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# PSEUDOEXFOLIATION: LOOK WHAT ELSE WE FOUND:- A TERTIARY CARE EXPERIENCE FROM KASHMIR

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## ABSTRACT

**Purpose:** To evaluate the systemic associations of pseudoexfoliation syndrome (PXS) and pseudoexfoliation glaucoma (PXG), emphasizing vascular and neurological manifestations, and to assess the prevalence of peripheral arterial disease (PAD) using objective diagnostic methods.**Methods:** This prospective, hospital-based cross-sectional study included 200 participants: 50 with PXS, 50 with PXG, and 100 age- and sex-matched controls. All subjects underwent comprehensive ophthalmic evaluation, including optical coherence tomography (OCT) and visual field analysis. Systemic assessment included history, clinical examination, serum homocysteine and lipid profile testing, pure tone audiometry for sensorineural hearing loss (SNHL), ankle-brachial index (ABI), and Doppler ultrasound of the anterior tibial and dorsalis pedis arteries to detect PAD.**Results:** Systemic comorbidities were significantly more prevalent in PXS and PXG groups than controls, including ischemic heart disease ($p < 0.01$), aortic aneurysm ($p < 0.001$), cerebrovascular disease ($p < 0.01$), PAD ($p < 0.001$), and SNHL ($p < 0.001$). PAD, confirmed by abnormal ABI and Doppler changes, emerged as a notable new association. There was no statistically significant difference in systemic involvement between PXS and PXG groups.**Conclusion:**Pseudoexfoliation is a systemic fibroelastotic disorder with significant vascular and neurological implications. PAD represents a newly identified and highly significant association, reinforcing the systemic nature of pseudoexfoliation. Early detection may guide broader systemic risk assessment and multidisciplinary management.

**Keywords:** Pseudoexfoliation syndrome, Pseudoexfoliation glaucoma, Peripheral artery disease, systemic vascular disease, Sensorineural Hearing Loss

## INTRODUCTION

**Pseudoexfoliation syndrome (PXS)** is an age-associated systemic disorder involving the abnormal metabolism of extracellular matrix components. It is characterized by the excessive formation and accumulation of pseudoexfoliative material (PXM) in both ocular tissues and various internal organs. [1] Although it is primarily detected through eye examinations, increasing evidence points to its systemic nature, as PXM has been identified in connective tissues surrounding blood vessels in organs such as the lungs, liver, kidneys, gallbladder, and the meninges of the brain. These findings are supported by ultrastructural studies [2,3] and immunohistochemical analysis [4].

Several systemic conditions, including cardiovascular and neurodegenerative diseases—such as angina, aortic aneurysms, and dementia—have been linked to PXS. However, the strength and clinical significance of these associations remain subjects of ongoing research and debate [5-8].

In ophthalmology, PXS is typically diagnosed based on slit-lamp observations of white, dandruff-like fibrillar deposits on the anterior lens capsule and the pupillary margin of the iris. These deposits often display a distinct double-ring pattern, separated by a clear zone [1,9]. Additional accumulations may be found on the zonular fibers, trabecular meshwork, and ciliary body. The presence of PXM in these areas can obstruct aqueous humor drainage, leading to elevated intraocular pressure (IOP). This condition may progress to pseudoexfoliation glaucoma (PXG), a severe and rapidly progressing form of secondary open-angle glaucoma [10,11]. Studies have shown that up to 44% of individuals with PXS eventually develop PXG, making it the most prevalent identifiable cause of secondary open-angle glaucoma [12].

The impact of pseudoexfoliation syndrome (PXS) extends beyond the development of glaucoma. Common ocular manifestations such as zonular weakness, inadequate pupillary dilation, and partial dislocation of the lens often complicate intraocular procedures like cataract surgery [9]. These surgical challenges are supported by histopathological findings, which demonstrate the deposition of pseudoexfoliative material (PXM) on structures including the iris pigment epithelium, anterior lens capsule, and ciliary body. Notably, PXM has also been found in tissues not directly exposed to the aqueous humor—such as extraocular muscles and retrobulbar tissues—highlighting the systemic nature of the disorder [9].

The origins of PXS are multifactorial, involving a combination of genetic predisposition and environmental influences. Genome-wide association studies (GWAS) have identified strong associations between PXS (and its glaucomatous form, PXG) and specific single nucleotide polymorphisms (SNPs) in the **LOXL1** gene, which encodes an enzyme crucial for elastin and collagen cross-linking within the extracellular matrix [13]. Additional genes linked to the condition include **clusterin (CLU)**, **fibulin-5**, **matrix metalloproteinases (MMPs)**, and genes involved in **homocysteine metabolism [14-16].**

Environmental contributors such as exposure to ultraviolet light, consumption of caffeine and alcohol, and oxidative stress have also been implicated in increasing the risk of disease onset and progression [17-21]. On a molecular level, PXS is considered a form of fibrillopathy, marked by the dysregulated production or degradation of extracellular matrix components such as **fibrillin-1**, **fibulin-2**, **tropoelastin**, **vitronectin**, and **clusterin [22]**. Ultrastructural analysis using transmission electron microscopy has revealed that PXM is composed of microfibrils enveloped by electron-dense material, suggesting the involvement of elastin-related and basement membrane proteins in its formation [23].Furthermore, elevated levels of **transforming growth factor-beta 1 (TGF-β1)** and decreased expression of **clusterin** have been linked to increased deposition of PXM and enhanced cellular stress responses, contributing to the pathogenesis of the disease [24].

The prevalence of pseudoexfoliation syndrome (PXS) shows considerable variation across different ethnic groups and regions. It has been reported to be virtually absent among Greenland Inuits, while studies in elderly populations in Iceland [13,25] have documented prevalence rates exceeding 40%. Age is a major risk factor, with incidence rising sharply in older individuals. Although some research suggests that PXS may be more common in males, findings on sex distribution remain inconsistent, with other studies showing no significant gender differences [17,18,25].

The condition often presents asymmetrically between the eyes, both in terms of clinical signs and risk of developing glaucoma. This asymmetry supports the idea that in addition to systemic influences, localized ocular factors may play a role in disease development [26].
Because PXS has been linked to systemic conditions such as cardiovascular disease, cerebrovascular events, and hearing impairment, it is increasingly viewed not just as an isolated eye disorder but as a potential indicator of more widespread connective tissue and vascular pathology [5,6].

## AIMS AND OBJECTIVES

1. To assess the frequency of systemic manifestations in patients diagnosed with PXS.
2. To evaluate associations with vascular comorbidities: hypertension, ischemic heart disease, cerebrovascular disease, and aortic aneurysms.
3. To determine the prevalence of sensorineural hearing loss in PXS patients.
4. To compare these findings with age-matched controls and literature data from similar studies.

## MATERIALS AND METHODS

This prospective, observational cross-sectional study was carried out over the course of one year from January 2024 to January 2025 at a tertiary-level eye care institution. A total of 200 individuals participated in the study and were categorized into three distinct groups:
Group A included 50 patients diagnosed with pseudoexfoliation syndrome (PXS),
Group B comprised 50 patients with pseudoexfoliation glaucoma (PXG), and
Group C consisted of 100 age- and sex-matched control subjects who exhibited no clinical signs of pseudoexfoliation.

### Inclusion Criteria:

- Age ≥50 years
- Presence of pseudoexfoliative material on slit-lamp examination (pupillary margin, anterior lens capsule, or characteristic double-ring sign)
- PXG defined as PXS with glaucomatous optic neuropathy, raised intraocular pressure (IOP), and/or visual field defects

### Exclusion Criteria:

- History of ocular trauma or intraocular surgery
- Secondary glaucoma not related to PXS
- Autoimmune or connective tissue disorders
- Chronic corticosteroid use

**Ophthalmic Evaluation:** All participants underwent a comprehensive eye examination, including, Slit-lamp biomicroscopy, IOP measurement, Gonioscopy, Dilated fundus examination and Visual field testing and optic nerve imaging (for glaucoma suspects)

### Optical Coherence Tomography (OCT) of the retinal nerve fiber layer (RNFL)

A comprehensive medical history and systemic examination were conducted to identify coexisting conditions such as hypertension, diabetes mellitus, ischemic heart disease, aortic aneurysm, cerebrovascular disease, and peripheral arterial disease (PAD).
To evaluate sensorineural hearing loss (SNHL), pure tone audiometry was performed. PAD screening involved measurement of the Ankle-Brachial Index (ABI) and Doppler ultrasonography of the anterior tibial and dorsalis pedis arteries, along with their distal branches. The vascular assessment focused on detecting intimo-medial thickening, identifying plaque characteristics, and analyzing spectral waveform abnormalities such as loss of triphasic pattern, monophasic flow, and decreased flow velocity.
Informed written consent was obtained from all participants prior to inclusion. The study received approval from the institutional ethics committee. Statistical analysis was performed using SPSS

version 25.0. Categorical variables were assessed using the Chi-square test, while continuous variables were analyzed using ANOVA or independent samples t-test. A p-value less than 0.05 was considered statistically significant.

In this study, the prevalence of systemic comorbidities was evaluated across three groups: individuals with pseudoexfoliation syndrome (PXS), those with pseudoexfoliation glaucoma (PXG), and age- and sex-matched control participants. Hypertension was observed in 44% of the PXS group and 50% of the PXG group, compared to 36% among controls. Although the prevalence was numerically higher in the pseudoexfoliation groups, the difference was not statistically significant when compared to controls ($p = 0.08$), and no meaningful difference was found between the PXS and PXG subgroups ($p = 0.53$). These findings suggest that while hypertension is prevalent in the elderly population, this study did not demonstrate a significant association with pseudoexfoliation.

A similar trend was observed for diabetes mellitus, which was reported in 40% of PXS patients, 48% of PXG patients, and 41% of control participants. The differences were not statistically significant ($p = 0.62$), and no notable variation was seen between the PXS and PXG groups ($p = 0.41$). Therefore, in this cohort, no clear link was found between pseudoexfoliation and diabetes mellitus.

Ischemic heart disease (IHD) was found to be significantly more prevalent among individuals with pseudoexfoliation. It was present in 24% of those with PXS and 36% of PXG patients, compared to only 10% in the control group ($p < 0.01$). While the difference between the PXS and PXG groups was not statistically significant ($p = 0.21$), the higher frequency of IHD in both suggests a potential vascular association with pseudoexfoliation pathology.

Aortic aneurysms were detected in 10% of PXS patients and 16% of those with PXG, whereas none were reported among controls—a statistically significant finding ($p < 0.001$). The absence of a significant difference between the two pseudoexfoliation groups ($p = 0.38$) implies that the risk of such vascular structural abnormalities may be inherent to pseudoexfoliation itself, regardless of glaucoma development.

Cerebrovascular disease also showed a marked increase in prevalence within the pseudoexfoliation cohort. It was reported in 18% of the PXS group and 22% of PXG patients, in contrast to only 5% among controls ($p < 0.01$). However, the difference between the PXS and PXG subgroups was not statistically significant ($p = 0.62$), reinforcing the hypothesis that pseudoexfoliation may be linked to systemic vascular dysfunction, independent of glaucoma status.

A particularly significant finding in this study was the elevated prevalence of peripheral arterial disease (PAD) among patients with pseudoexfoliation. PAD was identified in 28% of individuals with PXS and 42% of those with PXG, in stark contrast to just 7% in the control group—a statistically significant difference ($p < 0.001$). The comparison between the PXS and PXG subgroups did not yield statistical significance ($p = 0.17$), suggesting that pseudoexfoliation itself, regardless of glaucoma status, may be linked to systemic peripheral vascular involvement.

Similarly, sensorineural hearing loss (SNHL) was found to be significantly more common in individuals with pseudoexfoliation. It affected 60% of the PXS group and 76% of those with PXG, compared to only 12% among controls ($p < 0.001$). Although the difference between the PXS and PXG groups was not statistically significant ($p = 0.09$), the notably high prevalence of SNHL in both groups supports the hypothesis that pseudoexfoliation may impact microvascular systems beyond the eye, potentially involving structures such as the cochlea.

Smoking history, considered a potential vascular risk factor, was more commonly reported among individuals with pseudoexfoliation. It was present in 36% of the PXS group and 42% of the PXG group, compared to 25% of control participants. The difference between the combined pseudoexfoliation groups and controls was statistically significant ($p = 0.03$). However, no significant variation was found between the PXS and PXG subgroups ($p = 0.63$), indicating that while smoking may contribute to overall vascular risk, it does not appear to be associated with the progression from PXS to PXG.

| Table 1: Systemic Comorbidities and Clinical Findings in PXS, PXG, and Controls | | | | | |
|---|---|---|---|---|---|
| **Systemic Condition** | **PXS (n=50)** | **PXG (n=50)** | **Controls (n=100)** | **p-value (PXS+PXG vs Controls)** | **p-value (PXS vs PXG)** |
| Hypertension | 22 (44%) | 25 (50%) | 36 (36%) | 0.08 | 0.53 |
| Diabetes Mellitus | 20 (40%) | 24 (48%) | 41 (41%) | 0.62 | 0.41 |
| Ischemic Heart Disease | 12 (24%) | 18 (36%) | 10 (10%) | <0.01 | 0.21 |
| Aortic Aneurysm | 5 (10%) | 8 (16%) | 0 (0%) | <0.001 | 0.38 |
| Cerebrovascular Disease | 9 (18%) | 11 (22%) | 5 (5%) | <0.01 | 0.62 |
| Peripheral Arterial Disease (PAD) | 14 (28%) | 21 (42%) | 7 (7%) | <0.001 | 0.17 |
| Sensorineural Hearing Loss | 30 (60%) | 38 (76%) | 12 (12%) | <0.001 | 0.09 |
| Smoking History | 18 (36%) | 21 (42%) | 25 (25%) | 0.03 | 0.63 |

Peripheral vascular evaluation through the Ankle-Brachial Index (ABI) and Doppler ultrasound examination of the anterior tibial, dorsalis pedis, and distal arteries demonstrated significant systemic involvement in patients with pseudoexfoliation. An ABI value below 0.9, which indicates peripheral arterial disease, was observed in 24% of individuals with PXS and 40% of those with PXG, compared to just 6% in the control group. This difference was statistically significant ($p < 0.001$), though no significant difference was found between the PXS and PXG groups ($p = 0.11$), suggesting that peripheral vascular impairment is associated with pseudoexfoliation regardless of glaucoma presence.

Furthermore, Doppler ultrasound identified intimo-medial thickening in 28% of PXS patients and 44% of PXG patients, whereas only 7% of controls showed this feature. The prevalence of this vascular change was significantly higher in the pseudoexfoliation groups compared to controls ($p < 0.001$), but the difference between PXS and PXG groups was not statistically significant ($p = 0.14$). This thickening may reflect early or subclinical atherosclerotic alterations linked to pseudoexfoliation.

Plaque deposits, varying from hypoechoic to calcified types, were detected in 20% of patients with PXS and 34% of those with PXG, compared to only 3% of controls, a difference that was statistically significant ($p < 0.001$). Despite this, there was no significant distinction between the PXS and PXG groups ($p = 0.16$), highlighting the systemic vascular involvement associated with pseudoexfoliation regardless of glaucoma status.

Spectral Doppler evaluations revealed abnormal blood flow patterns, such as loss of the normal triphasic waveform and the presence of monophasic flow, in 24% of PXS and 38% of PXG patients, versus just 4% of controls ($p < 0.001$). Additionally, reduced blood flow velocity was observed in 20% of PXS and 32% of PXG participants, compared with 3% in the control group ($p < 0.001$). No significant differences were found between the PXS and PXG groups for these Doppler findings ($p = 0.18$ and $p = 0.20$, respectively), suggesting that vascular abnormalities are inherent to pseudoexfoliation itself and are not limited to those who develop glaucoma.

| Table 2: Peripheral Arterial Disease – Doppler and ABI Findings in PXS, PXG and Controls | | | | | |
|---|---|---|---|---|---|
| **Doppler Finding** | **PXS (n=50)** | **PXG (n=50)** | **Controls (n=100)** | **p-value (PXS+PXG vs Controls)** | **p-value (PXS vs PXG)** |
| Abnormal ABI (<0.9) | 12 (24%) | 20 (40%) | 6 (6%) | <0.001 | 0.11 |
| Intimo-medial Thickening | 14 (28%) | 22 (44%) | 7 (7%) | <0.001 | 0.14 |
| Plaque Presence | 10 (20%) | 17 (34%) | 3 (3%) | <0.001 | 0.16 |
| Loss of Triphasicity / Monophasic Flow | 12 (24%) | 19 (38%) | 4 (4%) | <0.001 | 0.18 |
| Reduced Flow Velocity | 10 (20%) | 16 (32%) | 3 (3%) | <0.001 | 0.20 |

## DISCUSSION

This hospital-based cross-sectional study was designed to investigate the systemic associations of pseudoexfoliation, including both pseudoexfoliation syndrome (PXS) and pseudoexfoliation glaucoma (PXG). While traditionally viewed as a disease affecting only the eye, pseudoexfoliation is increasingly recognized as a systemic fibroelastotic disorder with potential involvement of multiple organ systems. Our findings strongly support this perspective, revealing significant links between pseudoexfoliation and various systemic vascular conditions such as ischemic heart disease, aortic aneurysm, cerebrovascular disease, peripheral arterial disease (PAD), and sensorineural hearing loss (SNHL). These results align with emerging research suggesting that pseudoexfoliation reflects widespread dysfunction of the extracellular matrix and microvascular damage.

Patients with pseudoexfoliation (both PXS and PXG) were notably older on average compared to control subjects, consistent with the established understanding of pseudoexfoliation as an age-related disease. This observation is supported by earlier epidemiological studies, including the Reykjavik Eye Study, which reported a prevalence of up to 40.6% in individuals aged over 80 years (Arnarsson AM, 2009)25. The progressive buildup of pseudoexfoliative material (PXM) with advancing age is thought to result from ongoing changes in extracellular matrix metabolism and reduced efficiency in clearing this material (Schlotzer-Schrehardt U, Naumann GO, 2006)[1].

Hypertension was common among all study groups, with rates of 44% in PXS patients, 50% in those with PXG, and 36% in the control group; however, these differences were not statistically significant. This finding aligns with the study by Sarenac-Vulovic TS et al. (2014)[27], who similarly reported a high but comparable prevalence of hypertension across PXS, PXG, and control populations. The absence of a significant link may be due to the generally high prevalence of hypertension among older adults, which could obscure any disease-specific associations.

In contrast, ischemic heart disease (IHD) demonstrated a significant relationship with pseudoexfoliation. It was found in 24% of patients with PXS and 36% of those with PXG, compared to only 10% of controls ($p < 0.01$). Although the difference between PXS and PXG groups was not statistically significant, the overall elevated presence of IHD in the pseudoexfoliation groups highlights the vascular involvement of the condition. These results are consistent with prior research by Sarenac-Vulovic et al. (2014)[27], which reported IHD in 25% of PXG and 20% of PXS patients. Additionally, Elhawy E et al. (2012)[28] emphasized that pseudoexfoliative material contributes to systemic endothelial dysfunction, oxidative stress, and disruptions in extracellular matrix remodeling, factors that may increase the risk of coronary artery disease.

Aortic aneurysm, a significant vascular complication, was identified in 10% of patients with PXS and 16% of those with PXG, while no cases were detected in the control group, a difference that

was statistically significant ($p < 0.001$). These results are consistent with earlier research, such as the study by Sarenac-Vulovic TS et al. (2014)[27], which reported aortic aneurysms in up to 15% of PXG patients. The accumulation of pseudoexfoliative material (PXM) within the walls of large blood vessels is believed to contribute to decreased elasticity and structural weakening, providing a possible explanation for this association. Histopathological studies have confirmed the presence of fibrillar PXM deposits in vascular walls (Schlotzer-Schrehardt UM et al., 1992[29]; Bleich S et al., 2004[30]).

Similarly, cerebrovascular disease was more prevalent among those with pseudoexfoliation, affecting 18% of PXS patients and 22% of PXG patients, compared to 5% in the control group ($p < 0.01$). These findings are in line with prior observations by Sarenac-Vulovic TS et al. (2014)[27], who reported cerebrovascular involvement in 15–25% of patients with PXS or PXG compared to controls. The underlying mechanism is thought to involve PXM-induced disruption of cerebral microcirculation and endothelial function, potentially increasing the risk of ischemic cerebrovascular events (Mastronikolis S et al., 2022)[11].

A notable finding from our study was the high occurrence of sensorineural hearing loss (SNHL) in patients with pseudoexfoliation. SNHL was detected in 60% of individuals with PXS and 76% of those with PXG, compared to just 12% of the control group ($p < 0.001$). This aligns with prior research, such as the work by Sarenac-Vulovic TS et al. (2014)[27], which reported SNHL in 55% of PXS and 75% of PXG patients. The accumulation of pseudoexfoliative material within the cochlear blood vessels, along with microvascular insufficiency and oxidative stress, likely contributes to hearing impairment. Supporting this, histological analyses by Yuksel N et al. (2001)[31] and Hammer T et al. (2000)[32] have demonstrated PXM deposits in the cochlear vasculature and inner ear structures.

A key and novel aspect of our research was the assessment of peripheral arterial disease (PAD) using objective measures like the ankle-brachial index (ABI) and Doppler ultrasound of lower limb arteries. PAD was significantly more common in patients with pseudoexfoliation, occurring in 28% of those with PXS and 42% of those with PXG, compared to only 7% of controls ($p < 0.001$). Doppler studies further revealed vascular abnormalities—including increased intimo-medial thickness, presence of atherosclerotic plaques, and altered spectral waveforms characterized by loss of triphasic flow and reduced velocities—which were significantly more frequent among PXS and PXG patients than controls. Although vascular changes tended to be more pronounced in the PXG group than in the PXS group, these differences were not statistically significant, indicating that systemic vascular involvement may begin prior to the development of glaucoma in pseudoexfoliation patients. The similar systemic and vascular profiles between the PXS and PXG subgroups suggest that the systemic effects are primarily driven by the accumulation of pseudoexfoliative material itself rather than by glaucomatous damage. This supports the concept of pseudoexfoliation as a systemic condition manifesting ocular signs, rather than a purely eye-limited disorder with incidental systemic findings.

The mechanisms underlying these systemic effects are thought to involve genetic and molecular pathways. The LOXL1 gene, which plays a crucial role in elastin fiber formation and maintenance, has been repeatedly linked to pseudoexfoliation in diverse populations (Patil A et al., 2022)[33]. Other factors include Clusterin, a molecular chaperone that aids in protein folding and clearance, and transforming growth factor-beta 1 (TGF-β1), a cytokine involved in fibrosis and vascular remodeling (Yilmaz A et al., 2005[34]; Ritch R, 2014[35]).

## CONCLUSION

The results of this cross-sectional study reinforce the growing recognition of pseudoexfoliation as a systemic condition with notable vascular, neurological, and auditory implications. Both patients with pseudoexfoliation syndrome (PXS) and pseudoexfoliation glaucoma (PXG) demonstrated significantly higher rates of systemic comorbidities such as ischemic heart disease, aortic aneurysm, cerebrovascular disease, peripheral arterial disease (PAD), and sensorineural hearing loss when compared to age-matched control subjects. Notably, these systemic associations were present in

both groups without significant differences, indicating that systemic involvement likely occurs early in the disease course rather than being solely a result of glaucoma progression.

Peripheral arterial disease was a particularly prominent finding, highlighted by abnormal ankle-brachial index measurements and Doppler ultrasound abnormalities, further emphasizing the systemic vascular component of pseudoexfoliation. These findings highlight the need to view pseudoexfoliation not just as an eye disease but also as a potential indicator of underlying systemic vascular pathology.

Recognizing pseudoexfoliation early could allow for timely systemic evaluation and risk assessment, especially for cardiovascular and cerebrovascular conditions. This underscores the importance of coordinated care involving ophthalmologists, cardiologists, neurologists, and vascular medicine specialists to ensure comprehensive management. Larger prospective studies are essential to clarify causal relationships and elucidate the underlying mechanisms connecting pseudoexfoliation with systemic diseases.

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