Association between obstructive sleep apnea hypopnea syndrome and normal tension glaucoma

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KEYWORDS
Normal tension glaucoma; Obstructive sleep apnea hypopnea syndrome; Apnea hypopnea index; Cup to disk ratio; Intraocular pressure; Visual field defects

Abstract Background and objective: To study the prevalence of glaucoma among a group of patients with obstructive sleep apnea hypopnea syndrome and to test the hypothesis that OSAS should be considered as a significant risk factor for normal tension glaucoma (NTG).

Subjects and methods: The study included forty subjects recently confirmed to have OSA and fifteen obese subjects without OSAHS as control group. Control subjects were matched to patients regarding coexisting comorbid conditions. All patients were planned for full polysomnographic study, and a complete ophthalmologic examination within 48 h of the PSG.

Results: Glaucoma was diagnosed in fourteen (14) out of 40 patients with OSAHS yielding an estimate prevalence of 35% among patients with OSAHS compared to only one case of glaucoma in obese patients without OSAHS as control group. Control subjects were matched to patients regarding coexisting comorbid conditions. All patients were planned for full polysomnographic study, and a complete ophthalmologic examination within 48 h of the PSG.

Results: Glaucoma was diagnosed in fourteen (14) out of 40 patients with OSAHS yielding an estimate prevalence of 35% among patients with OSAHS compared to only one case of glaucoma in obese patients without OSAHS that is to say 6.7% with statistically significantly difference between the two groups ($\chi^2 = 4.415$, $p = 0.045$). We found that mean ± SD CD ratio was statistically significantly higher in patients with OSAHS compared to controls without OSAHS as follows: 0.40 (0.20–0.80), and 0.30 (0.20–0.60) respectively ($Z = 2.435^*$, $p = 0.015$). Comparing subgroup of patients: with glaucoma ($n = 14$) to those without glaucoma ($n = 26$), statistically significantly higher CD ratio 0.70 (0.60–0.80) was noted in those with glaucoma compared to those without glaucoma 0.30 (0.20–0.40) ($Z = 5.292^*$, $p = 0.001$). Statistically a significantly positive correlation existed between CD ratio and AHI in patients with OSAHS with $r = 0.566$ at $p < 0.001$ as well as both subgroups with and without glaucoma with $r = 0.902, 0.638$ respectively at $p < 0.001$. Statistically significantly positive correlation existed between CD ratio and DI in patients with OSAHS with $r = 0.622$ at $p < 0.001$ as well as both subgroups with and without glaucoma with $r = 0.847, 0.678$ respectively at $p < 0.001$. Statistically significantly negative correlation existed between CD ratio and lowest SaO2 during sleep in patients with OSAHS with $r = −0.561$ at $p < 0.001$ as well as both subgroups with and finding of a higher than expected prevalence of glaucoma in our patient population with sleep apnea suggests that clinicians may need to consider the possibility that unrecognized glaucoma is present in patients with newly diagnosed or existing sleep apnea. In conclusion, OSAS should be considered as a significant risk factor for NTG. So it is
Introduction

Normal-tension glaucoma (NTG) is an optic neuropathy associated with a glaucomatous optic nerve head, progressive, retinal nerve fiber layer thinning, characteristic visual field defects, open anterior chamber angle on gonioscopy, and a maximum intraocular pressure (IOP) below 21 mmHg [1].

Currently, identified risk factors for NTG include abnormal ocular blood flow, abnormal blood coagulation, systemic hypotension, ischemic vascular disorders, and autoimmune disease [2–4]. However, pathogenesis of the condition remains unclear.

Obstructive sleep apnea syndrome (OSAS) is a common yet under diagnosed condition that may be associated with significant morbidity if left untreated. It is characterized by recurrent interruption of normal breathing during sleep, owing to upper airway obstruction (apneic spells) [5]. The apneic spells can cause a decrease in the arterial oxygen saturation and a rise in the carbon dioxide saturation during sleep. OSAS has been associated with many vascular diseases including cardiovascular disease, hypertension and stroke [6–8].

It is also suggested that OSAS could create transient hypoxemia and increase vascular resistance, which may compromise optic nerve head perfusion and oxygenation and cause glaucomatous optic neuropathy [3,9].

The objective of our study was to study the prevalence of glaucoma among a group of patients with obstructive sleep apnea hypopnea syndrome and to test the hypothesis that OSAS should be considered as a significant risk factor for normal-tension glaucoma (NTG).

Subjects and methods

Forty subjects were selected from patients referred for sleep related breathing disorder evaluation at the sleep lab in the department of chest diseases, Faculty of Medicine, Alexandria University, Egypt – for possible OSA and confirmed to have OSA. These patients were eligible for the study. Patients with obstructive sleep apnea, who had a previous established diagnosis of glaucoma, and/or who were already on treatment for glaucoma were not included in the prevalence calculation. Only patients who could undergo an overnight PSG and ophthalmologic examination were included.

Fifteen obese subjects without OSAHS mostly recruited from surgery clinics at the Alexandria Main University hospital, and Medical Research Institute as patients with no obvious sleep complaints, being prepared for bariatric surgery to lose weight were included as the control group. Control subjects were matched to patients regarding coexisting comorbid conditions. Accidental diagnosis of unsuspected OSAHS excluded immediately the subject from the study. Only those who were free of sleep related breathing disorders (not OSAHS) were included.

All patients were planned for full polysomnographic study. This latter was carried out using somnoscreen plus RC combi 39, which included the following channels: flow (cannula and/or thermistor), snore (cannula and/or microphone), thoracic movement, abdominal movement, oxygen saturation, plethysmogram, pulse rate, electrocardiogram, periodic leg movement, electrooculogram, electroencephalogram and CPAP/BiPAP pressure.

The polysomnographic analysis was done automatically but was imperatively coupled with manual scoring. Respiratory events were scored using standard criteria [10,11]. The apnea hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep. As indices of nocturnal hypoxemia we considered the oxygen desaturation index (this is the number of times that the oxygen saturation falls by more than 3% or 4% per hour of sleep), T90 (the fraction of sleep time spent below an oxygen saturation of 90%) and the minimal value recorded during sleep (minimal SaO₂) [10,11].

Patients underwent a complete ophthalmologic examination within 48 h of the PSG. All ophthalmologic examinations were performed by a single glaucoma specialist and included the measurement of intraocular pressure (IOP and fundoscopic assessment) for the presence of glaucomatous optic disk changes. The diagnostic criteria used by the examiner were in strict adherence to the latest Primary Open Angle Glaucoma Preferred Practice Pattern’s definition and diagnostic recommendations [12].

At the time of the ophthalmologic examination, the results of the polysomnogram (degree of sleep apnea) were unknown to the examiner.

All subjects were enrolled in the study after a written informed consent according to the protocol approved by the Ethics Committee of the Hospital.

Results

Demographic data of the studied population

Among 40 studied patients with OSAHS, 13 (32.5%) were males whereas 27 (67.5%) were females. While for control obese population without OSAHS, males were 7 in number that is to say 46.7% while females were 8 in number that is to say 53.3% with no statistical significant differences between the two groups.

Statistically significantly higher values of mean ± SD age of patients with OSAHS were found compared to obese patients without OSAHS with values 58.95 ± 11.25 years, and 39.73 ± 7.79 years respectively (t = 6.077 at p < 0.001). Age distribution was as follows: in the range of 20 to 40 years;
only one patient with OSAHS was noted while 11 obese patients without OSAHS fell in this age group. In the range of 40 to 60 years; 20 patients with OSAHS were in this age group compared to 4 obese patients without OSAHS only. Finally 19 patients with OSAHS were 60 years or older whereas no obese patient without OSAHS reached 60 years of age. This reflects a statistically significantly older population with OSAHS compared to those without OSAHS.

Statistically significantly higher values of mean ± SD weight and BMI were noted in obese patients without OSAHS compared to patients with OSAHS. Mean ± SD weight of patients without OSAHS was 133.33 ± 29.12 kg, while that of patients with OSAHS was 116.02 ± 19.12 kg (t = 2.136 at p = 0.046). Consequently statistically significantly higher BMI values 49.14 ± 8.96 kg/m² compared to 43.53 ± 8.98 kg/m² (t = 2.065 at p = 0.044), were retrieved from obese patients without OSHS versus those with OSAHS respectively (see Table 1 and Figs. 1–5).

Comorbidities in the studied patients

Regarding prevalence of concomitant systemic comorbidities as well as frequencies of these comorbidities: hypertension, diabetes mellitus and Coronary artery disease (CAD) were the most frequently encountered ones in both patients and obese control subjects respectively as follows; hypertension in 65%, and 66.7%, diabetes mellitus in 55% and 73.3%, and CAD in 20% and 13.3% respectively. Obese control subjects without OSAHS were matched with patients regarding existing concomitant diseases. Other coexisting concomitant comorbidities with fewer frequencies were hypothyroidism, depression, heart failure, COPD, GERD and others (see Table 2).

Nocturnal sleep studies

All patients were planned for full polysomnographic study. This latter was carried out using Somnoscreen plus RC combi 39. AHI was statistically significantly higher (p < 0.001) in patients with OSAHS (50.78 ± 23.33 events/h) as compared to obese patients without OSAHS (4.09 ± 1.61 events/h). The average SaO₂ and minimum SaO₂ were statistically significantly lower in patients with OSAHS compared to patients without OSAHS (89.83 ± 6.68, 95.07 ± 1.33% respectively, p = 0.001 and 70.40 ± 13.35, 90.80 ± 3.71% respectively, p < 0.001). T90 was statistically significantly higher in patients with OSAHS (27.5%) compared to patients without OSAHS (0.0) with p < 0.001. The mean value of ODI in patients with OSAHS (43.52 ± 21.49) was statistically significantly higher (p < 0.001) as compared to patients without OSAHS (2.93 ± 1.29) (see Table 3 and Figs. 6–9).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison between the two studied groups according to demographic data.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n = 40)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (32.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (67.5%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>20 to &lt;40</td>
<td>58.95 ± 11.25</td>
</tr>
<tr>
<td>40 to &lt;60</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>≥60</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td>Weight</td>
<td>116.02 ± 19.12</td>
</tr>
<tr>
<td>Height (meters)</td>
<td>1.64 ± 0.09</td>
</tr>
<tr>
<td>BMI</td>
<td>43.53 ± 8.98</td>
</tr>
</tbody>
</table>

Qualitative data were described using number and percent and was compared using χ². Normally quantitative data were expressed as mean ± SD and compared using student t-test.

* Statistically significant at p ≤ 0.05.
Prevalence of normal tension glaucoma and pattern of glaucomatous visual defects

Glaucoma was diagnosed in fourteen (14) out of 40 patients with OSAHS yielding an estimate prevalence of 35% among patients with OSAHS OSAHS that is to say 6.7% with statistically significantly difference between the two groups ($\chi^2 = 4.415, p = 0.045$).

The diagnostic criteria used by the examiner were in strict adherence to the latest Primary Open Angle Glaucoma Preferred Practice Pattern’s definition and diagnostic recommendations (reference). Accordingly: mean ± SD value of IOP were 16.73 ± 2.39 mmHg, and 15.53 ± 1.92 mmHg in both patients and controls respectively with no statistically significant difference between the two groups.

Mean ± SD CD ratio was statistically significantly higher in patients compared to controls as follows: 0.40 (0.20–0.80), and 0.30 (0.20–0.40) respectively ($Z = 2.435^*, p = 0.015$).

Visual fields were defined as glaucomatous by following selected guidelines that were taken from the modified Collaborative Initial Glaucoma Treatment Study guidelines. 15 Visual field defects included the presence of one or more of the following abnormalities in the visual field in the absence of other explanations for a field defect in the following locations with a cluster of three adjacent depressed points on the pattern standard deviation plot a nasal step or scotoma, inferior or superior arcuate scotoma, paracentral scotoma, or generalized depression (see Tables 4 and 5, Figs. 10 and 11).

Comparing a subgroup of patients with glaucoma ($n = 14$) to those without glaucoma ($n = 26$), statistically significantly higher CD ratio 0.70 (0.60–0.80) was noted in those with glaucoma compared to those without glaucoma 0.30 (0.20–0.40) ($Z = 5.292^*, p = 0.001$). No statistically significantly

Table 2  Comparison between the two studied groups according to coexisting co-morbid conditions.

<table>
<thead>
<tr>
<th></th>
<th>Patients ($n = 40$)</th>
<th>Control ($n = 15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>26 (65.0%)</td>
<td>10 (66.7%)</td>
</tr>
<tr>
<td>DM</td>
<td>22 (55.0%)</td>
<td>11 (73.3%)</td>
</tr>
<tr>
<td>CAD</td>
<td>8 (20.0%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Other systemic diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6 (15.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hypothyroidism with ischemic cardiomyopathy</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dyslipidemia, hyperuricemia</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>GERD</td>
<td>1 (2.5%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>History of falling and fracture of thoracic vertebrae with failure of definite surgical repair because of obesity</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Spondylolisthesis in the lower thoracic vertebrae- severe back ache</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Disk prolapse</td>
<td>0 (0.0%)</td>
<td>1 (6.7%)</td>
</tr>
</tbody>
</table>

Qualitative data were described using number and percent.
differences were noted in mean ± SD value of IOP between
the two subgroups of patients with OSAHS (see Table 6).
 Concerning polysomnographic respiratory parameters of
patients with OSAHS, subgroup of patients with glaucoma
demonstrated statistically significantly higher mean ± SD val-
ues of AHI, and DI (61.21 ± 26.96/h, and 55.14 ± 25.24/h)
respectively compared to subgroups of patients without glau-
coma (45.15 ± 19.43/h, and 37.27 ± 16.52) respectively with
t = 2.174 at p = 0.036 and t = 2.389 at p = 0.027 respec-
tively. Subgroup of patients with glaucoma suffered from sta-
tistically significantly lower to lowest SaO2 during sleep 63.57
± 14.50 mmHg compared to subgroups of patients without
glaucoma 74.08 ± 11.34 mmHg with t = 2.533 at p = 0.016
(see Table 7).

Correlations

(1) There was no significant relation between diagnosis of
glaucoma and age or BMI or associated comorbidities
in patients with OSAHS.
(2) Statistically significantly positive correlation existed
between value of IOP and t90 in group of patients with
OSAHS with r = 0.414 at p = 0.008 (see Fig. 12).
(3) Statistically significantly negative correlation existed
between value of IOP and average SaO2 during sleep
in the group of patients with OSAHS with r = 0.405
at p = 0.009 (see Fig. 13).
(4) Statistically significantly positive correlation existed
between the value of IOP and t90 in the subgroup of
patients with glaucoma with r = 0.658 at p = 0.011
(see Fig. 14).

(5) Statistically significantly negative correlation existed between the value of IOP and average SaO2 during sleep in the subgroup of patients with glaucoma with \( r = -0.563 \) at \( p = 0.0036 \) (see Fig. 15).

(6) Statistically significantly positive correlation existed between CD ratio and AHI in patients with OSAHS with \( r = 0.566 \) at \( p < 0.001 \) as well as both subgroups with and without glaucoma with \( r = 0.902, 0.638 \) respectively at \( p < 0.001 \) (see Fig. 16).

(7) Statistically significantly positive correlation existed between CD ratio and DI in patients with OSAHS with \( r = 0.622 \) at \( p < 0.001 \) as well as both subgroups with and without glaucoma with \( r = 0.847, 0.678 \) respectively at \( p < 0.001 \) (see Fig. 17).

(8) Statistically significantly negative correlation existed between CD ratio and lowest SaO2 during sleep in patients with OSAHS with \( r = -0.561 \) at \( p < 0.001 \) as well as both subgroups with and without glaucoma with \( r = -0.69, -0.566 \) respectively at \( p < 0.001 \) (see Fig. 18).

Discussion

Our study demonstrated that normal tension glaucoma was diagnosed in fourteen (14) out of 40 patients with OSAHS yielding an estimate prevalence of 35% among patients with OSAHS compared to only one case of glaucoma in obese patients without OSAHS that is to say 6.7% with statistically significantly difference between the two groups (\( \chi^2 = 4.415, p = 0.045 \)). Control subjects were matched to patients regarding coexisting comorbid conditions. The only limitation of our study group was that population with OSAHS was statistically significantly older compared to those without OSAHS.

Bilgin in 2014\[13\] recruited 24 patients with normal tension glaucoma and 24 age and sex matched controls who were also similar for systemic risk factors such as diabetes mellitus (DM), hypertension (HT) and hypercholesterolemia. All patients and controls underwent over-night polysomnography (PSG) for the diagnosis of OSAS. Patients and controls were statistically similar in terms of age, sex, gender, smoking, systemic risk factors, and neck circumference and body mass index. The subjects with AHI \( \geq 20 \) were accepted as OSAS. Bilgin found that ten (41.7%) of 24 patients with normal tension glaucoma and 3 (12.5%) of 24 controls had OSAS (\( p < 0.05 \)). The prevalence of OSAS was higher in patients with normal tension glaucoma (NTG) and the difference between patient and control groups was statistically significant (\( p < 0.05 \)).

Table 4  Comparison between the two studied groups according to ocular examination findings.

<table>
<thead>
<tr>
<th>Patients (n = 40)</th>
<th>Control (n = 15)</th>
<th>Test of sig.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP 16.73 ± 2.39</td>
<td>15.53 ± 1.92</td>
<td>( t = 1.732 )</td>
<td>0.089</td>
</tr>
<tr>
<td>C/D ratio 0.40 (0.20–0.80)</td>
<td>0.30 (0.20–0.60)</td>
<td>( Z = 2.435^* )</td>
<td>0.015^*</td>
</tr>
</tbody>
</table>

Normally quantitative data was expressed as mean ± SD and compared using student \( t \)-test, while abnormally distributed data was expressed using Median (Min. – Max.) and was compared using the Mann Whitney test.

^* Statistically significant at \( p \leq 0.05 \).

Table 5  Comparison between the two studied groups according to prevalence of glaucoma and pattern of glaucomatous visual defects.

<table>
<thead>
<tr>
<th>Patients (n = 40)</th>
<th>Control (n = 15)</th>
<th>( \chi^2 )</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma No glaucoma 26 (65.0%)</td>
<td>14 (93.3%)</td>
<td>( \chi^2 = 4.415^* )</td>
<td>0.045^*</td>
</tr>
<tr>
<td>Have glaucoma 14 (35.0%)</td>
<td>1 (6.7%)</td>
<td>(n = 14)</td>
<td>(n = 1)</td>
</tr>
<tr>
<td>Glaucomatous visual field defects Nasal step 2 (14.3%)</td>
<td>1 (100.0%)</td>
<td>( \chi^2 = 3.775 )</td>
<td>MC, ( p = 0.338 )</td>
</tr>
<tr>
<td>Bjerrum scotoma 6 (42.9%)</td>
<td>0 (0.0%)</td>
<td>(n = 14)</td>
<td>(n = 1)</td>
</tr>
<tr>
<td>Arcuate scotoma 4 (28.6%)</td>
<td>0 (0.0%)</td>
<td>(n = 14)</td>
<td>(n = 1)</td>
</tr>
<tr>
<td>Paracentral scotoma 2 (14.3%)</td>
<td>0 (0.0%)</td>
<td>(n = 14)</td>
<td>(n = 1)</td>
</tr>
</tbody>
</table>

Qualitative data were described using number and percent and was compared using \( \chi^2 \), Monte Carlo test or Fisher Exact test.

^* Statistical significance.
Mojon et al. [14] observed OSAS in 7 of the 16 normal tension glaucoma (NTG) patients (44%). However, their controls were all male subjects from a previously published study. Thus, they did not use an age and sex matched control group.

Marcus et al. [15] described the rate of sleep apnea among patients with normal tension glaucoma (NTG) as 55.5%. They did not observe any OSAS cases in their control group.

In another prospective study of 6 patients with known normal tension glaucoma (NTG) and symptomatic snoring, Blumen Ohana et al. [16] reported that 3 of the patients subsequently were diagnosed with OSAS on PSG testing. However, both Marcus et al. and Blumen Ohana et al. offered PSG only to those who reported a positive history of sleep disturbance or snoring. Since subjective reports often underestimate the prevalence of OSAS, this may create a statistical bias in both of these studies.

### Table 6

Comparison between two studied subgroups (with and without glaucoma) according to ocular examination findings.

<table>
<thead>
<tr>
<th></th>
<th>No glaucoma (n = 26)</th>
<th>Have glaucoma (n = 14)</th>
<th>Test of sig.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP</td>
<td>16.58 ± 2.27</td>
<td>17.0 ± 2.66</td>
<td>t = 0.530</td>
<td>0.599</td>
</tr>
<tr>
<td>C.D ratio</td>
<td>0.30 (0.20–0.40)</td>
<td>0.70 (0.60–0.80)</td>
<td>Z = 5.292*</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
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Normally quantitative data were expressed as mean ± SD and compared using student t-test, while abnormally distributed data were expressed using Median (Min. – Max.) and was compared using the Mann Whitney test.

* Statistically significant at p ≤ 0.05.

### Table 7

Relation between glaucoma with demographic and clinical data in patient groups.

<table>
<thead>
<tr>
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<th>Test of sig.</th>
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<tbody>
<tr>
<td>AHI</td>
<td>45.15 ± 19.43</td>
<td>61.21 ± 26.96</td>
<td>t = 2.174*</td>
<td>0.036</td>
</tr>
<tr>
<td>DI</td>
<td>37.27 ± 16.52</td>
<td>55.14 ± 25.24</td>
<td>t = 2.389*</td>
<td>0.027*</td>
</tr>
<tr>
<td>T90</td>
<td>27.5 (0.0–100)</td>
<td>30 (1.0–100)</td>
<td>Z = 0.766</td>
<td>0.443</td>
</tr>
<tr>
<td>Average SaO2 during sleep</td>
<td>89.08 ± 7.50</td>
<td>91.21 ± 4.73</td>
<td>t = 0.964</td>
<td>0.341</td>
</tr>
<tr>
<td>Lowest SaO2 during sleep</td>
<td>74.08 ± 11.34</td>
<td>63.57 ± 14.50</td>
<td>t = 2.533*</td>
<td>0.016*</td>
</tr>
</tbody>
</table>

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* Statistically significant at p ≤ 0.05.

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* Statistically significant at p ≤ 0.05.
Mojon et al. in 2000 [17] performed overnight transcutaneous finger oximetry to 30 consecutive patients having primary open-angle glaucoma. They assessed the oximetry disturbance index during night sleep, a parameter used to diagnose sleep apnea syndrome and to grade its severity. They found that sleep apnea syndrome was more prevalent among primary open-angle glaucoma patients compared to normal historic controls of the same age and sex distribution. The oximetry disturbance index grade was significantly larger in the primary open-angle glaucoma group compared to normal controls. According to the oximetry disturbance index, 20% (6/30) of primary open-angle glaucoma patients had sleep apnea syndrome.

Bendel RE et al. in 2008 [18] studied one hundred patients with moderate to severe obstructive sleep apnea to determine the prevalence of glaucoma in patients with obstructive sleep apnea. Glaucoma was diagnosed in 27 of 100 patients yielding an estimated prevalence of 27%.

Mojon et al. [19] reported a case series of 114 patients referred for polysomnography (PSG) for the evaluation of...
OSA. Sixty-nine patients had OSA confirmed by PSG, and 5 (7.2%) of these patients were diagnosed with glaucoma.

Two studies have found no association of OSA with glaucoma. Geyer et al. [20] examined 228 patients diagnosed with OSA from a single sleep center and found the prevalence of glaucoma to be 2%, the same as expected in a general Caucasian population. In that study, patients previously studied and found to have sleep apnea were recalled to participate in the study. The time lapse between the sleep study and the eye examination was not noted by the authors. It is likely that most of those who participated in the study were receiving some form of therapy for OSA with the majority receiving nasal continuous positive airway pressure (nCPAP).

Girkin et al. [21] looked for associated diagnoses of sleep apnea in 667 newly diagnosed glaucoma patients in a single institution’s database and compared the association with a control group and did not find it to be significantly different, although a trend of more prevalent glaucoma diagnosis in patients with OSA was noted. Girkin et al. [21] examined three International Classification of Diseases Ninth Revision (ICD9) diagnostic codes for newly diagnosed glaucoma over a 4-year time frame and also searched for sleep apnea diagnoses under a single diagnostic ICD9 code. The investigators acknowledge that this methodology favors the null outcome of an association between glaucoma and sleep apnea. Additionally, a review of ICD9 codes reveals that at least nine other additional codes for sleep apnea are available, which were not considered by these investigators, as they searched for only one ICD9 diagnostic code, leaving a potential for patients diagnosed with another sleep apnea code not to be detected. Additionally, the investigators have no way of determining which patients may have been obtaining eye care or care of their OSA outside of the institution, in which case an unknown quantity of diagnoses would not be in their database.

In our study we found that mean ± SD CD ratio was statistically significantly higher in patients with OSAHS compared to controls without OSAHS as follows: 0.40 (0.20–0.80), and 0.30 (0.20–0.60) respectively (Z = 2.435*, p = 0.015). Comparing subgroup of patients: with glaucoma (n = 14) to those without glaucoma (n = 26), statistically significantly higher CD ratio of 0.70 (0.60–0.80) was noted in those with glaucoma compared to those without glaucoma 0.30 (0.20–0.40) (Z = 5.292*, p = 0.001). Statistically significantly positive correlation existed between CD ratio and AHI in patients with OSAHS with r = 0.566 at p < 0.001 as well as both subgroups with and without glaucoma with r = 0.902, 0.638 respectively at p < 0.001. Statistically significantly positive correlation existed between CD ratio and DI in patients with OSAHS with r = 0.622 at p < 0.001 as well as both subgroups with and without glaucoma with r = 0.847, 0.678 respectively at p < 0.001. Statistically significantly negative correlation existed between CD ratio and lowest SaO2 during sleep in patients with OSAHS with r = −0.561 at p < 0.001 as well as both subgroups with and without glaucoma with r = −0.69, −0.566 respectively at p < 0.001.

The previous findings in our research are in accordance with Kargi et al. [22] who found that the thickness of retinal nerve fiber layer (RNFL) was reduced in patients with OSAS compared to controls. The decrease in RNFL was found to be correlated with the severity of sleep apnea (r = 0.78, p = 0.01). They concluded that sleep apnea syndrome is correlated with a proportional decrease in the RNFL. Decreased ocular perfusion related to hypoxia and vasoconstriction associated with OSAS may cause RNFL thinning, which may precede clinically detectable glaucoma. Early detection of RNFL thinning offers an opportunity to detect glaucoma at its earlier stages [23,24].

During sleep, repetitive episodes of airway occlusion, consequent hypoxemia, hypercapnia, and changes in intrathoracic pressure elicit changes in the autonomic, hemodynamic, humoral, and neuroendocrine responses that can affect the circulation of the optic nerve with loss of ganglion cells [25].

Kargi et al. [22] found that RNFL was thinner in patients with OSAS without any evident glaucoma as patients with clinical signs of glaucoma were excluded from the study.

With the increasing severity of OSAS, mean oxygen saturation values are reduced and relative hypoxia occurs. They found that as the disease becomes more severe, RNFL thinning is proportionally more prominent. This supports the correlation found between hypoxia and RNFL thinning in our study.

Two possible mechanisms for RNFL thinning in OSAS were proposed: the first mechanism may be due to the following sequence: the sleeping state in OSAS is associated with a reduction in the ventilatory drive caused by hypoxia and hypercapnia. This causes a decrease in pO2 and an increase in pCO2. Hypoxemia results in increased levels of the vasoconstrictor endothelin production. The endothelial cells also produce nitric oxide, a vasodilator [26–28]. In patients with OSAS, the endothelium-mediated vasodilator response is markedly impaired [28]. Thinning of RNFL may be caused by a loss of ganglion cells caused in some way by the hypoxia secondary to this OSAS-induced imbalance between nitric oxide and endothelin [26,27,29].

The second speculation is that the nocturnal vascular changes caused by OSAS may be the cause of RNFL thinning. Hypoxia indirectly increased intracranial pressure during sleep and decreased cerebral perfusion pressure may disturb blood supply of the optic nerve in patients with OSAS [29–31].

Vascular disturbances may result in diffuse loss or localized defects of the RNFL before the initiation of glaucoma [32]. When vascular dysregulation in OSAS is added to nocturnal
systemic hypotension, RNFL damage and consequent thinning may occur [33]. Reporting that the decrease in RNFL thickness correlated with the severity of OSAS.

A further support for the relationship between NTG and OSAS was reported by Kremmer et al. [34] who demonstrated a positive influence of OSAS therapy with nasal continuous positive airways pressure (nCPAP) ventilation on both disease courses [34]. The glaucomatous damage was shown to be stable after nCPAP treatment [34]. Thus, OSAS may be a treatable cause of circulatory deficiency in the optic nerve head.

In contradiction to our study and other previous studies [32–34], the lack of a correlation between AHI and the presence of glaucoma in the study performed by Bendel et al. in 2008 [18] might have been attributed to factors that affect oxygenation of the optic nerve, other than AHI, that may have played a role. These include blood pressure, cardiac output, and neurohormone levels. The measurement of AHI has become the standard for a statistical review in studies of sleep apnea patients, but it is far from being the only measure of the effect of disordered breathing on haemodynamics, metabolic function, and daytime symptoms.

In addition, in any given patient, the AHI does not always reflect the degree of hypoxemia or the hemodynamic derangements, which are also influenced by the baseline respiratory status, baseline cardiac output, and the length of individual apneas and hypopneas.

This issue was supported by the fact that non-apneic snoring has been independently associated with hypertension, suggesting that patients with obstructive sleep apnea and much lower AHI levels have significant changes in hemodynamic [35].

The finding of a higher than expected prevalence of glaucoma in our patient population with sleep apnea suggests that clinicians may need to consider the possibility that unrecognized glaucoma is present in patients with newly diagnosed or existing sleep apnea.

In conclusion, OSAS should be considered as a significant risk factor for NTG. So it is advisable to take an accurate sleep history (including questions about snoring, nocturnal gasping-choking, daytime sleepiness and morning headaches) from patients with NTG and refer these patients for PSG test and nCPAP therapy.

**Conflict of interest**

No conflict of interest.

**References**


