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MISCELLANEOUS

Retinal and optic nerve evaluation by optical coherence tomography in adults with obstructive sleep apnea–hypopnea syndrome (OSAHS)

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Abstract
Objective To assess the peripapillary retinal nerve fiber layer (RNFL) thickness, optic nerve head (ONH) morphologic parameters, and macular thickness and volume in patients affected by obstructive sleep apnea–hypopnea syndrome (OSAHS).
Methods This prospective, observational case-control study consisted of 96 eyes of 50 OSAHS patients (mean age of 50.9±12.4 years, best-corrected visual acuity ≥20/20, refractive error less than 3 spherocylindrical diopters, and intraocular pressure <21 mmHg) who were enrolled and compared with 64 eyes of 33 age-matched controls. Peripapillary RNFL thickness, ONH parameters, macular thickness and volume were measured by optical coherence tomography (OCT).
Results OSAHS patients showed a significant reduction of the nasal quadrant RNFL thickness (74.7±15.8 μm) compared with those values observed in control patients (81.1±16.6 μm, p=0.047, Student's t-test). No differences in peripapillary RNFL thickness were observed when dividing the OSAHS group in accordance with disease severity. Vertical integrated rim area (VIRA) (0.67±0.41 mm^3 in OSAHS vs 0.55±0.29 mm^3 in controls; p=0.043, Student's t-test), horizontal integrated rim width (HIRW) (1.87±0.31 mm^2 in OSAHS vs 1.8±0.25 mm^2 in controls; p=0.039, Student's t-test) and disc area (2.74±0.62 mm^2 in OSAHS vs 2.48±0.42 mm^2 in controls; p=0.002, Student's t-test) showed significant differences, all of them being higher in the OSAHS group. Severe OSAHS had significant higher disc area (2.8±0.7 mm^2) than controls (2.5±0.4 mm^2; p=0.016, ANOVA test). Temporal inner macular thickness was significantly higher in mild–moderate OSAHS patients (270±12 μm) than in severe OSAHS patients (260±19 μm; p=0.021, ANOVA test).
Conclusions OSAHS patients showed decreased peripapillary nasal RNFL thickness, and increased ONH area and volume parameters when they were evaluated by OCT. These findings suggest that neuronal degeneration might be present in the retina of OSAHS patients, as previously observed in some neurodegenerative disorders

Keywords Macular volume · Optical coherence tomography · OCT · Retinal nerve fiber layer thickness · Obstructive sleep apnea–hypopnea syndrome · OSAHS

The authors confirm that they were fully involved in the study and preparation of the manuscript, and that the material within has not been and will not be submitted for publication elsewhere. The authors have full control of all primary data, and they agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data upon request. The authors have no financial interests in any aspect of this study.

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Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is part of a broad group of disorders known as "sleep-related

breathing disorders". OSAHS is characterized by brief episodes of complete or partial upper airway collapse during sleep, causing an increased thoraco-abdominal effort and a decreased arterial oxygen saturation, leading to an arousal response [1] which takes the form of apneas and periodic hypopneas during sleep. This produces an excessive daytime sleepiness. There are a great deal of evidence that local and systemic inflammation play an important role in the pathogenesis of OSAHS, contributing to anatomic narrowing of the upper airway, increased collapsibility of the airway tissues, and abnormalities in reflexes that affect upper respiratory tract caliber and pharyngeal inspiratory muscle function [2].

OSAHS has recently been associated with numerous ophthalmological disorders, such as floppy eyelid syndrome, visual field defects, retinal vein occlusion, central serous chorioretinopathy, and certain optic nerve dysfunctions [3–5]. Thus, papilledema and increased intracranial pressure have been reported in OSAHS patients [6, 7], improving after continuous positive airway pressure (CPAP) treatment [8, 9]. Non-arteritic anterior ischemic optic neuropathy has also been reported to be associated with OSAHS [10]. Likewise, an increased incidence of glaucoma in OSAHS patients is assumed [11–14]. Nevertheless, the pathogenesis of optic disc damage in OSAHS is complex and remains unknown. Frequent episodes of nocturnal hypoxemia would compromise optic nerve perfusion and oxygenation, leading to optic neuropathy [15]. Clinical features of OSAHS have inspired studies about brain structural abnormalities in this disease. Magnetic resonance imaging studies have reported a loss of gray and white matter in certain brain areas, suggesting a premature degeneration of the central nervous system in patients suffering from OSAHS [16, 17].

Optical coherence tomography (OCT), a relatively new noninvasive imaging technique, provides reproducible, high-resolution cross-sectional imaging of the retinal nerve fiber layer (RNFL) and optic nerve head (ONH) topography, providing an objective tool to diagnose axonal damage. OCT is used in various ophthalmological disorders, including glaucoma [18] and macular diseases [19]. Likewise, a significant reduction in the peripapillary RNFL thickness has been reported in patients with various neurologic disorders [20], such as multiple sclerosis [21, 22], Alzheimer's disease [23, 24], Parkinson's disease [25, 26], and schizophrenia [27], suggesting that this technology might also prove useful in other neurodegenerative diseases. Recently, a decreased RNFL thickness measured with OCT has been found in patients with moderate/severe OSAHS [28].

The goals of our study were to determine, by using OCT, the differences in the ONH parameters, peripapillary RNFL thickness, macular thickness and volume, between OSAHS patients and control subjects, as well as to assess whether a correlation exists between the OCT measurements and the clinical severity of the disease.

Material and methods

Ninety-six eyes from 50 patients (41 males and nine females) with OSAHS were consecutively recruited in the Department of Otolaryngology at the Miguel Servet University Hospital in Zaragoza, Spain. The selected patients, whose age was 50.9± 12.4 years (14–75), have a newly discovered and previously untreated mild to severe OSAHS diagnosed according to clinical features and an apnea–hypopnea index (AHI) greater than 4. Before OSAHS was confirmed, the patients completed a questionnaire concerning epidemiological data (age, height, weight, co-morbidities, smoking, previous treatment, and past surgeries) and information about symptoms such as loud snoring, observed apnea, or excessive daytime sleepiness. The most common vascular risk factors, hypertension, diabetes, and hyperlipidaemia, were studied and treated if necessary. All smoker OSAHS patients were encouraged to stop the habit. After appropriate information, written informed consent of all subjects was obtained.

Every OSAHS patient was diagnosed with a full sleep study during an entire attended night. This investigation consisted of continuous polygraphic recording of two electroencephalographic leads, right and left electrooculographic leads, and chin electromyography for sleep staging. Ribcage and abdominal motion were monitored by inductive plethysmography (Alice 4, Philips, Eindhoven, Holland), airflow by thermistor (Ambulatory Monitoring, Inc., Ardsley, NY, USA), and arterial oxyhaemoglobin saturation by finger pulse oximetry (OhmedaBiox 3700, Ohmeda, Boulder, CO, USA). Sleep stage scoring was done for 30-s intervals by trained technicians according to standard criteria [29]. Apnea was defined as the complete cessation of airflow, and hypopnea as a discernible reduction in airflow or thoraco-abdominal excursion lasting for 10 s or more, accompanied by a decrease in oxygen saturation of at least 4 %. AHI was defined as the total number of apneas and hypopneas per hour during sleep. In patients with a confirmed diagnosis, an individualized multidisciplinary treatment was initiated according to the sleep study, the severity of clinical symptoms and signs, the exploration of the superior airway, and the wishes of the patient [30].

The control group was formed by 64 eyes of 33 age-matched healthy control subjects (19 males and 14 females), with a mean age of 49.1±14.3 years (15–74), who were recruited from the Department of Ophthalmology at the Lozano Blesa University Clinic Hospital in Zaragoza, Spain. The same epidemiological data as in the OSAHS group were collected. Smoking habit and vascular risk factors were treated in the same way.

Patients and controls were subsequently referred for a comprehensive ophthalmological examination at the ophthalmologic department at "Lozano Blesa" University Clinic Hospital from December 2010 to December 2011. Patients who had a history of stroke with central apnea, chronic uveitis, antiglaucomatous drug usage, optic neuropathy, and previous ocular trauma or surgeries were excluded from this study. After appropriate information, written informed consent of all subjects was obtained. The research followed the tenets of the Declaration of Helsinki, and the protocol was approved by the local ethics committee.

All OSAHS patients and control subjects underwent a complete ophthalmologic examination, including assessment of best-corrected visual acuity (BCVA), ocular motility, pupillary reflexes, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, Humphrey automated visual field (HVF) examination, and dilated fundus examination. The examiners were masked to the diagnosis. All participants had a BCVA of 20/20 or better with a refractive error lower than 3 spherical diopters and 2 diopters of astigmatism. Eyes with HVF defects compatible with glaucoma (nasal step, paracentral or arcuate scotomas, or arcuate blind spot enlargement), applanation intraocular pressure (IOP) >21 mmHg, posterior pole pathology such as macular degeneration or diabetic retinopathy, or patients with media opacification such as cataract or vitreous hemorrhage which prevented ocular and OCT examination, were excluded.

OCT was performed with the Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) following 1 % tropicamide instillation for dilation of the pupils. Only high-quality images (signal strength ≥7) were included. Each patient underwent scans to measure peripapillary RNFL thickness, ONH parameters, and macular thickness and volume at the same visit. Peripapillary RNFL thickness was automatically calculated by the fast RNFL algorithm. Three 360° circular scans with a diameter of 3.4 mm centered on the optic disc were performed. The software allows the mapping of the thickness data according to both quadrant-by-quadrant and clock hour analyses. We considered the average values of three different measurements per quadrant (superior, inferior, nasal and temporal): the overall data obtained in all quadrants were identified as overall RNFL thickness. ONH measurements were obtained by the fast optical disc scanning protocol, which consists of six radial scans centered on the ONH. ONH parameters were automatically calculated, including vertical integrated rim area (VIRA, measurement of neurorretinal rim volume, in mm^3), horizontal integrated rim width (HIRW, measurement of neurorretinal rim area, in mm^2), disc area, cup/disc area ratio, horizontal cup/ disc ratio, and vertical cup/disc ratio. Macular thickness measurements were obtained by the fast macular thickness protocol, which consists of six radial scans (each 6 mm) in a spoke-like pattern centered on the fovea, with each radial scan spaced 30° apart. To fill the gaps between scans, the OCT uses interpolation. Stratus OCT software calculates retinal thickness as the distance between the first signal from the vitreoretinal interface and the signal from the anterior boundary of the retinal pigment epithelium. The map is composed of nine sectorial thickness measurements in three concentric circles with diameters of 1 mm, 3 mm, and 6 mm. The area bounded by the outer (6-mm) and middle (3-mm) circles forms the outer ring, and the area bounded by the middle (3-mm) and inner circles (1-mm) forms the inner ring. The central 1-mm circular region represents the foveal area. Total average macular thickness, average macular thicknesses in the inner (1–3 mm) and outer (3–6 mm) rings, and the central 1-mm fovea thickness were analyzed in the study. Total macular volume was calculated automatically by the OCT software (Fig. 1).

Statistical analysis

Data analysis was conducted using SPSS software version 19.0 (SPSS, Inc, Chicago, IL, USA). Values were presented as mean ± standard deviation (SD) and expressed in microns (μm) for the peripapillary RNFL thickness and macular retinal thickness, and in mm^3 for macular volume. Qualitative differences between the study variables were assessed using Pearson's chi-squared test. Discriminant analysis, with Wilks' lambda determination, was performed in order to evaluate parameters that better define the cases. The relationship between AHI and ophthalmologic significant variables was evaluated using Pearson's correlation coefficient. A p value <0.05 was considered statistically significant.

We conducted two separate analyses. In the first one, mean values of the studied variables obtained in all OSAHS patients were compared with those obtained in the control group (only taking into account the presence of OSAHS, regardless of severity), the two-sample Student t-test was used for determining whether the values of a particular quantitative variable differ between OSAHS and the control eyes.

In the second analysis, the OSAHS patients sample was divided according to the severity of OSAHS (measured by AHI) into two groups: those with mild–moderate OSAHS (group 1, AHI ≥5 and <30); and those with severe OSAHS (group 2, AHI ≥30). Quantitative differences between the studied variables in the three groups were compared using one-way ANOVA test. Post-hoc analyses with Bonferroni adjustments were performed. We joined mild and moderate OSAHS patients, assuming that severe OSAHS patients would show more differences when compared with the control group.

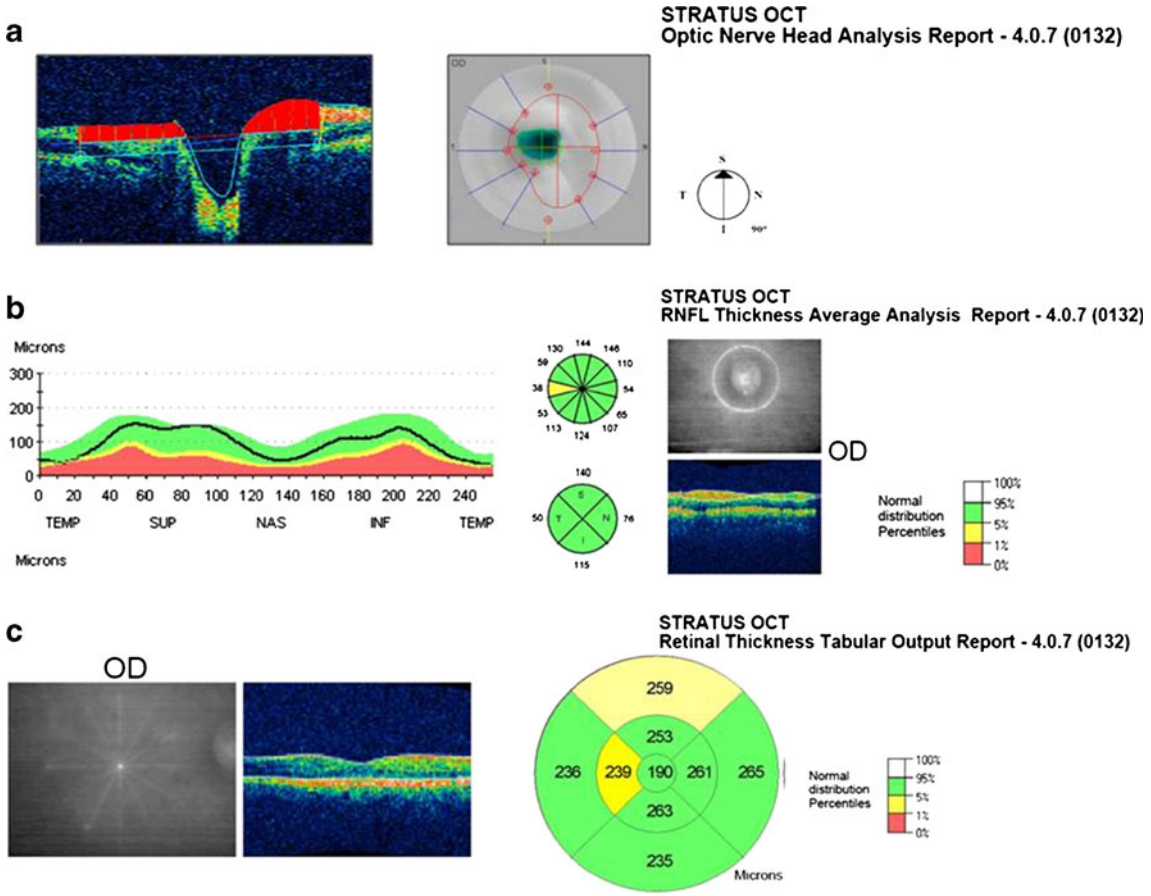

Fig. 1 **a** Optic nerve head examination. Vertical cross-section representation. **b** Retinal nerve fiber layer analysis report. Average values (microns) per quadrant (*S* superior. *N* nasal. *I* inferior. *T* temporal). **c** Macular thickness report; nine sectorial thickness measurements in three concentric circles with diameters of 1 mm, 3 mm, and 6 mm

Results

All the patients screened from the otolaryngology department were informed in advance, and asked if they wanted to participate in the study. They were warned that to agree with the study did not necessarily imply participating in it, depending on the exclusive ophthalmologic findings. The reasons for not participating in the study were problems for medical visits (due to physical or mental condition) or disagreement with the study. Of 63 consecutive OSAHS patients who accepted to participate, 51 (80.9 %) were included in the study, whereas 12 (19.1 %) were excluded. Eight subjects were excluded because of refractive defect greater than 3 spherical diopters or 2 diopters of astigmatism, two with mature cataracts which prevented ocular and OCT examination, and two other patients because of diabetic macular edema and non-exudative age-related macular degeneration respectively. Three of the 86 people (3.5 %), including controls and cases, did not fulfill the quality criteria for OCT. Finally, 83 Caucasian individuals were included in the analysis, 50 OSAHS patients and 33 healthy controls, whose demographic data are summarized in Table 1. Both eyes of each patient were included, except when an exclusion criteria appeared in one eye, assuming that OSAHS influence could be asymmetric [31, 32]. Age showed no statistically significant difference between both groups (p=0.401, Student's t-test). In both groups, more men than women were enrolled; although the difference was statistically significant (p<0.05; chi-squared test), gender has no effect on RNFL evaluation as previously mentioned [33]. BCVA was similar in both groups (p=0.577). Body mass index (BMI) was not matched. The mean BMI was higher in SAOS patients (29.6±4.5) than that in controls (24.9±4.3) (p<0.05, Student's t-test). Nevertheless, no significant differences in vascular risk factors and prevalence of smoking habit between cases and controls were found (p=0.09, chi-squared test). Table 2 summarizes polysomnographic data in OSAHS patients according to severity.

First analysis: OCT parameters in OSAHS patients versus non-OSAHS individuals

Table 3 shows the results of IOP, HVF indices, optic disc parameters, and macular and peripapillary RNFL thickness

Table 1 Demographic data of OSAHS patients and controls

	Total OSAHS cases	Mild–moderate OSAHS cases	Severe OSAHS cases	Controls
Number of patients	50	19	31	33
Age (years)	50.9±12.4 (14–75)	50.7±14.0 (14–71)	51.0±11.5 (18–75)	49.1±14.3 (15–74)
Sex				
Male	41 (82 %)	16 (84.2 %)	25 (80.6 %)	19 (57.6 %)
Female	9 (18 %)	3 (15.8 %)	6 (19.4 %)	14 (42.4 %)

measurements in OSAHS patients vs controls. IOP values were higher in OSAHS group than those in controls ($p<0.001$, Student's *t*-test). Humphrey visual field results, such as visual field index (VFI), mean deviation (MD), and pattern standard deviation (PSD), were significantly altered in patients with OSAHS patients as compared with the control group ($p=0.009$, $p=0.002$, $p=0.014$ respectively by Student's *t*-test). VIRA, HIRW, and disc area values were higher in the OSAHS group than those in controls. These differences were statistically significant ($p<0.05$, Student's *t*-test). Only the nasal quadrant of the peripapillary RNFL showed a decreased thickness in OSAHS patients (74.7± 15.8 μm) compared with that in control subjects (81.1± 16.6 μm) ($p=0.016$, Student's *t*-test). No statistically significant difference was observed regarding the macular thickness and volume ($p>0.05$; Student's *t*-test).

Discriminant analysis included disc area and peripapillary RNFL thickness of the nasal quadrant as differentiating variables, with a lambda value of 0.958 ($p=0.011$) and 0.929 ($p=0.004$) respectively. Standardized canonical discriminant function coefficients showed that disc area was the most important predictor variable (0.747). Thus, the larger the disc area in the discriminant function, the greater the tendency to classify the subject as OSAHS. Peripapillary RNFL thickness of the nasal quadrant had a negative value (−0.652), which implies that if patients with equal scores in the remaining variables have a thicker peripapillary RNFL in nasal quadrant, they will show a lower score in the discriminant function, and therefore they will be more easily classified as controls. AHI showed no correlation with any of the significant variables: VIRA ($r=0.045$, $p=0.672$, $n=96$), HIRW ($r=0.082$, $p=0.439$, $n=96$), disc area ($r=0.063$, $p=0.554$, $n=96$), and peripapillary RNFL thickness in nasal quadrant ($r=-0.061$, $p=0.565$, $n=96$).

Second analysis: OCT parameters in mild–moderate OSAHS versus severe OSAHS patients

When dividing the OSAHS group according to its severity in mild/moderate and severe cases, age showed no statistically significant difference between the different pairs: controls/-mild–moderate OSAHS (49.1±14.3 years vs 50.7±14.0 years respectively; $p>0.05$, ANOVA test); controls/severe OSAHS (49.1±14.3 years vs 51.0±11.5 respectively; $p>0.05$, ANOVA test); mild–moderate OSAHS/severe OSAHS (50.7 ±14.0 years vs 51.0±11.5 respectively; $p>0.05$, ANOVA test).

HVF data are shown in Table 4. VFI and PSD were not significantly altered in patients with mild–moderate or severe OSAHS as compared with the control group. MD value was significantly altered in the mild–moderate OSAHS group as compared with controls ($p=0.005$, ANOVA test).

Table 4 also contains mean values of IOP, optic disc measurements, and macular and peripapillary RNFL thickness measurements in OSAHS patients, classified according to IAH. Severe OSAHS eyes revealed higher disc area values than those in control group ($p=0.016$, ANOVA test). No differences in IOP values were found among the three groups. Temporal inner macular thickness was significantly higher in mild–moderate OSAHS patients compared to the severe OSAHS group. No differences in peripapillary RNFL thickness among the three groups were observed. Only the nasal quadrant in the severe OSAHS group showed an almost statistically significant decrease when comparing with controls ($p=0.057$).

Discriminant analysis just included temporal inner macular thickness as a differentiating variable between individuals with OSAHS and controls, with a lambda value of 0.532 ($p<0.001$). The standardized canonical discriminant function coefficients showed a value of −0.400. Thus, patients with equal scores in the remaining variables, but

Table 2 Comparison of polysomnographic data in OSAHS patients according to the disease severity

	Mild–moderate OSAHS cases	Severe OSAHS cases	*P* value[a]
AHI	19.5±8.2 (6–29)	64.6±31.3 (30–136)	<0.01
BMI (kg/m^2)	29.3±4.5 (24.6–41.7)	29.9±4.9 (24–41)	0.507
DeS index	12.9±7.4 (1–24)	42.4±22.6 (10–95)	<0.01
mO2	93.7±1.5 (91–96)	92±2.5 (86–95)	0.016
LSat	83.6±8.3 (53–92)	78.31±8.8 (55–92)	0.016

AHI apnea–hipopnea index; *BMI* body mass index; *DeS Index* desaturation index; *mO2* mean saturation of oxygen; *LSat* lowest oxygen saturation

[a] Mann–Whitney U test

Table 3 Comparison of IOP, Humphrey visual field (HVF) indices, optic nerve head (ONH) values, macular thickness, and volume and peripapillary RNFL thickness measurements between OSAHS patients and controls

	OSAHS	Controls	*P* value[a]
IOP (mmHg)	16. 8±2.9 (11–22)	15.2±1. 6 (12–18)	0.003
HVF			
VFI	98.5±2.3 (87–100)	99.2±0.8 (97–100)	0.009
MD	−0.64±1.38 (−4.87 to 1.65)	0.07±1.01 (−2.78 to 1.79)	0.002
PSD	1.77±1.09 (0.9–8.46)	1.47±0.26 (1.04–2.03)	0.014
Optic disc parameters			
VIRA (mm^3)	0.67±0.41 (0.09–2.31)	0.55±0.29 (0.18–1.23)	0.043
HIRW (mm^2)	1.87±0.31 (1.11–2.56)	1.77±0.25 (1.34 – 2.45)	0.039
Disc area (mm^2)	2.7±0.6 (1.7–5)	2.5±0.4 (1.6–3.8)	0.002
Cup area (mm^2)	0.73±0.81 (0.03–5.01)	0.57±0.44 (0.01–2.79)	NS
Rim area (mm^2)	2.0±0.7 (0–3.4)	1.9±0.5 (0–3.2)	NS
C/D area	0.25±0.23 (0.01–1)	0.23±0.18 (0.005–1)	NS
C/D horizontal	0.48±0.21 (0.1–1)	0.48±0.17 (0.080–1)	NS
C/D vertical	0.43±0.2 (0.08–1)	0.42±0.16 (0.055–1)	NS
Macular thickness (μm)			
IMR	274.9±15.9 (235–312)	274.6±15.4 (249–312)	NS
EMR	237.8±12.3 (210–264)	238.5±13.2 (211–272)	NS
Fovea	208.5±27.9 (137–291)	204.5±23.4 (161–254)	NS
TIM	264.3±17.6 (166–299)	264.8±15.7 (237–296)	NS
SIM	279±15.2 (242–316)	276.7±16.5 (242–317)	NS
NIM	279.2±19.1 (223–326)	279.8±16.4 (255–323)	NS
IIM	277.1±18.7 (231–329)	277.1±19.5 (203–313)	NS
TOM	220.7±12.5 (192–253)	220.4±13.5 (193–254)	NS
SOM	239.9±12.5 (213–268)	240.1±14.1 (212–282)	NS
NOM	258.6±16.6 (208–300)	260.8±16.6 (227–305)	NS
IOM	231.9±15.6 (199–278)	232.6±15.6 (198–259)	NS
Macular volume (mm^3)	6.92±0.37 (6.07–7.77)	6.92±0.38 (6.21–7.92)	NS
RNFL thickness(μm)			
Average	98.2±10.4 (75.5–125.3)	99.9±9.3 (81.2–120.2)	NS
Superior	124.8±17.4 (80–162)	123.2±15.1 (87–159)	NS
Nasal	74.7±15.8 (40–117)	81.1±16.6 (52–126)	0.016
Inferior	123.3±16.9 (84–166)	125.5±15.7 (99–175)	NS
Temporal	70.1±13.2 (41–100)	69.9±12.1 (47–97)	NS

IOP intraocular pressure; *VFI* visual function index; *MD* mean deviation; *PSD* pattern standard deviation; *VIRA* vertically integrated rim area (mm^3); *HIRW* horizontally integrated rim width (mm^2); *C/D* cup/disk; *IMR* average thickness inner macular ring; *EMR* average thickness external macular ring; *TIM* temporal inner macular thickness; *SIM* superior inner macular thickness; *NIM* nasal inner macular thickness; *IIM* inferior inner macular thickness; *TOM* temporal outer macular thickness; *SOM* superior outer macular thickness; *NOM* nasal outer macular thickness; *IOM* inferior outer macular thickness. *RNFL* retinal nerve fiber layer; *NS* non-significant

[a]Student's *t*-test

thicker temporal inner macula, will be more easily classified as controls.

We found no correlation between IAH and the significant different parameters when the OSAHS group was divided according to its severity. Disc area in severe OSAHS (r=0.071, p=0.606, n=58); temporal inner macular thickness in severe OSAHS (r=0.11, p=0.416, n=58); temporal inner macular thickness in mild–moderate OSAHS (r=0.325, p=0.057, n=38).

Discussion

During sleep, apneic episodes with consequent drop in oxygen saturation lead to the activation of the adrenergic system, proinflammatory mechanisms, endothelial dysfunction, oxidative stress, procoagulant mechanisms, and metabolic deregulation [34]. There is some evidence that OSAHS is a risk factor for neurovascular and cardiovascular diseases. Arterial hypertension, cardiac arrhythmia and/or ischemia, congestive heart failure, and cerebrovascular disease are events more likely in the presence of the obstructive sleep disturbance [35, 36]. This vascular phenomenon may compromise optic nerve perfusion and oxygenation, ultimately leading to optic neuropathy.

Several authors have reported a higher prevalence of glaucomatous neuropathy in OSAHS patients [7, 13], characterized by increased size of the optic disc cup and associated thinning of peripapillary RNFL. Moreover, some authors have reported a significant presence of visual field

Table 4 Comparison of IOP, Humphrey visual field (HVF) indices, optic nerve head (ONH) values, macular thickness and volume and peripapillary RNFL thickness measurements between controls, mild–moderate OSAHS patients and severe OSAHS patients

	Controls	Mild–moderate OSAHS	Severe OSAHS	*P* value[a]	
IOP (mmHg)	15.2±1.6 (12–18)	16.9±2.4 (14–22)	16.7±3.1 (11–21)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
HVF					
VFI	99.2±0.8 (97–100)	98.2±2.8 (87–100)	98.6±1.9 (90–100)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
MD	0.07±1.01 (−2.78 to 1.79)	−0.89±1.5 (−4.87 to 1.2)	−0.47±1.3 (−4.06 to 1.65)	Controls/mild–moderate	0.005
				Controls/severe	NS
				Mild–moderate/severe	NS
PSD	1.47±0.26 (1.04– 2.03)	1.67±0.6 (0.96–3.4)	1.84±1.3 (0.9–8.46)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Disc parameters					
VIRA (mm^3)	0.55±0.29 (0.19–1.24)	0.6±0.4 (0.1–2.1)	0.67±0.39 (0.11–2.31)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
HIRW (mm^2)	1.8±0.3 (1.3–2.5)	1.9±0.3 (1.1–2.5)	1.9±0.3 (1.2–2.6)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Disc area (mm^2)	2.5±0.4 (1.6–3.8)	2.7±0.6 (1.7–4)	2.8±0.7 (1.7–5)	Controls/mild–moderate	NS
				Controls/severe	0.016
				Mild–moderate/severe	NS
Cup area (mm^2)	0.6±0.4 (0.0–2.8)	0.9±0.8 (0.0–3.3)	0.6±0.8 (0.0–5)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Rim area (mm^2)	1.9±0.5 (0–3.2)	1.8±0.7 (0.0–3.1)	2.1±0.7 (0–3.4)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
C/D area	0.2±0.2 (0.0–1)	0.3±0.3 (0.0–1)	0.2±0.2 (0.0–1)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
C/D horizontal	0.5±0.2 (0.1–1)	0.5±0.2 (0.1–1)	0.5±0.2 (0.1–1)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
C/D vertical	0.4±0.2 (0.1–1)	0.5±0.2 (0.1–1)	0.4±0.2 (0.1–1)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Macular thickness (μm)					
IMR	274.6±15.4 (249–312.2)	279.7±13.9 (252.7–312.7)	271.9±16.6 (235–311)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
EMR	238.5±13.2 (211.5–272.5)	239.2±10.3 (213–259)	236.9±13.4 (210.2–264)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Fovea	204.5±23.4 (161–254)	214.3±22.1 (186–265)	204.9±30.7 (137–291)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS

Table 4 (continued)

	Controls	Mild–moderate OSAHS	Severe OSAHS	*P* value[a]	
TIM	264.8±15.7 (237–296)	270.4±12.5 (251–299)	260.6±19.2 (166–296)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	0.021
SIM	276.7±16.5 (242–317)	283.1±14.2 (257–316)	276.5±15.4 (242–311)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
NIM	279.8±16.4 (255–323)	283.5±15.5 (253–323)	276.6±20.7 (223–326)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
IIM	277.1±19.5 (203–313)	281.9±16.5 (250–323)	274.2±19.6 (231–329)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
TOM	220.4±13.5 (193–254)	223.2±10 (203–248)	219.2±13.7 (192–253)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
SOM	240.1±14.1 (212–282)	242.6±10.8 (220–266)	238.3±13.2 (213–268)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
NOM	260.8±16.6 (227–305)	258.6±14.2 (227–288)	258.6±18 (208–300)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
IOM	232.6±15.6 (198–259)	232.4±14.5 (199–268)	231.7±16.3 (202–278)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Macular volume (mm^3)	6.92±0.38 (6.2–7.92)	6.98±0.33 (6.29–7.69)	6.88±0.39 (6.07–7.77)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
RNFL thickness (μm)					
Average	99.9±9.3 (81.2–120.2)	99.5±11.3 (75.5–125.3)	97.4±9.9 (76–117.9)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Superior	123.2±15.1 (87–159)	125.4±15.3 (85–160)	124.4±18.6 (80–162)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Nasal	81.1±16.6 (52–126)	75.5±17.2 (40–117)	74.2±14.7 (45–115)	Controls/mild–moderate	NS
				Controls/severe LIMITE	0.057
				Mild–moderate/severe	NS
Inferior	125.5±15.7 (99–175)	126.5±18.9 (84–166)	121.3±15.5 (84–163)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS
Temporal	69.9±12.1 (47–97)	70.6±11.9 (50–96)	69.8±14 (41–100)	Controls/mild–moderate	NS
				Controls/severe	NS
				Mild–moderate/severe	NS

IOP intraocular pressure; *VFI* visual function index; *MD* mean deviation; *PSD* pattern standard deviation; *VIRA* vertically integrated rim area (mm^3); *HIRW* horizontally integrated rim width (mm^2); *C/D* cup/disk; *IMR* inner macular ring; *EMR* external macular ring; *TIM* temporal inner macular thickness; *SIM* superior inner macular thickness; *NIM* nasal inner macular thickness; *IIM* inferior inner macular thickness; *TOM* temporal outer macular thickness; *SOM* superior outer macular thickness; *NOM* nasal outer macular thickness; *IOM* inferior outer macular thickness; *RNFL* retinal nerve fiber layer; *NS* non-significant

[a] One-way ANOVA test

defects in patients with OSAHS, even with an improvement of this defects following treatment with CPAP in one OSAHS patient [37, 38]. This glaucomatous functional loss is thought to be preceded by thinning of RNFL in some years [39]. Thus, the first quantifiable sign of glaucomatous neuropathy in OSAHS patients is an axonal loss measured by OCT. In our study, we just included patients with normal IOP values (less than 22 mmHg), normal gonioscopy, and no perimetric evidence of glaucomatous neuropathy, in order to assess an hypothetical reduction of peripapillary RNFL thickness secondary to the respiratory disorder. Despite this, we found significantly higher IOP values as well as alterations in indices of VF in OSAHS patients compared to controls. In the present study, as in previous studies [15, 28, 40], and after excluding patients with glaucoma, nasal peripapillary RNFL thickness was found to be decreased in patients harboring OSAHS compared with controls. Moreover, several ONH parameters such as disc area, VIRA, and HIRW were increased in OSAHS patients compared to the controls. Therefore, patients with OSAHS not harboring glaucoma might already show some signs of a neuronal degeneration.

Peripapillary RNFL thickness measurement reflects neuronal axons, and would allow quantification of ganglion cell axonal loss. Macular thickness and volume values would reflect neurons, including bodies of retinal ganglion cells, and allowing quantification of neuronal loss. Retinal ganglion cells have been reported to be particularly sensitive to mild systemic hypoxic stress [41]. Thus, in hypoxic conditions, cell death has been classified as apoptotic or necrotic. The last one presents swelling of cell body, disruption of plasma membrane, and alterations in nuclear DNA [42]. It is possible that this nuclear swelling could induce an increased macular thickness preceding atrophy secondary to neuron death (reflected as a decreased peripapillary RNFL thickness). In our results, temporal inner macular thickness was significantly higher in mild–moderate OSAHS patients compared to severe OSAHS patients and controls. This fact would support the attractive hypothesis that a previous inflammatory edema, with an increased macular thickness, might be an expression of VEGF, nitric oxide, and other proinflammatory mediators in early stages of OSAHS, preceding a final stage with loss of neuronal population and subsequent functional repercussion.

The significant increase in morphological ONH parameters, such as VIRA, HIRW, and disc area, in OSAHS patients compared with those in controls, especially disc area in severe OSAHS patients, might be justified by a hypothetical and slight optic nerve swelling caused by intracranial vascular dysfunction. Moreover, according to the discriminant analysis, disc area is the most distinguishing feature between patients and controls. Purvin et al. analyzed the relationship between intracranial pressure, papilledema, and OSAHS [6]. They suggested episodic hypoxia and hypercapnia as cause of papilledema in the OSAHS group, which would be secondary to a cerebral vasodilation phenomenon. It seems that frequent changes in the oxygenation of OSAHS patients would induce vascular problems in cerebral autoregulation. This fact might imply changes in intracranial volume due to vasodilation and increased brain water content [7]. Likewise, Lee et al. found an improvement of idiopathic intracranial hypertension when nocturnal oxygenation treatment was established [8]. O'Donoghue et al. [9] reported a 4 % decrease in total brain volume following treatment with positive pressure nocturnal oxygen in patients with OSAHS. The perpetuation of nerve fiber layer swelling could lead to a nerve fiber loss, with the consequent thinning of RNFL as the disease progresses. This would be consistent with the nasal peripapillary RNFL nasal thinning observed in severe OSAHS group. Future studies comparing the RNFL thickness before and after treatment of sleep apnea might add more information at this point.

A major limitation of the present study is the relatively small sample size, mainly when OSAHS patients were divided into two types according to their severity. Furthermore, a referral bias could be present because patients were referred for sleep disorder and, therefore, they might not be representative of the entire OSAHS population, mostly undiagnosed. In fact, we were not able to determine the exact duration of the respiratory disease. It is possible that the greater the severity and longer duration of the hypoxia, the greater the RNFL alterations.

In conclusion, these findings suggest that peripapillary RNFL thickness and optic disc area might be used as a biomarker to early diagnosis and classification of OSAHS patients. Further studies would be necessary to determine the usefulness of these OCT measurements in this disorder.

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