Automated Evaluation of Parapapillary Choroidal Microvasculature in Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma

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• OBJECTIVE: To determine whether parapapillary choroidal microvasculature (PPCMv) density as measured by optical coherence tomography angiography differs between pseudoexfoliation syndrome (PXS) and pseudoexfoliation glaucoma (PXG).

• DESIGN: Cross-sectional study.

• METHODS: One hundred ninety-two eyes of 120 subjects from 2 academic referral institutions were enrolled. Automated PPCMv density was calculated using custom Matlab software in inner and outer annuli around the optic nerve region in addition to peripapillary superficial vasculature. Linear modeling was used to compare vessel densities among groups.

• RESULTS: Data from 64 eyes with PXS, 84 eyes with PXG, and 44 eyes healthy control subjects were analyzed. The differences of visual field mean deviation and peripapillary retinal nerve fiber layer thickness among study groups were statistically significant with lower values in PXG eyes compared with the PXS and control groups. Peripapillary superficial retinal vessel densities were significantly reduced in patients with PXG compared with patients with PXS and normal control subjects (all $P < .001$) without a difference between PXS and control eyes. Customized outer annular PPCMv density in the PXG group with a value of 11.1% (SD 5.1%) was lower than that in PXS with a value of 13.2% (SD 5.3%; $P = .001$). Similarly, PXS values were lower than those of control eyes with a value of 18.6% (SD 5.1%; $P < .001$).

• CONCLUSION: A progressive decrease in outer PPCMv from the control group to those with PXS without glaucoma to those with PXS and glaucoma (PXG) showed deep peripapillary vasculopathy in pseudoexfoliation syndrome. Choroidal vessel density may be affected early in the course of pseudoexfoliation before glaucoma develops. (Am J Ophthalmol 2021;224:178–184. © 2020 Elsevier Inc. All rights reserved.)

PSEUDOEXFOLIATION (EXFOLIATION) SYNDROME (PXS) is characterized by abnormal fibrillar extracellular material deposits throughout the body, including the walls of posterior ciliary arteries and the optic nerve sheaths. PXS is the most common identifiable cause of glaucoma worldwide, accounting for majority of open-angle glaucoma in some countries.[1] In fact, the presence of PXS was shown as the most important independent risk factor for glaucoma progression and the glaucoma conversion rate was higher in patients with ocular hypertension and PXS than in those without PXS.[2,3] Glaucoma in PXS has a more serious clinical course and poorer prognosis than primary open-angle glaucoma (POAG) with higher severity of optic nerve damage.[1–3] The reasons for this development and progression of glaucoma might be the abnormalities of optic disc structure and/or optic disc vascular supply. Earlier studies have shown thinning of the lamina cribrosa of the optic nerve head in nonglaucomatous PXS and PXG subjects than in control subjects.[4,5] PXG is also associated with a vasculopathy and endothelial basement membrane abnormalities.[6] Iris blood vessel lumens are often narrowed and may become obliterated in PXS, leading to iris hypoperfusion and microneovascularization.[1] Choroidal thinning was observed in moderate/advanced PXG eyes.[4] We previously investigated peripapillary superficial retinal capillary density in eyes with PXG and POAG using custom software and found that the vessel densities were significantly lower in eyes with PXG.[7] However, deep choroidal layer microvasculatures within the parapapillary area are more likely related to optic nerve blood flow given that this area is downstream from the short posterior ciliary artery, which also provides a vascular supply to the prelaminar and laminar potions of the optic nerve head.[8]

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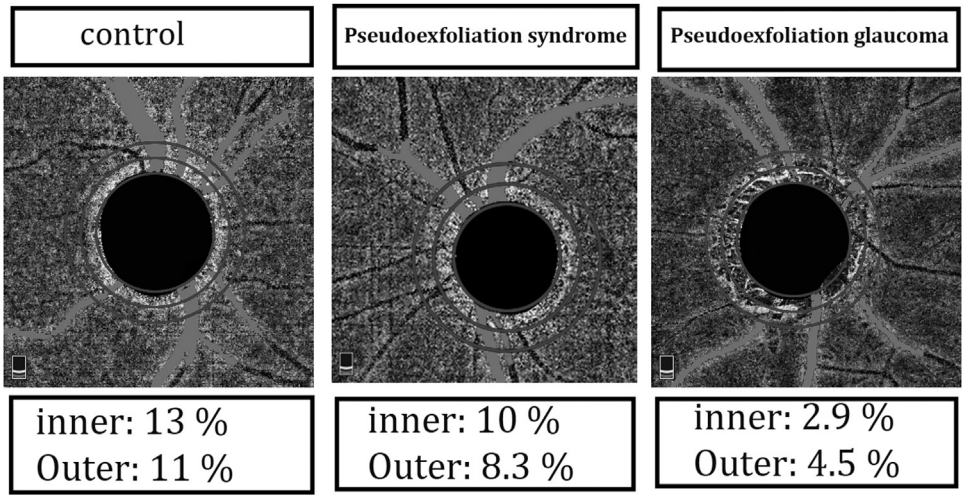

FIGURE 1. Parapaillary choroidal microvasculature in subjects in the control group (Left), patients with pseudoexfoliation syndrome (Middle), and patients with pseudoexfoliation glaucoma (Right). Vessel density values of inner and outer circles are shown as percentages.

Therefore, evaluation of the deep optic nerve and choroidal microvasculature in PXS and PXG, which is feasible with optical coherence tomography-angiography (OCT-A), is of particular clinical interest. Previous OCTA studies have shown choroidal microvascular dropout immediately around the optic disc in glaucomatous eyes (without PXG).[9–12] However, to our knowledge, just 1 study has used OCTA by manually delineating the vascular dropout area to assess the deep microvasculature in eyes with PXG and there have been no reports of the prevalence of deep vessel density in PXS.[13] The current study aimed to evaluate parapapillary deep vessel density in both PXG and PXS using our automated image processing method of choroidal microvessel quantification.[14,15]

METHODS

THIS COMPARATIVE CROSS-SECTIONAL STUDY WAS CONducted from June 2017 to October 2019 in Farabi Eye Hospital and Ramathibodi Hospital after approving study protocol by the Institutional Review Board of Tehran University of Medical Science and Mahidol University (Bangkok, Thailand) in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants. Participants with a spherical refraction within ±2.5 diopters (D), and cylinder correction within ±1.5 D were included. Patients with other optic neuropathy (except PXG) and macular pathology were excluded. For all subjects, a complete ophthalmologic examination including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann tonometry and axial length measurement (IOL Master; Carl Zeiss Meditec, Jena, Germany) were performed. Subjects then underwent OCT and OCT-A imaging using the AngioVue imaging system (RTVue XR, version 2018.0.0.18; Optovue, Inc., Fremont, CA, USA).

Three major groups of subjects were defined in the present study: the PXS group, the PXG group, and the control group.

- **PXS GROUP:** Patients were enrolled in the PXS group if they had visible pseudoexfoliation material on the anterior lens capsule or pupillary margin after mydriasis on slit-lamp, an intraoperative pressure (IOP) <22 mm Hg with no history of increased IOP, an absence of glaucomatous disc appearance, and a normal visual field defined by mean deviation and pattern standard deviation within 95% confidence interval limits and a Glaucoma Hemifield Test within normal limits.

- **PXG GROUP:** Presence of pseudoexfoliation material on the anterior lens capsule and/or pupillary margin after mydriasis on slit-lamp biomicroscopy, enlarged vertical cup-to-disc ratio, diffuse or focal thinning of the neuroretinal rim, an open iridocorneal angle on gonioscopy, presence of a pattern standard deviation outside 95% normal limits (confirmed on ≥2 consecutive, reliable tests), and a glaucoma hemifield test outside normal limits were used for PXG diagnosis.[14] Presence or absence of peripapillary atrophy was not an inclusion or exclusion criterion.

- **CONTROL GROUP:** This group included hospital staffs with age >42 years (which was the lower limit age of PXG subjects), a best-corrected visual acuity ≥20/30, IOP <22 mm Hg, no history of increased IOP or diabetes mellitus, an absence of glaucomatous disc appearance an open angle with normal optic disc appearance on fundus

TABLE 1. Demographic Features and Structural Data in 3 Subject Groups

	Normal	PXS	PXG	*P* Value		
				Normal vs PXS	Normal vs PXG	PXS vs PXG
Subjects with both eyes (n)	18	29	24	—	—	—
Age (y)	65.2 (6.20) [52-81]	69.5 (8.70) [50-86]	67.0 (7.9) [42-87]	.017	.551	.212
Axial length (mm)	22.9 (1.1) [20-25]	23.26 (0.9) [21-25.3]	23.2 (0.7) [21.8-25.3]	.738	.708	>.99
Visual field MD (dB)	−2.0 (2.4) [−10.0 to 1]	−2.54 (3.3) [−10.1 to 2.9]	−16.0 (10.4) [−32.4 to −0.8]	>.99	<.001	<.001
Visual field PSD (dB)	2.5 (1.1) [1-5.4]	2.8 (1.5) [0-7]	6.8 (3.4) [1.6-13.8]	>.99	<.001	<.001
Average RNFL (μm)	101.7 (8.9) [80-119]	97.3 (10.1) [71-118]	74.7 (12.7) [49-100]	.423	<.001	<.001
Superior RNFL (μm)	103.4 (9.4) [88-121]	99.6 (10.4) [70-115]	75.7 (14.3) [45-101]	.889	<.001	<.001
Inferior RNFL (μm)	100.9 (10.0) [70-118]	95.4 (11.2) [72-121]	73.6 (12.3) [52-99]	.347	<.001	<.001

MD = mean deviation; PSD = pattern standard deviation; PXG = pseudoexfoliation glaucoma; PXS = pseudoexfoliation syndrome; RNFL = retinal nerve fiber layer.

Values are mean (standard deviation) [range]. Comparisons are based on linear mixed model analysis with Bonferroni correction after adjusting for age.

examination, no visual field defects, and no evidence of pseudoexfoliation material on the anterior lens capsule or pupillary margin after mydriasis on slit-lamp biomicroscopy in either eye.

• **SPECTRAL-DOMAIN OCT AND OCT-A:** All subjects underwent OCT and OCT-A imaging using the AngioVue imaging system. A standard circular scan was used to measure retinal nerve fiber layer (RNFL) thickness and the mean and each sector RNFL values were recorded.

For OCT-A, we used blood flow information at the radial peripapillary capillary layer as a vessel density map (%) in a 4.5- × 4.5-mm rectangle scan centered on the optic disc. Both all vessels and small vessel density were measured in peripapillary areas and its superior and inferior sectors. Then, we used choriocapillary en face imaging and used customized MATLAB software (The MathWorks, Inc., Natick, Massachusetts, USA) for calculating a customized parapapillary choroidal microvasculature (PPCMv) density after removing the shadows of the large retinal vessels and ignoring the information inside the disc as published previously.[14,15] Briefly, 3 concentric circles were overlaid on the en face image (Figure 1). The information in the inner and outer coaxial annular regions of interest with widths of 0.5 mm and their superior and inferior halves were then used for reporting PPCMv density values in populations. The customized PPCMv density algorithm consists of 3 main stages: constructing the binary location of large retinal vessel shadows, parapapillary capillary segmentation using modified Otsu algorithm, and calculating PPCMv density values. We previously validated the performance of our automated customized PPCMv density by comparing manual and automated methods, which showed a small bias (difference) between two methods.[14]

• **STATISTICAL ANALYSIS:** Normally distributed variables were described as the mean, standard deviation (SD), and range and categorical variables were compared using the χ^2 test. A linear mixed model was used to evaluate the differences of variables among the groups using the Bonferroni correction for multiple comparisons and intereye correlation after adjusting for age. In this method the correlation in outcomes between paired eyes of a subject was accounted for by adding a random effect. Relationships between average RNFL thickness and vessel density of superficial and choroidal vessels were evaluated using simple linear and second-order polynomial (or quadratic) models in all study eyes. Statistical analysis was performed with the SPSS software (version 22.0; IBM Corp., Armonk, New York, USA). $P < .05$ was considered statistically significant.

RESULTS

ONE HUNDRED NINETY-TWO EYES OF 120 SUBJECTS WERE enrolled in this study after excluding 20 eyes from the PXS group, 12 eyes from the PXG group, and 8 eyes from the control group because of macular pathology and poor image condition. Another 4 eyes from the control group were excluded because of the participants were younger in age. Therefore, 64 eyes of 35 patients with PXS, 84 eyes of 59 patients with PXG, and 44 eyes of 26 healthy control subjects were used for the final analysis. Of the participants, 61.9%, 54.7%, and 61.4% were male ($P = .64$, χ^2) with mean ages of 67.0 (SD 7.9), 69.5 (SD 8.7), and 65.2 (SD 6.2) years in the PXG, PXS, and control groups, respectively. Functional and structural characteristics of study eyes are shown in Table 1. The differences of visual

TABLE 2. Peripapillary Superficial Vessel Densities in 3 Subject Groups

Superficial Vessel Density (%)	Normal	PXS	PXG	P Value		
				Normal vs PXS	Normal vs PXG	PXS vs PXG
Peripapillary small vessels	52.0 (2.4) [47.5-57.1]	48.9 (6.7) [22.4-58.6]	37.8 (9.1) [19.5-56.3]	.353	<.001	<.001
Peripapillary all vessels	58.4 (2.5) [52.6-62.9]	54.6 (6.4) [27.6-61.9]	44.6 (8.5) [26.4-61.5]	.096	<.001	<.001
Superior small vessels	52.1 (2.7) [46.4-58.4]	49.8 (6.2) [22.4-60.5]	37.7 (9.8) [17.8-58.4]	.756	<.001	<.001
Superior all vessels	58.7 (2.8) [52.9-63.8]	55.3 (6.3) [28.3-64.5]	44.7 (9.0) [25.1-63.8]	.189	<.001	<.001
Inferior small vessel	51.9 (2.6) [45.2-56.2]	48.5 (7.1) [22.4-56.6]	37.8 (8.9) [21.3-54.3]	.195	<.001	<.001
Inferior all vessels	57.9 (2.5) [51.6-62.0]	54.0 (7.0) [26.8-62.8]	44.4 (8.4) [27.8-59.8]	.089	<.001	<.001

MD = mean deviation; PSD = pattern standard deviation; PXG = pseudoexfoliation glaucoma; PXS = pseudoexfoliation syndrome.
Values are mean (standard deviation) [range]. Comparisons are based on linear mixed model analysis with Bonferroni correction after adjusting for age.

field mean deviation and pattern standard deviation among study groups were statistically significant with more visual field loss in the PXG compared with the PXS and control groups. There was no significant difference of visual field between the PXS and control groups. PXG eyes also manifested lower peripapillary RNFL thickness than those with PXS and control groups ($P < .001$, linear mixed model adjusting for age with Bonferroni correction). Peripapillary RNFL thickness was not different between PXS and control eyes (Table 1).

• **PERIPAPILLARY SUPERFICIAL RETINAL VESSEL DENSITIES:** Small and all vessel densities of the radial peripapillary capillary layer (within the RNFL layer) in the circular area and superior and inferior hemifields are shown in Table 2. Small vessel densities were significantly reduced in patients with PXG compared with the PXS and normal subject groups (all $P < .001$). We demonstrated peripapillary superficial small vessel densities of 37.8% (SD 9.1%) in the PXG versus 48.9% (SD 6.7%) and 52.0% (SD 2.4%) in the PXS and control groups, respectively (both $P < .001$). There was no difference in peripapillary vessel density between PXS and control eyes.

• **PARAPAPILLARY CHOROIDAL MICROVASCULATURE:** Automated customized PPCMv density was measured in inner and outer annuli and inferior and superior hemifields around the optic nerve head. Mean outer annular vessel density in the PXG group with value of 11.1% (SD 5.1%) was lower than that in PXS (13.2% [SD 5.3%]; $P = .03$; Figure 1). Similarly, PXS values were lower than that of control eyes (18.6% [SD 5.1%]; $P < .001$). Furthermore, PXG and PXS groups had significantly reduced inner PPCMv with amounts of 14.1% (SD 6.7%) and 16.1% (SD 6.6%), respectively, compared with normal control subjects (24.7% [SD 6.5%]; both $P < .001$). Inner PPCMs did not differ significantly between PXG and PXS groups ($P = .12$). All outer and inner ring hemifields also had lower density in PXG and PXS than in the control group (Table 3).

Correlation analysis showed that mean peripapillary superficial small vessel density was significantly correlated with average RNFL thickness in all study eyes ($r^2 = 0.60$, $P < .001$). The scatter plot in Figure 2 shows that each 1-mm loss in RNFL thickness was associated with 0.46 using univariate linear regression analysis. However, the quadratic model was better than the linear model in assessing the relationship between superficial vessel density measurements and average RNFL thickness.

For choroidal vessel density parameters, both linear and quadratic models performed similarly. Inner and outer annuli PPCMv were also correlated with average RNFL ($r^2 = 0.16$, $P < .001$ and $r^2 = 0.19$, $P < .001$, respectively, for the linear model) (Figure 2).

DISCUSSION

THIS STUDY INVESTIGATED DIFFERENCES OF SUPERFICIAL (within RNFL) and deep (choroidal) parapapillary vessel densities in PXG, PXS, and healthy control subjects using automated OCT-A analysis. Superficial vascular density was significantly lower in patients with PXG than that in patients with PXS and control subjects, with no differences between patients with PXS and control subjects.

The PXG group had significantly reduced PPCMv density compared with patients with PXS and normal subjects. Similarly, outer PPCMv density of PXS eyes was lower than control eyes. In other words, outer PPCMs demonstrated a progressive decrease from control subjects to those with PXS to eyes with PXG.

Exfoliation syndrome has been associated with vascular pathology, including anterior segment ischemia, retinal vein occlusion, cardiovascular and cerebrovascular disease caused by accumulating exfoliation material, and endothelial basement membrane disruption.[1,16] The increase in vasoactive peptide endothelin-1 and the decrease in aqueous levels of nitric oxide in PXS lead to obliterative vasculopathy and reduced ocular and retrobulbar blood flow.[17,18] Moghimi

TABLE 3. Parapapillary Choroidal Vasculature Densities in 2 Circles Around the Optic Nerve Head in 3 Groups

Parapapillary Choroid (%)	Normal	PXS	PXG	*P* Value		
				Normal vs PXS	Normal vs PXS	Normal vs PXS
Inner annulus	24.7 (6.5) [9.2-38.3]	16.1 (6.6) [3.5-31.3]	14.1 (6.7) [1.9-32.7]	<.001	<.001	.126
Inner hemi-superior	25.4 (7.3) [7.3-41.8]	16.5 (6.9) [3.9-32.5]	14.3 (7.4) [1.0-38.4]	<.001	<.001	.138
Inner hemi-inferior	23.9 (7.7) [9.9-48.7]	16.0 (7.0) [2.7-36.1]	13.8 (7.5) [0.9-35.2]	<.001	<.001	.135
Outer annulus	18.6 (5.1) [7.7-31.1]	13.2 (5.3) [2.1-23.6]	11.1 (5.1) [1.5-24.6]	<.001	<.001	.033
Outer hemi-superior	19.4 (5.7) [5.9-34.5]	13.5 (5.7) [2.4-24.8]	11.3 (5.8) [4.0-27.5]	<.001	<.001	.040
Outer hemi-inferior	17.8 (5.9) [6.6-32.7]	12.9 (5.9) [1.1-28.3]	10.8 (5.4) [0.6-24.3]	.006	<.001	.085

MD = mean deviation; PSD = pattern standard deviation; PXG = pseudoexfoliation glaucoma; PXS = pseudoexfoliation syndrome.
Values are mean (standard deviation) [range]. Comparisons are based on linear mixed model analysis with Bonferroni correction after adjusting for age.

and associates[4] have shown that moderate to advanced PXG eyes had thinner choroid when compared with mild PXG, PXS, and healthy control eyes, indicating the role of choroidal vasculature in pathogenesis of advanced PXG. To evaluate PXS vasculopathy, a few studies have recently reported the peripapillary superficial retinal vasculature in PXS, PXG, and its comparison with POAG with various results.[7,13,19–21] Indeed, we previously demonstrated a decreased superficial capillary density in patients with PXS compared with control subjects.[7] Recent studies also showed that PXG eyes had lower vessel values compared with POAG eyes after adjusting for age and stage using Optovue OCT-A.[7,19] Park and associates[20] found a significant reduction in superficial peripapillary vessel density in the inferonasal and nasal sectors but not in the other sectors of eyes with PXG compared with POAG using a swept-source OCT-A device. On the other hand, 2 recent studies showed that PXG eyes had a similar level of peripapillary and superficial macular vessel densities compared with open angle glaucoma eyes both using Optovue OCT-A.[13,21] Those studies did not address the superficial vessel density values in PXS without glaucoma. In the present study, we found no difference in superficial peripapillary vessel density between PXS and control eyes and lower superficial vessel density in PXG compared with PXS eyes.

However, the parapapillary microvasculature of the deep optic nerve and choroid may represent a potential risk factor for glaucoma progression; given the underlying PXS vasculopathy, its evaluation is worth studying. In fact, PPCMs focal loss is associated with progressive RNFL thinning in glaucoma,[11] and baseline PPCMv within the β-zone parapapillary atrophy was also associated with progression of glaucoma as measured by visual field than did baseline RNFL thickness. It means together with previously known risk factors for progression such as baseline visual field mean deviation, the presence of disc hemorrhage, higher IOP, PPCMs dropout should be considered as a new risk factor, which proposed the role of PPCMs in the perfusion of the optic nerve.[22] In this study, an automated technique was used to measure PPCMs in inner and outer annuli around the optic nerve in PXS and PXG. In line with previous studies of POAG,[11,12,22] and 1 report of PXG (without PXS)[13] we found focal loss of deep vessels in the inner and outer annuli in PXG eyes compared to control eyes.[11–13,22] Of note, for the first time, the present study showed an outer PPCMs dropout not only in PXG, but also in PXS with a progressive dropout from control to PXS eyes to PXG eyes. Focal loss of choroidal microvessels in PXS might suggest choroidal vasculopathy and a greater loss of PPCMs in PXG manifests the additive vascular damage which might occur in the pathogenesis of glaucoma. In other words, our data showed that choroidal vessel density may be affected early in the course of pseudoexfoliation before glaucoma develops. The pathogenesis of choroidal vasculopathy in PXS might be related to identification of exfoliation fibers in the walls of posterior ciliary arteries which supply parapapillary choroid.[1] In the present study, we also found similar superficial retinal vessel density in control and PXS eyes. This suggests that even though PXS vascular dysregulation could not affect superficial parapapillary vessel, it reduces parapapillary deep choroidal vasculature. Moreover, superficial vessel density was strongly correlated to peripapillary RNFL and therefore in our PXS eyes without RNFL loss, superficial vessel loss was not anticipated. Stronger correlation of peripapillary RNFL with peripapillary superficial vessel density (r^2=0.60) than correlation of RNFL with PPCMv density (r^2 = 0.19) may also suggest secondary superficial vessel rarefaction in contrast to primary PXS-associated PPCMv dropout. Indeed, we previously showed that different optic neuropathies (regardless of the cause of the optic neuropathy) manifested similar superficial peripapillary vessel density rarefaction, which correlated with RNFL thickness.[23,24] It appears that superficial vessel density loss in the PXG eyes might prominently happen secondary to RNFL damage.

The current study has a number of limitations. Cross-sectional design and small sample size limited the power of our findings. Second, while we took into account the effect of retinal vessel shadows over the choroidal slab,

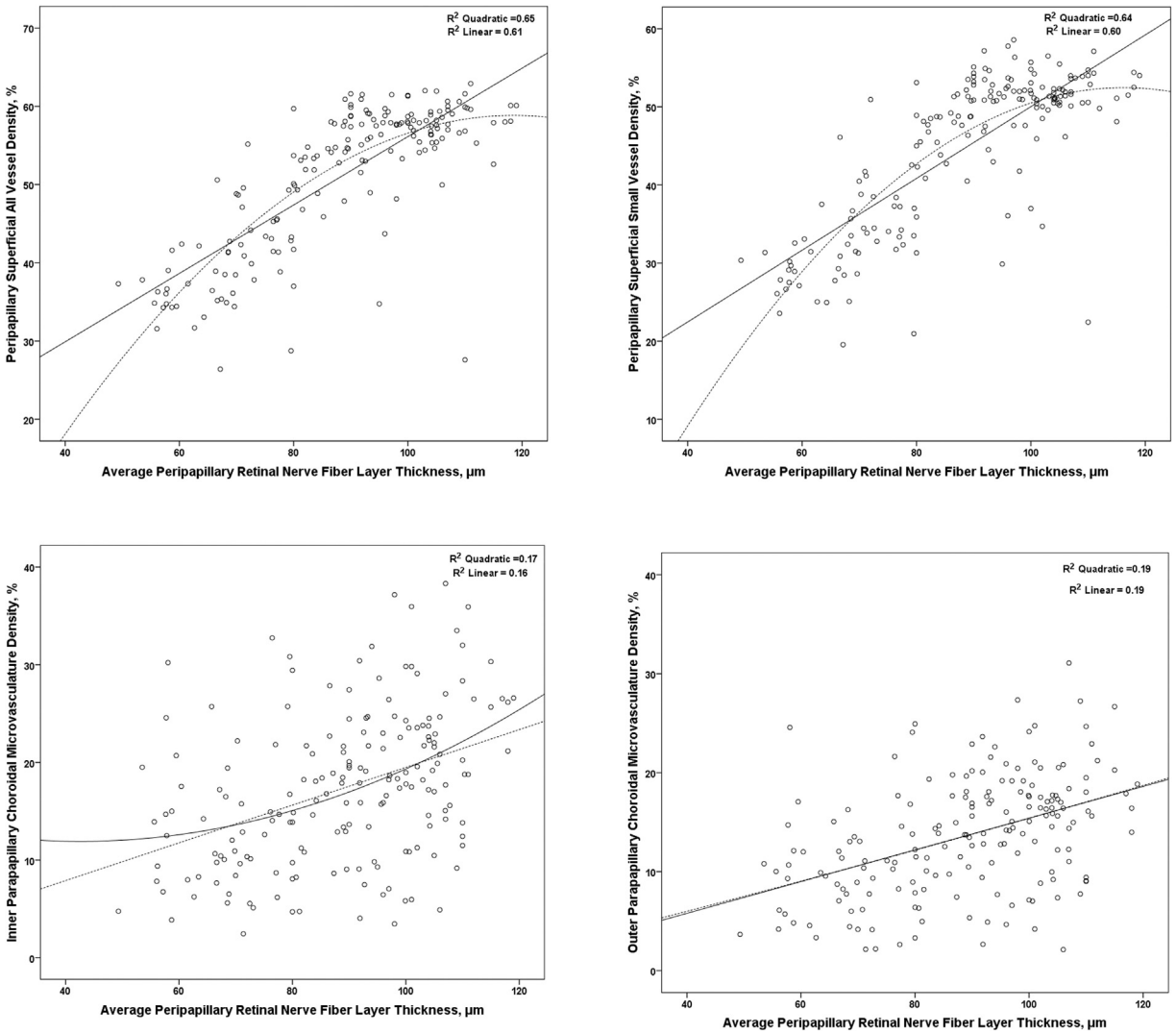

FIGURE 2. Scatter plot showing the linear (dotted line) and curvilinear (quadratic fit, dotted lines) association of peripapillary retinal nerve fiber layer thickness with peripapillary small and all retinal vessel densities (Top) and peripapillary inner and outer choroidal microvasculature densities (Bottom).

limited resolution of images and artifacts around shadows should be considered. Third, we ignored the impact of myopia for the study eyes although we included subjects with a spherical refraction within ±2.5 diopters (D), and cylinder correction within ±1.5 D and three groups axial length were matched. While we previously showed the effect of myopia on peripapillary superficial vessels,[25] another study did not find myopia effect on PPCMv.[26] Finally, some reports of systemic vascular comorbidities in XFS/XFG remain inconsistent[27] and vascular rarefaction in our cases could be a secondary phenomenon rather that primary event in exfoliation syndrome.

In conclusion, in PXS with and without glaucoma and control eyes, peripapillary vascular density dropout in superficial retina (radial peripapillary capillary) and deep choroidal layers differed significantly. While superficial vessel density was lower in PXG compared to the other groups, this vessel density was not different between controls and PXS. PPCMv exhibited a progressive decrease from the control group to those with PXS without glaucoma to those with PXS and glaucoma (PXG). This difference may reflect the parapapillary deep vasculopathy in PXS, but further study is indicated to determine the pathogenic role that such changes may play.

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All authors have completed and submitted the ICMJE form for disclosure of potential conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.

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