density in a thick retinal slab from internal limiting membrane to retinal pigment epithelium, whereas our results focused on vessel density in a more superficial layer, from the internal limiting membrane to the RNFL posterior boundary. In a study by Wang et al(53) disc flux index in the glaucomatous eyes was statistically significantly correlated with the visual field loss expressed as MD across all the stages of POAG, which was also observed in our study. The average RNFL thickness showed statistically significant positive correlation with the average vessel density and average flux index in control and severity stages of POAG groups . Also, the RNFL thickness in the four quadrants showed statistically significant positive correlation with vessel density and flux index in the four quadrants in control and severity stages of POAG groups. Our findings also corroborate analyses with the previous similar studies. (15,45,46,47)

In this study, we found a reduction in the disc perfusion parameters (disc flux index and vessel density) in the glaucomatous eyes, which correlated with the severity of glaucoma damage. Furthermore, our analysis revealed that altered perfusion parameters were correlated with MD and RNFL thickness. Altered perfusion parameters were also found to be good indicators of eyes with POAG, especially the severe POAG. All these suggest that OCTA disc perfusion parameters showed excellent correlation with the severity of glaucoma.

The ability to detect POAG with a non-invasive examination such as OCT-A can become a useful part of annual health examinations. Karczewicz et al.(54) previously reported that blood flow in the ophthalmic artery and the central retinal artery was significantly decreased in patients with myopia and POAG as compared to that in myopic eyes without POAG. Together with our results, this suggests that disc blood flow index and vessel density may aid in the diagnosis and monitoring of POAG, especially in myopic eyes, in which shallow cupping and pale neuroretinal rims make ONH assessment difficult, and where RNFL thickness measured by OCT has been less effective at discriminating glaucoma. (55)

By using OCT-A technology for ocular hemodynamic evaluations not only offers the upper hand of providing a quantitative assessment of ocular circulation at a level of precision that has not been achieved with previous instruments that measured blood flow but also its feasibility from a clinical standpoint suggests that OCT-A may be a useful modality that may reflect hemodynamic considerations relevant to glaucoma management. Moreover, the device's ability to visualize the vascular networks in easily interpretable images and density maps may provide new clinically relevant information that can easily be incorporated into the routine management of patients with glaucoma. In our study we could show that the close correlation between the average flux index/vessel density and MD and RNFL thickness suggesting that OCT-A might also be useful in glaucoma assessment and monitoring the progression of POAG

In conclusion, OCT-A is a sensitive non-invasive reproducible investigation that will aid in clinical monitoring of vascular changes in glaucoma, and also it could potentially complement to our understanding of the pathophysiology of the disease, specifically its underlying vascular mechanism. Also there exists a spatial correlation between the OCT-A parameters and the OCT RNFL thickness parameters and visual function measured by visual field testing, in glaucomatous eyes.

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