



Evaluation of Plasma Spermine and Spermidine Levels in Primary Open-Angle Glaucoma and Exfoliation Glaucoma

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Abstract

Objectives: This study aimed to compare plasma spermine and spermidine concentrations in patients with primary open-angle glaucoma (POAG), patients with exfoliation glaucoma (EG), and healthy individuals, and to explore their potential association with disease severity.

Materials and Methods: This prospective case-control study was conducted at a tertiary referral center and included patients with an established diagnosis of POAG or EG for more than two years. The control group consisted of age- and sex-matched healthy individuals. Participants with predefined systemic comorbidities or ocular conditions that could potentially confound the study findings were excluded. Plasma concentrations of spermine and spermidine were measured using enzyme-linked immunosorbent assay. Glaucoma severity was assessed using the modified Hodapp-Parrish-Anderson glaucoma staging system.

Results: Significant differences in spermine and spermidine concentrations were observed among the three study groups ($p=0.005$ and $p=0.037$, respectively). Post-hoc analyses showed that spermine levels were significantly elevated in both the POAG and EG groups relative to controls, whereas spermidine levels were significantly increased only in the POAG group. In the EG group, spermidine levels showed a weak inverse correlation with glaucoma severity (Kendall's tau-b = -0.317, $p=0.037$).

Conclusion: The observed alterations in plasma spermine and spermidine concentrations suggest a potential association between systemic polyamine metabolism and glaucoma. Given the proposed roles of polyamines in neurodegenerative processes, further studies are warranted to clarify the biological significance of these findings in glaucoma.

Keywords: Primary open-angle glaucoma, exfoliation glaucoma, spermine, spermidine, polyamines, neurodegeneration

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Introduction

Glaucoma is a leading cause of permanent vision impairment and is characterized by ongoing structural and functional deterioration of the optic nerve, particularly the optic nerve head and retinal nerve fiber layer.^{1,2} As life expectancy increases, the incidence of glaucoma is expected to rise. However, the underlying mechanisms driving its onset and progression remain poorly understood. Elevated intraocular pressure (IOP) remains the only confirmed modifiable risk factor linked to retinal ganglion



cell degeneration, making its regulation the cornerstone of glaucoma management. Nevertheless, vision loss may progress even in patients whose IOP has been normalized through medical or surgical interventions.^{1,3} These findings support the multifactorial nature of glaucomatous optic nerve damage.¹ Emerging evidence links glaucomatous degeneration to neurodegenerative processes, leading to growing interest in neuroprotective strategies as a complementary approach to disease management.³

Polyamines are low-molecular-weight organic cations synthesized from ornithine, structurally defined by a terminal primary amino group and a chain of alternating secondary amino groups.^{4,5} The principal members of the polyamine family include spermidine, spermine, putrescine, and cadaverine.^{4,6} Polyamines are involved in a broad range of cellular activities, such as promoting cell proliferation, regulating programmed cell death, maintaining DNA structural stability, and influencing gene expression through transcriptional and translational control.^{5,6,7} Furthermore, polyamine levels have been linked to key neurobiological processes, including neuritogenesis, brain development, and neuronal survival.⁸ Although limited in number, studies examining the association between polyamines and neurodegenerative diseases have yielded inconsistent findings. Notably, polyamine levels have been shown to decline with age, while exogenous supplementation has been associated with lifespan extension in experimental models.⁹ This age-related decline is particularly noteworthy given reports of markedly altered polyamine levels in the blood or tissues of individuals with age-related neurodegenerative disorders, including Alzheimer's¹⁰ and Parkinson's disease.¹¹ Collectively, these findings—along with evidence supporting their therapeutic potential—suggest that polyamines may exert pleiotropic, adaptive, and pathogenic effects in neurodegenerative disorders.⁹

Despite increasing evidence supporting the involvement of polyamine metabolism in oxidative homeostasis, neurodegeneration, and neuronal survival, there are still limited clinical data regarding circulating spermine and spermidine levels in patients with glaucoma. Moreover, it remains unclear whether circulating polyamine profiles differ between primary open-angle glaucoma (POAG) and exfoliation glaucoma (EG), and whether these alterations are associated with glaucoma severity.

Given the neurodegenerative nature of glaucoma and the potential involvement of polyamines in neurodegenerative processes, we hypothesized that circulating polyamine levels would be altered in patients with glaucoma and might be associated with disease severity. Accordingly, this study aimed to compare plasma spermine and spermidine concentrations among patients with POAG, patients with

EG, and healthy controls, and to evaluate the association between these concentrations and glaucoma severity.

Materials and Methods

Study Design

This prospective case-control study was conducted between February and July 2020 and included patients with an established diagnosis of glaucoma for more than two years prior to enrollment. The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: GO 18/933-14; project number: GO 18/933; date: 11 December 2018) and conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants.

A priori power analysis was performed to estimate the minimum sample size required. Based on previously reported spermine and spermidine levels in humans^{5,12} and assuming an α error of 5% with a statistical power of 80-90%, it was estimated that 36 to 46 participants per group (totaling 108 to 138 subjects) would be necessary to achieve adequate power.

Glaucoma Diagnosis and Participant Selection

Patients with POAG or EG and a disease duration longer than two years were consecutively enrolled in the study.

The diagnosis of POAG was based on the following criteria: absence of exfoliation material in both eyes upon maximal pupillary dilation; IOP >21 mmHg; open anterior chamber angle confirmed by gonioscopy (Shaffer grade 3 or 4); characteristic glaucomatous changes in the optic nerve head (e.g., rim thinning or notching in the superior or inferior temporal quadrant, or total cupping); and corresponding glaucomatous visual field defects (e.g., paracentral, arcuate, or Seidel's scotoma, or a nasal step).

The diagnosis of EG was established based on the presence of characteristic exfoliative material deposits in the anterior segment structures (cornea, lens, and/or pupillary margin) in one or both eyes, along with fulfillment of the other POAG diagnostic criteria stated above. All patients with glaucoma were receiving topical combination therapy consisting of dorzolamide hydrochloride 2% and timolol maleate 0.5% (Cosopt; Merck Sharp & Dohme, Istanbul, Türkiye) and brimonidine tartrate 0.15% (Alphagan P; AbbVie, Istanbul, Türkiye) at the time of blood sampling. The control group included healthy individuals over the age of 50 who were matched for age and sex and had no ocular conditions other than refractive errors.

To prevent potential confounding effects, strict exclusion criteria were applied across all three groups. Individuals with a known or suspected history of systemic conditions, including diabetes mellitus, hypertension, coronary artery disease, obesity (body mass index [BMI] ≥ 30 kg/m²), or neurodegenerative disorders such as Alzheimer's or Parkinson's disease, were not included in the study. Additionally, individuals with inflammatory ocular disease, a history of ocular trauma, or systemic medication use were excluded.

Data Collection and Clinical Examination

Detailed medical histories were obtained from all participants. Each participant underwent a comprehensive ophthalmic examination, including visual acuity testing, slit-lamp biomicroscopy of the anterior segment, IOP measurement using Goldmann applanation tonometry, dilated fundus examination, gonioscopy, and standard automated perimetry with the 24-2 threshold program (Humphrey Instruments; Carl Zeiss Meditec, Dublin, CA).

Glaucoma severity was classified into six stages (0-5) using the modified Hodapp-Parrish-Anderson (HPA) glaucoma staging system described by Mills et al.¹³ HPA classification could not be determined for patients whose visual field examinations remained unreliable despite repeated testing.

After a 12-hour fast, venous blood samples were collected from all participants. The samples were then centrifuged at $1500 \times g$ for 10 minutes to isolate plasma. The plasma was aliquoted and stored at -80°C until analysis. Plasma concentrations of spermine and spermidine were quantified in the Research Laboratory of the Department of Medical Biochemistry at Hacettepe University using commercially available enzyme-linked immunosorbent assay (ELISA) kits, in accordance with the manufacturers' protocols (Human Spermine ELISA Kit, Mybiosource, USA; Human Spermidine ELISA Kit, Cloud Clone Corp., USA).

Statistical Analysis

All statistical analyses were performed using SPSS software, version 25.0 for Windows (IBM Corp., Armonk, NY, USA). Quantitative variables were presented as mean $\pm$ standard deviation (SD). Normality of distribution was assessed using the Shapiro-Wilk test and evaluation of kurtosis and skewness values, with an absolute threshold of 0.5. Comparisons of quantitative variables among the three groups were conducted using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, based on the distribution of the data. Post-hoc pairwise comparisons were performed using Dunn's test with adjustment for

multiple comparisons following the Kruskal-Wallis test, and Bonferroni-adjusted pairwise comparisons following one-way ANOVA. Categorical variables were presented as counts and percentages (n, %), and group comparisons were performed using Pearson's chi-squared test. Associations between quantitative variables were evaluated using Spearman's rank correlation coefficients (ρ), while Kendall's tau-b was used to assess correlations between ordinal variables (HPA stage) and continuous measures. A p value ≤ 0.05 was considered indicative of statistical significance. Spermidine and spermine concentrations were graphically represented by group using median values and interquartile ranges, plotted with GraphPad Prism version 8.4.2 (GraphPad Software, San Diego, CA, USA).

Results

A total of 134 participants were included in the study. Sex distribution, age, and BMI were comparable across the three groups ($p=0.425$, $p=0.067$, and $p=0.886$, respectively) ([Table 1](#)).

Among patients with classifiable HPA stages, most had mild-to-moderate glaucoma, and relatively few had advanced disease. A significant difference in glaucoma severity was observed between the two glaucoma groups ($p=0.019$) ([Table 1](#)).

Significant differences in spermine and spermidine concentrations were observed among the three study groups ($p=0.005$ and $p=0.037$, respectively; [Table 1](#), [Figures 1](#) and [2](#)). Post-hoc pairwise comparisons indicated that spermidine levels were significantly higher in the POAG group compared to the control group ($p<0.05$), whereas differences between the remaining group pairs did not reach statistical significance. Post-hoc analysis of spermine levels demonstrated no significant difference between the POAG and EG groups. However, both groups exhibited significantly elevated concentrations compared to controls ([Table 1](#)).

Correlation analysis revealed a weak positive association between age and spermine concentration in the POAG group ($\rho=0.324$, $p=0.020$). In the EG group, spermine and spermidine concentrations were moderately and positively correlated ($\rho=0.463$, $p=0.002$). Furthermore, HPA stage exhibited a weak positive correlation with age in the POAG group ($\text{tau-b}=0.242$, $p=0.031$) and a weak negative correlation with spermidine levels in the EG group ($\text{tau-b}=-0.317$, $p=0.037$). No other statistically significant correlations were identified, including those between age and spermidine or spermine levels in the control group. The statistically significant correlation analyses are summarized in [Table 2](#).

Table 1. Comparison of the groups in terms of characteristics, glaucoma severity, and plasma spermine and spermidine concentrations

	POAG (n=51)	EG (n=44)	Control (n=39)	p value
Sex, n (%)				
Female	30 (58.8)	20 (45.5)	20 (51.3)	0.425*
Male	21 (41.2)	24 (54.5)	19 (48.7)	
Age (years), mean $\pm$ SD	66.7 $\pm$ 9.2	67.0 $\pm$ 6.6	63.9 $\pm$ 7.6	0.067 [†]
BMI (kg/m ²), mean $\pm$ SD	24.4 $\pm$ 3.2	24.3 $\pm$ 3.4	24.6 $\pm$ 3.0	0.886 [‡]
Modified Hodapp-Parrish-Anderson stage, n (%)				
Stage 0	6 (11.8)	1 (2.3)	39 (100)	POAG vs. EG 0.019*
Stage 1	22 (43.1)	5 (11.4)	0	
Stage 2	11 (21.6)	12 (27.3)	0	
Stage 3	10 (19.6)	4 (9.1)	0	
Stage 4	1 (2.0)	4 (9.1)	0	
Stage 5	1 (2.0)	2 (4.5)	0	
Unknown (no data)	0	16 (36.4)	0	
Spermine (ng/mL), mean $\pm$ SD	358.7 $\pm$ 124.7 ^a	354.3 $\pm$ 131.8 ^a	307.0 $\pm$ 157.5	0.005[†]
Spermidine (ng/mL), mean $\pm$ SD	5.08 $\pm$ 1.45 ^a	4.86 $\pm$ 1.38 ^{a,b}	4.34 $\pm$ 1.13 ^b	0.037[‡]

POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma, BMI: Body mass index, SD: Standard deviation. *Pearson chi-square, [†]Kruskal-Wallis, [‡]One-way ANOVA. p values in bold indicate the presence of statistical significance. Same letters denote the lack of statistical significance in pairwise comparisons (Dunn's test with adjustment for multiple comparisons following Kruskal-Wallis; Bonferroni-adjusted pairwise comparisons following one-way ANOVA)

Discussion

Compared with healthy controls, patients with POAG and EG exhibited elevated circulating spermine levels, whereas spermidine concentrations were significantly increased only in the POAG group. Additionally, glaucoma severity classified using the modified HPA system showed a weak positive correlation with age in the POAG group and a weak negative correlation with spermidine levels in the EG group. Taken together, these findings indicate that circulating polyamine levels are altered in glaucoma, whereas their associations with disease severity appear to be limited.

Recent evidence increasingly characterizes glaucoma as a complex neurodegenerative disease in which retinal ganglion cell loss is associated not only with elevated IOP but also with mitochondrial dysfunction, metabolic stress, impaired axonal transport, oxidative stress, and neuroinflammation.^{14,15,16,17} A recent review by Ekici and Moghimi¹⁸ further highlighted the multifactorial nature of glaucomatous neurodegeneration, emphasizing the interconnected contributions of elevated IOP, impaired ocular blood flow, extracellular matrix remodeling, excitotoxicity, oxidative stress, and neuroinflammation to retinal ganglion cell dysfunction and loss. Although IOP remains the only established modifiable risk factor, disease progression may occur despite adequate IOP control,

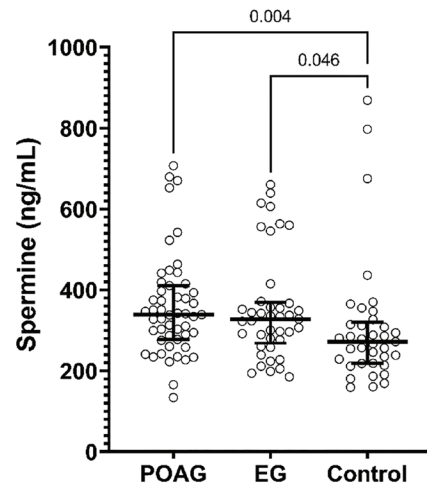


Figure 1. Scatterplot of plasma spermine concentrations in the glaucoma and control groups. Data are presented as individual values; horizontal lines indicate the median and error bars represent the interquartile range. Pairwise comparisons were performed using Dunn's test following the Kruskal-Wallis test. The comparison between POAG and EG was not statistically significant ($p>0.999$, not shown in the figure)

POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma

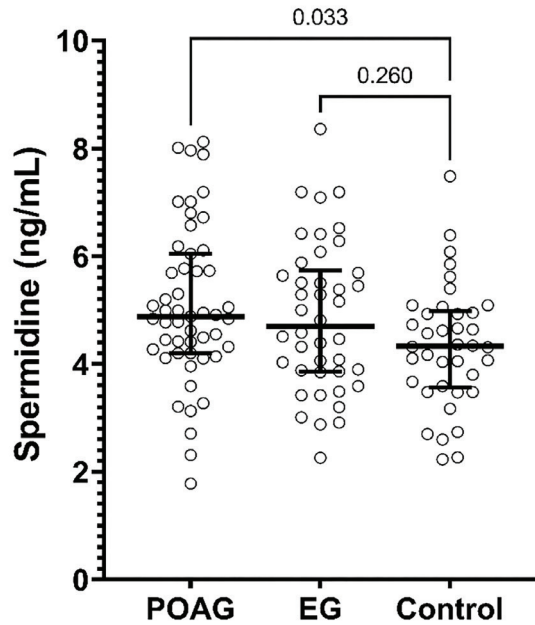


Figure 2. Scatterplot of plasma spermidine concentrations in the glaucoma and control groups. Data are presented as individual values; horizontal lines indicate the median and error bars represent the interquartile range. Pairwise comparisons were performed using Bonferroni correction following one-way ANOVA. The comparison between POAG and EG was not statistically significant ($p > 0.999$, not shown in the figure)

POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma

underscoring the need for neuroprotective approaches targeting retinal ganglion cell survival. Experimental studies have demonstrated that spermidine exerts neuroprotective effects in models of retinal ganglion cell injury and optic nerve damage.¹⁹ Given that clinical studies evaluating circulating spermine and spermidine concentrations in glaucoma remain scarce, these experimental findings provide a biological rationale for investigating circulating polyamines in patients with glaucoma. Furthermore, recent reviews indicate that neuroprotective strategies targeting retinal ganglion cell metabolism, mitochondrial function,

and oxidative stress may complement conventional IOP-lowering therapy.^{16,20}

Consistent with this biological framework, circulating spermine levels were elevated in both POAG and EG, whereas increased spermidine levels were observed only in patients with POAG. In light of the neuroprotective effects of spermidine reported in experimental models of neurodegeneration and optic nerve injury,¹⁹ the observed increase in circulating spermidine may reflect an adaptive response to glaucomatous neurodegeneration. It may also represent altered systemic polyamine metabolism accompanying the disease process. Nevertheless, whether increased circulating spermidine represents a compensatory response, a marker of altered systemic polyamine metabolism, or an epiphenomenon of the disease process cannot be determined from the present cross-sectional study.

In addition to their experimentally demonstrated neuroprotective effects, polyamines are involved in oxidative homeostasis, mitochondrial function, autophagy, and cellular stress responses.^{21,22} These biological properties provide a plausible mechanistic link between altered polyamine metabolism and glaucomatous neurodegeneration. Mitochondrial dysfunction and oxidative stress are also implicated in retinal ganglion cell degeneration, reinforcing interest in metabolic and neuroprotective therapeutic strategies.^{15,16,23} Nevertheless, whether circulating polyamine levels directly reflect retinal oxidative stress or neuroprotective activity in human glaucoma remains uncertain.

Spermine and spermidine are naturally occurring polyamines that are abundant in the central nervous system and retina, where they are predominantly localized to astrocytes and contribute to neuronal homeostasis.²⁴ Polyamine metabolism is tightly regulated through coordinated biosynthetic and catabolic pathways, allowing dynamic interconversion among spermine, spermidine, and their metabolic precursors.^{6,25} Consequently, changes in circulating polyamine levels may reflect tissue-specific disturbances in polyamine homeostasis associated with glaucomatous neurodegeneration rather than alterations in a single metabolic pathway.

Table 2. Summary of significant correlation analyses

Study group	Variables	Correlation method	Correlation coefficient	p value
POAG	Age - Spermine	Spearman's rho	0.324	0.020
EG	Spermine - Spermidine	Spearman's rho	0.463	0.002
POAG	HPA grade - Age	Kendall's tau-b	0.242	0.031
EG	HPA grade - Spermidine	Kendall's tau-b	-0.317	0.037

POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma, HPA: Hodapp-Parrish-Anderson; the modified grading system was used

Age-related changes in polyamine metabolism appear to be tissue-specific. Experimental studies have demonstrated declining spermidine levels with age in several animal tissues, whereas human studies have reported distinct age-related patterns for different organs.²⁶ These observations further suggest that circulating spermine and spermidine levels should be interpreted cautiously, as systemic concentrations may not directly reflect local retinal polyamine metabolism. In addition, previous studies have associated both spermine and spermidine with antioxidant and anti-inflammatory effects in neurodegenerative disorders, including Alzheimer's disease.²³ Collectively, this evidence supports the biological plausibility of altered circulating polyamine levels in glaucoma, although the underlying mechanisms remain incompletely understood.

The distinct polyamine profiles observed in POAG and EG may also reflect differences in their underlying pathophysiology. Although oxidative stress is implicated in both conditions, POAG is primarily characterized by progressive retinal ganglion cell degeneration and neuroaxonal dysfunction, whereas EG is additionally associated with exfoliative material deposition, extracellular matrix remodeling, and characteristic alterations in anterior segment tissues. However, the specific mechanisms linking these pathophysiological variations to systemic polyamine metabolism remain to be elucidated. Because the study did not assess polyamine-related enzyme activity or interconversion, the basis of the observed groupwise pattern remains uncertain.

The clinical significance of altered circulating polyamine levels remains uncertain, including whether these alterations reflect disease activity, progression, or treatment response. Taken together, the present findings support further investigation of polyamine metabolism as a potential mechanistic pathway and circulating polyamines as candidate biomarkers in glaucoma, rather than providing direct evidence for a neuroprotective role of circulating polyamines.

Study Limitations

Although patients with varying degrees of glaucoma severity were included, their uneven distribution across HPA categories may have influenced the strength of the observed correlations between disease severity and polyamine levels and might limit the generalizability of these findings across the full disease spectrum. Furthermore, HPA classification data were unavailable for a subset of patients with EG because reliable visual field examinations (required for HPA grading) could not be obtained despite repeated testing. Consequently, fewer patients were available for the

severity-based analyses, potentially reducing their statistical power. However, the primary comparisons of circulating spermine and spermidine concentrations between study groups were independent of HPA stage.

Although overall disease severity was categorized using the modified HPA grading system, individual clinical parameters of glaucomatous damage, including baseline and current IOP, visual field indices (mean deviation, pattern SD, visual field index), and optical coherence tomography-derived retinal nerve fiber layer measurements, were not incorporated into the final analytical dataset. Consequently, the present study could not assess whether circulating spermine and spermidine concentrations were associated with these specific structural and functional clinical parameters beyond the HPA-based severity classification.

All patients with glaucoma received comparable topical combination therapy, but the potential influence of these medications on circulating polyamine concentrations cannot be excluded. In addition, the cross-sectional design of the study precludes the assessment of temporal changes in these concentrations across different stages of glaucoma and limits the interpretation of their relationship with disease progression.

The absence of additional parameters related to polyamine metabolism, including aqueous-humor polyamine concentrations and relevant enzyme activity and gene expression, represents another limitation that may have constrained a more comprehensive interpretation of the findings. Although age distributions did not differ significantly across the study groups, age-related alterations in spermine and spermidine metabolism may still have acted as a confounding factor. Despite these limitations, a strength of the present study is the inclusion of participants without clinically significant systemic comorbidities, thereby reducing the potential influence of systemic diseases on circulating spermine and spermidine levels.

Conclusion

This study demonstrated alterations in circulating polyamine levels in glaucoma when compared with controls, with elevated spermine concentrations in both POAG and EG but increased spermidine concentrations only in patients with POAG. These findings suggest that systemic polyamine metabolism may be altered in glaucoma. However, the biological and clinical significance of these changes remains uncertain. Although experimental evidence supports potential neuroprotective effects of polyamines, the present cross-sectional findings do not establish whether the observed alterations represent an adaptive response to glaucomatous neurodegeneration,

a consequence of the disease process, or other changes in systemic polyamine metabolism. Further prospective longitudinal studies that span the full spectrum of glaucoma severity and integrate circulating and ocular polyamine measurements with structural and functional clinical parameters are warranted to clarify the relationship between polyamine metabolism and glaucoma.

Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: GO 18/933-14; project number: GO 18/933; date: 11 December 2018) and conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments.

Informed Consent: Written informed consent was obtained from all participants.

Declarations

Authorship Contributions

Surgical and Medical Practices: O.A., Ö.D., S.K., M.İ., Concept: O.A., Ö.D., A.Y.G., M.İ., Design: O.A., Ö.D., A.Y.G., M.İ., Data Collection or Processing: O.A., Ö.D., A.Y.G., Analysis or Interpretation: O.A., A.Y., H.A.Ö., Literature Search: O.A., Ö.D., M.İ., Writing: O.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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