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PREVALENCE OF PRIMARY GLAUCOMA AND OCULAR HYPERTENSION AMONG THE POPULATION WITH DIABETES MELLITUS IN SOUTHERN SERBIA: A CROSS-SECTIONAL EPIDEMIOLOGICAL STUDY

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Glaucoma is considered one of the most common causes of irreversible loss of vision. Diabetes mellitus (DM) is a known risk factor associated with glaucoma and the development of glaucomatous optic neuropathy. The aim of this study was to examine the prevalence of ocular hypertension (OHT) and primary glaucoma (defined as primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) combined) in patients with DM, as well as possible differences in prevalence according to gender. The research was conducted as cross-sectional epidemiological study, included 1703 patients, of different ages from 40 to 86 years. After an ophthalmological assessment and meticulous patient history-taking, we included the patients with a previously established diagnosis of DM and the place of residence in Southern Serbia in the territory of the Nišava, Jablanica and Pčinja districts. Statistical analysis revealed the total prevalence of primary glaucoma was 8.98%, the prevalence of OHT was 12.98%. A statistically significant difference in the prevalence of PACG

between genders was determined ($p<0.001$). Compared to male, female subjects had 6.47 times higher chances of suffering from PACG (OR=6.47; $p<0.001$). For POAG, no statistically significant difference in prevalence between genders was observed ($p<0.001$). Although women are 1.34 times more likely to develop POAG, the difference did not reach statistical significance (OR=1.34; $p=0.138$). The evidence from our study indicates that DM is a risk factor for the development of glaucoma and point out the importance of more frequent ophthalmological examinations and glaucoma screening among the diabetic population.

Key words: prevalence, primary open-angle glaucoma, primary angle-closure glaucoma, ocular hypertension, diabetes mellitus

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PREVALENCIJA PRIMARNIH GLAUKOMA I OKULARNE HIPERTENZIJE MEĐU POPULACIJOM OBOLELOM OD DIJABETES MELLITUSA U JUŽNOJ SRBIJI: EPIDEMIOLOŠKA STUDIJA PRESEKA

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Glaukom se smatra jednim od najčešćih uzroka trajnog gubitka vida. Dijabetes melitus (DM) je poznati faktor rizika povezan sa glaukomom i razvojem glaukomatozne optičke neuropatije. Cilj ove studije bio je da se ispita prevalencija okularne hipertenzije (OHT) i primarnog glaukoma (definisanog kao kombinacija primarnog glaukoma otvorenog ugla (POAG) i primarnog glaukoma zatvorenog ugla (PACG)) kod pacijenata sa DM, kao i moguće razlike u prevalenciji prema polu. Istraživanje je sprovedeno kao epidemiološka studija preseka, obuhvatilo je 1703 pacijenta, različite starosti od 40 do 86 godina. Nakon oftalmološkog pregleda i detaljnog uzimanja anamneze pacijenata, uključili smo pacijente sa prethodno utvrđenom dijagnozom DM i mestom prebivališta u Južnoj Srbiji na teritoriji Nišavskog, Jablaničkog i Pčinjskog okruga. Statističkom analizom dobijena je ukupna prevalencija primarnog glaukoma 8,98%, a prevalencija OHT 12,98%. Utvrđena je statistički značajna razlika u prevalenciji PACG između polova ($p<0,001$). U poređenju sa muškarcima, ženske osobe su imale 6,47 puta veće šanse da obole od PACG (OR=6,47; $p<0,001$). Za POAG nije uočena statistički

značajna razlika u prevalenciji između polova (p<0,001). Iako je kod žena 1,34 puta veća verovatnoća da će razviti POAG, razlika nije dostigla statističku značajnost (OR=1,34; p=0,138). Dokazi iz naše studije ukazuju da je DM faktor rizika za razvoj glaukoma i ističu važnost češćih oftalmoloških pregleda i skrininga za glaukom među dijabetičarskom populacijom.

Ključne reči: prevalencija, primarni glaukom otvorenog ugla, primarni glaukom zatvorenog ugla, očna hipertenzija, dijabetes melitus

Introduction

Glaucoma is considered one of the most common causes of irreversible loss of vision. (1) Additionally, it is characterized by an optic neuropathy with damage and a decrease in the number of ganglion cells of the retina and their axons in the optic nerve, manifested as visual field (VF) loss and a slow but irreversible loss of vision if not treated. (2,3) The prevalence of glaucoma is estimated to be circa 3.5 % in population between 40 and 80 years of age, with increasing trend over time. In 2014, it amounted to 64.3 million, with an estimated increase to 76.0 million in 2020 and even 111.8 million people by 2040. (4, 5)

Diabetes mellitus (DM) is a known risk factor associated with glaucoma and the development of glaucomatous optic neuropathy, which predominantly affects optic disc and the anterior chamber angle. (6) Numerous studies have been conducted on the prevalence of glaucoma in individuals with DM, and the prevalence ranged from 4.96% to 14.6%. (7,8) According to official data from the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut", it is estimated that approximately 600,000 people or 8.1% of the population is affected by DM in Serbia in 2023. Diabetes mellitus type II (T2DM) is much more prevalent in the population (95%) compared to diabetes mellitus type I (T1DM). (9) As reported by the research of the International Diabetes Federation Diabetes Atlas, an increase in the number of people affected by DM in the world is expected, it is estimated that the global prevalence of DM in 2019 is 9.3% (463 million people), then they predict an increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. (10)

The impact of DM on the level of the optic nerve develops through damage to the mircovasculature of the retina and the optic disc, which disturbs their normal function and makes them more sensitive to damage caused by increased intraocular pressure (IOP). (6,11) In certain cases, long-term elevated blood glucose levels may precipitate damage to the iridocorneal angle, more specifically in the trabecular meshwork and consequently disrupt the normal flow of the aqueous humor and increase the risk of primary open-angle glaucoma (POAG). (12)

Although extensive research on this topic have been carried out in the world, in our country there are limited data on the prevalence of glaucoma in people with DM. The aim of this study was to examine the prevalence of ocular hypertension (OHT) and primary glaucoma (defined as POAG and primary angle-closure glaucoma (PACG) combined) in patients with DM, as well as possible

differences in prevalence according to gender, among the population in the territory of Southern Serbia.

Materials and Methods

This cross-sectional epidemiological study was conducted in the period from June 2023 to June 2024. The research included 1703 patients, of different ages from 40 to 86 years, of which 868 were men and 835 were women. In our study, the criteria for the inclusion of the participants were a previously established diagnosis of DM and the place of residence of the participants in Southern Serbia in the territory of the Nišava, Jablanica and Pčinja districts. Comparison of the association between primary glaucoma and the non-diabetic population was not included in our study.

Patient demographic data, clinical characteristics of DM (T1DM and T2DM) and duration of therapy for the underlying disease were collected by taking anamnestic data from the participants. Ophthalmological examination consisted of visual acuity examination according to Snellen, examination of the anterior segment of the eye using a biomicroscope, measurement of IOP with Goldman applanation tonometry, direct and indirect ophthalmoscopy. In the case of participants suspected of having glaucoma based on the ophthalmological examination, additional analyzes were performed in the form of a tonometric curve, optical coherence tomography (OCT) recording of the optic nerve head, VF testing and gonioscopy to confirm or rule out the diagnosis of glaucoma.

Statistical analysis

Statistical data analysis was performed using SPSS software package, SPSS 22.0 (SPSS Inc, Chicago, USA). The following descriptive statistical methods were used: absolute numbers, arithmetic mean, range, frequency, percentages, confidence interval (95% CI). The prevalence of glaucoma in people with DM was calculated, and variables associated with glaucoma were evaluated. The chi-square (χ^2) test with Yates continuity correction was used to examine the difference in the prevalence of ocular conditions (primary glaucoma and OHT) between genders. Yates correction was applied to 2x2 contingency tables. A p-value level of statistical significance beneath 0.001 is considered significant.

To assess the association between gender and the prevalence of a specific type of glaucoma, odds ratios with corresponding 95% confidence intervals (CI) were also calculated, with a statistically significant p-value of $p < 0.05$.

Results

Our study included 1703 participants with DM of various ages, ranging from 40 to 86 years old, average age of 63 years. The structure of respondents by gender consisted of 868 (51%) men and 835 (49%) women.

All participants in our study have been previously diagnosed with DM, among them 221 (12.98%) is affected by OHT, 111 (6.52%) suffer from POAG, 42 (2.46%) from PACG, while 1329 participants are not affected by any form of elevated IOP (Table 1).

The total prevalence of primary glaucoma in our sample was 8.98% (95% CI: 7.6–10.3), whereas the prevalence of OHT in the same sample was 12.98% (95% CI: 11.4–14.6) (Table 2).

Within our female patient population, the prevalence of primary glaucoma and OHT was higher than in the male population from our group and amounted to 7.43% (95% CI: 5.6–9.2) for POAG, 4.31% (95% CI: 2.9–5.7) for PACG and 18.80% (95% CI: 16.2–21.5) for OHT (Table 3).

A statistically significant difference in the prevalence of PACG between genders was determined by using the Chi-square test ($\chi^2 = 23.19$, $df = 1$, $p < 0.001$). This difference also remains significant after applying Yates' correction for continuity ($\chi^2 = 21.71$, $df = 1$, $p < 0.001$). Compared to male subjects, female subjects had 6.47 times higher chances of suffering from PACG (OR = 6.47; 95% CI: 2.7–15.4; $p < 0.001$). It is also noted a statistically significant difference in the prevalence of OHT between genders after administering the Chi-square test ($\chi^2 = 49.23$, $df = 1$, $p < 0.001$), also this difference remains significant even after applying Yates' correction for continuity ($\chi^2 = 48.22$, $df = 1$, $p < 0.001$). While for POAG, no statistically significant difference in prevalence between genders was observed even after applying the Chi-square test with Yates' continuity correction ($\chi^2 = 14.52$, $df = 1$, $p < 0.001$) (Table 3). Although women are 1.34 times more likely to develop POAG, the difference did not reach statistical significance (OR = 1.34; 95% CI: 0.91–1.97; $p = 0.138$).

Table 1. Demographic characteristics of the examined patients

Variable	Diabetic patients with ocular hypertension (OHT)	Diabetic patients with primary open-angle glaucoma (POAG)	Diabetic patients with primary angle-closure glaucoma (PACG)	Diabetic patients without OHT and glaucoma	Total number of patients
	Number (Percentage)	Number (Percentage)	Number (Percentage)	Number (Percentage)	Number (Percentage)
Gender					
Male	64 (3.76%)	49 (2.88%)	6 (0.35%)	749 (43.98%)	868 (50.97%)
Female	157 (9.22%)	62 (3.64%)	36 (2.11%)	580 (34.06%)	835 (49.03%)
Total number of patients	221 (12.98%)	111 (6.52%)	42 (2.46%)	1329 (78.04%)	1703 (100%)
Age range of all participants (Years)	40-86				

Table 2. The total prevalence of ocular hypertension (OHT), primary glaucoma, primary open-angle glaucoma (POAG) or primary angle-closure glaucoma (PACG)

Ocular condition	Total number of patients	Total prevalence (%)	95% CI †
OHT	221	12.98	11.4–14.6
Primary glaucoma	153	8.98	7.6–10.3
POAG	111	6.52	5.35–7-7
PACG	42	2.47	1.7–3.2

† CI – Confidence Interval

Table 3. The prevalence by gender of ocular hypertension (OHT), primary glaucoma, primary open-angle glaucoma (POAG) or primary angle-closure glaucoma (PACG)

Ocular condition	Prevalence male (%)	95% CI†	Prevalence female (%)	95% CI†	χ^2 ‡	*p	χ^2‡ with Yates continuity	*p

							correctio n	
OHT	7.37	5.6–9.1	18.80	16.2–21.5	49.2273	**<0.001**	48.2205	**<0.001**
Primary glaucoma	6.34	4.7–7.9	11.74	9.6–13.9	15.1777	**<0.001**	14.5244	**<0.001**
POAG	5.65	4.1-7.2	7.43	5.6-9.2	2.213	0.137	1.9305	0.165
PACG	0.69	0.14-1.24	4.31	2.9-5.7	23.1873	**<0.001**	21.7068	**<0.001**

† CI – Confidence Interval, ‡ Chi-square with Yates continuity correction,*p – level of statistical significance (obtained by the chi-square test)

Discussion

Both glaucoma and DM are multifactorial and highly prevalent diseases. Glaucoma is considered the second leading cause of vision loss (4), while DM is considered the fifth predominant cause of moderate to severe vision loss. (13) The total prevalence of glaucoma among diabetics in our study was 8.98% (95% CI: 7.6–10.3), where the total prevalence of POAG amounted to 6.52% (95%-CI: 5.35–7-7) and PACG 2.47% (95%-CI: 1.7–3.2).

Dharmadhikari et al also included only subjects with DM in their study, compared to our research they obtained a higher prevalence of glaucoma 15.6% (95% CI: 13.1-18.1) and the prevalence of POAG 7.8%, which can be attributed to the difference in the age of the population which is older in their research. (14) The Singapore Malay Eye Study from 2009 showed the total prevalence of glaucoma among diabetic participants was 4.7%, and for POAG 3.3%, which are lower prevalences in comparison to our study. (15) Both studies included only diabetic patients of a similar age rang, also a complete ophthalmological examination was performed, with gonioscopy and VF testing, while our study additionally included OCT examination of the optic nerve head. This difference in prevalence is possible due to the time period of conducting the research, as well as newer diagnostic procedures

compared to studies from an earlier period, which allow the detection of glaucoma in earlier stages of the disease . (16)

In comparison with the study by Tham et al, which shows a lower prevalence in the general population, including both diabetic and non-diabetic patients, the prevalence of POAG in Europe was 2.51% (95% CI, 1.54–3.89), the prevalence of PACG was 0.42% (95% CI, 0.13–0.98), and glaucoma (POAG and PACG combined) 2.93% (95% CI, 1.85–4.40). This discrepancy may be attributed to the difference in the specificity of the sample between these two studies, all of our subjects are diabetics and DM has already been described as a risk factor for glaucoma, and therefore a higher prevalence in our sample is expected in comparison to the prevalence in the general population. Also, our results are slightly higher compared to the estimated prevalence for the general population aged 40–80 years in Europe in 2020. The prevalence of POAG was 5.67 (95% CI, 4.21–7.51), and the prevalence of PACG was 1.46 (95% CI, 0.45–3.49), and glaucoma (POAG and PACG combined) 7.12 (95% CI, 5.20–9.68). (5) Another potential explanation of higher prevalence of glaucoma in diabetics might be that patients with DM are more often referred for ophthalmological examinations compared to the general population, because it is already recognized that DM is a risk factor for a spectrum of eye diseases. And that more frequent visits to the ophthalmologist contribute to more frequent diagnoses and therefore to a higher prevalence of glaucoma in diabetics. (17)

Our results provide insight into the existence of a significant statistical association between female gender and the prevalence of PACG ($\chi^2 = 21.71$, df = 1, $p < 0.001$). Female subjects are 6.47 times more likely to suffer from PACG than males (OR = 6.47; 95% CI: 2.71–15.44; $p < 0.001$). Similar data have been found in other studies that indicate a higher prevalence of PACG in women. (5) Data obtained in this study are consistent with several meta-analysis. Which shows that PACG is more common in women, examined in a sample of the general population. (18, 19) The occurrence of angle-closure glaucoma in women is determined by the anatomical structure of the eye. In women, the eyes are slightly smaller and shorter than in men, and thus the anterior chamber is shallower and the chamber angle is narrower, which reduces the flow of aqueous humor. (20) This is confirmed by numerous studies that have noted a shallower anterior chamber and a narrower chamber angle in females. (21, 22, 23) Additionally, the difference in the hormonal status between genders is highlighted as significant cause for the more frequent occurrence of glaucoma in women, with focus on the importance of changes in the level of exogenous and endogenous estrogen in women. (20)

Although in the current study a trend of higher prevalence of POAG was observed in women, no statistically significant difference was found (OR = 1.34; 95% CI: 0.91–1.97; p < 0.001). Jiangnan et al also found no statistically significant difference in POAG prevalence between genders (P = 0.13). In contrast to our findings, a meta-analysis by Tham et al showed that men were at a higher risk of developing POAG than women (OR, 1.36; 95% CrI, 1.23–1.52). (5) Also, Zhang et al in their meta-analysis found that men are at a higher risk of POAG than women (RR 1.28, 95% CI 1.12 ~ 1.45, p < 0.01), and suggest that the exact reason for this is uncertain, but that the greater axial length of the eye and the deeper anterior chamber in males may be the reason. (24, 25) The existence of this trend deserves additional studies that could be conducted on a larger number of respondents.

There are several hypotheses about the relation and influence of DM on the development and progression of glaucoma. It has been reported in the literature that changes occur at the level of the microvasculature of the optic disc, then in the structure of the chamber angle of the anterior chamber, as well the influence of oxidative stress and the genetic connection between DM and glaucoma are also discussed.

Microvascular changes in the blood vessels of the optic nerve lead to reduced perfusion of the optic disc and retina and consequently lead to damage to the optic nerve itself and a loss of vision, and progression of glaucoma occurs. (26, 27)

In people with DM, an elevated level of glucose in the blood is accompanied by an increase in the level of glucose in the aqueous humor, this can cause increased production and deposition of fibronectin in the trabecular meshwork, which results in the reduction of the cells of the trabecular meshwork and disruption of the normal outflow of aqueous humor through the anterior chamber angle, contributing to the development of POAG. (12)

One of the hypotheses about the impact of DM on the development of glaucomatous changes in the optic nerve is influence on retinal ganglion cells metabolism. As a probable risk factor for the development of POAG, DM may act by contributing to additional vulnerability and apoptosis of retinal ganglion cells whose function is already compromised by elevated IOP. (11)

Wang et al found a significant genetic correlation between T2DM and POAG, and indicated that due to shared genetic mechanisms, metabolic disorders in T2DM patients may have an impact on the development of neurodegenerative changes in the optic nerve. (28)

The connection between glaucoma and DM was examined in several meta-analyses, which came to the conclusion that people with DM have increased risk of developing glaucoma. (17, 29, 30, 31) Therefore, it is necessary to point out that regular ophthalmological examinations and regular glaucoma screening are necessary for patients with DM. (17)

Conclusion

In conclusion, our observations contribute to epidemiological data in the field of glaucoma occurrence in diabetics in our region. The evidence from our study indicates that DM is a risk factor for the development of glaucoma. This epidemiological study point out the importance of more frequent ophthalmological examinations and glaucoma screening among the diabetic population, and highlights the significance of early detection of glaucoma in patients with DM for timely treatment and prevention of disease progression.

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