https://doi.org/10.5664/jcsm.9488

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Prospective evaluation of the comorbidity of obstructive sleep apnea in patients with glaucoma

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Study Objectives: This study aimed to identify prospectively the correlation between obstructive sleep apnea (OSA) severity, ocular microcirculation changes, and visual function changes in patients with glaucoma.

Methods: We prospectively enrolled patients with glaucoma who were willing to undergo overnight polysomnography. The enrolled patients were further divided into normal tension glaucoma, high-tension glaucoma, and control. Visual field progression was analyzed using sequential standard automated perimetry. Peripapillary and macular vessel density were assessed through optical coherence tomography angiography (OCT-angiography). The associations between polysomnography parameters, OCT-angiography parameters, and visual field progression were analyzed.

Results: A total of 22 patients with normal tension glaucoma, 30 patients with high-tension glaucoma, and 24 control patients were enrolled. Through regression analysis, glaucoma was found to be an independent predictor of moderate-to-severe OSA ($P = .035$); furthermore, moderate-to-severe OSA was significantly associated with visual field progression ($P = .008$ in the high-tension glaucoma subgroup and $P = .008$ in the overall glaucoma). Additionally, OSA severity was negatively correlated with the ganglion cell complex thinning rate in the normal tension glaucoma subgroup.

Conclusions: Presence of glaucoma increased the risk of moderate-to-severe OSA compared with the control group. OSA severity was related to visual field deterioration in patients with glaucoma and further associated with structural progression in the normal tension glaucoma subgroup. Careful monitoring of the comorbid OSA status of patients with glaucoma is essential to prevent disease progression.

Keywords: obstructive sleep apnea, glaucoma, polysomnography, visual field, optical coherence tomography angiography

Citation: Chan Y-H, Chuang L-H, Yu C-C, et al. Prospective evaluation of the comorbidity of obstructive sleep apnea in patients with glaucoma. *J Clin Sleep Med*. 2022;18(1):47–56.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Glaucoma and obstructive sleep apnea (OSA) are chronic progressive diseases. Despite the increased prevalence of glaucoma in patients with OSA, prospective studies evaluating the effect of OSA on glaucoma are limited.

Study Impact: We prospectively demonstrated that the severity of OSA was associated with the functional and structural progression of glaucoma. The result implies the importance of the regular and careful monitoring of comorbid OSA in patients with glaucoma.

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic, sleep-related breathing disorder that is potentially associated with comorbidities. The prevalence of OSA varies from 7.8 to 77.2% in adults aged 30–69 years.[1] Moreover, the prevalence was found to be higher among Asians, male individuals, older adults, and those with a high body mass index (BMI).[2,3] OSA is a multifactorial disorder, and anatomical factors (eg, upper airway occlusion) and nonanatomical factors (eg, impaired pharyngeal dilator muscle function, low respiratory arousal threshold, and high loop gain) are involved in the pathogenesis of OSA.[4,5] According to the American Academy of Sleep Medicine guidelines,[6] the gold standard diagnosis method for OSA is overnight polysomnography (PSG). The severity of respiratory events is graded as mild(an apnea-hypopnea index [AHI] of ≥ 5 events/h but < 15 events/h), moderate (an AHI of ≥ 15 events/h but < 30 events/h), or severe (an AHI of ≥ 30 events/h). Intermittent hypoxemia is recognized as a potential major factor contributing to the pathogenesis of OSA-related comorbidities. It increases oxidative stress, sympathetic activation, and vascular inflammation with endothelial dysfunction.[7] Ocular manifestations of OSA include floppy eyelid syndrome, nonarteritic anterior ischemic optic neuropathy, central serous retinopathy, retinal vein occlusion, optic neuropathy, diabetic retinopathy, geographic atrophy, and glaucoma.[8,9]

Glaucoma is a chronic progressive neurodegenerative disease; it is the leading cause of blindness in developed countries.[10] The pathogenesis is complex and not fully understood. Although conventional theory is that the main pathology is impairment in aqueous humor outflow resulting in elevated intraocular pressure (IOP), recent studies have found that decreased ocular blood flow

plays a crucial role in the pathogenesis.[8,11–14] Prolonged episodes of hypoxia in OSA cause oxidative stress and inflammation, which directly damage the optic nerve head, retinal ganglion cells, and their axons.[15–17] Hypoxia also induces an endothelin-1 and nitric oxide imbalance, which causes vascular dysregulation and results in insufficient blood supply and nourishment to the retinal nerve fiber layer (RNFL).[15,18]

Studies have reported a higher prevalence of glaucoma in patients with OSA.[15] Furthermore, studies using optical coherence tomography (OCT) have illustrated that the RNFL was significantly thinner in patients with OSA compared with normal controls, and it was negatively correlated with AHI and positively correlated with oxygen saturation.[19,20] Yu et al[21] evaluated vessel density (VD) in patients with OSA using OCT-angiography and demonstrated that VD in the peripapillary and parafoveal regions was significantly decreased in patients with OSA and negatively correlated with disease severity. Regarding functional changes, Ferrandez et al[22] employed standard automated perimetry (SAP) and illustrated that mean deviation (MD) and visual field index were significantly decreased in patients with OSA compared with controls, and AHI was significantly correlated with MD, pattern standard deviation (PSD), and visual field index. Although studies have examined visual function and changes in the retinal structure in patients with OSA, prospective studies evaluating OSA and the impacts on glaucoma progression are relatively scant. The main purpose of our prospective study was to identify the correlation of OSA severity with PSG parameters, microcirculation changes measured using OCT-angiography, and visual function changes tested using SAP in patients with glaucoma.

METHODS

This was a prospective, longitudinal, hospital-based, observational cohort study conducted from April 2017 through March 2020. According to the Helsinki Declaration of 1975 (1983 revision), this study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Keelung, Taiwan. The Institutional Review Board number was 201601196B0. All enrolled patients provided written informed consent.

We randomly surveyed patients who were willing to undergo overnight PSG. Subsequently, we referred these patients and enrolled those with a valid PSG examination at a sleep center. These patients had never received a diagnosis of OSA or had undergone PSG prior to enrollment. Exclusion criteria were a history of other optic neuropathy or retinopathy, including nonarteritic anterior ischemic optic neuropathy, arteritic anterior ischemic optic neuropathy, optic neuritis, diabetic retinopathy, hypertensive retinopathy, and other maculopathy.

Participants grouping

Participants were further divided into 3 groups: the normal tension glaucoma (NTG) subgroup, defined as normal IOP (lower than 21 mmHg) with open-angle and glaucomatous optic neuropathy; the high-tension glaucoma (HTG) subgroup, defined as elevated IOP (higher than 21 mm Hg) and glaucomatous optic neuropathy; and the control group (without IOP elevation or glaucomatous optic nerve change). Similar to our previous study,[23] an AHI of 15 events/h was used as the cutoff value for grading the severity of OSA. We categorized OSA into mild (an AHI of ≥ 5 events/h but < 15 events/h) and moderate to severe (an AHI of ≥ 15 events/h).

Data collection and design

All patients underwent PSG once after being enrolled. Serial SAP and OCT-angiography were performed in participants with glaucoma to examine their glaucoma progression. In addition, the following data were recorded: age, sex, concurrent systemic disease, BMI, neck circumference, and continuous positive airway pressure (CPAP) use after PSG examination. Neck circumferences of ≥ 38.75 for men and ≥ 34.5 cm for women were considered as cutoff points, which were obtained in a study[24] involving the Korean population and were thought to represent those applicable to Asian populations. In addition, the number of antiglaucoma agents used and the number of times patients underwent ocular surgery were recorded.

Procedures for PSG

PSG was performed at a sleep center by using a computerized PSG system (N7000 Embla, Broomfield, CO). The PSG included an electroencephalogram obtained using 6 electroencephalographic channels, an electrocardiogram, bilateral electrooculograms, a submental electromyogram, chest and abdominal movements measured through inductance plethysmography, airflow sensors (both nasal pressure cannula and oronasal thermistor), and arterial oxygen saturation determined through finger probe pulse oximetry. The examination was performed between 10:00 PM and 7:00 AM; a minimum recording time of 6 hours and a minimum total sleep time of 4 hours were required for the examination to be valid.

According to the American Academy of Sleep Medicine scoring criteria,[25] respiratory events were manually scored.

Apnea was defined as the absence of airflow for 10 seconds, whereas hypopnea was defined as a reduction of > 30% in airflow lasting for 10 seconds with either an arousal or 3% oxygen desaturation. Obstructive apnea was defined as the presence of respiratory effort combined with the absence of airflow, whereas central apnea was defined as the absence of both airflow and breathing movements. Mixed apnea was defined as a combination of central and obstructive apnea that persisted upon the resumption of respiratory effort.[26]

The AHI was defined as the sum of apnea (including obstructive, central, and mixed) and hypopnea events per hour of sleep. The oxygen desaturation index was defined as the number of desaturation events (desaturation ≥ 3%) per hour of sleep. The mean oxyhemoglobin saturation was determined through pulse oximetry during sleep time.

Ocular examination

The following data were recorded at the clinic prior to the sleep center referral: IOP (measured using an applanation tonometer; mm Hg), central corneal thickness measured with an optic pachymeter (Haag-Streit International, Koeniz, Switzerland; μm), and gonioscopy. An OCT-angiography imaging system

(AngioVue; Optovue, Inc., Fremont, CA) was used to measure the mean peripapillary RNFL thickness, mean ganglion cell complex (GCC) thickness, and peripapillary and macular capillary vessel density, and parameters were recorded according to version A2017,1,1,151. A split-spectrum amplitude decorrelation angiography algorithm combined with a projection artifact suppression algorithm in AngioVue was used to detect flow. The default enface displays were as follows. Superficial retinal capillary plexus: 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer; deep retinal capillary plexus: 15 μm below the inner plexiform layer to 70 μm below the inner plexiform layer. We adopted a 3.00 mm diameter macular scan area, whereas the optic disk area scanned was 4.5 mm in diameter.[27] The parafovea area was defined as an annular region with an inner diameter of 1 mm and outer diameter of 3 mm centered on the fovea avascular zone. The peripapillary area was defined as a 1.0-mm-wide annulus extending outward from the optic disk boundary. The radial peripapillary capillary mode was used to calculate the VD from the internal limiting membrane to the posterior boundary of the RNFL. SAP was performed with a Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, CA) set to 30-2 for all patients to collect the MD and PSD. Visual field (VF) exams and OCT-angiography images with low reliability (≥ 33% fixation losses, ≥ 10% false-positives, and ≥ 10% false-negatives and signal strength index < 50, respectively) were excluded from the analysis.

To compare changes in the visual function, the mean deviation (MD) slope was plotted and defined as the change in the MD value divided by time between 2 SAP studies. Similarly, structural progression was defined as the change in VD/RNFL/GCC divided by time between 2 OCT-angiography studies

Statistical analysis

For participants with glaucoma, data acquisition and analysis were performed only for the eye that exhibited typical patterns of glaucomatous VF defects. However, when both eyes presented with typical patterns, only the right eye was analyzed. For control, the right eye was analyzed. The Kolmogorov–Smirnov normality test was performed to examine normality distribution for quantitative data. Normally distributed quantitative data are presented as means with standard deviations, nonnormally distributed quantitative data are presented as median with the first and third quartile, and qualitative data are presented as proportions. To compare demographic data between subgroups, we analyzed the quantitative data using independent sample *t*-tests or Mann–Whitney *U* test, and qualitative data using chi-squared tests. Logistic regression was performed to analyze the univariate and multivariable associations of demographic data and ocular characteristics with moderate-to-severe OSA; generalized linear regression was performed to analyze univariate and multivariable associations between the change in the MD and demographic data or PSG parameters. Spearman's rank correlation coefficient was calculated to analyze the correlation between glaucoma-related changes in the retinal structure and OSA-associated parameters. The median split method was used to analyze nonnormally distributed quantitative independent variables in regression analysis. The false discovery rate was calculated using the Benjamini–Hochberg method[28] to control type I errors caused by multiple analyses. The false discovery rate was set as 25%. A P value of < .05 and a Q value (Benjamini–Hochberg adjusted P value) of < .25 were considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (SPSS, Inc, Chicago, IL).

RESULTS

In this prospective study, we enrolled a total of 76 patients who underwent a valid PSG examination at the same sleep center. Of these 76 patients, 22, 30, and 24 were enrolled in the NTG, HTG, and control groups. The mean number of antiglaucoma agents used was 1.77 ± 0.94 prior to PSG examination and 1.88 ± 0.9 at the end of the study period (P = .159, paired-sample t-test). No ocular surgery was performed during the study period. Moreover, none of our participants demonstrated a central apnea index of ≥ 5 events/h and none had ≥ 50% of respiratory events classified as central apnea. The mean periods between 2 SAP studies used to plot the MD slope were 27.7 ± 5.9, 26.0 ± 6.3, and 26.7 ± 6.3 months in the NTG subgroup, HTG subgroup, and overall glaucoma group, respectively. Furthermore, to analyze sequential structural changes through OCT-angiography, multiple OCT-angiography images were obtained for 12 patients in the NTG subgroup and 19 patients in the HTG subgroup. The mean periods between 2 OCT-angiography studies were 12.4 ± 6.1, 12.5 ± 5.2, and 12.5 ± 5.6 months in the NTG subgroup, HTG subgroup, and overall glaucoma group, respectively.

Participant characteristics

As shown in **Table 1**, we compared the demographic data of the glaucoma group (n = 52) and the control group (n = 24). A total of 14 (26.9%) patients in the glaucoma group received CPAP treatment after the initial PSG, whereas only 3 (12.5%) patients in the control group did; however, the difference between the 2 groups was not significant (P = .161). The results of the chi-squared test indicated that the proportion of patients with moderate-to-severe OSA (AHI ≥ 15 events/h) was significantly higher in the glaucoma group than in the control group (67.3% vs 41.7%, P = .034). However, after correcting for the type I error rate by using the Benjamini–Hochberg method, this result appeared to be false positive (Q = .544). None of the variables showed statistical significance after correcting the false discovery rate.

Comparison of characteristics between patients with mild OSA and moderate-to-severe OSA

We classified participants based on their OSA severity. The mild OSA and moderate-to-severe OSA groups included 21 and 45 participants, respectively. The proportion of male patients, patients with diabetes, and CPAP users was higher in the moderate-to-severe OSA group than in the mild OSA group (P = .021, P = .039, and P = .001 respectively; **Table 2**). Regarding ocular characteristics, although MD, PSD, GCC, RNFL, and vessel density showed no significant difference, the MD slope was significantly lower in the moderate-to-severe OSA group (P = .025). Male sex, diabetes mellitus, CPAP use, AHI, oxygen desaturation index, and MD

Table 1—Participant characteristics.

	Glaucoma Group (n = 52)	Control Group (n = 24)	*P* Value	Q Value
Age (years)	54.4 ± 13.4	52.2 ± 17.1	.536[a]	.780
Sex (male)	37 (71.2%)	15 (62.5%)	.451[b]	.722
DM (yes)	13 (25%)	5 (20.8%)	.691[b]	.790
HTN (yes)	20 (38.5%)	8 (33.3%)	.667[b]	.821
CPAP use (yes)	14 (26.9%)	3 (12.5%)	.161[b]	.515
BMI (kg/m^2)	22.6 ± 4.1	25.3 ± 3.2	.753[a]	.803
Large NC[d]	25 (48.1%)	11 (45.8%)	.856[b]	.856
AHI (events/h)	26.3 [10.4, 44.9]	12.7 [8.1, 26.0]	.071[c]	.568
AHI < 5	5 (9.6%)	5 (20.8%)	.179[b]	.409
5 ≤ AHI < 15	12 (23.1%)	9 (37.5%)	.191[b]	.382
AHI ≥ 15	35 (67.3%)	10 (41.7%)	.034[b]	.544
ODI	14.7 [4.3, 30.2]	8.0 [1.9, 15.1]	.087[c]	.464
Mean SaO_2 (%)	95.0 [93.3, 96.0]	95.0 [94.0, 96.0]	.624[c]	.832
IOP (mm Hg)	16.2 ± 3.02	15.1 ± 3.25	.164[a]	.437
CCT (μm)	544.2 ± 35.4	551.8 ± 45.1	.435[a]	.773
AXL (mm)	25.1 [23.4, 26.5]	23.9 [23.3, 25.8]	.159[c]	.636

Normally distributed quantitative data are presented as mean ± SD, and nonnormally distributed quantitative data are presented as median [Q_1, Q_3]. [a]Independent *t*-test. [b]Chi-squared test. [c]Mann–Whitney *U* test. [d]Neck circumferences of ≥ 38.75 cm for men and ≥ 34.5 cm for women were included in the analysis as large neck sizes (Large NC). AHI = apnea–hypopnea index, AXL = axial length, BMI = body mass index, CCT = central cornea thickness, CPAP = continuous positive airway pressure, DM = diabetes mellitus, HTN = hypertension, IOP = intraocular pressure, NC = neck circumference, ODI = oxygen desaturation index, SaO_2 = arterial oxyhemoglobin saturation.

slope all remained significantly associated with moderate-to-severe OSA after correcting for the type I error by using the Benjamini–Hochberg method (all $Q < .25$) .

Comparison of characteristics Between patients With NTG and HTG

As shown in **Table S1** in the supplemental material, a higher proportion of patients in the HTG subgroup had a larger neck circumference than did those in the NTG subgroup ($P = .002$ and $Q = .05$). Other variables were not found to be significant after correcting for the type I error. Regarding the visual function, no significant difference was observed in baseline MD, baseline PSD, or MD slope between the 2 subgroups. In addition, no difference in structural parameters or ocular microcirculation characteristics was noted between the 2 subgroups, as determined through OCT-angiography. These findings indicated that both glaucoma subgroups had similar disease severity.

Univariate and multivariable logistic regression analysis for assessing variables associated with moderate-to-severe OSA

In the univariate analysis (**Table 3**), male sex (odds ratio [OR] 3.750 [1.359, 10.345], $P = .011$), presence of diabetes mellitus (OR 4.667 [1.219, 17.864], $P = .024$), higher BMI (OR 1.182 [1.024, 1.366], $P = .023$), and history of glaucoma (including both NTG and HTG) (OR 2.882 [1.063, 7.813], $P = .037$) were positively correlated with the proportion individuals with moderate-to-severe OSA. Additionally, male sex and a history of glaucoma remained significant predictors of OSA in the multivariable model (OR 3.528 [1.143,10.891], $P = .028$ and OR 3.041 [1.009,9.167], $P = .048$, respectively).

Univariate and multivariable generalized linear regression analysis for assessing variables associated with the mean deviation slope

Furthermore, we attempted to determine whether OSA severity would influence the rate of VF deterioration. We conducted a generalized liner regression to analyze the univariate and multivariable associations related to the MD slope with demographics or PSG parameters (**Table 4**). In the HTG subgroup, moderate-to-severe OSA (AHI ≥ 15 events/h) alone was significant, and the regression line exhibited a negative gradient (B = −1.123 [−1.950, −0.297], $P = .008$). Sex, age, concurrent systemic disease, BMI, large neck circumference, oxygen desaturation index, and mean arterial oxyhemoglobin saturation were not significantly associated with the MD slope. In the overall glaucoma group (NTG + HTG), a history of diabetes mellitus and moderate-to-severe OSA were negatively and significantly associated with the MD slope (B = −0.640 [−1.167, −0.018], $P = .044$ and B = −0.875 [−1.422, −0.329], $P = .002$, respectively). Only moderate-to-severe OSA remained significant in the multivariable model (B = −0.766 [−1.332, −0.200], $P = .008$). In the NTG subgroup, moderate-to-severe OSA was not significant to the MD slope ($P = .054$).

Correlations between glaucoma progression and OSA-associated parameters

To analyze sequential structural changes through OCT-angiography, VD/RNFL/GCC slopes were compared with

Table 2—Comparison of characteristics between patients with mild OSA and those with moderate-to-severe OSA.

	Mild OSA (n = 21) (5 ≤ events/h AHI < 15 events/h)	Moderate-Severe OSA (n = 45) (AHI ≥ 15 events/h)	*P* Value	Q Value
Age (years)	52.7 ± 18.5	56.3 ± 11.9	.424[a]	.650
Sex (male)	11 (52.3%)	36 (80%)	.021[b]	.121*
DM (yes)	2 (9.5%)	15 (33.3%)	.039[b]	.150*
HTN (yes)	6 (28.6%)	20 (22.2%)	.219[b]	.504
CPAP use (yes)	0 (0%)	17 (37.8%)	.001[b]	.023*
BMI (kg/m^2)	25.2 ± 3.6	26.4 ± 3.9	.232[a]	.485
Large NC[d]	8 (38.1%)	25 (55.6%)	.186[b]	.535
AHI (events/h)	10.1 [8.1, 12.2]	37.9 [24.3, 49.6]	< .001[c]	.023*
ODI	5.7 [2.5, 7.0]	27.4 [13.8, 44.3]	< .001[c]	.023*
Mean SaO_2 (%)	95.0 [93.6, 97.0]	94.2 [93.1, 96.0]	.201[c]	.514
Glaucoma	12 (57.1%)	35 (77.8%)	.085[b]	.279
MD (dB)	−3.14 [−7.18, −0.46]	−2.12 [−5.97, −0.54]	.622[c]	.715
PSD (dB)	5.08 [2.12, 7.87]	2.54 [1.84, 8.29]	.478[c]	.647
MDSlope (dB/y)	0.58 ± 1.53 (n = 17)†	−0.38 ± 0.75 (n = 37)†	.025[a]	.115*
AXL (mm)	24.0 [23.4, 26.2]	24.5 [23.3, 26.1]	.961[c]	.961
RNFL (um)	87.1 ± 16.2	84.2 ± 16.7	.513[a]	.656
GCC (um)	87.0 [78.5, 94.5]	87.0 [76.0, 92.3]	.466[c]	.670
wiVD RPC (%)	46.1 [42.2, 49.6]	46.3 [42.1, 49.4]	.861[c]	.943
ppVD RPC (%)	48.6 [44.4, 51.5]	48.4 [42.1, 52.7]	.884[c]	.924
wi SL MVD (%)	42.1 [35.3, 46.5]	43.3 [40.5, 46.2]	.304[c]	.538
pf SL MVD (%)	43.3 ± 6.9	45.3 ± 6.0	.249[a]	.477
wi DL MVD (%)	49.6 ± 4.6	48.8 ± 4.6	.558[a]	.675
pf DL MVD (%)	53.7 [49.4, 55.3]	51.9 [48.0, 55.0]	.336[c]	.552

Normally distributed quantitative data are presented as mean ± SD, and nonnormally distributed quantitative data are presented as median [Q_1, Q_3]. *Benjamini–Hochberg adjusted *P* value (Q value) of < 0.25 was considered significant. †In the mild OSA group, we could not determine the MD slope value of 4 patients who did not undergo serial SAP; these patients were included in the control group. Similarly, 8 patients in the moderate-to-severe OSA group did not have an MD slope value. [a]Independent *t*-test. [b]Chi-squared test. [c]Mann–Whitney *U* test. [d]Neck circumferences of ≥ 38.75 cm for men and ≥ 34.5 cm for women were included in the analysis as large neck sizes (Large NC). AHI = apnea–hypopnea index, AXL = axial length, BMI = body mass index, CPAP = continuous positive airway pressure, DL = deep layer, DM = diabetes mellitus, GCC = ganglion cell complex, HTN = hypertension, IOP = intraocular pressure, MD = mean deviation, MVD = macula vessel density, NC = neck circumference, ODI = oxygen desaturation index, pf = parafovea, pp = peripapillary, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer, RPC = radial peripapillary capillary, SaO_2 = arterial oxyhemoglobin saturation, SL = superficial layer, VD = vessel density, wi = whole image.

OSA-associated parameters. Because of the nonnormal distribution of VD/RNFL/GCC slopes, Spearman's rank correlation coefficient was calculated. **Table 5** lists Spearman's rank correlation coefficients related to the GCC slope with OSA-associated parameters. In the NTG subgroup, the AHI was negatively correlated with the GCC slope ($r = -.584$, $P = .046$). Significance was not observed with VD/RNFL in the NTG subgroup or with VD/GCC/RNFL in the HTG and overall glaucoma group.

DISCUSSION

The results of our study demonstrated that glaucoma was strongly associated with the risk of moderate-to-severe OSA (AHI ≥ 15 events/h), and functional progression in the overall glaucoma group and the HTG subgroup was positively correlated with OSA severity.

Glaucoma, which is the leading cause of blindness, is a broad-spectrum disease characterized by chronic progressive neurodegeneration, and its diagnostic criteria include functional and structural examination. Although VF examination remains the gold standard[29] for evaluating optic nerve function, structural examination through OCT-angiography was designed for the quantitative and qualitative evaluation of the optic nerve peripapillary RNFL, macular GCC, and microcirculation characteristics. To our knowledge, glaucoma has a circadian rhythm; nocturnal changes in IOP have been demonstrated in glaucoma.[30–32] The causes of optic nerve head hypoperfusion have been implicated in the pathogenesis of glaucoma.[15] OSA is closely related to increased oxidative stress and impaired autoregulation.[7] Desaturation in OSA might aggravate the IOP nocturnal spike during sleep,[15,33] and the comorbidity of OSA in patients glaucoma is critical not only because of the high prevalence but also the interaction of 2 diseases.[34–37]

Table 3—Univariate and multivariable logistic regression for variables associated with moderate-to-severe OSA[a]

	Univariate Analysis		Multivariable Analysis[b]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.031 (0.998, 1.065)	.068		
Male sex	3.750 (1.359, 10.345)	.011*	3.528 (1.143, 10.891)	.028*
DM (yes/no)	4.667 (1.219, 17.864)	.024*	4.186 (0.900, 19.467)	.068
HTN (yes/no)	2.300 (0.849, 6.230)	.101		
BMI	1.182 (1.024, 1.366)	.023*	1.114 (0.949, 1.308)	.186
Large NC[c]	2.273 (0.886, 5.829)	.088		
AXL[d]	1.000 (0.395, 2.530)	1.000		
Glaucoma (yes/no)	2.882 (1.063, 7.813)	.037*	3.041 (1.009, 9.167)	.048*
CCT	1.001 (0.989, 1.013)	.888		
RNFL	0.989 (0.960, 1.018)	.450		
GCC[d]	0.794 (0.312, 2.025)	.630		
wi VD RPC[d]	0.938 (0.370, 2.372)	.892		
pp VD RPC[d]	0.749 (0.295, 1.900)	.542		
wi SL MVD[d]	1.336 (0.526, 3.389)	.542		
pf SL MVD	1.035 (0.961, 1.114)	.369		
wi DL MVD	0.964 (0.866, 1.074)	.508		
pf DL MVD[d]	0.749 (0.295, 1.900)	.542		

*$P < .05$, logistic regression. [a]Dependent variable: moderate-to-severe OSA. [b]For multivariable analyses, only variables significant in univariate analyses were included in the model. [c]Neck circumferences of ≥ 38.75 cm for men and ≥ 34.5 cm for women were included in the analysis as large neck sizes (Large NC). [d]For nonnormally distributed quantitative data, the median split method was used to convert a continuous variable into a categorical variable. The median value indicated below can be used as reference. AXL = axial length, BMI = body mass index, CCT = central cornea thickness, CI = confidence interval, DL = deep layer, DM = diabetes mellitus, GCC = ganglion cell complex, HTN = hypertension, MVD = macula vessel density, NC = neck circumference, pf = parafovea, pp = peripapillary, RNFL = retinal nerve fiber layer, RPC = radial peripapillary capillary, SL = superficial layer, VD = vessel density, wi = whole image.

The first aim of our study was to identify the higher prevalence of OSA in participants with glaucoma. Although several retrospective studies have demonstrated RNFL thinning and higher prevalence of glaucoma in patients with OSA, there is a paucity of prospective evaluations of the impact of OSA on patients with glaucoma. In the present study, the baseline demographics of patients with glaucoma were similar to those of controls, with no difference noted in other possible predisposing factors of OSA, including sex, age, BMI, and neck circumference. In addition, the disease severity of the glaucoma subgroups was similar at baseline. As for moderate-to-severe OSA (AHI ≥ 15 events/h), the glaucoma group failed to exhibited a significantly higher prevalence compared with controls after correcting the type I error. However, when demographics, PSG data, ocular examination, and microvasculature were considered covariates in a binomial logistic regression, the presence of glaucoma ($P = .048$) and the male sex ($P = .028$) were strongly associated with moderate-to-severe OSA (AHI ≥ 15 events/h) (**Table 3**). Supported by previous literature,[38,39] our prospective study firmly confirmed the hypothesis that OSA was not uncommon in the population with glaucoma, and moreover, the presence of glaucoma increased the risk of moderate-to-severe OSA.

Ferrandez et al[22] prospectively demonstrated that retinal sensitivity measured with SAP was significantly lower in OSA compared with controls. Several prevalence studies[40–s42] also reported significant differences in both MD and PSD in OSA compared with controls. However, whether OSA predisposes patients to more rapid glaucoma progression remains unknown. On the basis of our previous retrospective study,[23] OSA is considered a predisposing factor for NTG. Therefore, proceeding to a prospective-design study was essential to clarify whether OSA with higher AHI and/or oxygen desaturation index is associated with the progression of glaucoma. Our present results indicated that, although no difference was observed between mild OSA and moderate-to-severe OSA in terms of MD, PSD, RNFL, GCC, or VD, glaucoma progression, as determined based on the VF MD slope, was significantly faster in the moderate-to-severe OSA group (**Table 2**). Moreover, in participants with HTG and overall glaucoma, moderate-to-severe OSA was significantly and negatively correlated with the MD slope ($P = .008$ and $P = .008$ respectively) (**Table 4**). The IOP controls exhibited no difference from baseline, which reveals that desaturation status during sleep, as evaluated by PSG, had a negative effect on glaucomatous nerve progression presenting in the function examination.

A relevant prospective study[43] that focused on primary open-angle glaucoma demonstrated a high prevalence of OSA among patients with primary open-angle glaucoma but without significance compared with controls; thus, screening for OSA in patients with primary open-angle glaucoma was not supported. By contrast, the novelty of our study was that we demonstrated that overall glaucoma—including NTG and HTG—was associated with moderate-to-severe OSA. Furthermore, the glaucoma

Table 4—Univariate and multivariable generalized linear regression analysis for assessing variables associated with the mean deviation slope.[a]

Independent Variables	General Glaucoma (n = 52)				NTG (n = 22)				HTG (n = 30)			
	Univariate		Multivariable[b]		Univariate		Multivariable[b]		Univariate		Multivariable[b]	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Age	0.004 (−0.017, 0.025)	.733			−0.015 (−0.038, 0.007)	.189			0.011 (−0.020, 0.042)	.485		
Male sex	−0.570 (−1.167, 0.028)	.062			−0.240 (−0.800, 0.320)	.401			−0.826 (−1.782, 0.131)	.091		
DM	−0.640 (−1.262, −0.018)	.044*	−0.385 (−0.998, 0.229)	.219	−0.065 (−0.837, 0.707)	.869			−0.859 (−1.747, 0.028)	.058		
HTN	0.102 (−.472, 0.676)	.728			0.371 (−0.242, 0.984)	.236			0.040 (−0.846, 0.926)	.929		
BMI	−0.010 (−0.078, 0.058)	.776			0.016 (−0.069, 0.102)	.706			−0.013 (−0.113, 0.087)	.795		
Large NC[c]	0.039 (−0.521, 0.598)	.892			0.133 (−0.496, 0.763)	.678			0.113 (−0.825, 1.052)	.813		
AHI ≥ 15 events/h	−0.875 (−1.422, −0.329)	.002*	−0.766 (−1.332, −0.200)	.008*	−0.540 (−1.091, 0.010)	.054			−1.123 (−1.950, −0.297)	.008*		
ODI[d]	−0.469 (−1.030, 0.091)	.101			−0.353 (−0.862, 0.156)	.175			−0.831 (−1.665, 0.003)	.051		
Mean SaO_2[d]	−0.227 (−0.782, 0.329)	.424			0.290 (−0.226, 0.805)	.271			−0.556 (−1.419, 0.307)	.207		
CPAP use	−0.135 (−0.765, 0.494)	.673			0.135 (−0.457, 0.728)	.654			−0.339 (−1.333, 0.656)	.505		

*$P < .05$, unstandardized generalized linear regression coefficient. [a]Dependent variable: MD slope. [b]For multivariable analyses, only variables significant in univariate analyses were included in the model. [c]Neck circumferences of ≥ 38.75 cm for men and ≥ 34.5 cm for women were included in the analysis as large neck sizes (Large NC). [d]For nonnormally distributed quantitative data, the median split method was used to convert a continuous variable into a categorical variable. The median value indicated below can be used as reference. AHI = apnea–hypopnea index, BMI = body mass index, CI = confidence interval, CPAP = continuous positive airway pressure, DM = diabetes mellitus, HTG = high tension glaucoma, HTN = hypertension, NC = neck circumference, NTG = normal tension glaucoma, ODI = oxygen desaturation index, SaO_2 = arterial oxyhemoglobin saturation.

Table 5——Correlations of ganglion cell complex slope with OSA-related parameters.

	Mean ± SD	ρ	*P* Value
NTG (n = 12)			
NC (cm)	35.2 ± 3.2	0.030	.926
BMI (kg/m^2)	22.6 ± 2.5	0.293	.355
AHI (events/h)	27.3 ± 18.1	−0.584	.046*
ODI	20.8 ± 16.5	−0.452	.140
Mean SaO_2 (%)	95.2 ± 2.5	0.488	.108
HTG (n = 19)			
NC (cm)	39.0 ± 3.8	0.396	.093
BMI (kg/m^2)	25.8 ± 4.5	0.423	.071
AHI (events/h)	32.0 ± 25.8	0.273	.257
ODI	24.7 ± 26.8	0.347	.145
Mean SaO_2 (%)	94.7 ± 1.5	−0.305	.204
Glaucoma (n = 31)			
NC (cm)	37.5 ± 4.0	0.181	.330
BMI (kg/m^2)	24.6 ± 4.2	0.306	.094
AHI (events/h)	30.2 ± 22.9	−0.123	.510
ODI	23.2 ± 23.1	0.026	.889
Mean SaO_2 (%)	94.9 ± 1.9	0.131	.482

*$P < .05$, Spearman's rank correlation coefficient. AHI = apnea–hypopnea index, BMI = body mass index, HTG = high tension glaucoma, NC = neck circumference, NTG = normal tension glaucoma, ODI = oxygen desaturation index, SaO_2 = arterial oxyhemoglobin saturation.

functional progression rate was correlated with OSA severity. On the basis of this result, we suggest that to prevent the progression of glaucoma, careful monitoring of comorbid OSA status is essential.

Recent studies have focused on evaluating patients with OSA assisted by OCT or OCT-angiography. Lin et al[19] demonstrated RNFL thinning via OCT among Asian populations with OSA. Via OCT-angiography, Yu et al[21] demonstrated that among patients with OSA, parafoveal and peripapillary VD decreased with disease severity. Our prospective study revealed that patients with glaucoma and a higher AHI were at a higher risk of structural deterioration. With regard to parameters of OCT-angiography, AHI was significantly correlated with the GCC thinning slope in the NTG subgroup during the short follow-up period (12.4 ± 6.1 months) (**Table 5**). This finding is parallel to a relevant retrospective study that illustrated AHI to be an effective indicator of progression with structural change in glaucoma.[44]

Several limitations to this study should be noted. First, the study period was relatively short and with a sex predilection; the majority of patients were male. Another major limitation of this study is the small sample size. Although we surveyed many patients at our glaucoma clinic, we could enroll only 52 patients with glaucoma and 24 control participants with valid PSG examinations. However, the other patients we surveyed were not willing to undergo overnight PSG. Future large-scale studies are warranted to confirm the findings of this study. In addition, although CPAP compliance, CPAP usage duration, extensive sleep questionnaire, and sleep medication are crucial information, we did not evaluate these in detail; this could have confounded the results. Furthermore, we adopted a small macula scan area (3×3 mm), meaning we might have missed glaucomatous damage outside the area.[45] Last, we did not record blood pressure during the study period, which might have affected VD despite the relatively low association observed between blood pressure and retinal VD in patients with OCT-angiography in a previous study.[46]

CONCLUSIONS

Our prospective cohort study revealed glaucoma and male sex as the independent predictors of moderate-to-severe OSA. Furthermore, moderate-to-severe OSA was an independent predictor of VF deterioration in glaucoma.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CPAP, continuous positive airway pressure
GCC, ganglion cell complex
HTG, high tension glaucoma
IOP, intraocular pressure
MD, mean deviation
NTG, normal tension glaucoma
OCT, optical coherence tomography
OR, odds ratio
OSA, obstructive sleep apnea
PSD, pattern standard deviation

PSG, polysomnography
RNFL, retinal nerve fiber layer
SAP, standard automated perimetry
VD, vessel density
VF, visual field

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ACKNOWLEDGMENTS

The authors thank Hsin-Fen Lin of Raising Statistic Consultant Inc. for their statistical assistance.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December 30, 2020
Submitted in final revised form June 8, 2021
Accepted for publication June 9, 2021
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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. This study was funded by the Chang Gung Memorial Hospital, Keelung under Grant CMRPG2G0262. The authors report no conflicts of interest.