

The Impact of Serum Vitamin D Levels on Pseudoexfoliative Glaucoma Severity: Should It Be Considered Before Surgical Intervention?

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Background: Pseudoexfoliative glaucoma (PXG) is a secondary form of glaucoma characterized by the accumulation of extracellular protein deposits, leading to elevated intraocular pressure and progressive optic nerve damage. While pharmacological therapies can help control intraocular pressure, surgical intervention is often required in advanced cases. This study investigates the relationship between serum vitamin D levels and PXG severity, with a focus on their potential role in disease progression and treatment planning.

Materials and Methods: A total of 114 patients from the glaucoma clinic at Rouhani Hospital were enrolled in the study. Participants were divided into three groups: severe pseudoexfoliative glaucoma, mild-to-moderate pseudoexfoliative glaucoma, and a control group. The study assessed the association between serum vitamin D levels and the severity of pseudoexfoliative glaucoma, while accounting for potential confounding factors such as age, sex, and intraocular pressure.

Results: Our study found no significant association between serum vitamin D levels and the severity of pseudoexfoliative glaucoma ($p = 0.89$). Additionally, vitamin D levels did not show a statistically significant effect on disease severity within subgroups based on age, sex, or intraocular pressure (all $p > 0.05$). Notably, linear regression analysis identified age ($p < 0.001$, $\beta = 0.404$), female sex ($p < 0.001$, $\beta = 0.206$), and higher intraocular pressure ($p < 0.001$, $\beta = 0.344$) as significant independent factors associated with increased pseudoexfoliative glaucoma severity.

Conclusion: Serum vitamin D levels do not appear to directly influence the severity of pseudoexfoliative glaucoma or the necessity for surgical intervention. In contrast, factors such as age, sex, and intraocular pressure play a critical role in determining disease severity, highlighting their importance in clinical management.

Keywords: Pseudoexfoliative syndrome; glaucoma; 1,25 dihydroxyvitamin D; pseudoexfoliation; pseudoexfoliation glaucoma; vitamin D

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Introduction

Glaucoma is an optic neuropathy characterized by quantifiable functional deterioration and



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degeneration of the optic nerve, leading to diminished visual function and irreversible loss of visual field (1). It is the second leading cause of blindness worldwide. The prevalence of glaucoma varies due to factors such as gender, ethnicity, and age (1, 2).

Vitamin D, a prohormone, has diverse functions, including immunomodulatory, anti-inflammatory, antioxidative, and antineoplastic effects. Its antioxidative properties have been increasingly recognized, and vitamin D deficiency may contribute to the development of autoimmune disorders and cancer (3, 4). Additionally, vitamin D inhibits endothelial cell proliferation and reduces hypoxia-inducible factor levels, which in turn can regulate the expression of vascular endothelial growth factor (VEGF) (5). Although the active form of vitamin D is 1, 25-dihydroxyvitamin D, vitamin D status is typically assessed by measuring serum 25-hydroxyvitamin D levels. Several studies have explored the relationship between vitamin D and glaucoma (6, 7). Vitamin D influences the expression of certain proteins and related molecules involved in aqueous humor production by the ciliary epithelium. Moreover, experimental animal models have demonstrated that topical administration of vitamin D can lead to a reduction in intraocular pressure (IOP) (5,8, 9).

Pseudoexfoliation (PEX) syndrome is a multifactorial systemic disorder whose prevalence increases with age (5). In this condition, fibrillar extracellular materials accumulate not only in the eye but also in cardiac and vascular tissues, reflecting systemic involvement (10). Both genetic and non-genetic factors—such as race, age, autoimmune disorders, ultraviolet exposure, oxidative stress, inflammation, viral infections, and trauma—have been implicated in its pathogenesis (4,11,12). PEX materials appear as gray-white deposits and are typically found in ocular structures, including the pupillary border, iris, anterior hyaloid, iridocorneal angle, and lens. At the time of diagnosis, elevated intraocular pressure or glaucoma is present in approximately 20% of PEX cases (10, 11).

The management of pseudoexfoliative glaucoma (PEX) primarily aims to reduce intraocular pressure

(IOP) and prevent progressive optic nerve damage. Initial treatment typically involves medical therapies such as prostaglandin analogs, beta-blockers, and alpha agonists. In advanced or refractory cases, surgical interventions—including trabeculectomy, tube shunt surgery, and goniotomy—may be required to achieve adequate IOP control. Given emerging evidence suggesting a potential role of vitamin D in ocular health and disease progression, this study seeks to evaluate whether serum vitamin D levels are associated with the severity of PEX glaucoma.

Materials and methods

Study Design

This study employed a case-control design to investigate the potential association between serum vitamin D levels and the severity of pseudoexfoliative glaucoma (PEXG). A total of 114 participants were recruited from the glaucoma clinic at Rouhani Hospital, including 76 patients diagnosed with PEXG and 38 age- and sex-matched controls. The PEXG group was further stratified into mild-to-moderate and severe subgroups based on disease severity, as determined by mean deviation (MD) on visual field testing.

Participants

Case Group: Patients diagnosed with pseudoexfoliative glaucoma (PEXG) who attended the glaucoma clinic at Rouhani Hospital, either as new referrals or for follow-up visits.

Control Group: Individuals accompanying PEXG patients to the clinic, with no history of glaucoma or other ocular diseases, serving as age- and sex-matched controls.

Inclusion Criteria: All cases in glaucoma clinic of Rouhani Hospital for either PEXG diagnosis or follow-up (case group)

✓ Individuals accompanying PEXG patients to the clinic (control group)

Exclusion Criteria: Informed consent to participate in the study,

- ✓ Known gastrointestinal disorders affecting
- ✓ vitamin D absorption,
- ✓ Primary hyperparathyroidism,
- ✓ Chronic kidney failure,

- ✓ Liver failure,
- ✓ Pregnancy,
- ✓ Malignancies,
- ✓ Untreated thyroid disease,
- ✓ Vitamin D supplementation within the past 3-6 months,
- ✓ And use of medications affecting vitamin D metabolism

Sample Size

The sample size was determined using the formula for comparing three independent means. Based on a previously reported effect size of 0.719 (Yingjuan et al.), with a desired statistical power of 80% and an alpha level of 0.05, a minimum of 38 participants per group was required. This yielded a total sample size of 114 participants.

The sample size was calculated using the following formula:

$$n \geq (1 + \sqrt{g-1}) \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{d^2} + \frac{Z_{1-\frac{\alpha}{2}}^2 \sqrt{g-1}}{2(1 + \sqrt{g-1})}$$

Data Collection

Visual acuity was evaluated using the Snellen chart. Comprehensive ocular examination was performed with a slit-lamp biomicroscope to assess both anterior and posterior segments. The cup-to-disc (C/D) ratio was measured during fundoscopic examination. Intraocular pressure (IOP) was determined using Goldmann applanation tonometry (GAT). The anterior chamber angle was assessed via gonioscopy.

PEXG diagnosis was done based on the following criteria:

- ✓ IOP > 21 mmHg
- ✓ Observation of pseudoexfoliative (PEX) material at the pupil margin or anterior capsule of the lens after pupil dilation with 1% Tropicamide drops
- ✓ Open angle on gonioscopy
- ✓ Optic disc glaucoma on fundus examination
- ✓ Visual field changes (perimetry)

Serum vitamin D levels measured using a monobind ELISA kit in the laboratory of Rouhani Hospital. Participants were categorized as: (42)

- ✓ Adequate: Serum 25(OH)D \geq 30 ng/ml
- ✓ Inadequate: Serum 25(OH)D < 30 ng/ml
- ✓ Mild deficiency: Serum 25(OH)D 20-30 ng/ml

- ✓ Severe deficiency: Serum 25(OH)D < 20 ng/ml
- Disease Severity Assessment (PEXG Group Only)*
- ✓ Mild-to-moderate: MD < -12dB on visual field examination

- ✓ Severe: MD \geq -12dB on visual field examination

Data Analysis

Data were analyzed using SPSS software. Descriptive statistics, including mean, standard deviation, frequency, and percentage, were used to summarize participant characteristics and study variables. Independent t-tests and chi-square tests were applied to compare continuous and categorical variables, respectively, between the case and control groups. One-way ANOVA was used to evaluate differences in quantitative parameters across PEXG severity subgroups. Linear regression analysis, adjusted for potential confounding factors, was performed to assess the association between serum vitamin D levels and PEXG severity. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants following a detailed explanation of the study procedures, potential risks, and benefits. Patient confidentiality and anonymity were strictly maintained throughout the research process.

Results

A total of 114 participants were included in the study, comprising 38 patients with severe PEXG, 38 with mild-to-moderate PEXG, and 38 control participants without PEXG. Of the total cohort, 62 participants (54.4%) were male and 52 (45.6%) were female. Among the 76 PEXG patients, 50 (65.8%) were male and 26 (34.2%) were female. Participants' ages ranged from 18 to 90 years, with a mean age of 70.45 years. The mean age of female participants was 67.83 years, while that of male participants was 72.65 years.

Correlation between Vitamin D and PEXA

Among participants with severe vitamin D deficiency, 12 were in the severe PEXG group, 9 in the mild-to-moderate PEXG group, and 12 in the control

group. For those with mild vitamin D deficiency, 12 were from the severe PEXG group, 21 from the mild-to-moderate group, and 10 from the control group. Among participants with normal vitamin D levels, 14

belonged to the severe PEXG group, 8 to the mild-to-moderate group, and 16 to the control group.

Statistical analysis revealed no significant association between vitamin D status and PEXG severity across the three groups ($P = 0.89$) (Table 1).

Table 1. Frequency Distribution of Three Vitamin D Levels in Three Groups.

Vitamin D Deficiency	Severe	Mild to moderate	Control	Total	P value
Severe	12 36.40%	9 27.30%	12 36.40%	33 100.00%	0.089
Mild	12 27.90%	21 48.80%	10 23.30%	43 100.00%	
Normal	14 36.80%	8 21.10%	16 42.10%	38 100.00%	

Vitamin D Groups in Three Groups based on Age, Gender, and IOP

Among participants younger than 75 years ($n = 64$, 56.1%), 7 cases with severe vitamin D deficiency were in the severe PEXG group, 3 in the mild-to-moderate group, and 11 in the control group. For mild vitamin D deficiency, 6 cases were from the severe group, 6 from the mild-to-moderate group, and 8 from the control group.

Among those with normal vitamin D levels, 5 were in the severe PEXG group, 4 in the mild-to-moderate group, and 14 in the control group. There was no statistically significant association between vitamin D status and PEXG severity in participants under 75 years of age ($P = 0.581$).

Additionally, no significant differences were observed in age, intraocular pressure, or gender based on vitamin D status (Table 2)

Table 2. Frequency Distribution of Three Vitamin D Groups in Three Groups of Severe, Mild to Moderate, and Control According to Age, Gender, and IOP

Variable	D Deficiency	PEXG severity			P value
		Severe	Mild to moderate	Control	
Age < 75 years	Severe	7 33.30%	3 14.30%	11 52.40%	0.581
	Mild	6 30.00%	6 30.00%	8 40.00%	
	Normal	5 21.70%	4 17.40%	14 60.90%	
Age ≥ 75 years	Severe	5 41.70%	6 50.00%	1 8.30%	0.235
	Mild	6 26.10%	15 65.20%	2 8.70%	
	Normal	9 60.00%	4 26.70%	2 13.30%	
Male	Severe	10 45.50%	7 31.80%	5 22.70%	0.212
	Mild	7 35.00%	11 55.00%	2 10.00%	
	Normal	11 55.00%	4 20.00%	5 25.00%	
Female	Severe	2 18.20%	2 18.20%	7 63.60%	0.372

IOP ≤ 21 mmHg	Mild	5	10	8	0.079
		21.70%	43.50%	34.80%	
	Normal	3	4	11	
		16.70%	22.20%	61.10%	
IOP > 21 mmHg	Severe	11	9	12	0.688
		34.40%	28.10%	37.50%	
	Mild	9	19	10	
		23.70%	50.00%	26.30%	
IOP > 21 mmHg	Normal	13	7	16	0.688
		36.10%	19.40%	44.40%	
	Severe	1	0	0	
		100.00%	0.00%	0.00%	
IOP > 21 mmHg	Mild	3	2	0	0.688
		60.00%	40.00%	0.00%	
	Normal	1	1	0	
		50.00%	50.00%	0.00%	

Linear Regression Results

Linear regression analysis was used to evaluate the association of age, gender, IOP, and vitamin D with PEXG severity, using a stepwise approach. In the first model, age was significantly associated with increased glaucoma severity, with a 0.404-unit increase per year ($P < 0.001$, $\beta = 0.404$). In the second model, adding IOP showed that glaucoma severity increased by 0.344 units for each unit rise in IOP ($P < 0.001$, $\beta = 0.344$). In the third model, inclusion of gender indicated that severity was 0.266 units lower in women compared to men ($P < 0.001$, $\beta = 0.266$). Vitamin D levels, however, were not significantly associated with glaucoma severity in any model (Table 3).

Table 3. linear regression results

Model	Beta	P value
1 (Constant)		0.016
Age	0.404	<0.001
2 (Constant)		<0.001
Age	0.368	<0.001
IOP	0.344	<0.001
3 (Constant)		<0.001
Age	0.316	<0.001
IOP	0.366	<0.001
gender	-0.266	<0.001

Discussion

Pseudoexfoliative material has been shown to accumulate in the endothelium of the cornea, iris, pre-equatorial lens epithelium, trabecular ciliary epithelium, vascular endothelial cells, and other ocular tissues (10, 11). Changes in both intraocular and

extraocular tissues are attributed to a diffuse fibrotic matrix resulting from stress-induced elastosis (5).

In the present study, no significant association was observed between serum vitamin D levels and the severity of pseudoexfoliative glaucoma (PEXG) across different age groups. However, linear regression analysis revealed a significant increase in PEXG severity of 0.404 units per year of age. Although the control group was notably younger than the PEXG groups, there was no significant age difference between the mild-to-moderate and severe PEXG subgroups.

Elastosis related to cellular stress is associated with abnormally cross-linked elastic microfibrils that accumulate within fibrillary PEX aggregates (11). Oxidative stress has been shown to play a key role in the progression and pathogenesis of both primary open-angle glaucoma and PEX syndrome (12). Several studies have reported that conditions such as hypoxia, ischemia, and low-grade chronic inflammation exacerbate oxidative stress, contributing to PEX development (13). Erdurmuş et al. (14) demonstrated that increased oxidative stress and reduced antioxidant defenses are implicated in PEX and primary glaucoma. These findings suggest that oxidative stress is a critical factor in the management of glaucoma and PEX syndrome, and modulation of the antioxidant–prooxidant balance may represent a potential therapeutic target for disease prevention and treatment (15,16).

The findings of the present study are consistent with those of several previous investigations. For instance, Yongwun Cho et al. (2021) reported that serum vitamin D levels were lower in controls than in patients with open-angle glaucoma (OAG), although the difference was not statistically significant (17). Similarly, Laura et al. (2021) found no significant association between vitamin D levels and the incidence of glaucoma (6). Additionally, Seyhan Diki et al. (2018) observed no statistically significant differences in serum vitamin D levels among controls, patients with pseudoexfoliation glaucoma, and those with pseudoexfoliation syndrome (18). These results align closely with the findings of our study.

However, the results of our study are not consistent with all previous research. For instance, Ulhaq et al. (2020) reported that patients with glaucoma had significantly lower serum vitamin D levels compared to controls (7). Similarly, Chen et al. (2019) found that individuals with severe glaucoma exhibited lower vitamin D levels than those with mild glaucoma or healthy controls (3). In addition, a retrospective cross-sectional study by Atalay et al. (2018) demonstrated that control participants had significantly higher serum vitamin D levels than patients with primary open-angle glaucoma (POAG) (19).

These discrepancies suggest that the relationship between vitamin D and glaucoma severity may vary depending on study population, methodology, or other confounding factors.

The findings of this study have important implications for the management of pseudoexfoliative glaucoma, particularly in the context of surgical intervention. The lack of a significant association between serum vitamin D levels and glaucoma severity suggests that routine vitamin D supplementation is unlikely to influence disease progression or surgical outcomes. Instead, clinicians should focus on established risk factors such as age, gender, and intraocular pressure (IOP) when developing treatment plans and determining the timing of surgical interventions. In cases where medical therapy is insufficient to control IOP, procedures such as trabeculectomy or tube shunt surgery remain

essential for preserving visual function and preventing further optic nerve damage.

The researchers acknowledge several limitations in this study. First, the relatively small sample size may have limited the statistical power to detect significant associations between serum vitamin D levels and pseudoexfoliative glaucoma severity. Second, the study did not account for other potential risk factors, such as the presence of cataracts, thyroid disorders, or family history of glaucoma, which could influence disease progression. Based on these limitations, the researchers recommend that future studies involve larger, more diverse cohorts to further investigate the relationship between serum vitamin D and glaucoma, as well as to evaluate the impact of additional risk factors on the severity and progression of pseudoexfoliative glaucoma.

Conclusion

Based on our findings and in comparison with other studies, serum vitamin D levels do not appear to directly influence the severity of pseudoexfoliative glaucoma in Iranian patients. However, age, sex, and intraocular pressure were identified as significant factors associated with disease severity, emphasizing their importance in clinical management and the need to consider these variables when planning appropriate surgical interventions in advanced cases of PEX glaucoma.

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