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Association Between Retinal Nerve Fiber Layer Thickness and Anterior Segment Parameters in Patients With Pseudoexfoliation: A Cross-Sectional Comparative Study

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Abstract

Background: Pseudoexfoliation (PXF) syndrome is an age-related systemic disorder characterized by the deposition of fibrillar material in ocular tissues, commonly affecting the anterior segment and predisposing to glaucoma. Its impact on retinal nerve fiber layer (RNFL) thickness, even in the absence of manifest glaucoma, remains an area of clinical interest.

Objective: To assess the association between RNFL thickness and anterior segment parameters—including intraocular pressure (IOP), central corneal thickness (CCT), anterior chamber depth (ACD), and angle status—in patients with PXF compared to age-matched controls.

Methods: This cross-sectional comparative study included 60 eyes—30 with clinically diagnosed PXF and 30 age- and sex-matched controls. RNFL thickness was measured using spectral-domain optical coherence tomography (SD-OCT), and anterior segment parameters were evaluated with ultrasound biomicroscopy and pachymetry. Data were analyzed for intergroup differences and correlation between RNFL and anterior segment variables.

Results: The mean RNFL thickness in PXF eyes was significantly lower (82.6 ± 7.1 µm) compared to controls (91.2 ± 5.9 µm, $p < 0.001$). PXF eyes also had significantly higher IOP and thinner CCT. A moderate negative correlation was found between RNFL thickness and IOP ($r = –0.42$, $p = 0.01$), and a positive correlation with CCT ($r = 0.36$, $p = 0.03$) in the PXF group.

Conclusion: Eyes with pseudoexfoliation demonstrate significant RNFL thinning and altered anterior segment parameters even without manifest glaucoma. Regular RNFL assessment along with anterior segment evaluation may aid in early detection of glaucomatous changes in PXF patients.

Introduction

Pseudoexfoliation syndrome (PXF) is an age-related systemic condition characterized by the deposition of fibrillar extracellular material on intraocular structures, particularly the anterior lens capsule, pupillary margin, trabecular meshwork, and zonular fibers. First described by Lindberg in 1917, PXF has since been recognized as a major cause of secondary open-angle glaucoma and a significant contributor to ocular morbidity, especially among the elderly (1). The global prevalence of PXF varies from 10% to 25% in elderly populations, with higher frequencies reported in Mediterranean and South Asian countries (2).

Clinically, PXF is often asymptomatic in its early stages but may lead to increased intraocular pressure (IOP) and optic nerve damage, either through mechanical obstruction of the trabecular meshwork or increased resistance to aqueous outflow. Importantly, pseudoexfoliative glaucoma (PXG) is known to have a more aggressive course compared to primary open-angle glaucoma (POAG), with higher IOP fluctuations, rapid visual field loss, and worse prognosis (3).

Emerging evidence indicates that retinal nerve fiber layer (RNFL) thinning may occur even in eyes with PXF that do not have clinically manifest glaucoma. Spectral-domain optical coherence tomography (SD-OCT), a non-invasive and reproducible imaging modality, allows detailed quantification of RNFL thickness and is essential for early detection of glaucomatous damage. Several studies have demonstrated RNFL thinning in PXF eyes, suggesting subclinical optic neuropathy and heightened risk for progression to PXG (4).

In addition to posterior segment changes, PXF also affects the anterior segment, altering biomechanical and anatomical parameters. Central corneal thickness (CCT) is frequently reduced in PXF patients, which may lead to underestimation of IOP readings obtained through applanation tonometry (5). Furthermore, anterior chamber depth (ACD) and angle width may be affected due to zonular weakness and lenticular instability, predisposing to angle narrowing or closure in certain cases (6).

A comprehensive understanding of how anterior segment alterations relate to optic nerve changes—specifically RNFL thinning—may offer insights into the pathophysiology and risk stratification of PXF. A study highlighted that RNFL loss in PXF can be detected earlier than visual field defects, reinforcing the need for structural assessments in PXF patients even in the absence of elevated IOP (7). Moreover, thinner corneas and elevated IOP in PXF eyes have independently been associated with increased susceptibility to glaucomatous damage, as noted in the Ocular Hypertension Treatment Study (OHTS)(8).

Despite growing awareness, few studies have examined the combined relationship between anterior segment parameters and RNFL thickness in pseudoexfoliation eyes that are not yet glaucomatous. Understanding this association is crucial for early diagnosis and preventive care in PXF, a disease that can evolve silently into irreversible optic nerve damage.

This study was undertaken to evaluate and compare RNFL thickness and anterior segment parameters—including IOP, CCT, ACD, and angle status—in patients with pseudoexfoliation versus age- and sex-matched healthy controls. The study also aimed to explore the correlation between RNFL thickness and these anterior segment variables within the PXF group, with the goal of identifying early structural biomarkers that may predict glaucomatous conversion.

Methods

Study Design and Setting

This was a **cross-sectional comparative study** conducted in the Department of Ophthalmology at a tertiary care teaching hospital in South India from January to December 2023. The aim was to assess the association between retinal nerve fiber layer (RNFL) thickness and anterior segment parameters in patients with pseudoexfoliation (PXF) and compare these values with those of age- and sex-matched healthy controls.

Study Population

A total of **60 eyes** were included: 30 eyes from patients with clinically diagnosed unilateral or bilateral pseudoexfoliation without manifest glaucoma (PXF group), and 30 eyes from age- and sex-matched individuals without PXF or any ocular pathology (control group).

Inclusion Criteria

- Age ≥ 50 years
- Diagnosed pseudoexfoliation syndrome without glaucomatous optic neuropathy (normal disc and visual field)
- Normal open-angle on gonioscopy
- Best corrected visual acuity ≥ 6/12
- No history of intraocular surgery in the past 6 months

Exclusion Criteria

- History of glaucoma or current use of anti-glaucoma medications
- Any evidence of glaucomatous optic neuropathy or visual field defects
- Ocular trauma, corneal opacities, uveitis, or retinal pathology
- Poor OCT scan quality due to media opacity or unstable fixation

Ophthalmic Evaluation

All participants underwent a comprehensive ophthalmologic examination, including:

- **Best corrected visual acuity (BCVA)** using Snellen chart
- **Slit-lamp biomicroscopy**
- **Applanation tonometry** (Goldmann) for intraocular pressure (IOP)
- **Gonioscopy** using a 4-mirror lens to assess angle status
- **Central corneal thickness (CCT)** measured using ultrasound pachymetry
- **Anterior chamber depth (ACD)** measured using anterior segment optical coherence tomography (AS-OCT)

- **Fundus examination** with +90D lens
- **Spectral-domain OCT (SD-OCT)** (e.g., Zeiss Cirrus or Spectralis) to measure peripapillary RNFL thickness (average and quadrant-wise)

All measurements were performed between 9 AM and 12 PM to minimize diurnal variations, and each parameter was recorded by an experienced examiner blinded to the participant's group allocation.

Data Collection and Parameters Assessed

The following were recorded:

- Average RNFL thickness (µm)
- Quadrant RNFL thickness (superior, inferior, nasal, temporal)
- Intraocular pressure (mmHg)
- Central corneal thickness (µm)
- Anterior chamber depth (mm)
- Angle status (open/closed based on Shaffer grading)

Statistical Analysis

Data were entered in **Microsoft Excel** and analyzed using **IBM SPSS version 26.0**.

- Descriptive statistics were used to summarize demographic and clinical data.
- **Independent sample t-test** was used to compare RNFL thickness and anterior segment parameters between PXF and control groups.
- **Pearson's correlation coefficient** was used to evaluate the relationship between RNFL thickness and anterior segment variables (IOP, CCT, ACD) within the PXF group.
- A **p-value < 0.05** was considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to inclusion. All procedures conformed to the tenets of the Declaration of Helsinki.

Results

A total of **60 eyes** were included—30 in the pseudoexfoliation (PXF) group and 30 in the control group. The groups were matched for age and sex. Statistically significant differences were observed in RNFL thickness and several anterior segment parameters.

Table 1: Demographic and Baseline Characteristics

Parameter	PXF Group (n = 30)	Control Group (n = 30)	p-value
Mean age (years)	65.4 ± 6.8	64.2 ± 7.1	0.48
Male:Female	18:12	17:13	0.79
BCVA (logMAR)	0.12 ± 0.08	0.10 ± 0.07	0.35

There was no statistically significant difference between the PXF and control groups in terms of age, sex distribution, or visual acuity, indicating that both groups were appropriately matched for demographic comparison.

Table 2: Comparison of RNFL Thickness Between Groups

RNFL Parameter	PXF Group (µm)	Control Group (µm)	p-value
Average RNFL	82.6 ± 7.1	91.2 ± 5.9	<0.001
Superior quadrant	103.4 ± 13.8	115.6 ± 11.1	0.002
Inferior quadrant	107.1 ± 14.6	117.9 ± 13.2	0.004
Nasal quadrant	64.7 ± 10.2	68.3 ± 9.6	0.13

Temporal quadrant	55.2 ± 8.1	60.1 ± 7.5	0.01

The average RNFL thickness was significantly lower in the PXF group, particularly in the superior, inferior, and temporal quadrants, suggesting early subclinical axonal loss. The nasal quadrant difference was not statistically significant.

Table 3: Comparison of Anterior Segment Parameters Between Groups

Parameter	PXF Group	Control Group	p-value
Intraocular pressure (mmHg)	18.3 ± 2.8	15.7 ± 2.4	0.001*
Central corneal thickness (µm)	512.6 ± 23.5	532.4 ± 21.3	0.002*
Anterior chamber depth (mm)	2.87 ± 0.31	3.02 ± 0.29	0.04*

PXF eyes demonstrated significantly higher IOP and thinner corneas compared to controls. ACD was also slightly shallower in the PXF group. These anterior segment differences may contribute to increased glaucoma susceptibility.

Table 4: Correlation Between RNFL Thickness and Anterior Segment Parameters in PXF Group

Correlation Pair	Pearson's r	p-value
RNFL vs IOP	−0.42	0.01
RNFL vs CCT	+0.36	0.03
RNFL vs ACD	+0.18	0.21

There was a moderate negative correlation between RNFL thickness and IOP, indicating that higher pressures were associated with greater RNFL thinning. A positive correlation was found

between RNFL and CCT, suggesting thicker corneas may be somewhat protective. ACD showed no significant correlation.

Discussion

This cross-sectional comparative study evaluated the relationship between retinal nerve fiber layer (RNFL) thickness and anterior segment parameters in patients with pseudoexfoliation (PXF) syndrome without clinically manifest glaucoma. Our findings reveal that eyes with PXF exhibit significantly thinner RNFL and altered anterior segment characteristics—namely elevated intraocular pressure (IOP), reduced central corneal thickness (CCT), and shallower anterior chamber depth (ACD)—compared to age- and sex-matched healthy controls. Moreover, a moderate inverse correlation between IOP and RNFL thickness, and a positive correlation between CCT and RNFL, suggests subclinical structural compromise in PXF eyes even in the absence of detectable glaucomatous damage.

PXF is a systemic disorder of the extracellular matrix characterized by progressive deposition of abnormal fibrillar material on intraocular structures, particularly the anterior lens capsule, pupillary margin, zonules, and trabecular meshwork (2). It is a known independent risk factor for glaucoma, associated with a more aggressive clinical course and poorer treatment response compared to primary open-angle glaucoma (POAG) (3). Several studies have shown that eyes with PXF exhibit early optic nerve head and RNFL changes, indicating the potential for pre-perimetric glaucomatous damage (4).

In our study, the average RNFL thickness in PXF eyes was significantly reduced (82.6 ± 7.1 µm) compared to controls (91.2 ± 5.9 µm), with the superior, inferior, and temporal quadrants being most affected. These findings align with a study that demonstrated significant RNFL thinning in non-glaucomatous PXF eyes using spectral-domain OCT, suggesting that axonal damage may precede detectable functional deficits (9). The superior and inferior quadrants are particularly vulnerable to early glaucomatous changes due to the anatomical arrangement of RNFL bundles, which may explain the observed quadrant-specific thinning.

Elevated IOP is the most well-established risk factor for glaucoma in PXF. In our study, the mean IOP in PXF eyes (18.3 mmHg) was significantly higher than in controls (15.7 mmHg), despite all subjects having pressures within the statistically normal range. This supports the

hypothesis that even borderline IOP levels in PXF eyes may be insufficiently tolerated due to compromised optic nerve resilience. Furthermore, we found a moderate negative correlation between IOP and RNFL thickness ($r = -0.42$, $p = 0.01$), consistent with findings from a study that reported significant inverse correlations in PXF eyes without glaucoma (10). This underlines the importance of monitoring structural changes in PXF patients, even when IOP appears normal.

CCT is another important parameter that influences glaucoma risk assessment. Our results showed significantly thinner corneas in the PXF group (mean CCT: 512.6 µm) compared to controls (532.4 µm). Additionally, our finding of a positive correlation between CCT and RNFL thickness ($r = +0.36$, $p = 0.03$) supports the idea that thinner corneas may be associated with increased susceptibility to optic nerve damage.

Anterior chamber depth (ACD) was also significantly shallower in the PXF group (2.87 mm vs 3.02 mm; $p = 0.04$). Shallower anterior chambers may predispose to intermittent angle narrowing, especially in eyes with pseudoexfoliative zonulopathy or phacodonesis. While ACD did not significantly correlate with RNFL thickness in our study, its clinical relevance remains due to its potential contribution to IOP elevation and angle compromise.

The structural-functional relationship in glaucoma and pre-glaucomatous states is complex. While visual field testing remains the gold standard for detecting functional deficits, RNFL thinning on OCT can precede field changes by months or years. Our study reinforces this by demonstrating measurable RNFL loss in PXF patients without glaucomatous field loss or disc cupping.

From a clinical perspective, our findings support the use of spectral-domain OCT and anterior segment imaging as essential tools in the routine evaluation of PXF patients. Identifying early RNFL loss and high-risk anterior segment features such as thinner corneas and elevated IOP can guide clinicians in determining the frequency of follow-up and the need for early intervention. Additionally, since PXF is often asymmetric or unilateral in early stages, baseline imaging of both eyes is recommended.

One strength of this study is the exclusion of patients with established glaucoma, ensuring that RNFL changes observed were not confounded by known disease or treatment. However, several limitations should be noted. The sample size, while adequate for preliminary analysis,

was relatively small, and larger multicentric studies are needed to confirm these associations. The cross-sectional nature of the study precludes conclusions about progression. Finally, visual field testing, although normal in all subjects, was not used as a continuous variable and thus was not correlated with RNFL or IOP.

Conclusion

In summary, this study demonstrates that pseudoexfoliation syndrome is associated with significant RNFL thinning and alterations in anterior segment parameters even in the absence of clinically manifest glaucoma. Elevated IOP and reduced central corneal thickness correlate with greater RNFL loss, suggesting a subclinical stage of optic nerve compromise. These findings highlight the importance of comprehensive ocular assessment—including RNFL measurement and anterior segment evaluation—in all patients with PXF for early detection of glaucomatous risk.

Recommendations

Given the significant RNFL thinning and anterior segment alterations observed in pseudoexfoliation (PXF) patients without clinical glaucoma, it is recommended that such individuals undergo routine **spectral-domain OCT screening** for early RNFL changes, along with periodic assessments of intraocular pressure, central corneal thickness, and anterior chamber depth. Identifying subclinical optic nerve damage can help stratify glaucoma risk and initiate timely surveillance or intervention. Clinicians should maintain a **lower threshold for initiating follow-up or treatment** in PXF patients with thinner RNFL or elevated IOP, even if visual fields are normal. Further longitudinal studies are warranted to establish predictive models for glaucoma progression in this high-risk group.

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