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Complete List of Authors:	Cerquera Jaramillo, Maria; Hospital Militar Central, Bogota Moreno Mazo, Sara; Hospital Militar Central, Bogota Toquica Osorio, Jeanneth; Hospital Militar Central, Bogota
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TITLE

Prevalence of Primary Open-angle Glaucoma in Patients with Obstructive Sleep Apnea in a Colombian Population

NAMES AND AFFILIATIONS

María Alejandra Cerquera Jaramillo - Ophthalmology Resident - Department of Ophthalmology, *Universidad Militar Nueva Granada – Central Military Hospital*, Bogota, Colombia

Sara Edith Moreno Mazo – MD, Glaucoma Ophthalmologist – Department of Ophthalmology, *Universidad Militar Nueva Granada - Central Military Hospital,* Bogota, Colombia

Jeanneth Eloyne Toquica Osorio - Glaucoma Ophthalmologist – Department of Ophthalmology, *Universidad Militar Nueva Granada - Central Military Hospital*, Bogota, Colombia

Correspondence address: Jeanneth Eloyne Toquica Osorio, Department of Ophthalmology *Universidad Militar Nueva Granada - Central Military Hospital*, Bogotá, Colombia; Phone: +(57) 3138897669;

Email: eloyne@yahoo.com

ABSTRACT

Objective

Determine the prevalence, functional and structural alterations, of primary open-angle glaucoma (POAG) in patients with obstructive sleep apnea (OSA).

Setting

Tertiary hospital associated with a specialized center in ophthalmologic images in Bogota, Colombia.

Participants

Included 150 patients, for a sample of 300 eyes, 64 women (42.7%) and 84 men (57.3%) between 40 – 91 years old with a mean age of 66.8 (±12.1) and 150 patients were Hispanic.

Interventions

Patients were evaluated by the Glaucoma Clinic performing: visual acuity (VA), biomicroscopy, intraocular pressure (IOP), indirect gonioscopy, and direct ophthalmoscopy. Patients classified as glaucoma suspects underwent visual computerized campimetry (VCC) and optical coherence tomography (OCT) of the optic nerve

Outcome Measure

VA, biomicroscopy, IOP, indirect gonioscopy, and direct ophthalmoscopy, VCC and OCT of the optic nerve.

Results

The prevalence of glaucoma suspect was 12.6%, and for POAG was 17.3%. No alterations in the appearance of the optic nerve in 74.6%, focal or diffuse thinning of the neuroretinal rim (16.6%) was the most frequently alteration, followed by asymmetry of the disc > 0.2 mm (8.6%), (p=0.005). In the VCC, 54.4% had no alterations in the visual field (VF). The remaining 41% showed arcuate, nasal step, and paracentral focal defects. The mean nerve

fiber layer (RNFL) was normal in 74% of the mild OSA group, 93.8% of the moderate group, and 17.1% of the severe group. Similarly, normal ganglion cell complex (GCC) in 60%, 68%, and 75% respectively. Abnormal results in the mean RNFL were seen in 25.9%, 6.3%, and 23.4% of the mild, moderate, and severe groups respectively. In the GCC, 39.7%, 33.3% and 25% of the patients in the aforementioned groups.

Conclusion

It was possible to determine the relationship between structural changes in the optic nerve and the severity of OSA. No relationship with any of the other studied variables was identified.

Keywords: Descriptive Cross-Sectional Study, Glaucoma Suspect, Primary open-angle glaucoma, Obstructive sleep apnea, Visual field.

INTRODUCTION

Glaucoma is considered the second cause of irreversible blindness worldwide in people over 40 years of age, defined as optic neuropathy that generates loss of neural tissue in the optic nerve and, therefore, changes in the visual field (VF) (1). Its prevalence is estimated at 1.86% – 7% in Hispanic, Asian, and Native American ethnicities, and 5.6% in African Americans[1,2]. It is estimated that by 2020, more than 80 million people will be affected, 11.2 million of whom will have bilateral blindness, with an annual incidence of 2.4 million cases[3]. It is a progressive and silent disease; whose visual manifestations develop in advanced stages [3].

Obstructive Sleep Apnea (OSA) has been identified as a cause of glaucoma. Its prevalence has been estimated at 27%[4] but varies in different epidemiological studies. OSA is understood as a disorder characterized by repetitive partial or complete obstruction of the upper airway during sleep, causing oxygen desaturation and becoming a risk factor for cardiovascular and neurological diseases[5]. The main symptoms are snoring, daytime sleep, difficulty concentrating, and morning headache. Risk factors include obesity, gender, upper respiratory abnormalities, consumption and snoring[6].

Regarding pathophysiology, upper airway obstruction favors hypoxia, hypercapnia, increased vascular resistance, and sympathetic activation[5,7,8]. The relationship between glaucoma and OSA can be explained by the increase in IOP at night due to a supine position[4,9], which increases episcleral venous pressure[4], and periods of hypoxia followed by oxidative stress that generate an increased intracranial pressure, which, in turn, decreases cerebral perfusion pressure, subsequently altering the vascular supply to the optic nerve[5]. Sympathetic system is important because, during apnea episodes, the renin–angiotensin

system is activated, leading to a sustained increase in blood pressure during sleep[6]. Dysregulation of optic nerve vascularization secondary to repetitive hypoxia, associated to an imbalance between vasodilator vascular stimuli (nitric oxide) and vasoconstrictors (endothelin) which generates variations in ocular perfusion pressure and therefore susceptibility to ischemia in the optic nerve head[10]. Additionally, episodes of apnea and hypopnea contribute to the development of complications with endothelial dysfunction, vascular remodeling, and hypertension[11].

Due to the complexity of the relationship between these conditions and the controversy between their association[7,8], it is very important to be able to categorize the frequency of cases. Furthermore, by identifying the risk factor for OSA[12], a protocol that allows patients to be referred to ophthalmological consultation in a timely manner could be created in order to avoid visual sequelae. Additionally, patients requiring medical treatment in order to prevent optic nerve damage and avoid blindness can be timely identified[13].

The objective of this study is to characterize the prevalence of primary open-angle glaucoma, as well as its functional and structural alterations, in patients with OSA.

MATERIALS & METHODS

We included adult patients who were listed in Bogota's *Central Military Hospital* database as diagnosed with OSA between January 2013 and December 2019. These patients' medical histories were used to determine demographic data such as age and ethnicity as well as family history, arterial hypertension and diabetes mellitus histories. The findings in polysomnography determined the severity of OSA using the AHI (sum of apnea and

hypopnea events divided by total hours of sleep) to categorize it into one of three groups: mild (index 6–15), moderate (16–30), and severe (> 30).

Exclusion criteria include psychiatric or neurological disorders, optic neuropathy, any condition affecting the VF (such as intracranial or ocular lesions), coexisting retinal disease, sequelae of trauma and/or eye inflammation, congenital ocular anatomical alterations, intraocular surgery (with the exception of cataract surgery), history of hypertensive crisis, history of prolonged steroid use, uveitis, interstitial lung diseases, heart disease, cirrhosis, and chronic renal failure. Additionally, patients with closed-angle glaucoma by gonioscopy and patients who did not sign the informed consent.

Two clinical days were carried out. On the first day, two glaucoma specialists, performed visual acuity (VA) (Snellen chart), anterior segment (slit lamp), intraocular pressure (IOP) (Goldmann tonometer), and indirect gonioscopy (Posner lens). The ophthalmoscopy (90D lens Volk Optical Inc.) to determine alterations such as focal or diffuse thinning of the neuroretinal rim, optic disc hemorrhages, defects in the RNFL, and disc asymmetry > 0.2 mm.

Glaucoma suspects were selected with the following conditions: open angles by gonioscopy, optic nerve excavations > 0.5 mm, asymmetry of optic nerve excavations > 0.2 mm, IOP ≧

22 mmHg, IOP within normal limits linked to thinning of the neuroretinal rim, thinning of RNFL, optic nerve vessels causing “bayoneting” flexion or deformation, peripapillary hemorrhages, and loss of the ISNT rule.

On the second day, patients were invited to the *Instituto de Macula y Retina Oftalmocenter* where visual computerized campimetry (VCC) (Humphrey Field Analyzer model 750i, Carl Zeiss-Meditec, Dublin, USA, SITA Standard program) and optic nerve OCT (spectral domain with the Cirrus OCT team) exams were performed. In the VCC, the mean deviation (MD) and alterations in the VF (superior arcuate defect, inferior arcuate defect, generalized decrease in sensitivity, nasal step, focal and paracentral defects) were determined. The OCT measured the mean nerve fiber layer (RNFL) and ganglion cell complex (GCC). The examinations were analyzed by two glaucoma specialists and all data collected were grouped into groups for analysis.

The diagnosis of glaucoma suspect was assigned to patients that showed either risk factors linked to developing glaucoma or clinical signs suggesting the disease but without functional alterations in the VF or structural alterations in the OCT. Patients were classified as having primary open-angle glaucoma (POAG) when they showed functional alterations in the VF and/or structural alterations in the OCT.

The study was approved by the ethics committee of the *Hospital Militar Central* in the reunion of may 3, 2019 act No, 7. The committee has adherence to the guidelines of the declaration of Helsinki and all the patients singed a consent to participate in study, approved by the ethics committee.

For the statistical analysis, SPSS 23 software was used. A Chi-sq test to determine the association between variables and the severity of OSA. A Shapiro-Wilk test to identify if the

sample data followed a normal distribution, Levene's test to specify if the continuous variables had the same variance, and ANOVA test to compare the means of the continuous variables. Using their respective confidence intervals, we established the prevalence of glaucoma suspects as well as POAG with OSA. The frequency of each visual alteration in the patients was determined and the findings of the OCT and VF were described.

Regarding bias control, the medical records of all patients diagnosed with OSA who met the inclusion and exclusion criteria in the proposed time span were collected. The personnel in charge were trained to carry out the evaluation; the diagnostic equipment was properly calibrated and had the corresponding technological updates.

PATIENT AND PUBLIC INVOLMENT

Patients were informed telephonically of the purpose of the study and were invited to participate in the study. All data collected were grouped into four (4) groups for analysis. The first group analyzed the demographic data, and the second group analyzed the findings in the clinical history and ophthalmological examination (AHI, glaucoma family history, history of arterial hypertension or AV diabetes mellitus, basal IOP, gonioscopy, optic nerve excavation, and suspicious changes in the optic nerve). The third group evaluated the results of the VF (MD value classified as mild >-6.00 dB, moderate MD -6.00 to -12.00 dB and severe ≤-12.01) and the campimetry alterations already described, and in the fourth group the OCT results were categorized as normal, suspicious, or abnormal. The diagnosis of suspected glaucoma was assigned to patients that showed either risk factors linked to developing glaucoma or clinical signs suggesting the disease but without functional alterations in the VF or structural alterations in the OCT. Patients were classified as having

primary open-angle glaucoma (POAG) when they showed functional alterations in the VF and/or structural alterations in the OCT. All patients had a posterior ophthalmological consult in the the *Hospital Militar Central,* where they were informed of the results of the study.

focus groups were organ- ised with members of the community (women and men), healthcare workers and community health workers, to explore barriers to CC screening and further improve the programme and recruitment strategy. Patients were also involved at their arrival at the screening centre where they were offered a 1-hour information session on CC and sexual health by trained midwives. Furthermore, the public is kept informed about the progress of our research through the publication of biannual newslet- ters disseminated among health workers and the general community. Newsletters will be published until the end of the 3T study.

RESULTS

The study included 150 patients, (300 eyes). A total of 42.7% women and 57.3% men between 40 – 91 years old with a mean age of 66.8 (±12.1). All 150 patients were Hispanic, 1.3% had a family history of glaucoma, 64.7% high blood pressure and 20.7% diabetes mellitus (Table 1).

The AHI was categorized as 62% mild OSA, 17.3% as moderate, and 20.7% as severe. In total, 90 eyes were glaucoma suspects, which 52 eyes were POAG, for a prevalence of 17.3% for POAG and 12.6% for glaucoma suspect.

- ***Visual acuity:*** The most prevalent were between 20/20 and 20/60 in 94.6%, (p=0.057). The patients with good visual acuities were in the mild severity group (20/20, 28.5%; 20/25, 23.7%; 20/30, 19.4%; 20/40, 15.1%), followed by the lowest

VA in the moderate group (20/50, 11.5%; 20/150, 1.9%) and the severe group (20/60, 4.8%; 20/70, 3.2%; 20/80, 4.8%). (Table 2).

- ***Intraocular Pressure:*** The mean was 13 mmHg (± 2.6), 13.3 mmHg (± 0.2) for mild cases, 13.3 mmHG (± 0.3) for moderate cases, and 12.5 mmHg (± 0.3) for severe cases (p = 0.107). Regarding the excavation of the optic nerve, the mean was 0.4 mm (± 0.2), (p = 0.953) (Table 3-4).
- ***Optic nerve changes:*** 74.6% of the eyes showed no alterations, 16.6% have a focal or diffuse thinning of the neuroretinal rim. These findings were more prevalent in the mild OSA group (21.5%), followed by the moderate OSA group (15.4%), and the severe OSA group (3.2%). Disc asymmetry (> 0.2 mm) was observed in 8.6%, with a higher prevalence in the severe OSA group (16.1%), followed by the mild OSA group (8.2%), and finally the moderate group (7.7%), (p=0.005) (Table 2).

- ***Campimetry alterations:*** 54.4% were normal with no significant differences between the groups (mild OSA [55.2%], moderate [56.3%], and severe [50.0%]). The second alteration was superior arcuate defect in 14.4%, more commonly found in the mild OSA group (12.1%). The next alternation was focal defects in 13.3%, mainly in the mild group (13.8%), with an equal percentage in the moderate and severe groups (12.5%). The nasal step defect was present in 12.2%, most frequently in the moderate OSA group (18.8%), followed by the mild group (13.8%) and severe group (6.3%). To a lesser extent, a paracentral defect was seen in 3.3%—only in the mild OSA group (5.2%)—and an inferior arcuate defect was seen in 2.2% in the moderate (6.3%) and mild (1.7%) OSA groups. (p=0.583). (Table 5)

- The decrease in the **Mean Deviation** (MD) was mild (< -6 dB) in 83.3%, distributed as follows: moderate OSA (56.3%), mild OSA (55.2%), and severe OSA (50.0%). The moderate decrease in MD (-6 and -12 dB) occurred in 13.3%, distributed as follows: severe OSA (18.8%), mild OSA (12.1%), and moderate OSA (6.3%). The severe decrease in MD (> -12 dB) was 4.4%, distributed mostly in severe OSA (12.5%) vs. mild OSA (3.4%). (p=0.305).

- ***OCT of the optic nerve:*** The mean RNFL was normal in 74% of the mild OSA group, 93.8% of the moderate OSA group, and 17.1% of the severe OSA patients. Similarly, the GCC was normal in 60%, 68% and 75% of the respective OSA severity groups. Abnormalities in the mean RNFL were seen in 25.9%, 6.3% and 23.4% of the mild, moderate, and severe groups, respectively (p=0.081). Regarding GCC, abnormalities were found in 39.7%, 33.3% and 25% for these same groups (p=0.218). (Table 5)

DISCUSSION

OSA has been considered a possible risk factor for developing glaucoma. According to the pathophysiology of OSA, a vascular theory has been postulated that relates to the increase in vascular resistance secondary to hypoxia. This would cause dysregulation of optic nerve head vascularization[5,10]. There is also a mechanical theory that the increase of IOP caused by supine position and an increase of episcleral venous pressure linked to obesity could lead to this condition[4,9]. According to these theories, functional and structural changes would be generated in the optic nerve, leading glaucoma.

This study found the prevalence of POAG in patients with OSA was 17.3%, and glaucoma suspect was 12.6%. These prevalence values are similar to those of studies such as that of Bagabas *et al.*[14], which found a 16% prevalence, but were much lower than those found in studies such as Friedlander *et al.*[15] and Wozniac *et al.*[16]. In various meta-analyses, a link between OSA and glaucoma[5,17] has been identified; Shi *et al.*[18]— revealed a significant relationship between the prevalence of glaucoma and OSA in case-control studies (OR=1.96) and cross-sectional studies (OR=1.41).

Regarding to the risks factors for developing POAG, all the patients in this study were Hispanic, meaning ethnicity was not a differentiating factor, patients suffering from hypertension were found in the group of patients diagnosed with glaucoma.

A high number of patients have visual acuities between 20/20-20/60. This indicates that the visual state is preserved, and as such, the visual pathways are not significantly compromised. No statistical relationship was found regarding the severity of OSA and visual acuities, most likely indicating that OSA does not increase loss of vision.

IOP is recognized as the only modifiable risk factor associated with developing glaucoma, so timely identification would allow for rapid treatment in order to prevent the progression of glaucoma. Various studies have identified a relationship between OSA and IOP values, finding positive correlation with the supine position (Moghimi *et al.*[19], Sergio et al.[20], and Yee *et al.*[9]. This is contrary to studies described by Nowak *et al.*[21] and Shalaby *et al.*[22]. In studies such as that of Carnero et al.[23], patients with OSA experience upper limits of IOP.

Unlike the aforementioned, in our study, IOP occurred within normal, with no evidence of a correlation with the severity of OSA.

The excavation with greater sizes was reported in patients with glaucoma and no relation to OSA severity. Suspicious changes in the optic nerve were the only variable in which a statistical significance was found regarding the severity of OSA. This demonstrates how OSA can influence the optic nerve anatomy by favoring the development of optic neuropathy and, to some extent, the onset of POAG. A higher percentage of these changes was found in the severe OSA group. It was possible to identify that focal or diffuse thinning of the neuroretinal rim in the mild OSA group as a possible indicator of early and focal damage of the optic nerve. Additionally, asymmetry > 0.2 mm was identified in patients with severe OSA, indicating greater damage by a diffuse thinning of the neuroretinal rim, from which it could be inferred that the progression of optic nerve damage is related to the severity of OSA. This is similar to the findings of Tsang *et al.*, a case-control study that demonstrated an incidence of suspicious optic nerve changes four times higher in patients with moderate or severe OSA[24]. Another study by Uslu *et al.*, suggests an increased optic nerve excavation in patients with OSA, and it could be considered an indicator of neural damage in the early diagnosis of OSA[25]. In contrast to previous results, Lin *et al.*, showed that the optic nerve parameters did not differ between OSA severity groups[26], nor did it differ from the general population described by Salzgeber *et al.*[27].

As for the functional changes in the VF, authors such as Tsang *et al.* found abnormalities in DM and pattern standard deviations[24] correlated with OSA severity index[20], indicating a direct relationship between these pathologies. In contrast, this study identified that most of

the patients did not show functional alterations, which is similar to the findings of Swaminatha *et al.*[28] and Salzgeber *et al.*[27].

According to VF numerical parameters, a high percentage of patients showed a mild decrease in the mean deviation which predominated in the moderate OSA group. Meanwhile, a moderate to severe decrease was seen in the severe OSA group. This indicates that the greater the severity of OSA, the more compromised the VF; this signifies a possible link between these pathologies, although it could not be statistically demonstrated in this study.

It has been described that the first VF manifestations in patients with POAG are generalized depression, enlargement of the blind spot, Seidel's scotoma, or nasal step[29]. Subsequently, paracentral defects that may join with the blind spot, as well as temporary steps, and superior or inferior arcuate defects. Finally, progressive damage can lead to peripheral constriction of the VF, leaving central or temporal vision islands[29]. Comparing this to what was observed in this study, the functional alterations described are commonly identified in intermediate or advanced stages of POAG which occurred more frequently in the mild OSA group; therefore, it could be inferred that mild stages of OSA may be related to greater VF alterations.

The OCT showed that most of the patients were within normal ranges, patients with abnormal results showed an increased severity of structural nerve damage as the analysis went from mild and moderate to severe OSA. This is supported by meta-analyses that demonstrated a link between moderate and severe OSA with significant thinning of RNFL thickness—mainly in the upper, lower, and nasal quadrants[30-32]. Additionally, Fan *et al.* described greater progression of structural changes (RNFL thickness) in patients with mild OSA, obtaining an

8.448 risk of structural progression in patients with severe OSA[33]. This differs from the studies of Nowak *et al.*, Salzgeber *et al.,* and Kara *et al.*[21,27,34]. Moreover, Abdullayev *et al.* found no alteration of RNFL thickness in patients with OSA that correlated to its severity, but describe a decrease in GCC in patients with mild severity[35]. In contrast, Uslu *et al.* found no alterations in the GCC, but a decrease in the peripapillary RNFL thickness[25].

In the general population with POAG, structural changes have been observed as the first manifestation of glaucoma—before a compromised VF[29], which correspond to the decrease of the GCC in the initial stages with a subsequent decrease in the mean RNFL. When comparing these characteristics of the general population with POAG to the results of this study, it can be deduced that most of the patients with OSA and glaucoma first showed an alteration in the GCC, followed by alterations in the mean RNFL. Some of the patients experienced these alterations before VF alterations; therefore, it can be inferred that the development of glaucoma would manifest itself in the same way in patients with OSA as in the general population with glaucoma.

The main limitations of the study were the lack of a control group, and the performed of only one examination. As such, it was not possible to determine if the alterations found persisted or if the glaucoma progressed over time. Finally, due to the sample size, it could not be determined whether OSA correlated with the development of POAG.

In conclusion, this study found a prevalence of glaucoma suspects of 12.6% vs. a POAG prevalence of 17.3% in patients diagnosed with OSA. The study demonstrated a relationship between the structural changes of the optic nerve and the severity of OSA, suggesting that

OSA might influence the anatomy of the optic nerve and favor the development of optic neuropathy, and, to some extent, the onset of POAG. No relationship was identified with any of the other variables that were studied. Future research, studies, and follow-ups are recommended for patients with OSA to rule out glaucoma as one of its multiple systemic manifestations.

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TABLE 1 Demographic variables

DEMOGRAFIC VARIABLES		n (%)
SEX	1. Female	64 (42.7)
	2. Male	86 (57.3)
ETHNICITY	1. Hispanic	150 (100)
	2. Afro-descendant	0
	3. Indigenous	0
FAMILY HISTORY	1. Si	2 (1.3)
	2. No	148 (98.6)
HYPERTENSION	1. Si	97 (64.7)
	2. No	53 (35.3)
DIABETES MELLITUS	1. Si	31 (20.7)
	2. No	119 (79.3)

TABLE 2. Visual acuity and suspicious changes in the optic nerve

VARIABLE		OBSTRUCTIVE SLEEP APNEA SEVERITY			Total (n=300)	Valor p
		MILD (n=186)	MODERATE (n=52)	SEVERE (n=62)	n (%)	
VISUAL ACUITY	20/20	53 (28.5%)	14 (26.9%)	13 (21.0%)	80 (26.6)	0.031
	20/25	44 (23.7%)	11 (21.1%)	6 (9.7%)	61 (20.3)	
	20/30	36 (19.4%)	10 (19.2%)	22 (35.5%)	68 (22.6)	
	20/40	28 (15.1%)	7 (13.5%)	9 (14.7%)	44 (14.6)	
	20/50	15 (8.1%)	6 (11.5%)	3 (4.8%)	24 (8)	
	20/60	2 (1.1%)	2 (3.8%)	3 (4.8%)	7 (2.3)	
	20/70	3 (1.6%)	0	2 (3.2%)	5 (1.6)	
	20/80	1 (0.5%)	0	3 (4.8%)	4 (1.3)	
	20/100	2 (1.1%)	0	0	2 (0.6)	
	20/150	0	1 (1.9%)	1 (1.6%)	2 (0.6)	
	20/200	2 (1.1%)	0	0	2 (0.6)	
SUSPECTED CHANGES IN THE OPTIC NERVE	1. Focal or diffuse thinning of the neuroretinal rim	40 (21.5%)	8 (15.4%)	2 (3.2%)	50 (16.6)	0.005
	2. Disc Hemorrage	0	0	0	0	
	3. RNFL alterations	0	0	0	0	
	4. Disc asymmetry > 0.2	12 (8.2%)	4 (7.7%)	10 (16.1%)	26 (8.6)	
	No Alterations	134 (72.0%)	40 (76.9%)	50 (80.6%)	224 (74.6)	

TABLE 3. Quantitative variables

VARIABLE	MEDIAN	STANDARD DESVIATION
AGE (YEARS)	66.8	12.1
INTRAOCULAR PRESSURE (mmHg)	13	2.6
OPTIC NERVE EXCAVATION (mm)	0.4	0.2

OBSTRUCTIVE SLEEP APENA SEVERITY		INTRAOCULAR PRESSURE (mmHg)	OPTIC NERVE EXCAVATION	Total n
MILD	Median	13.3	0.4	186
	Standard Desviation	0.2	0,0	
MODERATE	Median	13.3	0.4	52
	Standard Desviation	0.3	0,0	
SEVERE	Median	12.5	0.4	62
	Standard Desviation	0.3	0,0	
ANOVA P value		0.107	0.953	

TABLE 4. Quantitative variables and Obstructive Sleep Apnea Severity

TABLE 5. Functional and structural findings in the visual field and optic nerve computerized tomography

VARIABLE		OBSTRUCTIVE SLEEP APNEA SEVERITY			Total (n=90)	P-VALUE
		MILD (n=58)	MODERATE (n=16)	SEVERE (n=16)	n (%)	
VISUAL FIELD	1. Superior Arcuate Defect	7 (12,1%)	1 (6.3%)	5 (3.1%)	13 (14.4)	0.583
	2. Inferior Arcuate Defect	1 (1.7%)	1 (6.3%)	0	2 (2.2)	
	3. General Diminished Sensitivity	0	0	0	0	
	4.Nasal Step	7 (12.1%)	3 (18.8%)	1 (6.3%)	11(12.2)	
	5. Focal Defects	8 (13.8%)	2 (12.5%)	2 (12.5%)	12 (13.3)	
	6. Paracentral Defects	3 (5.2%)	0	0	3 (3.3)	
	7. Normal	32 (55.2%)	9 (56.3%)	8 (50.0%)	49 (54.4)	
MEAN DEVIATION	1. DM <-6 dB	49 (84.5%)	15 (93.8%)	11 (68.8%)	75 (83.3)	0.305
	2. DM -6 a-12 dB	7 (12.1%)	1 (6.3%)	3 (18.8%)	11(12.2)	
	3. DM >-12 dB	2 (3.4%)	0	2 (12.5%)	4 (4.4)	
MEAN NERVE FIBER LAYER	1. Normal > 80 micras	43 (74.1%)	15 (93.8%)	12 (17.1%)	70 (77.7)	0.081
	2. Suspicious 70-79 micras	12 (20.7%)	0	1 (6.3%)	13 (14.4)	
	3. Abnormal < 70 micras	3 (5.2%)	1 (6.3%)	3 (18.8%)	7 (7.7)	
GANGLION CELL COMPLEX	1. Normal (green)	35 (60.3%)	11 (68.8%)	12 (75.0%)	58 (64.4)	0.218
	2. Suspicious (yellow)	11 (19.0%)	4 (25.0%)	0	15 (16.6)	
	3. Abnormal (red)	12 (20.7%)	1 (6.3%)	4 (25.0%)	17 (18.9)	
POAG	1. SI	35 (60.3%)	9 (56.3%)	8 (50.0%)	52 (57.8)	0.752
	2. NO	23 (39.7%)	7 (43.8%)	8 (50.0%)	38 (42.2)	
GLAUCOMA SUSPECTS	1. SI	23 (39.7%)	7 (43.8%)	8 (50.0%)	38 (42.2)	0.752
	2. NO	35 (60.3%)	9 (56.3%)	8 (50.0%)	52 (57.8)	

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9

		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Primary Open-angle Glaucoma in Patients with Obstructive Sleep Apnea in a Colombian Population: A Cross-Sectional Study

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TITLE

Primary Open-angle Glaucoma in Patients with Obstructive Sleep Apnea in a Colombian Population: A Cross-Sectional Study

NAMES AND AFFILIATIONS

María Alejandra Cerquera Jaramillo - Ophthalmology Resident - Department of Ophthalmology, *Universidad Militar Nueva Granada – Central Military Hospital*, Bogota, Colombia

Sara Edith Moreno Mazo – MD, Glaucoma Ophthalmologist – Department of Ophthalmology, *Universidad Militar Nueva Granada - Central Military Hospital,* Bogota, Colombia

Jeanneth Eloyne Toquica Osorio - Glaucoma Ophthalmologist – Department of Ophthalmology, *Universidad Militar Nueva Granada - Central Military Hospital*, Bogota, Colombia

Correspondence address: Jeanneth Eloyne Toquica Osorio, Department of Ophthalmology *Universidad Militar Nueva Granada - Central Military Hospital*, Bogotá, Colombia; Phone: +(57) 3138897669;

Email: eloyne@yahoo.com

ABSTRACT

Objective

Determine the prevalence, functional and structural alterations, of primary open-angle glaucoma (POAG) in patients with obstructive sleep apnea (OSA).

Design

Cross-Sectional

Setting

Tertiary hospital associated with specialized center in ophthalmologic images in Bogota, Colombia.

Participants

150 patients, for a sample of 300 eyes, 64 women (42.7%) and 84 men (57.3%) between 40 – 91 years old with a mean age of 66.8 (±12.1).

Interventions

Visual acuity, biomicroscopy, intraocular pressure, indirect gonioscopy, and direct ophthalmoscopy. Patients classified as glaucoma suspects underwent automated perimetry (AP) and optical coherence tomography (OCT) of the optic nerve

Outcome Measure

The primary outcomes are the determination of prevalence of glaucoma suspects and PAOG in patients with obstructive sleep apena. Secondary outcomes are the description of functional and structural alterations in computerized exams of patients with OSA.

Results

The prevalence of glaucoma suspect was 12.6%, and for POAG was 17.3%. Normal appearance of the optic nerve was seen in 74.6%, focal or diffuse thinning of the neuroretinal rim (16.6%) was the most frequently finding, followed by asymmetry of the disc > 0.2 mm

(8.6%), (p=0.005). In the AP 54.4% had normal findings in the visual field (VF). The remaining 41% showed arcuate, nasal step, and paracentral focal defects. The mean nerve fiber layer (RNFL) was normal in 74% of the mild OSA group, 93.8% of the moderate group, and 17.1% of the severe group. Similarly, normal ganglion cell complex (GCC) in 60%, 68%, and 75% respectively. Abnormal results in the mean RNFL was seen in 25.9%, 6.3%, and 23.4% of the mild, moderate, and severe groups respectively. In the GCC, 39.7%, 33.3% and 25% of the patients in the aforementioned groups.

Conclusion

It was possible to determine the relationship between structural changes in the optic nerve and the severity of OSA. No relationship with any of the other studied variables was identified.

Keywords: Descriptive Cross-Sectional Study, Glaucoma Suspect, Primary open-angle glaucoma, Obstructive sleep apnea, Visual field.

Strengths and limitations of this study

- Two stage design for collecting data, based in complete clinical ophthalmologic examination, followed by computerized exams to ensure diagnosis.
- The collected data and results were verified by two glaucoma specialists.
- The study reflects the situation in a tertiary hospital with a specialized ophthalmologic center in Bogota, Colombia. Generalizability of our study results needs to be verified

- The main limitations of the study were the lack of a control group, sample size, and the performed of only one examination, making not possible to determine if the alterations found persisted or if the glaucoma progressed over time.

INTRODUCTION

Glaucoma is considered the second cause of irreversible blindness worldwide in people over 40 years of age, defined as optic neuropathy that generates loss of neural tissue in the optic nerve and, therefore, changes in the visual field (VF)[1]. Its prevalence is estimated at 1.86% – 7% in Hispanic, Asian, and Native American ethnicities, and 5.6% in African Americans[1,2]. It is estimated that by the year 2020, more than 80 million people will be affected, 11.2 million of whom will have bilateral blindness, with an annual incidence of 2.4 million cases[3]. It is a progressive and silent disease; whose visual manifestations develop in advanced stages[3].

Obstructive Sleep Apnea (OSA) has been identified as a cause of glaucoma [4,5]. Its prevalence has been estimated at 27% but varies in different epidemiological studies[6]. OSA is understood as a disorder characterized by repetitive partial or complete obstruction of the upper airway during sleep, causing oxygen desaturation and becoming a risk factor for cardiovascular and neurological diseases[7]. The main symptoms are snoring, daytime sleep, difficulty concentrating, and morning headache. Risk factors include obesity, gender, upper respiratory abnormalities, consumption and snoring[8].

Regarding pathophysiology, upper airway obstruction favors hypoxia, hypercapnia, increased vascular resistance, and sympathetic activation[7,9,.10]. The relationship between glaucoma and OSA can be explained by the increase in IOP at night due to a supine position[6,11], which increases episcleral venous pressure[6], and periods of hypoxia followed by oxidative stress that generate an increased intracranial pressure, which, in turn, decreases cerebral perfusion pressure, subsequently altering the vascular supply to the optic nerve[7].

Sympathetic system is important because, during apnea episodes, the renin–angiotensin system is activated, leading to a sustained increase in blood pressure during sleep[8]. Dysregulation of optic nerve vascularization secondary to repetitive hypoxia, associated to an imbalance between vasodilator vascular stimuli (nitric oxide) and vasoconstrictors (endothelin) which generates variations in the ocular perfusion pressure and therefore susceptibility to ischemia in the optic nerve head[12]. Additionally, episodes of apnea and hypopnea contribute to the development of complications with endothelial dysfunction, vascular remodeling, and hypertension[13].

Due to the complexity of the relationship between these conditions and the controversy between their association[9,10], is very important to be able to categorize the frequency of cases. Furthermore, by identifying the risk factor for OSA[14], a protocol that allows patients to be referred to ophthalmological consultation in a timely manner could be created in order to avoid visual sequelae. Additionally, patients requiring medical treatment in order to prevent optic nerve damage and avoid blindness can be timely identified[15].

The objective of this study is to characterize the prevalence of primary open-angle glaucoma, as well as its functional and structural alterations, in patients with OSA.

MATERIALS & METHODS

We included all the legal adult patients who were listed in Bogota's *Central Military Hospital* database as diagnosed with OSA (by polysomnography) between January 2013 and December 2019. These patients' medical histories were used to determine demographic data such as age and ethnicity as well as family history, arterial hypertension (high blood

pressure), and diabetes mellitus histories. The findings in polysomnography determined the severity of OSA using the AHI (sum of apnea and hypopnea events divided by total hours of sleep) to categorize it into one of three groups: mild (index 6–15), moderate (16–30), and severe (> 30).

Exclusion criteria include psychiatric or neurological disorders, optic neuropathy, anterior ischemic optic neuropathy, heavy smoking (20 cigarettes per day), alcohol or psychoactive substance abuse, any condition affecting the VF (such as intracranial or ocular lesions), coexisting retinal disease, sequelae of trauma and/or eye inflammation, congenital ocular anatomical alterations, intraocular surgery (with the exception of cataract surgery), history of hypertensive crisis, history of prolonged steroid use, uveitis, bronchial asthma, interstitial lung diseases, heart disease, cirrhosis, and chronic renal failure. Additionally, patients with closed-angle glaucoma or suspected closure by gonioscopy and patients who did not sign the informed consent in the study were excluded.

Two clinical days were carried out. On the first day, two glaucoma specialists in the hospital's Department of Ophthalmology, performed a complete ophthalmological examination, including visual acuity (VA) using the Snellen chart, the anterior segment with a slit lamp, intraocular pressure (IOP) measurement utilizing a Goldmann tonometer, and an assessment of indirect gonioscopy employing a Posner lens. The ophthalmoscopy was performed with a 90D lens (Volk Optical Inc.) to determine alterations such as focal or diffuse thinning of the neuroretinal rim, optic disc hemorrhages, defects in the nerve fiber layer (RNFL), and disc asymmetry greater than 0.2 mm.

Suspects glaucoma patients were selected if they showed the following conditions as open angles by gonioscopy, optic nerve excavations greater than 0.6 mm and asymmetry of optic nerve excavations greater than 0.2 mm. Associated, IOP greater than or equal to 22 mmHg, and IOP within normal limits linked to thinning of the neuroretinal rim. Additionally, thinning of RNFL, optic nerve vessels causing "bayoneting" flexion or deformation, peripapillary hemorrhages, and loss of the ISNT rule.

On the second day, glaucoma suspects were invited to the *Instituto de Macula y Retina Oftalmocenter* in Bogota where AP (Humphrey Field Analyzer model 750i, Carl Zeiss-Meditec, Dublin, USA, SITA Standard program) and optic nerve OCT (spectral domain with the Cirrus OCT team) exams were performed. In the AP, the mean deviation (MD) and alterations in the VF (superior arcuate defect, inferior arcuate defect, generalized decrease in sensitivity, nasal step, focal defects, and paracentral and normal defects) were determined. The OCT measured the mean RNFL and GGC, as well as analyzed the optic disc. Subsequently, two glaucoma specialists participating in the study analyzed the examinations.

The data collected were grouped into four groups for analysis. The first group analyzed the demographic data and risk factors (glaucoma family history, history of arterial hypertension or diabetes mellitus). The second group analyzed the findings in the clinical history and ophthalmological examination (AHI, AV, basal IOP, gonioscopy, optic nerve excavation, and suspicious changes in the optic nerve). The third group evaluated the results of the VF (MD value classified as mild >-6.00 dB, moderate MD -6.00 to -12.00 dB and severe ≤-12.01) and the campimetry alterations. In the fourth group the OCT results were categorized

as normal (>80 μM), suspicious (70-79 μM), or abnormal (<70 μM) for RNFL and normal (P5-90%), suspicious (P1-5%) or abnormal (P<5%) for GCC.

The diagnosis of glaucoma suspect was assigned to patients that showed either risk factors linked to developing glaucoma or clinical signs suggesting the disease but without functional alterations in the VF or structural alterations in the OCT. Patients were classified as having POAG when they showed functional alterations in the VF and structural alterations in the OCT.

The study was approved by the ethics committee of the *Hospital Militar Central* in the reunion of may 3, 2019 act No, 7. The committee has adherence to the guidelines of the declaration of Helsinki and all the patients singed a consent to participate in study, approved by the ethics committee.

For the statistical analysis, SPSS 23 software was used. A Chi-sq test to determine the association between variables and the severity of OSA. A Shapiro-Wilk test to identify if the sample data followed a normal distribution, Levene's test to specify if the continuous variables had the same variance, and ANOVA test to compare the means of the continuous variables. Using their respective confidence intervals, we established the prevalence of glaucoma suspects as well as POAG with OSA. The frequency of each visual alteration in the patients was determined and the findings of the OCT and VF were described.

Regarding bias control, all clinical records of the patients diagnosed with OSA met the inclusion and exclusion criteria proposed. The personnel in charge were trained to carry out

the evaluation; the same person was in charge of a specific function. Data collected and results were supervised and analyzed by two glaucoma specialists. The data collected were grouped into four groups for analysis. It was used the same diagnostic equipment, which was properly calibrated and had the corresponding technological updates.

Patient and Public Involvement

Patients were contacted telephonically to assist a clinical consult, where they were informed of the purpose of the study, risks and possible interventions and were invited to participate in the study. All patients who accepted, signed the informed consent, and had an ophthalmological consult in the Hospital Militar Central, where they were informed of their own results of the study. No results were disseminated in the others study participants.

RESULTS

The study included 150 patients, (300 eyes). A total of 42.7% women and 57.3% men between 40 – 91 years old with a mean age of 66.8 (±12.1). All 150 patients were Hispanic, 1.3% had a family history of glaucoma, 64.7% high blood pressure and 20.7% diabetes mellitus (Table 1).

DEMOGRAFIC VARIABLES		n (%)
SEX	1. Female	64 (42.7)
	2. Male	86 (57.3)
ETHNICITY	1. Hispanic	150 (100)
	2. Afro-descendant	0
	3. Indigenous	0
FAMILY HISTORY	1. Yes	2 (1.3)
	2. No	148 (98.6)
HYPERTENSION	1. Yes	97 (64.7)
	2. No	53 (35.3)
DIABETES MELLITUS	1. Yes	31 (20.7)
	2. No	119 (79.3)

TABLE 1 Demographic variables

The AHI was categorized as 62% mild OSA, 17.3% as moderate, and 20.7% as severe. In total, 90 eyes were glaucoma suspects, which 52 eyes were POAG, for a prevalence of 17.3% for POAG and 12.6% for glaucoma suspect.

- ***Visual acuity:*** The most prevalent were between 20/20 and 20/60 in 94.6%, (p=0.057). The patients with good visual acuities were in the mild severity group (20/20, 28.5%; 20/25, 23.7%; 20/30, 19.4%; 20/40, 15.1%), followed by the lowest VA in the moderate group (20/50, 11.5%; 20/150, 1.9%) and the severe group (20/60, 4.8%; 20/70, 3.2%; 20/80, 4.8%). (Table 2).

VARIABLE		OBSTRUCTIVE SLEEP APNEA SEVERITY			Total (n=300)	p-value
		MILD (n=186)	MODERATE (n=52)	SEVERE (n=62)	n (%)	
VISUAL ACUITY	20/20	53 (28.5%)	14 (26.9%)	13 (21.0%)	80 (26.6)	0.031
	20/25	44 (23.7%)	11 (21.1%)	6 (9.7%)	61 (20.3)	
	20/30	36 (19.4%)	10 (19.2%)	22 (35.5%)	68 (22.6)	
	20/40	28 (15.1%)	7 (13.5%)	9 (14.7%)	44 (14.6)	
	20/50	15 (8.1%)	6 (11.5%)	3 (4.8%)	24 (8)	
	20/60	2 (1.1%)	2 (3.8%)	3 (4.8%)	7 (2.3)	
	20/70	3 (1.6%)	0	2 (3.2%)	5 (1.6)	
	20/80	1 (0.5%)	0	3 (4.8%)	4 (1.3)	
	20/100	2 (1.1%)	0	0	2 (0.6)	
	20/150	0	1 (1.9%)	1 (1.6%)	2 (0.6)	
	20/200	2 (1.1%)	0	0	2 (0.6)	
SUSPECTED CHANGES IN THE OPTIC NERVE	1. Focal or diffuse thinning of the neuroretinal rim	40 (21.5%)	8 (15.4%)	2 (3.2%)	50 (16.6)	0.005
	2. Disc Hemorrage	0	0	0	0	
	3. RNFL alterations	0	0	0	0	
	4. Disc asymmetry > 0.2	12 (8.2%)	4 (7.7%)	10 (16.1%)	26 (8.6)	
	No Alterations	134 (72.0%)	40 (76.9%)	50 (80.6%)	224 (74.6)	

TABLE 2. Visual acuity and suspicious changes in the optic nerve

- ***Intraocular Pressure:*** The mean was 13 mmHg (± 2.6), 13.3 mmHg (± 0.2) for mild cases, 13.3 mmHG (± 0.3) for moderate cases, and 12.5 mmHg (± 0.3) for severe cases (p = 0.107). Regarding the excavation of the optic nerve, the mean was 0.4 mm (± 0.2), (p = 0.953) (Table 3-4).

VARIABLE	MEDIAN	STANDARD DESVIATION
AGE (YEARS)	66.8	12.1
INTRAOCULAR PRESSURE (mmHg)	13	2.6
OPTIC NERVE EXCAVATION (mm)	0.4	0.2

TABLE 3. Intraocular pressure and Optic nerve excavation

OBSTRUCTIVE SLEEP APENA SEVERITY		INTRAOCULAR PRESSURE (mmHg)	OPTIC NERVE EXCAVATION	Total n
MILD	Median	13.3	0.4	186
	Standard Desviation	0.2	0,0	
MODERATE	Median	13.3	0.4	52
	Standard Desviation	0.3	0,0	
SEVERE	Median	12.5	0.4	62
	Standard Desviation	0.3	0,0	
ANOVA P value		0.107	0.953	

TABLE 4. Obstructive Sleep Apnea Severity, Intraocular pressure and Optic nerve excavation

- ***Optic nerve changes:*** 74.6% of the eyes showed no alterations, 16.6% have a focal or diffuse thinning of the neuroretinal rim. These findings were more prevalent in the mild OSA group (21.5%), followed by the moderate OSA group (15.4%), and the severe OSA group (3.2%). Disc asymmetry (> 0.2 mm) was observed in 8.6%, with a higher prevalence in the severe OSA group (16.1%), followed by the mild OSA group (8.2%), and finally the moderate group (7.7%), (p=0.005) (Table 2).

- ***Campimetry alterations:*** 54.4% were normal with no significant differences between the groups (mild OSA [55.2%], moderate [56.3%], and severe [50.0%]). The second alteration was superior arcuate defect in 14.4%, more commonly found in the mild OSA group (12.1%). The next alternation was focal defects in 13.3%, mainly in the mild group (13.8%), with an equal percentage in the moderate and severe groups (12.5%). The nasal step defect was present in 12.2%, most frequently in the moderate OSA group (18.8%), followed by the mild group (13.8%) and severe group (6.3%). To a lesser extent, a paracentral defect was seen in 3.3%—only in the mild OSA group (5.2%)—and an inferior arcuate defect was seen in 2.2% in the moderate (6.3%) and mild (1.7%) OSA groups. (p=0.583). (Table 5)

VARIABLE		OBSTRUCTIVE SLEEP APNEA SEVERITY			Total (n=90)	P-VALUE
		MILD (n=58)	MODERATE (n=16)	SEVERE (n=16)	n (%)	
VISUAL FIELD	1. Superior Arcuate Defect	7 (12,1%)	1 (6.3%)	5 (3.1%)	13 (14.4)	0.583
	2. Inferior Arcuate Defect	1 (1.7%)	1 (6.3%)	0	2 (2.2)	
	3. General Diminished Sensitivity	0	0	0	0	
	4.Nasal Step	7 (12.1%)	3 (18.8%)	1 (6.3%)	11(12.2)	
	5. Focal Defects	8 (13.8%)	2 (12.5%)	2 (12.5%)	12 (13.3)	
	6. Paracentral Defects	3 (5.2%)	0	0	3 (3.3)	
	7. Normal	32 (55.2%)	9 (56.3%)	8 (50.0%)	49 (54.4)	
MEAN DEVIATION	1. DM <-6 dB	49 (84.5%)	15 (93.8%)	11 (68.8%)	75 (83.3)	0.305
	2. DM -6 a-12 dB	7 (12.1%)	1 (6.3%)	3 (18.8%)	11(12.2)	
	3. DM >-12 dB	2 (3.4%)	0	2 (12.5%)	4 (4.4)	
MEAN NERVE FIBER LAYER	1. Normal > 80 µm	43 (74.1%)	15 (93.8%)	12 (17.1%)	70 (77.7)	0.081
	2. Suspicious 70-79 µm	12 (20.7%)	0	1 (6.3%)	13 (14.4)	
	3. Abnormal < 70 µm	3 (5.2%)	1 (6.3%)	3 (18.8%)	7 (7.7)	
GANGLION CELL COMPLEX	1. Normal (green)	35 (60.3%)	11 (68.8%)	12 (75.0%)	58 (64.4)	0.218
	2. Suspicious (yellow)	11 (19.0%)	4 (25.0%)	0	15 (16.6)	
	3. Abnormal (red)	12 (20.7%)	1 (6.3%)	4 (25.0%)	17 (18.9)	
PRIMARY OPEN ANGLE GLAUCOMA	1. Yes	35 (60.3%)	9 (56.3%)	8 (50.0%)	52 (57.8)	0.752
	2. No	23 (39.7%)	7 (43.8%)	8 (50.0%)	38 (42.2)	
GLAUCOMA SUSPECTS	1. Yes	23 (39.7%)	7 (43.8%)	8 (50.0%)	38 (42.2)	0.752
	2. No	35 (60.3%)	9 (56.3%)	8 (50.0%)	52 (57.8)	

TABLE 5. Functional and structural findings in the visual field and optic nerve computerized tomography

- The decrease in the **Mean Deviation** (MD) was mild (< -6 dB) in 83.3%, distributed as follows: moderate OSA (56.3%), mild OSA (55.2%), and severe OSA (50.0%). The moderate decrease in MD (-6 and -12 dB) occurred in 13.3%, distributed as follows: severe OSA (18.8%), mild OSA (12.1%), and moderate OSA (6.3%). The severe decrease in MD (> -12 dB) was 4.4%, distributed mostly in severe OSA (12.5%) vs. mild OSA (3.4%). (p=0.305).

- ***OCT of the optic nerve:*** The mean RNFL was normal in 74% of the mild OSA group, 93.8% of the moderate OSA group, and 17.1% of the severe OSA patients. Similarly, the GCC was normal in 60%, 68% and 75% of the respective OSA severity groups. Abnormalities in the mean RNFL were seen in 25.9%, 6.3% and 23.4% of the mild, moderate, and severe groups, respectively (p=0.081). Regarding GCC, abnormalities were found in 39.7%, 33.3% and 25% for these same groups (p=0.218). (Table 5)

DISCUSSION

OSA has been considered a possible risk factor for developing glaucoma. According to the pathophysiology of OSA, a vascular theory has been postulated that relates to the increase in vascular resistance secondary to hypoxia. This would cause dysregulation of optic nerve head vascularization[7,12]. There is also a mechanical theory that the increase of IOP caused by supine position and an increase of episcleral venous pressure linked to obesity could lead to this condition[6,11]. According to these theories, functional and structural changes would be generated in the optic nerve, leading glaucoma.

This study found the prevalence of POAG in patients with OSA was 17.3%, and glaucoma suspect was 12.6%. These prevalence values are similar to those of studies such as that of Bagabas *et al.*[16], which found a 16% prevalence, but were much lower than those found in studies such as Friedlander *et al.*[17] and Wozniac *et al.*[18]. In various meta-analyses, a link between OSA and glaucoma[7,19] has been identified; Shi *et al.*[20] revealed a significant relationship between the prevalence of glaucoma and OSA in case-control studies (OR=1.96) and cross-sectional studies (OR=1.41).

Regarding to the risks factors for developing POAG, all the patients in this study were Hispanic, meaning ethnicity was not a differentiating factor, patients suffering from hypertension were found in the group of patients diagnosed with glaucoma.

A high number of patients have visual acuities between 20/20-20/60. This indicates that the visual state is preserved, and as such, the visual pathways are not significantly compromised. No statistical relationship was found regarding the severity of OSA and visual acuities, most likely indicating that OSA does not increase loss of vision.

IOP is recognized as the only modifiable risk factor associated with developing glaucoma, so timely identification would allow for rapid treatment in order to prevent the progression of glaucoma. Various studies have identified a relationship between OSA and IOP values, finding positive correlation with the supine position (Moghimi *et al.*[21], Sergio et al.[22], and Yee *et al.*[11]. This is contrary to studies described by Nowak *et al.*[23] and Shalaby *et al.*[24]. In studies such as that of Carnero et al.[25], patients with OSA experience upper limits of IOP.

Unlike the aforementioned, in our study, IOP occurred within normal, with no evidence of a correlation with the severity of OSA.

The excavation with greater sizes was reported in patients with glaucoma and no relation to OSA severity. Suspicious changes in the optic nerve were the only variable in which a statistical significance was found regarding the severity of OSA. This demonstrates how OSA can influence the optic nerve anatomy by favoring the development of optic neuropathy and, to some extent, the onset of POAG. A higher percentage of these changes was found in the severe OSA group. It was possible to identify that focal or diffuse thinning of the neuroretinal rim in the mild OSA group as a possible indicator of early and focal damage of the optic nerve. Additionally, asymmetry > 0.2 mm was identified in patients with severe OSA, indicating greater damage by a diffuse thinning of the neuroretinal rim, from which it could be inferred that the progression of optic nerve damage is related to the severity of OSA. This is similar to the findings of Tsang *et al.*[26], a case-control study that demonstrated an incidence of suspicious optic nerve changes four times higher in patients with moderate or severe OSA. Another study by Uslu *et al.* [27], suggests an increased optic nerve excavation in patients with OSA, and it could be considered an indicator of neural damage in the early diagnosis of OSA. In contrast to previous results, Lin *et al.* [28], showed that the optic nerve parameters did not differ between OSA severity groups, nor did it differ from the general population described by Salzgeber *et al.*[29].

As for the functional changes in the VF, authors such as Tsang *et al.* [26] found abnormalities in DM and pattern standard deviations correlated with OSA severity index[22], indicating a direct relationship between these pathologies. In contrast, this study identified that most of

the patients did not show functional alterations, which is similar to the findings of Swaminatha *et al.* [30] and Salzgeber *et al.*[29].

According to VF numerical parameters, a high percentage of patients showed a mild decrease in the mean deviation which predominated in the moderate OSA group. Meanwhile, a moderate to severe decrease was seen in the severe OSA group. This indicates that the greater the severity of OSA, the more compromised the VF; this signifies a possible link between these pathologies, although it could not be statistically demonstrated in this study.

It has been described that the first VF manifestations in patients with POAG are generalized depression, enlargement of the blind spot, Seidel's scotoma, or nasal step[31]. Subsequently, paracentral defects that may join with the blind spot, as well as temporary steps, and superior or inferior arcuate defects. Finally, progressive damage can lead to peripheral constriction of the VF, leaving central or temporal vision islands[31]. Comparing this to what was observed in this study, the functional alterations described are commonly identified in intermediate or advanced stages of POAG which occurred more frequently in the mild OSA group; therefore, it could be inferred that mild stages of OSA may be related to greater VF alterations.

The OCT showed that most of the patients were within normal ranges, patients with abnormal results showed an increased severity of structural nerve damage as the analysis went from mild and moderate to severe OSA. This is supported by meta-analyses that demonstrated a link between moderate and severe OSA with significant thinning of RNFL thickness—mainly in the upper, lower, and nasal quadrants[32-34]. Additionally, Fan *et al.*[35] described greater progression of structural changes (RNFL thickness) in patients with mild OSA,

obtaining an 8.448 risk of structural progression in patients with severe OSA. This differs from the studies of Nowak *et al.* [23], Salzgeber *et al.* [29], and Kara *et al.*[36]. Moreover, Abdullayev *et al.*[37] found no alteration of RNFL thickness in patients with OSA that correlated to its severity, but describe a decrease in GCC in patients with mild severity. In contrast, Uslu *et al.* found no alterations in the GCC, but a decrease in the peripapillary RNFL thickness[27].

The general population with POAG, structural changes has been observed as the first manifestation of glaucoma—before a compromised VF [31], which correspond to the decrease of the GCC in the initial stages with a subsequent decrease in the mean RNFL. When comparing these characteristics of the general population with POAG to the results of this study, it can be deduced that most of the patients with OSA and glaucoma first showed an alteration in the GCC, followed by alterations in the mean RNFL. Some of the patients experienced these alterations before VF alterations; therefore, it can be inferred that the development of glaucoma would manifest itself in the same way in patients with OSA as in the general population with glaucoma.

The main limitations of the study were the lack of a control group, and the performed of only one examination. As such, it was not possible to determine if the alterations found persisted or if the glaucoma progressed over time. Finally, due to the sample size, it could not be determined whether OSA correlated with the development of POAG.

In conclusion, this study found a prevalence of glaucoma suspects of 12.6% vs. a POAG prevalence of 17.3% in patients diagnosed with OSA. The study demonstrated a relationship

between the structural changes of the optic nerve and the severity of OSA, suggesting that OSA might influence the anatomy of the optic nerve and favor the development of optic neuropathy, and, to some extent, the onset of POAG. No relationship was identified with any of the other variables that were studied. Future research, studies, and follow-ups are recommended for patients with OSA to rule out glaucoma as one of its multiple systemic manifestations.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(*e*) Describe any sensitivity analyses	Not Applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11

		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable
Outcome data	15*	Report numbers of outcome events or summary measures	10-16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-16
		(*b*) Report category boundaries when continuous variables were categorized	10-16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Primary Open-angle Glaucoma in Patients with Obstructive Sleep Apnea in a Colombian Population: A Cross-Sectional Study

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TITLE

Primary Open-angle Glaucoma in Patients with Obstructive Sleep Apnea in a Colombian Population: A Cross-Sectional Study

NAMES AND AFFILIATIONS

María Alejandra Cerquera Jaramillo - Ophthalmologist - Department of Ophthalmology, *Universidad Militar Nueva Granada – Central Military Hospital*, Bogota, Colombia

Sara Edith Moreno Mazo – MD, Glaucoma Ophthalmologist – Department of Ophthalmology, *Universidad Militar Nueva Granada - Central Military Hospital,* Bogota, Colombia

Jeanneth Eloyne Toquica Osorio - Glaucoma Ophthalmologist – Department of Ophthalmology, *Universidad Militar Nueva Granada - Central Military Hospital*, Bogota, Colombia

Correspondence address: María Alejandra Cerquera Jaramillo, Department of Ophthalmology *Universidad Militar Nueva Granada - Central Military Hospital*, Bogotá, Colombia; Phone: +(57) 3144781831; Email: malecerquera@hotmail.com

ABSTRACT

Objective

Determine the prevalence, functional and structural alterations, of primary open-angle glaucoma (POAG) in patients with obstructive sleep apnea (OSA).

Design

Cross-Sectional

Setting

Tertiary hospital associated with specialized center in ophthalmologic images in Bogota, Colombia.

Participants

150 patients, for a sample of 300 eyes, 64 women (42.7%) and 84 men (57.3%) between 40 – 91 years old with a mean age of 66.8 (±12.1).

Interventions

Visual acuity, biomicroscopy, intraocular pressure, indirect gonioscopy, and direct ophthalmoscopy. Patients classified as glaucoma suspects underwent automated perimetry (AP) and optical coherence tomography of the optic nerve

Outcome Measure

The primary outcomes are the determination of prevalence of glaucoma suspects and POAG in patients with OSA. Secondary outcomes are the description of functional and structural alterations in computerized exams of patients with OSA.

Results

The prevalence of glaucoma suspect was 12.6%, and for POAG was 17.3%. No alterations in the appearance of the optic nerve was seen in 74.6%, focal or diffuse thinning of the neuroretinal rim (16.6%) was the most frequently finding, followed by asymmetry of the disc

> 0.2 mm (8.6%), (p=0.005). In the AP 41% showed arcuate, nasal step, and paracentral focal defects. The mean nerve fiber layer (RNFL) was normal (>80 μM) in 74% of the mild OSA group, 93.8% of the moderate group, and 17.1% of the severe group. Similarly, normal (P5-90) ganglion cell complex (GCC) in 60%, 68%, and 75% respectively. Abnormal results in the mean RNFL was seen in 25.9%, 6.3%, and 23.4% of the mild, moderate, and severe groups respectively. In the GCC, 39.7%, 33.3% and 25% of the patients in the aforementioned groups.

Conclusion

It was possible to determine the relationship between structural changes in the optic nerve and the severity of OSA. No relationship with any of the other studied variables was identified.

Keywords: Descriptive Cross-Sectional Study, Glaucoma Suspect, Primary open-angle glaucoma, Obstructive sleep apnea, Visual field.

Strengths and limitations of this study

- Two stage design for collecting data, based in complete clinical ophthalmologic examination, followed by computerized exams to ensure diagnosis.
- The collected data and results were verified by two glaucoma specialists.
- The study reflects the situation in a tertiary hospital with a specialized ophthalmologic center in Bogota, Colombia. Generalizability of our study results needs to be verified

- The main limitations of the study were the lack of a control group, sample size, and the performed of only one examination, making not possible to determine if the alterations found persisted or if the glaucoma progressed over time.

INTRODUCTION

Glaucoma is considered the second cause of irreversible blindness worldwide in people over 40 years of age, defined as optic neuropathy that generates loss of neural tissue in the optic nerve and, therefore, changes in the visual field (VF)[1]. Its prevalence is estimated at 1.86% – 7% in Hispanic, Asian, and Native American ethnicities, and 5.6% in African Americans[1,2]. It is estimated that by the year 2020, more than 80 million people will be affected, 11.2 million of whom will have bilateral blindness, with an annual incidence of 2.4 million cases[3]. It is a progressive and silent disease; whose visual manifestations develop in advanced stages[3].

Obstructive Sleep Apnea (OSA) has been identified in some population study as a possible risk factor to glaucoma [4,5]. Its prevalence has been estimated at 27% but varies in different epidemiological studies[6]. OSA is understood as a disorder characterized by repetitive partial or complete obstruction of the upper airway during sleep, causing oxygen desaturation and becoming a risk factor for cardiovascular and neurological diseases[7]. The main symptoms are snoring, daytime sleep, difficulty concentrating, and morning headache. Risk factors include obesity, gender, upper respiratory abnormalities, consumption and snoring[8].

Regarding pathophysiology, upper airway obstruction favors hypoxia, hypercapnia, increased vascular resistance, and sympathetic activation[7,9,10]. The relationship between glaucoma and OSA can be explained by the increase in IOP at night due to a supine position[6,11], which increases episcleral venous pressure[6], and periods of hypoxia followed by oxidative stress that generate an increased intracranial pressure, which, in turn, decreases cerebral perfusion pressure, subsequently altering the vascular supply to the optic nerve[7].

Sympathetic system is important because, during apnea episodes, the renin–angiotensin system is activated, leading to a sustained increase in blood pressure during sleep[8]. Dysregulation of optic nerve vascularization secondary to repetitive hypoxia, associated to an imbalance between vasodilator vascular stimuli (nitric oxide) and vasoconstrictors (endothelin) which generates variations in the ocular perfusion pressure and therefore susceptibility to ischemia in the optic nerve head[12]. Additionally, episodes of apnea and hypopnea contribute to the development of complications with endothelial dysfunction, vascular remodeling, and hypertension[13].

Due to the complexity of the relationship between these conditions and the controversy between their association[9,10], is very important to be able to categorize the frequency of cases. Furthermore, by identifying the risk factor for OSA[14], a protocol that allows patients to be referred to ophthalmological consultation in a timely manner could be created in order to avoid visual sequelae. Additionally, patients requiring medical treatment in order to prevent optic nerve damage and avoid blindness can be timely identified[15].

The objective of this study is to characterize the prevalence of primary open-angle glaucoma, as well as its functional and structural alterations, in patients with OSA.

MATERIALS & METHODS

We included all the legal adult patients who were listed in Bogota's *Central Military Hospital* database as diagnosed with OSA (by polysomnography) between January 2013 and December 2019. These patients' medical histories were used to determine demographic data such as age and ethnicity as well as family history, arterial hypertension (high blood

pressure), and diabetes mellitus histories. The findings in polysomnography determined the severity of OSA using the AHI (sum of apnea and hypopnea events divided by total hours of sleep) to categorize it into one of three groups: mild (index 6–15), moderate (16–30), and severe (> 30)[16].

Exclusion criteria include psychiatric or neurological disorders, optic neuropathy, anterior ischemic optic neuropathy, heavy smoking (20 cigarettes per day), alcohol or psychoactive substance abuse, any condition affecting the VF (such as intracranial or ocular lesions), coexisting retinal disease, sequelae of trauma and/or eye inflammation, congenital ocular anatomical alterations, intraocular surgery (with the exception of cataract surgery), history of hypertensive crisis, history of prolonged steroid use, uveitis, bronchial asthma, interstitial lung diseases, heart disease, cirrhosis, and chronic renal failure. Additionally, patients with closed-angle glaucoma or suspected closure by gonioscopy and patients who did not sign the informed consent in the study were excluded.

Two clinical days were carried out. On the first day, two glaucoma specialists in the hospital's Department of Ophthalmology, performed a complete ophthalmological examination, including visual acuity (VA) using the Snellen chart, the anterior segment with a slit lamp, intraocular pressure (IOP) measurement utilizing a Goldmann tonometer, and an assessment of indirect gonioscopy employing a Posner lens. The ophthalmoscopy was performed with a 90D lens (Volk Optical Inc.) to determine alterations such as focal or diffuse thinning of the neuroretinal rim, optic disc hemorrhages, defects in the nerve fiber layer (RNFL), and disc asymmetry greater than 0.2 mm.

Suspects glaucoma patients were selected if they showed the following conditions as open angles by gonioscopy, optic nerve excavations greater than 0.6 mm and asymmetry of optic nerve excavations greater than 0.2 mm. Associated, IOP greater than or equal to 22 mmHg, and IOP within normal limits linked to thinning of the neuroretinal rim. Additionally, thinning of RNFL, optic nerve vessels causing "bayoneting" flexion or deformation, peripapillary hemorrhages, and loss of the ISNT rule.

On the second day, glaucoma suspects were invited to the *Instituto de Macula y Retina Oftalmocenter* in Bogota where AP (Humphrey Field Analyzer model 750i, Carl Zeiss-Meditec, Dublin, USA, SITA Standard program) and optic nerve optical coherence tomography (OCT) (spectral domain with the Cirrus OCT team) exams were performed. In the AP, the mean deviation (MD) defined as the average difference from normal expected value in the patient age group and alterations in the visual field (VF) (superior arcuate defect, inferior arcuate defect, generalized decrease in sensitivity, nasal step, focal defects, and paracentral and normal defects) were determined. The OCT measured the mean RNFL and GGC, as well as analyzed the optic disc. Subsequently, two glaucoma specialists participating in the study analyzed the examinations.

The data collected were grouped into four groups for analysis. The first group analyzed the demographic data and risk factors (glaucoma family history, history of arterial hypertension or diabetes mellitus). The second group analyzed the findings in the clinical history and ophthalmological examination (AHI, AV, basal IOP, gonioscopy, optic nerve excavation, and suspicious changes in the optic nerve). The third group evaluated the results of the VF (MD value classified as mild >-6.00 dB, moderate MD -6.00 to -12.00 dB and severe >-

12.00) and the campimetry alterations. In the fourth group the OCT results were categorized as normal (>80 μM), suspicious (70-79 μM), or abnormal (<70 μM) for RNFL and normal (P5-90%), suspicious (P1-5%) or abnormal (P<5%) for GCC.

The diagnosis of glaucoma suspect was assigned to patients that showed either risk factors linked to developing glaucoma or clinical signs suggesting the disease but without functional alterations in the VF or structural alterations in the OCT. Patients were classified as having POAG when they showed functional alterations in the VF and structural alterations in the OCT.

The study was approved by the ethics committee of the *Hospital Militar Central* in the reunion of may 3, 2019 act No, 7. The committee has adherence to the guidelines of the declaration of Helsinki and all the patients singed a consent to participate in study, approved by the ethics committee.

For the statistical analysis, SPSS 23 software was used. A Chi-sq test to determine the association between variables and the severity of OSA. A Shapiro-Wilk test to identify if the sample data followed a normal distribution, Levene's test to specify if the continuous variables had the same variance, and ANOVA test to compare the means of the continuous variables. Using their respective confidence intervals, we established the prevalence of glaucoma suspects as well as POAG with OSA. The frequency of each visual alteration in the patients was determined and the findings of the OCT and VF were described.

Regarding bias control, all clinical records of the patients diagnosed with OSA met the inclusion and exclusion criteria proposed. The personnel in charge were trained to carry out the evaluation; the same person was in charge of a specific function. Data collected and results were supervised and analyzed by two glaucoma specialists. The data collected were grouped into four groups for analysis. It was used the same diagnostic equipment, which was properly calibrated and had the corresponding technological updates.

Patient and Public Involvement

No patients were involved in the design, recruitment or conduct of the study. The results were informed directly to each participant of the study, but were not disseminated in the others study participants.

RESULTS

The study included 150 patients, (300 eyes). A total of 42.7% women and 57.3% men between 40 – 91 years old with a mean age of 66.8 (±12.1). All 150 patients were Hispanic, 1.3% had a family history of glaucoma, 64.7% high blood pressure and 20.7% diabetes mellitus (Table 1).

DEMOGRAFIC VARIABLES		n (%)
SEX	1. Female	64 (42.7)
	2. Male	86 (57.3)
ETHNICITY	1. Hispanic	150 (100)
	2. Afro-descendant	0
	3. Indigenous	0
FAMILY HISTORY	1. Yes	2 (1.3)
	2. No	148 (98.6)
HYPERTENSION	1. Yes	97 (64.7)
	2. No	53 (35.3)
DIABETES MELLITUS	1. Yes	31 (20.7)
	2. No	119 (79.3)

TABLE 1 Demographic variables

The AHI was categorized as 62% mild OSA, 17.3% as moderate, and 20.7% as severe. In total, 90 eyes were glaucoma suspects, which 52 eyes were POAG, for a prevalence of 17.3% for POAG and 12.6% for glaucoma suspect.

- ***Visual acuity:*** The most prevalent were between 20/20 and 20/60 in 94.6%, (p=0.057). The patients with good visual acuities were in the mild severity group (20/20, 28.5%; 20/25, 23.7%; 20/30, 19.4%; 20/40, 15.1%), followed by the lowest VA in the moderate group (20/50, 11.5%; 20/150, 1.9%) and the severe group (20/60, 4.8%; 20/70, 3.2%; 20/80, 4.8%). (Table 2).

VARIABLE		OBSTRUCTIVE SLEEP APNEA SEVERITY			Total (n=300)	p-value
		MILD (n=186)	MODERATE (n=52)	SEVERE (n=62)	n (%)	
VISUAL ACUITY	20/20	53 (28.5%)	14 (26.9%)	13 (21.0%)	80 (26.6)	0.031
	20/25	44 (23.7%)	11 (21.1%)	6 (9.7%)	61 (20.3)	
	20/30	36 (19.4%)	10 (19.2%)	22 (35.5%)	68 (22.6)	
	20/40	28 (15.1%)	7 (13.5%)	9 (14.7%)	44 (14.6)	
	20/50	15 (8.1%)	6 (11.5%)	3 (4.8%)	24 (8)	
	20/60	2 (1.1%)	2 (3.8%)	3 (4.8%)	7 (2.3)	
	20/70	3 (1.6%)	0	2 (3.2%)	5 (1.6)	
	20/80	1 (0.5%)	0	3 (4.8%)	4 (1.3)	
	20/100	2 (1.1%)	0	0	2 (0.6)	
	20/150	0	1 (1.9%)	1 (1.6%)	2 (0.6)	
	20/200	2 (1.1%)	0	0	2 (0.6)	
SUSPECTED CHANGES IN THE OPTIC NERVE	1. Focal or diffuse thinning of the neuroretinal rim	40 (21.5%)	8 (15.4%)	2 (3.2%)	50 (16.6)	0.005
	2. Disc Hemorrage	0	0	0	0	
	3. RNFL alterations	0	0	0	0	
	4. Disc asymmetry > 0.2	12 (8.2%)	4 (7.7%)	10 (16.1%)	26 (8.6)	
	No Alterations	134 (72.0%)	40 (76.9%)	50 (80.6%)	224 (74.6)	

TABLE 2. Visual acuity and suspicious changes in the optic nerve

- ***Intraocular Pressure:*** The mean was 13 mmHg (± 2.6), 13.3 mmHg (± 0.2) for mild cases, 13.3 mmHG (± 0.3) for moderate cases, and 12.5 mmHg (± 0.3) for severe cases (p = 0.107). Regarding the excavation of the optic nerve, the mean was 0.4 mm (± 0.2), (p = 0.953) (Table 3-4).

VARIABLE	MEDIAN	STANDARD DESVIATION
AGE (YEARS)	66.8	12.1
INTRAOCULAR PRESSURE (mmHg)	13	2.6
OPTIC NERVE EXCAVATION (mm)	0.4	0.2

TABLE 3. Intraocular pressure and Optic nerve excavation

OBSTRUCTIVE SLEEP APENA SEVERITY		INTRAOCULAR PRESSURE (mmHg)	OPTIC NERVE EXCAVATION	Total n
MILD	Median	13.3	0.4	186
	Standard Desviation	0.2	0,0	
MODERATE	Median	13.3	0.4	52
	Standard Desviation	0.3	0,0	
SEVERE	Median	12.5	0.4	62
	Standard Desviation	0.3	0,0	
ANOVA P value		0.107	0.953	

TABLE 4. Obstructive Sleep Apnea Severity, Intraocular pressure and Optic nerve excavation

- ***Optic nerve changes:*** 74.6% of the eyes showed no alterations, 16.6% have a focal or diffuse thinning of the neuroretinal rim. These findings were more prevalent in the mild OSA group (21.5%), followed by the moderate OSA group (15.4%), and the severe OSA group (3.2%). Disc asymmetry (> 0.2 mm) was observed in 8.6%, with

a higher prevalence in the severe OSA group (16.1%), followed by the mild OSA group (8.2%), and finally the moderate group (7.7%), (p=0.005) (Table 2).

- ***Campimetry alterations:*** 54.4% were normal with no significant differences between the groups (mild OSA [55.2%], moderate [56.3%], and severe [50.0%]). The second alteration was superior arcuate defect in 14.4%, more commonly found in the mild OSA group (12.1%). The next alternation was focal defects in 13.3%, mainly in the mild group (13.8%), with an equal percentage in the moderate and severe groups (12.5%). The nasal step defect was present in 12.2%, most frequently in the moderate OSA group (18.8%), followed by the mild group (13.8%) and severe group (6.3%). To a lesser extent, a paracentral defect was seen in 3.3%—only in the mild OSA group (5.2%)—and an inferior arcuate defect was seen in 2.2% in the moderate (6.3%) and mild (1.7%) OSA groups. (p=0.583). (Table 5)

VARIABLE		OBSTRUCTIVE SLEEP APNEA SEVERITY			Total (n=90)	P-VALUE
		MILD (n=58)	MODERATE (n=16)	SEVERE (n=16)	n (%)	
VISUAL FIELD	1. Superior Arcuate Defect	7 (12,1%)	1 (6.3%)	5 (3.1%)	13 (14.4)	0.583
	2. Inferior Arcuate Defect	1 (1.7%)	1 (6.3%)	0	2 (2.2)	
	3. General Diminished Sensitivity	0	0	0	0	
	4.Nasal Step	7 (12.1%)	3 (18.8%)	1 (6.3%)	11(12.2)	
	5. Focal Defects	8 (13.8%)	2 (12.5%)	2 (12.5%)	12 (13.3)	
	6. Paracentral Defects	3 (5.2%)	0	0	3 (3.3)	
	7. Normal	32 (55.2%)	9 (56.3%)	8 (50.0%)	49 (54.4)	
MEAN DEVIATION	1. MD <-6 dB	49 (84.5%)	15 (93.8%)	11 (68.8%)	75 (83.3)	0.305
	2. MD -6 a-12 dB	7 (12.1%)	1 (6.3%)	3 (18.8%)	11(12.2)	
	3. MD >-12 dB	2 (3.4%)	0	2 (12.5%)	4 (4.4)	
MEAN NERVE FIBER LAYER	1. Normal > 80 µm	43 (74.1%)	15 (93.8%)	12 (17.1%)	70 (77.7)	0.081
	2. Suspicious 70-79 µm	12 (20.7%)	0	1 (6.3%)	13 (14.4)	
	3. Abnormal < 70 µm	3 (5.2%)	1 (6.3%)	3 (18.8%)	7 (7.7)	
GANGLION CELL COMPLEX	1. Normal (green)	35 (60.3%)	11 (68.8%)	12 (75.0%)	58 (64.4)	0.218
	2. Suspicious (yellow)	11 (19.0%)	4 (25.0%)	0	15 (16.6)	
	3. Abnormal (red)	12 (20.7%)	1 (6.3%)	4 (25.0%)	17 (18.9)	
PRIMARY OPEN ANGLE GLAUCOMA	1. Yes	35 (60.3%)	9 (56.3%)	8 (50.0%)	52 (57.8)	0.752
	2. No	23 (39.7%)	7 (43.8%)	8 (50.0%)	38 (42.2)	
GLAUCOMA SUSPECTS	1. Yes	23 (39.7%)	7 (43.8%)	8 (50.0%)	38 (42.2)	0.752
	2. No	35 (60.3%)	9 (56.3%)	8 (50.0%)	52 (57.8)	

TABLE 5. Functional and structural findings in the visual field and optic nerve computerized tomography

- The decrease in the **Mean Deviation** (MD) was mild (< -6 dB) in 83.3%, distributed as follows: moderate OSA (56.3%), mild OSA (55.2%), and severe OSA (50.0%). The moderate decrease in MD (-6 and -12 dB) occurred in 13.3%, distributed as follows: severe OSA (18.8%), mild OSA (12.1%), and moderate OSA (6.3%). The severe decrease in MD (> -12 dB) was 4.4%, distributed mostly in severe OSA (12.5%) vs. mild OSA (3.4%). (p=0.305).

- ***OCT of the optic nerve:*** The mean RNFL was normal in 74% of the mild OSA group, 93.8% of the moderate OSA group, and 17.1% of the severe OSA patients. Similarly, the GCC was normal in 60%, 68% and 75% of the respective OSA severity groups. Abnormalities in the mean RNFL were seen in 25.9%, 6.3% and 23.4% of the mild, moderate, and severe groups, respectively (p=0.081). Regarding GCC, abnormalities were found in 39.7%, 33.3% and 25% for these same groups (p=0.218). (Table 5)

DISCUSSION

OSA has been considered a possible risk factor for developing glaucoma. According to the pathophysiology of OSA, a vascular theory has been postulated that relates to the increase in vascular resistance secondary to hypoxia. This would cause dysregulation of optic nerve head vascularization[7,12]. There is also a mechanical theory that the increase of IOP caused by supine position and an increase of episcleral venous pressure linked to obesity could lead to this condition[6,11]. According to these theories, functional and structural changes would be generated in the optic nerve, leading glaucoma.

This study found the prevalence of POAG in patients with OSA was 17.3%, and glaucoma suspect was 12.6%. These prevalence values are similar to those of studies such as that of Bagabas *et al.*[17], which found a 16% prevalence, but were much lower than those found in studies such as Friedlander *et al.*[18] and Wozniac *et al.*[19]. In various meta-analyses, a link between OSA and glaucoma[7,20] has been identified; Shi *et al.*[21] revealed a significant relationship between the prevalence of glaucoma and OSA in case-control studies (OR=1.96) and cross-sectional studies (OR=1.41).

A high number of patients have visual acuities between 20/20-20/60, indicating no mayor compromise of the visual acuity in the population studied. No statistical relationship was found regarding the severity of OSA and visual acuities, most likely indicating that OSA does not increase loss of vision.

IOP is recognized as the only modifiable risk factor associated with developing glaucoma, so timely identification would allow for rapid treatment in order to prevent the progression of glaucoma. Various studies have identified a relationship between OSA and IOP values, finding positive correlation with the supine position (Moghimi *et al.*[22], Sergio et al.[23], and Yee *et al.*[11]. This is contrary to studies described by Nowak *et al.*[24] and Shalaby *et al.*[25]. In studies such as that of Carnero et al.[26], patients with OSA experience upper limits of IOP. Unlike the aforementioned, in our study, IOP occurred within normal, with no evidence of a correlation with the severity of OSA.

The excavation with greater sizes was reported in patients with glaucoma and no relation to OSA severity. Suspicious changes in the optic nerve were the only variable in which a

statistical significance was found regarding the severity of OSA. This demonstrates how OSA can influence the optic nerve anatomy by favoring the development of optic neuropathy and, to some extent, the onset of POAG. A higher percentage of these changes was found in the severe OSA group. It was possible to identify that focal or diffuse thinning of the neuroretinal rim in the mild OSA group as a possible indicator of early and focal damage of the optic nerve. Additionally, asymmetry > 0.2 mm was identified in patients with severe OSA, indicating greater damage by a diffuse thinning of the neuroretinal rim, from which it could be inferred that the progression of optic nerve damage is related to the severity of OSA. This is similar to the findings of Tsang *et al.*[27], a case-control study that demonstrated an incidence of suspicious optic nerve changes four times higher in patients with moderate or severe OSA. Another study by Uslu *et al.* [28], suggests an increased optic nerve excavation in patients with OSA, and it could be considered an indicator of neural damage in the early diagnosis of OSA. In contrast to previous results, Lin *et al.* [29], showed that the optic nerve parameters did not differ between OSA severity groups, nor did it differ from the general population described by Salzgeber *et al.*[30].

As for the functional changes in the VF, authors such as Tsang *et al.* [27] found abnormalities in MD and pattern standard deviations correlated with OSA severity index[23], indicating a direct relationship between these pathologies. In contrast, this study identified that most of the patients did not show functional alterations, which is similar to the findings of Swaminatha *et al.* [31] and Salzgeber *et al.*[30].

According to VF numerical parameters, a high percentage of patients showed a mild decrease in the mean deviation which predominated in the moderate OSA group. Meanwhile, a

moderate to severe decrease was seen in the severe OSA group. This indicates that the greater the severity of OSA, the more compromised the VF; this signifies a possible link between these pathologies, although it could not be statistically demonstrated in this study.

It has been described that the first VF manifestations in patients with POAG are generalized depression, enlargement of the blind spot, Seidel's scotoma, or nasal step[32]. Subsequently, paracentral defects that may join with the blind spot, as well as temporary steps, and superior or inferior arcuate defects. Finally, progressive damage can lead to peripheral constriction of the VF, leaving central or temporal vision islands[32]. Comparing this to what was observed in this study, the functional alterations described are commonly identified in intermediate or advanced stages of POAG which occurred more frequently in the mild OSA group; therefore, it could be inferred that mild stages of OSA may be related to greater VF alterations.

The OCT showed that most of the patients were within normal ranges, patients with abnormal results showed an increased severity of structural nerve damage as the analysis went from mild and moderate to severe OSA. This is supported by meta-analyses that demonstrated a link between moderate and severe OSA with significant thinning of RNFL thickness—mainly in the upper, lower, and nasal quadrants[33-35]. Additionally, Fan *et al.*[36] described greater progression of structural changes (RNFL thickness) in patients with mild OSA, obtaining an 8.448 risk of structural progression in patients with severe OSA. This differs from the studies of Nowak *et al.* [24], Salzgeber *et al.* [30], and Kara *et al.*[37]. Moreover, Abdullayev *et al.*[38] found no alteration of RNFL thickness in patients with OSA that correlated to its severity, but describe a decrease in GCC in patients with mild severity. In

contrast, Uslu *et al.* found no alterations in the GCC, but a decrease in the peripapillary RNFL thickness[28].

The general population with POAG, structural changes has been observed as the first manifestation of glaucoma–-before a compromised VF [32], which correspond to the decrease of the GCC in the initial stages with a subsequent decrease in the mean RNFL. When comparing these characteristics of the general population with POAG to the results of this study, it can be deduced that most of the patients with OSA and glaucoma first showed an alteration in the GCC, followed by alterations in the mean RNFL. Some of the patients experienced these alterations before VF alterations; therefore, it can be inferred that the development of glaucoma would manifest itself in the same way in patients with OSA as in the general population with glaucoma.

The main limitations of the study were the lack of a control group, and the performed of only one examination. As such, it was not possible to determine if the alterations found persisted or if the glaucoma progressed over time. Finally, due to the sample size, it could not be determined whether OSA correlated with the development of POAG.

In conclusion, this study found a prevalence of glaucoma suspects of 12.6% vs. a POAG prevalence of 17.3% in patients diagnosed with OSA. The study demonstrated a relationship between the structural changes of the optic nerve and the severity of OSA, suggesting that OSA might influence the anatomy of the optic nerve and favor the development of optic neuropathy, and, to some extent, the onset of POAG. No relationship was identified with any of the other variables that were studied. Future research, studies, and follow-ups are

recommended for patients with OSA to rule out glaucoma as one of its multiple systemic manifestations.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(*e*) Describe any sensitivity analyses	Not Applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11

		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable
Outcome data	15*	Report numbers of outcome events or summary measures	10-16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-16
		(*b*) Report category boundaries when continuous variables were categorized	10-16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.