Evaluating Peripapillary Vessel Density And Retinal Nerve Fiber Layer Thickness In Pseudoexfoliation Syndrome: A Comparative Study

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ABSTRACT

Purpose: To evaluate the changes in the peripapillary vessel density and retinal nerve fiber layer thickness changes in pseudoexfoliation syndrome compared to healthy controls.

Methods: The changes were studied in thirty eyes of thirty patients with pseudoexfoliation syndrome using optical coherence tomography angiography. Peripapillary vessel densities and peripapillary nerve fiber layer thicknesses were used to compare the optic nerve head characteristics in eyes with PSX and twenty-five healthy control eyes.

Results: Average, superior, and inferior RNFL thicknesses were similar in both groups (p:0.055, p:0.052, p:0.116 respectively). Eyes with PSX had lower VD values compared to healthy control groups in peripapillary, superior, and inferior segments. (p:0.011, p:0.013, p:0.017 respectively). There were significant positive correlations between RNFL thickness and peripapillary vessel density in their corresponding sectors except for inferotemporal and temporal superior sectors. ($p<0.05$ except inferotemporal and temporal-superior sectors)

Conclusion: In this study, peripapillary vessel density was found lower in eyes with pseudoexfoliation syndrome compared to age and systemic co-morbidity matched control group. These findings suggest that reduced peripapillary vessel density which may lead to ischemia might cause vulnerability to glaucomatous damage at the optic nerve head. However, further research needs to be done to establish whether the reduction of vessel density is associated with the progression to the pseudoexfoliation glaucoma and increased vulnerability to the glaucomatous damage.

Keywords: Optic coherence tomography angiography, psudoexfoliation syndrome, peripapillary vessel density

INTRODUCTION

Pseudoexfoliation syndrome (PSX) is a systemic disorder characterized by the abnormal production and accumulation of extracellular fibrillar material, which affects multiple organs and tissues throughout the body.[1-5] This condition is primarily associated with aging, as its incidence significantly increases with advancing age.[2-4] Moreover, the prevalence of PSX varies greatly across different ethnic groups and geographical regions, reflecting genetic and environmental influences on its development. [2-4]

PSX is driven by the excessive synthesis of elastic microfibrils and their aberrant cross-linking, leading to the deposition of this pathological material in various tissues. [5,6] In the eye, the primary sites involved in the production of these microfibrillar aggregates include the iris, ciliary epithelium, corneal endothelium, lens epithelium, trabecular meshwork epithelium, and vascular endothelial cells. [6] These tissues contribute to the accumulation of PSX material, which is predominantly deposited in the lens zonules, ciliary body, lens capsule, and trabecular meshwork. [6,7]

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The ocular manifestations of PSX are particularly significant, as they can lead to a range of complications, including increased intraocular pressure, glaucoma, and difficulties during cataract surgery. The deposition of PSX material compromises the structural integrity of the lens zonules, increasing the risk of lens dislocation, while its accumulation in the trabecular meshwork impairs aqueous humor outflow, leading to secondary open-angle glaucoma. [7-9]. Consequently, early detection and monitoring of PSX are critical for preventing vision loss and managing associated complications.

PSX has been increasingly linked to systemic diseases, particularly cardiovascular conditions.[10,11] It is associated with a higher risk of ischemia, increased vascular resistance, reduced blood flow, arterial endothelial dysfunction, elevated plasma homocysteine levels, and hypertension. [11,12] These connections emphasize the systemic implications of PSX, especially regarding cardiovascular health. [10,12]

Optical coherence tomography angiography (OCT-A) is a novel non-invasive imaging technique increasingly utilized for detailed visualization of the retina and choroid. [13] This technology also enables the assessment of vessel densities and blood flow in the optic nerve head (ONH). [14,15] Recent studies have shown that changes in ONH vessel density (VD) and blood flow are associated with glaucomatous damage. [14,15] Furthermore, alterations in the vasculature of the optic nerve head have been found to correlate with visual field defects and topographic changes in the ONH.[14]

In light of the vascular changes observed in PSX, our study aims to investigate the optic nerve head vascular alterations in PSX cases without glaucoma. This research seeks to enhance our understanding of the early vascular involvement in PSX and its potential implications for disease progression.

MATERIALS AND METHODS

This cross-sectional study was conducted from January 2019 to May 2019 and approved by the local institutional review board. The work was executed following the Code of Ethics of the World Medical Association (Declaration of Helsinki). The data of the patients who underwent OCT-A examination during the routine examination were recorded retrospectively. Thirty-two patients with PSX and 25 healthy control eyes were included in the study.

During the detailed ophthalmologic examination, the visual acuity, intraocular pressure, fundus findings, anterior segment examination results, and axial lengths were recorded for all patients. Additionally, demographic data were collected. All patients also underwent visual field testing, and those with visual field defects suggestive of glaucoma were excluded from the study. Other exclusion criteria included refractive errors greater than 3 diopters, the presence of any retinal or optic nerve disease, and a history of ocular surgery, except for uncomplicated cataract surgery.

OCTA was performed in all participants by a single experienced technician. 4.5 x 4.5 mm optic disc scans were obtained using the AngioVue SD-OCT system RTVue-XR Avanti. Scans that have motion artifacts and signal strength lesser than 6/10 were excluded from the study. All vessel densities (VD) and retinal nerve layer fiber (RNFL) thicknesses were calculated with integrated AngioVue software. **(Figure 1)**

SPSS 26.0 software (SPSS Inc, Chicago, IL) was used. The distribution pattern of variables was evaluated with the help of visual and analytical methods. The Independent t-test was used for variables with normal distribution, while Mann Whitney u test was used for variables with non-normal distribution. The Chi-square test was used for categorical variables. The Spearman Rank Correlation Test was used for the investigation of the relationship between variables.

RESULTS

A total of 30 cases with PSX and 25 healthy control subjects were enrolled in this study. The demographic data and clinical characteristics of the patients are shown in **Table 1**. There was no significant difference in baseline IOP, age, gender, lens status, axial length, average RNFL thickness, or systemic diseases between the 2 groups.

Table 2 shows the average RNFL thickness and peripapillary vessel density (VD) parameters of the 2 groups. There was no significant difference in RNFL thicknesses between the same sectors of healthy and PSX eyes, except for the RNFL thickness in the inferotemporal sector **(Table 2).** However, the VD values of all the sectors significantly lower in the PSX group compared with the control group except nasal inferior, inferonasal, temporal inferior, temporal superior, superonasal sectors **(Table 2).**

There were significant positive correlations between RNFL thickness and peripapillary VD in their corresponding sectors except for inferotemporal and temporal superior sectors **(Table 3).**

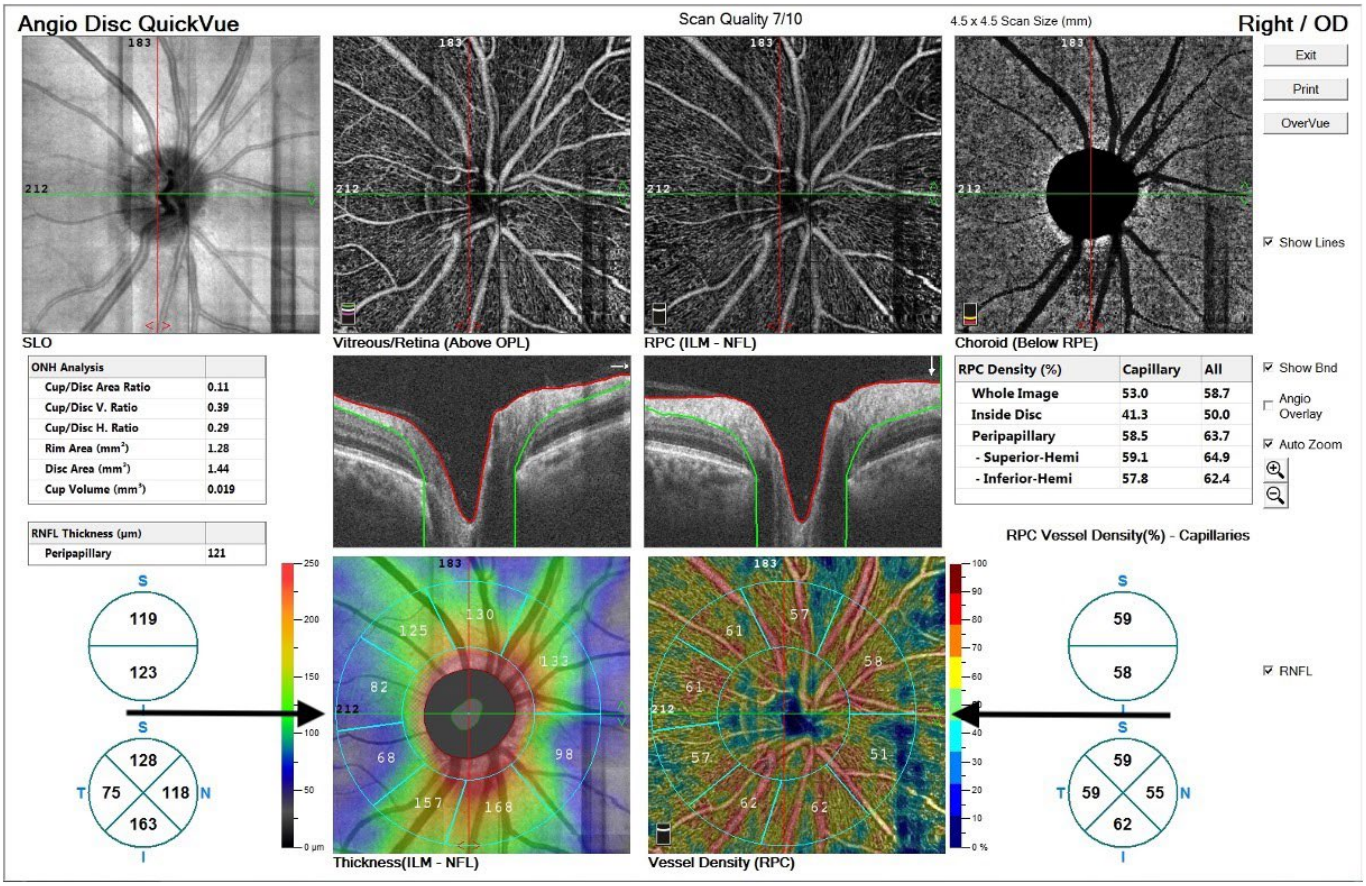

Figure 1: *Vessel densities (VD) and retinal nerve layer fiber (RNFL) thicknesses calculated with integrated AngioVue software are shown with the arrows.*

Table 1: *The demographic data of study participants*

	Pseudoexfoliation Group	**Control Group**	**p**
Age,years	65.44±8.9	62.56±4.82	0.125
Male,n (%)	18 (60%)	14 (56%)	
Female, n(%)	12 (40%)	11 (44%)	0.765
Pseudophakic, n (%)	12 (%40)	10 (%40)	1
Diaebetes Mellitus, n(%)	5 (16.7%)	5 (20%)	0,750
Systemic Hypertension (HT), n(%)	10 (33.3%)	6 (24%)	0.448
Axial Length (AL), mm	23.59±1.15	23.62±0.77	0.929
Hyperlipidemia	4 (13.3%)	4 (16%)	0.78
Baseline IOP, mmHg	15.31±1.96	14.88±2.1	0.427
Average RNFL Thickness, µm	105.34±17.74	113.04±10.46	0.063

Table 2: *The comparison of retinal nerve fiber layer thickness (RNFL) and vessel density (VD) values of PSX and control eyes according to sectors*

	Peripapillary Vessel Density (VD)			Peripapillary Retinal Nerve Fiber Layer (RNFL)		
Measurement Location, Sectors*	**Pseudoexfoliation Group**	**Control Group**	**p****	**Pseudoexfoliation Group**	**Control Group**	**p*****
Peripapillary	50.6±4.23	52.98±2.19	**0.011**	105.34±17.74	113.04±10.46	0.055
Superior	50.68±4.07	52.98±2.35	**0.013**	106.07±15.34	112.63±8.04	0.052
Inferior	49.64±6.77	52.97±2.50	**0.017**	104.93±21.15	112.24±12.22	0.116
Superotemporal	54.1±5.66	56.37±3.57	**0.001**	113.62±19.33	130.29±14.65	0.094
Nasalsuperior	47.17±8.10	51.66±2.84	**0.007**	101.47±35.84	112.44±11.27	0.122
Nasalinferior	46.407±7.89	49.30±3.96	0.084	92.07±33.61	93.20±14.06	0.079
Inferonasal	49.5±6.70	51.85±4.71	0.143	134.57±36.16	136.84±28.82	0.801
Inferotemporal	54.3±9.2	59.27±3.85	**0.015**	122.24±29.2	140.56±19.24	0.08
Temporalinferior	49.92±6.61	52.90±4.07	0.053	67.96±13.63	75.92±17.15	0.068
Temporalsuperior	53.79±4.17	55±3.34	0.300	76.82±20.93	78.81±8.73	0.689
Superonasal	49.57±5.51	49.85±3.44	0.821	123.96±21.53	129.38±20.21	0.388

*: Sectors were automatically set for the optic disc by the software of the Angiovue device.
**: p values for comparison between vessel densities of PSX and Control group
***: p values for comparison between RNFL thicknesses of PSX and Control group

Table 3: *The correlation analysis of vessel density (VD) and retinal nerve and fiber layer thickness (RNFL) values*

Vessel Density (VD)	Retinal Nerve Fiber Layer Thickness (RNFL)										
Measurement Location Sectors	Peripapillary	Superior	Inferior	Supertemporal	Nasal superior	Nasal inferior	Inferonasal	Inferotemporal	Temporal inferior	Temporal superior	Superonasal
Correlation Coefficient	**,693***	**,547***	**,507***	**,440***	**,500***	**,647***	**,579***	,176	**,597***	-,015	**,632***

*. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

PSX is the leading cause of secondary open-angle glaucoma. [1,7] While the exact reasons for the progression from PSX to pseudoexfoliative glaucoma (PSG) are not fully understood, PSG is generally considered to have a more severe and progressive course than primary open-angle glaucoma. [16] This increased severity is thought to result from factors such as fluctuations in intraocular pressure (IOP), consistently higher IOP levels, and asymmetry in IOP between the eyes. [16] In glaucoma cases, visual field loss typically becomes apparent only after 30-40% of retinal ganglion cells have been damaged. [17] Relying solely on visual field testing for diagnosis can thus lead to delayed detection and treatment.

To mitigate this delay, retinal nerve fiber layer (RNFL) thickness measurement has emerged as a valuable method for the early diagnosis and treatment of glaucoma. Additionally, optical coherence tomography angiography (OCT-A), a non-invasive technique, allows for visualization of the vascular network of the optic nerve head and assessment of its perfusion status. Recent studies have shown that optic nerve head vessel density (ONH VD) values are correlated with ganglion cell loss, glaucoma severity, RNFL thickness, and visual field mean deviation. Therefore, OCT-A can be an important tool not only for early disease detection but also for monitoring disease progression.

PSX is the most common cause of secondary open-angle glaucoma. [7] While the precise mechanisms that lead to the progression from PSX to PSG remain unclear, PSG is generally considered more aggressive and progressive than primary open-angle glaucoma. This increased severity is thought to be due to factors such as fluctuations in intraocular pressure (IOP), consistently higher IOP levels, and asymmetry in IOP between the eyes.[16] In cases of glaucoma, significant visual field loss often occurs only after 30-40% of retinal ganglion cells have already been damaged. [17] Therefore, relying solely on visual field testing for diagnosis can result in delayed detection and treatment of glaucoma. [17]

To address this challenge, retinal nerve fiber layer (RNFL) thickness measurement has become a widely used tool for the early diagnosis and management of glaucoma.[17,18] Additionally, optical coherence tomography angiography (OCT-A), as a non-invasive imaging technique, allows for the visualization of the optic nerve head (ONH) vascular network and the assessment of its perfusion status. [18,19] Recent studies have shown that ONH vessel density (VD) is closely linked to ganglion cell loss, glaucoma severity, RNFL thickness, and visual field mean deviation.[19] Thus, OCT-A has emerged as a valuable tool for the early detection of glaucoma as well as for monitoring disease progression over time.

In this study, OCT-A was used to evaluate the structural differences in optic disc head VD and RNFL thickness between PSX and healthy controls. No statistically significant difference was observed between the groups in terms of average, inferior, and superior RNFL thickness, while the average, inferior, and superior VD values were found to be reduced in the PSX group compared to the control eyes. A recent study examined the relationship between peripapillary VD and factors such as age, gender, diabetes (DM), and systemic hypertension (HTN). The study found that peripapillary VD was influenced only by HTN and gender.[20] To minimize potential confounding factors, the control group consisted of subjects matched for HTN, DM, axial length (AL), age, and gender.

RNFL loss, which can occur before any noticeable IOP elevation or optic nerve head (ONH) damage, is a critical indicator of early glaucomatous damage. [21] Thus, RNFL measurement is considered more effective for early glaucoma diagnosis than traditional methods like IOP measurement, fundus examination, and visual field testing. [21] Although some studies have reported a decrease in RNFL thickness in PSX cases compared to controls, there is no complete consensus. [22,23]

Sorkhabi et al. found a reduced mean RNFL in PSX cases compared to controls but noted no significant difference when RNFL was examined segmentally. [23] Aydin et al. similarly reported comparable RNFL thickness between PSX cases and controls, with the exception of the superior quadrant, which was thinner in the PSX group. [22] In our study, we also observed decreased RNFL thickness in the PSX group, with statistically significant differences found only in the inferotemporal segment.

PSX material is known to accumulate in various ocular vascular structures, potentially leading to ischemic diseases and impaired circulation.[24] Gilles et al. demonstrated an association between PSX and retinal vein occlusions.[25] Similarly, Naumann et al. found severe PSX deposition in iris veins, which could damage vessel walls and occlude lumens.[26] Doppler flowmetry in the same study also showed reduced blood flow in the iris vessels. Helbig et al. reported lower oxygen levels in the anterior chamber of eyes with PSX compared to controls.[27] Additionally, a recent study using a Heidelberg retinal flowmeter found decreased ONH and peripapillary retinal blood flow in PSX cases.[28]

In an earlier study, RNFL thickness and vessel diameters were compared between PSX and control cases, revealing no significant differences.[29] However, this study predated the availability of automated systems like OCT-A, making it difficult to detect subtle changes due to manual measurements. In a recent study by Simsek et al., both VD and RNFL values were lower in the fellow eyes of unilateral PSG cases compared to controls. [19,30] This suggests that glaucomatous damage might have already begun in the fellow eyes, with decreased VD possibly reflecting the impact of this damage.[30]

In contrast, our study found reduced VD in the PSX group compared to controls, while RNFL thicknesses were similar. Hayreh et al. hypothesized that reduced blood supply to the ONH could lead to glaucomatous damage, suggesting that vascular issues in PSX might contribute to the progression to PSG and more severe glaucomatous damage.[31]

The data here support the idea that VD differences in PSX and control cases with similar RNFL values may be linked to vascular changes caused by PSX, potentially leading to RNFL loss and PSG progression. Future research could explore whether vascular insufficiency primarily causes glaucomatous damage or if decreased ONH VD is secondary to tissue loss, reducing the demand for vascular supply.

A positive correlation was observed between RNFL thickness and VD, consistent with previous studies.[32] Given the relationship between VD and RNFL, recent publications suggest that VD could be used similarly to RNFL, particularly in situations where obtaining RNFL measurements is challenging.[18] Although the decrease in RNFL was not statistically significant in PSX cases, the reduction in VD was significant. This suggests that a decline in VD may indicate significant changes at an earlier stage than a decrease in RNFL, potentially making VD an important tool for early detection of glaucoma. However, further studies are needed to confirm this.

In summary, peripapillary VD was lower in eyes with PSX compared to the age- and disease-matched control group. These findings suggest that reduced peripapillary VD, potentially leading to ischemia, may increase vulnerability to glaucomatous damage at the optic nerve head. However, further research is needed to determine if the reduction in VD is associated with the progression to pseudoexfoliation glaucoma and increased susceptibility to glaucomatous damage.

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