Journal of Global Biosciences
Peer Reviewed, Refereed, Open-Access Journal
ISSN 2320-1355
Volume 10, Number 4, 2021, pp. 8497-8511
Website: www.mutagens.co.in
URL: www.mutagens.co.in/jgb/vol.10/04/100401.pdf

Research Paper

RELATIONSHIP BETWEEN OCULAR PERFUSION PRESSURE AND RESISTIVITY INDEX IN THE OPHTHALMIC ARTERY IN BOTH PRIMARY OPEN ANGLE GLAUCOMA AND NORMAL-TENSION GLAUCOMA PATIENTS AND CONTROLS IN A TERTIARY HOSPITAL IN NIGERIA

Uwah, Akaninyene Innocent[1], Elizabeth Akon Awoyesuku[2] and Emmanuel, O. Megbelayin[1]

[1]Department of Ophthalmology,
University of Uyo Teaching Hospital,
[2]Department of Ophthalmology,
University of Port Harcourt Teaching Hospital,
Rivers State,
Nigeria.

Abstract

AIM: To establish the relationship between ocular perfusion pressure and resistivity index in the ophthalmic artery in both primary open angle glaucoma and normal-tension glaucoma patients and controls in a tertiary hospital in Nigeria. **METHODS:** The study was an observational case-control study conducted between January 2019 and June 2019. One hundred and eight patients (54 glaucoma patients and 54 controls) were consecutively selected into the study. All participants underwent blood pressure measurement by using a standard mercury sphygmomanometer which was validated with a similar sphygmomanometer. Subjects were made to have at least 5 minutes of rest before the systolic and diastolic blood pressures were measured. The also had a Colour Doppler Imaging to measure resistivity index and blood flow velocity in the ophthalmic and central retinal arteries. For comparison between the two groups, all data were subjected to Student T-test. Pearson linear correlation test was performed to study the relationship between resistivity index and ocular perfusion pressure in the glaucoma and control groups. Statistical significance was set at $p<0.05$. **RESULTS**: There was a negative relationship between Resistivity Index in Ophthalmic artery and Diastolic Ocular Perfusion Pressure in glaucoma patients and this relationship was statistically significant. (r= -0.319, p=0.019). In controls, there was no significant relationship between Resistivity Index in Ophthalmic artery and Diastolic Ocular Perfusion Pressure (r= -0.015, p=0.914). There was however no statistically significant relationship between Resistivity Index in Ophthalmic Artery and Systolic Ocular Perfusion Pressure in glaucoma

patients (r= -0.208, *p*=0131). Similarly, no relationship was seen between Resistivity Index in Ophthalmic artery and Systolic Ocular Perfusion Pressure in controls (r= 0.088, *p*=0.527). **CONCLUSION**: The study also showed significant inverse relationship between diastolic ocular perfusion pressure and resistivity index in ophthalmic artery in glaucoma patients while no relationship was found in the controls. The study also showed that there was no significant relationship between systolic ocular perfusion pressure and resistivity index. This implies that systolic ocular perfusion pressure does not play a significant role in glaucoma development while the significant negative relationship between resistivity index ophthalmic artery and diastolic ocular perfusion pressure in the glaucoma suggests that impaired auto regulation is strongly involved in the glaucoma patients of Nigerian origin.
Key words: *Glaucoma, Ocular perfusion pressure, Resistivity index*.

INTRODUCTION

Ocular perfusion pressure is the pressure at which blood flows to the eye and refers to the difference between arterial and venous pressures.[1,2] While the venous pressure in the eye is slightly higher than intraocular pressure to allow for normal blood circulation, intraocular pressure can actually replace venous pressure when calculating ocular perfusion pressure.[3]

Low ocular perfusion pressure has been reported to have a strong association with prevalence of open-angle glaucoma in different population-based studies.[4-6] In a population-based prevalence survey in Baltimore where over 5000 subjects aged 40 years or older were studied, low diastolic ocular perfusion pressure was found to be strongly associated with a six-fold increase in prevalence of open-angle glaucoma compared to those whose perfusion pressures were higher than 50mmHg.[7] Similarly, a population-based study - the Proyecta VER, also evaluated about 5000 subjects of Hispanic origin and reported a four-fold increase in prevalence of open-angle glaucoma in subjects whose diastolic ocular perfusion pressures were less than 50mmHg compared to those with diastolic ocular perfusion pressure greater than 80mmHg.[5] The Egna-Neumarkt Eye Study has given supporting data on low diastolic ocular perfusion pressure as a risk factor for open-angle glaucoma. It was a population-based cross-sectional study of participants of Caucasian origin which reported that persons with diastolic pressure <60 mmHg to had a 2.5-fold higher risk for glaucoma compared with those with diastolic perfusion pressure >76 mmHg.[4]

The Barbados Eye Study (BES) – a longitudinal population-based study evaluated about 5000 subjects mostly of African origin over many years and reported as follows: low diastolic ocular perfusion pressure was found to be associated with a three-fold increased risk of open-angle glaucoma after a 4-year follow-up period.[8] After 9 years of follow-up, data from this same study also upheld their earlier findings but in addition, reported that low mean and systolic perfusion pressures were found to be associated with risk of developing glaucoma.[6] In the same vein, the Early Manifest Glaucoma Trial (EMGT) - a prospective randomized controlled clinical trial followed up participants over 8 years and reported that systolic perfusion pressure of 125mmHg or less was a risk factor for open-angle glaucoma progression.[9] Therefore, data from these longitudinal studies support the role of low ocular perfusion pressure as a risk factor in the incidence of primary open-angle glaucoma. The studies involved small sample sizes.

Glaucoma progression was reported to be a consequence of low perfusion pressure as it plays a role in its prevalence.[9] The EMGT also compared the role of initial treatment and no treatment in glaucoma progression and reported that glaucoma subjects with low systolic ocular perfusion pressure at the beginning of the study progressed at a faster rate than subjects with higher systolic ocular perfusion pressure.[9] The study also analyzed factors for progression individually for high and low intraocular pressure at baseline, as defined by a median split. A significant hazard ratio of 1.55 for ocular perfusion pressure was observed in glaucoma patients with high baseline intraocular pressure.

Controversies also surround the relationship between ocular perfusion pressure and glaucoma. The Rotterdam Study.[10,11] - a population-based longitudinal study evaluated nearly 4000 subjects over a mean follow-up period of 9.8 years. The study reported that there was no significant association between perfusion pressure and incidence of glaucoma when adjusted for baseline intraocular pressure, and concluded that the insignificant association was due to the intraocular pressure - a strong risk factor for open-angle glaucoma, being part of ocular perfusion pressure rather than the ocular perfusion pressure itself.

The aim of this study is therefore to establish the relationship between ocular perfusion pressure and resistivity index in the ophthalmic artery in both primary open angle glaucoma and normal-tension glaucoma patients and controls in our environment and generate much needed data to compare with global data.

MATERIALS AND METHODS

The study was an observational case-control study conducted between January 2019 and June 2019. One hundred and eight patients (54 glaucoma patients and 54 controls) were consecutively selected into the study. All participants underwent blood pressure measurement by using a standard mercury sphygmomanometer which was validated with a similar sphygmomanometer. Subjects were made to have at least 5 minutes of rest before the systolic and diastolic blood pressures were measured. The also had a Colour Doppler Imaging to measure resistivity index and blood flow velocity in the ophthalmic and central retinal arteries.

All data generated from the study was entered into a standard proforma and analyzed using commercially available statistical data management software - Statistical Package for Social Sciences - Version 21 (SPSS-21). Continuous variables were expressed as means (standard deviation) and compared by the Student's T-test. For comparison between the two groups, all data were subjected to Student T-test. A *p*-value of less than 0.05 was considered statistically significant. Pearson linear correlation test was performed to study the correlation between resistivity index and ocular perfusion pressure in the glaucoma and control groups

INCLUSION CRITERIA FOR GLAUCOMA SUBJECTS

1. Adults 18 years and older who were newly diagnosed with primary open angle glaucoma and normal-tension glaucoma yet to commence anti-glaucoma medications.
2. The diagnosis of primary open-angle glaucoma was based on;
   a. glaucomatous optic nerve head damage (vertical cup disc ratio, evaluation of symmetry, thickness, colour of neuro-retinal rim, notching and loss of retinal nerve fibre layer) seen with non-contact examination lens (+78D).
   b. Visual field changes on standard automated perimetry consistent with glaucoma, irrespective of severity.
3. Open angles and normal anterior chamber angles on gonioscopy $\geq 270^{o}$.
4. All levels of intraocular pressure.
5. Glaucoma patients who were willing to participate and gave written informed consent.

INCLUSION CRITERIA FOR CONTROLS (NON-GLAUCOMA SUBJECTS)

1. Apparently healthy adults, 18 years and older with no signs of any form of glaucomatous optic nerve damage.
2. Subjects were neither diagnosed with glaucoma nor treated for glaucoma.
3. Subjects with no family history of glaucoma.
4. Intraocular pressure ≤ 21mmHg in both eyes.
5. Healthy patients' caregivers, patients with presbyopia and small or no refractive error (≤±1.00 D)
6. Individuals who presented themselves for routine eye examination during the study period.

EXCLUSION CRITERIA FOR GLAUCOMA AND NON-GLAUCOMA SUBJECTS

1. Age <18 years.
2. Intraocular pressure >21mmHg for control group.
3. History of chronic disease such as diabetes mellitus and hypertension
4. Individuals with no history of diabetes who had a fasting blood sugar result of > 6.1 mmol/l (>100mg/dl) or random >11.1 mmol/l (>200mg/dl).
5. Individuals with systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg.
6. Chronic smoking
7. History of neuro-ophthalmic disease
8. History of ocular trauma
9. Ocular media opacity that precluded fundus examination
10. Family history of glaucoma

ETHICAL CONSIDERATIONS

Ethical Clearance was sought and obtained from the Health Research Ethical Committee of the University of Uyo Teaching Hospital, Uyo, Akwa Ibom State. All procedures were in accordance with the standards of the Declaration of Helsinki for research involving human subjects. Patients were educated properly and written informed consent was obtained.

Anti-glaucoma medications prescribed for the participants were provided for the patients free of charge. Any participant that was identified to have eye disease was appropriately referred for subsequent management.

RESULTS:

Table1: Demographics of study population

Total no	Male %	Female%	Age range	Mean age	p-value (Age)	p-value (Sex)
108	47.2	52.8	18-79	49.9±17.0	0.769	0.847

Table 11: Mean IOP, CCT and Corrected IOP in Glaucoma and Control Subjects

	Glaucoma		Control		
	Male	Female	Male	Female	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p value*
IOP (mmHg)	21.12±10.05	22.38±9.12	12.42±2.08	12.75±2.154	
Mean IOP	21.8±9.5		12.6±2.1		*<0.001**
CCT (µm)	530.40±25.83	535.72±18.54	536.7±17.65	538.7±22.68	
Mean CCT	533.26±22.16		537.78±20.25		*0.271*
Corrected IOP (mmHg)	22.140±9.959	23.02±9.03	13.02±2.28	13.19±2.36	
Mean	22.6±9.4		13.1±2.3		*<0.001**

* Statistically significant; IOP= Intraocular Pressure; CCT= Central Corneal Thickness**:**

Table III: Mean BP Measurement and Ocular Perfusion Pressure in Glaucoma and Control Subjects

	Glaucoma		Control		
	Male	Female	Male	Female	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p value*
SBP (mmHg)	122.92±10.79	118.76±9.51	121.38±7.22	116.06±10.56	
	120.69±10.24		118.63±9.41		*0.280*
DBP (mmHg)	74.00±9.10	74.21±7.74	75.85±6.41	72.25±9.24	
	74.11±8.32		73.98±8.13		*0.935*
SOPP (mmHg)	100.78±12.44	95.74±12.42	108.37±7.21	102.88±9.91	
	98.07 ± 12.57		105.52 ± 9.07		*<0.001**
DOPP (mmHg)	51.86±12.82	51.19±10.51	62.83±6.31	59.06±8.62	
	51.50 ± 11.53		60.87 ± 7.76		*<0.001**

* Statistically significant; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; SOPP= Systolic Ocular Perfusion Pressure; DOPP= Diastolic Ocular Perfusion Pressure

Table III shows that the mean SBP for glaucoma patients was 120.69±10.24mmHg and that for controls -118.63±9.41mmHg; this difference was however not statistically significant (*p*=0.280). Similarly, the mean DBP of glaucoma patients, though higher than controls (74.11±8.32mmHg vs 73.98±8.13mmHg), was not statistically significant (*p*=0.935).

The mean SOPP in glaucoma patients was found to be lower than in controls (98.07 ± 12.57mmHg vs 105.52 ± 9.07mmHg) and the difference was statistically significant (*p*=0.001). Similarly, the mean DOPP of glaucoma patients was 51.50 ± 11.53mmHg and that of controls - 60.87 ± 7.76mmHg; the difference was also statistically significant (*p*<0.001).

Table IV: Correlation between RI and Age in Glaucoma Patients and Controls

	RI of OA		RI of CRA	
	r	*P value*	r	*p value*
Age [Glaucoma]	-0.161	*0.243*	0.079	*0.568*
Age [Controls]	0.593	*<0.001**	0.174	*0.209*

* Statistically significant RI= Resistivity Index; OA = Ophthalmic Artery; CRA= Central Retinal Artery

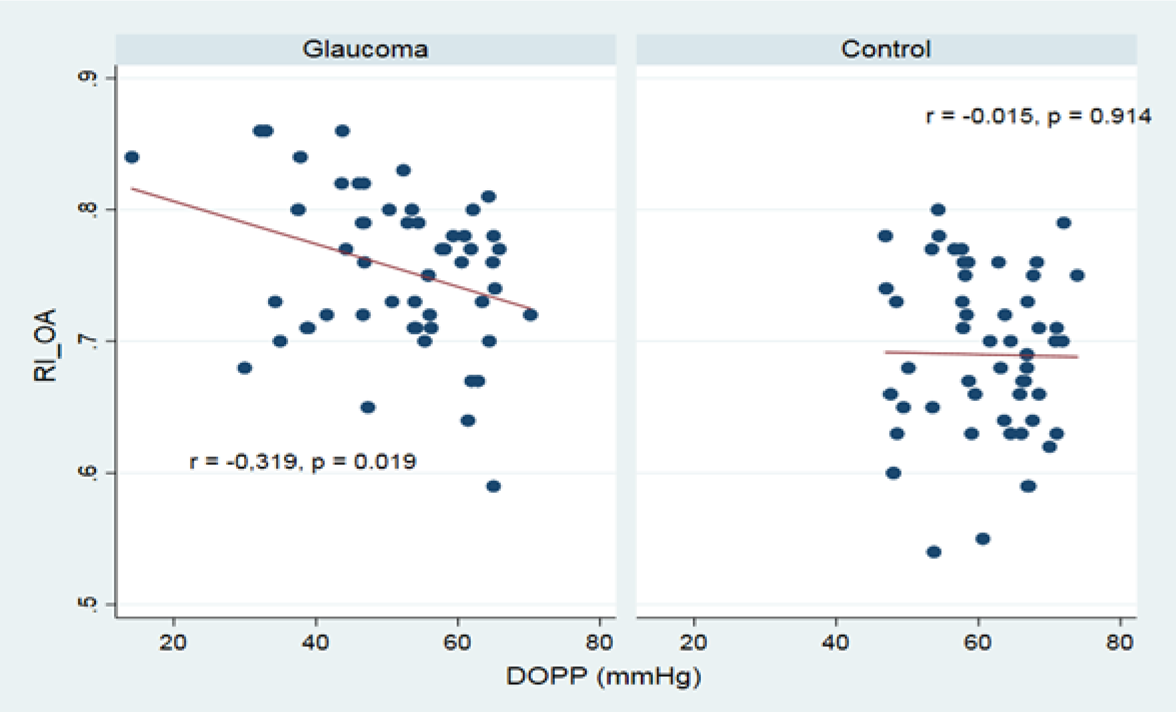
Table IV shows the correlation between OA and CRA RI and Age. In glaucoma patients, RI of OA and CRA did not significantly correlate with Age (*p*=0.243 and 0.568 respectively). However, in controls, there was a positive correlation between RI of OA and Age. This correlation was statistically significant (*p*<0.001). RI of CRA did not have significant correlation with Age in controls. (*p*=0.209).

Table V: Comparison of SOPP and DOPP Between Primary Open Angle Glaucoma Patients, Normal-Tension Glaucoma Patients and Controls

	Primary Open Angle Glaucoma	**Normal-Tension Glaucoma**	**Controls**	***F value***	***P value***
Ocular Perfusion Pressure					
SOPP (mmHg)	92.19±2.78	102.78±9.49	105.52±9.07	*13.998*	*<0.001**
DOPP (mmHg)	44.56±11.51	57.05±8.13	60.87±7.76	*32.658*	*<0.001**

* Statistically significant; SOPP= Systolic Ocular Perfusion Pressure; DOPP= Diastolic Ocular Perfusion Pressure; Pt = Patients

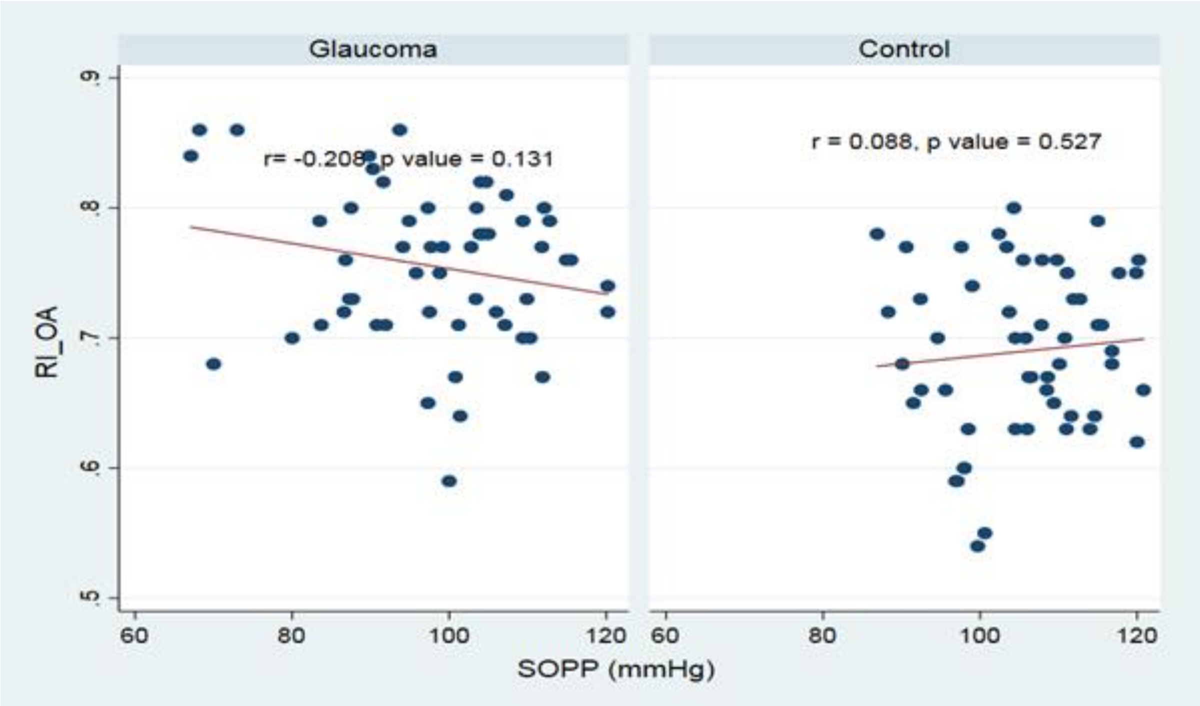
In Table V, SOPP was found to be the lowest in primary open angle glaucoma patients (92.19±2.78mmHg), followed by normal-tension glaucoma patients (102.78±9.49mmHg) and then controls (105.52±9.07mmHg). The difference in mean across the groups was statistically significant (*p* <0.001). A similar trend was noted for DOPP where the mean in primary open angle glaucoma patients was 44.56±11.51mmHg, followed by normal-tension glaucoma patients at 57.05±8.13mmHg and controls (60.87±7.76mmHg). The difference in mean across groups was statistically significant (*p* < 0.001).



RI= Resistivity Index; OA= Ophthalmic Artery; DOPP= Diastolic Ocular Perfusion Pressure

Figure 1: Relationship between RI in OA and DOPP in Glaucoma Patients and Controls

Figure 1 is a scatter-plot showing the relationship between RI in OA and DOPP in glaucoma patients and controls. There was a negative relationship between RI in OA and DOPP in glaucoma patients and this relationship was statistically significant. (r= -0.319, p=0.019). In controls, there was no significant relationship between RI in OA and DOPP (r= -0.015, p=0.914).



RI= Resistivity Index; OA= Ophthalmic Artery; SOPP= Systolic Ocular Perfusion Pressure

Figure 2: Relationship between RI in OA and SOPP in Glaucoma Patients and Controls

Figure 2 shows that there was no statistically significant relationship between RI in OA and SOPP in glaucoma patients (r= -0.208, *p*=0131). Similarly, no relationship was seen between RI in OA and SOPP in controls (r= 0.088, *p*=0.527).

Table VI: Relationship between RI in Ophthalmic Artery and Ocular Perfusion Pressure in Primary Open Angle Glaucoma and Normal-Tension Glaucoma Patients

	Resistivity Index of Ophthalmic Artery			
	POAG		NTG	
	r	*p*	r	*p*
DOPP	**-0.304**	***0.149***	**-0.267**	***0.154***
SOPP	**-0.240**	***0.258***	**-0.073**	***0.703***

DOPP= Diastolic Ocular Perfusion Pressure; Ocular Vessels = OA and CRA; RI= Resistivity Index

Table VI shows the relationship between RI in OA and DOPP; and between RI in OA and SOPP in primary open angle glaucoma and normal-tension glaucoma patients. There was no significant relationship between RI in OA and DOPP in primary open angle glaucoma (p=0.149) and normal-tension glaucoma patients (*p*=0.154). Similarly, there was no significant relationship between RI in OA and SOPP in primary open angle glaucoma (*p*=0.258) and normal-tension glaucoma patients (p=0.703).

DISCUSSION

Intraocular pressure remains an integral component of ocular perfusion pressure and the normal range of intraocular pressure is 10 – 21mmHg. Goldmann applanation tonometry is the gold standard for measuring intraocular pressure and it was first acknowledged by Goldman and Smith[12] that differing central corneal thickness significantly affected intraocular pressure. Subsequently, other studies also confirmed the marked influence of corneal thickness on intraocular pressure hence, the need for central corneal thickness adjusted intraocular pressure.[13–15] Normal anatomical conditions and physiological mechanisms are maintained when the intraocular pressure is within this range.[16] Raised intraocular pressure in the long term may cause damage to the optic nerve and subsequent visual field loss. This damage to the optic nerve may be as a result of the effect of chronic hypoperfusion of the optic nerve head or from the direct mechanical effect of high pressures on the optic nerve.[3] Perfusion pressure is affected by levels of intraocular pressure which is controlled by several factors such as aqueous humour, blood pressure and blood volume.[17-19] Aqueous humour which is produced largely by active secretion greatly influences intraocular pressure. A minor pathway of aqueous production - the ultrafiltration is predominantly influenced by intraocular pressure, plasma oncotic pressure within the capillaries and ciliary body. Production of aqueous is largely constant, therefore intraocular pressure will increase if trabecular drainage reduces or episcleral venous pressure rises. The relationship between blood pressure and intraocular pressure has been explained by suggesting that autonomic nervous system which regulates blood pressure may produce circadian rhythm of aqueous humour production with subsequent changes in intraocular pressure.[17] Secondly, angiotensin converting enzyme which also affects blood pressure may reduce intraocular pressure by increasing prostaglandin synthesis or inhibition of cholinesterase activity.[18]

Blood volume also influences intraocular pressure levels as evident in a comparative study by Patil et al.[19] In their study, an increase in blood volume was shown to significantly increase intraocular pressure. Elevated intraocular pressure distorts the lamina cribrosa causing compression of blood vessels at the optic nerve head with subsequent reduction in ocular perfusion pressure, thus causing regional hypoxia.[20] Failure of autoregulatory mechanism leads to ischaemia which is consistent with findings of reduced optic nerve head blood flow in glaucoma patients.[21] Therefore, despite this complex relationship between intraocular pressure, blood pressure and ocular perfusion pressure, a good regulatory process must be in place to ensure optimal perfusion of ocular tissues.

This study showed a significant relationship between diastolic ocular perfusion pressure (DOPP) and resistivity index in ophthalmic artery in glaucoma patients. Galassi et al.[15] reported similar findings. This significant relationship may be because the participants were newly diagnosed glaucoma patients with corrected intraocular pressure, thereby removing possible errors from incorrect IOP that may affect diastolic ocular perfusion pressure calculation. Similar finding was reported by Gherghel et al.[22] who noted significant negative correlation between ophthalmic artery resistivity index and mean ocular perfusion pressure in patients with progressive glaucomatous damage but not in those with stable visual fields. The negative correlation between RI in ophthalmic artery and DOPP in this study means that as DOPP reduces RI increases in ophthalmic artery. Furthermore, this increase in resistivity index signifies greater resistance in the vascular bed and a reduced blood flow to the optic nerve. Gherghel and his Colleagues[22] explained that the reduced ocular perfusion pressure with subsequent increase in RI of ophthalmic artery leads to diminished optic nerve blood flow in glaucoma patients as a direct consequence of vascular dysregulation. This study supports the suggestion that vascular dysregulation is present in normal-tension glaucoma and primary open angle glaucoma.[23] In contrast, the study by Samsudin et al.[24] did not show a significant correlation between ocular perfusion pressure and resistivity index of ophthalmic artery in glaucoma patients. This is probably because the normal-tension glaucoma patients were on both anti-glaucoma medications and treatment for systemic diseases such as diabetes and hypertension. No significant correlation was observed between ocular perfusion pressure and resistivity index of ophthalmic artery of glaucoma patients according to reports of the study by Garhofer and Colleagues[25] probably because their study had glaucoma patients who were receiving anti-glaucoma medications. However, this study did not show any significant relationship between resistivity index in ophthalmic artery and DOPP in both primary open angle glaucoma and normal-tension glaucoma study groups. This is not unexpected because of the relatively small sample size of the individual groups. Interestingly, only one published study specifically assessed the relationship between diastolic ocular perfusion pressure and resistivity index in normal-tension glaucoma and reported a significant positive correlation between resistivity index in ophthalmic artery and diastolic ocular perfusion pressure.[26] Although both studies included newly diagnosed normal-tension glaucoma patients, the significant result in their study could have occurred because they had a larger sample size. In addition, this different finding may not be unconnected with the fact this current study examined Nigerian participants while the other study was done in a Caucasian population.

In the controls, there was no significant correlation between diastolic ocular perfusion pressure and resistivity index in ophthalmic artery. This is similar to the reports of Gherghel et al.[22] and Galassi et al.[26] However, a significant positive correlation between resistivity index of ophthalmic artery and ocular perfusion pressure was noted in healthy controls in the study by Garhofer and Colleagues.[25] This is probably due to the fact that they studied a larger sample size. Another reason for this finding may be because the controls in their study had higher systolic and diastolic blood pressures (-considered systolic and diastolic hypertension) compared to this study.

There was no relationship between systolic ocular perfusion pressure (SOPP) and resistivity index of ophthalmic artery in glaucoma patients and controls. Similarly, Galassi et al.[26] also reported that there was no significant relationship between systolic ocular perfusion pressure and resistivity index of ophthalmic artery in glaucoma patients and controls. There were no other studies done on the relationship between systolic ocular perfusion pressure and resistivity index or other Doppler indices. The reason for the lack of relationship between systolic ocular perfusion pressure and resistivity index is probably because systolic ocular perfusion pressure does not have significant contribution to glaucoma pathogenesis.

CONCLUSION

The study also showed significant inverse relationship between diastolic ocular perfusion pressure and resistivity index in ophthalmic artery in glaucoma patients while no relationship was found in the controls. The study also showed that there was no significant relationship between systolic ocular perfusion pressure and resistivity index.

This implies that systolic ocular perfusion pressure does not play a significant role in glaucoma development while the significant negative relationship between resistivity index ophthalmic artery and diastolic ocular perfusion pressure in the glaucoma suggests that impaired auto regulation is strongly involved in the glaucoma patients of Nigerian origin.

REFERENCES

1. Bill A. The uveal venous pressure. *Arch Ophthalmol.* 1963;69:780–782.
2. Morgan WH, Yu DY, Cooper RL, Alder VA, Cringle SJ, Constable IJ. Retinal artery and vein pressures in the dog and their relationship to aortic, intraocular, and cerebrospinal fluid pressures. *Microvasc Res.* 1997;53:211–21.
3. Hayreh SS. Blood Flow in the Optic Nerve Head and Factors that may Influence it. *Prog Retin Eye Res.* 2001;20:595–624.
4. Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology.* 2000;107:1287–93.
5. 90. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol.* 2001;119:1819–26.
6. 91. Leske MC, Wu S-Y, Hennis A, Honkanen R, Nemesure B. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. *Ophthalmology*. 2008;115:85–93.
7. Tielsch JM, Katz J, Singh K, Quigley HA, Gottsch JD, Javitt J, et al. A Population-based Evaluation of Glaucoma Screening : The Baltimore Eye Survey. *Am J Epidemiol*. 1991;134:1102–10.
8. Leske MC, Wu S-Y, Nemesure B, Hennis A. Incident open-angle glaucoma and blood pressure. *Arch Ophthalmol.* 2002;120:954–9.
9. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114:1965–72.

10. Ramdas WD, Wolfs RCW, Hofman A, Jong PTVM De, Vingerling JR, Jansonius NM. Ocular Perfusion Pressure and the Incidence of Glaucoma : Real Effect or Artifact ?: The Rotterdam Study. *Invest Ophthalmol Vis Sci*. 52:6875–6881.
11. Hulsman CAA, Vingerling JR, Hofman A, Witteman JCM, de Jong PTVM. Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. *Arch Ophthalmol*. 2007;125:805–12.
12. Goldmann H, Schmidt T. Uber Applanationsonometric. *Ophthalmologica*. 1957;134:221–42.
13. Babalola OE, Kehinde A V, Iloegbunam AC, Akinbinu T, Moghalu C, Onuoha I. A comparison of the Goldmann applanation and non-contact (Keeler Pulsair EasyEye) tonometers and the effect of central corneal thickness in indigenous African eyes. *Ophthalmic Physiol Opt*. 2009;29:182–8.
14. Nzelu- Egwuonwu N. Relationship between Central Corneal Thickness and Intraocular Pressure in Indigenous Africans in Nigeria. *Invest Ophthalmol Vis Sci.* 201316;54:5622.
15. Adegbehingbe SA, Olusanya BA, Ajayi BGK, Ashaye AO, Bekibele CO. Central Cornea Thickness in Glaucoma and Non- Glaucoma African Population. *Ophthalmol Res*. 2017;6:1–8.
16. Murgatroyd H, Bembridge J. Intraocular pressure. *Contin Educ Anaesth Crit Care Pain*. 2008;8:100–3.
17. Gherghel D, Hosking SL, Orgul S. Autonomic nervous system, circadian rhythms, and primary open-angle glaucoma. *Surv Ophthalmol*. 2004;49:491–508.
18. Shah GB, Sharma S, Mehta AA, Goyal RK. Oculohypotensive effect of angiotensin-converting enzyme inhibitors in acute and chronic models of glaucoma. *J Cardiovasc Pharmacol.* 2000;36:169–75.
19. Patil SS, Dharwadkar AA, Dharwadkar AR, Herur A, Ankad B. A Comparative and Interrelationship Study between Blood Pressure and Intraocular Pressure in Young Healthy Male Adults after Water Ingestion. *Int J Collab Res Intern Med Public Heal.* 2011;3:466–73
20. Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. *Arch Ophthalmol*. 1981;99:635–49.
21. Riva CE, Salgarello T, Logean E, Colotto A, Galan EM, Falsini B. Flicker-evoked

response measured at the optic disc rim is reduced in ocular hypertension and early glaucoma. *Invest Ophthalmol Vis Sci*. 2004;45:3662–8.

22. Gherghel D, Orgu S, Gleta K, Gekkieva M, Flammer J. Relationship Between Ocular Perfusion Pressure and Retrobulbar Blood Flow in Patients With Glaucoma With Progressive Damage. *Am J Ophthalmol*. 2000;130:597–605
23. Kondo Y, Niwa Y, Yamamoto T, Sawada A, Harris A, Kitazawa Y. Retrobulbar Hemodynamics in Normal-tension Glaucoma With Asymmetric Visual Field Change and Asymmetric Ocular Perfusion Pressure. *Am J Ophthalmol.* 2000;30:454–60.
24. Samsudin A, Isaacs N, Tai MS, Ramli N, Mimiwati Z, Choo MM. Ocular perfusion pressure and ophthalmic artery flow in patients with normal tension glaucoma. *BMC Ophthalmol.* 2016;16:39.
25. Garhofer G, Fuchsjager G, Vass C, Pemp B, Hommer A, Schmetterer L. Retrobulbar Blood Flow Velocities in Open Angle Glaucoma and Their Association with Mean Arterial Blood Pressure. *Invest Ophthalmol Vis Sci.* 2010;51:6652–7.
26. Galassi F, Giambene B, Varriale R. Systemic Vascular Dysregulation and Retrobulbar Hemodynamics in Normal-Tension Glaucoma. *Invest Ophthalmol Vis Sci*. 2011;52:4467–71.