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# Evaluation of Resistivity Index in Ophthalmic and Central Retinal Arteries of Primary Open Angle Glaucoma and Normal-Tension Glaucoma Patients Using Colour Doppler Imaging at University of Uyo Teaching Hospital

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### Abstract

**Aim:** To evaluate the resistivity index in Ophthalmic and central retinal arteries of the optic nerve head in glaucoma patients and compare it with age and sex-matched controls at University of Uyo Teaching Hospital, using Colour Doppler Imaging.

**Methods:** The study was an observational case-control study conducted between January 2019 and June 2019. Fifty-four newly diagnosed primary open angle glaucoma patients and 54 age and sex-matched controls from the Ophthalmology Clinic were consecutively selected into the study. All participants underwent 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:** The study showed that the resistivity indices of the ophthalmic and central retinal arteries were significantly higher in glaucoma patients than controls ($p < 0.001$). The resistivity indices of ophthalmic and central retinal arteries were also found to be independent of age in glaucoma patients ($p > 0.05$), but in controls, RI of the ophthalmic artery significantly increased with age ($p < 0.001$). Resistivity indices of ophthalmic and central retinal arteries were noted to be higher in primary open angle glaucoma patients than controls ($p < 0.001$). Similarly, resistivity indices of both arteries were also noted to be higher in normal-tension glaucoma patients than controls.

***Keywords:*** *Central Retina Artery; Glaucoma; Ophthalmic Artery; Resistivity Index*

## Introduction

Glaucoma is the commonest cause of irreversible blindness globally [1,2] and it is also recognized as the second leading cause of blindness in the world [3]. Glaucoma contributed 8.4 million to the 39 million people estimated to be bilaterally blind in the world in 2010 and this population is projected to reach 11.1 million in the year 2020 [3]. The number of individuals diagnosed with glaucoma is expected to increase from an estimated 60.5 million in 2010 to 79.6 million in 2020 [3]. Review of related population-based studies have reported that sub-Saharan Africa has the highest glaucoma prevalence of 4% - with the highest populations in West Africa compared to Southern, Eastern and Central Africa [4].

The Nigeria National Blindness and Visual Impairment Survey (NNBVIS) - a population-based study carried out between 2005 and 2007 showed a similar trend with glaucoma ranking as the second leading cause of blindness in people aged 40 years and older, with a prevalence of 0.7% [5]. Another community-based study in Nigeria also showed that glaucoma ranked next to cataract as the leading cause of blindness [6]. The prevalence of glaucoma in Nigeria is 5.02%, and this is higher than the global prevalence with primary open angle glaucoma being the commonest type [7].

Glaucoma is defined as a group of progressive multifactorial optic neuropathies in which intraocular pressure amongst other risk factors is responsible for a characteristically acquired loss of retinal ganglion cell axons leading to atrophy of the optic nerve with demonstrable visual field defects [8]. Intraocular pressure is an important modifiable risk factor in glaucoma and in most cases, it is the only risk factor identified. In the past, intraocular pressure was used to distinguish normal from abnormal pressures and also to determine when to commence ocular hypotensive treatment. The assumption that only high pressures cause glaucomatous optic nerve damage while normal pressures do not is untrue [9]; as some glaucoma patients have pressures that are consistently within normal limits - a situation considered normal tension glaucoma. The Baltimore Eye Survey (BES) reported that more than 50% of their study subjects had pressures within the normal range and would be missed if the screening was based entirely on intraocular pressure [10]. The Taijimi study - conducted in Japan in 2004 also reported a that about 90% [11] of their patients had normal intra-ocular pressures, which further reiterates the fact that intraocular pressure alone is not adequate as screening tool for glaucoma.

Lowering of intraocular pressure still remains the proven method for reducing the progression of glaucoma including normal tension glaucoma [15]. However, intraocular pressure cannot be the only mechanism of glaucomatous damage, because it has been reported that despite adequate intraocular pressure reduction, a remarkable number of patients still have progressive glaucomatous optic nerve damage and visual field loss [12,13]. Results from the Ocular Hypertension Treatment Study (OHTS) showed that over 90% of subjects in the observation group did not develop glaucoma over the five-year period despite high intraocular pressure, further strengthening the theory that there are other risk factors apart from intraocular pressure-related [14].

The disproval of elevated intraocular pressure as the sole mechanism for glaucoma progression has led to the search for other factors responsible for glaucomatous optic nerve damage. There are growing reports on non-intraocular pressure-related risk factors and some studies have focused on abnormalities of vascular regulation with increasing evidence of involvement of dysfunctional arterial autoregulatory mechanisms in the pathogenesis of glaucoma [15-17]. Autoregulation means that the vascular system maintains a relatively stable blood flow, vascular resistance, arteriolar caliber and nutrient supply as the perfusion pressure changes [18]. In the ocular system, autoregulation functions in maintaining the blood flow to the optic nerve head irrespective of the ocular perfusion pressure changes [19]. Autoregulation is effective when the ocular perfusion pressure is within a normal range and it is demonstrated that retinal and optic nerve head blood flow reduces as the systemic blood pressure and perfusion pressure fall below the defined range [20] and increases as the blood pressure rises above the defined range [21].

Some authors have argued that poor stability in the regulation of optic nerve head blood rather than blood flow reduction is the underlying pathogenic mechanism for glaucomatous optic nerve damage [22,23]. It is also suggested that underlying wider circadian fluctuations in ocular perfusion pressure is implicated in glaucoma progression [24]. In the past few decades, vascular risk factors other than systemic hypertension have been demonstrated to have circadian rhythm - such factors as ocular blood flow [25] and ocular perfusion pressure [26]. Inadequate optic nerve head perfusion may be the main mechanism or could occur as a result of vascular dysregulation occurring during diurnal fluctuations in some cases of glaucoma [27].

Different techniques have been employed in measuring optic nerve head blood flow. Some visualize the retinal vessels and directly measure blood flow while others are able to investigate the vasculature of the retrobulbar structures of the eye including the optic nerve and choroid [28-30]. However there is no standard technique for optic nerve head blood flow measurement as each modality for measurement has limitations and also measures different aspects of blood flow.

The various techniques used to evaluate ocular blood flow include Colour Doppler Imaging [31], Doppler Fourier domain-optical coherence tomography [32], Laser Doppler velocimetry [29], confocal scanning laser Doppler flowmetry [30] and retinal functional imager [33].

Colour Doppler Imaging (CDI) has become popularly used in ophthalmology to measure blood velocity and vascular resistance in ophthalmic artery, central retinal artery, and short posterior ciliary arteries [17,34].

This study seeks to directly assess the status of blood flow to optic nerve in glaucoma patients of Nigerian ethnicity and compare these to controls. The study will not only fill the gap in present knowledge about the subject, but also provide a database and guide in future management of glaucoma patients in Nigeria.

## Materials and Methods

This was an observational case-control hospital-based study conducted between the 2nd of January 2019 and 30th of June 2019.

### Study population

The study population was made up of Nigerians of different ethnic background, but predominantly Ibibios who are indigenes of South-south of Nigeria. The participants also had different social (occupational, marital and tribe), religious (Christian, Islam and traditional) and educational (no formal education, primary, secondary and tertiary) backgrounds.

### Sample size determination

The sample size for both Cases and Controls was calculated using the formula for comparison of two means [35] as shown below:

$$n = \frac{2 (Z_\alpha + Z_\beta)^2 \sigma^2}{(\mu_1 - \mu_0)^2}$$

Where:

n = Minimum required sample size

$Z_\alpha$ = Standard deviation corresponding to α (level of significance) of 5% = 1.96

$Z_\beta$ = Standard deviation corresponding to β (power = 95%) = 1.65

$\sigma^2$ = Standard deviation of mean End Diastolic Velocity of ophthalmic artery in glaucoma patients = 2.82 $cm^{-1}$, from a previous study in Ife, Nigeria [17]

$\mu_1 - \mu_0$ = expected minimum detectable difference in mean End Diastolic Velocity of ophthalmic artery between glaucoma and control groups, Ife = 2.06 $cm^{-1}$ [17]

$$n = \frac{2\,(1.96 + 1.65)^2 \times 2.82^2}{2.06^2}$$

n = 49

Allowance for non-responders (10%) = 49 + 5 = 54

Therefore, minimum sample size = 108 (including 54 glaucoma patients and 54 age- and sex-matched controls).

### Sampling technique

A consecutive sampling method was used at the Ophthalmology clinic. On each day, all newly diagnosed glaucoma patients who gave a written informed consent were included in the study. The Ophthalmology Clinic held on four days every week - on Mondays, Tuesdays, Thursdays and Fridays, so subject selection continued weekly until the estimated minimum sample was reached.

Control group for the study included age and sex-matched healthy patients' caregivers, patients with presbyopia and small or no refractive error (≤ ± 1.00 D) and individuals who presented themselves for routine eye examination during the study period. Also included were staff of University of Uyo and University of Uyo Teaching Hospital, who met the inclusion criteria.

### Subject selection

All consecutive newly diagnosed glaucoma patients, seen at the Eye Clinic of the hospital - who met the inclusion criteria and gave written informed consent, were recruited into the study. The control study group was made up of age and sex-matched healthy subjects.

### 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 ≥ 270°.
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 ≤ 21 mmHg 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 > 21 mmHg 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 (> 100 mg/dl) or random > 11.1 mmol/l (> 200 mg/dl).
5. Individuals with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.
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 were obtained.

### Benefits to participants

Benefits included screening and monitoring for glaucoma. 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.

### Procedure for colour doppler imaging

After the procedure was explained to the subject, the examination was conducted with the subject lying in supine position with the eyes closed without squeezing the eyelids while looking straight. The examiner sat behind the head of the patient and rested his hand on the subject's forehead to steady the hand and reduce excessive pressure on the globe. A coupling gel was applied on the closed eyelid, a 7 MHz probe was used for the examination according to the technique described by Odunlami., *et al* [17].

In the B-scan mode, the back of the eyeball and retrobulbar structures were identified with the use of optic nerve as a landmark. Colour Doppler was then applied to identify the retrobulbar arteries (ophthalmic and central retinal arteries). The ophthalmic artery was identified and measured about 17 mm posterior to the globe, parallel and lateral to the optic nerve. The central retinal artery was identified within the shadow of the optic nerve with the Doppler sample gate (≤ 2 mm) set 3 mm posterior to the surface of the optic disc. Measurement of the central retinal artery was then taken. The sample volume depth was set at about 40 mm with angle correction where possible, and sample volume placed about 3 mm behind the surface of the optic disc for measurement of the ophthalmic artery. When the examiner was satisfied with tracing, three consecutive readings of peak systolic and end diastolic velocities for each artery were taken and the mean calculated. Resistivity index for the ophthalmic and central retinal arteries were calculated as (PSV - EDV)/PSV [36]. Calculation of Resistivity index for both arteries was already programmed in the ultrasound machine, thus values were generated after measurement of peak systolic and end diastolic velocities were recorded.

### Pilot study

A pilot study was conducted between 19th November and 14th December 2018 to assess the workability of the protocol adopted for carrying out the research and necessary adjustments were made. The study protocol and other aspects of the examination were tested on 10 glaucoma patients and 10 age and sex-matched healthy controls who were selected from the Eye Clinic of University of Uyo Teaching Hospital. All the subjects recruited for the pilot study were not included in the main study.

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.

## Results

A total of 108 subjects including 54 newly diagnosed glaucoma patients and 54 controls participated in the study.

| | **Glaucoma** | | | **Control** | | |
|---|---|---|---|---|---|---|
| **Age group (years)** | **Male n (%)** | **Female n (%)** | **Total n (%)** | **Male n (%)** | **Female n (%)** | **Total n (%)** |
| ≤20 | 1 (4.0) | 2 (6.9) | 3 (5.6) | 1 (3.8) | 2 (7.1) | 3 (5.6) |
| 21 - 30 | 2 (8.0) | 5 (17.2) | 7 (13.0) | 5 (19.2) | 2 (7.1) | 7 (13.0) |
| 31 - 40 | 3 (12.0) | 5 (17.2) | 8 (14.8) | 4 (15.4) | 4 (14.3) | 8 (14.8) |
| 41 - 50 | 5 (20.0) | 2 (6.9) | 7 (13.0) | 4 (15.4) | 3 (10.7) | 7 (13.0) |
| 51 - 60 | 5 (20.0) | 6 (20.7) | 11 (20.4) | 5 (19.2) | 6 (21.4) | 11 (20.4) |
| 61 - 70 | 8 (32.0) | 6 (20.7) | 14 (25.9) | 5 (19.2) | 9 (32.1) | 14 (25.9) |
| > 70 | 1 (4.0) | 3 (10.3) | 4 (7.4) | 2 (7.7) | 2 (7.1) | 4 (7.4) |
| Total | 25 (100.0) | 29 (100.0) | 54 (100.0) | 26 (100.0) | 28 (100.0) | 54 (100.0) |
| % Sex | 46.3 | 53.7 | 100.0 | 48.1 | 51.9 | 100 |
| Overall Mean (yrs) | 50.4 ± 17.2 | | | 49.5 ± 16.8 | | |
| Range (years) | 18 - 79 | | | 18 - 78 | | |
| p-value (Age) = 0.769 | | | | p-value (Sex) = 0.847 | | |

***Table 1:*** *Age and sex distribution of study participants.*

Table 1 shows that the age of glaucoma patients ranged from 18 - 79 years with a mean of 50.4 ± 17.2 years. The Controls had a similar age range of 18 - 78 years with a mean of 49.5 ± 16.8 years. The difference in the mean ages between the two groups was however not significant (p = 0.769). The modal age group of both glaucoma patients and controls was 61 - 70 years. The least represented in the glaucoma study group and controls were those 20years and younger (5.6% and 9.3% respectively). Majority of the glaucoma patients were over 40 years (68.5%).

The sex distribution of glaucoma patients showed a female preponderance in all age groups except those 41 - 50 years and 61 - 70 years while for the control group, females had higher representation only in two age categories. Overall, majority of the study subjects were females in both groups: 53.7% in glaucoma subjects and 51.9% in controls. This difference in sex distribution was not statistically significant (p = 0.847).

| | Glaucoma n (%) | Controls n (%) | Stat test | p value |
|---|---|---|---|---|
| **Education** | | | | |
| None | 3 (5.6) | 1 (1.9) | | |
| Primary | 12 (22.2) | 9 (16.7) | Fishers Exact | 0.536 |
| Secondary | 21 (38.9) | 27 (50.0) | | |
| Tertiary | 18 (33.3) | 17 (31.5) | | |

***Table 2A**: Educational level of study participants.*

Table 2A shows that majority of the study participants had either secondary or tertiary education and both levels of education accounted for 72.2% and 81.5% in the glaucoma and control groups respectively

| Occupation | Glaucoma (n = 54) | Controls (n = 54) | Stat test | p value |
|---|---|---|---|---|
| Artisan | 2 (3.7) | 5 (9.3) | | |
| Business* | 5 (9.3) | 9 (16.7) | | |
| Civil servant | 11 (20.4) | 9 (16.7) | | |
| Farmer | 6 (11.1) | 10 (18.5) | | |
| Housewife | 4 (7.4) | 6 (11.1) | Fishers | 0.428 |
| Professional** | 2 (3.7) | 2 (3.7) | | |
| Retired | 7 (13.0) | 2 (3.7) | | |
| Student | 8 (14.8) | 6 (11.1) | | |
| Trader | 9 (16.7) | 5 (9.3) | | |

***Table 2B:** Occupation of study participants.*

**: Business included (Contractors and Entrepreneurs). **: Professionals included (Nurses and Engineers).*

Table 2B shows that the highest proportion of glaucoma patients were civil servants, traders and students (51.9%) while farming, business and public service constituted the commonest occupation among controls (51.9%).

| | Glaucoma | | Control | | |
|---|---|---|---|---|---|
| | Male Mean ± SD | Female Mean ± SD | Male Mean ± SD | Female 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* |

***Table 3:*** *Mean IOP, CCT and corrected IOP in glaucoma and control subjects.*

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

Table 3 shows that the mean IOP in glaucoma patients was 21.8 ± 9.5 mmHg compared to 12.6 ± 2.1 mmHg in controls and this difference was statistically significant (p < 0.001). The mean CCT was higher in the control group at 537.78 ± 20.25 μm compared to the glaucoma patients at 533.26 ± 22.16 μm. This difference was not statistically significant (p = 0.271). The mean corrected IOP of glaucoma patients was significantly higher than that of controls (p < 0.05).

| | IOP | Corrected IOP | p value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Glaucoma | 21.8 ± 9.5 | 22.6 ± 9.4 | < 0.001* |
| Control | 12.6 ± 2.1 | 13.1 ± 2.3 | 0.010* |

***Table 4:*** *Comparison of mean IOP and corrected IOP in glaucoma and control subjects.*

**: Statistically significant; IOP: Intraocular Pressure.*

Table 4 shows that after correcting for the CCT, the mean IOP increased to 22.6 ± 9.4 mmHg (p = < 0.001) in glaucoma patients. For the controls, it also increased (12.6 ± 2.1 mmHg compared to 13.1 ± 2.3 mmHg, p = 0.01).

| | 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 |

***Table 5:*** *Correlation between RI and Age in Glaucoma Patients and Controls.*

**: Statistically significant, RI: Resistivity Index; OA: Ophthalmic Artery; CRA: Central Retinal Artery.*

Table 5 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).

| | Doppler Indices | Glaucoma Pt Mean ± SD | Control Mean ± SD | p value |
|---|---|---|---|---|
| OA | PSV (cm/s) | 28.81 ± 5.72 | 32.50 ± 8.77 | 0.011* |
| | EDV (cm/s) | 7.02 ± 2.17 | 10.08 ± 3.31 | < 0.001* |
| | RI | 0.76 ± 0.06 | 0.69 ± 0.06 | < 0.001* |
| CRA | PSV (cm/s) | 10.82 ± 3.63 | 13.11 ± 3.71 | 0.002* |
| | EDV (cm/s) | 3.90 ± 1.57 | 5.23 ± 1.70 | < 0.001* |
| | RI | 0.66 ± 0.07 | 0.60 ± 0.06 | < 0.001* |

***Table 6:*** *Comparison of mean RI of OA and CRA of glaucoma patients and controls.*

**: Statistically Significant; PSV: Peak Systolic Velocity; EDV: End Diastolic Velocity; RI: Resistivity Index; OA: Ophthalmic Artery; CRA: Central Retinal Artery.*

Table 6 compares mean RI of OA and CRA between glaucoma patients and controls. The comparison of other Doppler indices such as PSV and EDV are also depicted on the table. In the ophthalmic artery, the mean PSV for glaucoma patients was 28.81 ± 5.72 cm/s compared to 32.50 ± 8.77 cm/s in controls; the difference was statistically significantly (p = 0.011). The mean EDV in glaucoma patients was 7.02 ± 2.17cm/s compared to 10.08 ± 3.31 in controls and this difference was statistically significant (p < 0.001). Mean RI in glaucoma patients was 0.76 ± 0.06 compared to 0.69 ± 0.06 in controls and the difference was significant (p < 0.001).

In the CRA, mean PSV of glaucoma patients was 10.82 ± 3.63 cm/s compared to 13.11 ± 3.71 cm/s in controls and this difference was significant (p = 0.02). Similarly, mean EDV was significantly lower in glaucoma patients than controls - 3.90 ± 1.57 cm/s vs 5.23 ± 1.70 cm/s (p < 0.001). Mean RI of CRA was 0.66 ± 0.07 in glaucoma patients and 0.60 ± 0.06 in controls and this difference was significant (p < 0.001).

| | Doppler Indices | Primary Open Angle Glaucoma | Normal-Tension Glaucoma | Controls | | |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Mean ± SD | Mean ± SD | F value | P value |
| OA | PSV (cm/s) | 27.77 ± 5.42 | 29.64 ± 5.90 | 32.50 ± 8.77 | 3.775 | 0.026* |
| | EDV (cm/s) | 6.40 ± 1.72 | 7.51 ± 2.39 | 10.08 ± 3.31 | 17.380 | < 0.001* |
| | RI | 0.77 ± 0.06 | 0.75 ± 0.06 | 0.69 ± 0.06 | 16.061 | < 0.001* |
| CRA | PSV (cm/s) | 9.63 ± 3.32 | 11.77 ± 3.63 | 13.11 ± 3.71 | 7.826 | < 0.001* |
| | EDV (cm/s) | 3.33 ± 1.27 | 4.36 ± 1.65 | 5.23 ± 1.70 | 12.079 | < 0.001* |
| | RI | 0.68 ± 0.05 | 0.63 ± 0.08 | 0.60 ± 0.06 | 13.995 | < 0.001* |

***Table 7:*** *Comparison of mean RI Between primary open angle glaucoma patients, normal-tension glaucoma patients and controls.*

**: Statistically Significant; PSV: Peak Systolic Velocity; EDV: End Diastolic Velocity; RI: Resistivity Index; OA: Ophthalmic Artery; CRA: Central Retinal Artery.*

Table 7 compares RI and other Doppler indices between three groups: primary open angle glaucoma patients, normal-tension glaucoma patients and Controls. In the OA, the difference in the mean PSV between primary open angle glaucoma patients (27.77 ± 5.42 cm/s), normal-tension glaucoma patients (29.64 ± 5.90 cm/s) and controls (32.50 ± 8.77 cm/s) was statistically significant ($p = 0.026$). Mean EDV was 6.40 ± 1.72 cm/sec in primary open angle glaucoma patients, 7.51 ± 2.39 cm/sec in normal-tension glaucoma patients and 10.08 ± 3.31 cm/sec in controls. This difference in mean across the groups was statistically significant ($p < 0.001$). The differences in mean RI in OA in primary open angle glaucoma patients (0.77 ± 0.06), normal-tension glaucoma patients (0.75 ± 0.06) and controls (0.69 ± 0.06) was statistically significant ($p < 0.01$).

In CRA, the difference in mean PSV between primary open angle glaucoma patients, normal-tension glaucoma patients and controls was statistically significant - 9.63 ± 3.32 cm/s vs 11.77 ± 3.63 cm/s vs 13.11 ± 3.71 cm/s ($p < 0.001$). Mean EDV was lowest in primary open angle glaucoma patients (3.33 ± 1.27 cm/sec), followed by normal-tension glaucoma patients (4.36 ± 1.65 cm/sec) and high in controls (5.23 ± 1.70 cm/sec). This difference was statistically significant ($p < 0.001$). Resistivity index was highest in primary open angle glaucoma patients (0.68 ± 0.05), followed by normal-tension glaucoma patients (0.63 ± 0.08) and lowest in controls (0.60 ± 0.06); and this difference was statistically significant ($p < 0.001$).

## Discussion

### Socio-demographic characteristics

All participants were adults and their mean ages were 50.4 ± 17.2 years for glaucoma patients and 49.5 ± 16.8 years for controls. This mean age was similar to that of Mokbel., *et al*. [37] in Egypt, but lower than that reported by Odunlami., *et al*. [17] in Ile-Ife, Western Nigeria. The reason is not apparent as the study did not group participants in age categories. Different from this study, Butt., *et al*. [38] in Scotland reported a higher mean age of their study subjects. This is not surprising their study included patients with diabetes mellitus and hypertension - diseases known to be commoner in older individuals. Most of the glaucoma patients were older than 40years, consistent with the study by Olawoye., *et al*. [39] and the Nigerian National Blindness and Visual Impairment Survey [7].

More females than males participated in the study; similar to the study by Odunlami., *et al* [17]. This is probably because women have better eye health seeking behavior than men as reported by Thompson., *et al* [40].

Systolic and diastolic blood pressures were not significantly different in glaucoma patients and controls as systemic hypertension was excluded from both groups. This finding is similar to the study by Samsudin., *et al*. [41] where systemic hypertension was also excluded from both groups. In contrast, Butt., *et al*. [38] reported significantly higher systolic blood pressure in glaucoma patients than in controls. This is probably due to the fact they included glaucoma patients with systemic hypertension but for controls, those with systemic hypertension were excluded. In this study, the difference in the mean central corneal thickness in glaucoma patients and controls was not statistically significant and this is similar to finding in a study by Adegbehingbe., *et al*. [42] in Southwest Nigeria. This may be unconnected with the fact that both studies where carried out in Southern Nigeria and these study populations have close proximity to each other as well as share similar demographic characteristics.

The mean intraocular pressure and corrected IOP were significantly higher in glaucoma patients than controls in this study ($p < 0.001$ for both comparisons). However, these values (mean IOP and corrected IOP) were lower than those reported by Odunlami., *et al* [17]. In their study only glaucoma patients with intraocular pressure higher than 22 mmHg where recruited, which may explain the higher values reported. The difference between mean IOP and corrected mean IOP was statistically significant for both glaucoma patients and controls ($p < 0.001$ and 0.010 respectively).

In this study, primary open angle glaucoma patients constituted 44.4% while normal-tension glaucoma patients made up 55.6% of all glaucoma patients. This proportion may have been possible because majority of the POAG patients were excluded from the study either because they had systemic hypertension or diabetes mellitus. A study by Omoti., *et al*. [43] has given support to this finding as they reported that POAG patients had significantly higher association with systemic hypertension and diabetes mellitus than non-glaucoma patients. The finding is contrary to the study by Olawoye and Tarella [44] where primary open angle glaucoma patients constituted a far higher proportion of 51.2% compared 19.6% for normal-tension glaucoma patients.

### Pattern of resistivity index in glaucoma patients and controls

This study showed that in glaucoma patients, resistivity index (RI) in both ophthalmic artery and central retinal artery were independent of age. In contrast, Butt., *et al*. [45] reported that in glaucoma patients, resistivity index in ophthalmic artery significantly increased with age while that of central retinal artery was independent of age. This difference may not be unconnected with the fact that glaucoma patients who had systemic conditions such as diabetes, hypertension and cerebrovascular accidents were part of their study population. The incidences of these systemic conditions are known to increase and worsen with age and their additive effect could have contributed to the increasing resistivity index with age.

In controls, resistivity index increased with advancing age in both ophthalmic and central retinal arteries; however, this increase in resistivity index with age was only significant in the ophthalmic artery ($p < 0.001$). Harris., *et al*. [46] reported a similar result in their study. This similarity may be because both studies had subjects with similar age range. Also similar to this study, Ustymowicz., *et al*. [47] reported an increase in resistivity index with age in both ophthalmic and central retinal arteries, but the increase in resistivity index with age was only significant in the central retinal artery ($p < 0.001$). This minor difference in observation could have occurred because their study had a larger sample size of 140 healthy volunteers but, various similarities such as mean age and age range of participants, and also similar male-female ratio. In the same vein, the study by Baxter., *et al*. [48] reported no significant increase in resistivity index of ophthalmic artery with age but a significant correlation in central retinal artery. Their study utilized a larger sample size which could explain the difference It is widely reported in the literature that blood flow to arterial beds reduces with age [49,50] as a result of either increased peripheral vascular resistance or decreased cardiac output or both.

### Comparison of resistivity index in glaucoma patients and controls

In this study, mean resistivity index of ophthalmic and central retinal arteries were significantly higher in glaucoma patients than in controls ($p < 0.001$). This is similar to the study by Ishola., *et al*. [51] where mean resistivity indices of POAG and NTG patients were compared to that of controls. Similar findings were also reported by Odunlami., *et al* [17]. Even though their study utilised similar sample size (50 cases and 50 controls), only primary open angle glaucoma patients constituted the glaucoma patients unlike this study that included normal-tension glaucoma patients. This result suggests an increase in vascular resistance and reduction in blood flow to the optic nerve head in POAG irrespective of whether the IOP was high or within normal limits. Mokbel., *et al*. [37] in Egypt, also reported similar findings in their study subjects. In the Mokbel study, the higher resistivity index values seen in glaucoma patients could have been because they used median resistivity index compared to this study which used mean resistivity index. In addition, they also had a smaller sample size and a narrower age range compared to this study. In India, Sharma., *et al*. [52] had similar results even though they used a smaller sample size and some of the glaucoma patients had undergone medical and/or laser treatment before enrolment in the study. Other studies with similar results were those of Butt., *et al*. [45] and Galassi., *et al*. [15] these studies however used only patients with normal pressure glaucoma. This similarity in the results of these studies is probably because there is reduced that optic nerve perfusion in glaucoma irrespective of intraocular pressure level.

In order to remove bias of intraocular pressure as a confounder in this study, the glaucoma patients were divided into two groups - primary open angle glaucoma patients and normal-tension glaucoma patients. The mean resistivity index in the ophthalmic and central retinal arteries of primary open angle glaucoma patients were significantly higher than the mean RI in controls - similar to the report by Odunlami., *et al*. [17] and Mokbel., *et al*. [37] who both compared only primary open angle glaucoma patients with controls. Similarly, in normal-tension glaucoma patients, the mean resistivity index in ophthalmic and central retinal arteries were significantly higher than those of controls. This result is in agreement with that of Butt., *et al.* [45] who had similar sample size in the normal-tension glaucoma patients but included those with systemic disease such as diabetes mellitus, hypertension and history of previous cerebrovascular accidents. Galassi., *et al*. [15] also reported higher mean resistivity index in ophthalmic and central retinal arteries compared to controls, even though they had a larger sample size and a higher mean age of cases and controls. On the other hand, Samsudin., *et al*. [52] found no significant difference in the mean resistivity index of ophthalmic artery between normal-tension glaucoma patients and controls. This may be due to the fact the glaucoma patients were on anti-glaucoma medications; they also did not exclude those with diabetes and hypertension.

In this study, mean resistivity indices of ophthalmic and central retinal arteries were significantly higher in primary open angle glaucoma patients than those of normal-tension glaucoma patients. This result may be explained by the fact that resistivity index is shown to increase with intraocular pressure [17] and therefore, this additive effect on resistivity index may cause a higher resistance and a lower optic nerve perfusion in primary open angle than normal-tension glaucoma patients. In contrast, Yamazaki., *et al*. [53] reported that there was no significant difference in resistivity indices of both arteries in primary open angle and normal-tension glaucoma patients. This could have occurred because both the primary open angle and normal-tension glaucoma patients were being treated with anti-glaucoma medications and the bias of intraocular pressure was removed. Another contrasting result was reported by Butt., *et al*. [38] where mean resistivity of ophthalmic artery was greater in primary open angle glaucoma patients than normal-tension glaucoma patients but the difference did not reach significant levels. However, in the central retinal artery, mean resistivity indices in both groups were the same. Their study did not exclude glaucoma patients with systemic diseases such as diabetes mellitus, systemic hypertension and cerebrovascular disease which could have added bias to their result. The reason for these contrasting findings in the different studies is likely due to differences in methodologies of the studies.

This study showed that the mean peak systolic velocity (PSV) and end diastolic velocity (EDV) of ophthalmic artery in glaucoma patients were significantly lower than those of controls. Similarly, mean PSV and EDV of central retinal artery in glaucoma patients were also significantly lower than in controls. This reflects a reduction in blood flow in glaucoma patients. Odunlami., *et al*. [17] also reported similar findings for peak systolic and end diastolic velocities in a Nigerian population. Another study by Sharma and Bangiya [52] in an Indian population also reported significantly slower blood flow velocities in ophthalmic and central retinal arteries of POAG patients compared to controls. These two studies had similar results to the current study despite using only primary open angle glaucoma patients who represented the POAG study group. This suggests that optic nerve perfusion is reduced in glaucoma irrespective of glaucoma is primary open angle or normal-tension. In contrast, Mokbel., *et al.* [37] in Egypt, reported that there was no difference between median peak systolic and end diastolic velocities of ophthalmic artery in glaucoma patients and controls. In addition, they reported that median end diastolic velocity of the central retinal artery was lower in glaucoma than in controls, while noting no difference in median peak systolic velocity of glaucoma patients compared to controls. This difference may be due to the fact that median values were used for comparison in their study instead of mean values which was used in this study.

This study also showed that the mean peak systolic velocity and end diastolic velocity in ophthalmic and central retinal arteries of primary open angle glaucoma patients were significantly lower than those of controls ($p < 0.001$). Other studies also reported similar finding [17,53]. Similarly, the means peak systolic velocity and end diastolic velocity in ophthalmic and central retinal arteries of normal-tension glaucoma patients was significantly lower than controls ($p < 0.001$). The reason for these similarities in results is probably because there is reduced optic nerve perfusion in glaucoma regardless of intraocular pressure and this is evident where similar findings were reported in other studies with normal-tension glaucoma patients [15,45].

However, Huber., *et al*. [54] comparing peak systolic velocity and end diastolic velocity in normal-tension glaucoma patients and healthy volunteers, found no significant difference between the two groups. This may not be unconnected with the fact that peak systolic and end diastolic velocities of both ophthalmic and central retinal artery have great variability as shown in different studies [17,37,45,52,54]. This apparent disadvantage is overcome by the resistivity index which is a velocity ratio and is substantially independent of Doppler angle and thus useful in evaluating the functional parameters of ocular vascular bed noted to be altered in glaucoma [55]. These reduced end diastolic velocity and increased resistivity index show that changes in resistance affect diastolic blood flow more than systolic velocity thereby worsening organ ischaemia [56]. Thus, reduced blood velocity and increased resistivity index can lead to optic nerve ischaemia which is ultimately causes glaucomatous optic nerve damage [57].

## Conclusion

From the findings in this research work, it can be concluded that there is reduced optic nerve blood flow in glaucoma patients of Nigerian origin as well as the presence of defective autoregulation in the optic nerve vascular bed of these glaucoma patients. Furthermore, mean resistivity indices of ophthalmic and central retinal arteries were significantly higher in primary open angle glaucoma patients with all levels of intraocular pressure than in controls. Similarly, the mean peak systolic velocity and end diastolic velocity were significantly lower in cases than in controls. These suggest increased resistance to blood flow and reduced perfusion of the optic nerve head leading to glaucomatous optic neuropathy.

A significant inverse relationship also exists between diastolic ocular perfusion pressure and resistivity index in ophthalmic artery in glaucoma patients while no relationship was found in the controls. This relationship indicates that there is impaired autoregulation in the measured vascular bed (ophthalmic artery) as suggested by Panerai [18]. In addition, it means that the higher resistivity index which represents increased vascular resistance distal to the point measured and reduced blood flow in the vascular beds occurs with low diastolic ocular perfusion pressure in glaucoma patients.

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