

## **Systemic Arterial Hypertension And Glaucoma in a Population-based Study from South of Brazil**

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## **ABSTRACT**

**Purpose:** To evaluate the relationship between glaucoma and systemic arterial hypertension (SAH), and between blood pressure (BP) and intraocular pressure (IOP) in a population-based study of the South region of Brazil.

**Methods:** Subjects over 40 years of age underwent a screening examination which included medical interview, BP measurements, slit-lamp exam, tonometry, and fundoscopy. Glaucoma was diagnosed based on the ISGEO classification. SAH was diagnosed in subjects with previous diagnosis of SAH in treatment for BP control, or not using hypotensive drugs but with a mean systolic BP  $\geq 140$  mmHg and/or mean diastolic BP  $\geq 90$  mmHg. New SAH cases were diagnosed in subjects with a mean systolic BP  $\geq 140$  mmHg and/or mean diastolic BP  $\geq 90$  mmHg. Diabetes (DM) was diagnose in subjects in treatment for glycemia control, and new diagnoses were based on glycemia levels  $>200$ mg/dl. Diastolic perfusion pressure (DPP) was defined as the difference between diastolic BP and IOP. To assess the relation between SAH and glaucoma and intra-ocular pressure (IOP) vs. BP, multivariate analyses were performed, using age, race, gender, and diabetes as independent variables. Odds ratio were calculated with logistic regression analyses.

**Results:** A total of 1636 subjects were examined (76.5% participation rate). Glaucoma was found in 56 subjects (crude prevalence of all glaucoma: 3.4%; 95% CI, 2.5-4.3), and SAH prevalence was diagnosed in 960 subjects (crude prevalence: 58.7%; 95% CI 56.2-61.1). Glaucoma prevalence among in the SAH group was 3.85% (37), and in the non-SAH group was 2.8% (19) ( $p=0.31$  - chi square test). SAH was not associated with glaucoma (odds ratio [OR] 0.72, 95% CI 0.40-1.25). Subjects with diastolic perfusion pressure  $<50$  mmHg showed an odds ratio of 3.98 (95% CI, 1.02-13.24). Among normal subjects (no glaucoma), multivariate analysis showed that systolic BP, diabetes, age, and race were significantly correlated to IOP ( $r^2= 0,025$ ,  $p<.001$ ,  $p=.001$ ,  $p=.003$ ,  $p=.017$ ,  $p=.027$ , respectively).

**Conclusion:** In this population-based study from the South Region of Brazil, SAH was not significantly associated to glaucoma, but BP was independently correlated with IOP. There was an inverted association between low DPP and glaucoma.

## INTRODUCTION

Vascular factors have been investigated in the pathogenesis of open-angle glaucoma (OAG)<sup>1-9</sup>, particularly the blood pressure (BP) levels and perfusion pressure (PP) at the optic nerve head. Although it remains a quite controversial subject, most studies did not observe an significant association between Systemic Arterial Hypertension (SAH) and glaucoma, however, most of the studies found an inversed association between diastolic PP and glaucoma, and also, a positive correlation between IOP and BP levels.<sup>2,10-14</sup>

Tielsch JM<sup>15</sup> considered age as a predictive factor of time of evolution of SAH, and observed that in subjects with less than 60 years of age (early stage of SAH), SAH showed an inversed association with glaucoma. The authors of this study hypothesized that higher levels of BP could improve blood flow at the retina and optic nerve head. Thus, early stage of SAH could represent a protective factor for the development of glaucoma. On the other hand, subjects over 70 years of age (advanced stage of SAH) would already show lesions of small vessels (atherosclerosis), which would compromise blood flow to the optic nerve head. Thus, in these patients, SAH would represent a risk factor for the development of glaucoma. However, a recent the longitudinal study Barbados Incidence Study of Eye Diseases evaluated 3,222 patients between 40 to 84 years during a mean follow-up period of 9 years, and observed that increasing levels of systolic BP was associated to a reduced risk for OAG incidence.<sup>16</sup>

The purpose of this study was to evaluate the relationship between SAH and glaucoma, BP and IOP, and also between PP and glaucoma in subjects over 40 years old living in the South region of Brazil.

## METHODS

*Projeto Glaucoma* was a population-based prevalence study conducted from June 2000 to December 2003, in two districts of Piraquara city - located in the south region of Brazil, 250 miles south from Sao Paulo. Piraquara city has 72,886 habitants, 72% of the population is White, and the annual gross domestic product is approximately U\$1,560.00 per capita (approximately half of the value observed in Brazil U\$3,815.00 per capita).<sup>17</sup> Informed consent was obtained from all participants. The Ethic Committee at the Universidade Federal do Parana approved all protocols, and the methods described adhered to the tenets of the Declaration of Helsinki.

This study aimed to determine the prevalence and clinical characteristics of glaucoma in residents aged 40 years or older of two districts in Piraquara city: Vila-Macedo and Jardim-Primavera. These two districts were chosen due to well organized records of their respective residents, and the remarkable motivation of the local HealthCare Units employees and local community leaders - who helped motivate residents to participate in the study by explaining the glaucomatous disease process and the importance of screening/early detection. HealthCare Units employees used their records of residents to identify participants who lived in the two districts. In addition, before analyzing the data, we checked each participant address against district maps, and we excluded all participants whose addresses did not belong to Vila-Macedo and Jardim-Primavera. Using the records of residents, we identified all subjects over 40 years old who had not attended the screening examination, and we visited their homes to try to encourage their participation.

The screening examination was performed in HealthCare Units located in the two districts. Identification and demographic data were obtained, and racial groups were defined by self-description (based on classification used by the National Census Agency – IBGE).<sup>17</sup> The screening examination included an interview on medical history, capillary blood glucose measurements (using Dextrostix Elite reagent strips), oblique flash light test, anterior segment evaluation at the slit-lamp, Goldmann applanation tonometry and direct funduscopy (all exams performed by properly trained Ophthalmology residents). Blood pressure measurements were performed with the patients at the sitting position, after 10 minutes of rest. If the systolic BP was  $\geq 140$  mmHg and/or the diastolic BP was  $\geq 90$  mmHg, BP measurement was repeated after 5 minutes of additional rest at the sitting position.

The optic disc was examined after each pupil was dilated with 1 drop of tropicamide, unless contraindicated by the oblique flashlight test and/or the presence of a shallow anterior chamber depth at the slit lamp examination. The vertical cup-disc ratio (VCDR) was estimated for each eye. The rim border was determined based on the course of the blood vessels and the gradation of color, shadows, and texture. A suspect appearance of the optic disc (glaucomatous-appearing optic disc; GAOD) was defined in eyes with VCDR  $\geq 0.6$ , asymmetry of the VCDR between the two eyes  $\geq 0.2$ , focal thinning of the neuroretinal rim, localized or diffuse retinal nerve fiber layer defect, and/or optic disc hemorrhage. A glaucoma specialist confirmed the presence of a GAOD in the participants. Participants with GAOD status and/or intraocular pressure (IOP) measurements  $> 21$  mm Hg at the screening underwent a definitive examination at the Ophthalmologic Clinic of our University, which included at least two more visits.

In the first visit, patients underwent a complete ophthalmologic examination, including review of medical history, BP measurements, measurement of visual acuity (VA) with best correction, retinoscopy and refractive exam, biomicroscopy of anterior segment, Goldmann applanation tonometry, pachimetry and white on white visual field test with automated perimetry (Topcon, 24-2), gonioscopy, fundoscopy and measurement of the BP. In the second visit, 10 months after the first one, new white on white visual field test was performed in Humphrey 24-2 Full-Threshold or 24-2 SITA-Standard.

Gonioscopy was performed by a glaucoma specialist. The optic disc was evaluated by two specialists by direct fundoscopy and/or fundus biomicroscopy. The mean vertical cup/disc ratio (VCDR) determined by the two examiners, masked to each other evaluation, was calculated.

An abnormal VF exam was determined by the presence of one of the following criteria: 1. glaucoma hemifield test (GHT) outside normal limits; 2. presence of a cluster of  $\geq 3$  contiguous points at the Pattern Deviation (PD) Probability Plot with  $p < 5\%$  or worse (within the same hemifield).<sup>18</sup> A reliable visual field test was defined as an exam with less than 33% of fixation losses, false-positive and false negative. One glaucoma specialist (KS) verified if VF defects were consistent with glaucoma.

## Diagnosis Criteria

Based on the classification proposed by American Society of Hypertension and the Brazilian Cardiology Society, SAH was diagnosed in subjects with a mean systolic BP  $\geq 140$  mmHg and/or mean diastolic BP  $\geq 90$  mmHg, and/or in subjects with a previous diagnosis of SAH using hypotensive drugs, or not using hypotensive drugs for any reason but with a mean systolic BP  $\geq 140$  mmHg and/or mean diastolic BP  $\geq 90$  mmHg. The perfusion pressure was calculated using the formula:  $PP = BP - IOP$ .

DM diagnosis was based on reported previous history of DM, and/or a capillary blood glucose over 200 mg/dl (fasting or non-fasting).

Glaucoma was diagnosed according to the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification, which uses three levels of evidence.<sup>18</sup> Briefly, the highest level of evidence requires optic disc abnormalities (VCDR  $>97.5^{\text{th}}$  percentile in the “hypernormal” population) and VF defect compatible with glaucoma. In the second level of evidence, if a VF test could not be performed satisfactorily, a severely damaged optic disc (VCDR  $>99.5^{\text{th}}$  percentile of the “hypernormal” population) would be sufficient to make the diagnosis. Lastly, if the optic disc could not be examined because of media opacity (and, hence no VF test was also possible), a visual acuity  $<20/400$  and an IOP exceeding the  $99.5^{\text{th}}$  percentile of the “hypernormal” population, or evidence of previous glaucoma filtering surgery, may be taken as sufficient for a diagnosis of glaucoma.

Since our study protocol did not include VF tests in the screening examination, the VCDR and IOP cut-off points described at TABLE 1 were based on the  $97.5^{\text{th}}$  and  $99.5^{\text{th}}$  percentiles for “hypernormals” (subjects with normal VF results) in surveys described by Foster et al.<sup>18</sup> TABLE 1 summarizes the criteria for glaucoma diagnosis adopted by our study. Glaucoma was also classified in primary glaucoma and secondary glaucoma, according to the ISGEO criteria.

## Statistical Analysis

Parametric (Student-t test) and non-parametric tests (Mann-Whitney test) were used to compare continuous variables, according to data distribution. The Chi-square ( $\chi^2$ ) or Fisher exact test was used to compare categorical data. For analysis purposes, we classified all

participants in White and non-White groups. Multivariate analysis was performed to assess the relationship between glaucoma and SAH, and between IOP and BP. Variables such as age, race, gender, DM diagnosis, were included as covariates. A p value <0.05 was considered statistically significant. Statistical analyses were performed using software JMP 5 (SAS Institute, Inc., Cary, NC, USA) and MedCalc (Mariakerke, Belgium).

## RESULTS

The estimated number of subjects aged 40 years or older in the districts of Vila-Macedo and Jardim-Primavera is 2139 (according to the National Census in 2000). Comparing the demographic characteristics of the enumerated sample with the total population of Piraquara city, subjects aged over 70 years of age were under-represented in the sample (9.0% in the sample versus 14.4% in Piraquara city), but otherwise, the demographics of these two populations was similar.

Of 2139 eligible subjects, 1636 were examined in the screening examination, yielding a participation rate of 76.5%. The mean age of the responder was  $53.7 \pm 10.7$  years, 71.5% were White, 18.2% were Mixed (Black/White), 5.9% were Black, 0.2% Yellow/Native Indian, and 4.2% self-described undetermined race. Using the two districts population determined by the National Census 2000 as the standard population, we assessed the participation rate for each age group and demographic information on responders and non-responders. The participation rate among men and women in all age groups was higher than 80%. However, men in the younger age group (40-49 years) were less likely to participate (participation rate of 52%,  $p < 0.001$ ).

The overall prevalence of glaucoma was 3.42% (56 patients). There were 52 patients with primary glaucoma (40 open angle glaucoma and 12 angle closure glaucoma), and 4 patients with secondary glaucoma.

The prevalence rate of SAH was 58.7% (960 patients). Table 2 shows the demographic characteristics of SAH and non-SAH groups. A total of 697 subjects reported a previous diagnosis of SAH, of whom only 34% of them were under good BP control (systolic BP < 140mmHg and diastolic BP < 90mmHg).

In the SAH group, 37 subjects (3.85%) had glaucoma; and in the non-SAH group 19 subjects (2.8%) had glaucoma. There was no statistically significant difference in the prevalence of glaucoma between subjects with or without SAH ( $p = 0.31$ ; chi-square test). The mean IOP in the SAH group was significantly higher than in non-SAH group was ( $15.94 \pm 4.3$ mmHg vs.  $15.07 \pm 3.67$ mmHg,  $p < .001$ ).



In multivariate analysis that assessed the factors associated with glaucoma, both age and IOP was significantly associated with glaucoma ( $r^2 = 0.145$ ,  $p < .001$ ); while SAH, gender, race and diabetes were not associated with glaucoma. When the relationship between SAH and glaucoma was evaluated within age ranges (quartiles), there was no significant association between these variables in any age range (data not shown).

In multivariate analysis that assessed the factors associated with IOP in normal subjects (no glaucoma), the following covariates were included in the model: age, race, gender, systolic BP, diagnosis of DM. It was observed that the mean systolic BP, diagnosis of DM, and age were significantly associated with IOP ( $r^2=0.025$ ,  $p < .001$ ,  $p=0.001$ ,  $p=0.047$ ,  $p=0.003$ , respectively).

Table 3 shows the odds ratio for glaucoma according to the diastolic BP and diastolic perfusion pressure ranges, adjusted for age, race, and gender. Subjects with diastolic perfusion pressure  $<50$  mmHg showed an odds ratio of 3.98 (95% CI, 1.02-13.24).

## DISCUSSION

In this study, there was no significant association between SAH and glaucoma, and it was not observed any significant association between SAH and glaucoma in any age group (younger than 45 years, or older than 65 years). The lack of association between these two diseases was also observed by several different authors in different regions of the world.<sup>2, 7, 16,18,19</sup> Different diagnosis criteria for both glaucoma and SAH, the duration of the disease, the efficacy of SAH treatment, the type of drug used to treat SAH, and the complexity of the involved mechanisms may represent some of the factors accounting for these contradictory results.

In spite of the lack of association between glaucoma and SAH, it was observed a positive correlation between the systolic BP and IOP ( $p < .001$ , adjusted for age, race, gender, diabetes). This association has been observed by other authors in different part of the world. The Barbados Eye Study also observed that the systolic BP was positively correlated with the IOP after the exclusion of subjects with OAG.<sup>18</sup> The Baltimore Longitudinal Study also showed a positive correlation between IOP and systolic BP. However, in most of the studies, the actual change in IOP with increasing BP is relatively small. In fact, longitudinal studies such as the Barbados Incidence Study of Eye Diseases<sup>16</sup> and Early Manifest Glaucoma Trial<sup>20</sup> observed that a higher SBP was a protective factor for glaucoma incidence and glaucoma progression, respectively. The results of these longitudinal studies may be suggesting that although higher BP is associated with higher IOP levels, lower BP may be associated to a deleterious effect on the optic nerve head.

Ocular perfusion pressure is evaluated as systolic or diastolic perfusion pressure, and these parameters aim to reflect the blood flow at the optic nerve head. In agreement with previous studies,<sup>2,9,10,12,20</sup> the current study observed that lower diastolic perfusion pressure was associated with glaucoma. Thus, it is possible that lower levels of diastolic perfusion pressure may result in ischemia and optic nerve damage, particularly in subjects with abnormal ocular blood flow autoregulation. However it is important to note that the calculation of ocular perfusion pressure is rather simple, and it may not accurately reflect the true blood flow at the level of the retina and optic nerve head. Further studies need to better clarify the role of this potential vascular factor in glaucoma pathogenesis, and the role of BP control in glaucoma management.

Our study had limitations. Of note, many of the SAH patients of the current study were not under adequate control of their disease (even the ones that have reported to be under regular treatment). The BP measurements were obtained during different time of the day, and IOP measurements were also obtained during different time of the day. There was no reliable information on the duration of SAH disease, and it was assume that age may reflect, at least partially, the duration of the disease. There was no data or confirmation of reported data about the different types of drugs used to reduce BP levels. The lack of objective data of these variables limits the analyses to better understand the complex relationship between SAH and glaucoma.

## **Conclusion**

In summary, although the systolic BP demonstrated a positive correlation with the IOP, no association was found between SAH and glaucoma in this population from the South Region of Brazil. However, there was an inverted association between low DPP and glaucoma.

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## TABLES

TABLE 1. The criteria for primary open angle glaucoma diagnosis

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**Category 1 – Structural and functional evidence:**

- VCDR  $\geq 0.7$ , and/or VCDR asymmetry  $\geq 0.2$ , and/or neuro-retinal rim width  $\leq 0.1$  (between 11-1 and 5-7 o'clock)
- associated to a glaucomatous VF defect (not explained by other diseases)

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**Category 2 – Advanced Structural damage with unproved VF loss:**

- VCDR  $\geq 0.9$  and/or VCDR asymmetry  $\geq 0.3$

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**Category 3- Optic disc not seen and VF test impossible:**

- VA  $< 20/400$  with IOP  $\geq 26$ mmHg, and/or evidence of glaucomatous surgery
- 

VCDR – vertical cup disc ratio, VA – visual acuity, IOP – intra-ocular pressure.

Diagnostic criteria based on the 97.5<sup>th</sup> and 99.5<sup>th</sup> percentile for hypernormals in surveys described by Foster et al.<sup>15</sup>

TABLE 2. Demographic characteristics of subjects with and without systemic arterial hypertension (SAH).

	Total	SAH	Non-SAH	P values
N	1636	960	676	
Age ( years old )	53.7±10.8	55.9±10.9	50.7±9.8	<.001
Gender (Female )	940 (57.4%)	586 (61.0%)	355 (52.5%)	<.001
Race				
<i>Whites</i>	1169 (71.4%)	679 (70.7%)	490 (72.5%)	0.33
<i>Non-Whites</i>	398 (24.3%)	243 (25.3%)	155 (22.9%)	
Undetermined	69 (4.2%)	38 (3.9%)	31 (4.6%)	

TABLE 3. Adjusted odds ratio for glaucoma according to diastolic blood pressure and diastolic perfusion pressure ranges.

	<b>Subjects</b>	<b>Glaucoma cases</b>	<b>Adjusted Odds Ratio for glaucoma (95% CI)</b>
<b>Diastolic Blood Pressure</b>			
< 65 mmHg	106	6	3.93 (0.82-15.58)
65-74 mmHg	254	3	0.13 (0.01-0.62)
75-85 mmHg	540	17	1.18 (0.42-3.48)
> 85 mmHg	736	30	1 [reference]
<b>Diastolic Perfusion Pressure</b>			
< 50 mmHg	108	8	3.98 (1.02-13.24)
50-57.5 mmHg	202	5	0.37 (0.07-1.38)
57.5-65.0 mmHg	332	14	1.28(0.44-3.53)
> 65 mmHg	982	29	1 [reference]

Adjusted for age, gender, and race.