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CLINICAL STUDY

Peripapillary retina nerve fiber layer thickness and macular ganglion cell layer thickness in patients with obstructive sleep apnea syndrome

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Abstract

Purpose **To investigate the association of the severity of obstructive sleep apnea syndrome (OSAS) with peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell-inner plexiform layer (GC-IPL).**

Materials and methods **In this cross-sectional study, 145 patients with OSAS and 40 healthy subjects were enrolled. OSAS patients were further divided into mild ($n=50$), moderate ($n=36$), and severe ($n=59$) OSAS groups according to their apnea–hypopnea index (AHI) values. Spectral-domain optical coherence tomography was used to measure the peripapillary RNFL and GC-IPL thicknesses.**

Results **There was no statistical difference between the RNFL thickness in OSAS and control groups ($P>0.05$). Both average GC-IPL and minimum GC-IPL thicknesses were significantly *lower* in severe OSAS group than in healthy controls ($P<0.05$ for both). There was a significant negative correlation between AHI and both average GC-IPL ($r=-0.232$, $P=0.005$) and minimum GC-IPL ($r=-0.233$, $P=0.005$) thicknesses.**

Conclusions **Our study results suggest that although RNFL thickness did not differ significantly between OSAS and control groups, ganglion cell layer thickness in OSAS patients is much lower than in healthy population. Ganglion cell thickness showed a significant correlation with the severity of OSAS.**

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Introduction

Obstructive sleep apnea syndrome (OSAS) is defined as repetitive complete or partial obstruction of upper airway during sleep that results in reduction in oxygen saturation and intermittent hypoxia. This, in turn, induces oxidative stress, inflammation, and endothelial dysfunction, and consequently leads to impaired vascular autoregulation. OSAS has been associated with numerous ophthalmic disorders, including floppy eyelid syndrome, non-arteritic anterior ischemic optic neuropathy, glaucoma, papilledema, central serous choroidoretinopathy, and retinal vein occlusion.[1–8]

Glaucoma is the most investigated ocular conditions in patients with OSAS. Although numerous previous studies have reported high glaucoma prevalence in patients with OSAS, only few investigators have indicated any association between OSAS and glaucoma.[5,9–18] Additionally, it has been suggested that OSAS may also influence the retina nerve fiber layer (RNFL) and macular ganglion cell complex (GCC).[9,14,15,19]

Nowadays optical coherence tomography (OCT) is commonly used for qualitative and quantitative assessment of retina. Structural alterations in peripapillary RNFL and macular GCC thickness are often detected with OCT. Although several studies have investigated the impact on RNFL thickness in patients with OSAS, there is limited information regarding the effect of OSAS on GCC thickness. The aim of our study is to evaluate the association of the severity of OSAS with peripapillary RNFL and macular ganglion cell-inner plexiform layer (GC-IPL)

Materials and methods

Study population and design

This prospective comparative study was performed in the Department of

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Ophthalmology, Kanuni Sultan Suleyman Education and Research Hospital and Chest Diseases and Sleep Center, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee. All participants received oral and written study-related information, and each participant provided written informed consent.

Eligibility criteria

Both study and control groups were recruited in Chest Diseases and Sleep Center, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. Patients presenting to the sleep center with complaints of snoring, witnessed apnea, and excessive daytime sleepiness underwent polysomnographic investigation. Obstructive sleep apnea syndrome was diagnosed and graded according to the following apnea–hypopnea index (AHI) values: mild (>5 to ≤ 15), moderate (>15 to <30), and severe (≥ 30). Newly diagnosed, treatment-naïve OSAS patients were enrolled in this study. Control subjects had an AHI value <5 and were age and sex matched with the OSAS group participants. The subjects who had a myopia or hyperopia ($>+3$ or -3 D of spherical equivalent), glaucoma, intraocular pressure >21 mm Hg, posterior pole pathology such as macular degeneration or diabetic retinopathy, a history of intraocular surgery, ocular trauma, uveitis, and poor image due to cataract or unstable fixation were excluded.

Sleep study (polysomnography)

A standard overnight polysomnography was performed at the Chest Diseases and Sleep Center, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. All patients underwent an overnight polysomnography in a quiet room, which included the following variables: electroencephalography, submental electromyography, electro-oculography, airflow (nasal and oral) by thermistors, and pulse oximetry measurements. The AHI (times/h) was calculated by calculating the average number of episodes of apnea plus hypopnea per hour of sleep or recording time. An apneic event was defined as the cessation of airflow for at least 10 s with an effort to breathe. A hypoapneic event was described as a minimum of 30% fall in airflow for at least 10 s with 3% or greater oxygen desaturation compared with baseline.

Ocular examination protocol and measurements

All ocular examination and measurements were performed at the Department of Ophthalmology, Kanuni Sultan Suleyman Education and Research Hospital. All subjects underwent detailed ophthalmic examinations, including slit-lamp biomicroscopy, tonometry, and fundus examination. All participants were examined with Cirrus HD-OCT 4000 (Carl Zeiss Meditec Inc., Dublin, CA, USA). A single well-trained examiner blinded to the study groups took the ocular images. All measurements were performed between 0900 and 1200 hours. OCT scans with signal strength >6 were included for analysis. The GCC mapping was conducted based on macular protocol centered on fovea with a cube of 512×128 with automated measurement of the GC-IPL thickness. Data for RNFL thickness were acquired using the 'Optic Disc Cube 200×200' protocol. One eye of each participant was randomly selected for statistical analysis.

Outcome measures

Outcomes measures were the ganglion cell thickness including average and minimum GC-IPL thicknesses, and RNFL thickness parameters including average, temporal, superior, nasal, and inferior thicknesses.

Statistical analysis

All statistical analyzes were performed using SPSS 16.0 (SPSS, Chicago, IL, USA). The normality of all data samples was checked using the Shapiro–Wilk test. Comparisons among the groups were performed using one-way analysis of variance test, followed by the Bonferroni–Dunn *post hoc* test. χ^2 tests were used for categorical variables. The Pearson's correlation coefficient was used to determine the relationship between the AHI and OCT parameters. Differences were considered statistically significant for P-values <0.05.

Results

A total of 185 subjects met the study criteria, including 40 eyes in the control group, 50 eyes in the mild OSAS group, 36 eyes in the moderate OSAS group, and 59 eyes in the severe OSAS group. The demographic and clinical characteristics of the groups are shown in Table 1. There was no difference between OSAS and control groups with respect to age, gender, intraocular pressure, axial length, refractive values, and existence of systemic diseases, including diabetes and hypertension.

Table 2 shows RNFL and GC-IPL thickness between the patients with OSAS and control subjects. Although RNFL thickness was not significantly different between the

Table 1 Demographic and clinical characteristics of the groups

	Mean ± SD				
	Control (n = *40*)	*Mild-OSAS* (n = *50*)	*Moderate OSAS* (n = *36*)	*Severe OSAS* (n = *59*)	P-*value*
Gender, F/M	17/23	20/30	17/19	21/38	0.721[a]
Age (years)	46 ± 7	47 ± 9	49 ± 10	50 ± 8	0.102[b]
AL	23.0 ± 0.8	23.4 ± 0.8	22.9 ± 0.6	23.4 ± 0.9	0.061[b]
SE	0.28 ± 0.68	0.24 ± 0.91	0.57 ± 1.0	0.09 ± 0.97	0.429[b]
IOP	16.6 ± 2.9	16.07 ± 2.5	16.1 ± 3.1	16.9 ± 2.9	0.135[b]
AHI score	1.9 ± 1.1	9.5 ± 2.5	21.3 ± 4.34	57.2 ± 22.1	**0.000**[b]
BMI	27.5 ± 4.6	29.3 ± 4.9	31.8 ± 5.2	34.4 ± 6.4	**0.000**[b]
DM (+/−)	8/32	9/41	6/30	9/50	0.939[a]
HT (+/−)	11/29	11/39	12/24	20/39	0.525[a]

Abbreviations: AL, axial length; BMI, body mass index; DM, diabetes mellitus; F, female; HT, hypertension; IOP, intraocular pressure; M, male; OSAS, obstructive sleep apnea syndrome; SR, spherical refraction. Bold values are statistically significant for $P < 0.05$.
[a]χ^2 test. [b]One-way ANOVA test.

groups, the average GC-IPL thickness and minimum GC-IPL thickness were significantly lower in the OSAS group ($P<0.05$ for both).

The GC-IPL thickness measurements of the groups are shown in Table 3. A pairwise comparison between the groups revealed that severe OSAS group has statistically significant thinner average GC-IPL thickness and minimum GC-IPL thickness than the control group and mild OSAS group ($P<0.05$ for all). Table 4 shows the results of Pearson's correlation analysis between the AHI and OCT parameters. The AHI index was significantly negatively correlated with average GC-IPL ($r=-0.232$, $P=0.005$) and minimum GC-IPL ($r=-0.233$, $P=0.005$) thicknesses.

RNFL thickness measurements are shown in Table 5. No significant differences were found between the groups ($P>0.05$ for all). The results of Pearson's correlation analysis showed that the RNFL thickness measurements were not correlated with the AHI ($P>0.05$ for all) (Table 4)

Table 2 Comparison of RNFL and GC-IPL thicknesses in OSAS and Control groups

	Mean ± SD		
	Control	*OSAS*	P-*value*[a]
RNFL			
Average	95.3 ± 9.3	94.2 ± 9.9	0.553
Superior	118.3 ± 15.4	116.5 ± 16.2	0.577
Nasal	72.9 ± 15.4	70.4 ± 12.3	0.226
Inferior	124.9 ± 16.2	122.8 ± 18.2	0.490
Temporal	65.8 ± 10.7	67.0 ± 12.5	0.466
GC-IPL			
Average	86.6 ± 4.7	81.4 ± 10.0	**0.005**
Minimum	82.4 ± 6.7	77.0 ± 11.5	**0.012**

Abbreviations: GC-IPL, ganglion cell-inner plexiform layer; OSAS, obstructive sleep apnea syndrome; RNFL, retina nerve fiber layer. [a]Student's *t*-test. Bold values are statistically significant for $P < 0.05$.

Discussion

In this prospective cross-sectional study, we investigated the RNFL thickness and ganglion cell thickness in patients with OSAS and compared the results with a control group. To our knowledge, this study included one of the largest number of subjects with OSAS in the published literature. Our results suggested that the GC-IPL thickness in patients with severe OSAS was significantly lower than that of normal subjects; also, there was a significant negative correlation between the AHI and both average and minimum GC-IPL thicknesses.

Several previous studies have indicated an association between OSAS and glaucoma.[5,9–14] Previous studies have reported that patients with OSAS had a high incidence and prevalence of glaucoma.[4,5,20] Moreover, patients with primary open-angle glaucoma or normal-tension glaucoma constitute a high-risk population for OSAS.[11,12,21] Conversely, a few studies have reported that the prevalence of glaucoma in patients with OSAS was similar to that in the general Caucasian population.[15,17]

Glaucomatous optic neuropathy is characterized by degeneration of retinal ganglion cells (RGCs) and resulting changes in the optic nerve head such as reduction in RNFL thickness. Numerous studies have shown that early detection of decreased peripapillary RNFL thickness has a diagnostic ability to detect early glaucoma.[22,23] It has also been reported that 40% of RGC axon loss may have already occurred before a visual field defect is detected on a standard automated perimetry.[24,25] Several previous studies have investigated RNFL parameters in OSAS patients.[5,14,20,26] While most studies have reported decreased RNFL thickness in patients with OSAS,[10,14,27–32] some other studies found no reduction[33,34] or relationship between the RNFL thickness and disease severity.[28,29] In our study, RNFL thickness was not significantly different between the OSAS groups

Table 3 Comparison of GC-IPL thickness in OSAS subgroups and Control group

GC-IPL	*Mean ± SD*				P-*value*[a]	*Pairwise comparison*[b]					
						Groups					
	Control (1)	*Mild OSAS (2)*	*Moderate OSAS (3)*	*Severe OSAS (4)*		*1–2*	*1–3*	*1–4*	*2–3*	*2–4*	*3–4*
Average	86.6 ± 4.7	84.7 ± 5.7	81.9 ± 9.0	77.8 ± 15.4	0.000	0.183	0.298	**0.000**	0.814	**0.004**	0.348
Minimum	82.4 ± 6.7	81.9 ± 5.7	76.7 ± 11.7	72.6 ± 17.2	0.000	0.675	0.226	**0.000**	0.724	**0.000**	0.623

Abbreviations: GC-IPL, ganglion cell-inner plexiform layer; OSAS, obstructive sleep apnea syndrome. Bold values are statistically significant for $P < 0.05$.[a] One-way ANOVA test. [b] Bonferroni–Dunn *post hoc* test.

Table 4 Pearson's correlation analyses between the AHI and RNFL and GC-IPL thicknesses in patients with OSAS

	RNFL					*GC-IPL*		
	Average	*Superior*	*Nasal*	*Inferior*	*Temporal*	*Average*	*Minimum*	
AHI								
r	− 0.002	− 0.068	− 0.062	− 0.001	0.105		**− 0.232****	**− 0.233****
P-value	0.965	0.214	0.261	0.981	0.055	**0.005**	**0.005**	

Abbreviations: AHI, apnea–hypopnea index; GC-IPL, ganglion cell-inner plexiform layer; OSAS, obstructive sleep apnea syndrome; RNFL, retinal nerve fiber layer. Bold values are statistically significant for $P < 0.05$.

Table 5 Comparison of RNFL thickness in OSAS subgroups and Control group

RNFL	*Mean ± SD*				
	Control	*Mild OSAS*	*Moderate OSAS*	*Severe OSAS*	P-*value*[a]
Average	95.3 ± 9.3	94.6 ± 9.8	94.7 ± 10.2	93.5 ± 10.0	0.829
Superior	118.3 ± 15.4	116.5 ± 16.0	118.9 ± 12.3	114.2 ± 19.7	0.495
Nasal	72.9 ± 15.4	69.9 ± 12.4	72.7 ± 13.4	68.8 ± 11.5	0.336
Inferior	124.9 ± 16.2	124.0 ± 17.7	121.8 ± 20.0	122.6 ± 17.9	0.869
Temporal	65.8 ± 10.7	67.5 ± 13.2	65.5 ± 11.4	68.0 ± 12.7	0.720

Abbreviations: OSAS, obstructive sleep apnea syndrome; RNFL, retina nerve fiber layer. [a] One-way ANOVA test.

and control group in all quadrants. Moreover, no significant correlation was observed between AHI and RNFL thicknesses. Similarly, a study performed in Turkish population reported that RNFL thickness did not differ between healthy and OSAS subjects.[35] Another study by Ferrandez *et al*[36] reported that RNFL thickness measured with OCT did not differ significantly between groups.

There may be several factors responsible for the varying results among the studies. First factor, which may lead to differences among the studies, is difference in mean age of the study participants. Two previous studies and this study found that AHI was not correlated with RNFL thickness. The mean age in these studies was under 52 years.[27,29] A study by Shiba *et al*[31] found a significant correlation between the AHI and RNFL thickness and the mean age in that study was 61.9 years old. It may be postulated that if the patients were older we would see a thinner RNFL thickness. Moreover, we do not know exactly how long the patients suffered from OSAS before diagnosis. RNFL thickness may decrease gradually over long periods of time with the OSAS. A second possible factor can be ethnical differences among the studies. Similar to our study, a study by Adam *et al*[35] investigated RNFL thickness in Turkish patients with OSAS and did not find any difference between OSAS and control groups.

Recently, in addition to the evaluation of peripapillary RNFL thickness, measurement of the macular ganglion cell thickness by OCT has been used in several ocular and neurological conditions, particularly glaucoma. There are limited studies on ganglion cell thickness in patients with OSAS, which may lead to glaucoma and reduction in RNFL thickness. Ferrandez *et al*[37] showed that neither GC-IPL nor GCL thickness were reduced in OSAS patients compared with healthy controls.[37] Conversely, Huseyinoglu *et al*[30] found lower ganglion cell thickness in patients with severe OSAS compared to the control group. In addition, there was a significant negative correlation between AHI and GC thickness. In our study, both average and minimum GC-IPL thicknesses were significantly reduced in patients with severe OSAS in

comparison with healthy controls. Also, both average and minimum GC-IPL thicknesses showed a significant correlation with OSAS severity (AHI). The thinner ganglion cell layer thickness without a decrease in RNFL thickness in our patients with OSAS may suggest that measurement of the GC-IPL thickness may be a more effective method to detect early structural progression than measurement of RNFL thickness. Some recent studies have reported that the measurement of ganglion cell layer thickness may have an advantage over measurement of RNFL thickness in detecting the early glaucomatous structural changes.[38,39] It may be expected that RNFL thickness may gradually decrease over time in patients with OSAS even if this hypothesis remains to be demonstrated.

The underlying pathophysiology of ocular complications in OSAS has not been clearly elucidated; however, it appears to be multifactorial and is closely linked to hypoxia.[40,41] In patients with OSAS, hypoxia caused by repetitive episodes of upper airway obstruction results in a subsequent of increase in $PaCO_2$ and decrease in PaO_2.[42] Long-term abnormal blood flow and hypoxia can lead to retinal layer cell damage. RGCs have been reported to be particularly sensitive to acute, transient, and mild systemic hypoxic stress.[43] It has also been indicated that RGCs are more sensitive to ischemia than the more distal retinal cells.[44,45] Retinal hypoxia leads to increase in some mediators including vascular endothelial growth factor, nitric oxide, glutamate, inflammatory cytokines, and reactive oxygen species. Enhanced expression of these mediators causes RGCs loss by disruption of blood retinal barrier, excitotoxicity, and increased accumulation of intracellular Ca^{2+}.[36]

The current study had some limitations. First, we evaluated the only retinal structural changes with OCT. The functional evaluation of retina should be analyzed in future studies using visual field testing with 10-2 program and pattern electroretinography in these subjects. Also, we do not know how long our patients suffered from OSAS before their diagnosis; peripapillary RNFL and GC-IPL thickness may alter gradually over long periods of time with the disease. A prospective longitudinal study is required for a better understanding of the peripapillary RNFL and GC-IPL thickness changes in OSAS patients.

In conclusion, we observed that severe OSAS patients had lower GCC thickness compared to mild OSAS patient or control group. We also found significant correlations between the severity of apnea (AHI) and GCC thickness. Future studies including monitoring of these participants with RNFL thickness and visual field measurements may indicate the role of this study in detection of early glaucomatous changes in patient with OSAS.

Summary

What was known before

- Several previous studies have reported an association between OSAS and glaucoma. Also most studies have reported decreased RNFL thickness in patients with OSAS.

What this study adds

- This study suggested that the ganglion cell thickness in patients with severe OSAS was significantly lower than that of normal subject; also, there was a significant negative correlation between the OSAS severity and ganglion cell thicknesses.

Conflict of interest

The authors declare no conflict of interest.

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