Original Article

Peripapillary and fovea avascular zone optical coherence tomography angiography parameters in exfoliation glaucoma versus primary open-angle glaucoma versus healthy eyes

Ofira Zloto, Ronel Veksler, Iris Moroz, Hila Goldberg, Hani Levkovitch-Verbin

Purpose: To examine the differences in the peripapillary vascular parameters and foveal-avascular-zone (FAZ) vascularity parameters between primary open-angle-glaucoma (POAG) patients versus exfoliation-glaucoma (XFG) patients versus healthy subjects. **Methods:** This is cross-sectional study and a comparative clinical study. POAG and XFG patients and healthy subjects underwent a comprehensive ophthalmic examination, including visual field optical coherence tomography (OCT) and OCT angiography (OCTA) of the optic disc and FAZ. Differences in peripapillary vessel density (VD), perfusion density (PD), and FAZ area and circularity were examined between all groups, as well as correlations between clinical parameters and vascularity parameters for each glaucoma group. **Results:** A total of 109 subjects (one eye for each patient) were analyzed, including 45 with POAG, 30 with XFG, and 34 controls. The average peripapillary VDs were the lowest among the XFG patients and the highest among the controls ($P < 0.05$, ANOVA). The average peripapillary PD of the central ring was the lowest in the XFG group and the highest in the control group ($P = 0.02$, ANOVA). A significant negative correlation was found between the average peripapillary VDs and PDs of the inner ring and full ring and disease severity of the POAG patients. There was a significant positive correlation between the average peripapillary PDs of the central rings and full ring and the central macular thickness of the XFG patients ($P < 0.01$ and $P < 0.04$, respectively, Pearson correlation). **Conclusion:** The peripapillary vascular parameters of the POAG and XFG patients were lower compared to those of normal participants. A correlation between clinical characteristics of POAG and XFG patients and PD was found. This may hint to a vascular mechanism in glaucoma either primary or secondary to intra-ocular pressure/OAG damage.

Key words: OCTA, POAG, PXF

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Glaucoma is one of the leading causes of irreversible blindness worldwide, affecting more than 70 million people.[1] It is a group of optic neuropathies characterized by a progressive degeneration of retinal ganglion cells and their axons. There are typical peripapillary retinal nerve fiber layer (RNFL) changes, typical macular changes that can be seen on optical coherence tomography (OCT), and the corresponding visual field (VF) defects.[2-4] Primary open-angle glaucoma (POAG) is the most common form of glaucoma.[2] Risk factors associated with progression of POAG include advanced age, elevated intra-ocular pressure (IOP), and a positive family history.[5] Exfoliation glaucoma (XFG) is the most common secondary OAG, accounting for up to 25% of glaucoma cases worldwide.[6] It is an ocular manifestation of exfoliation syndrome (XFS), an age-related systemic disorder that leads to the accumulation of extra-cellular fibrillar material throughout the body.[6] Compared to POAG, XFG is associated with a greater mean IOP, more advanced VF loss at diagnosis, and poorer response to medical treatment.[7]

Although the specific pathogenesis of glaucoma is not fully known,[1] there is increasing evidence that vascular factors play a role in its development.[8,9] However, until recently, studies on ocular vasculature in glaucoma have been a challenge because of limitations of imaging modalities.[10] OCT angiography (OCTA) is a relatively new non-invasive imaging modality that can be used to characterize vasculature in various retinal layers, providing quantitative assessment of the blood vessel density as well as perfusion in the optic nerve head, macula, and peripapillary area.[11-13] Several pioneering studies have recently applied OCTA to examine differences between POAG and XFG in peripapillary vessel density,[14,15] and one study examined the changes of the vasculature of the macula in XFG compared to POAG.[16] However, there is no consensus between them on the results.

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We therefore designed the present study with four objectives: (1) to compare peripapillary vascular parameters in POAG patients versus XFG patients versus healthy subjects, (2) to examine the vascularity parameters of the foveal avascular zone (FAZ) in POAG patients versus XFG patients versus healthy subjects, (3) to examine the correlations between peripapillary circulation and functional parameters, and (4) to examine the correlations between FAZ and functional parameters.

Methods

Patients and data

Adult POAG and XFG patients and adult subjects without glaucoma or any other intra-ocular diseases were prospectively recruited from February 2018 to April 31, 2019 at the Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel. The study was approved by the local institutional review board of the Sheba Medical Center and adhered to the tenets of the Declaration of Helsinki.

Inclusion criteria for patients with POAG were an open angle on gonioscopy, glaucomatous cupping of the optic disc, glaucomatous VF damage, and any unknown reason for glaucoma. Inclusion criteria for patients with XFG were an open angle on gonioscopy, evidence of exfoliation in the anterior chamber, glaucomatous cupping of the optic disc, and glaucomatous VF damage.

Inclusion criteria for the healthy subjects were an IOP ≤21 mm Hg with no history of elevated IOP, normal-appearing optic discs and intact neuroretinal rims on clinical examination, average and quadrant RNFL thicknesses within 99% confidence limits, the absence of optic neuropathy of any etiology, and normal VF.

Exclusion criteria for all groups were previous intra-ocular surgeries, systemic vascular disease, systemic drugs causing either dilatation or constriction of the vascular diameter or anti-coagulants, known retinal disease, optic neuropathy of

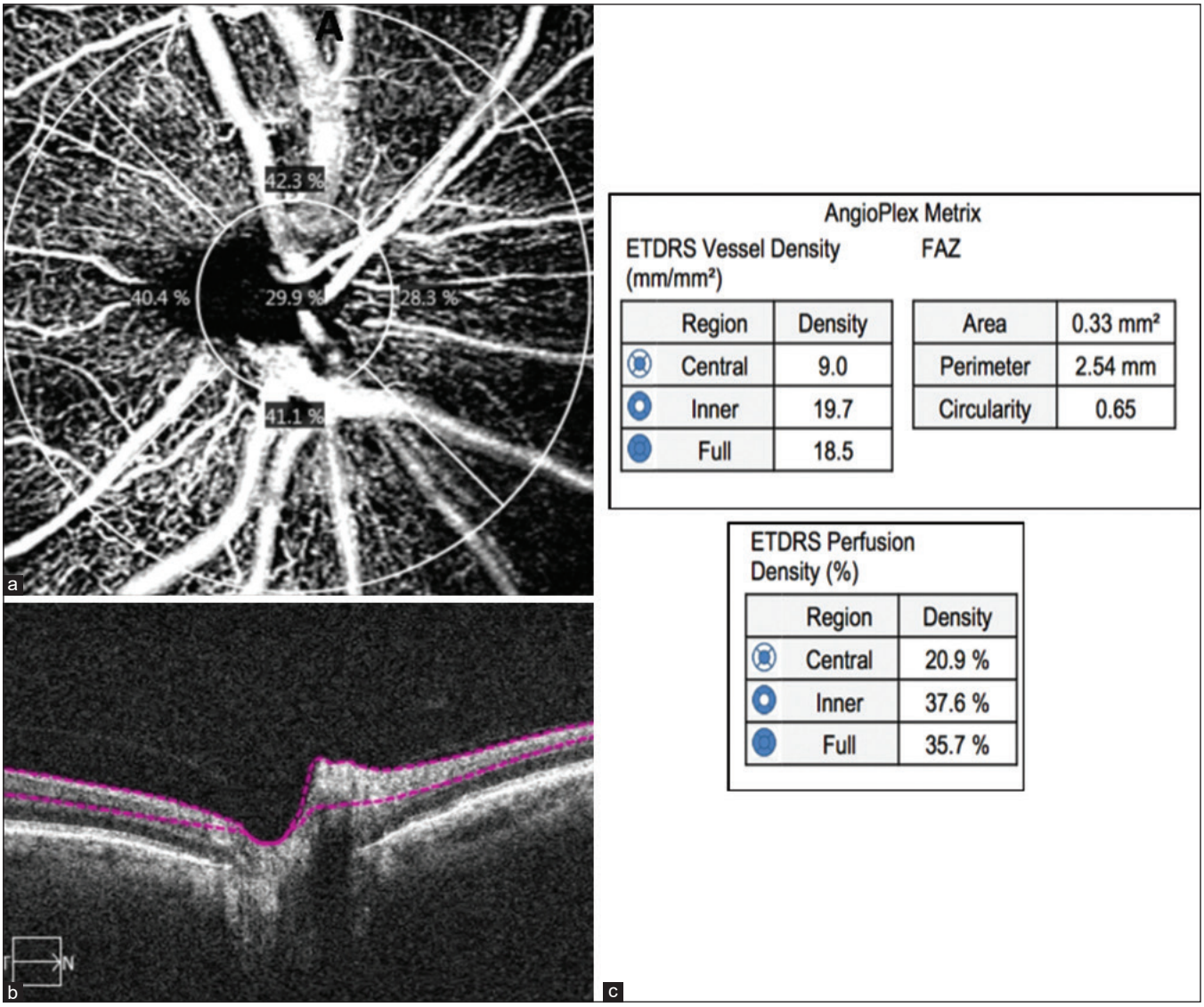

Figure 1: Micro-vascular measuremen ts in the Angioplex OCT-A technology. (a) OCTA scan image centered on the optic disc. The en face image of the superficial layer overlaid with the Early Treatment of Diabetic Retinopathy Study grid. (b) Segmentation boundaries automatically set from the ILM to the inner plexiform layer. (c) Tables with data of the automatically calculated values for vessel densities, perfusion densities, and FAZ

any etiology, hypotony of IOP of <6.5 mmHg, and significant media opacity preventing high-quality imaging.

All the study participants underwent a comprehensive ophthalmic examination, which included evaluation of VA, IOP measurements with Goldman applanation tonometry, slit-lamp examination of the anterior and posterior segments, and inspection of the optic nerve.

VF

The VF test was performed with the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA, USA) Swedish Interactive Threshold Algorithm 24–2 strategy. Reliable VF data were used in the current study, which considered a false-positive rate to be <20% and a false-negative rate to be <15%. The results of the mean deviation (MD) and the pattern standard deviation (PSD) from the 24-2 threshold test were collected for analysis. Glaucoma patients were classified by stage based on a 24-2 perimetry as follows: mild was defined as an MD greater than (-6) decibels (dB), moderate as (-6) to (-12) dB, and severe as less than (-12) db.

OCT image

All study participants underwent spectral-domain OCT (SD-OCT) (Cirrus HD-OCT 5000; Carl Zeiss Meditec, Inc., Dublin, CA, USA) and OCTA imaging on the same day and by the same operator. Before OCTA, standard peripapillary RNFL thickness (RNFLT) analysis was performed with a 3.46 mm scan centered over the optic nerve head. A macular cube 512 × 128 combination scan mode was used for central macular thickness (CMT). Ganglion cell-inner plexiform layer (GC) thicknesses were also measured by SD-OCT. Only OCT images with a signal strength ≥7 and the absence of artifacts, poor centration, or segmentation errors were included.

OCTA

A commercial OCTA device (AngioPlex; CIRRUS HD-OCT 5000, 10.0, Carl Zeiss Meditec) was used to image the micro-vasculature around the optic disk in a 3 mm × 3 mm optic disk region [Fig. 1a]. The boundaries of the superficial layer of the retina were automatically determined from the internal limiting membrane to the inner plexiform layer [Fig. 1b]. The Angioplex Metrix field automatically provides the values of perfusion density (PD) and vessel density (VD) for this superficial retinal layer, both in a tabular form and as vascular density maps according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) sub-fields [Fig. 1c]. VD is the total length of perfused vasculature per unit area in the region of measurement, and PD is the total area of perfused vasculature per unit area in the region of measurement. VD and PD were automatically measured by the OCTA software, and an analysis of the average peripapillary VD and peripapillary PD of the central ring, inner ring (according to the ETDRS – a central foveal ring 1 mm in diameter and an inner macular ring 3 mm in diameter), and full area was produced.

The values for the total area, perimeter, and circularity of the FAZ were extracted with in-built software of the Zeiss Cirrus Angioplex [Fig. 1c]. Circularity is a measure of compactness of a shape relative to a circle, and it was calculated as $4\pi A/P$, where A was the area and *P* was the perimeter.[17]

Table 1: Study participants' demographics and clinical characteristics

Variable	Control Group (34 patients)	POAG Group (45 patients)	XFG Group (30 patients)	*P*	*P* POAG vs. XFG	*P* XFG vs. Control	*P* POAG vs. Control
Age (yrs) mean±SD (range)	69.10±16.30 (39-88)	71.00±13.00 (51-89)	76.90±9.50 (58-93)	0.070	0.067	0.063	0.078
Sex, *n* (%)				0.024*	0.060	0.104	0.277
Men	17 (50.0)	17 (37.8)	21 (70.0)				
Women	17 (50.0)	28 (62.2)	9 (30.0)				
IOP mean±SD (range)	15.50±3.00 (11-21)	16.48±3.70 (11-26)	17.06±5.9 (10-30)	0.369	0.959	0.469	0.987
Visual field MD mean±SD (range)	-1.94±1.25 (-0.92-(-3.74))	-7.65±6.03 (-0.48-(-23.29))	-8.10±6.12 (-0.63-(-21.51))	0.182	0.969	0.023*	0.021*
Visual field PSD mean±SD (range)	3.12±1.72 (1.47-4.93)	6.00±3.70 (1.28-15.05)	5.79±3.45 (1.66-12.37)	0.304	0.830	0.511	0.375
Stage, *n* (%)							
Mild	0 (0)	20 (44.45)	11 (36.67)	0.377	0.184	<0.01*	0.553
Moderate	0 (0)	14 (31.11)	9 (30.00)				
Severe	0 (0)	11 (24.44)	10 (33.33)				
RNFL thickness. µm mean±SD (range)	78.04±15.77 (43-103)	74.41±15.14 (43-102)	74.92±11.28 (46-91)	0.662	0.966	0.980	0.900
Ganglion cell average, mean±SD (range)	68.72±14.73 (32-87)	64.45±12.17 (42-88)	65.58±11.18 (46-86)	0.432	0.681	0.670	0.591
Central macular thickness, µm mean±SD (range)	301.54±83.81 (234-456)	268.00±62.96 (194-425)	256.88±68.80 (190-405)	0.077	0.993	0.090	0.206

*Significantly different. POAG=primary open-angle glaucoma; XFG=exfoliation glaucoma; IOP=intra-ocular pressure; MD=mean deviation; SD=standard deviation; PSD=pattern standard deviation; RNFL=retinal nerve fiber layer

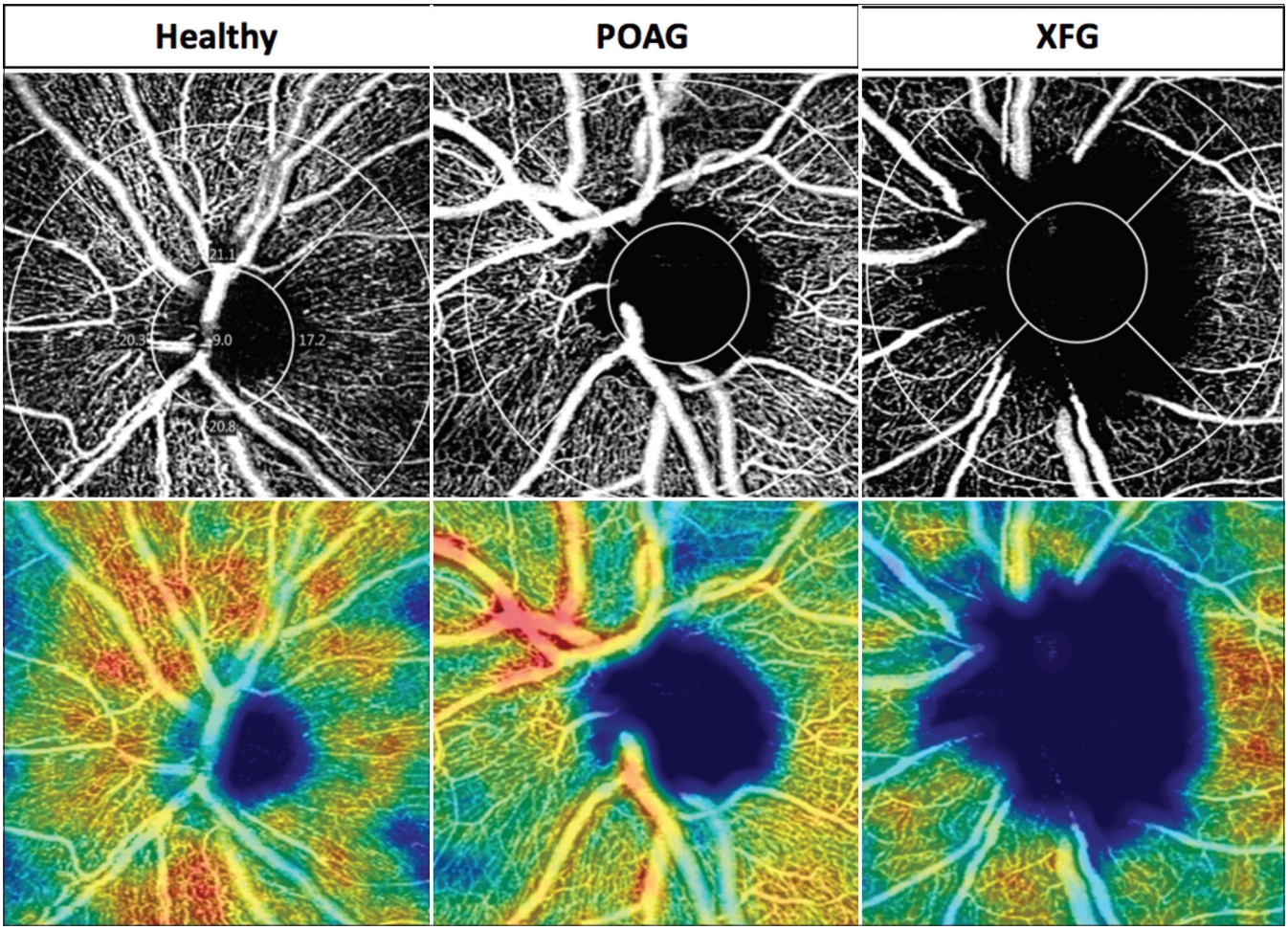

Figure 2: OCTA images in a gray scale and color-perfused capillary density

Table 2: Peripapillary vessel density

Variable	Control Group	POAG Group	XFG Group	*P*	*P* POAG vs. Control	*P* XFG vs. Control	*P* POAG vs. XFG
Central ring (mm^{-1}) mean±SD	9.61±6.87	8.43±7.00	6.88±4.37	0.233	0.272	0.991	0.122
Inner ring (mm^{-1}) mean±SD	17.84±3.55	16.20±3.93	15.66±3.43	0.050*	0.288	0.044*	0.900
Full area (mm^{-1}) mean±SD	16.57±3.46	10.37±8.09	11.61±6.46	<0.01*	<0.01*	0.036*	0.877

*Significantly different. POAG=primary open-angle glaucoma; XFG=exfoliation glaucoma; SD=standard deviation

Table 3: Peripapillary perfusion density

Variable	Control Group	POAG Group	XFG Group	*P*	*P* POAG vs. Control	*P* XFG vs. Control	*P* POAG vs. XFG
Central ring (%) mean±SD	0.16±0.93	0.10±0.94	0.09±0.07	0.02*	0.04*	0.01*	0.746
Inner ring (%) mean±SD	0.43±0.36	0.31±0.07	0.33±0.06	0.153	0.147	0.193	0.384
Full area (%) mean±SD	0.35±0.05	0.30±0.06	0.29±0.06	<0.01*	<0.01*	<0.01*	0.457

*Significantly different|POAG=primary open-angle glaucoma; XFG=exfoliation glaucoma; SD=standard deviation

Statistical analysis

One eye per patient was selected for the analysis. It was randomly selected in the control group, and the affected eye was selected in the XFG and POAG groups unless both eyes met the inclusion criteria, whereupon only the right eye was selected. Quantitative variables were described as mean, range, and standard deviation. Categorical variables were described as absolute and relative frequencies. Significant differences between the IOP, MD, RNFLT, CMT, GCC, VD, PD, and FAZ parameters across groups were tested with analysis of variance (ANOVA) with a Bonferroni post hoc analysis. The correlations between parameters were tested

with Pearson's correlation analysis. A P value of <0.05 was defined as statistically significant, and the confidence interval was set at 95%. To achieve a power of 80%, we calculated the required number of subjects needed for each group (Power and Precision Biostat, Englewood, NJ). Statistical analysis was carried out with Microsoft Excel 16.12 (Microsoft Corporation, Redmond, WA, USA) and SPSS software version 23.0 (SPSS, Inc., Chicago, IL, USA).

Results

Study participants

The 109 study participants (55 males and 54 females) included 45 patients in the POAG group, 30 patients in the XFG group, and 34 subjects in the control group.

There were significant differences between the three groups in gender (p = 0.02, Chi-square). However, when comparing genders between the control group to POAG and the control group to the PXG group, no differences in gender were found (p = 0.277, 0.104, accordingly, Chi-square). The patients in the POAG and XFG groups were being treated by eye drops to reduce IOP; therefore, the absence of any significant group differences in IOP was expected [Table 1]. No significant differences were found between the POAG, PXG, and control groups in age. Significant differences were found between POAG and PXF groups to the control group in visual field parameters and severity of the disease. The participants' demographics and clinical characteristics are summarized in Table 1.

Peripapillary VD

The average peripapillary VDs of the inner ring and full ring of the XFG group were the lowest of the three groups, whereas the average peripapillary VDs of the inner ring and full ring of the control group were the highest [Fig. 2]. The differences in the average peripapillary VDs of the central ring, inner ring, and full ring between the three groups were statistically significant (P = 0.05, 0.049 and P < 0.01, ANOVA). There were no significant differences between the POAG and PXG groups in VDs [Table 2].

Peripapillary PD

There were significant differences between the three groups in the average peripapillary PDs of the central ring and the full ring. The average peripapillary PD of the central ring was the lowest for the PXF group and the highest for the control group (P = 0.02, ANOVA). The average peripapillary PD of the full ring was the lowest for the POAG group and the highest for the control group (P < 0.01, ANOVA) [Table 3]. There were no significant PD differences between the POAG and PXG groups.

Correlation between clinical characteristics and vascular parameters

The clinical parameters of glaucoma, including IOP, glaucoma severity stage, RNFLT, CMT, and GC thickness were correlated with the OCTA vascular parameters [Table 4]. The average peripapillary VDs of the inner ring and full ring were significantly negatively correlated with disease severity in the

Table 4: Correlation between clinical characteristics and vascular parameters

Variable Correlation (P)	POAG Group					XFG Group				
	IOP	Stage	RNFL Thickness	Central Macular Thickness	Average Ganglion Cell	IOP	Stage	RNFL Thickness	Central Macular Thickness	Average Ganglion Cell
Vascular densities										
Central ring	-0.276 (0.777)	-0.012 (0.633)	0.658 (0.342)	0.28 (0.890)	0.25 (0.259)	-0.098 (0.634)	0.127 (0.604)	0.253 (0.327)	0.01 (0.942)	0.52 (0.01)*
Inner ring	-0.31 (0.877)	-0.462 (0.021)*	0.441 (0.559)	-0.290 (0.143)	0.13 (0.527)	0.117 (0.569)	0.281 (0.245)	-0.053 (0.900)	0.16 (0.441)	0.44 (0.036)*
Full area	0.139 (0.488)	-0.533 (0.022)*	0.740 (0.260)	-0.323 (0.100)	-0.32 (0.770)	0.096 (0.641)	0.279 (0.247)	0.130 (0.855)	0.15 (0.478)	0.49 (0.02)*
Perfusion densities										
Central ring	-0.166 (0.730)	-0.455 (0.042)*	0.239 (0.698)	0,80 (0.09)	0.04 (0.82)	-0.137 (0.503)	0.090 (0.715)	0.600 (0.288)	0.50 (0.01)*	0.04 (0.82)
Inner ring	-0.101 (0.608)	-0.333 (0.122)	0.141 (0.821)	0.01 (0.98)	0.14 (0.50)	0.075 (0.715)	0.235 (0.332)	-0.053 (0.891)	0.37 (0.08)	0.14 (0.50)
Full area	-0.56 (0.777)	-0.452 (-0.047)*	0.217 (0.725)	0.07 (0.91)	0.12 (0.56)	0.052 (0.799)	0.231 (0.342)	0.122 (0.324)	0.43 (0.04)*	0.12 (0.56)

*Significantly different. POAG=primary open-angle glaucoma; XFG=exfoliation glaucoma; IOP=intra-ocular pressure; MD=mean deviation; RNFL=retinal nerve fiber layer

Table 5: Fovea avascular zone parameters

Variable	Control Group	POAG Group	XFG Group	P	P POAG vs. Control	P XFG vs. Control	P POAG vs. XFG
FAZ area (mm^2) mean±SD	0.24±0.06	0.18±0.09	0.18±0.13	0.653	0.991	0.991	0.999
FAZ perimeter (mm) mean±SD	2.26±0.17	1.87±0.58	1.79±0.68	0.502	0.974	0.744	0.993
FAZ circularity mean±SD	0.58±0.13	0.67±0.11	0.65±0.11	0.521	0.777	0.982	0.978

*Significantly different. POAG=primary open-angle glaucoma; XFG=exfoliation glaucoma; FAZ=fovea avascular zone; SD=standard deviation

POAG group ($P = 0.021$ and $P = 0.022$, respectively, Pearson correlation). The average peripapillary VDs of the inner ring, central ring, and full ring were significantly positively correlated with the average GCC thickness of the XFG patients ($P = 0.01$, $P = 0.036$, and $P = 0.02$, respectively, Pearson correlation). The average peripapillary PDs of the central ring and full ring were significantly negatively correlated with the POAG disease severity stage ($P = 0.042$ and $P = 0.047$, respectively, Pearson correlation). The average peripapillary PDs of the central ring and full area were significantly positively correlated with the CMT of the XFG patients ($P = 0.01$ and $P = 0.04$, respectively, Pearson correlation).

FAZ parameters

There were no significant differences between the groups in the average FAZ area, circularity, or perimeter. The FAZ parameters of the three groups are summarized in Table 5. In the POAG group, FAZ circularity was not correlated with IOP, MD, CMT, GC thickness, or average RNFL ($P = 0.914$, $P = 0.158$, $P = 0.810$, and $P = 0.210$, respectively, Pearson correlation). In the XFG group, FAZ circularity did not correlate with IOP, MD, CMT, GC thickness, or average RNFLT ($P = 0.248$, $P = 0.886$, $P = 0.829$, $P = 0.513$, and $P = 0.969$, respectively, Pearson correlation).

Discussion

Accumulating evidence has revealed that vascular dysfunction plays a role in the pathogenesis of glaucoma. In 1969, Hayreh[18] histologically demonstrated significant defects in the micro-circulation of the posterior ciliary artery in glaucomatous eyes. Later studies applied fluorescein angiography and indocyanine green angiography and showed alterations in blood flow of the choriocapillary layer in glaucoma eyes.[19,20] These works were followed by findings on Heidelberg retinal tomography of an association between changes in optic nerve head morphology and retinal blood flow in patients with OAG.[21,22] Color Doppler imaging and laser Doppler flowmetry revealed impaired retrobulbar hemodynamics in eyes with XFG.[23] All those methodologies, however, provided a qualitative rather than a quantitative assessment of blood flow. Moreover, some of them are invasive and have serious side effects. OCTA has recently emerged as a promising new technology for studying ocular vascularization in glaucoma patients.[12,24] We compared OCTA parameters of the disc and fovea between 34 healthy participants, 45 POAG patients, and 30 XFG patients. Our results showed that peripapillary VD and peripapillary PD were significantly lower in the POAG and PXG groups compared to the control group. To the best of our knowledge, this is the first assessment by AngioPlex of all those parameters in two groups of glaucoma patients and a control group.

Suwan *et al*.[25] compared the peripapillary VD among eyes with XFS, XFG, POAG, and healthy control eyes by AngioVue. Those authors found that the POAG and XFG eyes had decreased VD values compared with controls. After adjusting for age and disease stage, they observed that the XFG eyes demonstrated lower VD values than the POAG eyes. Park *et al*.[26] compared peripapillary VDs between eyes with XFG and eyes with POAG by a swept source OCT device. They found that the former patients had a lower peripapillary VD than the latter patients. PD parameters were not examined in those two studies, nor were characteristics of clinical and vascular findings or correlations between them and FAZ circularity investigated. The current study investigated both VD and PD and found that the control group had higher VD and PD values compared to the two glaucoma groups (in 8 out of 12 parameters of OCTA) but that there were no differences in VD and PD between the PXG group and the POAG group. The differences between studies may derive from VD having been examined by different OCTA devices that may have different sensitivities and different interpretations.

Rebolleda *et al*.[14] examined the differences between Angiovue and AngioPlex in 20 POAG and 20 PXG patients and reported that only Angiovue detected a significantly lower VD in XFG patients compared to POAG patients with similar glaucoma-related damage to the VF. However, both Angiovue and Angioplex demonstrated a lower VD in glaucoma eyes compared to healthy eyes. Furthermore, Angiovue vascular parameters showed a correlation between functional and structural parameters in glaucoma patients that Angioplex did not detect.

We demonstrated a significant correlation between vascular parameters and clinical severity of POAG. This is in accordance with Yarmohammadi *et al*.'s[27] study in which they found that each 1% decrease in VD was associated with a 0.66 decibel loss in MD. This raises the possibility that VD as measured by OCTA in POAG patients can be used as a predictive tool for a future decrease in visual field test findings. Long-time studies with OCTA at different time points are warranted in order to examine this hypothesis.

We found a significant correlation between GC thickness and average peripapillary VDs in the XFG group as well as a significant correlation between CMT and average peripapillary PD in the XFG group. To the best of our knowledge, this is the first study to examine this correlation, and these results call for further studies to examine those correlations and determine whether those factors can predict disease deterioration in XFG. However, we did not find correlation between vascular parameters and OCT parameters in the POAG group. This may hint that the pathogenesis of POAG and XFG is different and maybe that pathogenesis of XFG includes vascular factors more than in POAG. This assumption need to be examined in further studies.

We also compared vascularization of the FAZ in POAG, XFG, and healthy controls and found no group differences in FAZ circularity. Suwan *et al*.[25] examined vascularity parameters in FAZ in 26 XFG patients and compared their findings to the same parameters in 28 POAG patients of Alnawaiseh *et al*.[24] They also did not find any significant differences between those two groups. It may be because the glaucomatous vascular injury begins in the perifovea area and, respectively, the parafoveal area and finally affects the FAZ parameters. Therefore, just in patients with severe glaucoma, the FAZ will be damaged. In this study, the patients were in different stages of the disease, so maybe some of them had a mild disease without any effect on the FAZ. Further studies need to examine the FAZ circularity parameters in patients with severe XFG, severe POAG, and healthy patients.

We are aware that this study is not without limitations. One limitation derives from it being a cross-sectional study, whereupon there was no assessment of the influence of differences in vascular parameters between glaucoma groups

on disease progression over time. Moreover, the small sample size may limit the generalizability of the results. Furthermore, OCTA is a relatively new technology that has recognized artifacts, and using different image-obtaining and data-analyzing techniques may provide very different results. This must be taken into account when comparing the results of different studies with different measuring methodologies.

Conclusion

In conclusion, the findings of this study revealed that the vascular parameters of peripapillary VD and peripapillary PD were lower in POAG and XFG patients compared to normal participants. Moreover, peripapillary VDs were in correlation to the severity of the disease in the POAG group, and peripapillary VDs and peripapillary PDs were in correlation to macular morphologic characteristics in the PXG group. This may hint to a vascular mechanism in glaucoma either primary or secondary to IOP/OAG damage.

Further long-term studies are warranted on the roles of OCTA as a diagnostic parameter for predicting the risk of glaucoma development and progression and for determining the correlation between OCTA progression and functional parameter progression.

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Conflicts of interest

There are no conflicts of interest.

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