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Review

# DIFFERENCES BETWEEN AQUEOUS HUMOR AND SERUM CONCENTRATIONS OF BDNF AND PPARG GENETIC VARIANTS IN GLAUCOMA PATIENTS

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SUMMARY – Brain-derived neurotrophic factor (BDNF) is essential for neuronal development, differentiation and survival, and aberrant BDNF expression in retina is associated with glaucoma. Peroxisome proliferator-activated receptor gamma (PPAR-γ) in retinal pigment epithelium plays a significant role in ocular pathophysiology. *PPARG* c.34C>G (rs1801282) (p.Pro12Ala) modulates transcriptional activity. This study aimed to determine whether BDNF in aqueous humor and serum could be used as a biomarker for primary open angle glaucoma (POAG) and to examine differences between *PPARG* genotype and BDNF concentrations in aqueous humor and serum in POAG patients. The study included 140 POAG patients and 87 non-glaucoma controls. BDNF concentrations were measured by ELISA methods and *PPARG* genotype was determined by PCR-RFLP. BDNF concentrations in aqueous humor were significantly higher in POAG patients compared to controls (p=0.001). A significant difference in aqueous humor BDNF concentration was observed between early and moderate (p=0.008) and early and advanced stages of POAG (p=0.022). There was no significant difference between BDNF concentration in aqueous humor and PPARG genotype in POAG patients (p=0.184). BDNF in aqueous humor may serve as a dynamic biomarker for POAG. No significant differences were found between *PPARG* genotypes and BDNF concentrations.

Key words: *Glaucoma; POAG; BDNF; Aqueous humor; Serum, PPARG genotype*

## Introduction

Glaucoma is a chronic progressive optic neuropathy associated with apoptotic loss of retinal ganglion cells (RGCs) and gradual degeneration of the optic nerve fibers resulting in a characteristic pattern of visual field loss[1]. Primary open angle glaucoma (POAG) is the most common type of glaucoma.

Many studies have been conducted to understand the pathophysiology of glaucoma. Among promising theories is one based on neurotrophins. One of the most extensively studied neurotrophic factors is the brain-derived neurotrophic factor (BDNF), crucial for synaptic and structural plasticity. Unique BDNF

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functions in neuronal development, differentiation, and survival in the developing and adult nervous system have been recognized. The neuroprotective role of BDNF is achieved directly through the tropomyosin receptor kinase B (TrkB) expressed in RGCs, and/or indirectly through TrkB expressed in glia. BDNF is also produced by the amacrine cells in the retina and can be transported retrogradely *via* axons to the retina from the brain[2-4]. BDNF deficiency may be a trigger for RGC apoptosis. By promoting survival of RGCs, BDNF plays a neuroprotective role and can therefore serve as a biomarker in neurodegenerative diseases such as glaucoma, as well as a therapeutic tool in glaucoma management[4,5].

Reduced serum and aqueous humor BDNF concentrations were found in people suffering from glaucoma[2,6-12]. Aberrant BDNF expression and the underlying signaling pathways in the visual system could have an important, even key role in the pathophysiology of glaucoma[5].

Peroxisome proliferator-activated receptor gamma (PPAR-γ) was also found important in ocular pathophysiology[13]. It belongs to the nuclear receptor superfamily with important function in the control of gene expression linked to a variety of physiological processes and neurodegenerative conditions[14,15]. Apart from being most widely expressed in adipose tissue, it is also expressed in inflammatory cells (e.g., macrophages, monocytes), gastrointestinal tract, skeletal muscle, heart, kidney, liver, lung, and eye[13,16,17]. In the eye, it is expressed in retinal pigment epithelium, and it mediates various pathologic processes in the eye such as glaucoma, diabetic retinopathy, choroidal neovascularization, diabetic macular edema, and other retinal diseases.

Ligands bind PPAR-gamma and promote downstream gene target transcription[18]. The *PPARG* c.34C>G (rs1801282), substitution of proline to alanine in codon 12 (p.Pro12Ala) was found to be relevant for modulation of transcriptional activity. The Ala variant reduces affinity for the response element in target genes, resulting in less effective stimulation of target genes[19]. Consequently, *PPARG* variants may be associated with structural and functional changes increasing the risk of glaucoma progression.

Considering the still incompletely elucidated mechanisms in the pathophysiology of glaucoma, the search for relevant molecular and biochemical biomarkers can contribute to better understanding of the processes leading to RGC death in glaucoma. Moreover, discovery of reliable biomarkers could serve in early detection of pathologic changes and could be a target for glaucoma therapy. The *PPARG* gene variant c.34C>G (p.Pro12Ala) and BDNF may be an important therapeutic biochemical and genetic biomarker for glaucoma.

The aim of this study was to determine whether BDNF in aqueous humor and serum could be used as a biomarker for POAG and to examine differences in *PPARG* genotype and BDNF protein concentrations between aqueous humor and serum in POAG patients.

## Patients and Methods

This cross-sectional study included 227 subjects aged 45-80 years from the Glaucoma Referral Center, Ministry of Health of the Republic of Croatia, Department of Ophthalmology, Sestre milosrdnice University Hospital Center. The study was conducted between 2019 and 2022. Subjects were divided into two groups of patients with POAG and non-glaucoma patients with cataract as controls. Ethical approval for this study was obtained from the Sestre milosrdnice University Hospital Center Ethics Committee (EP-2823-14) and Ethics Committee of the School of Medicine, University of Zagreb (EP-10106-23-111/120). The study was conducted in accordance with the Declaration of Helsinki, with written informed consent obtained from all participants. Glaucoma patients underwent trabeculectomy with mitomycin, while control group with cataract underwent phacoemulsification. A thorough examination including gonioscopy, IOP measuring, and lens status was conducted. Additionally, glaucoma patients performed both Octopus perimetry (Haag-Streit International, Koeniz, Switzerland) and optical coherence tomography (RTVue XR Avanti, Optovue Inc., Freemont, CA, USA) and were graded into glaucoma stages according to the Hoddap Parish Anderson (HPA) classification. Inclusion criteria were age over 45 years, confirmed diagnosis of glaucoma according to the European Glaucoma Society (EGS) guidelines with clear crystalline lens or cataract, and informed consent form

signed by the patient[20]. Exclusion criteria were hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infection, any malignant disease, diabetes, past stroke or brain injury, and any neurodegenerative disease. Non-inclusion criteria were any history of ocular or adnexal surgery, presence of other ocular diseases, and positive family history of glaucoma. These criteria were established to minimize the potential confounding factors, as various ocular conditions are known to alter the inflammatory status of the eye and can influence BDNF concentrations, thereby potentially affecting retinal ganglion cell function independently of glaucoma.

In this study, serum and aqueous humor concentration of BDNF and *PPARG* genotype were investigated in 140 glaucoma patients with different stages of POAG. Blood samples for BDNF determination were obtained from peripheral vein before surgery (trabeculectomy or phacoemulsification) and collected in 3.5-mL tubes with serum separator clot activator (Greiner Bio-One International GmbH, Kremsmünster, Austria). The samples were centrifuged for 10 min at 10,000 xg. The serum samples obtained were divided into plastic tubes (1.5 mL; Kartell, Noviglio, Italy) and stored immediately at -80 °C until determination of BDNF concentration. Aqueous humor samples (100-200 μL) were collected from the anterior chamber of the eye at the beginning of surgical procedures and immediately stored at -80°C. Enzyme-linked immunosorbent assay (ELISA) was performed within one year, and the stability of BDNF was not investigated.

Concentrations of BDNF in serum samples and aqueous humor were analyzed by ELISA (R&D, Minneapolis, USA; Aviscera Bioscience, California, USA) according to the manufacturers' instructions. Detection range of the ELISA kits used in this study was 23.4-1500 pg/mL and 1.25-125 pg/mL.

Standard curve was obtained from standards of known concentrations. Blood samples for genotyping analysis were collected in tubes with EDTA anticoagulant (Becton, Dickinson and Company, USA). Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood leukocytes using the standard salting-out method[21].

Since PPAR-γ can be involved in the modulation of BDNF expression, the association between BDNF concentrations and *PPARG* genotypes in glaucoma patients was investigated in this study. DNA samples were analyzed for *PPARG* c.34C>G gene variants[22]. *PPARG* genotyping was performed with standard polymerase chain reaction (PCR) followed by digestion with restriction enzyme BstUI.

The PCR mix was performed in a final volume of 25 μL and contained 200 ng of genomic DNA, 1 U of Taq DNA polymerase (Roche, Switzerland), 2.5 μL of 10X PCR buffer with 15 mM $MgCl_2$ (Roche, Switzerland), 2.5 μL of 5 mM dNTP mix (Roche, Switzerland) and 1 μL of each primer (5 μM), forward 5'-GCCAATTCAAGCCCAGTC-3' and reverse 5'-GATATGTTTGCAGACAGTGTATCAGTGAAGGAATCGCTTTCC-3' (Tib MolBiol, Germany). The PCR conditions were initial denaturation at 94 °C for 10 min, followed by 30 cycles of denaturation at 94 °C for 1 min, annealing at 60 °C for 35 s, extension at 72 °C for 1 min, and final extension at 72 °C for 10 min.

Five μL of PCR products were digested with 0.5 μL of 10 U/μL restriction endonuclease BstUI (New England Biolabs, UK) and 1 μL of enzyme buffer overnight at 60 °C, then separated by electrophoresis on a 2% agarose gel stained with GelRed (Olerup SSP, Sweden) and visualized by exposing them to UV light. After digestion, the expected products were as follows: 270 bp for wildtype homozygotes (CC), 227 and 43 bp for mutated homozygotes (GG), and 270, 227, and 43 bp for heterozygotes (CG).

***Statistics***

Statistical analysis was done using JASP 0.16.4 statistical software (JASP Team, 2023). The normality of distribution was tested using the Shapiro-Wilk method, which indicated that none of the variables followed normal distribution. Descriptive statistics were presented as median and interquartile range (IQR). Consequently, nonparametric methods were employed throughout the analysis. The Kruskal-Wallis test was used to compare differences across all groups for both age and BDNF variables. When the Kruskal-Wallis test revealed statistically significant differences, Dunn's *post hoc* test with Holm correction was applied to perform pairwise comparisons. This method was selected to control Type I errors while maintaining statistical power. Statistical significance was set at $p<0.05$.

## Results

The study included 140 POAG patients and 87 non-glaucoma patients as a control group. The POAG group included 59 males, median age 68 (61-75) years, and the non-glaucoma group as control group included 30 males, median age 73 (range 67-77) years.

In two subjects, serum BDNF concentrations were not analyzed due to hemolysis of blood samples, which could affect assay accuracy. Additionally, aqueous humor BDNF concentrations were not analyzed in fifteen subjects. In these cases, either the volume of aqueous humor collected was insufficient for analysis or the BDNF concentration was below detectable range of the assay.

Clinical characteristics of the study groups and BDNF concentration are shown in Tables 1-3. There was no statistically significant difference in serum BDNF concentration between the POAG and control group (p=0.323). A statistically significant difference was found in BDNF concentration in aqueous humor between the POAG and control group (p=0.001), and in aqueous humor in POAG group between early and moderate (p=0.008) and early and advanced stage (p=0.0022).

As shown in Tables 4 and 5, there were no statistically significant differences in BDNF concentrations in aqueous humor in POAG group according to *PPARG* genotypes (p=0.065). Serum concentrations of

*Table 1. BDNF concentration in serum and aqueous humor in POAG patients and control group*

| **Analyte** | **POAG**<br>**Median (IQR), n** | **Control group**<br>**Median (IQR), n** | **p** |
|---|---|---|---|
| Age (years) | 68 (61-75), 140 | 72 (67-78), 87 | <0.001 |
| BDNF (serum, ng/mL) | 12.5 (9.9-14.9), 139 | 12.9 (9.4-16.3), 86 | 0.323 |
| BDNF (AH, pg/mL) | 4.1 (2.7-5.2), 132 | 3.2 (2.0-3.9), 80 | 0.001 |

POAG = primary open angle glaucoma; n = number; IQR = interquartile range; BDNF = brain-derived neurotrophic factor; AH = aqueous humor

*Table 2. BDNF concentration in different POAG stages*

| **Analyte** | **Early**<br>**Median (IQR), n** | **POAG stage** | | **p** |
|---|---|---|---|---|
| | | **Moderate**<br>**Median (IQR), n** | **Advanced**<br>**Median (IQR), n** | |
| Age (years) | 66 (59-75), 41 | 68 (61-74), 44 | 69 (62-75), 55 | 0.598 |
| BDNF (AH, pg/mL) | 2.6 (1.6-4.3), 41 | 4.4 (3.8-5.3), 43 | 4.3 (3.2-5.9), 55 | <0.001 |
| BDNF (serum, ng/mL) | 12.7 (10.2-15.2), 41 | 13.7 (10.7-15.6), 43 | 11.6 (9.7-14.0), 48 | 0.086 |

POAG = primary open angle glaucoma; IQR = interquartile range; n = number, BDNF = brain-derived neurotrophic factor; AH = aqueous humor

*Table 3. Post hoc Dunn analysis*

| | **POAG stage** | | |
|---|---|---|---|
| **Analyte** | **Early-moderate**<br>**p** | **Early-advanced**<br>**P** | **Moderate-advanced**<br>**p** |
| BDNF (AH, pg/mL) | 0.008 | 0.022 | 0.577 |

POAG = primary open angle glaucoma; BDNF = brain-derived neurotrophic factor; AH = aqueous humor

*Table 4. Serum and aqueous humor BDNF concentration in three genotype subgroups in control group*

| Analyte | *PPARG* c.34C>G genotype | | | p |
|---|---|---|---|---|
| | CC<br>Median (IQR), n | CG<br>Median (IQR), n | GG<br>Median (IQR), n | |
| BDNF (serum, ng/mL) | 12.9 (9.6-16.4), 63 | 12.4 (9.0-15.1), 21 | 15.7 (14.4-17.0), 2 | 0.403 |
| BDNF (AH, pg/mL) | 3.2 (2.0-4.0), 58 | 3.2 (1.6-3.4), 20 | 5.1 (4.3-6.0), 2 | 0.298 |

*PPARG* = peroxisome proliferator-activated receptor gamma; n = number; IQR = interquartile range; BDNF = brain-derived neurotrophic factor; AH = aqueous humor

*Table 5. Serum and aqueous humor BDNF concentration in three genotype subgroups in POAG group*

| Analyte | *PPARG* c.34C>G genotype | | | p |
|---|---|---|---|---|
| | CC<br>Median (IQR), n | CG<br>Median (IQR), n | GG<br>Median (IQR), n | |
| BDNF (serum, ng/mL) | 12.5 (10.0-14.8), 105 | 12.1 (9.6-15.4), 29 | 12.1 (10.5-14.2), 3 | 0.995 |
| BDNF (AH, pg/mL) | 4.0 (2.4-4.8), 100 | 3.5 (2.7-5.3), 26 | 10.1 (7.1-10.3), 3 | 0.184 |

*PPARG* = peroxisome proliferator-activated receptor gamma; n = number; IQR = interquartile range; BDNF = brain-derived neurotrophic factor; AH = aqueous humor

*Table 6. Frequency of PPARG genotypes in POAG and control group*

| Group | PPARG genotype | | |
|---|---|---|---|
| | CC (%), n | CG (%), n | GG (%), n |
| POAG | 76.6, 105 | 21.2, 29 | 2.2, 3 |
| Control group | 72.4, 63 | 25.3, 22 | 2.3, 2 |

*PPARG* = peroxisome proliferator-activated receptor gamma; POAG = primary open angle glaucoma; n = number; CC, GG, GC = genotypes

BDNF were not statistically different among *PPARG* genotype groups in POAG group (p=0.995).

The PPARG gene CC, CG, GG frequency was 76.6%, 21.2% and 2.2% in the POAG group, and 72.4%, 25.3% and 2.3% in the control group, respectively (Table 6).

## Discussion

This study explored the concentrations of BDNF between POAG patients and controls, and differences in BDNF concentrations among POAG stages, as well as the potential influence of PPARG c.34C>G genotype on BDNF concentrations in both serum and aqueous humor. Most studies published so far explored BDNF concentration in serum but only a few of them also examined BDNF in aqueous humor in patients with POAG[6-9,12]. In contrast to previously published studies, our study found significantly higher concentrations of BDNF in aqueous humor in POAG patients than in control group. This could be due to a combination of factors such as differences in patient characteristics (age, ethnicity and comorbidities), sample size or disease stage. In POAG, retinal ganglion cells undergo stress and degeneration, which may lead to altered BDNF secretion as a compensatory response. Since BDNF plays a role in synaptic plasticity and neuronal repair, its increased concentration could be a response to neurodegeneration and an attempt to

preserve retinal ganglion cells. It is important to note that BDNF concentrations in aqueous humor exhibit significant variability, and the exact concentration of BDNF remains undetermined[9]. There is a lack of standardized protocols for sample collection, storage, and timeframe for performing analysis. Variations in the methods used to measure BDNF may have led to differences in the results obtained and published so far.

In the POAG subgroups, the lowest concentrations of BDNF in aqueous humor were found in early glaucomatous optic neuropathy, and higher in moderate and advanced stages of glaucoma. These results were consistent with those reported by Shpak *et al.*[8]. Possible explanation is that BDNF deficiency might be one of the factors that initiate the glaucoma process while a relative increase in BDNF concentration in the next stages of the disease may be a compensatory/neuroprotective response[8].

The statistically significant difference in BDNF concentration in aqueous humor between POAG patients and controls observed in this study may have important clinical implications. Although overall BDNF concentrations were higher in the POAG group compared to controls, stratifying patients by disease stage revealed a more complex pattern, i.e., BDNF concentrations were significantly lower in early-stage POAG, even falling below those recorded in the control group, and concentrations progressively increased in moderate and advanced stages. This suggests a potential stage-dependent role of BDNF, where initial depletion may reflect early neurodegenerative changes, followed by a compensatory upregulation in later stages as part of an intrinsic neuroprotective response. These findings support the potential utility of BDNF as a dynamic biomarker for glaucoma progression, with possible applications in early detection, disease staging, and personalized treatment strategies. Our findings showed no significant difference in serum BDNF concentrations between POAG group and control group. This suggests that circulating serum BDNF may not be a reliable marker for POAG diagnosis or progression. In both study groups, serum BDNF concentration was significantly higher compared to aqueous humor (ng *vs.* pg), which is consistent with findings from earlier research[6-8]. This difference can be attributed to the widespread expression of BDNF in neurons, as well as various other cells in the body, including those in the retina, trabecular meshwork, and platelets[8]. The difference in BDNF concentration between serum and aqueous humor indicates that BDNF is not transported from the bloodstream into the eye but is rather produced in the eye[8].

The possible role of the *PPARG* c.34C>G variant and BDNF was examined in this study. There is a lack of literature data, and only several experimental and clinical studies have published results on the relevance of *PPARG* variability in ocular pathologic processes and treatment response[13,16,23]. A limitation of this study was the unknown stability of BDNF protein before analysis, and a small number of samples of PPARG GG genotype frequency. This study did not find significant difference between PPARG genotypes and BDNF concentrations in either POAG patients or controls; however, the difference observed in aqueous humor approached statistical significance in POAG group, suggesting the necessity of further studies on a larger cohort. To our knowledge, this was the first study to investigate the difference between the *PPARG* genotype and BNDF protein concentration in aqueous humor and serum in glaucoma patients, therefore we could not compare and evaluate our results.

The findings in this study suggest that biomarkers BDNF and PPARG should be further investigated in different ethnic groups and on a larger number of people to understand the relationship between BDNF concentration, PPARG genotype, and pathogenesis of glaucoma.

Our study demonstrated a statistically significant difference in BDNF concentrations in the aqueous humor between POAG patients and healthy controls, with higher levels observed in the overall POAG group. However, significant differences were observed among glaucoma patients in different stages of the disease. This stage-dependent pattern suggests that BDNF may serve as a dynamic biomarker of glaucoma, reflecting both early neurodegenerative changes and later compensatory responses. Notably, the reduction in BDNF observed in early-stage POAG may indicate glaucomatous changes even before structural or functional damage becomes clinically detectable, underscoring its potential value for early diagnosis and timely intervention. As such, monitoring BDNF concentrations in aqueous humor could provide valuable insights into disease progression and potentially guide

treatment strategies. Although routine aqueous humor sampling is currently limited to intraoperative settings, the observed relationship between BDNF levels and glaucoma stages lays the groundwork for future exploration of less invasive sampling methods, and potentially, for BDNF-modulating therapies aimed at neuroprotection. Therefore, the significant difference in aqueous humor BDNF concentrations between POAG patients and controls is not only statistically relevant, but is also clinically meaningful**,** providing valuable insight into glaucoma pathophysiology and opportunities for improved patient management. Also, this study did not find significant differences between *PPARG* genotypes and BDNF concentrations.

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Sažetak

## RAZLIKE IZMEĐU KONCENTRACIJA BDNF-A U OČNOJ VODICI I SERUMU I PPARG GENETSKIH VARIJANATA KOD BOLESNIKA S GLAUKOMOM

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Moždani neurotrofni faktor (BDNF) ključan je za razvoj, diferencijaciju i preživljavanje neurona, a nepravilna ekspresija BDNF-a u mrežnici povezana je s glaukomom. Receptor za aktivator proliferacije tip gama (PPAR-γ) u retinskom pigmentnom epitelu ima značajnu ulogu u očnoj patofiziologiji. PPARG c.34C>G (rs1801282) (p.Pro12Ala) modulira transkripcijsku aktivnost. Cilj ovog istraživanja bio je utvrditi može li BDNF u očnoj vodici i serumu poslužiti kao biomarker za primarni glaukom otvorenog kuta (POAG) te ispitati razlike između genotipa PPARG i koncentracije BDNF u očnoj vodici i serumu kod bolesnika s POAG-om. U istraživanje je uključeno 140 bolesnika s POAG-om i 87 ispitanika u kontrolnoj skupini bez glaukoma. BDNF je određen ELISA-om, a genotip PPARG PCR-RFLP-om. Koncentracija BDNF-a u očnoj vodici kod bolesnika s POAG-om bila je značajno viša nego u kontrolnoj skupini (p=0,001). Pronađena je značajna razlika u koncentraciji BDNF-a u očnoj vodici između ranog i umjerenog (p=0,008) te između ranog i uznapredovalog stadija POAG-a (p=0,022). Nije bilo značajne razlike između koncentracije BDNF-a u očnoj vodici i genotipa PPARG kod bolesnika s POAG-om (p=0,184). BDNF može poslužiti kao dinamički biomarker za POAG. Nije bilo značajne razlike između genotipova PPARG i koncentracija BDNF-a.

Ključne riječi: *Glaukom; POAG; BDNF; Očna vodica; Serum; genotip PPARG*