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Glaucomatous Optic Neuropathy Associated with Nocturnal Dip in Blood Pressure: Findings from the Maracaibo Aging Study

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Abstract

Purpose—To determine which nocturnal blood pressure (BP) parameters (low levels or extreme dipper status) are associated with an increased risk of glaucomatous damage in Hispanics.

Design—Observational cross-sectional study.

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Disclosure

None of the authors declare any conflicts of interest.

Participants—A subset (n=93) of the participants from the Maracaibo Aging Study (MAS) who met the study eligibility criteria were included. These participants — who were at least 40 years of age — had measurements for optical tomography coherence, visual field tests, 24-hour BP, office BP, and intraocular pressure <22 mm Hg.

Methods—Univariate and multivariate logistic regression analyses under the generalized estimating equations (GEE) framework were used to examine the relationships between glaucomatous damage and BP parameters, with particular attention to drops in nocturnal BP.

Main Outcome Measures—Glaucomatous optic neuropathy (GON) based on the presence of optic nerve damage and visual field defects.

Results—The mean age was 61.9 years, and 87.1% were women. Of 185 eyes evaluated, 50 (27.0%) had signs of GON. Individuals with GON had significantly lower 24-hour and nighttime diastolic BP levels than those without. However, results of the multivariate GEE models indicated that the glaucomatous damage was not related to the average systolic or diastolic BP levels measured over 24 hours, daytime, or nighttime. In contrast, extreme drops in nighttime systolic and diastolic BP (>20% compared with daytime BP) were significant risk factors for glaucomatous damage (odds ratio=19.78 and 5.55, respectively).

Conclusions—In this population, the link between nocturnal BP and GON is determined by extreme dipping effects rather than low nocturnal BP levels alone. Further studies considering extreme drops in nocturnal BP in individuals at high risk of glaucoma are warranted.

Graphical Abstract

In a Hispanic population-based cohort, the risk of glaucomatous optic neuropathy conferred by nocturnal blood pressure is explained by extreme dipping of diurnal systolic or diastolic blood pressure and not by blood pressure levels.

Keywords

Glaucoma; Nocturnal blood pressure; Blood pressure; Dipper status; Aging

Introduction

Glaucoma is an acquired and progressive optic neuropathy that is a leading cause of irreversible blindness worldwide.[1] Identifying and controlling risk factors in the early stages of glaucomatous damage are important to preventing blindness. To date, elevated intraocular pressure (IOP) is the only modifiable risk factor proven to be effective in preventing and controlling glaucoma progression.[1] However, glaucoma can develop and progress in eyes with IOP in the normal range.[2] Thus, the identification of new modifiable risk factors could open new therapeutic approaches to glaucoma prevention and therapy.[3]

The role of systemic blood pressure (BP) in glaucoma pathogenesis has been increasingly gaining attention. However, its role based on conventional snapshot BP measurements of glaucomatous damage is unclear given the diurnal variations of BP.[4–6] Twenty-four-hour ambulatory BP monitoring (ABPM) provides information on changes in BP during the day and at night, as well as mean BP levels. Studies using ABPM have suggested that nocturnal

hypotension is important to glaucoma progression[4,7]; it is unclear, however, which nocturnal BP parameter (low average nighttime BP vs. extreme dipper status) is the most relevant risk factor. Furthermore, previous studies using ABPM included only patients with glaucoma[4,7–9]; hence, it appears important to study the relationships between ABPM components and glaucoma risk in the general population.

The present study examined a subset of study participants from the Maracaibo Aging Study (MAS) to test the hypothesis that extreme dipper status (an exaggerated nighttime drop in systolic and/or diastolic BP), and not simply low average nighttime BP levels, contributes to glaucomatous optic neuropathy (GON).

Methods

Sample population

We studied 93 MAS participants who were evaluated for eye health and who met the selection criteria described below.[10] The MAS — a population-based epidemiological study of age-related traits — currently includes approximately 3000 individuals, ≥40 years of age, living in the Santa Lucia neighborhood[10] or in the nearby community of Santa Rosa de Agua[11] in Maracaibo, Venezuela; all MAS participants received standardized assessments.[10] Randomly selected participants were invited to undergo an ophthalmological assessment. To be included in this study, individuals had to have completed optical tomography coherence (OCT) scans, visual field (VF) tests, ABPM, and office BP measurements. We decided to exclude one individual with an IOP ≥22 mm Hg, which we believed would only add uncertainty to results. Ninety-three individuals met the criteria. Each participant signed an informed consent, which was approved by the Institutional Review Boards of the Cardiovascular Institute at University of Zulia and Columbia University.

Ophthalmological assessment

Ophthalmologists conducted an ocular assessment of both eyes. This assessment included clinical ocular history; best-corrected visual acuity; a slit lamp examination (gonioscopy); and a dilated evaluation of the lens, vitreous, and retina. IOP was estimated with Goldmann tonometry. Standard automated perimetry was performed with the Heidelberg Edge Perimeter (Heidelberg Engineering, GmBH, Heidelberg, Germany). Spectralis spectral domain (SD)-OCT (software version 5.4.7.0; Heidelberg Engineering, GmBH) was used to measure the thickness of the peripapillary retinal nerve fiber layer (RNFL). Peripapillary RNFL measurements were obtained in a circle scan centered on the optic disc. The RNFL analysis used an automated computer algorithm to identify the anterior and posterior margins of the RNFL, from which the RNFL thickness was calculated. In addition, if the visual acuity was 20/20 or better in each eye according to the Standard Early Treatment Diabetic Retinopathy Study protocol at 4 m, refraction was the lensometer reading of the individual’s spectacle or plano. Otherwise, we performed a noncycloplegic autorefraction (Humphrey autorefractor model Hark 599, C. Zeiss, Meditec, Dublin). For individuals with visual acuity less than 20/20, subjective refraction was performed following standard protocols.

Glaucomatous optic neuropathy diagnosis based on clinical examination and confirmation with SD-OCT abnormalities had to include at least two peripapillary sectors flagged as "borderline" ($p < .05$) or one sector "outside normal limits" ($p < .01$). All patients underwent clinical examination with indirect ophthalmoscopy with a 78/90 D lens. In addition, reflectance images of the optic disc were evaluated, looking for signs of cupping and RNFL thinning. Finally, the attending clinician and OCT/VF reader followed the recommendations of the American Academy of Ophthalmology Preferred Practice Patterns.[12] OCT RNFL b-scans had to be free of segmentation errors and blinking/eye movement artifacts. VF abnormalities required at least three neighboring points that were 5%, 5%, and 1% probability, or 5%, 2%, and 2% probability or poorer within a hemifield on pattern deviation plots, with only one point allowed on the edge of the visual field. VF results had false-negative, false-positive, and fixation-loss rates less than 30%. *Glaucoma* was diagnosed during the clinical optic disc evaluation and was confirmed with SD-OCT peripapillary RNFL thickness measurements, based on the presence of GON and visual field abnormalities. *Suspected glaucoma* was diagnosed if the patient met the criteria for GON, but not for visual field abnormality. The ophthalmologist determined, via gonioscopy, that all cases of GON identified in our population were open-angle. An abnormal optic disc was defined as *diffuse or focal narrowing, or notching, of the optic disc rim, or optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue*. An abnormal VF, when present, was defined as 1) VF damage consistent with RNFL damage (e.g., nasal step, arcuate field defect, or paracentral depression in clusters of test sites) based on the presence of abnormal clusters; 2) VF defects consistent with glaucomatous optic nerve damage.

The diagnosis of glaucoma or suspected glaucoma was performed by one of the investigators (CGDM) from the Optic Nerve and Visual Field Reading Center at Columbia University Medical Center in New York. Due to the small number of individuals with glaucoma in the study, we combined the two diagnostic groups (i.e., glaucoma and suspected glaucoma) as the main outcome measure of glaucomatous optic neuropathy.

Blood pressure measurements

The office systolic BP and diastolic BP were obtained for each participant by trained nurses at the Cardiovascular Institute of the University of Zulia, using a validated automated device (Dynamap, XL). After participants had rested in a sitting position for 5 to 10 minutes, 5 consecutive (one per minute) BP measurements were taken in a sitting position and averaged. ABPM devices (validated oscillometric 90202 or 90207 SpaceLabs monitors, Redmond, Washington) were programmed to obtain readings every 15 minutes during daytime hours (06:00–22:59) and every 30 minutes during nighttime (23:00–05:59).

The hypertension diagnosis followed the guidelines of the European Societies of Cardiology and Hypertension, 2013. Office hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertensive drugs. The 24-hour BP, daytime BP, and nighttime BP measurements were the average BP recordings during the appropriate intervals. Ambulatory hypertension was defined as 24 hours of systolic BP ≥130, diastolic BP ≥80 mm Hg, or the use of antihypertensive drugs.

Dipper statuses were defined as follows: (i) extreme dipper: an abnormal decrease in the nocturnal BP levels more than 20% in relation to diurnal BP levels; (ii) dipper: a normal decrease in the nocturnal BP levels between 20% and 10% in relation to diurnal BP levels; (iii) nondipper: a minor or no decrease in nocturnal BP levels, ranging from 10% to 0%; and finally (iv) reverse dipper: an abnormal increase in nocturnal BP levels in relation to daytime BP levels. To identify the decrease or increase in nocturnal BP levels in relation to daytime BP levels, we used the ABPM to calculate the night/day BP ratio, as suggested by Fagard and colleagues.[13] Night/day BP ratios ≤0.8 indicated an extreme dipper, >0.8 to 0.9 indicated a dipper, >0.9 to 1.0 indicated a nondipper, and >1.0 indicated a reverse dipper. Dipper status was determined separately for systolic BP and diastolic BP. We combined reverse dippers with nondippers for analysis due to the small number of participants who were reverse dippers, and the fact that nondipper and reverse dipper status did not add any significant risk for GON (Table S1).

Other information

Participants provided their medical history, including age, sex, level of education, smoking history, alcohol intake, and antihypertensive drug treatment. In addition, clinical and laboratory assessments were performed to measure total cholesterol, LDL cholesterol, triglycerides, and HbA1c. Body mass index (BMI) was calculated by kg/m2. Diabetes mellitus was defined as a glucose serum level ≥126 mg/dl, HbA1c ≥6.5%, or intake of anti-diabetic drugs.

Statistical analyses

Categorical variables were compared for the two groups using the chi-squared test, and continuous variables were compared using Student's t-test. To assess various BP parameters as risk factors for glaucomatous damage, we performed univariate and multivariate logistic regression analyses under the generalized estimating equations (GEE) framework to take into account nonindependence of the two eyes within an individual. Confounders were identified using a threshold of $p < .1$ in the comparison of baseline characteristics. However, despite the p value, the IOP was selected as a confounder due to its alluded role in the pathogenesis of GON. One multivariate model was adjusted only for age, and another model was fully adjusted for age, education level, BMI, LDL-cholesterol, creatinine, conventional hypertension, refractive error and IOP. All the analyses were performed using SPSS 23 (IBM Corp.). Statistical significance was accepted at $p < .05$ for two-tailed tests.

Results

Sample Population

The mean age of the participants was 61.9 years, and 87.1% were women (Table 1). Some 28.0% were smokers and 9.7% reported consuming alcohol. Approximately 14.0% had diabetes. The prevalence of hypertension based on office BP and ABPM were 64.5% and 55.9%, respectively, and 47.3% of those with office hypertension were taking anti-hypertensive medications. Table S1 shows the comparison of the baseline characteristics between nonincluded and included individuals. Nonincluded individuals in the present study were older, were less frequently women, had fewer years of education, were more often

smokers, had a higher proportion of alcohol intake, had a lower BMI, were more like to have hypertension, had lower levels of LDL cholesterol, had a history of cardiovascular diseases, had poorer treatment of hypertension, and had higher levels of conventional and ambulatory BP.

Of the 93 participants, 26 (30.0%) had at least one eye with GON (Table 1). A total of 185 eyes were evaluated, and 49 (26.6%) were identified as having GON: 19 (10.3%) as glaucoma and 30 (16.1%) as suspected glaucoma. One individual with an IOP ≥22 mm Hg in one eye was excluded from the analysis. Individuals with GON were significantly older, had lower levels of education, a lower BMI, and were more likely to have refractive errors than individuals with healthy eyes. The type of anti-hypertensive treatment was not associated with GON (Table S3).

Blood Pressure Levels and Glaucomatous Eyes

Office systolic BP levels were significantly higher in participants with GON than in individuals with healthy eyes (Table 2). In contrast, systolic BP levels based on 24-hour ABPM did not differ between GON and healthy eyes, but levels of diastolic BP, especially nighttime diastolic BP, were significantly lower in individuals with GON when compared with BP levels in those with healthy eyes. However, the two multivariate adjusted GEE models showed levels of diastolic BP were no longer significantly associated with glaucomatous damage (Table 3).

Dipper Status and Glaucomatous Risk

We then further examined 24-hour BP by determining whether BP dipper status influenced GON. When the proportions of extreme dippers were compared between individuals with GON eyes vs. healthy eyes, 18.4% of the glaucomatous eyes had extreme dipper status by systolic BP, whereas just 3.0% of the healthy eyes did. Similarly, 34.7% of the glaucomatous eyes had extreme dipper status by diastolic BP, whereas 17.8% of the healthy eyes did (Figure 1). Under the fully adjusted multivariate GEE models, extreme dippers (systolic and diastolic) had a significantly higher risk of having glaucomatous eyes when compared with normal dippers (Table 4). Meanwhile, non-dipper and reverse dipper effects were not associated with an increased risk of GON.

Discussion

The present study suggests that the extreme drop in BP as defined by a decrease >20% of nocturnal BP levels compared with daytime BP levels, rather than nocturnal hypotension *per se*, increases glaucoma risk. Individuals with low nighttime BP levels did not show elevated risk. Overall, our study demonstrated that after adjusting for confounders, systolic BP and diastolic BP levels, averaged for 24-hour, daytime, and nighttime intervals were not significant risk factors for presence of GON, whereas either extreme dipper systolic and diastolic status were associated with increased risk of GON.

The rates of glaucoma (10.3%), suspected glaucoma (16.1%), and GON (26.6%) were high in our study in contrast with Black-Hispanics living in Barbados[6], or Mexican-Americans living in Los Angeles[14] or Arizona,[15] but were similar to rates of suspected glaucoma

among Hispanics of Caribbean origin residing in New York[16]. Populations from Maracaibo have a proportion of ancestral European, African, and Native American genetic contributions that have more in common with other Caribbean populations than with Mexican populations[17], which could explain the different proportion of individuals with glaucomatous damage. In addition, environmental exposures might explain the high rates of GON in the MAS population, including low socioeconomic status and the low Human Development Index that characterize this population.[18] On the other hand, of particular importance for glaucoma risk is the high prevalence and low treatment and control rates of hypertension among the studied population.[18]

The relationship between systemic BP levels and glaucoma pathogenesis has been extensively examined, and nocturnal hypotension is known to be a major risk factor for the prognosis and progression of glaucoma diseases.[7,8,19,20] The proposed mechanism implicated is chronic ischemia.[19,20] When BP levels decrease sharply during the night, systemic perfusion of the eye is inadequate.[20–22] Autoregulation of eye circulation can normalize the perfusion, but autoregulation might be compromised in individuals with glaucoma. In those individuals, the extreme reduction of perfusion pressure in the optic nerve head can lead to ischemia and, ultimately, to GON.[19] Interestingly, low nighttime BP levels were not significantly associated with glaucomatous damage unless there was an extreme dipping effect.

Approximately 15%–25% of individuals aged ≥40 years have an extreme dipper pattern, which has been linked to increased duration of heart ischemic episodes, cognitive decline, and silent brain infarction.[23,24] Furthermore, extreme dipping status is associated with progression of glaucoma.[20,25] Our study extends these findings in that (i) individuals with extreme dipping effect exhibited the highest increased risk for GON; (ii) our results were determined in the general Hispanic population.

Our study showed that nocturnal BP measurements as measured by ABPM are more insightful indicators of glaucomatous damage than one-time measurements of office BP. Previous studies similarly found that ABPM is a reliable predictor of hypertensive retinopathy, diabetic retinopathy, macular alterations, VF defects, and glaucoma.[26–28] ABPM is also a better predictor of risk to other organs,[29,30] including chronic kidney disease, stroke, and cardiac events.[31,32] However, our study is the first to compare ABPM and office BP as indicators of glaucoma risk in the general population, and it suggests that measures from ABPM can be considered as a useful tool for clinicians to identify at-risk individuals long before symptoms of glaucomatous damage appear.

IOP was not found to be a risk factor for GON in our study. The role of IOP as a risk factor for glaucoma in normotensive eyes is well-established.[33] Specifically, studies have attributed IOP to the progression of glaucomatous damage (as visual field defect progression or increased cup disc ratio).[33] Given we were unable to follow up, we could not establish whether IOP is related to progression of GON in our study. On the other hand, in contrast with other population-based studies[5,34,35], our IOP average (12.7±3.0 mm Hg for total population; 13.3±3.6 for GON; and 12.4±2.8 for healthy eyes) is lower; 14.4±3.5 mm Hg,[5] 14.6±3.1 mm Hg,[34] and 14.7±2.4 mm Hg, respectively (among individuals 40–49 years of

age).[35] The discrete difference of IOP between our sample and other studies might not provide a reliable explanation supporting that IOP is not a risk factor in our population; however, there is evidence suggesting that the relationship between IOP and GON is astonishingly weak, especially at the lower end of IOP levels, indicating that other risk factors are involved in GON.[36] Extrapolating that argument, our mean IOP is nearer to the lower limit of IOP (10 mm Hg) than the average mean of the other studies. Thus, we suggest that IOP has less impact on GON in our population sample than in other population-based studies.

The main limitation of the study is the small sample size that precludes us from comparing extreme dipper status as a risk factor for glaucomatous damage in individuals with normal vs. low average nighttime BP, and from comparing the risk of individuals exhibiting non-dipper and reverse dipper status vs. dippers. In addition, the combined analyses of glaucoma and suspected glaucoma might hinder specific associations related to glaucoma. However, there is sufficient overlap between suspected glaucoma and early glaucoma to suggest that their shared elements are substantial and are worth detecting. Another aspect that needs to be clarified is whether risk factors for extreme dipper status, such as physical activity,[37] sleep quantity and quality,[38] and timing of antihypertensive medications[39] are more closely associated with GON than extreme dipper status. Lastly, although we measured conventional BP in a sitting position, we were not able to control the positional changes during ABPM recordings. This note is relevant because positional changes are linked with changes in BP levels. We hope to examine that issue in the future.

In summary, our results support the hypothesis that the association between nocturnal hypotension and GON is determined by having extreme dipping effect and not by low average nighttime BP levels. Further studies examining the progression to glaucoma in individuals identified as high risk would clarify the usefulness of extreme dipper status as a risk factor. Our results support the use of ABPM to help identify individuals with extreme dipper status who are at high risk of GON and who should undergo further ophthalmological assessment. Therapies that modify glaucoma risk are urgently needed, and new approaches to avoiding the extreme dipper effect, such as changes in the timing of antihypertensive drug intake, might be effective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
BMI	body mass index
BP	blood pressure
GEE	generalized estimating equations
GON	glaucomatous optic neuropathy
MAS	Maracaibo Aging Study
OCT	optical coherence tomography

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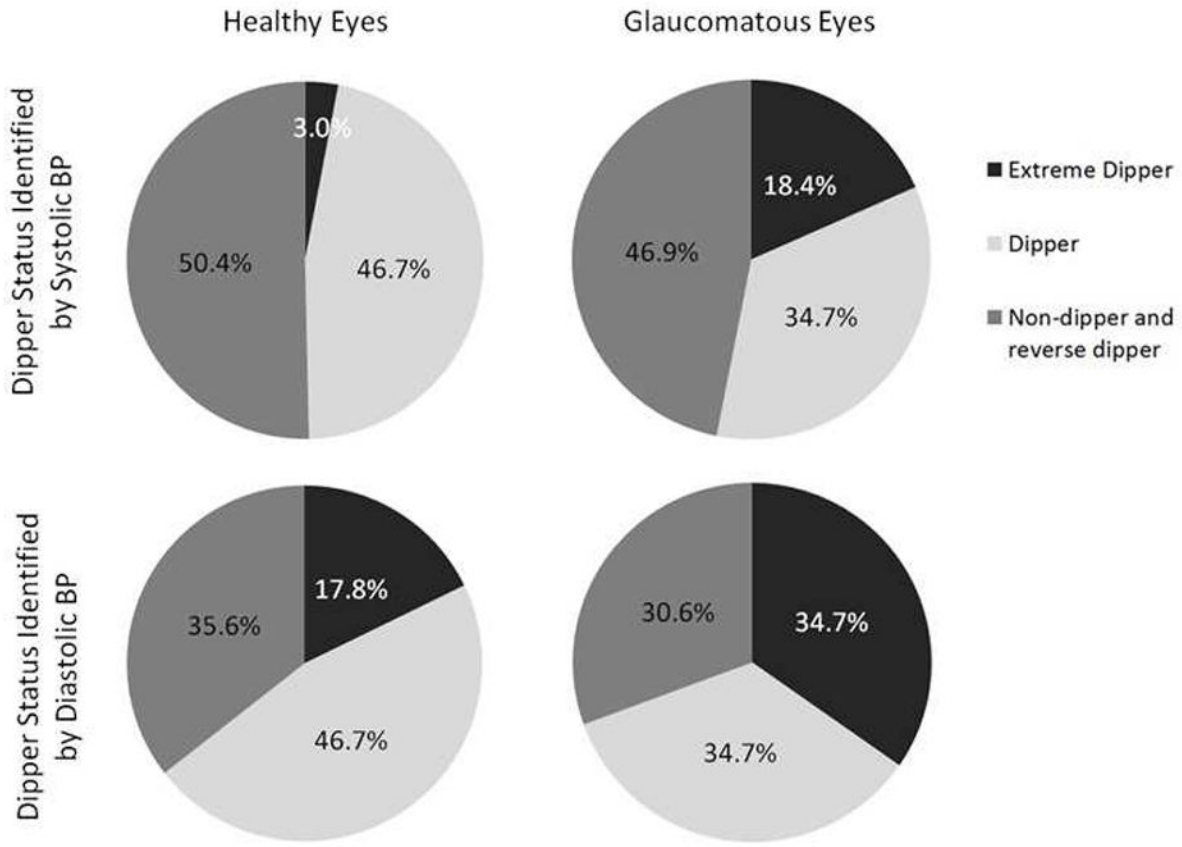

Figure 1.
Proportion of dipper status in healthy and glaucomatous eyes.

Table 1

Baseline Characteristics of the Total Population, Stratified by Individuals with Glaucomatous Optic Neuropathy and Healthy Eyes

Baseline characteristics	Total population (n = 93)	Individuals with Glaucomatous Optic Neuropathy* (n = 26)	Individuals with Healthy eyes (n = 67)	*p* value†
Age, years	61.9±13.3	70.9±12.1	58.4±12.1	<0.001
Women, n (%)	81 (87.1)	23 (88.5)	58 (86.6)	0.807
Education, years	7.6±5.0	5.4±3.4	8.4±5.3	0.009
History of smoking, n (%)	26 (28.0)	9 (34.6)	17 (25.4)	0.373
Alcohol intake, n (%)	9 (9.7)	3 (11.5)	6 (9.0)	0.705
Body mass index,	28.2±5.1	26.5±6.0	28.8±4.7	0.007
Diabetes mellitus, n (%)	13 (14.0)	5 (19.2)	8 (11.9)	0.363
Total Cholesterol, mg/dl	196.8±46.9	188.3±47.6	199.7±46.6	0.325
LDL cholesterol, mg/dl	125.5±53.8	109.3±42.1	131.0±56.4	0.100
HDL cholesterol, mg/dl	44.1±11.4	46.3±9.9	43.4±11.8	0.299
Triglycerides, mg/dl	140.8±81.0	130.0±83.3	144.5±80.6	0.471
Creatinine, mg/dl	0.9±0.3	1.0±0.3	0.8±0.2	0.066
HbA1c, %	5.8±0.7	5.8±0.4	5.7±0.5	0.513
Conventional hypertension, n (%)	60 (64.5)	20 (76.9)	40 (57.7)	0.119
Ambulatory hypertension, n (%)	52 (55.9)	16 (61.5)	36 (53.7)	0.496
Antihypertensive treatment, n (%)‡	44 (47.3)	14 (53.8)	30 (44.8)	0.432
Refractive Errors, n (%)	38 (40.9)	15 (57.7)	23 (34.3)	0.040
IOP, mmHg	12.7±3.0	13.3±3.6	12.4±2.8	0.199

Proportion of glaucoma diagnosis cases = suspected glaucoma 30 (16.2%); glaucoma 20 (10.8%); and glaucomatous optic neuropathy 50 (27.0%).

LDL= low-density lipoprotein; HDL= high-density lipoprotein; IOP= intraocular pressure.

*Among those 26 individuals with glaucomatous optic neuropathy, 30 (16.1%) eyes had suspected glaucoma while 19 (10.3%) eyes had glaucoma. A total of 49 (26.6%) eyes were identified as eyes with glaucomatous optic neuropathy.

†*p* value of the baseline comparison between individuals with glaucomatous optic neuropathy and healthy eyes.

Table 2

Distribution of Blood Pressure Levels in the Total Population and Between Individuals with Glaucomatous Optic Neuropathy and with Healthy Eyes

	Total population (n = 93)	Individuals with Glaucomatous Optic Neuropathy* (n = 26)	Individuals with Healthy eyes (n = 67)	*p* value*
Conventional BP				
Systolic BP	141.0±22.8	148.7±26.1	138.0±20.8	0.041
Diastolic BP	76.0±8.3	74.4±10.0	76.6±7.5.	0.247
Ambulatory BP				
24-hour BP				
Systolic BP	122.2±15.0	121.9±17.4	122.3±14.2	0.911
Diastolic BP	70.4±8.5	67.0±8.5	71.8±8.2	0.014
Daytime BP				
Systolic BP	123.7±14.2	124.1±17.1	123.5±13.1	0.847
Diastolic BP	72.1±8.5	69.3±8.9	73.1±8.2	0.053
Nighttime BP				
Systolic BP	118.0±18.6	116.8±20.5	118.4±18.0	0.722
Diastolic BP	66.0±10.0	61.7±9.8	67.6±9.6	0.009

BP= blood pressure; MAP = mean arterial pressure.

*p value of the blood pressure comparison between individuals with glaucomatous and healthy eyes.

Table 3

Multivariate Logistic Regression Analysis Using the General Estimating Equation to Determine the Association Between Blood Pressure Levels and Glaucomatous Optic Neuropathy

	Risk Estimate for Glaucomatous Optic Neuropathy			
	Adjusted*		Fully-adjusted†	
Office and ambulatory blood pressure	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Conventional BP				
Systolic BP	1.00 (0.98–1.02)	0.831	1.00 (0.98–1.02)	0.913
Diastolic BP	0.98 (0.92–1.06)	0.652	0.99 (0.92–1.06)	0.724
Ambulatory BP				
24-hour BP				
Systolic BP	0.99 (0.96–1.02)	0.390	0.99 (0.96–1.02)	0.541
Diastolic BP	0.96 (0.89–1.02)	0.192	0.96 (0.90–1.03)	0.221
Day-time BP				
Systolic BP	0.99 (0.96–1.03)	0.674	1.00 (0.96–1.03)	0.858
Diastolic BP	0.98 (0.92–1.04)	0.425	0.98 (0.92–1.04)	0.490
Nighttime BP				
Systolic BP	0.98 (0.95–1.01)	0.221	0.99 (0.96–1.01)	0.305
Diastolic BP	0.95 (0.89–1.01)	0.089	0.95 (0.89–1.01)	0.101

BP= blood pressure; CI = confidence interval; MAP = mean arterial pressure.

*Model adjusted by age.

†Fully adjusted, was performed by age, education, body mass index, creatinine, refractive error and IOP.

Table 4

Multivariate Logistic Regression Analysis Using the General Estimating Equation to Determine the Association Between Dipper Status and Glaucomatous Optic Neuropathy

	Risk Estimate for Glaucomatous Optic Neuropathy			
	Adjusted*		Fully-adjusted†	
Dipper Status	**Odds ratio (95% CI)**	***p* value**	**Odds ratio (95% CI)**	***p* value**
Model 1				
Systolic dipper status#				
Extreme dipper	9.44 (1.70–52.2)	0.010	19.78 (2.23–175.50)	0.007
Dipper	**1.00 (Reference)**		**1.00 (Reference)**	
Non-dipper and reverse dipper	0.63 (0.21–1.90)	0.411	1.62 (0.50–5.54)	0.446
Model 2				
Diastolic dipper status#				
Extreme dipper	4.64 (1.34–16.1)	0.016	5.55 (1.04–29.62)	0.045
Dipper	**1.00 (Reference)**		**1.00 (Reference)**	
Non-dipper and reverse dipper	1.02 (0.30–3.38)	0.980	0.90 (0.30–3.01)	0.860

OD = odds ratio; CI = confidence interval; IOP = intraocular pressure; MAP = mean arterial pressure.

*Model adjusted by age.

†Fully adjusted, was performed by age, education, body mass index, creatinine, refractive error and IOP.

#Dipper status follows the definition of Fagard et al.,[15] in which night/day BP ratios ≤0.8 indicated extreme dipper, >0.8 to 0.9 indicated dipper, >0.9 to 1.0 indicated non-dipper and >1.0 indicated reverse dipper.