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Original Article

Oxidative DNA Damage and Antioxidant Depletion: A Systemic Profile in Primary Open-Angle Glaucoma

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Purpose: To evaluate systemic oxidative stress by comparing serum 8-hydroxy-2′-deoxyguanosine (8-OHdG), coenzyme Q10 (CoQ10), malondialdehyde (MDA), and 25-hydroxyvitamin D (25(OH)D) levels between primary open-angle glaucoma (POAG) patients and healthy controls.

Methods: This prospective case-control study included 37 POAG patients and 35 age-matched controls. Serum levels were measured via enzyme-linked immunosorbent assay. Nonparametric tests (Mann-Whitney *U*-test and Spearman correlations) and multivariate linear regression adjusting for age and sex were used.

Results: POAG patients showed significantly higher MDA (3.01 vs. 2.46 nmol/mL, $p = 0.021$) and 8-OHdG (9.34 vs. 6.52 ng/mL, $p < 0.001$), but lower CoQ10 (7.28 vs. 8.98 ng/mL, $p < 0.001$) and 25(OH)D (15.02 vs. 17.45 ng/mL, $p = 0.013$). MDA and 8-OHdG showed a strong positive correlation (rho = 0.855, $p < 0.001$). CoQ10 and 8-OHdG showed a moderate positive correlation (rho = 0.466, $p = 0.004$). No significant correlation was found between 25(OH)D and 8-OHdG (rho = −0.118, $p = 0.488$). After adjusting for age and sex, POAG remained independently associated with lower CoQ10 ($p < 0.001$). No oxidative marker correlated with intraocular pressure, visual field mean deviation, or retinal nerve fiber layer thickness in POAG patients (all $p > 0.05$).

Conclusions: POAG patients exhibit systemic oxidative imbalance with elevated oxidative damage and reduced antioxidant capacity. The positive CoQ10–8-OHdG correlation may suggest a compensatory relationship. This imbalance is associated with POAG but does not correlate with clinical severity cross-sectionally, suggesting it reflects a systemic disease component rather than a direct severity marker.

Key Words: 8-Hydroxy-2′-deoxyguanosine, Coenzyme Q10, Glaucoma, Malondialdehyde, Oxidative stress

Glaucoma is a chronic progressive optic neuropathy characterized by retinal ganglion cell loss and corresponding visual field defects, representing a leading cause of irreversible blindness worldwide [1]. Primary open-angle glaucoma (POAG) is the most common form, involving impaired aqueous humor outflow through an open anterior chamber angle, leading to elevated intraocular pressure (IOP), the primary modifiable risk factor [2]. However, many patients develop glaucomatous damage despite nor-

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mal IOP, highlighting the contribution of IOP-independent mechanisms including vascular dysregulation, genetic factors, and oxidative stress [3].

Oxidative stress results from an imbalance between reactive oxygen species production and antioxidant defenses. In glaucoma, mechanical stress from elevated IOP and ischemia-reperfusion injury can generate excessive oxidative damage [4]. Malondialdehyde (MDA), an end-product of lipid peroxidation, serves as a biomarker for oxidative damage to cellular membranes [5]. An 8-hydroxy-2′-deoxyguanosine (8-OHdG) represents oxidative DNA damage and is considered a sensitive marker of overall oxidative stress [6].

The endogenous antioxidant system includes enzymatic and nonenzymatic components. Coenzyme Q10 (CoQ10), a lipophilic antioxidant and essential mitochondrial component, has demonstrated neuroprotective effects in neurodegenerative conditions [7]. Vitamin D exhibits antioxidant, anti-inflammatory, and neuroprotective properties [8], and vitamin D deficiency has been associated with various ocular diseases including glaucoma [9].

While individual oxidative stress markers have been studied in glaucoma, their interrelationships and combined assessment remain limited. This study aimed to comprehensively evaluate the systemic oxidative stress profile in POAG patients by simultaneously measuring markers of oxidative damage (8-OHdG, MDA) and antioxidant defense (CoQ10, 25-hydroxyvitamin D [25(OH)D]), and investigate their correlations with clinical parameters.

Materials and Methods

Ethics statement

The study protocol was approved by the Ataturk University Clinical Research Ethics Committee (No. B.30.2.ATA.01.00/42) and adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study population

This prospective case-control study was conducted at the Department of Ophthalmology, Ataturk University Faculty of Medicine between June 2021 and December 2022. Sample size was calculated using G*Power 3.1 based on previous studies examining MDA levels in glaucoma [10]. With $\alpha = 0.05$, $\beta = 0.20$, and effect size $d = 0.80$, 34 participants per group were required. We enrolled 37 POAG patients and 35 controls.

Inclusion and exclusion criteria

POAG patients met these criteria as follows: (1) characteristic glaucomatous optic neuropathy (cup to disc ratio >0.7, asymmetry >0.2, or focal rim thinning); (2) corresponding visual field defects (Glaucoma Hemifield Test outside normal limits); (3) open angles on gonioscopy; and (4) untreated IOP >21 mmHg on two occasions. All POAG patients had high-tension glaucoma; no patients with normal-tension glaucoma were included in this cohort. The mean number of topical antiglaucoma medications used was 2.83 ± 0.08.

Control subjects had (1) IOP ≤21 mmHg, (2) normal optic discs, (3) normal visual fields, and (4) no glaucoma family history.

Exclusion criteria for both groups included secondary glaucoma; prior intraocular surgery (except uncomplicated cataract surgery >6 months earlier), ocular trauma, retinal diseases, diabetes mellitus, chronic kidney disease, liver dysfunction, autoimmune diseases, malignancy, pregnancy/lactation, antioxidant/vitamin D supplementation within 3 months, and smoking >10 cigarettes per day.

Clinical evaluation

All participants underwent comprehensive examination: best-corrected visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry (average of three measurements), gonioscopy, dilated fundus examination, standard automated perimetry (Humphrey Field Analyzer 750i, 24-2 SITA Standard; Carl Zeiss Meditec), and spectral-domain optical coherence tomography (Cirrus HD-OCT 5000, Carl Zeiss Meditec) for peripapillary retinal nerve fiber layer (RNFL) thickness.

Biochemical analysis

Peripheral venous blood was collected after 12-hour fasting. Serum was separated by centrifugation at 3,500×*g* for 10 minutes and stored at –80 °C until analysis. Serum concentrations were measured using commercial en-

zyme-linked immunosorbent assay (ELISA) kits as follows: (1) 8-OHdG (high sensitivity ELISA Kit, MyBioSource), (2) MDA (lipid peroxidation ELISA Kit, MyBioSource), (3) CoQ10 (human coenzyme Q10 ELISA Kit, MyBioSource). The assay measured total CoQ10 levels (reported in ng/mL), and (4) 25(OH)D (25-hydroxyvitamin D ELISA Kit, MyBioSource). All assays were performed in duplicate by a blinded investigator. Intra-assay and inter-assay coefficients of variation were <10% for all assays.

Statistical analysis

Data analysis used IBM SPSS ver. 25.0 (IBM Corp.). Normality was assessed using the Shapiro-Wilk test. Continuous variables with normal distribution were expressed as mean ± standard deviation or median (interquartile range), as appropriate, and compared using the independent *t*-test. Nonnormally distributed variables were expressed as median (interquartile range) and compared using the Mann-Whitney *U*-test. Categorical variables were compared using the chi-square test. Correlations were analyzed using Spearman rank correlation coefficient (rho). To account for the significant differences in age and sex between groups, multivariate linear regression models were constructed for CoQ10 and 25(OH)D levels, with POAG status as the independent variable and age and sex as covariates. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

Demographic and clinical characteristics

Seventy-two participants (37 POAG, 35 controls) were included. Table 1 presents demographic and clinical characteristics. Groups differed significantly in age ($p = 0.039$) and sex distribution ($p = 0.001$). As expected, POAG patients had higher IOP ($p < 0.001$), worse visual field mean deviation ($p < 0.001$), and thinner RNFL ($p < 0.001$).

Comparison of oxidative stress markers

As shown in Table 1 and Fig. 1A–1D, POAG patients had significantly higher levels of oxidative damage markers (8-OHdG, MDA) and lower levels of antioxidant/neuroprotective markers (CoQ10, 25(OH)D) compared to controls.

Correlation analyses among oxidative markers

Spearman correlation analysis within the POAG group (Fig. 2A–2C) revealed a strong positive correlation be-

Table 1. Demographic and clinical characteristics of the study population

Parameter	POAG group (n = 37)	Control group (n = 35)	*p*-value
Age (yr)	64.86 ± 11.52	58.57 ± 13.79	0.039*
Sex			0.001*
Female	21 (56.8)	7 (20.0)	
Male	16 (43.2)	28 (80.0)	
IOP (mmHg)	17.15 ± 1.29	14.70 ± 1.51	<0.001†
Visual field MD (dB)	−6.82 ± 1.60	−0.81 ± 0.52	<0.001†
RNFL thickness (μm)	75.6 ± 5.5	92.2 ± 5.1	<0.001†
No. of medications	2.83 ± 0.50	-	-
8-OHdG (ng/mL)	9.34 (6.79–21.55)	6.52 (4.59–8.20)	<0.001‡
MDA (nmol/mL)	3.01 (2.42–8.34)	2.46 (1.63–3.17)	0.021‡
CoQ10 (ng/mL)	7.28 (5.78–9.52)	8.98 (7.81–25.50)	<0.001‡
25(OH)D (ng/mL)	15.02 (11.48–24.95)	17.45 (14.82–31.63)	0.013‡

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).
POAG = primary open-angle glaucoma; IOP = intraocular pressure; MD = mean deviation; RNFL = retinal nerve fiber layer; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; MDA = malondialdehyde; CoQ10 = coenzyme Q10; 25(OH)D = 25-hydroxyvitamin D.
*Chi-square test; †Independent samples *t*-test; ‡Mann-Whitney *U*-test.

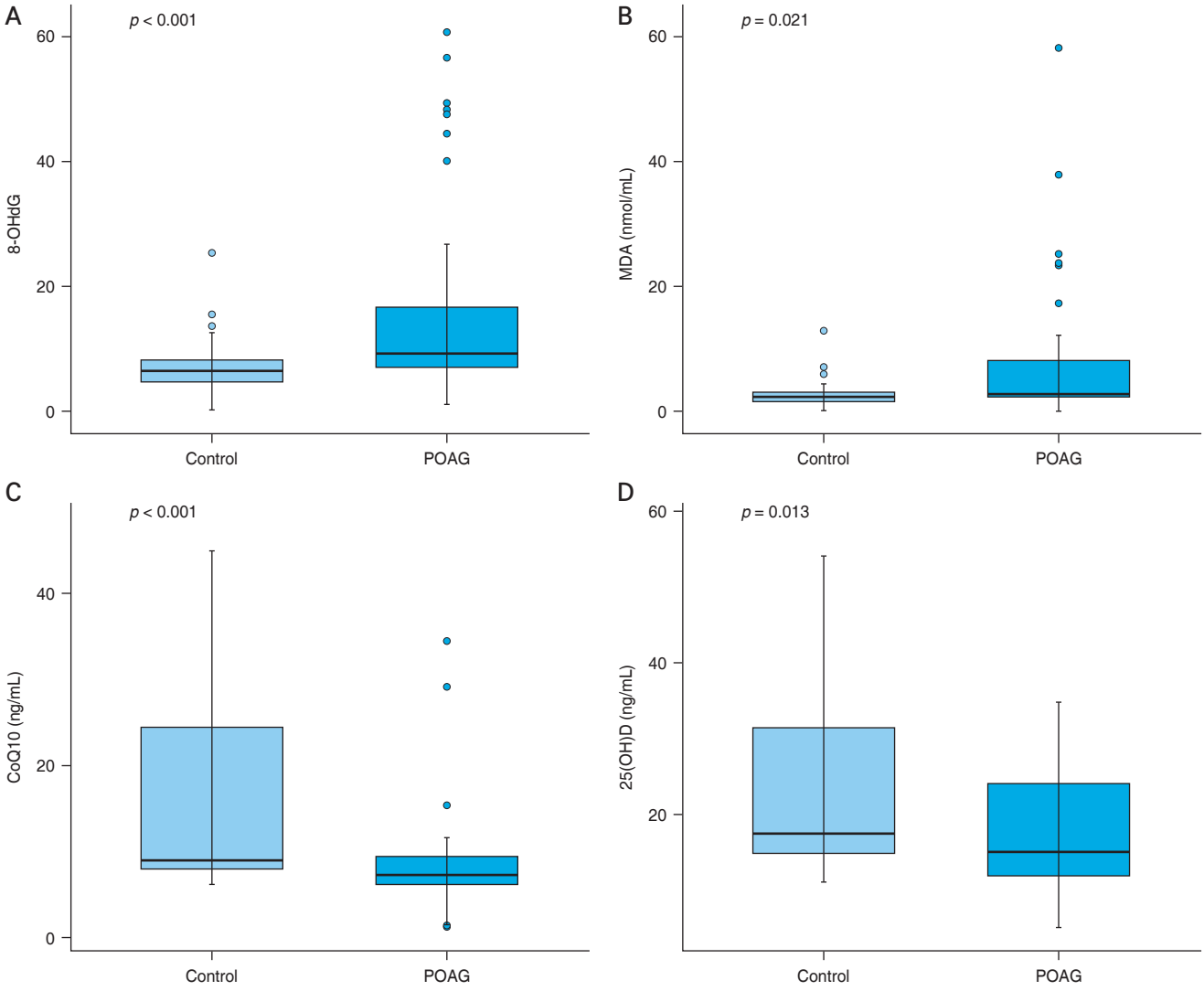

Fig. 1. Comparison of serum oxidative stress markers and vitamin D levels between the primary open-angle glaucoma (POAG) and control groups; (A) 8-hydroxy-2'-deoxyguanosine (8-OHdG), (B) malondialdehyde (MDA), (C) coenzyme Q10 (CoQ10), and (D) 25-hydroxyvitamin D (25(OH)D). Data are presented as box plots showing the median, interquartile range, and individual data points. Differences between groups were analyzed using the Mann-Whitney *U*-test.

tween MDA and 8-OHdG levels (rho = 0.855, $p < 0.001$). A moderate positive correlation was observed between CoQ10 and 8-OHdG levels (rho = 0.466; $p = 0.004$). No significant correlation was found between 25(OH)D and 8-OHdG levels (rho = –0.118, $p = 0.488$).

Correlation between oxidative markers and clinical parameters

No significant correlations were found between any of the oxidative markers (8-OHdG, MDA, CoQ10, 25(OH)D) and clinical parameters (IOP, visual field mean deviation, RNFL thickness) in the POAG group (all $p > 0.05$) (Supplementary Table 1). RNFL thickness showed a strong positive correlation with visual field mean deviation (rho = 0.878, $p < 0.001$), confirming structure-function concordance (Supplementary Table 2).

Multivariate regression analysis

Age- and sex-adjusted linear regression models (Table 2) were constructed. POAG status remained independently associated with significantly lower CoQ10 levels ($\beta = –9.55$, $p < 0.001$). For 25(OH)D, POAG status was associated with

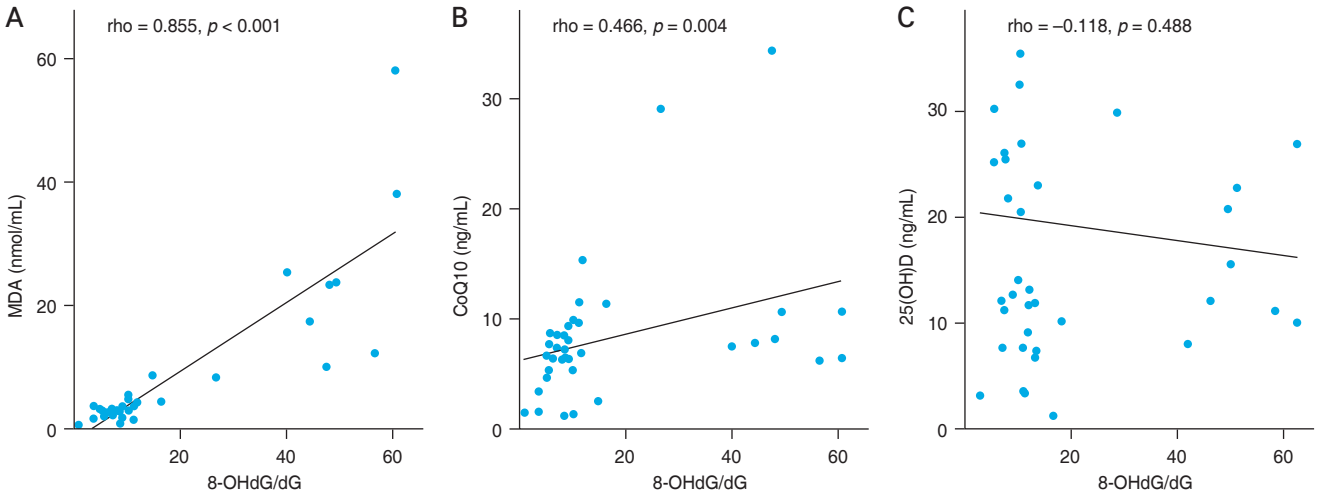

Fig. 2. Correlation analyses between oxidative stress markers in the primary open-angle glaucoma group. (A) Strong positive correlation between malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels (rho = 0.855, $p < 0.001$). (B) Moderate positive correlation between coenzyme Q10 (CoQ10) and 8-OHdG levels (rho = 0.466, $p = 0.004$). (C) No significant correlation between 25-hydroxyvitamin D (25(OH)D) and 8-OHdG levels (rho = –0.118, $p = 0.488$).

Table 2. Multivariate linear regression analysis of CoQ10 and 25(OH)D levels adjusted for age and sex

Variable	CoQ10 model		25(OH)D model	
	β (SE)	*p*-value	β (SE)	*p*-value
Intercept	15.03 (5.59)	0.009	26.45 (6.16)	<0.001
POAG (vs. control)	–9.55 (2.51)	<0.001	–5.37 (2.76)	0.056
Female (vs. male)	2.86 (2.56)	0.267	–3.65 (2.82)	0.199
Age (yr)	0.02 (0.09)	0.832	–0.02 (0.10)	0.844
Model R^2/adjusted R^2	0.179 / 0.143	-	0.120 / 0.081	-
Model *p*-value	0.004	-	0.033	-

CoQ10 = coenzyme Q10; 25(OH)D = 25-hydroxyvitamin D; SE = standard error; POAG = primary open-angle glaucoma.

lower levels with borderline statistical significance after adjustment (β = –5.37, $p = 0.056$). Age and sex were not significant independent predictors in the final models.

Discussion

This study demonstrates a distinct systemic oxidative stress profile in POAG patients, characterized by elevated oxidative damage markers (8-OHdG, MDA) and reduced antioxidant/neuroprotective factors (CoQ10, 25(OH)D). Our findings support the involvement of oxidative stress in glaucomatous neurodegeneration while providing insights into interrelationships among oxidative pathways.

The elevation in 8-OHdG and MDA levels aligns with previous reports of increased oxidative DNA damage and lipid peroxidation in glaucoma [11–13]. The strong correlation between MDA and 8-OHdG underscores a concurrent assault on lipids and DNA. The systemic elevation suggests oxidative stress in glaucoma may extend beyond ocular tissues.

The reduction in CoQ10 levels is noteworthy given its role in mitochondrial function and antioxidant defense. The observed moderate positive correlation between CoQ10 and 8-OHdG in our POAG group is intriguing; while counterintuitive, it may reflect a compensatory up-regulation or shared regulatory pathways in a state of high oxidative burden. This warrants further investigation.

Although vitamin D is not a classic antioxidant, we included it due to its recognized neuroprotective, anti-inflammatory, and indirect antioxidant properties [14]. Its reduction in our POAG patients adds to the evidence linking

vitamin D insufficiency to glaucoma [15,16]. The lack of direct correlation with oxidative damage markers suggests its role in glaucoma may be mediated through other pathways, such as immunomodulation or direct neuroprotection.

A key finding was the absence of significant correlations between systemic oxidative/antioxidant markers and clinical measures of glaucoma severity (IOP, mean deviation, RNFL thickness). This contrasts with some studies [17], but aligns with others [18]. This dissociation suggests that the measured systemic oxidative imbalance may represent a generalized susceptibility factor or a parallel systemic manifestation of POAG, rather than a direct driver of focal retinal ganglion cell loss. It may be more relevant to disease initiation or systemic comorbidities than to tracking cross-sectional severity.

Our study has several limitations. First, its cross-sectional design precludes causal inference. Second, we did not collect data on potential confounders like body mass index, detailed smoking history, dietary habits, sunlight exposure, or precise disease duration, which may influence oxidative stress levels. Third, our cohort consisted exclusively of high-tension POAG patients, limiting generalizability to normal-tension glaucoma. Fourth, the observed sex imbalance, though adjusted for statistically, remains a demographic difference. Finally, we measured systemic rather than local (aqueous humor or retinal) levels of these markers.

Despite these limitations, our findings highlight a systemic oxidative burden in POAG. This supports the rationale for investigating systemic antioxidant strategies as potential adjuncts in glaucoma management, as suggested by some trials [19,20], though more robust evidence is needed.

Future longitudinal studies measuring both systemic and local markers, in conjunction with genetic and lifestyle data, are needed to clarify the temporal relationship and clinical utility of oxidative stress biomarkers in glaucoma.

In conclusion, our study demonstrates a distinct systemic profile of increased oxidative damage and reduced antioxidant capacity in patients with POAG. The unexpected positive correlation between CoQ10 and 8-OHdG suggests a potential compensatory relationship in a state of high oxidative burden, warranting further mechanistic investigation. While this systemic imbalance did not correlate with cross-sectional clinical measures of disease severity, its presence supports oxidative stress as a critical systemic contributor to POAG pathophysiology. These markers may be more indicative of a systemic susceptibility state rather than tools for assessing current structural or functional severity. Further longitudinal studies are needed to explore the temporal dynamics and clarify the clinical utility of these biomarkers, including their potential role in disease stratification and monitoring.

Conflicts of Interest: None.
Acknowledgements: None.
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Supplementary Materials

Supplementary Table 1. Shapiro-Wilk test results for normality assessment of the study variables
Supplementary Table 2. Spearman correlation analysis between serum biochemical markers and clinical parameters in the primary open-angle glaucoma group (n = 37)
Supplementary materials are available from https://doi.org/10.3341/kjo.2025.0130

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Supplementary Table 1. Shapiro-Wilk test results for normality assessment of the study variables

Variable	Group	Shapiro-Wilk statistic	df	*p*-value
Age (yr)	Control	0.981	35	0.776
	POAG	0.978	37	0.675
8-OHdG (ng/mL)	Control	0.669	35	<0.001
	POAG	0.599	37	<0.001
MDA (nmol/mL)	Control	0.600	35	<0.001
	POAG	0.412	37	<0.001
CoQ10 (ng/mL)	Control	0.588	35	<0.001
	POAG	0.509	37	<0.001
25(OH)D (ng/mL)	Control	0.818	35	<0.001
	POAG	0.914	37	0.043
IOP (mmHg)	Control	0.965	35	0.314
	POAG	0.934	37	0.031
Visual field MD (dB)	Control	0.977	35	0.645
	POAG	0.987	37	0.935
RNFL thickness (μm)	Control	0.984	35	0.871
	POAG	0.977	37	0.615

df = degrees of freedom; POAG = primary open-angle glaucoma; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; MDA = malondialdehyde; CoQ10 = coenzyme Q10; 25(OH)D = 25-hydroxyvitamin D; IOP = intraocular pressure; MD = mean deviation; RNFL = retinal nerve fiber layer.

Supplementary Table 2. Spearman correlation analysis between serum biochemical markers and clinical parameters in the primary open-angle glaucoma group (n = 37)

Biochemical marker	RNFL thickness		IOP		Visual field MD	
	Spearman rho	*p*-value	Spearman rho	*p*-value	Spearman rho	*p*-value
8-OHdG	–0.303	0.069	0.207	0.219	–0.243	0.148
MDA	–0.307	0.065	0.208	0.216	–0.255	0.128
CoQ10	–0.045	0.790	0.118	0.488	–0.079	0.642
25(OH)D	–0.052	0.760	0.122	0.472	–0.124	0.464

RNFL = retinal nerve fiber layer; IOP = intraocular pressure; MD = mean deviation; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; MDA = malondialdehyde; CoQ10 = coenzyme Q10; 25(OH)D = 25-hydroxyvitamin D.