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Arterial Hypertension and Diabetes Mellitus in the Pathogenesis of Primary Open-Angle Glaucoma: A Balkan Perspective

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primary open angle glaucoma, risk factors, diabetes, arterial hypertension, glaucoma screening

Purpose. *To identify specific risk factors and protective factors to inform tailored screening and management strategies for high-risk individuals.*
Methods. *This case-control study included a total of 800 eyes from 400 individuals, comprising 200 pairs of eyes diagnosed with primary open-angle glaucoma (POAG) and 200 glaucoma-free (the control group). Data were collected through structured questionnaires and comprehensive ophthalmologic examinations. Statistical analyses were performed to assess the association between POAG and systemic conditions such as diabetes and hypertension, as well as various sociodemographic factors.*
Results. *Systolic arterial hypertension was identified as a risk factor ($p<0.05$), while diastolic hypertension showed a protective effect ($p<0.05$). Contrary to expectations, diabetes mellitus was not statistically associated with an increased risk of POAG ($p>0.05$).*
Conclusion. *The results emphasize the importance of arterial hypertension in the pathogenesis of POAG. The lack of significant association with diabetes in this cohort may be due to population-specific factors, such as genetic background or lifestyle. These findings support the need for tailored screening programs targeting individuals with risk factors.*
This study highlights the complex interaction of systemic diseases in the development of POAG. While arterial hypertension is confirmed risk factor, diabetes did not play a significant role in this cohort. Early detection through targeted screening of high-risk groups could improve the management and outcomes of glaucoma patients.

Introduction. Primary open-angle glaucoma (POAG) is a chronic and progressive optic nerve disease and one of the major causes of irreversible vision impairment worldwide. Open-angle glaucoma is a disease evidenced by optic neuropathy with a progressive loss of peripheral visual field. It is marked by optic nerve damage, usually associated with elevated intraocular pressure (IOP), that gradually leads to vision loss. POAG is typically asymptomatic, often going unnoticed until significant vision loss has occurred, posing a serious threat to eyesight [1].

Identification and management of POAG are particularly challenging because of its complexity. While high IOP is a known risk factor, it is certainly not the only factor contributing to disease progression. Systemic conditions such as diabetes mellitus (DM) and high blood pressure are also believed to increase the risk of developing POAG. This interplay of eye-specific and systemic health factors highlights the need to understand their impact on POAG's development [2].

Glaucoma, often referred to as "slow thief of vision", is significant in terms of quality of life, making it a substantial public health concern. Many people seek medical care only after losing up to 60% of their retinal nerve fibre layer (RNFL), leading to irreversible vision loss and greatly impacting the quality of life. As a chronic illness, POAG imposes a burden on healthcare systems, requiring ongoing monitoring, treatments, and, in some cases, surgery. These expenses are further increased by indirect costs, such as reduced work productivity, greater dependence on others, and the need for caregiving [3].

Diabetes mellitus, particularly type 2 diabetes (DM2), is a well-established risk factor for microvascular complications, including diabetic retinopathy. However, its relationship with POAG has been the subject of ongoing debate. Several epidemiological studies have suggested a positive association between diabetes and POAG, while others have failed to find such a link [4].

Arterial hypertension, another common systemic disease, is associated with the pathogenesis and progression of POAG. Hypertension leads to microvascular damage, impairing blood flow autoregulation to various tissues, including the optic nerve. Studies have documented the relationship between systemic blood pressure (BP) and IOP, showing that high systolic blood pressure levels are linked to elevated IOP.

Interestingly, the relationship between blood pressure and POAG appears to be more complex than a simple lin-

ear association. Some studies have proposed a ”U-shaped” relationship, where both high and low blood pressure increase the risk of POAG. The Egna-Neumarkt and Blue Mountains studies demonstrated a strong association between elevated blood pressure, ocular perfusion pressure (OPP) and POAG [5]. However, the Barbados, Proyecto Ver, and Early Manifest Glaucoma Trial (EMGT) studies did not find a connection between BP and POAG. The relationship between BP, OPP, and POAG remains controversial [6]. It also highlights the need for further research to unravel the complex interactions between systemic blood pressure, ocular perfusion, and IOP in the pathogenesis of glaucoma [7].

Purpose: to investigate the associations between systemic diseases, particularly type 2 diabetes mellitus and systemic arterial hypertension, and the development of primary open-angle glaucoma in a population from Sombor, Republic of Serbia. By identifying specific risk factors and protective factors, the study aims to inform tailored screening and management strategies for high-risk individuals.

Material and Methods

This study employs a case-control design to investigate the relationship between POAG and systemic conditions, including DM2 and arterial hypertension. The study was conducted at the Eye Department of the General Hospital “Dr. Radivoj Simonović” and aimed to explore the role of these risk factors in the progression and onset of POAG within the population. It has been approved by the Ethics Committee of the General Hospital "Dr Radivoj Simonović" Sombor, Serbia.

This study included a total of 800 eyes from 400 individuals, divided equally into two groups: 200 pair of eyes diagnosed with POAG (the case group) and 200 glaucoma-free (the control group). The sample size was determined using the G*Power 3 program, designed for estimating the statistical power of tests and the required sample size. All participants were aged 40 years or older. Individuals with other types of glaucoma, ocular conditions affecting visual fields, or secondary causes of glaucoma were excluded to maintain focus on primary open-angle glaucoma. All participants provided informed consent prior to their inclusion in the study. The study was conducted in accordance with the Helsinki Declaration.

Data collection involved a detailed medical history, clinical examination, and questionnaire to gather information on socioeconomic status and systemic diseases. Blood pressure measurements were taken for all participants using a standard sphygmomanometer, and participants were categorized based on current clinical guidelines. Additionally, diabetic status was assessed based on fasting blood sugar levels and diagnosis. Train ophthalmologists conducted ocular examinations, including visual acuity test (VA) with Snellen charts, IOP measurements using Goldmann applanation tonometry, visual field assessment with automated perimetry, and optic nerve head evaluation. Optic nerve evaluation was obtained using binocular indirect ophthalmoscopy via slit lamp biomicroscope and 66 D, 78D, 90D lens or Superfield lens. Optical coherence tomography was not used for purpose of this study.

The inclusion criteria for the study group are: individuals diagnosed with primary open-angle glaucoma, stable body weight over the past six months, participants not using medication that affects body composition, intraocular pressure (diuretics, antidepressants, anxiolytics, corticosteroids), lipid and lipoprotein status.

The exclusion criteria from the study are: individuals younger than 40 years old, corneal diseases, ocular inflammatory diseases, retinal changes (except for diabetic retinopathy), patients who have undergone any ophthalmic surgery (cataract, glaucoma, vitrectomy, etc.), patients on hemodialysis, chemotherapy, or those with severe kidney impairment (glomerular filtration rate reduced by more than 20%) and patients with type 1 diabetes.

The data were analyzed using SPSS statistical software. A binary logistic regression model and Mann-Whitney test were used to assess the relationship between POAG and the independent variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the strength of associations. Statistical significance was defined as a p-value < 0.05 (8).

Results

Sociodemographic Factors and Their Association with POAG

We examined the relationship between sociodemographic factors (age, gender, marital status, place of residence, employment status, education level, family history of glaucoma) and POAG. Distribution of sociodemographic factors is divided in two groups: patients with primary open-angle glaucoma (POAG) and healthy controls, along with statistical associations obtained through binary logistic regression analysis. The criterion variable represents group membership (0-glaucoma patients; 1-control group). Predictive variables include age, gender, marital status, place of residence, employment status, education and family history of POAG (Table 1).

Gender and Age: The distribution of males and females is similar in both groups ($p=0.388$, $B=0.221$) and it is not dependent on the age group ($p=0.286$, $B=0.021$).

Marital Status: Being divorced ($p<0.001$, $B=1.482$) or single ($p<0.001$, $B=3.782$) is more frequent among patients from the study group.

Residence: Living in urban areas is slightly more frequent among POAG patients (61% vs. 59%) but not statistically significant ($p=0.079$, $B=0.447$).

Education Level: Individuals with secondary level of education ($p<0.001$, $B=1.729$) and higher level of education ($p<0.001$, $B=1.427$) are found to be less likely to be diagnosed with glaucoma compared with primary level of education.

Employment Status: Being unemployed ($p=0.101$, $B=0.696$) or retired ($p=0.764$, $B=-0.111$) is not associated with a risk of POAG. On the other hand, farmers have

Table 1. Sociodemographic Factors and Their Association with POAG

Sociodemographic Characteristic	Study group (n, %)	Control group (n, %)
Gender		
Male	110 (55.0%)	102 (51.0%)
Female	90 (45.0%)	98 (49.0%)
Age (Male)		
45–54	17 (15.5%)	15 (14.7%)
55–64	29 (26.4%)	39 (38.2%)
65–74	45 (40.9%)	32 (31.4%)
>75	19 (17.3%)	16 (15.7%)
Age (Female)		
45–54	15 (16.7%)	30 (30.6%)
55–64	46 (51.1%)	41 (41.8%)
65–74	21 (23.3%)	21 (21.4%)
>75	8 (8.9%)	6 (6.1%)
Marital Status		
Married	151 (75.5%)	109 (54.5%)
Divorced	16 (8.0%)	22 (11.0%)
Widowed	23 (11.5%)	12 (6.0%)
Single	10 (5.0%)	12 (6.0%)
Place of Residence		
Urban	122 (61.0%)	118 (59.0%)
Rural	78 (39.0%)	82 (41.0%)
Level of Education		
Primary	57 (28.5%)	24 (12.0%)
Secondary	74 (37.0%)	127 (63.5%)
Higher	49 (24.5%)	19 (9.5%)
University	11 (5.5%)	30 (15.0%)
Incomplete Primary	9 (4.5%)	0 (0.0%)
Employment Status		
Employed	74 (37.0%)	91 (45.5%)
Unemployed	15 (7.5%)	30 (15.0%)
Retired	73 (36.5%)	71 (35.5%)
Farmer	28 (14.0%)	3 (1.5%)
Other	10 (5.0%)	5 (2.5%)
Family History		
First-degree Relative	67 (33.5%)	43 (21.5%)
Second-degree Relative	6 (3.0%)	5 (2.5%)
None	109 (54.5%)	152 (76.0%)

Note: n – number of participants, % – percentage of participants.

been more often diagnosed with POAG compared with employed individuals ($p<0.05$, B=-1.598).

Family History: Having a first-degree relative diagnosed with POAG significantly increase the risk ($p<0.001$, B=-1.164) of having POAG, supporting the role of genetic predisposition in the disease. Second-degree relatives do not show an association ($p=0.722$, B=-0.252).

These results suggest that education level, employment status, and family history play significant roles in the risk of developing POAG (Table 1).

Arterial Blood Pressure as a risk factor for POAG

To determine whether the values of arterial blood pressure influence the development of POAG, binary logistic regression was applied. The criterion variable represents group membership (0-patients with glaucoma; 1-control group). Predictor variables include systolic and diastolic blood pressure, use of antihypertensive therapy, and duration of therapy were examined. Higher systolic blood pressure ($p<0.001$, B=-0.055) and the duration of antihypertensive therapy ($p=0.041$, B=-0.098) were associated with the occurrence of POAG, while subjects with higher diastolic blood pressure were less likely to develop glaucoma ($p<0.001$, B=0.055) (Table 2).

Ocular Perfusion Pressure as a Risk Factor for POAG

To compare the values of systolic (SOPP) and diastolic ocular perfusion pressure (DOPP) between the control group and the group of glaucoma patients, the Mann-Whitney test was applied. The group of affected patients showed higher scores on SOPP, while the control group had higher scores on DOPP (Table 3).

Glycoregulation as a Risk Factor for POAG

To determine the impact of glycoregulation on the onset of POAG, we investigated blood sugar levels (BSL), glycated hemoglobin (HbA1C), the presence of DM2, the duration of type 2 diabetes therapy, and the type of DM treatment. Diabetes was not a risk factor for the onset of POAG ($p>0.05$, B=1.609), and this relationship was independent of the duration of DM ($p>0.05$, B=-0.013). Neither insulin therapy ($p>0.05$, B=0.589), tablets ($p>0.05$, B=0.754), nor diet ($p>0.05$, B=-0.816) was associated with the development of glaucoma (Table 4).

Table 2. Relationship Between Systemic Arterial Blood Pressure and POAG

Variable	B	p-value
Systolic BP	-0.055	0.000
Diastolic BP	0.055	0.000
Medication	0.718	0.052
Duration of therapy	-0.098	0.041

Note: B – standardized regression coefficient; p – statistical significance; model significant at $p<0.05$.

Table 3. Relationship between OPP and the onset of POAG

OPP	S	K	MR Affected	MR Control	Z-test	p-value
SOPP	1.76	5.76	227.46	173.54	-4.67	0.000
DOPP	1.24	7.47	179.65	221.36	-3.61	0.000

Note: MR – mean rank; Z – Mann-Whitney statistical test; p – statistical significance; model significant at p<0.05.

Table 4. Relationship between Type 2 Diabetes Mellitus and the onset of POAG

Variable	B	p-value
DM2	1.609	0.054
Duration of therapy	-0.013	0.824
DM therapy:		
Diet: none	-0.816	0.544
Tablets: none	0.754	0.504
Insulin: none	0.589	0.587

Note: B – standardized regression coefficient; p – statistical significance, model significant at p<0.05.

Table 5. Relationships between glycoregulation predictors and POAG

Variable	Odds ratio	Confidence Interval (LCI and UCI)	p-value
Diabetes (< 10 years duration)	3.100	0.358 - 26.846	0.304
Diabetes (> 10 years duration)	3.331	0.282 - 39.402	0.340
HbA1C (> 47.5 mmol/mol)	8.337	3.510 - 19.801	0.000
BSL (> 7 mmol/l)	0.333	0.100 - 1.112	0.074

Note: LCI – lower confidence interval; UCI – upper confidence interval; p-statistical significance; model significant at p< 0.05.

The association between glaucoma and diabetes therapy duration of more than 10 years was specifically examined. It was not found that therapy lasting more than 10 years had an impact on the onset of POAG (p>0.05, OR=3.100). Additionally, the treatment duration shorter than 10 years was not associated with the onset of glaucoma (p>0.05, OR=3.100). HbA1C values above 47.5 mmol/mol were positively associated with the onset of POAG (p<0.001, OR=8.337). BSL was not associated with the onset of glaucoma (p>0.05, OR=0.337) (Table 5).

Discussion

In our study, we investigated whether arterial blood pressure values influence the onset of POAG. The effects of systolic blood pressure, diastolic blood pressure, antihypertensive therapy, and the duration of therapy were specifically examined. Higher systolic blood pressure (p<0.001) and the duration of antihypertensive therapy (p<0.05) were positively associated with the development of POAG. Subjects with higher diastolic pressure were less likely to develop glaucoma (p<0.001).

It is known that systemic hypertension causes microvascular changes, leading to atherosclerotic changes and alterations in the autoregulatory vascular system. On the other hand, hypotension reduces local perfusion and leads to ischemic changes. Literature provides contradictory data; for instance, the Rotterdam and Beaver Dam studies indicate that systemic hypertension is a risk factor for glaucoma development, whereas the Barbados Eye Study does not find this association. Some studies, such as the Latino Eye and Blue Mountains studies, describe a "U-shaped" relationship where both high and low blood pressure are associated with the onset of POAG [9-13].

A parameter known as ocular perfusion pressure was introduced to better explain the relationship between BP and glaucoma progression. OPP represents the difference between systolic blood pressure (SBP) or diastolic blood pressure (DBP) and IOP. OPP is the pressure that drives blood through intraocular vascular structures, delivering oxygen and nutrients to the optic nerve head. The perfusion is opposed by resistance to flow and the vascular structure's resistance. Studies such as the Singapore Malay, Los Angeles Latino, Barbados, EMGT and Egna-Neumarkt studies report a significant relationship between low OPP values and an increased risk of POAG. On the other hand, the Beijing study did not find a relationship between OPP and the onset of glaucoma [14, 15].

In our study, we examined the influence of systolic and diastolic ocular perfusion pressure on the occurrence of glaucoma. It was found that SOPP was higher in people with POAG compared to the control group, while DOPP was lower in those affected by POAG. This suggests that changes in SOPP (Z=-4.67; p<0.05) and DOPP (p<0.05, Z=-3.61) influence the vascular perfusion of the optic nerve head and contribute to the development of glaucoma.

According to the results of our study, diabetes mellitus is not a risk factor for the onset of POAG (p>0.05), and this relationship is independent of the duration of diabetes (p>0.05) or diabetes therapy. HbA1C values above 47.5 mmol/mol (>6.5%) were positively associated with the onset of POAG (p<0.001). According to the European Glaucoma Society (EGS), diabetes is considered a con-

troversial factor in the onset of POAG. Several studies have found a positive association between diabetes and glaucoma, and this relationship is explained by mechanical and vascular effects. However, there are studies that refute this influence or even suggest that diabetes may be a protective factor in the onset of POAG. They explain their stance by frequent ophthalmologist visits among diabetic patients and non-glaucomatous changes in the optic nerve [16, 17].

Diabetes causes microvascular changes and affects the vascular autoregulation of the retina and optic nerve. Vascular changes reduce blood flow and lead to ischemia. Oxygen is essential for the proper functioning of cells; however, this also leads to reactive oxygen species (ROS) formation. Thus, oxygen has a dual nature; it is essential, but at the same time, it is toxic. The balance between oxidative processes and antioxidant capacity maintains the stability and functioning of living cells. If this balance is disrupted due to increased ROS production, decreased antioxidant protection, or both, oxidative stress occurs. Such changes, combined with hyperglycemia, insulin resistance, glycation end products, and specific lipid and lipoprotein disorders, lead to endothelial dysfunction. Atherosclerosis in diabetic patients is a complex interaction of various factors, but the initial lesion occurs at the endothelial cell level. An intact epithelium maintains a dynamic balance of relaxation and contraction factors, ensuring optimal vessel diameter and tissue perfusion [2, 18]. The endothelium releases numerous substances, some of which act as vasodilators, such as nitric oxide (NO) and acetylcholine. Angiotensin II has a vasoconstrictive effect, while the most well-known growth factor is vascular endothelial growth factor (VEGF). This plays a role in the vascular theory of glaucoma onset.

The mechanical theory posits that in chronic hyperglycemia, glucose is converted to sorbitol. This process reduces levels of NADPH (nicotinamide adenine dinucleotide phosphate), a cofactor for endothelial nitric oxide synthase (eNOS), which is essential for regenerating antioxidant molecules. Since sorbitol cannot easily cross cell membranes, it accumulates, leading to osmotic stress and increased water retention. This accumulation can result in elevated intraocular pressure [17-20]. IOP in individuals with diabetes is typically only a few millimetres of mercury (mmHg) higher than in non-diabetic individuals. However, even such modest increases can accelerate and exacerbate optic nerve damage. Studies attribute this to the impact of elevated IOP on vascular ischemia, reduced perfusion of the optic nerve head, mechanical compression of the lamina cribrosa, and decreased axoplasmic transport [4, 21]. Due to microcirculation disturbances, the optic nerve becomes significantly more susceptible, so even slight increases in IOP can cause changes not observed in the healthy population. Additionally, sorbitol in the aqueous humour exerts an osmotic effect, leading to fluid accumulation and retention in the eye's chambers. Over time, the accumulated fluid mechanically damages the eye's sensitive structures. All these changes in diabetic patients lead to microvascular damage, particularly in the blood vessels of the kidneys, retina and nerves. Given that approximately 71% of individuals with diabetes also have elevated blood pressure, it is assumed that this additionally increases the risk of POAG [2, 22].

To conclude, primary aim of this study is to raise public awareness about the risk factors associated with primary open-angle glaucoma, emphasizing the importance of regular eye examinations, especially among at-risk populations. Early detection and intervention are essential due to the absence of any early symptoms and because the condition is insidious. Various factors are involved regarding the late presentation of POAG. The approach to cope with the POAG burden needs to be multilevel. First, public awareness must be raised about risk factors for glaucoma. Public health campaigns on systemic diseases like type 2 diabetes mellitus and systemic arterial hypertension playing a pinnacle role in the development of POAG may encourage more towards early screening. Second, advances in novel screening technologies and a valid, cost-effective screening test for POAG would revolutionise the early detection of the disease.

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Abbreviation. *POAG – primary open angle glaucoma, VA – visual acuity, IOP – intraocular pressure, RNFL – retinal nerve fibre layer, BP – blood pressure, DM – diabetes mellitus, DM2 – type 2 diabetes mellitus, OPP – ocular perfusion pressure, OR – odds ratio, CI – confidence interval, LCI – lower confidence interval, UCI – upper confidence interval, SBP – systolic blood pressure, DBP – diastolic blood pressure, SOBP – systolic ocular perfusion pressure, DOPP – diastolic ocular perfusion pressure, NHS – National Health Service, BSL – blood sugar level, HbA1C – glycated hemoglobin, EGS – European Glaucoma Study, EMGT – Early Manifest Glaucoma Trial, ROS – reactive oxygen species, NO – nitric oxide, NADPH – nicotinamide adenine dinucleotide phosphate, VEGF – vascular endothelial growth factor, eNOS – endothelial nitric oxide synthase, AGEs – advanced glycation end products, B – standardized regression coefficient, p – statistical significance, MR – mean rank, , Z – Mann-Whitney statistical test*