Original Article

A comparative control study of ophthalmic artery Doppler velocimetry in patients with primary open angle glaucoma in Kano, Nigeria

Adamu Ibrahim Gombe, Isyaku Kabiru[1], Ismail Anas[1], Yahuza Mansur Adamu[1], Hassan Sadiq[2]

Department of Radiology, State Specialist Hospital, Gombe, Departments of [1]Radiology and [2]Ophthalmology, College of Health Sciences, Bayero University Kano, Nigeria

Abstract

Objective: The objective of the study is to sonographically determine the hemodynamic changes in ophthalmic arteries of patients with primary open angle glaucoma (POAG) at Kano, Nigeria.

Subjects and Methods: We conducted a prospective case–control study at Aminu Kano Teaching Hospital, Nigeria, on 108 newly diagnosed POAG and 108 control subjects. Intraocular pressure (IOP) and Doppler ultrasound velocimetry of ophthalmic arteries were assessed. Peak systolic velocity (PSV), end diastolic velocity (EDV), resistive indices (RIs), pulsatility indices (PIs) and systolic/diastolic (S/D) ratios of the ophthalmic arteries were evaluated and documented.

Results: The mean IOP values of POAG group in the right and left eyes were higher than the values of the right and left eyes of the control group. This was statistically significant ($P = 0.000$). The mean PSV, EDV, RI, PI, and S/D values in the POAG group of the right and left eyes were lower than values for the right and left eyes of the control group, which was also statistically significant ($P = 0.000$). The IOP showed positive correlation with PSV and EDV in both eyes of POAG cases but negative correlation with PI and S/D in both eyes in the POAG group. It however correlated positively with RI in the right eye and negatively with RI in the left eye.

Conclusions: The study showed significant differences between ophthalmic artery Doppler indices of patients with POAG and the healthy control subjects.

Keywords: Doppler velocimetric indices, ophthalmic artery, primary open angle glaucoma

Address for correspondence: Dr. Adamu Ibrahim Gombe, Department of Radiology, State Specialist Hospital, Gombe, Nigeria.
E-mail: ibrogombe@gmail.com

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INTRODUCTION

Glaucoma is an optic neuropathy that is characterized by changes in the optic disc and a defective visual field corresponding to a structural loss of neural tissue in the optic nerve head (ONH), subsequent visual field loss, and usually associated with raised intraocular pressure (IOP) greater than 21 mmHg.[1] It follows cataract among the causes of visual loss and blindness in Nigeria and the world (16.7%).[2] According to the most recent World Health Organization alert, it is estimated that more than

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100 million people may probably have glaucoma, over 20 million suffer from glaucoma, and over 5 million people are blind as a result of the disease.[3] Its prevalence in Africa is about 15%, and this is the highest compared to other parts of the world.[2] In Nigeria, its prevalence is about 0.7%.[4] Most previous studies indicate that glaucoma occurs more frequently in Africans than in Caucasians.[1,2] It is divided into congenital, juvenile-onset, and adult-onset categories.

The search for other possible etiologies leads to the identification of vascular factors as possible causative agents. Patients with glaucoma have been found to have diseases associated with systemic vascular factors such as peripheral vasospasm, systemic hypotension, and migraine.[5,6] Evidence has also suggested that vascular factors play a role in glaucoma pathogenesis.[5,6]

Erickson *et al*.[7] introduced orbital color Doppler imaging (CDI) in 1989 and that provided the opportunity for assessment of orbital blood vessels. CDI is a noninvasive ultrasonic tool that assesses blood flow velocity. CDI is usually preferred to other imaging modalities because it is noninvasive, is not affected by poor ocular media, requires no contrast medium or radiation, and has been used in ophthalmology since 1989.[7] The ability of CDI to access retrobulbar blood flow which is directly related to ONH perfusion makes it a potential tool for the evaluation of early changes in vascular flow related to glaucoma.[8]

The purpose of this study is to compare the various differences in ophthalmic artery velocimetric indices in patients with primary open angle glaucoma (POAG) and healthy controls. If abnormality (ies) in velocimetric indices of patients with glaucoma is/are found, corrective measures would be instituted by the clinicians early before onset of complications.

SUBJECTS AND METHODS

This was a hospital-based, cross-sectional study conducted at Aminu Kano Teaching Hospital, Kano on 216 subjects – comprising 108 subjects with POAG and the same number of age- and sex-matched controls. The study was approved by the Research and Ethics Committee of the hospital. It was conducted within 6 months from February 2018 to August 2018, and the Helsinki declaration tenets were strictly adhered to.

The diagnosis of POAG was made by a consultant ophthalmologist based on glaucomatous optic disc changes on fundoscopy (Heine Direct Ophthalmoscope), reproducible visual field defects typical of glaucoma (Humphrey Field Analyzer, Carl Zeiss, Germany, Sita full threshold standard program 30-2), raised IOP of >21 mmHg (Goldmann applanation tonometer, type AT 900 HAAG STREIT, 2000 AG) as well as open and normal angles on gonioscopy (3 MIRROR GONIO/FUNDUS LENS). Ophthalmic artery Doppler ultrasonography was then carried out by the researcher as described in the section under "Sonographic technique of ophthalmic artery Doppler." The study subjects included 108 newly diagnosed adult patients with POAG attending outpatient clinic as well as age- and sex-matched volunteers with normal IOP (<21 mmHg) and no clinical evidence of glaucoma to serve as the control group. Patients on the treatment for glaucoma, cigarette smokers, hypertensives, and diabetics and those with previous history of surgery for glaucoma or other ocular diseases were excluded from the study. Patients with cataract or corneal opacity preventing posterior segment assessment as well as those with head trauma, ocular, cranial, or facial masses and inflammatory ocular conditions were also excluded.

Sonographic technique of ophthalmic artery Doppler ultrasound examination

The procedure was explained to the patients and consent was obtained before commencement. All the patients and the control subjects were scanned by the researcher. The scanning was done between 10 am and 2 pm daily on 108 consecutive subjects. Patients were examined in the supine position with eyes closed and gaze directed at the ceiling. The head was also tilted approximately 15° cephalad. A thick layer of acoustic gel was applied to the closed eyelid with the transducer positioned horizontally without applying pressure to the eye to avoid alteration of the flow velocity measurements. A Mindray DC-6 Ultrasound Machine with 7.5 MHz Linear Array Transducer (Biomed Electronics, Shenzhen, China, 2007) was used. Both eyes of the POAG patients and the control group were scanned. The angle of insonation between the ultrasound beam and the vessel was adjusted to ≤60°,[9] while the Doppler sample gate was adjusted to 2 mm. Color Doppler was applied and the sample volume was oriented superiomedially to the optic nerve. The ophthalmic artery is just medial to the hypoechoic stripe of the optic nerve[10] [Figure 1]. Spectral waveforms of the ophthalmic artery were obtained and the velocimetric indices were obtained automatically, namely peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI), pulsatility index (PI), and systolic/diastolic (S/D) mean velocity ratio. Three separate Doppler readings were taken for every subject and the average value recorded. Thereafter, the coupling gel on the subject's eyes was carefully cleaned, and the ocular scan findings were recorded and explained to the subjects.

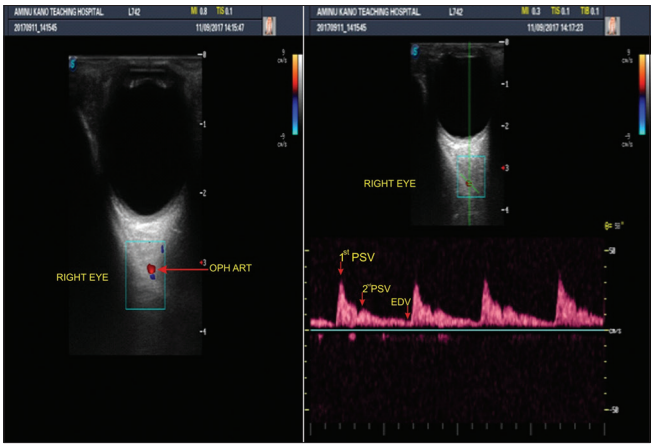

Figure 1: Doppler ultrasound image showing the ophthalmic artery and its spectral waveform in a normal subject. PSV = Peak Systolic velocity, EDV = End Diastolic Velocity, Oph Art = Ophthalmic artery

Methods of data analysis

The data was analyzed using a statistical package for social sciences (SPSS) version 22.0 software (SPPS Inc, Chicago, Illinois, USA). In addition to descriptive statistics, possible association between the observed velocimetric indices and IOP was examined with correlation coefficient at 95% confidence interval. The results obtained were presented in tables, figures, and charts. Qualitative variables were presented as percentage and proportion. The Pearson's correlation coefficient was used in correlating intraocular pressure and ophthalmic artery Doppler velocimetric indices, i.e. PSV, EDV, RI, PI, and S/D; Student's independent *t*-test was used to compare age, intraocular pressures, as well as ophthalmic artery Doppler velocimetric indices (PSV, EDV, RI, PI, and S/D) of the cases and that of the control subjects. A $P \leq 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the subjects

The age ranges for the POAG cases and control subjects were 18–72 years and 18–73 years, respectively. The mean ages for the POAG cases and control subjects were 51.8 ± 14.0 years and 52.0 ± 14.00 years, respectively [Table 1].

The mean IOPs in the right and left eyes of POAG group were 27.1 ± 5.7 mmHg and 27.1 ± 5.8 mmHg, respectively, while that for the control group were 16.3 ± 2.5 mmHg and 15.8 ± 2.7 mmHg, respectively, for the right and left eyes.

Doppler velocimetric characteristics of the subjects

The mean values of the PSV in the POAG cases were 29.2 ± 4.6 cm/s and 29.3 ± 5.0 cm/s for the right and left eyes, respectively, while those of the control group measured were 37.9 ± 5.3 cm/s and 38.1 ± 5.4 cm/s for the right and left eyes, respectively. They both showed statistically significant difference in both the right eyes (29.2 ± 4.6 cm/s vs. 37.9 ± 5.3 cm/s, $t = -13.03$, $P \leq 0.001$) and the left eyes (29.3 ± 5.0 cm/s vs. 38.1 ± 5.4 cm/s, $t = -12.43$, $P \leq 0.001$) [Table 2 and Figure 2].

Table 1: Age distribution of the subjects

Age (years)	POAG cases			Control subjects		
	Males	Females	Total	Males	Females	Total
18-27	1	8	9	1	8	9
38-47	8	5	13	8	5	13
48-57	13	16	29	13	16	29
58-67	28	8	36	28	8	36
68-77	3	7	10	3	7	10
Total	57	51	108	57	51	108

POAG: Primary open angle glaucoma

The mean values of the EDVs were 7.8 ± 2.2 cm/s and 7.7 ± 2.2 cm/s for the right and left eyes of the POAG cases, respectively, and 12.3 ± 2.2 cm/s and 12.5 ± 2.0 cm/s for the right and left eyes, respectively, of the control groups. They also both showed statistically significant difference (right eyes: 7.8 ± 2.2 cm/s vs. 12.3 ± 2.2 cm/s, $t = -14.97$, $P \leq 0.001$ and left eyes: 7.7 ± 2.2 cm/s vs. 12.5 ± 2.0 cm/s, $t = -16.54$, $P \leq 0.001$) [Table 2 and Figure 2].

The mean values for the resistive indices were 0.74 ± 0.07 on both the right and left eyes for the POAG cases and 0.67 ± 0.05 and 0.66 ± 0.06 respectively for the right and left eyes of the control group. They both showed statistically significant difference (right eyes: 0.74 ± 0.07 vs. 0.67 ± 0.05, $t = 8.68$, $P \leq 0.001$ and left eyes: 0.74 ± 0.07 vs. 0.66 ± 0.06, $t = 10.26$, $P \leq 0.001$) [Table 2 and Figures 3, 4].

The mean values of the PIS for the POAG cases were 1.6 ± 0.4 and 1.6 ± 0.5 for the right and left eyes, respectively, while the control group showed mean values of 1.4 ± 0.3 and 1.3 ± 0.3 for the respective right and left eyes. They both showed statistically significant difference (right eyes: 1.6 ± 0.4 vs. 1.4 ± 0.3, $t = 3.84$, $P \leq 0.001$ and left eyes: 1.6 ± 0.5 vs. 1.3 ± 0.3, $t = 4.74$, $P \leq 0.001$) [Table 2 and Figures 3 and 4].

The mean values of the S/D were 4.0 ± 1.1 and 4.0 ± 1.2 for the right and left eyes of the POAG cases, respectively, while the control group showed mean values of 3.2 ± 0.5 and 3.2 ± 0.5 for the respective right and left eyes. They also both showed statistically significant difference (right eyes: 4.0 ± 1.1 vs. 3.2 ± 0.5, $t = 7.00$, $P \leq 0.001$ and left eyes: 4.0 ± 1.2 vs. 3.2 ± 0.5, $t = 7.20$, $P \leq 0.001$) [Table 2 and Figures 4].

There was no statistically significant difference in the correlation values of the IOP and the ophthalmic artery Doppler velocimetric indices in both the POAG cases and the control subjects of both eyes.

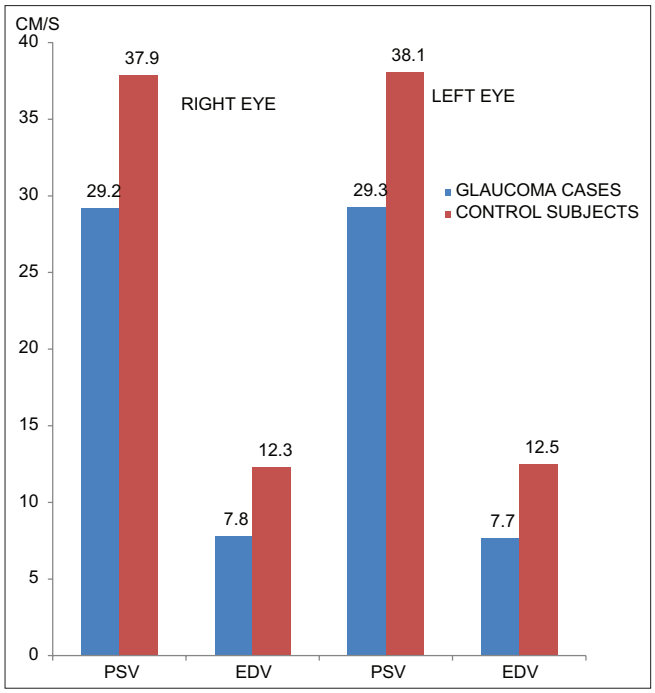

Figure 2: Histogram showing means of peak systolic velocity and end diastolic velocity of the ophthalmic arteries of both eyes. PSV: Peak systolic velocity, EDV: End diastolic velocity

There was a weak positive correlation (correlation value of ≤+0.3) between the right IOP and the right PSV in both the POAG cases and the control subjects (r = 0.04 and r = 0.06, respectively).

The EDV however showed a weak positive correlation with the right IOP in the POAG cases but a weak negative correlation (correlation value of ≤−0.3) with the right IOP in the control subjects (r = 0.08 and r = −0.03, respectively).

There was a weak positive correlation between the right IOP and the right RI in both the POAG cases and the control subjects (r = 0.01 and r = 0.04, respectively).

The PI however showed a weak negative correlation with the right IOP in the POAG cases but a weak positive correlation with the right IOP in the control subjects (r = −0.12 and r = 0.02, respectively).

Similarly, the S/D showed a weak negative correlation with the right IOP in the POAG cases but a weak positive correlation with the right IOP in the control subjects (r = −0.04 and r = 0.05, respectively).

There was a weak positive correlation between the left IOP and the left PSV in both the POAG cases and the control subjects (r = 0.04 and r = 0.01, respectively).

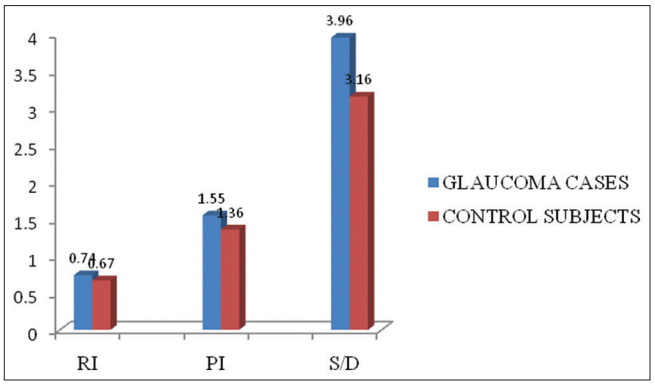

Figure 3: Histogram showing means of resistive index, pulsatility index, and systolic/diastolic ratios of the ophthalmic arteries of the right eyes. RI: Resistive index, PI: Pulsatility index, S/D: Systolic/diastolic

Table 2: Range of ophthalmic artery Doppler velocimetric indices of the primary open angle glaucoma cases and the control subjects of the right and left eyes

Doppler parameter	POAG cases		Control subjects	
	Right eye	Left eye	Right eye	Left eye
PSV (cm/s)	20.8-37.0	20.1-39.8	30.1-53.9	30.2-53.9
EDV (cm/s)	4.4-12.3	4.4-12.3	10.0-19.8	10.1-18.9
RI	0.6-0.9	0.6-0.9	0.5-0.7	0.5-0.7
PI	0.8-2.8	0.7-2.8	0.7-2.1	0.6-1.9
S/D	2.6-7.9	0.1-7.9	2.0-5.2	2.0-4.2

POAG: Primary open angle glaucoma, PSV: Peak systolic velocity, EDV: End diastolic velocity, RI: Resistive index, PI: Pulsatility index, S/D: Systolic/diastolic

Similarly, there was a weak positive correlation between the left IOP and the left EDV in both the POAG cases and the control subjects (r = 0.09 and r = 0.02, respectively).

The RI however showed a weak negative correlation with the left IOP in the POAG cases but a weak positive correlation with the left IOP in the control subjects (r = −0.01 and r = 0.01, respectively).

Similarly, the PI showed a weak negative correlation with the left IOP in the POAG cases but a weak positive correlation with the left IOP in the control subjects (r = −0.13 and r = 0.04, respectively).

The S/D however showed a weak negative correlation with the left IOP in both the POAG cases and the control subjects (r = −0.05 and r = −0.07, respectively).

There was no statistically significant difference in all the parameters (IOP, PSV, EDV, RI, PI, and S/D) measured in the right and left eyes of both the POAG cases and control group.

DISCUSSION

Glaucoma is a chronic disease-causing neurodegenerative change of the optic nerve. High IOP has long been

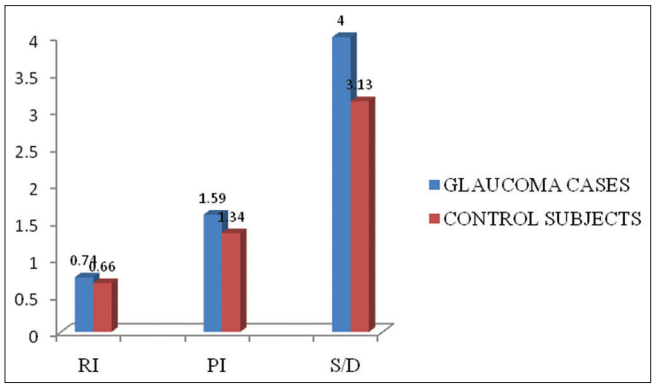

Figure 4: Histogram showing means of resistive index, pulsatility index, and systolic/diastolic ratios of the ophthalmic arteries of the left eyes RI: Resistive index, PI: Pulsatility index, S/D: Systolic/diastolic

considered the most important risk factor for the onset and progression of glaucoma.[11] Yet, glaucomatous optic nerve damage progresses even when IOP is controlled.[12] Progress made in the past few years in medical research has opened a new approach to the pathophysiology of glaucoma.[11] Previous studies have shown a link between ocular perfusion pressure and glaucoma, as it is known that glaucoma can progress despite normal IOP.[12] Most of these studies have reported that blood flow velocities are lower and RI is higher in patients with POAG compared to normal subjects.[10,13]

In this study, there were 57 (52.8%) males and 51 (47.2%) females, with a male-to-female ratio of 1.2:1. This is similar to previous studies where prevalence of POAG was found to be higher in males than females.[1,2,14] The mean ages of the subjects in the POAG cases and control group were 51.8 ± 14.0 and 52.0 ± 14.0, respectively. These were lower than the mean ages of 60.4 ± 17.7 and 60.1 ± 17.5 reported by Adeyinka *et al*.[10] in Ile-Ife, Southwestern Nigeria. This variation could be explained by the fact that previous studies in Southwestern Nigeria have indicated that significant number of patients with glaucoma is seen in the older age group (7th decade and above),[1,15] whereas most patients with glaucoma in Northern Nigeria are seen in the sixth decade and below.[2,16] This difference in age in the two studies could be attributed to higher life expectancy and literacy level obtained in the Southwestern region of the country compared to the northern part.[17] The values were also lower than the mean ages of 68.4 ± 8.5 and 68.1 ± 8.6, respectively, in the POAG cases and control subjects reported by Singh *et al*.[13] in India; 64.4 ± 8.5 and 67.3 ± 9.2, respectively, in the cases and control subjects reported by Sekeroglu *et al*.[18] in Turkey; and 55.1 ± 7.4 and 55.2 ± 6.0, respectively, in the POAG cases and control subjects reported by Ulickiene and Paunksnis[19] in Lithuania. The variation in mean age between this study and the ones mentioned above is also likely due to longer life span obtained in India, Turkey, and Lithuania compared to Nigeria,[20] thus resulting in higher proportion of people who may have been having POAG for a long period of time. There was no statistically significant difference in the mean ages of the patients and the control subjects ($P = 0.92$) as well as the gender because they were age and sex matched.

In this study, the mean IOPs of the POAG cases were lower than those of the control subjects. The mean values were 27.1 ± 5.7 mmHg and 16.3 ± 2.5 mmHg, respectively, for the POAG cases and control subjects of the right eyes while they were 27.1 ± 5.8 mmHg and 15.8 ± 2.7 mmHg, respectively, for the POAG cases and control subjects of the left eyes. Similar mean values of 26.0 ± 2.3 mmHg and 15.3 ± 2.1 mmHg in POAG cases and control subjects were obtained by Singh *et al*.[13] in India. However, Ulickiene and Paunksnis[19] in Lithuania obtained a lower mean IO*P* value of 22.1 ± 5.2 mmHg in the POAG cases but similar mean value of 16.0 ± 2.3 mmHg in the control subjects. The difference in IOP in the glaucoma cases may be accounted by the fact that the sample size used in their study (of 13 subjects) was far smaller than the present study which was 108. Another factor that may have contributed for the low intraocular pressure in the study by Ulickiene and Paunksnis[19] was the IOP in their study was not measured in the morning hours. Previous studies have shown that maximum IOP is obtained mostly between 9 am to 3 pm.[21,22] The statistically significant difference between the IOP in the POAG cases and that of the control group ($P = 0.00$) in this study agrees with the findings of Singh *et al*.[13] in India.

This study found that the PSV in patients with POAG was lower than the PSV in the control group. This finding is similar to previous study of Sekeroglu *et al*.[18] in Turkey. However, Chiou *et al*.[23] in Taiwan did not find any difference in the PSV between the POAG cases and control subjects. The difference in the PSV with the study by Chiou *et al*.[23] may be because they examined patients with hypertension and diabetes mellitus and patients who had laser therapy and other antiglaucoma medications which would have affected the values obtained in their study. A study by Raut *et al*.[24] in India showed that ophthalmic artery Doppler velocimetric indices may return to normal after treatment. This is not the case here where all patients with POAG with other comorbidities that affect the ophthalmic artery were excluded from the study.

This study also found a positive linear correlation between IOP and the PSV though not statistically significant (right eye: $R = 0.04$, $P = 0.68$; left eye: $R = 0.04$, $P = 0.69$). This

finding is similar to what Garhöfer *et al*.[25] in Austria found, where there was a weak positive correlation ($r = 0.33$) between the IOP and the PSV; however, this is in contrast to what was reported by Adeyinka *et al*.[10] in Nigeria where there was strong negative correlation between the IOP and PSV. This is likely because their sample size was smaller which affected the correlation value. Previous studies have shown that as the sample size increases, the confidence in the estimate increases, uncertainty decreases, and there is greater precision.[26,27,28]

Similarly, this study found a decreased EDV in patients with POAG when compared with the control subjects. This finding is also similar to previous studies by Siesky *et al*.[29] in America and Marineta *et al*.[30] in Romania. However, Januleviciene *et al*.[4] found much lower values of EDV than in this study. This could be explained by the fact that the mean age of their subjects (55 years for control and 58 years for the POAG) were higher than that of this study and ocular blood flow is much reduced with increasing age.

There was also positive linear correlation between IOP and the EDV though not statistically significant (right eye: $R = 0.08$, $P = 0.39$; left eye: $R = 0.09$, $P = 0.37$). This finding is similar to what Garhöfer *et al*.[25] in Austria found. This is however in contrast to what Eniola *et al*.[31] in Nigeria reported where there was negative correlation between the IOP and EDV. This is likely due to the fact that the sample size in their study was smaller than this study which affected the correlation value.[26-28]

The findings of lower PSV and EDV values in patients with POAG is likely due to loss of vascular autoregulation seen in most patients with POAG that have elevated IOP. Many studies have shown that the ophthalmic vessels can autoregulate to maintain constant blood flow, but this autoregulatory mechanism is impaired with high IOP. A study conducted by Raut *et al*.[24] in India showed that after antiglaucoma treatment, IOP was reduced and subsequently PSV and EDV were increased from their baseline values toward normalization.[24]

The RIs in this study were found to increase in patients with POAG when compared with the values obtained in the control subjects. This finding is similar to the report by Meng *et al*.[8] in Asia. However, Abegão Pinto *et al*.[6] did not find difference in the RI between the POAG cases and the control subjects. This is because their patients were on antiglaucoma treatments which would likely affect the Doppler readings. Another reason could be due to different study design with this study.

There was also weak positive linear relationship between IOP and the RI on the right side and weak negative relationship between IOP and RI in the left eye though not statistically significant (right eye: $R = 0.01$, $P = 0.89$; left eye: $R = -0.01$, $P = 0.94$). This finding is similar to what Garhöfer *et al*.[25] in Austria found, where there was positive correlation between the IOP and the RI while Eniola *et al*.[31] in Nigeria found a high positive correlation between the IOP and the RI. The increase in RI in glaucomatous subjects implies an increased peripheral resistance to flow in causing direct impedance to blood flow in retinal circulation.[10] RI has advantage in that its value does not depend on Doppler angle as opposed to PSV and EDV, as it is a ratio and its value can be used for comparison of results even in different studies which are not suitable for PSV and EDV since their values depend on Doppler angle.[31,32]

The PIs in this study were found to increase in patients with POAG when compared with the values obtained in the control subjects. This finding is also similar to the report by Raut *et al*.[24] in India and Asejczyk-Widlicka *et al*.[33] in Poland who found increased PI in patients with POAG when compared with the control subjects. However, Luis *et al*.[34] found no difference in the PI in the two groups. The reason could be due to higher age group (70.1 years) used in their study which reduced the blood flow significantly when compared with this study.

There was a weak negative linear relationship between IOP and the PI on both the right and left eyes though not statistically significant (right eye: $R = -0.12$, $P = 0.21$; left eye: $R = -0.13$, $P = 0.18$). The impedance indices, i.e. RI and PI, yield important information on decreased vascular compliance and resistance downstream from the measuring location. The increased PI may be due to distal resistance and perfusion pressure which gets elevated with increase in flow velocities pulsation before loss of autoregulation.

Similarly, the S/D ratio indices in this study were found to increase in patients with POAG when compared with the values obtained in the control subjects. This finding is similar to the report by Jimenez-Aragon *et al*.[7] and Calvo *et al*.[35] both in Spain where the S/D value in glaucomatous subjects was higher than the control group. However, Pinto *et al*.[5] in Belgium found a lower S/D value in glaucomatous patients when compared to the control subjects. It is likely that their patients had more progressing disease than the ones used in this study.

There was a weak negative linear relationship between IOP and the S/D values on both the right and left eyes though not statistically significant (right eye: $R = -0.04$,

$P = 0.66$; left eye: $R = -0.05$, $P = 0.61$). The higher value of S/D obtained in this study could suggest that the EDV is more affected than the PSV in glaucomatous subjects, hence making the ratio to be higher when compared with the control subjects.

In this study, it was also found that there was no statistically difference in the IOPs as well as the ophthalmic artery Doppler velocimetric indices of the right and left eyes in both the glaucoma and the control subjects. This is consistent with previous similar studies.[5,10]

CONCLUSIONS

The study showed significant differences between ophthalmic artery Doppler indices of patients with POAG and the healthy control subjects.

Limitations of the study

1. The study did not include patients on antiglaucoma treatment that would have shown the effect of medications on the ophthalmic artery Doppler velocimetric indices
2. Measurements of ocular blood flow were limited to only the ophthalmic arteries, thereby excluding readings from other smaller ocular vessels suchas the retinal and posterior ciliary arteries
3. There were challenges obtaining readings of ophthalmic arteries from some of the subjects due to its small size and anatomic variations. This was overcome by replacing with other patients
4. Furthermore, there may be heat production to the eye by the transducer.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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