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Optic Nerve Head Vessel Density in Different Stages of Pseudoexfoliation Disease

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Abstract

Purpose: To evaluate the superficial vascular density of the optic nerve head in different stages of pseudoexfoliation disease using optical coherence tomography angiography (OCTA).

Methods: In this cross-sectional study, 57 normal eyes, 41 eyes with pseudoexfoliation syndrome (PXS), 82 eyes with pseudoexfoliation glaucoma (PXG), and 27 non-glaucomatous fellow eyes of PXG (NL-PXG) that had OCTA were included. Circumpapillary RNFL (cpRNFL) thickness and circumpapillary capillary density (cpCD) were compared among the groups after adjusting for confounders using linear mixed model.

Results: PXG eyes had thinner global RNFL and lower cpCD ($74.2\pm14.3\mu m$ and 36.7 ± 10.0 %) than control (103.3 ± 8.6 μm and 52.5 ± 2.3 %), PXS (96.8 ± 8.8 μm and 51.5 ± 2.3 %), and NL-PXG eyes (96.3 ± 11.1 μm and 50.1 ± 3.9 %) ($P<0.001$). After adjustment for age, gender, and signal strength index, global cpRNFL thickness was comparable among control, PXS and NL-PXG. NL-PXG had the lowest cpCD ($P= 0.045$) and sectoral cpCD compared to PXS and control eyes. Although cpCD was comparable between control and PXS ($P=0.425$) eyes, sectoral differences ($P = 0.009$ and 0.004, for inferonasal and temporal-inferior cpCD, respectively) were detectable between the two groups. AUROC for differentiating NL-PXG eyes from normal were better for cpCD (0.78) compared to cpRNLF (0.69).

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Conclusions: OCTA can detect reduced capillary density before significant changes in cpRNFL in fellow eyes of PXG patients. This can enable earlier detection of glaucomatous loss in pseudoexfoliation disease and enhance management of the disease.

Keywords

glaucoma; optic nerve head; vessel density; optical coherence tomography; pseudoexfoliation

Introduction

Pseudoexfoliation syndrome (PXS) is the most common identifiable cause of open-angle glaucoma worldwide, and approximately half of PXS patients will develop secondary glaucoma during their life. Pseudoexfoliation glaucoma (PXG) accounts for nearly 25 % of all open angle glaucoma cases.[1 2] Although high intraocular pressure (IOP) and large IOP fluctuations can lead to higher rates of development or progression of PXG, there is increasing evidence that IOP-independent factors such as impaired ocular perfusion and lamina cribosa abnormalities may also contribute to its pathogenesis and progression. [3–6] Systemic vascular dysfunction secondary to the wide distribution of XFM deposits throughout the body has been reported in PXS.[7] Ocular vasculature, including the central retinal artery, short posterior ciliary arteries, ciliary circulation, iris vessels and vortex veins have been also shown to be affected in PXS.[3]

Impaired ocular and retrobulbar blood flow have been demonstrated using color Doppler imaging and laser Doppler flowmetry in PXS and PXG.[3 4 8 9] Unlike the existing technologies for evaluation of retinal perfusion, OCTA is a noninvasive 3-dimentional imaging technique that provides quantitative and qualitative assessment of the microvasculature in the different retinal layers.[10] Prior OCTA studies have shown reduced circumpapillary superficial vessel density (cpVD) in PXG compared to POAG as well as in unilateral PXS and its fellow eye.[11–16]

Although PXS can present unilaterally, it actually has bilateral involvement with asymmetricrepresentation. [2 3] In apparent unilateral cases, exfoliation fibers are almost invariably present on electron microscopy in the conjunctiva of the fellow eyes.[17] Puska et al found that 40% of patients with unilateral PXS converted to bilateral PXS in 10 years. [18] They also reported that 40% of unaffected fellow eyes of PXS developed PXG in that period. This suggests that unilateral involvement of PXS could be a clinical sign for bilateral involvement.[1]

As PXG can be a progressive disease with a poor prognosis, early detection would be of great value for timely management.[1 2] Understanding the changes in microvasculature in different stages of the disease may shed light on the pathophysiology of the disease and facilitate early detection of the disease. In the present study, we evaluated the OCTA-measured superficial vessel density of optic nerve head in non-glaucomatous fellow eyes of PXG patients and compared it with PXS eyes and control eyes.

Methods

This is a prospective, cross-sectional study. Patients with established or newly diagnosed unilateral PXG, bilateral PXG, PXS and normal eyes examined at Farabi Eye Hospital between May 2016 and October 2019 were enrolled. The study was approved by the research ethics committee of the Tehran University of Medical Science (IRB number: IR.TUMS.FARABIH.REC.1396.3245). Written informed consent was obtained from each patient before study entry.

All participants were older than 18 years of age, had BCVA 20/60 or better and, refractive error within ±6.00 Sphere and ±3.00 Cylinder. Each underwent an ophthalmic examination, which included slit-lamp biomicroscopy, IOP measurement (Goldman applanation tonometry), best corrected visual acuity (BCVA), gonioscopy, dilated fundus and optic disc examination, axial length measurement (IOL Master; Carl Zeiss Meditec) and visual field testing (Humphrey Visual Field Analyzer, Carl Zeiss Meditec, Dublin, CA).

Four main groups of participants were defined:

I. PXS: Eyes with pseudoexfoliative material on the anterior lens capsule or pupillary margin after mydriasis on slit-lamp examination, IOP <22 mmHg with no history of elevated IOP, healthy optic nerve head appearance, and a reliable normal visual field defined by a pattern standard deviation (PSD) within 95% confidence limits and a glaucoma hemifield test (GHT) result within normal limits. The fellow eyes did not have PXG.

II. PXG: Eyes with pseudoexfoliative material on the anterior lens capsule or pupillary margin after mydriasis on slit-lamp examination with a) glaucomatous optic nerve appearance (neuroretinal rim thinning or notching or RNFL defect); b) reliable and consistent glaucomatous visual field damage on Humphrey SITA 24–2 perimetry. Glaucomatous visual field damage was defined as 3 contiguous points at a 5% level of significance on the pattern deviation plot with 1 of the 3 points at a 1% level of significance, or a glaucoma hemifield test outside normal limits, or a pattern standard deviation (PSD) outside normal limits ($P < 0.05$), consistent with a glaucomatous pattern.

III. Non-glaucomatous fellow eyes of PXG patients (NL-PXG): This group included contralateral fellow eyes of patients in the PXG group if they had no visible pseudoexfoliative material on the anterior lens capsule or pupillary margin after mydriasis on slit-lamp examination, IOP <22 mmHg with no topical medication, healthy optic nerve head appearance, and a reliable normal visual field.

IV. Control group: a BCVA 20/30, IOP <22 mmHg without any anti-glaucoma medication and no history of elevated IOP, open angle with normal optic disc appearance and RNFL on fundus examination, a reliable normal visual field and no evidence of pseudoexfoliative material on the anterior lens capsule or pupillary margin after mydriasis on slit-lamp examination in both eyes.

Patients were excluded from the study with a history of any intraocular surgery, retinal disease, uveitis, non-glaucomatous optic neuropathy and ocular trauma, or significant media opacity preventing high-quality imaging.

Spectral-Domain Optical Coherence Tomography and Optical Coherence Tomography Angiography

OCT and OCTA imaging was performed in all subjects with AngioVue (Software Version 2018.0.0.18, Optovue, Fremont, CA). A standard circular scan (3.45 mm in diameter centered on ONH) was used to measure circumpapillary RNFL (cpRNFL) thickness. Global and each 45 degree sector RNFL values were recorded.

As described previously,[10] the AngioVue OCTA system uses an 840-nm light source and has a 70 KHz axial line rate. In each volume which contains 304×304 A-scans, two consecutive B-scans captured at each fixed A-scan position. This system uses Split-Spectrum Amplitude-Decorrelation Angiography (SSADA) algorithm to capture the dynamic motion of moving scatters such as red blood cells and provides a high-resolution three-dimensional (3D) visualization of perfused vasculature at various retinal layers. The optic disc scan covers an area of 4.5×4.5 mm centered on the ONH. Vessel density, defined as the proportion of measured area occupied by flowing blood vessels defined as pixels having decorrelation values above the threshold level, was automatically calculated within the optic disc scan. Circumpapillary vessel density (cpVD) was calculated in the region defined as a 750-μm-wide elliptical annulus extending from the optic disc margin. After automated removal of large vessels from the 4.5×4.5 rectangular optic disc scan and the 750-μm-wide annulus, whole image capillary density (wiCD) and circumpapillary capillary density (cpCD) were calculated respectively.

Two investigators (MS, AS) reviewed the quality of scans and excluded poor quality scans from the analysis if one of the following criteria were met: (1) signal strength index (SSI) less than 48; (2) poor clarity images; (3) motion artifacts; and (4) segmentation failure.

Statistical analysis

The mean and SD were calculated for the continuous variables. Linear mixed-effects model was used for comparing thickness and vessel density parameters among the groups while adjusting for inter-eye correlations. Multivariable model was constructed with age, SSI, and other variables with p<0.1 in univariable analysis. Factors related to cpCD were explored in univariable and multivariable analysis. Area under the receiver operating characteristic curve (AROC) was used to reveal the parameters that were best qualified to identify the PXS or Nl-PXG from control eyes and sensitivities (at 90% specificity) were calculated. Statistical analyses were performed using statistical software Stata 14.2 (StataCorp LLC, College Station, TX) and by SPSS software Version 25.0 (IBM Corp., Armonk, NY). P-value less than 0.05 was considered statistically significant.

Results

Two hundred and seven eyes of 152 subjects with good quality scans were enrolled in the study, consisting of 57 eyes of 36 normal subjects, 41 eyes of 28 PXS, 27 eyes of 27

NL-PXG and 82 eyes of 61 PXG. Demographic and ocular characteristics of study subjects are shown in Table 1. There was no significant difference in axial length among the study groups (P= 0.940). The differences in C/D ratio, IOP, MD and PSD were significant among the groups (p<0.001). The PXG eyes had greater C/D ratio and higher IOP compared to other groups. PXG eyes had more functional visual field loss in terms of MD and PSD compared to control, PXS and NL-PXG eyes. cpRNFL thickness, wiCD and cpCD differed significantly among the 4 groups (P< 0.001). PXG eyes had thinner global RNFL and lower vessel densities (cpCD and wiCD) than control, PXS and NL-PXG eyes (P<0.001 for all).

Although the differences in global cpRNFL thickness were not significant among control, PXS and NL-PXG after adjustment for age, gender, and SSI (P=0.437), some sectors had lower RNFL thickness in NL-PXG compared to PXS and control. We demonstrated superotemporal RNFL thickness of 124.6 ±19.7 μm in NL-PXG versus 132.1 ±16.3 μm in PXS (P=0.02). The inferotemporal sector had thinner RNFL in NL-PXG (120.8 ±15.6 μm) compared to PXS (128.9 ±14.2 μm) and Control (140.9 ±15.5 μm; P= 0.01 and 0.002 respectively) (Table 2).

The average cpCD value was reduced in NL-PXG (50.1 ±3.9 %) compared to PXS (51.5 ±2.3 %) after adjustment (P= 0.014). The reduction of capillary density was significant in the inferior hemifield of the NL-PXG compared to control and PXS (P=0.008 and 0.004, respectively). After adjustment, inferotemporal and temporal-inferior cpCD was lower in NL-PXG than PXS and inferonasal and temporal-inferior cpCD was lower in NL-PXG than control. cpCD did not differ significantly between control and PXS (P=0.425). (Table 2)

Factors associated with cpCD in all the groups were explored; older age (β (95% CI) = −0.20 (−0.33, −0.07), P=0.003), male gender (−5.71 (−8.26, −3.16), P<0.001), lower cpRNFL (0.26 (0.18, 0.35), P<0.001), and lower SSI (0.26 (0.18, 0.35), P<0.001) were associated with lower cpCD in univariable analysis. In multivariable analysis male gender (−2.37 (−4.3, −0.44), P=0.17) and lower cpRNFL (0.51 (0.46, 0.56), P<0.001) were associated with lower cpCD (Figure 1).

Although cpCD had a better performance for discriminating NL-PXG eyes and normal eyes (AUROC (95% CI) =0.78 (0.66– 0.90)) compared to the cpRNFL (0.69 (0.56– 0.84), both parameters had weak performance in discriminating PXS eyes and normal eyes (AUROC (95% CI) =0.69 (0.55–0.83) vs. 0.71 (0.58–0.84), for cpCD and cpRNFL, respectively) (Figure 2). The sensitivities (at 90% specifically) for detection of NL-PGX were 35.0 % and 17.2 % for cpCD and cpRNFL, respectively. The sensitivities (at 90% specifically) for detection of PXS were 19.2 % and 31.0 % for cpCD and cpRNFL, respectively.

Discussion

In the present study, peripapillary RNFL thickness and vessel densities in different stages of pseudoexfoliative syndrome were evaluated. We demonstrated that while cpRNFL is comparable among PXS eyes, non-glaucomatous fellow eyes of PXG eyes, and control eyes, the non-glaucomatous fellow eyes of PXG eyes had lower cpCD than PXS eyes and control eyes. This suggests that vessel density may be affected early in the course

of pseudoexfoliation before any structural or functional glaucomatous damage appears and it could be considered a risk factor for glaucoma development in pseudoexfoliative disease. Moreover, localized cpRNFL thinning and vessel density drop-out were found in PXS, non-glaucomatous fellow eyes of PXG eyes, and PXG eyes; thinner RNFL thickness was associated with lower vessel density. These findings may help clinicians diagnose pseudoexfoliative glaucoma patients earlier and allow for timely treatment of this aggressive disease.

In this study, we observed that NL-PXG eyes had lower average OCTA-measured cpCD compared to both PXS and control eyes. Ocular involvement in PXS is mostly bilateral. Even in unilateral PXS, the fellow eye often has abnormal aqueous humor dynamics or glaucomatous damage, which is less noticeable than the involved eye.[1 19] Ultrastructural alterations in anterior segment tissues and conjunctiva have also been reported in the clinically uninvolved fellow eye. A previous study in unilateral PXG demonstrated that the nonexfoliative fellow eyes had reduced peripapillary blood flow values when using a Heidelberg retinal flowmeter[9]. Similarly, Ocakoglu et al[3] evaluated peripapillary and optic nerve head blood flow values in PXS using a Heidelberg retinal flowmeter and reported lower blood flow in fellow eyes of PXS patients in comparison to healthy control eyes. With the advent of OCTA, there has been increased interest in investigating the role of the microvasculature within the peripapillary region in pathogenesis of PXG, which presents unilaterally but is actually a bilateral process. The difference in vessel density was significant in inferior hemifield, inferotemporal and temporal-inferior sectors in NL-PXG compared to PXS, and in inferior hemifield, inferonasal and temporal-inferior sectors in NL-PXG compared to control. Our results are consistent with a prior study that found lower mean cpVD in fellow eyes of PXG compared to controls.[20] They measured peripapillary vascular density in PXG and its normal fellow eye. Their results showed a significant cpVD decrease in the superior hemifield, and most of the sectors in the fellow eyes of PXG eyes compared to the control eyes.

About one quarter of the PXS patients need treatment for ocular hypertension or glaucoma at its presentation[21], whereas glaucomatous damage has been shown in about 40% of the fellow eyes of unilateral PXG. The fellow eyes of unilateral PXG are have high risk of glaucomatous damage[22]. The normotensive PXS eyes converted to PXG had initial smaller rim areas and rim/disc ratios[18]. Possible mechanisms for involvement in non-glaucomatous contralateral eyes of unilateral glaucoma cases (with or without PXS) have been suggested. These mechanisms includes[23]: 1) Reactivation of astroglial cell and transmission to the contralateral retina, 2) post-chiasmatic contralateral axonal degeneration, and 3) changes in ocular flow and vasculature in the contralateral eye[4 9].

Although the cpCD in NL-PXG was lower than in PXS, the differences in cpCD measurement between PXS and control were comparable after adjustment for age, gender, and SSI. Contrary to our finding, two recent studies demonstrated lower peripapillary vessel density in PXS compared to control eye.[11 16] Suwan et al reported a gradual decrease in cpCD from control to PXS to POAG and to PXG. This inconsistency may be due to their method of quantifying vessel density. They used a custom software to measure cpCD, which may have affected the results. In another study, PXS eyes had lower cpVD compared to

normal fellow and control eyes [16]. A possible explanation for their contradictory results might be that PXS eyes in their study had some loss of RNFL thickness. PXS in our study, unlike the previous ones, did not associate with thin cpRNFL.[11 16 24] In addition, these investigations did not present the SSI adjusted comparision. Recent studies have shown that lower scan quality and older age are associated with lower vessel density and that this should be addressed in the analysis.[25–28]

In the present study, although global RNFL thickness was not different among PXS, NL-PXG and control group, localized RNFL thinning and vessel density drop-out were detectable in NL-PXG eyes. Inferotemporal and supratemporal RNFL thinning was observed in NL-PXG subjects compared to PXS and control, after adjustment for confounders. This is consistent with the previous studies showing that inferotemporal and/or supratemporal RNFL loss preferentially occurs in preperimetric glaucoma[29 30]. With regards to vessel density, inferonasal and inferotemporal microvascular dropout were seen in NL-PXG group which correlated with corresponding sector RNFL thinning. Decreased ONH and retinal vessel density along with RNFL thinning have been reported in preperimetic glaucoma and the unaffected fellow eye of POAG;[31–33] however, in our study, vessel density was a better parameter for differntiating unaffected fellow eye of glaucoma from healthy normal.

Our findings demonstrated that cpCD had acceptable diagnostic accuracy (AUROC=0.78) in differentiating between fellow eyes of PXG from normal eyes, similar to a report by Simsek et al[20] However, cpCD had lower accuracy in differentiating PXS eyes from normal (AUROC=0.69). Of note, cpRNFL thickness had low performance for differentiating both PXS eyes and NL-PXG eyes from normal controls (AUROC= 0.71 and 0.69, respectively). cpRNFL thickness was comparable between the NL-PXG, PXS and Control groups. This is in line with a recent study by Goker et al[16] which compared the non-glaucomatous fellow eye of PXG patients and normal eyes which observed microvascular defects at the ONH before any RNFL defect became evident. They postulated that the microcirculation impairment in pseudoexfoliation disease may be a precursor to RNFL loss.

This study does have some limitations. The relatively small sample size could affect the power of results. Because of the cross-sectional design of the study, we were not able to assess progression over time. Moreover, we did not evaluate the importance of the fluctuation of IOP as a contributory factor in PXG and PXS. It has been reported to be larger in PXS patients[34]. Possible confounding factors that could influence VD, including systemic hypertension, diabetes mellitus, and vasoactive medications (both topical and systemic) were not excluded. Finally, the healthy group was younger than the other groups and there were differences in some ocular and systemic characteristics among the study groups. It is possible that all the factors that might affect OCTA damage were not adequately controlled despite adjusting for age and gender in multivariable analysis.

In conclusion, this study identifies capillary density dropout in non-glaucomatous fellow eyes of PXG patients at comparable cpRNFL thickness. Vessel density drop-out was detectable mostly in the inferior regions in early stages of pseudoexfoliation disease. These findings suggest that OCTA can detect microcirculation disturbances in eyes at high risk of developing glaucoma before detectable structural or functional damage. Longitudinal studies

are needed to determine the role of OCTA in detecting glaucoma development or predicting glaucoma progression in pseudoexfoliation disease.

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Synopsis:

Capillary density dropout can be detected in non-glaucomatous fellow eyes of pseudoexfoliative glaucoma patients at comparable retinal fiber layer thickness and can be helpful for earlier detection of glaucomatous change in pseudoexfoliation disease.
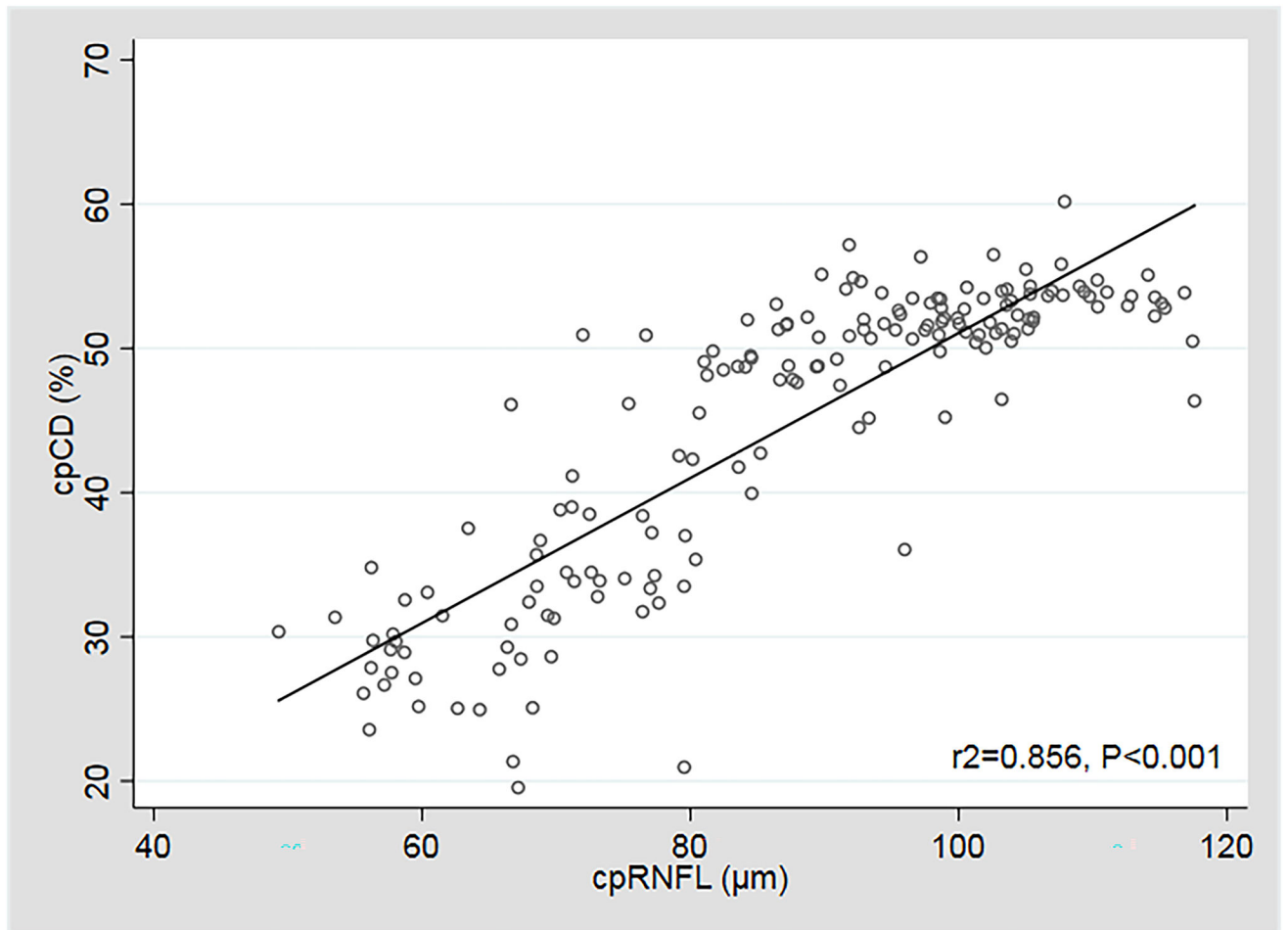
Figure 1-
Scatterplot Demonstrating a Positive Correlation of Circumpapillary (cpCD) and
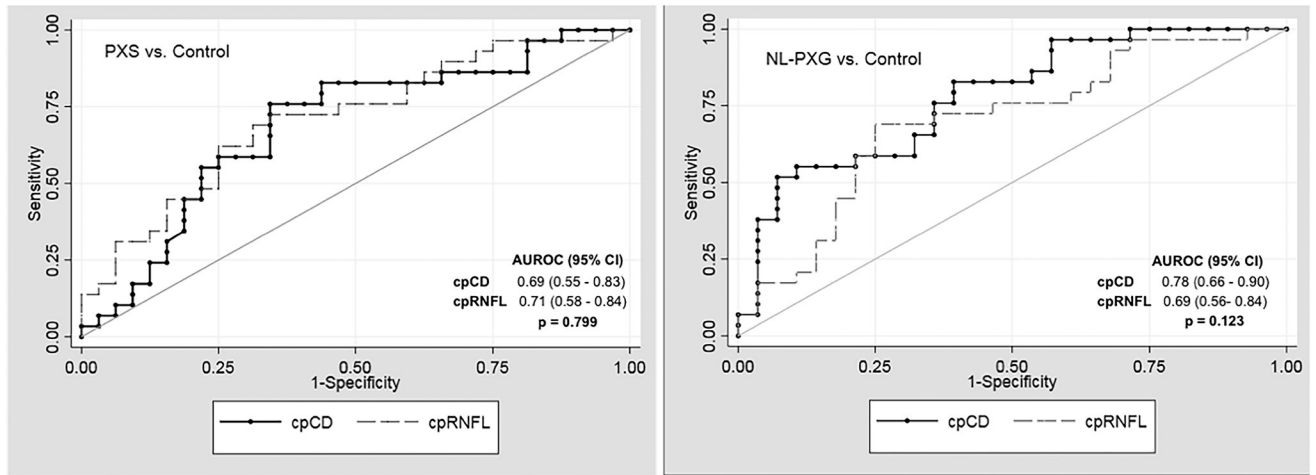Circumpapillary Retinal Nerve Fiber Layer Thickness (cpRNFL) in the Study Subjects.

Figure 2.
Area Under the Receiver Operating Characteristic (AUROC) Curves of Circumpapillary Capillary Density (cpCD), and Circumpapillary Retinal Nerve Fiber Layer (cpRNFL) for Discriminating Between Pseudoexfoliation Syndrome (PXS) and Healthy Controls (Right) and Non-Glaucomatous Fellow Eyes of Pseudoexfoliation Glaucoma Patients (NL-PXG).

Table 1-

Demographics and Ocular Characteristics of Study Population

Characteristic	Control	PXS	NL-PXG	PXG	P-value
Number of eyes	57	37	27	82	
Age (yrs), mean± SD	58.4 ±11.2	71.9 ±7.3	67.3 ±7.4	67.7 ±8.1	**<0.001**
Gender (F/M)	38/19	7/30	7/24	12/70	**<0.001**
C/D Ratio, mean± SD	0.4 ±0.2	0.3 ±0.1	0.4 ±0.2	0.8 ±0.2	**<0.001**
IOP (mmHg), mean± SD	14.7 ±2.2	15.8 ±3.1	15.9 ±3.6	23.4 ±11.4	**<0.001**
Axial Length (mm), mean± SD	23.5 ±0.5	23.5 ±0.6	23.1 ±0.9	23.2 ±0.8	0.940
MD (dB), mean± SD	−1.4 ±0.8	−1.3 ±1.2	−2.1 ± 3.9	−17 ±10.4	**<0.001**
PSD (dB), mean± SD	2.6 ±1.6	2.8 ±2.9	2.6 ±3.5	7.1 ±3.3	**<0.001**
cpRNFL (μm), mean± SD	103.3 ±8.6	96.8 ±8.8	96.3 ±11.1	74.2 ±14.3	**<0.001** **(0.001)** [*]
wiCD (%), mean± SD	49.9 ±2.1	48.4 ±2.2	47.4 ±3.7	36.2 ±7.3	**<0.001** **(0.001)** [*]
cpCD (%), mean± SD	52.5 ±2.3	51.5 ±2.3	50.1 ±3.9	36.8 ±9.3	**<0.001** **(0.001)** [*]

PXS= Pseudoexfoliation syndrome; PXG= pseudoexfoliation glaucoma; NL-PXG= Non-glaucomatous fellow eyes of PXG; SD= standard deviation; F= female, M= male; C/D= Cup to Disc; IOP= intraocular pressure; MD= mean deviation; dB= decibels; PSD= pattern standard deviation; cpRNFL= circumpapillary retinal nerve fiber layer; wiCD= whole image capillary density; cpCD= circumpapillary capillary density.

[*] Adjusted for age gender, and SSI

Boldface specifies statistically significant difference.

Table 2.

Comparison of circumpapillary Retinal Nerve Fiber Layer (cpRNFL) Thickness and Vessel Density among 3 groups: Pseudoexfoliation synderome (PXS), Fellow Eye of Pseudoexfoliation Glaucoma (NL-PXG) and Control.

	Control A.	PXS B.	NL-PXG C.	P-value (adjusted)*	P-value A. vs. B. (adjusted)	P- value A. vs. C. (adjusted)	P-value B. vs. C. (adjusted)
cpRNFL Thickness (µm), mean± SD							
Global	103.3 ±8.6	96.8 ±8.8	96.3 ±11.1	0.029 (0.437)	0.017 (0.815)	0.019 (0.614)	0.839 (0.214)
Hemi-Superior	106.3 ±8.7	100.3 ±9.9	98.8 ±12.5	**0.039 (0.287)**	**0.038 (0.519)**	**0.019 (0.757)**	0.602 (0.115)
Hemi-Inferior	100.3 ±9.6	93.3 ±9.2	93.8 ±10.8	**0.041 (0.688)**	**0.016 (0.812)**	**0.035 (0.506)**	0.844 (0.513)
Temporal-upper	84.3 ±8.3	77.1 ±10.4	75.7 ±12.7	**0.004 (0.209)**	**0.005 (0.503)**	**0.005 (0.088)**	0.649 (0.300)
Superotemporal	139 ±14.2	132.1 ±16.3	124.6 ±19.7	**0.013 (0.050)**	0.101 (0.712)	**0.004 (0.164)**	0.099 **(0.020)**
Superonasal	114 ±15.2	108.8 ±16.2	111.7 ±16.4	0.572 (0.754)	0.298 (0.491)	0.633 (0.457)	0.512 (0.921)
Nasal-upper	88 ±11.4	83.2 ±11.6	83.1 ±13.9	0.323 (0.360)	0.174 (0.163)	0.196 (0.464)	0.981 (0.357)
Nasal-Lower	75.3 ±9.6	72.1 ±10.6	75.4 ±10.9	0.207 (0.304)	0.264 (0.363)	0.969 (0.131)	0.263 (0.544)
Inferonasal	113.5 ±16.4	106.6 ±18.4	112.1 ±19.6	0.392 (0.769)	0.209 (0.734)	0.795 (0.944)	0.280 (0.471)
Inferotemporal	140.9 ±15.5	128.9 ±14.2	120.8 ±15.6	**<0.001 (0.002)**	**0.007 (0.353)**	**<0.001 (0.002)**	**0.035 (0.010)**
Temporal-Lower	71.5 ±8.8	65.7 ±10.7	66.9 ±13.1	0.068 (0.969)	**0.028 (0.885)**	0.134 (0.952)	0.707 (0.803)
OCTA vessel density (%), mean± SD							
wi CD	49.9 ±2.1	48.4 ±2.2	47.4 ±3.7	**0.001 (0.050)**	**0.003 (0.397)**	**0.001 (0.085)**	0.175 **(0.016)**
cpCD	52.5 ±2.3	51.5 ±2.3	50.1 ±3.9	**0.008 (0.045)**	0.073 (0.425)	**0.003 (0.072)**	0.062 **(0.014)**
Hemi-superior cpCD	52.8 ±2.7	51.9 ±3.0	51.0 ±4.3	0.120 (0.238)	0.204 (0.284)	**0.046 (0.459)**	0.280 (0.098)
Hemi-Inferior cpCD	52.2 ±2.3	51.1 ±2.4	49.1 ±3.9	**<0.001 (0.008)**	0.051 (0.741)	**<0.001 (0.008)**	**0.017 (0.004)**
Nasal-Superior cpCD	50.5 ±3.2	49.1 ±4.3	48.6 ±5	0.121 (0.578)	0.118 (0.462)	0.069 (0.719)	0.610 (0.309)
Nasal- Inferior cpCD	48.7 ±3.6	46.9 ±4.3	45.9 ±5.5	**0.019 (0.389)**	0.053 (0.398)	**0.017 (0.408)**	0.437 (0.172)
Inferonasal cpCD	50.9 ±3.8	49.6 ±4.8	47.7 ±5.4	**0.019 (0.030)**	0.211 (0.392)	**0.006 (0.009)**	0.142 (0.156)
Inferotemporal cpCD	57.4 ±4.6	57.4 ±3.8	55.2 ±5.5	**0.006 (0.087)**	**0.007 (0.257)**	**<0.001 (0.312)**	0.035 **(0.028)**
Temporal-Inferior cpCD	53.1 ±4.8	52.3 ±3.9	49.0 ±5	**0.002 (0.004)**	0.422 (0.968)	**0.001 (0.004)**	**0.007 (0.003)**
Temporal-Superior cpCD	56 ±3	55.3 ±3.5	54 ±5.5	0.248 (0.190)	0.382 (0.647)	0.075 (0.071)	0.381 (0.215)

	Control A.	PXS B.	NL-PXG C.	P-value (adjusted)*	P-value A. vs. B. (adjusted)	P- value A. vs. C. (adjusted)	P-value B. vs. C. (adjusted)
Superotemporal cpCD	55.4 ±3.9	54 ±6.4	53.6 ±5.6	0.797 (0.257)	0.276 (0.101)	0.135 (0.717)	0.275 (0.322)
Superonasal cpCD	50 ±4.4	50.2 ±5.5	48.7 ±4.9	0.380 (0.330)	0.842 (0.277)	0.263 (0.773)	0.203 (0.149)

SD= standard deviation; CD=capillary density; cpCD=circumpapillary capillary density; wiCD= whole image capillary density.

*
adjusted for age, gender, and SSI

Boldface specifies statistically significant difference.