



Thinning of the inner and outer retinal layers, including the ganglion cell layer and photoreceptor layers, in obstructive sleep apnea and hypopnea syndrome unrelated to the disease severity

Soner Guven · Deniz Kilic · Omer Faruk Bolatturk

Received: 17 September 2020 / Accepted: 18 June 2021 / Published online: 25 June 2021
© The Author(s), under exclusive licence to Springer Nature B.V. 2021

Abstract

Purpose The aim of this study was to analyze the segmented layers of the macula in patients with obstructive sleep apnea and hypopnea syndrome (OSAS) using spectral domain optical coherence tomography (SD-OCT).

Material and Methods This single-center, cross-sectional study included 31 OSAS patients and 31 age- and gender-matched control subjects. SD-OCT and overnight polysomnography were performed on all participants. The OSAS patients were categorized according to disease severity (mild, moderate, severe). The groups were compared in respect of each segmented macular layer through the use of segmentation software on SD-OCT. Total retinal thickness (RT), peripapillary retina nerve fiber layer (pRNFL) thickness, central corneal thickness (CCT) and intraocular pressure (IOP) values were also compared between the groups.

Results Mean CCT ($p:0.015$) and nasal pRNFL values ($p:0.042$) were lower and mean IOP was higher ($p:0.018$) in OSAS patients than in the control group. The statistical analysis revealed significantly thinner

total RT, inner retinal layers (IRL), outer retinal layers (ORL), photoreceptor layers (PRL) and ganglion cell layer (GCL) thicknesses in the OSAS groups compared to healthy subjects. No significant differences were found between the three OSAS subgroups in all segmented macular layers and pRNFL measurements. **Conclusion** The results of this study showed relatively thinner nasal pRNFL, total RT, IRL, ORL, PRL and GCL layers in OSAS patients compared to healthy subjects. Moreover, this thinning of the segmented layers was unrelated to disease severity.

Keywords Disease severity · Macular segmentation · Obstructive sleep apnea and hypopnea syndrome · SD-OCT

Introduction

Obstructive sleep apnea and hypopnea syndrome (OSAS) is a sleep disorder characterized by nocturnal hypoxemia and discontinuation of breathing episodes of more than 10 s during sleep [1]. Complete or partial obstruction of the upper airway during sleep leads to attempts to raise the thoraco-abdominal area with diminished arterial oxygenation [1]. Chronic fatigue, excessive daytime sleepiness, loud snoring, weight gain and a decline in cognitive functions are the main complaints of OSAS patients [1]. Obesity, alcohol

S. Guven (✉) · D. Kilic
Department of Ophthalmology, Kayseri City Hospital,
Mevlana mh. Tamer cd. 5/14, Talas, Kayseri, Turkey
e-mail: drsonerguven@yandex.com.tr

O. F. Bolatturk
Department of Neurology, Kayseri City Hospital, Kayseri,
Turkey

consumption, a large neck circumference, male gender and upper respiratory tract anomalies are common risk factors for OSAS. The gold standard method in the diagnosis of OSAS is overnight polysomnography (PSG) with observation [1].

Patients with OSAS have been linked to increased abnormalities with a neurodegenerative basis, such as Parkinson's disease and Alzheimer's disease [2, 3]. In addition, recent meta-analyses have reported a higher glaucoma prevalence, higher visual field defects and lower retinal nerve fiber (RNFL) and ganglion cell layer (GCL) thicknesses in OSAS [4–6]. The pathophysiology of this neurodegeneration seems to be multifactorial: Hypoxia/hypercapnia episodes, abnormal blood flow changes, oxidative stress, ischemic mediators and inflammation are potential contributory factors [7, 8].

Different eye abnormalities have been linked to OSAS including floppy eyelid syndrome, glaucoma, papilledema and non-arteritic anterior ischemic optic neuropathy [4, 9–11]. Previous studies have mostly focused on the association between OSAS and glaucoma either with RNFL thinning, visual field defects or ganglion cell loss [4–6]. Recently, a specific type of retinal ganglion cell melanopsin expressing intrinsically photosensitive retinal ganglion cells (ipRGC) was linked to sleep disorders including daytime sleepiness, pupil control, circadian rhythms and mood control [12, 13]. In a recently published article, the inner (ipRGC) and outer (rod and cone) retinal participation in pupillary light response (PLR) in OSAS was analyzed using stimuli with different wavelengths [13]. However, spectral domain optical coherence tomography (SD-OCT) is a reliable diagnostic tool widely used in ophthalmology practice, which is also noninvasive and non-contact. SD-OCT can generate cross-sectional high-resolution retinal images. An automated segmentation software added to SD-OCT allows quantification of each of the macular layers and of the peripapillary retinal nerve fiber layer (pRNFL). To the best of our knowledge, there is a lack of information about the quantification of the potential effects of hypocapnia/apnea episodes on the separate retinal layers of the macula in OSAS patients.

The main aim of this study was to evaluate the thickness profile of the segmented individual macular layers in OSAS patients using SD-OCT. The secondary aim was to compare the different OSAS

subgroups (mild, moderate, severe) in respect of macular layers and pRNFL.

Methods

Study design and population

This case–control study was conducted in accordance with the Declaration of Helsinki after approval granted by the Local Ethics Committee (Kayseri Erciyes University Clinical Investigations Ethics Committee; 2020/132). Written informed consent for participation in the study was obtained from all the participants. All the study subjects comprised patients with complaints of snoring who were referred to the Neurology Clinic of Kayseri City Hospital for polysomnography (PSG) between February 2020 and April 2020. All participants underwent overnight PSG. The subjects with apnea and hypopnea index (AHI) score > 5 were assigned as the patient group. The control group was formed of age-, gender- and body mass index (BMI)-matched participants with suspected OSAS and AHI score < 5 , thereby not meeting the criteria of OSAS diagnosis. In the OSAS patient group, the severity of the disease was assessed according to the AHI scores: mild (5–15), moderate (15–30) and severe (> 30) [14]. The patients included in the study were those who were diagnosed with OSAS for the first time and had no history of previous treatment.

All the study subjects underwent a detailed ophthalmic examination including best corrected visual acuity (BCVA), intraocular pressure (IOP) (Goldman applanation tonometer), central corneal thickness (CCT) with ultrasonic pachymetry (Ocuscan RXP-Alcon, Inc, California, USA) and slit lamp examination with dilated fundus. The following ocular criteria were defined as study inclusion criteria; spherical and cylindrical refractive error of $\leq \pm 3.00$ diopters, BCVA of 20/20 and IOP of ≤ 21 mmHg. Patients were excluded from the study if they had any type of ocular disease including retinal and optic disc pathologies, had a history of ocular surgery (including cataract), were using any topical or systemic medication or had any additional systemic diseases [including hypertension (HT) and diabetes mellitus (DM)] or neurodegenerative diseases (Parkinson's disease, multiple sclerosis, Alzheimer's disease). Internal medicine consultations to rule out any undiagnosed HT and

DM were made prior to the study. Subjects with IOP ≤ 21 mmHg with suspected normal tension glaucoma underwent standard automated perimetry visual field examinations. Subjects diagnosed for glaucoma were also excluded from the study.

Polysomnography

Overnight PSG was performed under appropriate conditions using Philips Respironics Alice LDe, (Amsterdam, 1096 BC Netherlands) under the observation of an experienced examiner (O.F.B). The procedure was performed with additional electroencephalography, electro-oculography, electrocardiogram, a thermistor, a nasal cannula, piezo-crystal effort belts, tibial electromyography and finger pulse oximetry recordings. Sleep-related breathing abnormalities were analyzed and calculated by one of the investigators (O.F.B) in accordance with the American Academy of Sleep Medicine criteria [15]. AHI was calculated from the total number of apnea episodes (the interruption of airflow for at least 10 s accompanied by arousal to be able to breathe) and hypopnea (a decline of at least 30% in airflow lasting > 10 s causing a 3% oxygen saturation change) per sleep hour.

Spectral domain optical coherence tomography imaging and analysis

The Heidelberg Spectralis SD-OCT device (Heidelberg Engineering, Heidelberg, Germany) was used for posterior segment measurements after pupil dilatation with tropicamide. As no significant differences were determined between the right and left eyes, only the measurements of right eyes were used for analysis to avoid 'double-organ bias.' All the measurements were taken in the morning (0900–1200) to avoid diurnal variations. At least 3 consecutive measurements were performed for each eye and only the best quality images were used for analysis. Images with artifacts and quality index < 20 were excluded. Macular scans containing 61 single lines of 15 frames with 30 × 25 volume scan centered at the fovea were used for macular layers segmentation. The quantification of the separate macular layers was obtained automatically from the segmentation software of the device after selecting retinal thickness map analysis. In all subjects, manual inspection of all automated

segmentations to detect any potential segmentation errors was performed by one of the authors (D.K) blinded to groups (patients or control). Manual corrections were also made to suspected segmentation errors in a blinded fashion. Numerical averages for each macular layer were calculated from a 3.45-mm-diameter circle. Only the numerical average values acquired from the outermost of the circle were used for analysis (Fig. 1). The automatically segmented layers in the macula were as follows: (1) total retinal thickness, (2) nerve fiber layer (mRNFL), (3) ganglion cell layer (mGCL), (4) inner plexiform layer (mIPL), (5) inner nuclear layer (mINL), (6) outer plexiform layer (mOPL), (7) outer nuclear layer (mONL), (8) retina pigment epithelium (RPE), (9) inner retinal layers (IRL—internal limiting membrane to external limiting membrane) and (10) outer retinal layers (ORL—external limiting membrane to Bruch membrane) (Fig. 1). As strict boundaries for photoreceptor layer connections have not been well established [16], a composite layer was created for photoreceptor interactions: photoreceptor layers (PRLs)—the total of the segmentation results for mOPL + mONL + outer retinal layers. Likewise, an inner composite layer was used for statistical analysis: ganglion cell complex (GCC)—the total of segmentation results for mRNFL + mGCL + mIPL.

A standard 3.46-mm-diameter circle software targeted on the optic nerve head was selected for pRNFL thickness measurements. The pRNFL thickness values were obtained from 9 different quadrants [global, superior (S), inferior (I), nasal (N), temporal (T) and sectors superior temporal (TS), superior nasal (NS), inferior nasal (NI) and inferotemporal (TI)]. Choroidal thickness (CT) measurements were taken manually only in the subfoveal area with an enhanced depth imaging program.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS version 23 software for Mac, licensed to Erciyes University. Conformity of the data to normal distribution was assessed using the Shapiro–Wilk test, histograms and Q–Q plots. Baseline descriptive characteristics [gender, age, BMI, IOP, spherical equivalent (SE), AHI score] were compared between the OSAS and control group using the Student's *t*-test or the Mann–Whitney *U*-test according to the normality

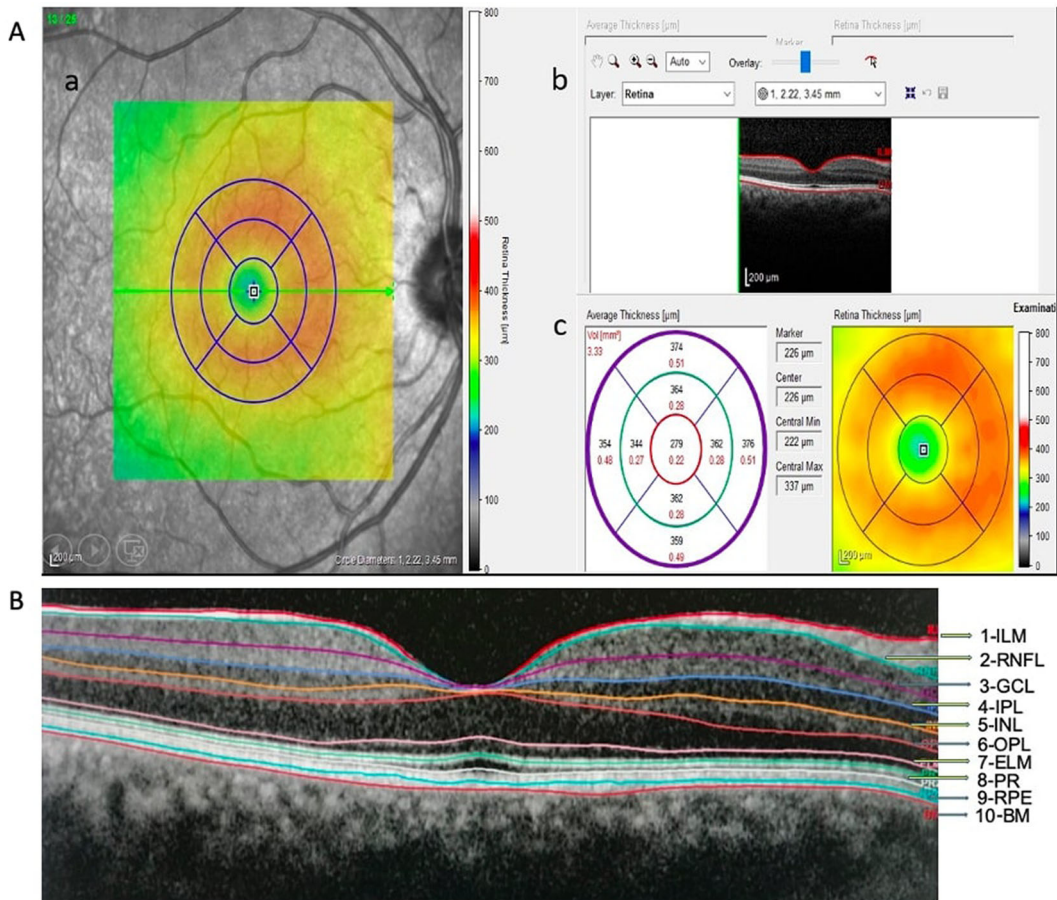


Fig. 1 **A** Macular segmentation measurements of a participant on SD-OCT. **a** Retinal thickness color mapping and 3 circles with different diameters (1–2.2–3.45 mm). **b** Layer segmentation choice default of the device. Total retinal thickness was chosen in this participant. **c** Average thickness and volume measurements of the selected retinal layer in 4 different quadrants. The diameters of the circles: red circle: 1 mm, green

circle: 2.2 mm, purple circle: 3.45 mm. **B** Retinal layer segmentation on SD-OCT. Layers: 1–2 = retina nerve fiber layer (RNFL), 3 = ganglion cell layer (GCL), 4 = inner plexiform layer (IPL), 5 = inner nuclear layer (INL), 6 = outer plexiform layer (OPL), 7 = external limiting membrane (ELM), 8 = photoreceptor layer (PR), 9 = retina pigment epithelium (RPE), 10 = Bruch membrane (BM)

of distribution. The comparisons of OSAS subgroups with the healthy control group were made using either the Kruskal–Wallis test or one-way ANOVA test with Bonferroni–Dunn post hoc test. Statistical corrections for multiple comparisons were also performed. The Chi-square test was applied to categorical variables. The groups were compared (OSAS-control and OSAS subgroups-control) in respect of subfoveal CT, pRNFL (in 9 different zones) and different macular layers (total retinal thickness (RT), mRNFL, mGCL, mIPL, mINL, mOPL, mONL, RPE, IRL, ORL, GCC, PRLs). A value of $p < 0.05$ was accepted as statistically significant.

Results

A total of 86 subjects initially agreed to participate in the study. Exclusions were made from the patient group of 8 determined with glaucoma in perimetry investigations, 2 with IOP > 21 mm hg, 6 with DM, 3 with HT, 2 with SE > 3 diopters, 2 with low image quality due to dense posterior subcapsular cataract and 1 with a history of previous OSAS treatment. Finally, a total of 62 subjects (31 eyes of OSAS patients and 31 eyes of healthy subjects) met the criteria and were included in this study.

Demographics and clinical characteristics of groups

The numbers of patients in the mild, moderate and severe OSAS subgroups were 10, 11 and 10 respectively. Both the patient and control groups, and the three OSAS subgroups were similar in terms of gender ($p:0.78$, $p:0.87$), age (42.9 ± 9.1 , 41.54 ± 6.6 years; $p:0.50$ and 42.8 ± 10.4 , 43.4 ± 7.9 and 42.54 ± 9.9 years; $p:0.91$), SE (0.39 ± 0.3 and 0.35 ± 0.3 D; $p:0.58$ and 0.38 ± 0.3 , 0.53 ± 0.3 and 0.28 ± 0.2 D; $p:0.19$) and BMI (29.09 ± 2.7 and 29.67 ± 2.7 kg/m²; $p:0.40$ and 27.8 ± 2.1 , 29.1 ± 2.8 and 30.27 ± 2.7 kg/m²; $p:0.16$) respectively. The OSAS patients had significantly higher IOP (15.9 ± 2.9 and 14.16 ± 2.8 mmHg; $p:0.018$) and significantly thinner CCT (508.16 ± 28.6 and 522.77 ± 15.1 μm; $p:0.015$) values compared to the control group. Further analysis revealed that the difference was only statistically significant between the severe subgroup of OSAS and the control group in respect of IOP (17.0 ± 3.0 and 14.16 ± 2.8 mmHg; $p:0.033$) and CCT (498.54 ± 19.2 and 522.77 ± 15.1 μm; $p:0.019$) (not shown). The AHI scores were significantly different between the three

subgroups (9.0 ± 2.3 , 22.7 ± 4.1 and 37.63 ± 5.3 ; $p:0.000$) (Table 1).

Retina nerve fiber layer thicknesses of groups

The patient and control groups were similar in terms of pRNFL values except for nasal quadrant. OSAS patients had significantly thinner nasal pRNFL values compared to healthy subjects (74.1 ± 15.3 and 82.51 ± 16.2 μm; $p:0.042$). In all regions, pRNFL thicknesses did not significantly differ between the OSAS subgroups (mild, moderate and severe) (Table 2).

Individual macular layer thicknesses of groups in segmentation analysis

The central macular thickness, mRNFL, mIPL, mOPL, mONL, GCC, mINL, RPE layer thicknesses of the patient group and control group were statistically similar ($p > 0.05$). The difference between these layers remained insignificant between the three OSAS subgroups ($p > 0.05$). The subfoveal CT value was similar in the whole patient group and the control group (298.0 ± 63.3 and 312.41 ± 40.7 μm; $p:0.29$). In the subgroup analyses, moderate OSAS patients had

Table 1 Demographics and clinical characteristics of groups

	OSAS patients (n:31)	Control subjects (n:31)	<i>p</i>	Mild OSAS (n:10)	Moderate OSAS (n:11)	Severe OSAS (n:10)	<i>p</i>
Sex—male	21 (68%)	20 (65%)	0.788*	7 (70%)	6 (60%)	8 (73%)	0.878*
Age, years	42.9 ± 9.1	41.54 ± 6.6	0.505†	42.8 ± 10.4	43.4 ± 7.9	42.54 ± 9.9	0.919‡
IOP, mmHg	15.9 ± 2.9	14.16 ± 2.8	0.018†	15.2 ± 2.9	15.4 ± 2.5	17.0 ± 3.0	0.044‡
SE, D	0.39 ± 0.3	0.35 ± 0.3	0.581†	0.38 ± 0.3	0.53 ± 0.3	0.28 ± 0.2	0.193‡
CCT, μm	508.16 ± 28.6	522.77 ± 15.1	0.015†	507.8 ± 25.6	519.1 ± 37.6	498.54 ± 19.2	0.017‡
AHI score	23.58 ± 12.6	1.8 ± 1.3	0.000†	9.0 ± 2.3	22.7 ± 4.1	37.63 ± 5.3	0.000‡
BMI, kg/m ²	29.09 ± 2.7	29.67 ± 2.7	0.401†	27.8 ± 2.1	29.1 ± 2.8	30.27 ± 2.7	0.162‡

Data are presented as mean ± standard deviation or number (%), where appropriate

OSAS obstructive sleep apnea syndrome, IOP intraocular pressure, SE spherical equivalent, CCT Central corneal thickness, AHI apnea-hypopnea index, D diopter, BMI body mass index

*Chi-square test

†Independent Student’s *t* test

‡One-way ANOVA test (subgroup comparisons were achieved with Bonferroni post hoc corrections)

Table 2 Retina nerve fiber layer thicknesses of groups (mean \pm standard deviation)

μm	OSAS patients (n:30)	Control subjects (n:31)	p^*	Mild OSAS (n:10)	Moderate OSAS (n:11)	Severe OSAS (n:9)	p^\dagger
RNFL-Global	99.53 \pm 14.6	105.09 \pm 11.3	0.101	102.7 \pm 10.6	94.6 \pm 19.6	101.3 \pm 12.5	0.185
RNFL-T	69.76 \pm 13.2	72.58 \pm 9.8	0.347	73.6 \pm 7.8	65.4 \pm 17.4	70.3 \pm 12.7	0.335
RNFL-TS	139.63 \pm 22.2	144.83 \pm 19.7	0.336	144.4 \pm 14.3	128.8 \pm 30.3	145.7 \pm 16.5	0.174
RNFL-TI	142.26 \pm 32.1	148.61 \pm 22.4	0.373	147.3 \pm 19.6	126.4 \pm 38.9	153.1 \pm 31.5	0.109
RNFL-N	74.1 \pm 15.3	82.51 \pm 16.2	0.042	76.6 \pm 13.3	72.0 \pm 18.4	73.7 \pm 15.3	0.212
RNFL-NS	107.03 \pm 20.7	116.58 \pm 23.4	0.097	113.3 \pm 15.8	98.1 \pm 19.5	109.7 \pm 24.7	0.152
RNFL-NI	107.03 \pm 20.7	116.58 \pm 23.4	0.222	111.8 \pm 24.2	102.1 \pm 33.9	113.2 \pm 20.1	0.440

OSAS obstructive sleep apnea syndrome, RNFL retina nerve fiber layer, T temporal, TS superior temporal, TI inferior temporal, N nasal, NS superior nasal

*Independent Student's *t* test

†One-way ANOVA test

significantly thinner subfoveal CT compared to the control group (259.7 \pm 62.5 and 312.41 \pm 40.7 μm ; p :0.034) and mild OSAS patients (259.7 \pm 62.5 and 321.8 \pm 78.5 μm ; p :0.047) (not shown). Total RT (334.27 \pm 16.0 and 345.33 \pm 19.7 μm ; p :0.018), IRL (256.88 \pm 15.9 and 266.24 \pm 18.6 μm ; p :0.037), ORL (77.76 \pm 2.5 and 79.36 \pm 2.4 μm ; p :0.013), PRL (172.84 \pm 6.4 and 178.57 \pm 9.8 μm ; p :0.008) and mGCL (52.62 \pm 6.8 and 55.07 \pm 5.2 μm ; p :0.019) thicknesses were significantly lower in OSAS patients compared to the control subjects. Further analysis revealed no significant difference between the three subgroups in respect of the aforementioned layer comparisons ($p > 0.05$) (Table 3).

Discussion

The results of the current study showed that OSAS patients had thinner nasal pRNFL, total RT, IRL, ORL, PRL and mGCL thicknesses compared to healthy subjects. Moreover, the difference between the two groups in respect of the above-mentioned thickness values was not statistically significant when evaluated according to disease severity. This finding indicates that the thicknesses of total, inner, outer, ganglion cell and photoreceptor layers of macula are significantly decreased in OSAS patients irrespective of disease severity. Furthermore, OSAS patients had significantly thinner CCT and higher IOP values than the control subjects, and this difference remained

statistically significant in the subgroup comparisons. In contrast to this finding, the CCT and IOP values seem to be unaffected until the late stages of the disease.

CCT and IOP values in OSAS patients have been analyzed in several studies. Koseoglu et al. [17] reported that CCT tended to be thinner with increasing disease stages. Likewise, Ekinci et al. [18] reported that CCT measurements were significantly lower compared to the control group. IOP values have also been investigated in previous studies. In a case-control study, Casas et al. [19] reported higher IOP values in OSAS patients, but unlike the current study findings, no differences were found in the IOP values between the three OSAS subgroups. In contrast, Lin et al. [20] reported no differences between OSAS and control subjects in respect of IOP values. In a cross-sectional study investigating the prevalence of glaucoma in OSAS, it was argued that IOP values were not a risk factor for glaucoma in OSAS subjects and did not significantly differ between subjects with and without glaucoma [21]. Although OSAS patients tended to have higher IOP and thinner CCT values in the current study, further evaluation of additional risk factors (age, family history, race etc.) and signs (visual field and optic nerve head changes, gonioscopy etc.) observed in glaucoma patients should be applied to diagnose glaucoma in OSAS.

The choroidal and pRNFL thickness alterations are the most thoroughly investigated parameters in OSAS patients. In recent meta-analyses, both the subfoveal

Table 3 Individual macular layer thicknesses of groups in segmentation analysis

μm	OSAS patients (n:31)	Control subjects (n:31)	<i>p</i>	Mild OSAS (n:10)	Moderate OSAS (n:11)	Severe OSAS (n:10)	<i>p</i>
	<i>Mean \pm standard deviation/median (min–max)</i>						
mRNFL	28.38 \pm 3.6/ 28 (17–37)	29.46 \pm 3.6/ 30 (14–23)	0.243*	29.27 \pm 3.1/ 30.8 (22–32)	27.5 \pm 4.7/ 28 (17–33)	28.38 \pm 3.1/ 27.8 (26–37)	0.469 [†]
mGCL	52.62 \pm 6.8/ 52 (26–61)	55.07 \pm 5.2/ 55.8 (42–64)	0.019 [‡]	52.8 \pm 3.8/ 53.5 (45–57)	50.8 \pm 9.8/ 51.7 (26–61)	51.31 \pm 5.9/ 52 (39–60)	0.127**
mIPL	40.54 \pm 4.0/ 41 (27–46)	41.87 \pm 3.3/ 42.8 (32–48)	0.160*	40.85 \pm 2.4/ 41.4 (38–44)	40.72 \pm 5.7/ 42.5 (27–46)	40.11 \pm 3.7/ 40.5 (33–45)	0.536 [†]
mINL	41.38 \pm 3.6/ 40.8 (34–55)	41.0 \pm 3.2/ 41.25 (33–49)	0.866 [‡]	40.7 \pm 3.0/ 41.8 (34–43)	43.35 \pm 4.8/ 43.5 (38–55)	40.22 \pm 2.1/ 40.3 (37–44)	0.288**
mOPL	31.11 \pm 2.5/ 31 (27–36)	31.82 \pm 2.9/ 32 (27–39)	0.303*	30.0 \pm 1.9/ 29.3 (27–33)	32.35 \pm 2.5/ 32.5 (28–36)	31.0 \pm 2.6/ 30.3 (27–34)	0.178 [†]
mONL	63.96 \pm 6.6/ 65.5 (51–77)	67.38 \pm 7.7/ 68.8 (42–79)	0.065*	65.47 \pm 3.0/ 65.8 (62–70)	63.4 \pm 9.4/ 60.4 (52–77)	63.11 \pm 6.3/ 66.3 (51–70)	0.263 [†]
RPE	13.99 \pm 1.8/ 13.8 (11–22)	14.13 \pm 1.1/ 14.3 (12–18)	0.303 [‡]	13.97 \pm 0.9/ 13.8 (13–15)	14.52 \pm 2.9/ 13.4 (12–22)	13.52 \pm 1.1/ 14 (12–15)	0.627**
Subfoveal CT	298.0 \pm 63.3/ 309 (157–475)	312.41 \pm 40.7/ 314 (239–380)	0.290*	321.8 \pm 78.5/ 332 (207–475)	259.7 \pm 62.5/ 256.5 (157–375)	311.18 \pm 27.1/ 310 (265–363)	0.025 [†]
CMT	216.74 \pm 22.4/ 218 (122–243)	220.45 \pm 13.9/ 224 (183–256)	0.436*	210.7 \pm 33.8/ 217 (122–238)	224.4 \pm 13.8/ 224 (202–243)	215.27 \pm 14.3/ 211 (197–240)	0.333 [†]
Total RT	334.27 \pm 16.0/ 334.8 (299–370)	345.33 \pm 19.7/ 349 (299–372)	0.018*	337.42 \pm 10.2/ 337.3 (315–349)	333.85 \pm 21.5/ 328.8 (299–370)	331.79 \pm 15.6/ 334.8 (300–349)	0.113 [†]
GCC	120.56 \pm 13.7/ 122.8 (70–141)	126.41 \pm 10.0/ 129 (103–142)	0.059*	122.92 \pm 8.7/ 124.1 (104–132)	119.02 \pm 19.7/ 122.6 (70–140)	119.81 \pm 11.6/ 118.5 (98–141)	0.252 [†]
IRL	256.88 \pm 15.9/ 256.8 (221–292)	266.24 \pm 18.6/ 272 (223–289)	0.037*	259.2 \pm 10.7/ 259.5 (234–271)	257.15 \pm 21.3/ 254.6 (221–292)	254.54 \pm 15.3/ 255.8 (226–275)	0.200 [†]
ORL	77.76 \pm 2.5/ 78 (74–82)	79.36 \pm 2.4/ 79.3 (75–84)	0.013*	78.52 \pm 2.6/ 78 (75–82)	77.62 \pm 1.9/ 78.1 (75–80)	77.2 \pm 2.9/ 76.5 (74–82)	0.054 [†]
PRL	172.84 \pm 6.4/ 173.3 (158–186)	178.57 \pm 9.8/ 179.3 (149–193)	0.008*	174 \pm 5.1/ 175.8 (167–181)	173.38 \pm 7.7/ 171 (166–186)	171.31 \pm 6.6/ 173.3 (158–179)	0.060 [†]

OSAS obstructive sleep apnea syndrome, CT choroidal thickness, CMT central macular thickness, RT retinal thickness, mRNFL retina nerve fiber layer, mIPL macular inner plexiform layer, mOPL macular outer plexiform layer, mONL macular outer nuclear layer, GCC ganglion cell complex, IRL inner retinal layers, ORL outer retinal layers, PRL photoreceptor layers, mGCL macular ganglion cell layer, mINL macular inner nuclear layer, RPE retina pigment epithelium

*Independent Student's *t* test

[†]One-way ANOVA test (Subgroup comparisons were achieved with Bonferroni post hoc corrections)

[‡]Mann–Whitney *U* test

**Kruskal–Wallis test

CT and pRNFL thicknesses have been found to be thinner in OSAS patients compared to healthy subjects. Furthermore, the reduction in subfoveal CT and pRNFL values tended to be increased with increasing disease severity [5, 22]. In the current study, the only OSAS subgroup which significantly differed from the

control group in terms of subfoveal CT was the moderate OSAS subgroup. This finding might be due to the small sample size of the subgroups in this series compared with previous reports. Zhao et al. [5] reported in a meta-analysis that the most affected quadrant of pRNFL was the inferior quadrant. In

contrast, a significant decrease in pRNFL thickness was observed in the nasal quadrants of pRNFL in the current study patients. Moreover, the difference was not evident in the subgroup comparisons in this study. Similar to the current study, Casas et al. [19] reported significant nasal pRNFL thinning in OSAS subjects, but the difference did not reach statistical significance at different disease stages. It was speculated that hypoxemia and hypercapnia episodes in OSAS lead to papilledema, which also causes nerve fiber loss secondary to prolonged RNFL swelling. Thus, there is no evident consensus about the affected pRNFL quadrants in OSAS and the association between pRNFL thinning and disease severity.

The striking finding of this study was the significantly reduced values of IRL, ORL, PRL and GCL in patients compared to control subjects, indicating that OSAS affects both the inner and outer retinal layers including photoreceptors and ganglion cells. The possible confounding pathological mechanisms causing significant loss in both mentioned layers might be a neural network abnormality in the input region (outer retina) reaching through to the output region (inner retina) or vice versa. It was hypothesized in the current study that ipRGCs might be a potential candidate for this type of retinal loss observed in OSAS patients. Even though there are no objective data indicating the functional role of ipRGCs in OSAS, the segmentation analysis findings of the current study echoed this speculation. First, ipRGCs have the largest identified retinal ganglion cell dendritic fields forming a photoreceptive network concentrated parafoveally, from where the measurements in segmentation analysis (3.45 mm) were obtained [23]. Second, pupil constriction seen in PLR is initiated by the outer retina (rods and cones) and sustained by ipRGCs when high retinal irradiance is applied, as measured with the post-illumination pupil response amplitude (PIPR) [24]. Moreover, the results of another recent study showed that outer retinal photoreceptor contributions to PLR were significantly altered in OSAS patients [13]. Third, ipRGCs play a pivotal role in circadian photoentrainment, sleep regulation and mood modulation, which are also impaired in OSAS patients [25–28]. Gracitelli et al. [12] also reported a significant association between daytime sleepiness and PLR (ipRGCs) in glaucoma patients. There is only one study which has focused on the contributions of three photoreceptors (rods, cones and ipRGCs) to PLR in

OSAS, and in that study, it was reported that the response to PLR was reduced in the outer retina (rods and cones) but no significant change was detected in the inner retina (ipRGCs). Unlike the current study, only moderate/severe OSAS patients were included in that study [13]. Furthermore, only the functional results were analyzed, whereas anatomic and morphological alterations might have already occurred before being reflected in the functional results. However, all the above-mentioned studies require more advanced technical and expensive equipment, which is not available in every ophthalmology clinic.

Another theory to explain the relatively global thinning of retinal layers might be the evidence-based association of neurodegeneration observed in OSAS [2, 3, 29]. It has been shown that apnea episodes alone lead to neuronal loss (apoptosis) in various parts of the brain [30]. In a study exploring the use of optic disc parameters and pRNFL via OCT to detect neurodegenerative brain changes in OSAS, the use of OCT was not recommended due to confounding central nervous system disorders (intracranial hypertension, papilledema, brain atrophy etc.) [29]. Moreover, a human postmortem retina tissue study showed marked thinning of both inner and outer retinal layers in Alzheimer's disease [31]. That study added new information to previous studies which had reported that neurodegenerative diseases alone affect inner retinal layers [31].

Direct neurodegeneration and/or vascular abnormalities (hypoxia-hypercapnia, endothelial dysfunction, free radicals or ocular blood pressure variations etc.) seem to result in a disintegration in retinal layers. Trans-synaptic disruption in one retinal layer either in the photoreceptor layer, ganglion cell layer or intermediate layers could contribute to the retinal degeneration cycle. In a recent study, it has been reported that damage of photoreceptors may also cause a thinning of the ganglion cell layer because of a post-receptor neuronal loss phenomenon in eyes with intermediate age-related macular degeneration [32]. Although no ocular perfusion measurements were performed in the current study, the effect of OSAS on periocular blood vessels, choroidal flow and vascular density changes has been analyzed in various previous studies [33–35]. Findik et al. [33] recently showed a linear increase in posterior ciliary artery pulsatile index and resistive index values with the AHI values in OSAS patients obtained by colored Doppler

sonography. Findik et al. [33] also argued that this finding may cause more serious ischemic optic neuropathy as the OSAS severity increases. In an OCT angiography study, it was shown that peripapillary and parafoveal vessel densities were significantly reduced in OSAS patients compared to control subjects [34]. Furthermore, Yu et al. [34] reported that this vessel density decrease was more prominent in the peripapillary area and was also related to disease severity. Unlike the above-mentioned studies, Tonini et al. [35] found no significant choroidal vascular reactivity in OSAS subjects compared to control subjects. The main limitation of that study was that Tonini et al. [35] included only 16 newly diagnosed males with OSAS without comorbidities in the study. A possible link between ischemia and retinal thinning may be hypothesized to explain the results of the current study. However, proving this hypothesis was beyond the scope of this study, and it can only be speculated that the retinal thinning cycle could possibly be multifactorial. Additional studies are needed to determine the exact initiator of this retinal thinning process. It is also possible that all individual retinal layers could be affected at the same time in OSAS.

Interestingly, the current study results showed that the thinning of the retinal layers was not related to the disease severity. A possible explanation of this is that the duration of the disease could be more important than the severity of the disease in causing an anatomic effect.

Single-center, case–control design of the study and small sample size are the main limitations of this report. The authors are also aware that anatomic changes do not always correlate with functional outcomes. Further microscopic, biochemical or post-mortem studies are needed to determine the exact functional effects of OSAS on the macula, especially the impact on ipRGCs. Another limitation was that the duration of the disease in the current study subjects was not known. Moreover, as strict exclusion criteria for glaucoma were applied, it was not possible to perform automatic perimetry investigations for all participants. Therefore, it is likely that some of the study subjects might have had undiagnosed glaucoma. Furthermore, the population under investigation may not be fully representative of the population of subjects with OSAS who have DM due to exclusion of DM patients. It was also not possible to apply

magnetic resonance imaging of the brain to the study subjects, which could have shown possible neurodegeneration in the central nervous system.

However, this study is a preliminary report showing segmental anatomic changes in the macula in OSAS patients for the first time. Furthermore, new information is added to the GCL thinning observed in OSAS patients with additional reduction of thicknesses of the PRLs, IRLs and ORLs. This is the first study to have reported that thinning of the specified macular layers is independent of disease severity.

In conclusion, macular layer thinning including both the inner and outer retina with photoreceptor and ganglion cell layers, unrelated to the disease severity is remarkable in OSAS patients. Future large-scale studies are needed to explore the exact physiopathological mechanisms resulting in this finding.

Author contributions SG, DK and OFB designed the study, collected the data, drafted the manuscript and created the tables.

Data availability The data are available upon request.

Declarations

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Ethics approval Ethics approval for this study was obtained from Kayseri Erciyes University, Clinical Investigations Ethics Committee, 2020/132.

References

- Guilleminault C (1994) Clinical features and evaluation of obstructive sleep apnea, 2nd edn. W B Saunders Co, Philadelphia, pp 667–677
- De Cock VC, Benard-Serre N, Driss V, Granier M, Charif M, Carlander B, Desplan M, Langenier MC, Cugy D, Bayard S (2015) Supine sleep and obstructive sleep apnea syndrome in Parkinson's disease. *Sleep Med* 16(12):1497–1501. <https://doi.org/10.1016/j.sleep.2014.09.014>
- Buratti L, Viticchi G, Falsetti L, Cagnetti C, Luzzi S, Bartolini M, Provinciali L, Silvestrini MJ (2014) Vascular impairment in Alzheimer's disease: the role of obstructive sleep apnea. *J Alzheimers Dis* 38(2):445–453. <https://doi.org/10.3233/JAD-131046>
- Liu S, Lin Y, Liu XJ (2016) Meta-analysis of association of obstructive sleep apnea with glaucoma. *J Glaucoma* 25(1):1–7. <https://doi.org/10.1097/IJG.0000000000000357>

5. Zhao X-J, Yang C-C, Zhang J-C, Zheng H, Liu P-P, Li QJ (2016) Obstructive sleep apnea and retinal nerve fiber layer thickness: a meta-analysis. *J Glaucoma* 25(4):e413–e418. <https://doi.org/10.1097/IJG.0000000000000349>
6. Kara N, Sayin N, Bayramoglu S, Savas A (2018) Peripapillary retina nerve fiber layer thickness and macular ganglion cell layer thickness in patients with obstructive sleep apnea syndrome. *Eye (Lond)* 32(4):701. <https://doi.org/10.1038/eye.2017.279>
7. Abdal H, Pizzimenti JJ, Purvis CC (2006) The eye in sleep apnea syndrome. *Sleep Med* 7(2):107–115. <https://doi.org/10.1016/j.sleep.2005.08.010>
8. Dhillon S, Shapiro CM, Flanagan J (2007) Sleep-disordered breathing and effects on ocular health. *Can J Ophthalmol* 42(2):238–243. <https://doi.org/10.3129/canjophthalmol.i07-029>
9. Leibovitch I, Selva D (2006) Floppy eyelid syndrome: clinical features and the association with obstructive sleep apnea. *Sleep Med* 7(2):117–122. <https://doi.org/10.1016/j.sleep.2005.07.001>
10. Purvin VA, Kawasaki A, Yee RD (2000) Papilledema and obstructive sleep apnea syndrome. *Arch Ophthalmol* 118(12):1626–1630. <https://doi.org/10.1001/archophth.118.12.1626>
11. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL (1994) Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *Am J Ophthalmol* 117(5):603–624. [https://doi.org/10.1016/s0002-9394\(14\)70067-4](https://doi.org/10.1016/s0002-9394(14)70067-4)
12. Gracitelli CP, Duque-Chica GL, Moura ALda, Roizenblatt M, Nagy BV, de Melo GR, Borba PD, Teixeira SH, Tufik S, Ventura DF (2016) Relationship between daytime sleepiness and intrinsically photosensitive retinal ganglion cells in glaucomatous disease. *J Ophthalmol*. <https://doi.org/10.1155/2016/5317371>
13. Duque-Chica GL, Gracitelli CP, Moura AL, Nagy BV, Vidal KS, de Melo G, Paranhos A, Cahali MB, Ventura DF (2019) Contributions of the melanopsin-expressing ganglion cells, cones, and rods to the pupillary light response in obstructive sleep apnea. *Invest Ophthalmol Vis Sci* 60(8):3002–3012. <https://doi.org/10.1167/iovs.19-26944>
14. (2014) International classification of sleep disorders. American Academy of Sleep Medicine, Darien
15. Iber C (2007) The AASM manual for the scoring of sleep and associated events: Rules Terminology and Technical Specification
16. Spaide RF, Curcio CA (2011) Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: literature review and model. *Retina* 31(8):1609. <https://doi.org/10.1097/IAE.0b013e3182247535>
17. Koseoglu HI, Kanbay A, Ortak H, Karadağ R, Demir O, Demir S, Gunes A, Doruk S (2016) Effect of obstructive sleep apnea syndrome on corneal thickness. *Int Ophthalmol* 36(3):327–333. <https://doi.org/10.1007/s10792-015-0122-2>
18. Ekinci M, Huseyinoglu N, Cagatay HH, Ceylan E, Keles S, Gokce G (2013) Is there a relationship between sleep apnea and central corneal thickness? *Curr Eye Res* 38(11):1104–1109. <https://doi.org/10.3109/02713683.2013.804578>
19. Casas P, Ascaso FJ, Vicente E, Tejero-Garcés G, Adiego MI, Cristóbal JA (2013) Retinal and optic nerve evaluation by optical coherence tomography in adults with obstructive sleep apnea–hypopnea syndrome (OSAHS). *Graefes Arch Clin Exp Ophthalmol* 251(6):1625–1634. <https://doi.org/10.1007/s00417-013-2268-9>
20. Lin P-W, Friedman M, Lin H-C, Chang H-W, Wilson M, Lin M-CJ (2011) Normal tension glaucoma in patients with obstructive sleep apnea/hypopnea syndrome. *J Glaucoma* 20(9):553–558. <https://doi.org/10.1097/IJG.0b013e3181f3eb81>
21. Bendel R, Kaplan J, Heckman M, Fredrickson P, Lin S (2008) Prevalence of glaucoma in patients with obstructive sleep apnoea—a cross-sectional case-series. *Eye* 22(9):1105. <https://doi.org/10.1038/sj.eye.6702846>
22. He M, Han X, Wu H, Huang W (2016) Choroidal thickness changes in obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Sleep Breath* 20(1):369–378. <https://doi.org/10.1007/s11325-015-1306-8>
23. Dacey DM, Liao H-W, Peterson BB, Robinson FR, Smith VC, Pokorny J, Yau K-W, Gamlin PD (2005) Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature* 433(7027):749. <https://doi.org/10.1038/nature03387>
24. Gamlin PD, McDougal DH, Pokorny J, Smith VC, Yau K-W, Dacey DM (2007) Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. *Vision Res* 47(7):946–954. <https://doi.org/10.1016/j.visres.2006.12.015>
25. Zaidi FH, Hull JT, Peirson SN, Wulff K, Aeschbach D, Gooley JJ, Brainard GC, Gregory-Evans K, Rizzo JF III, Czeisler CA (2007) Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. *Curr Biol* 17(24):2122–2128. <https://doi.org/10.1016/j.cub.2007.11.034>
26. Berson DM, Dunn FA, Takao M (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295(5557):1070–1073. <https://doi.org/10.1126/science.1067262>
27. Provencio I, Rodriguez IR, Jiang G, Hayes WP, Moreira EF, Rollag MDJ (2000) A novel human opsin in the inner retina. *J Neurosci* 20(2):600–605. <https://doi.org/10.1523/JNEUROSCI.20-02-00600.2000>
28. Butler MP, Smales C, Wu H, Hussain MV, Mohamed YA, Morimoto M, Shea SA (2015) The circadian system contributes to apnea lengthening across the night in obstructive sleep apnea. *Sleep* 38(11):1793–1801. <https://doi.org/10.5665/sleep.5166>
29. Huseyinoglu N, Ekinci M, Ozben S, Buyukuysal C, Kale MY, Sanivar HS (2014) Optic disc and retinal nerve fiber layer parameters as indicators of neurodegenerative brain changes in patients with obstructive sleep apnea syndrome. *Sleep Breath* 18(1):95–102. <https://doi.org/10.1007/s11325-013-0854-z>
30. Fung SJ, Xi M, Zhang J, Sampogna S, Chase MH (2012) Apnea produces excitotoxic hippocampal synapses and neuronal apoptosis. *Exp Neurol* 238(2):107–113. <https://doi.org/10.1016/j.expneurol.2012.08.006>
31. Asanad S, Ross-Cisneros FN, Nassisi M, Barron E, Karanjia R, Sadun AA (2019) The retina in Alzheimer’s disease: histomorphometric analysis of an ophthalmologic biomarker. *Invest Ophthalmol Vis Sci* 60(5):1491–1500. <https://doi.org/10.1167/iovs.18-25966>

32. Borrelli E, Abdelfattah NS, Uji A, Nittala MG, Boyer DS, Sadda SR (2017) Postreceptor neuronal loss in intermediate age-related macular degeneration. *Am J Ophthalmol* 181:1–11. <https://doi.org/10.1016/j.ajo.2017.06.005>
33. Fındık H, Çeliker M, Aslan MG, Çeliker FB, İncikli MF, Dursun E, Okutucu M, Şahin Ü (2019) The relation between retrobulbar blood flow and posterior ocular changes measured using spectral-domain optical coherence tomography in patients with obstructive sleep apnea syndrome. *Int Ophthalmol* 39(5):1013–1025. <https://doi.org/10.1007/s10792-018-0892-4>
34. Yu J, Xiao K, Huang J, Sun X, Jiang C (2017) Reduced retinal vessel density in obstructive sleep apnea syndrome patients: an optical coherence tomography angiography study. *Invest Ophthalmol Vis Sci* 58(9):3506–3512. <https://doi.org/10.1167/iov.17-21414>
35. Tonini M, Khayi H, Pepin J-L, Renard E, Baguet J-P, Lévy P, Romanet J-P, Geiser MH, Chiquet C (2010) Choroidal blood-flow responses to hyperoxia and hypercapnia in men with obstructive sleep apnea. *Sleep* 33(6):811–818. <https://doi.org/10.1093/sleep/33.6.811>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.