The role of lipid dysregulation and vascular risk factors in glaucomatous retrobulbar circulation

Monika Modrzejewska[1], Wilhelm Grzesiak[2], Daniel Zaborski[2*], Anna Modrzejewska[3]

[1]Department of Ophthalmology, Pomeranian Medical University, Szczecin, Poland, [2]Laboratory of Biostatistics, West Pomeranian University of Technology, Szczecin, Poland, [3]Department of Ophthalmology, Pomeranian Medical University Hospital, Szczecin, Poland

ABSTRACT

The aim of this study was to evaluate selected lipid-related and vascular factors and their effect on retrobulbar hemodynamics in glaucoma. Fifty-six patients with primary open-angle glaucoma (POAG) [POAG group; mean age 68.32 years (SD±0.21)] and 54 patients in control group [CG, mean age 68.1 years (SD±5.34)] were examined. Peak systolic velocity, end-diastolic velocity, mean velocity, pulsatility index, and resistive index of the ophthalmic artery, the central retinal artery, and the posterior ciliary arteries were measured by Color Doppler Imaging. Selected lipid-related, systemic and local vascular parameters were evaluated. Statistical methods included Shapiro-Wilk, Student-t and Mann-Whitney U tests, and Spearman rank correlations. In POAG group systolic arterial blood pressure, diastolic arterial blood pressure, total cholesterol, low-density lipoprotein cholesterol (LDL-ch), and intraocular pressure were significantly higher; while ocular perfusion pressure, high-density lipoprotein cholesterol (HDL-ch) and diastolic ocular perfusion pressure were significantly lower ($p \leq 0.05$). Color Doppler Imaging confirmed blood flow abnormalities in all investigated arteries. In addition, significant correlations of HDL-ch, LDL-ch and triglycerides (TG) with peak systolic velocity, end-diastolic velocity and mean velocity were found in individual arteries ($p \leq 0.05$). Also, significant associations of systolic arterial blood pressure, ocular perfusion pressure, systolic ocular perfusion pressure and diastolic ocular perfusion pressure with peak systolic velocity, end-diastolic velocity, mean velocity and resistive index were revealed in the posterior ciliary arteries ($p \leq 0.05$). Dysregulation of lipid-related and vascular factors, as well as statistical correlation between the above and retrobulbar blood flow indices, might imply their role in vasoconstrictive processes during glaucomatous endotheliopathy.

KEY WORDS: Primary open angle glaucoma; retrobulbar circulation; color Doppler imaging; vascular and lipid-related risk factors; ocular hemodynamics

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INTRODUCTION

Alterations of both retrobulbar hemodynamics and autoregulatory mechanisms are well-documented risk factors for primary open-angle glaucoma (POAG) as early as at the initial onset of the disease [1–4]. Many researchers are involved to identify the causes of glaucoma, other than intraocular pressure. Fluctuations in retrobulbar blood flow, intraocular pressure and ocular perfusion pressure accompanied by the changes in blood composition and viscosity. In addition, variations in diastolic arterial blood pressure, may play a crucial role in POAG pathogenesis [1–3,5]. Glaucoma may be associated with lipid dysregulation expressed not only as peripheral arterial disease, but also as ocular vascular pathology [6–8].

*Corresponding author: Daniel Zaborski, PhD
Laboratory of Biostatistics, West Pomeranian University of Technology, Doktora Judyma 10, 71-460 Szczecin, Poland, Phone: +48914496813, Fax: +48914496800, E-mail: daniel.zaborski@zut.edu.pl

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Prolonged disturbances to plasma lipids may lead to degenerative changes in the retinal and choroidal arterioles, venules, and capillaries, which may result in early ischemic retino-neural angiopathy [9,10]. A consequence of this process is hypoperfusion, causing microcirculation disorders related to ganglion cells, which may provoke permanent visual disturbances [4]. Changes in the inner diameter of the retinal arteries and veins result in altered blood flow velocity and vascular resistance indices in the retrobulbar arteries. So far, only a few studies emphasized the fact that lipid-related risk factors, apart from vascular ones, may affect the alteration of retrobulbar circulation in glaucoma. The above factors, together with the blood flow velocities and vascular resistance parameters measured by Color Doppler Imaging (CDI) might be considered as prognostic indicators of the disease development [4,11–13].

The aim of this study was to investigate the association of selected lipid and vascular parameters with retrobulbar blood flow velocities and resistance indices in the ophthalmic artery (OA), the central retinal artery (CRA) and the posterior ciliary

arteries (PCA): nasal (NPCA) and temporal (TPCA), in the POAG patients.

MATERIALS AND METHODS

Study population

CDI of the retrobulbar arteries was performed in glaucoma patients and healthy volunteers, who agreed to participate in the study. The study was in accordance with the Declaration of Helsinki for research involving human subjects. An informed consent was received from all the patients and healthy subjects, and the study was approved by the University Ethics Committee (approval no. F147/08). Two study groups were identified for comparison: a group of 56 patients with POAG [POAG group; 56 examined eyeballs; age range 60-72 years; mean age 68.32 years (SD±0.21)] and a control group comprising healthy individuals [CG; 54 subjects, 54 examined eyeballs, age range 59-74 years; mean age 68.1 years (SD±5.34)]. All the participants were age and gender matched.

Exclusion criteria for controls included: cardiovascular and carotid or vertebral artery diseases, hypertension, diabetes, proliferative diabetic retinopathy, smoking, alcohol consumption, ophthalmic disease with high refractive myopia, optical disorders, ocular trauma or use of any general medications as well as estrogen replacement therapy in women [14]. Moreover, prior to CDI, each subject was requested to abstain from caffeine, intense exercise and consumption of large meals.

The POAG group, treated with anti-glaucomatous beta-blocker topical drops, consisted of patients in whom chronic POAG [mean duration of the disease 8.34 years (SD±2.31)] was confirmed by the results of a detailed ophthalmologic examination involving: typical glaucomatous optic neuropathy changes in indirect ophthalmoscopy and GDX (scanning laser polarimeter, Carl Zeiss AG, Germany), visual field lesions in threshold static automated perimetry and intraocular pressure elevation in applanation tonometry. Moreover, atheromatic plaques in the internal carotid arteries in CDI were seen in all the studied patients, but they did not affect hemodynamic blood flow.

Ophthalmic and physical examinations

The ophthalmic examination included the best-corrected visual acuity (Snellen Letter Chart), anterior segment slit lamp and indirect ophthalmoscopic fundus examinations (Volk glass 90D and XL, USA), gonioscopy and Goldmann applanation for intraocular pressure.

Data on mean arterial blood pressure, measured in a supine position before CDI examination, were collected directly from the subjects. The ranges between ≤ 120 mmHg and ≤ 80 mmHg (for systolic and diastolic arterial blood pressure, respectively) were considered normal. Vascular markers, such as systolic and diastolic systemic arterial blood pressure, ocular perfusion pressures, systolic and diastolic ocular perfusion pressure, were estimated according to the formulae [15]:

$$OPP = 2/3\ [ABPd + (ABPs - ABPd)/3] - IOP \quad (1)$$

$$OPPs = ABPs - IOP \quad (2)$$

$$OPPd = ABPd - IOP \quad (3)$$

where: OPP – ocular perfusion pressure; OPPs – systolic ocular perfusion pressure; OPPd – diastolic ocular perfusion pressure; ABPs – systolic arterial blood pressure; ABPd – diastolic arterial blood pressure; IOP – intraocular pressure.

Biochemical analyses

Selected plasma lipids levels: total cholesterol, HDL-ch, LDL-ch, and triglycerides were established using Roche kits and Clinilab automatic analyzer (bioMerieux, Craponne, France). The following reference values were used: total cholesterol ≤180 mg/dl, HDL-ch≥45–75 mg/dl, LDL-ch ≤65–100 mg/dl, triglycerides ≤150 mg/dl.

Imaging analyses

CDI of the OA, CRA, NPCA and TPCA was performed using Voluson 730 PRO, GE Medical Systems device (Milwaukee, WI, USA), with a multi-frequency 7.5-MHz linear probe. Each measurement was calculated three times for each vessel and averaged, maintaining a constant Doppler angle of about 30° in the CRA and both NPCA and TPCA, and 60° in the OA. The examinations were performed by the same experienced investigator, who automatically and, later on, manually, identified the peak, trough and velocity waveform according to the technique proposed by Harris ***et al.*** [16], in accordance with the guidelines recommended in the literature [16,17].

The following parameters were evaluated: peak systolic velocity (cm/s), end-diastolic velocity (cm/s), mean velocity (cm/s), pulsatility index, and vascular resistance index. The highest velocity value achieved during the cardiac systole was defined as peak systolic velocity and was calculated from the frequency of the peak in the Doppler-shifted waveform. End-diastolic velocity was described as the minimum velocity occurring during the diastole and was recorded as the frequency of the trough in the Doppler-shifted waveform. The pulsatility index, also referred to as the Gosling index, was defined as the ratio of the difference between the systolic and diastolic velocity to the mean blood flow velocity. Pourcelot's vascular resistance index was defined as the ratio of the difference between the systolic and diastolic velocity to the systolic blood flow velocity.

Statistical analysis

Calculations were performed on the logarithmically transformed data, except for the mean and standard deviation of the original data, which are presented in the descriptive analysis. The Shapiro-Wilk, Student-t and Mann-Whitney U tests were applied using Statistica 10 software (StatSoft, Inc., Tulsa, OK, USA). Statistical significance of the differences between the mean values of the analyzed blood flow velocity parameters was determined. In addition, statistical correlations of the vascular and lipid-related risk factors with blood flow velocity parameters were calculated. Due to the variability of the measurements and, consequently, a significant departure from the normal distribution, the Spearman rank correlation test was employed to estimate the relationships between the parameters. Statistical significance was considered at $p \leq 0.05$.

RESULTS

In glaucoma patients, the best-corrected visual acuity with full optical correction (Snellen Letter Chart) was 0.65 (SD±0.28), whereas it was 0.98 (SD±0.12) in healthy individuals. Intraocular pressure was elevated and differed markedly from that in the controls. Arterial blood pressure (systolic and diastolic) was significantly higher in the POAG group (Table 1), whereas ocular perfusion pressure and diastolic ocular perfusion pressure were significantly lower. Total cholesterol and LDL-ch were markedly elevated in the POAG group, while HDL-ch was significantly lower in comparison with CG group. Triglycerides concentration remained within the normal ranges.

In POAG group, CDI confirmed blood flow abnormalities in all the investigated arteries (OA, CRA and PCAs), with significantly lower blood flow velocities (except for peak systolic velocity in the OA) and increased resistance indices (except for resistance index in the OA), as compared with CG (Table 2).

Statistically significant and negative moderate correlations between vascular factors and ocular blood flow velocity parameters were found only in the TPCA and NPCA. These included the correlations of peak systolic velocity, end-diastolic velocity, mean velocity and resistance index with arterial blood pressures (correlation coefficients ranging from r=-0.58 to r=-0.47 for the TPCA and from r =-0.46 to r=-0.27 for the NPCA) and those of peak systolic velocity and mean velocity with ocular perfusion pressure (r=-0.31 and r=-0.35, respectively, for the TPCA and r=-0.29 and r=-0.33, respectively, for the NPCA). Moreover, peak systolic velocity, end-diastolic velocity, mean velocity and resistance index were correlated with systolic ocular perfusion pressure (correlation coefficients ranging between r=-0.58 and r=-0.41 for the TPCA and between r=-0.41 and r=-0.28 for the NPCA) and diastolic ocular perfusion pressure (except for resistance index in the NPCA, correlation coefficients ranging from r=-0.58 to r=-0.47 for the TPCA and from r=-0.48 to r=-0.26 for the NPCA).

Statistically significant low to moderate correlations were also observed between lipid-related factors and ocular blood flow velocity parameters in the OA, CRA, TPCA, and NPCA. These included the correlations of peak systolic velocity with HDL-ch (r=0.40), as well as peak systolic velocity

TABLE 1. Comparisons of values of arterial blood pressure, ocular perfusion pressure, intraocular pressure and plasma lipid profile in glaucoma patients (POAG, n=56) and controls (CG, n=54)

Parameter	POAG		CG		*p*-value
	Mean	SD	Mean	SD	
ABPs (mmHg)	130.71	12.01	116.21	7.32	0.000
ABPd (mmHg)	84.42	6.86	79.16	4.19	0.000
OPP (mmHg)	40.62	5.95	55.11	2.22	0.000
OPPs (mmHg)	114.83	13.21	103.28	6.44	0.065
OPPd (mmHg)	60.05	7.39	61.33	3.45	0.049
IOP (mmHg)	20.02	4.11	16.13	1.25	0.000
TCH (mg/dl)	200.17	22.09	165.15	44.95	0.000
LDL-ch (mg/dl)	133.12	30.14	83.22	26.45	0.000
HDL-ch (mg/dl)	38.29	4.07	44.12	14.26	0.004
TG (mg/dl)	110.41	50.97	97.86	24.39	0.104

SD: Standard deviation; TCH: Total cholesterol; LDL-ch: Low density lipoprotein fraction cholesterol; HDL-ch: High density lipoprotein fraction cholesterol; TG: Triglycerides, ABPs: Systolic arterial blood pressure, ABPd: Diastolic arterial blood pressure; OPP: Ocular perfusion pressure; OPPs: Systolic ocular perfusion pressure; OPPd: Diastolic ocular perfusion pressure; IOP: Intraocular pressure

TABLE 2. Comparisons of values of systolic velocity, end-diastolic velocity, mean velocity, pulsatility and resistance indices in the retrobulbar arteries in glaucoma patients (POAG, n=56) and controls (CG, n=54)

Arteries	Parameter	POAG		CG		*p*-value
		Mean	SD	Mean	SD	
OA	PSV	49.44	5.31	50.27	5.46	0.420
	EDV	13.83	2.06	17.03	3.52	0.000
	MV	21.90	3.17	23.11	3.03	0.043
	PI	1.79	0.37	1.58	0.33	0.002
	RI	0.75	0.14	0.70	0.04	0.051
CRA	PSV	7.26	1.54	12.63	3.53	0.000
	EDV	1.89	0.56	5.26	2.14	0.000
	MV	4.05	1.00	7.54	2.22	0.000
	PI	1.71	0.21	1.63	0.16	0.027
	RI	0.78	0.04	0.60	0.03	0.000
TPCA	PSV	9.43	1.92	17.03	3.86	0.000
	EDV	2.46	0.76	6.41	2.55	0.000
	MV	4.95	1.20	9.67	2.40	0.000
	PI	1.74	0.21	1.40	0.25	0.000
	RI	0.74	0.03	0.60	0.04	0.000
NPCA	PSV	8.98	1.69	17.01	3.17	0.000
	EDV	2.45	0.71	6.32	2.30	0.000
	MV	4.71	1.31	9.59	2.34	0.000
	PI	1.69	0.14	1.41	0.26	0.001
	RI	0.74	0.03	0.59	0.04	0.000

SD: Standard deviation; PSV (cm/s): Peak systolic velocity; EDV (cm/s): End-diastolic velocity; MV (cm/s): Mean velocity; PI: Pulsatility index; RI: Resistance index; OA: The ophthalmic artery, CRA: The central retinal artery, TPCA: The temporal posterior ciliary artery, NPCA: The nasal posterior ciliary artery

and end-diastolic velocity with LDL-ch (r=-0.47 and r=-0.42, respectively) in the OA. Moreover, peak systolic velocity was correlated with HDL-ch, LDL-ch and triglycerides (correlation coefficients ranging between r=-0.37 and r=0.30) in the CRA, while peak systolic velocity and mean velocity were associated with HDL-ch (r=0.31 and r=0.31, respectively) and LDL-ch (r=-0.38 and r=-0.25, respectively) in the TPCA. Finally, peak systolic velocity and mean velocity were also correlated with HDL-ch (r=0.29 and r=0.29, respectively) and LDL-ch (r=-0.34 and r=-0.25) in the NPCA.

DISCUSSION

Atherosclerosis is hardly ever taken into account as a risk factor for glaucoma incidence [18–20]. Damage to the vessel wall (hypertension, bacterial toxins, atherogenic lipoproteins aggregation) and uncontrolled smooth muscle cell proliferation facilitate the process of atherosclerotic plaque formation. Reduced level of endothelial substances exhibiting a relaxing activity is also worth mentioning [21–23]. The aforementioned risk factors, including also genetic predisposition to low HDL-ch (<35 mg/dl), as well as free radical oxidation of LDL-ch and lipoprotein Lp(a) fractions, hyperbetalipoproteinemia, homocystinuria, oxidative modification of LDL-ch, together with the so-called uninhibited stimulated inflammatory response of leukocytes/endothelial cells, induce the cascade of atherosclerotic processes [2,3,10,23–25]. Apart from lipid-related factors, the role of disturbances in the level of vasodilatory nitric oxide (NO) and vasoconstrictive endothelin-1 (ET-1) agents affecting the retino-choroidal microcirculation is emphasized in the literature. The results of decreased NO and increased ET-1 levels in glaucoma patients have been widely described [18,22,26–31].

In this study, the importance of vascular factors such as decreasing ocular perfusion pressure, instability of blood pressure and lipid profile alterations were shown in glaucoma. It is known that glaucomatous ischemia and hemodynamic dysregulation might be caused ***e.g.*** by the lack of NO/ET-1 balance, being a response to endotheliopathy [32,33]. Moreover, the agents above are also involved in the apoptosis of glaucomatous retinal ganglion cells and dysregulation of aqueous outflow through the trabecular meshwork [28,29,34]. Experimental studies indicated that a local production of ET-1 can be stimulated by oxidized LDL (Ox-LDL), the compound indicative of hypercholesterolemia, which may intensify vasoconstrictive stimulation of ciliary arteries [32,34–38].

The outcomes of the present study emphasize the role of lipid dysregulation in the phenomenon mentioned above. It was confirmed by a significant increase in some lipids, especially total cholesterol and LDL-ch, and a decrease in HDL-ch level (with reference to laboratory standards) in contrast to triglycerides, which did not demonstrate any significant alterations (Table 1). Moreover, statistically significant correlations of LDL-ch with peak systolic velocity and end-diastolic velocity in the OA may partially confirm our previously formulated hypothesis. The study has proved that the effect of atherosclerotic factors on the ocular circulation disturbances in glaucoma cannot be excluded.

In the studied glaucoma group, significantly decreased blood flow velocities were also associated with higher blood pressure. This may confirm the hypothesis that the disturbances of retrobulbar circulation may appear as a response to systemic pressure alteration, conceivably occurring as a vascular spasm or vasoconstrictive hypersensitivity [33,39]. Such a relationship was shown by Jonas ***et al.*** [40], Rader ***et al.*** [41], and Kerr ***et al.*** [42] in the region of peripapillary retinal vessels.

It should be mentioned that a statistically significant decrease in blood flow velocities in all the retrobulbar glaucomatous arteries has been confirmed by Doppler measurements in many studies [4,9–13,43,44].

Martinez and Sanchez [4] and Galassi ***et al.*** [45], reported a six-fold higher risk of the progression of glaucomatous visual field deficiency with an end-diastolic velocity decrease and a vascular resistance increase above 0.78, in the OA. It is also known that the rise in the risk of glaucoma development to about 90.5% appears with resistance index higher than 0.72. Taken together, our study results are compliant with the above mentioned ones, indicating a rise in resistance index in the OA, CRA, and PCAs, although in the case of the OA, this increase was not statistically significant.

According to Swietliczko and David [46], similar follow-ups in healthy individuals with an experimentally increased intraocular pressure indicated hemodynamic alterations of the short posterior ciliary arteries. The results of ***in vitro*** studies by Spencer ***et al.*** [47] showed a linear increase of resistance index, provoked by a spasm involving the vessels of the smallest size, concurrent with an increase in intraocular pressure [22,43]. Similar observations were made in the present study.

The phenomenon worth mentioning and observed in the studied POAG patients was a decrease in blood flow velocity parameters accompanied by increased vascular resistance indices in the retrobulbar arteries, despite applying beta-blocker ophthalmic drops. Considering the effects of beta-blockers on lipid profiles, this suggests their subtle influence on the retrobulbar circulation [8]. Opinions on the mechanisms behind the effects of these drugs on the retino-choroidal microcirculation remain controversial. Steigerwalt ***et al.*** [48], and Grunwald ***et al.*** [25] did not report any significant differences in the retrobulbar blood flow in eyeballs with either high or normal intraocular pressure. However, Collignon and Collignon-Brach [49] described an extension of retinal vessel diameter

after 12-24 months of betaxolol therapy in comparison with placebo.

Among the vascular factors affecting blood flow in the glaucomatous optic nerve, the decreases in ocular perfusion pressure and diastolic ocular perfusion pressure have been the most often emphasized recently, especially their fall below 30 and even 50 mmHg, respectively [50,51]. These data have been confirmed in the Egna-Neumarkt study [1], Baltimore Eye Survey [51], ProYecto VER project [52] and the Barbados Incidence Study of Eye Diseases [53]. Additionally, Tielsch ***et al***. [51] reported a six-fold higher risk of glaucoma occurrence with ocular perfusion pressure <30 mmHg in relation to about 50 mmHg in healthy individuals, taking also into account significant differences in systolic and diastolic ocular perfusion pressure. According to Leske ***et al***. [53,54], diastolic ocular perfusion pressure lower than normal was associated with three times higher risk of POAG prevalence.

Choi ***et al***. [55] proved that the changes in ocular perfusion pressure induced by the circadian fluctuation of blood pressure might account for the progression index in normal tension glaucoma.

It is believed that hypertension may cause an increase in blood flow velocity in the peripapillary vessels. However, it is also acknowledged that, concurrently, a long-lasting process of maintaining excessive hypertension, changes the threshold of autoregulatory mechanisms with a consequence of their dysregulation and decrease in the retrobulbar blood flow [2,26]. An example of the above may be statistically significant correlations between systolic arterial blood pressure, systolic ocular perfusion pressure, diastolic ocular perfusion pressure and blood flow parameters in the PCAs revealed in our study.

Finally, two limitations of our work need to be discussed. Firstly, beta-blockers in our research did not have a significant effect on resistance parameters in retrobulbar vessels. Moreover, a few reports in the literature emphasize the fact that these drugs alter lipid levels in the blood serum, which needs to be confirmed by further research with relation to the ischemic origin of glaucoma. Secondly, the sample size used in our study was relatively small. Therefore, we consider that our observations on lipid dysregulation require confirmation on a larger group of glaucoma patients. With a greater number of subjects, it would also be possible to apply regression analysis, which would allow more meaningful interpretation of the relationships among lipid-related and vascular factors and retrobulbar blood flow parameters in comparison with the correlation coefficients alone. Regression equations can also be used for predictions, provided that the magnitude of the coefficient of determination be sufficiently large. Correlation analysis provides only an overview of the relations between the investigated factors and the values of correlation coefficients only suggest the existence of such associations, which should also be proved by other methods.

CONCLUSION

In summary, our preliminary observations on lipid dysregulation and the coexistence of fluctuations in blood pressure, ocular perfusion pressure, and intraocular pressure might suggest a vasoconstrictive role of the lipid-related and vascular factors in the glaucomatous endotheliopathy. This hypothesis is additionally supported by concomitant correlations between the selected lipid and vascular factors and retrobulbar blood flow velocities found in our study. Decreased blood flow velocities and increased resistance indices observed not only in the CRA (nourishing mainly retinal ganglion cells) but also in both PCAs (supplying the optic nerve axons) might indicate a significance of these parameters in the ischemic origin of glaucoma.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

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