Original Article

Relationship between systemic hypertension, perfusion pressure and glaucoma: A comparative study in an adult Indian population

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Aims: To study the relationship between blood pressure (BP), intraocular pressure (IOP), mean ocular perfusion pressure (MOPP) and primary open angle glaucoma (POAG) in patients with hypertension and compare it to a control group of normotensives. **Design:** Cross-sectional observational study. **Materials and Methods:** A total of 108 subjects with primary hypertension and 100 age-matched controls without hypertension were enrolled for the study. IOP measurement using Noncontact Tonometer and dilated fundus evaluation using + 90 D lens were done for all cases. Single recording of BP was taken. Gonioscopy, Humphrey's central visual fields, optical coherence tomography and pachymetry were done for all subjects with IOP > 21 mm Hg or C: D ratio ≥ 0.5 or asymmetry of > 0.2. **Statistical Analysis:** Univariate and multivariate multinomial regression models were used to determine the association between covariates and risk of glaucoma or glaucoma suspect. **Results:** There was no difference in the glaucoma status between subjects with and without hypertension. Subjects on antihypertensive medications were 1½ times more likely to have suspicious glaucoma (odds ratio [OR] =1.56] and nearly twice as likely to have POAG (OR = 1.85). In addition, we found a 31% and 12% reduction in risk of having POAG (95% confidence interval [CI] =13–45%, *P* = 0.001) and glaucoma suspect (95% CI = 2–21%, *P* = 0.03) respectively with every 1 mm Hg increment in MOPP. **Conclusion:** Subjects on antihypertensive medications are more likely to have either glaucoma or glaucoma suspect, and higher ocular perfusion pressure offers relative protection from glaucomatous damage.

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Glaucoma is a chronic progressive optic neuropathy characterized by retinal ganglion cell death and associated visual field loss.[1] The exact pathophysiological mechanism of optic nerve damage in glaucoma is not fully understood.[2] Besides the mechanical effect of raised intra ocular pressure (IOP) on optic nerve head (ONH),[3] several vascular risk factors such as systemic hypertension, atherosclerosis, vasospasm etc., have also been implicated as potential factors capable of increasing the risk of open-angle glaucoma (OAG).[2,4] The vascular hypothesis of OAG states that a low blood pressure (BP) relative to IOP can lead to low mean ocular perfusion pressure (MOPP), thus impairing perfusion of the ONH with resultant glaucomatous cupping and visual field loss.[2,5-8] Assessment of the diurnal fluctuations in IOP and MOPP is, therefore, clinically relevant in glaucoma patients.[9] Systemic hypertension as such may directly damage the small vessels of the optic disc and increase the risk of glaucoma. However, despite prior studies, the association between systemic hypertension, BP, or perfusion pressure and OAG remains unclear.[2] Understanding the relationship between these parameters is important to determine the risk factors influencing OAG development. This study examined a cohort of patients with systemic hypertension with the aim of studying its relationship with IOP and OAG and compared it to a control group of normotensives in an adult Indian population.

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Materials and Methods

The study was carried out at the Department of Ophthalmology in a tertiary health care center in South India from August 2010 to March 2012. Ethical clearance was obtained from the Institutional Ethical Committee. It was a cross-sectional observational study consisting of two groups of subjects with and without systemic hypertension. Informed consent was obtained from all the subjects. Participants were recruited from a convenient sample of patients attending the outpatient department of the institute. Enrolled subjects were all above 40 years of age. The study group included 108 subjects with essential hypertension, either self-reported hypertension or newly diagnosed cases (defined as ≥140 mm Hg systolic BP [SBP] and/or ≥90 mm Hg diastolic BP [DBP]). Participants with hypertension due to secondary causes (endocrine or kidney disease/steroid induced) were excluded. Control group included 100 age and sex-matched subjects without hypertension. Each individual with hypertension was asked about the number of years of hypertension, details of antihypertensive medications and associated diabetes mellitus. Single measurement of BP was taken for all the subjects in the right upper arm in sitting position using a mercury sphygmomanometer (auscultatory technique using the first, and fifth phases of the Korotkoff sounds as per the American Heart Association BP measurement recommendations).[10] IOP was measured in both the eyes using a NonContact Tonometer (TOPCON CT-80) while dilated fundus examination was performed using a +90 D lens for all the subjects by two equally experienced observers. Mean arterial pressure (MAP) was calculated as DBP + 1/3 (SBP–DBP). MOPP was calculated using a standardized formula (MOPP = 2/3 × MAP–IOP).[11,12] All subjects with high IOP (>21 mm of Hg) or C: D ratio ≥ 0.5 or asymmetry of > 0.2 were further evaluated with Humphrey's

central visual fields(24-2 SITA Standard Threshold protocol, Carl Zeiss Meditec, Germany), ultrasonic pachymetry, gonioscopy, optic disc photography and optical coherence tomography (OCT) - fast retinal nerve fiber layer (RNFL) and ONH protocols of stratus OCT.

Primary OAG (POAG) was diagnosed if glaucomatous cupping and characteristic field defects were present along with thinned RNFL and neuroretinal rim (NRR) on OCT and open angles on gonioscopy with or without raised IOP. The patient was classified as a glaucoma suspect if optic discs were suspicious, but IOP, RNFL thickness and visual fields were normal. If only IOP was >21 mm Hg with normal disc and fields, the patient was labeled as ocular hypertension.

Statistical analysis

Continuous data were presented as mean with a standard deviation and analyzed using Student's *t*-test or Mann–Whitney test. Chi-square or Fischer's exact test was used to compare the categorical variables. Association between IOP and BP was analyzed using age adjusted linear regression. Pearson's correlation coefficients (*r*) were used to analyze the relationships between IOP and BP and between MOPP and glaucoma status. Univariate and multivariate multinomial regression models were used to determine the association between covariates and risk of glaucoma or glaucoma suspect. Reference group included subjects without glaucoma. To determine the association between hypertension and its treatment on the glaucoma status, covariates included in Model 1 were age, gender, and presence of hypertension, antihypertensive medications and duration of diabetes. Model 2 was the same as Model 1 with the addition of MOPP and IOP to determine the association of these variables on glaucoma status.

All statistical analyses were carried out using Stata I/C version 12.0 (Stata Corp., College Station, TX) and *P* value < 0.05 was considered as significant.

Results

A total of 208 participants (108 in the hypertensive group and 100 in the control group) were included in our study. Table 1 shows a comparison of the demographic parameters, BP and IOP of the subjects with and without hypertension. In the hypertensive group, IOP varied from 10 to 24 mm Hg with a mean IOP of 15.37 mm Hg ± 2.01 mm Hg (216 eyes of 108 patients). In the control group, IOP varied between 9 and 23 mm Hg with a mean IOP of 13.41 mm Hg ± 2.82 mm Hg (200 eyes of 100 participants). Using unpaired *t*-test, the means in the two groups were found to differ significantly ($P < 0.0001$). Fig. 1 shows the median IOP and the distribution of IOP between the two groups. Subjects with hypertension also had a significantly higher MOPP compared with the controls ($P < 0.001$) [Fig. 2]. As the MOPP for both eyes are almost identical, we have shown the values for the right eye only in Fig. 2. Fifteen (13.9%) subjects in the hypertensive group and seven (7%) in the control group were glaucoma suspects. There were no cases of ocular hypertension in either group. Seven (6.54%) subjects in the hypertensive group and three (3%) in the control group were diagnosed as POAG. There was no difference in the glaucoma status between subjects with and without hypertension ($P = 0.15$, Fischer's test).

In the hypertensive group, 48% subjects were on treatment with calcium channel blocker (amlodipine), 22% on angiotensin-converting enzyme inhibitor (enalapril), 5% on β blocker (propranolol), 7% on multiple medications and the remaining 18% were on salt restricted diet.

Using age adjusted linear regression analysis, we observed 0.55 mm Hg rise in IOP per 10 mm Hg increment in SBP (95% confidence interval [CI] =0.28–0.83 mm Hg, $P < 0.001$) and 0.96 mm Hg rise in IOP per 10 mm Hg increment in DBP (95% CI = 0.49–1.43, $P < 0.001$). IOP was also seen to have a moderately positive correlation with MAP ($r = 0.29$) that was not statistically significant ($P = 0.12$). Fig. 3a and b show this relation in both the eyes using a locally weighted scatter plot smoothening curve. MOPP showed a moderately negative but insignificant correlation with glaucoma status ($r = -0.22$, $P = 0.18$) [Fig. 4].

Univariate multinomial regression analysis using "no glaucoma" as the comparison group showed a significant association between use of antihypertensive medications and glaucoma suspect status. Similarly, POAG was found to have a significant association with antihypertensive medications, MOPP and IOP [Table 2]. In multivariate multinomial regression adjusted for age, gender, hypertension status and duration of diabetes; subjects on antihypertensive medications were 1½ times more likely to have suspicious glaucoma (odds ratio (OR) =1.56, 95% CI = 1.01–2.48, $P = 0.05$) and nearly twice more likely to have POAG (OR = 1.85, 95% CI = 0.92–3.7, $P = 0.08$). On adding MOPP and IOP to the above covariates, we found that treatment with antihypertensive medications had a stronger and more significant impact on both suspicious glaucoma (OR = 1.74, 95% CI = 1.05–2.87, $P = 0.03$)

Table 1: Comparison of demographic, BP and IOP parameters between subjects with and without HTN

Variable	Normotensive (*n*=100) %	Hypertensive (*n*=108) %	*P* value
Age	55.1 (7.1)	55.5 (6.2)	0.44[$]
Gender (% males)	47 (47)	66 (61)	0.04[$]
Duration of HTN		42.7 months (56.4)	-
Diabetes mellitus (years)	3.8 (10.9)	1.9 (4.8)	0.13[$]
SBP (mm Hg)	126.6 (10.6)	142.6 (10.1)	<0.001[#]
DBP (mm Hg)	77.5 (4.9)	86.7 (7.0)	<0.001[$]
MAP (mm Hg)	93.9 (5.9)	105.3 (7.2)	<0.001[$]
IOP (OD) (mm Hg)	13.5 (2.7)	15.2 (2.4)	<0.001[$]
IOP (OS) (mm Hg)	13.5 (2.9)	15.6 (1.9)	<0.001[$]
Mean C: D ratio (OD)	0.36 (0.11)	0.36 (0.16)	0.85[#]
Mean C: D ratio (OS)	0.36 (0.12)	0.36 (0.15)	0.87[#]
Mean perfusion pressure (mm Hg)	48.5 (5.4)	54.1 (53.9)	<0.001[$]
Glaucoma status (% of subjects)			
No glaucoma	90	79.6	0.15[¥]
Glaucoma suspect	7	13.9	
POAG	3	6.5	

Continuous variable=Mean±SD, Categorical variable=*n* (%).[#]Student's *t*-test, [$]Ranksum test, [§]Chi-square test, [¥]Fischer's test. HTN: Hypertension, BP: Blood pressure, IOP: Intraocular pressure, OD: Right eye, OS: Left eye, POAG: Primary open angle glaucoma, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, SD: Standard deviation

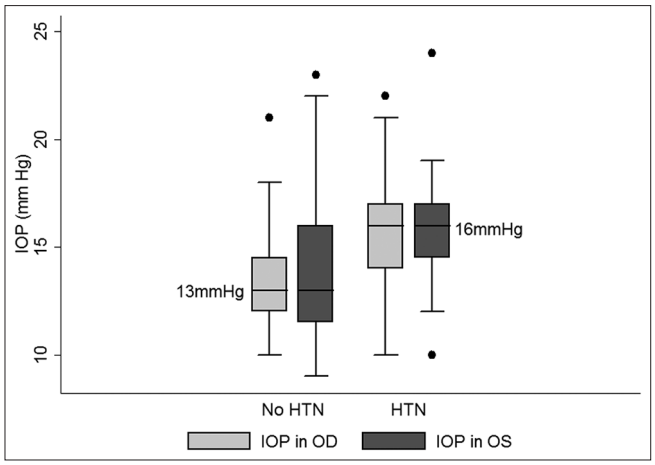

Figure 1: Box and Whisker plot showing distribution of IOP in both eyes in subjects with (n = 108) and without hypertension (n = 100)

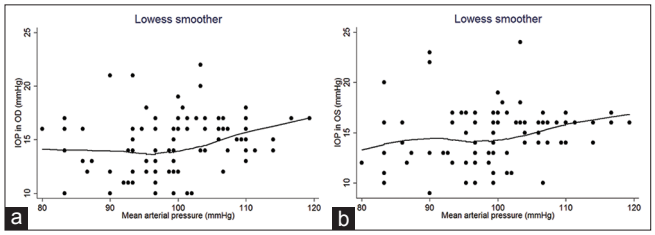

Figure 3: (a) Locally weighted scatter plot smoothening curve (unadjusted) showing relationship between mean arterial pressure and intra ocular pressure in right eye (n = 208 eyes). (b) Locally weighted scatter plot smoothening curve (unadjusted) showing relationship between mean arterial pressure and intra ocular pressure in left eye (n = 208 eyes)

and POAG status (OR = 2.49. 95% CI = 1.00–6.21, P = 0.05). In addition, we found a 31% and 12% reduction in the risk of having POAG (95% CI = 13–45%, P = 0.001) and suspicious glaucoma (95% CI = 2–21%, P = 0.03) respectively with every 1 mm Hg increment in MOPP.

Discussion

In our study, we had found that the presence of systemic hypertension alone did not lead to the increased likelihood of having glaucoma or glaucoma suspect. Association between systemic hypertension and POAG has been evaluated in various population based studies that yield contradictory results. In the Blue Mountain Eye Study, a significant association was seen between hypertension and OAG. Association was strongest in those with poorly controlled hypertension (OAG prevalence 5.4%) as compared to those with normal BP (OAG prevalence 1.9%).[13] In the Egna-neumarkt study, the association was found between primary OAG and systemic hypertension.[14] A positive correlation was also found between systemic BP and IOP. In the Rotterdam study, however, the presence of systemic hypertension was not significantly associated with OAG, similar to our results.[15] Although hypertension was common in the Barbados Eye Study participants, it was unrelated to the prevalence of OAG.[16] Studies by Vijaya *et al*. in a rural and urban south Indian population similar to ours, found no association of POAG with systemic hypertension.[17,18]

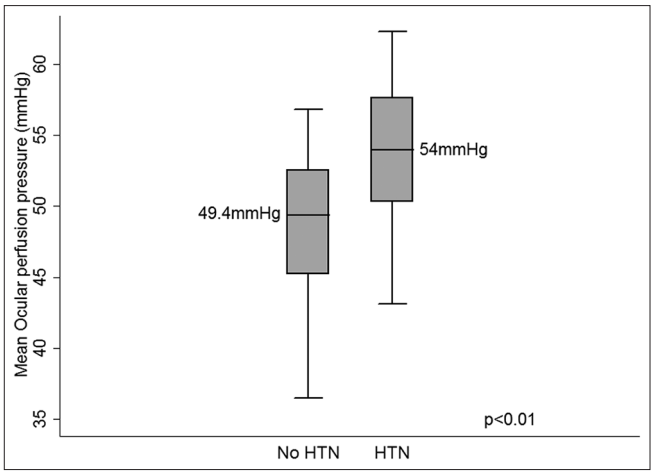

Figure 2: Box and Whisker plot showing distribution of mean ocular perfusion pressure in right eye of subjects with (n = 108) and without hypertension (n = 100)

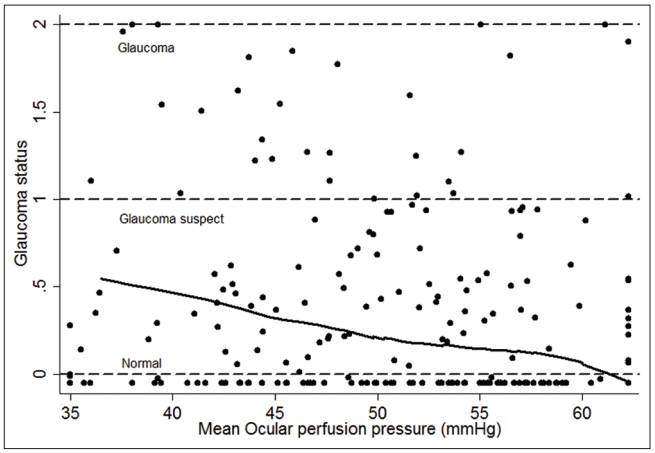

Figure 4: Locally weighted scatter plot smoothening curve showing relationship between glaucoma status and mean ocular perfusion pressure across the entire sample. (The mean ocular perfusion pressure represents a mean of the mean ocular perfusion pressure in right eye and left eye for all the eyes in the study)

We found that subjects on antihypertensive medications had two- to three-fold increased likelihood of having glaucoma or glaucoma suspect. One potential reason may be related to the bedtime dosing of the antihypertensive medications which cause a drop in nocturnal BP and subsequent reduction in ONH perfusion. Pache and Flammer reported hypotension and in particular, a nocturnal drop in BP as an important risk factor for OAG.[19] Similarly, investigators from the Thessaloniki eye study[20] reported that DBP lower than 90 mm Hg resulting from antihypertensive treatment was associated with increased cupping and a decreased rim area of the optic disc, a finding confirmed by others.[21-26] Contrary to this, Tokunaga *et al*. studied the association between visual field progression and nocturnal BP dip in normal-tension glaucoma (NTG) and high tension OAG patients.[25] Subjects were classified based on the percentage of nocturnal BP dip into nondippers (<10% drop), physiologic dippers (10–20% drop) and extreme dippers (>20% drop in BP). Visual field progression was evident in both the extreme dipper and the nondipper groups thus suggesting an

Table 2: Univariate and multivariate multinomial regression analysis to determine the association between independent variables and glaucoma status (dependent variable) (*n*=208)

Variable	Interval	(OR (95% CI))		
		Univariate	Model 1*†	Model 2**†
		Glaucoma suspect		
Age	1 year older	0.97 (0.9-1.04)	0.96 (0.88-1.04)	0.96 (0.89-1.04)
Gender	Versus female	0.84 (0.3-2.1)	0.64 (0.24-1.66)	0.68 (0.25-1.82)
Hypertension	Versus normotensive	2.2 (0.9-5.7)	1.10 (0.22-5.41)	1.78 (0.32-9.93)
Treatment	Versus no treatment	1.43 (1.1-1.9)*	1.56 (1.01-2.48)*	1.74 (1.05-2.87)*
Diabetes duration (years)	1 year more	1.02 (0.9-1.1)	1.03 (0.98-1.08)	1.03 (0.98-1.08)
Mean OPP	1 mm Hg higher	0.95 (0.8-1.03)	-	0.88 (0.79-0.98)*
IOP	1 mm Hg higher	1.15 (0.9-1.4)	-	1.04 (0.85-1.27)
		POAG		
Age	1 year older	1.08 (0.9-1.2)	1.07 (0.98-1.18)	1.10 (0.98-1.22)
Gender	Versus female	1.96 (0.5-7.8)	1.71 (0.40-7.24)	2.84 (0.49-16.5)
Hypertension	Versus normotensive	2.41 (0.6-9.6)	4.4 (0.4-5.31)	4.97 (0.17-140.8)
Treatment	Versus no treatment	1.57 (1.1-2.3)*	1.84 (0.92-3.68)	2.49 (1.00-6.21)*
Diabetes duration (years)	1 year more	1.00 (0.9-1.1)	1.01 (0.92-1.09)	1.00 (0.91-1.11)
Mean OPP	1 mm Hg higher	0.85 (0.8-0.9)*	-	0.69 (0.55-0.87)§
IOP	1 mm Hg higher	1.44 (1.1-1.8)*	-	1.21 (0.89-1.64)

†Multinomial regression analysis was computed. Not having glaucoma served as the referent group. *Statistical significant association: $P<0.05$, §$P<0.01$, *Model 1: Age, gender, hypertension, treatment, duration of diabetes, **Model 2: Same as model 1 with the addition of mean perfusion pressure and IOP. OPP: Ocular perfusion pressure, OR: Odds ratio, CI: Confidence interval, IOP: Intraocular pressure, POAG: Primary open-angle glaucoma

underlying vascular dysregulation, and not merely nocturnal hypotension, as a contributory factor for glaucomatous damage.

Another possible explanation for the observed association between antihypertensive medications and OAG in our study is that the subjects on antihypertensive medications are likely to have more severe disease and hence, greater disruption of auto regulatory mechanisms of blood flow in the ONH. Chronically elevated BP results in arteriosclerosis, changes in the size of the precapillary arterioles and capillary dropout leading to increased resistance to blood flow and thus reduced perfusion.[27]

In our study, the mean IOP in the hypertensive group was significantly higher than those without hypertension. IOP was also seen to have a positive correlation with MAP. The Baltimore Eye Survey identified high IOP and systemic hypertension as potential risk factors in the development of glaucomatous optic nerve damage.[28] Other population based studies have reported an increase in IOP ranging from 0.16 to 0.52 mm Hg with every 10 mm Hg increment in systolic pressure, similar to our results, and 0.35–0.52 mm Hg for every 10 mm Hg increment in DBP.[27,29,30] The magnitude of the effect of DBP on IOP was slightly higher in our study with almost 1 mm Hg rise with every 10 mm Hg rise in DBP. This may reflect an overestimation of the effect and could partially be due to this being a clinic based study at a tertiary center, where subjects with advanced systemic disease are referred. The implications of the disturbed milieu between DBP, IOP and perfusion pressure is unknown and requires further study in the Indian population.

The perfusion parameters of the lamina cribrosa and NRR are implicated in various studies to be significantly correlated with visual field defects as measured with scanning laser Doppler flowmeter.[31,32] Oku *et al*. had found in a study that ONH ischemia could contribute to the enlargement and excavation of the disc cup independent of the IOP level.[33] In addition, circadian fluctuation of ocular perfusion pressure is an important contributing factor in the pathogenesis of glaucomatous optic neuropathy.[9,11] Increase in MOPP in our study, was associated with reduced risk of glaucoma in a dose dependent manner, that is, risk reduction was higher with POAG than with glaucoma suspect. In other words, lower the MOPP, greater the risk of developing glaucoma. Similar results were found in various studies on ocular perfusion pressure and its relation with glaucoma. Among various ocular perfusion pressure risk variables studied, 24-h MOPP fluctuation was found to be the most consistent clinical risk factor for determining glaucoma severity in patients with NTG.[34] Sehi *et al*. had demonstrated in a study that the percentage decrease in diurnal MOPP was significantly larger in patients with untreated POAG than in normal subjects, suggesting that relative diurnal change in MOPP may be a risk factor for POAG.[35] Two studies by Quaranta *et al*. on 24-h diastolic OPP (DOPP) fluctuations in newly diagnosed, untreated POAG patients have shown that the calculated DOPP peaked in the evening.[36,37] Similarly, a study by Costa *et al*. in two groups of healthy adults and POAG patients had shown that both groups had higher IO*P* values at night. In POAG patients, however, the night time IOP increase was accompanied by a simultaneous decrease in DBP, resulting in the reduction of DOPP.[38] Inadequate auto regulatory mechanisms in glaucoma patients could prevent maintenance of adequate blood flow in the face of nighttime changes in IOP and BP.[9] Choi *et al*. suggested that MOPP fluctuations may be a risk factor for NTG, as reductions of OPP may lead to short-term ocular tissue ischemia, followed by reperfusion injury and consequent

loss of retinal ganglion cells.[34] Similar findings of increased risk of developing glaucoma with lower diastolic, systolic or mean perfusion pressures have been reported in various other population based studies.[14-16,27,29,30,39]

Calculation of mean OPP using theoretical formula may not reflect the real physiological status of ocular perfusion. Direct measurement of ocular blood flow could result in different outcomes. Furthermore, there are inevitable measurement inaccuracies during assessment of BP and IOP and also the scales of measurement differ (IO*P* values are in the range of 10-30 mm Hg while BP values approximate 100 mm Hg). Despite these limitations, several large studies have shown that calculated OPP is a highly relevant parameter in glaucoma.[9] We acknowledge that BP and IOP are both influenced by diurnal variations; therefore, having a single elevated/normal BP or IOP reading may not be representative of an individual's true BP or IOP status. Therefore, though tedious, a study carried out with 24 hours ambulatory BP monitoring and recording of diurnal variation of IOP may be more appropriate. Continuous IOP monitoring technologies are currently emerging that can contribute significantly to the study of IOP rhythms.[40-42] They may provide an invaluable tool toward a better understanding of long- and short-term IOP fluctuations.

A drawback of our study was that the C: D ratio was estimated by two different observers leading to a potential for inter-observer variability, which we did not adjust for in the analysis. Inter-observer variability in estimation of C: D ratio has been documented in various studies.[43-46] In addition, we did not follow our patients for development or progression of glaucoma status. A longitudinal study to follow up the hypertensive and normotensive subjects with visual fields and other parameters to see for risk of glaucoma would be more appropriate. Ours was a hospital based study and hence the real incidence of glaucoma among hypertensives could be confounded.

Conclusion

The results of the present study suggest a potential role of MOPP in the pathogenesis of glaucoma in subjects on antihypertensive medications. It may be prudent to avoid night time administration of antihypertensive drugs in subjects with suspicious or proven OAG. However, longitudinal studies are further needed to confirm this.

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