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Original Article

Evaluation of the macular choroidal thickness using spectral optical coherence tomography in patients with obstructive sleep apnoea syndrome

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Abstract

Background: To assess the choroidal thickness (CT) in patients with obstructive sleep apnoea syndrome (OSAS) and healthy controls.

Design: Prospective, cross-sectional study

Participants: Ninety-two eyes of 92 patients with OSAS and 32 eyes of 32 aged and body mass index-matched healthy subjects were enrolled.

Methods: OSAS patients were further divided into mild, moderate and severe OSAS groups according to their apnoea hypopnea index (AHI) values. The macular CT and peripapillary retinal nerve fibre layer (RNFL) thickness measurements of the subjects were obtained using spectral domain optical coherence tomography (RTVue-100, Optovue). The CT and RNFL thickness measurements of the groups were compared, and correlations among the AHI values and these measurements were calculated.

Main Outcome Measures: Choroidal thickness.

Results: There were no significant differences in subfoveal and temporal CT measurements of the groups. A pairwise comparison between the groups revealed that severe OSAS group has significantly thinner CT than mild OSAS group at 3.0 mm nasal to the fovea. Also, compared with severe OSAS group, the CT measurements at 1.5 mm and 3.0 mm nasal to the fovea were significantly thicker in control eyes (both, $P < 0.05$). There were weak negative correlations between the nasal CT measurements and AHI in the OSAS group (nasal 1.5 mm, $P = 0.002$, $r = -0.358$; nasal 3.0 mm, $P = 0.004$, $r = -0.336$). Compared with controls, severe OSAS group had significantly thinner nasal and superior RNFL thickness measurement.

Conclusions: Sleep apnoea patients had choroidal structural alterations that may have significance on the pathophysiology of the ophthalmic disorders associated with OSAS.

Key words: choroidal thickness, obstructive sleep apnoea syndrome, spectral-domain optical coherence tomography.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common medical condition which is characterized by repeated episodes of upper airway obstruction during sleep combined with daytime sleepiness.[1] Because of its association with many systemic disorders including hypertension, coronary artery disease, heart failure and stroke, OSAS has become an important public health issue.[2,3]

Recent evidence in the literature suggests that many ophthalmological disorders are also associated with OSAS including floppy eyelid

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syndrome, glaucoma, non-arteritic ischemic optic neuropathy, central serous chorioretinopathy and papilloedema.[4,5] The established link between sleep apnoea and these disorders has not been fully elucidated but is generally believed to be due to hypoxemia, vascular dysregulation and increased sympathetic activity.[6] In OSAS, hypoxia secondary to repetitive apneic episodes leads to blood pressure variations and hemodynamic changes. Also, inspiratory efforts against collapsed airways decrease intrathoracic pressure and arouse the patient from sleep. These intermittently activate sympathetic system which could result in abnormal neural, humoral, thrombotic, metabolic and inflammatory responses.[7,8]

Although OSAS is increasingly being linked to cardiac and vascular disease, to the best of our knowledge, little is known about the effects of OSAS on the choroid; one of the most highly vascularized tissues of the body.[9] The established imbalance between vasoactive substances, especially nitric oxide and endothelin in OSAS might have an influence on the choroid because it was shown that endothelin-1 is a major determinant of choroidal blood flow.[10,11] Also, choroidal blood flow shares some regulatory properties with cerebral blood flow, such as hypercapnia induced vasodilatation, and contrary to the retinal and optic nerve head vasculature, choroid vessels are subject to the autonomic regulation.[12] These make choroid more vulnerable to the effects of OSAS, since sleep apnoea causes autonomic dysfunction and hypercapnia.[13]

But, because of its localization between the overlying pigmented retinal pigment epithelium and the underlying opaque and rigid fibrous sclera, the choroid is difficult to visualize. Fortunately, in recent years, a number of commercially available spectral domain optical coherence tomography (SD-OCT) systems enable us to measure the choroidal thickness (CT) *in vivo*.[14] Imaging choroid using SD-OCT is an easy, reproducible, non-invasive and effective tool to understand choroidal changes.[15]

In this study, we aimed to evaluate the CT and retinal nerve fibre layer (RNFL) thickness measurements in eyes of patients with OSAS and healthy controls to determine the effects of the OSAS on CT and RNFL by using SD-OCT. We hypothesized that patients with OSAS would demonstrate CT changes, and this might be the way of better understanding the pathogenesis of the ophthalmological disorders associated with OSAS.

Methods

This prospective study was approved by the local ethical committee and was performed in accordance with the ethical principles described in the Declaration of Helsinki. All subjects enrolled in the study agreed to participate, met the inclusion criteria and signed an informed consent agreement before any procedures were performed. Patients with diabetes mellitus, systemic arterial hypertension, cardiovascular disease, dyslipidemia or any known systemic diseases other than OSAS, retinal disease (i.e. macular degeneration), ocular surgery, ocular trauma, glaucoma, ocular inflammation or refractive errors outside −5 to +3 D were excluded. Smoking was also an exclusion criterion. None of the subjects was taking medications. All subjects underwent detailed ophthalmologic examination including the axial length measurement with optical biometry (Lenstar LS 900, Haag-Streit AG, Köniz, Switzerland) and visual field examination with the Humphrey perimetry (Carl Zeiss Meditec, Dublin, CA, USA) with the 30-2 programme.

All participants underwent diagnostic overnight polysomnography (PSG) at the sleep laboratory at Bozok University Faculty of Medicine, Yozgat, Turkey. The recordings were analysed according to the guidelines of the American Academy of Sleep Medicine.[16]

Patients with OSAS were newly diagnosed and never treated for OSAS. Obstructive sleep apnoea syndrome was diagnosed and graded according to the following apnoea hypopnea index (AHI) values: mild: $5 \leq AHI < 15$; moderate $15 \leq AHI < 30$, and severe: $AHI \geq 30$. Those with $AHI \geq 5$ were included in this study. Controls had an AHI value < 5, and were matched with the case group in terms of age, sex and body mass index.

Image acquisition and processing

Subjects were scanned using the RTVue SD-OCT system (RTVue-100; software version 6.1, Optovue Inc, Fremont, CA, USA) from 10 a.m. to 12 a.m. after pupil dilation. The system works at 830 nm wavelength and is capable of a scan speed of 26 000 axial scan per second. The depth resolution of the system is 5 μm in tissue.

Both retinal nerve fibre layer and macular choroidal thickness measurements for each participant were taken on the same day. For measurement of CT, the retina cross line scan pattern which consists of two orthogonally oriented 6-mm lines consisting of 1024 A-scans, was used. After the patient's chin and forehead were correctly positioned, the instrument pushed towards the eye while the patient maintained fixation on the internal fixation light until the retinal image was inverted. Only the nasal temporally oriented line was used for the measurement. The image is automatically inverted so that the chorioretinal interface is adjacent to the zero delay. The retina cross-line scan has 32 frames averaged, 16

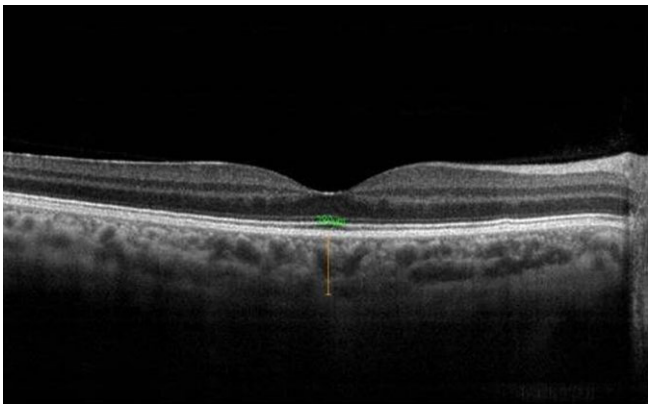

Figure 1. Optical coherence tomography scan showing the choroidal thickness. Yellow line indicates the choroidal thickness measurement at the fovea.

per direction, without tracking. After all eyes were imaged, two independent physicians who were masked to the diagnosis of the subjects used the manual segmentation function to delineate the boundaries of the choroid by using RTVue manual measurement tools. The CT is measured perpendicularly (from the outer edge of the hyper-reflective retinal pigment epithelium to the inner sclera) at the fovea, and 1.5 mm temporal, 3.0 mm temporal, 1.5 mm nasal and 3.0 mm nasal to the fovea (Fig. 1). The measurements from the two observers were then averaged together for analysis; the differences between readings of the masked physicians were found to be within 10% of the mean.

For measurement of the peripapillary RNFL thickness, 'RNFL 3.45 mode' was used. The RNFL 3.45 mode measure peripapillary RNFL along a circle 3.45 mm in diameter around the optic disc. RNFL thickness parameters selected as main outcome measures included average, temporal, superior, nasal and inferior RNFL thickness. The OCT software automatically derives the RNFL thickness measurements. One eye of each subject was chosen for the study according to a random-number sequence (dichotomatic sequence 0 and 1). This was done in an attempt to avoid the correlation that often exists between two eyes of the same person.

Statistical analysis

All data were analysed using SPSS software (version 16.0 SPSS, Inc, Chicago, IL, USA). The descriptive statistics were presented as mean ± standard deviation (SD). The one-way analysis of variance test was used to compare the groups, with a Bonferroni adjustment for multiple comparisons. The chi-squared test was used to make comparisons between the categorical data. The correlations between the AHI and the CT, RNFL measurements were analysed by Pearson correlation coefficients. A P value less than 0.05 was considered statistically significant.

Results

Ninety-two consecutive OSAS patients and 32 control subjects who are devoid of the ocular and systemic exclusion criteria that might affect the results were included in the study. Table 1 summarizes demographic and clinical characteristics of subjects by groups. The mean age, intraocular pressure, body mass index and axial length values were similar in the OSAS and control groups (all, $P > 0.05$). The AHI was significantly different between the groups.

The mean CT measurements of the groups at each location are shown in Table 2. A pairwise comparison between the groups revealed that severe OSAS group has significantly thinner CT than mild OSAS group at 3.0 mm nasal to the fovea. Also, compared with severe OSAS group, the CT measurements at 1.5 mm and 3.0 mm nasal to the fovea were significantly thicker in the control group (both, $P < 0.05$).

RNFL thickness measurements are shown in Table 3. Significant differences were found in the nasal quadrant and superior quadrant RNFL thickness measurements between the groups. Post hoc tests revealed that severe OSAS and moderate OSAS groups had significantly thinner nasal RNFL thickness measurements than controls ($P = 0.04$ and $P = 0.003$, respectively). Compared with controls, severe OSAS group had also significantly thinner superior RNFL thickness measurement ($P = 0.044$).

There were weak negative correlations between the nasal CT measurements and AHI in the OSAS group (nasal 1.5 mm, $P = 0.002$, $r = -0.358$; nasal 3.0 mm, $P = 0.004$, $r = -0.336$). However, the correlations between the CT measurements and AHI were not significant in the control group. There was no significant correlation between the RNFL thickness measurements and AHI both in the OSAS group and controls.

Discussion

The pathogenesis of the ophthalmic manifestations of OSAS is not fully understood; however, several reports have proposed a vascular etiology.[10,17,18] The choroid of the eye is primarily a vascular tissue, and it is the major blood supply to the retina.[12] A structurally and functionally normal choroidal vasculature is essential for the retinal function: abnormal choroidal blood volume and/or compromised flow can result in photoreceptor dysfunction and death.[19] Consequently, the choroid is suggested to play a role in the pathophysiology of many conditions that are also associated with OSAS, such as

Table 1. Demographic and clinical characteristics of subjects by groups

Parameter	Control (n = 32)	Mild OSA (n = 33)	Moderate OSA (n = 28)	Severe OSA (n = 31)	P-value
Age (years)	47.31 ± 10.53	48.50 ± 7.72	50.47 ± 8.11	52.0 ± 10.54	0.321
Sex (male/female)	17/15	18/15	13/15	17/14	0.457
IOP (mmHg)	15.27 ± 2.74	14.92 ± 3.36	15.68 ± 4.55	15.77 ± 2.43	0.782
AXL (mm)	23.44 ± 0.66	23.26 ± 1.18	23.79 ± 0.66	23.53 ± 0.94	0.284
BMI (kg/mm^2)	31.78 ± 7.53	31.84 ± 5.63	33.37 ± 6.34	35.67 ± 6.48	0.115
AHI (no./h of sleep)	2.45 ± 1.47	8.46 ± 2.72	21.86 ± 3.79	67.80 ± 22.20	<0.001

AHI, apnoea hypopnea index; AXL, axial length; BMI, body mass index; IOP, intraocular pressure; OSA, obstructive sleep apnoea.

Table 2. Choroidal thickness measurements (μm) by groups

Measurement site	Control (n = 32)	Mild OSA (n = 33)	Moderate OSA (n = 28)	Severe OSA (n = 31)	P-value
Subfoveal	248.31 ± 47.53	241.53 ± 42.88	228.05 ± 31.56	221.92 ± 43.67	0.125
1.5 mm nasal to the fovea	223.31 ± 41.94	218.96 ± 33.51	208.15 ± 28.73	193.40 ± 38.38	0.021
3.0 mm nasal to the fovea	208.72 ± 29.68	203.46 ± 45.84	194.42 ± 38.94	174.74 ± 33.30	0.010
1.5 mm temporal to the fovea	227.27 ± 39.63	227.88 ± 42.51	217.84 ± 30.65	207.11 ± 46.96	0.235
3.0 mm temporal to the fovea	217.0 ± 53.31	222.38 ± 42.32	209.05 ± 32.57	196.88 ± 40.79	0.167

OSA, obstructive sleep apnoea.

Table 3. RNFL thickness measurements (μm) by groups

Parameter	Control (n = 32)	Mild OSA (n = 33)	Moderate OSA (n = 28)	Severe OSA (n = 31)	P-value
Average RNFL (μm)	110.3 ± 9.8	109.4 ± 7.6	106.7 ± 9.1	103.5 ± 12.2	0.076
Temporal quadrant RNFL (μm)	82.3 ± 11.7	87.4 ± 12.4	83.8 ± 9.1	82.6 ± 12.8	0.394
Superior quadrant RNFL (μm)	136.3 ± 16.9	133.3 ± 11.7	131.2 ± 13.8	124.4 ± 16.7	0.044
Nasal quadrant RNFL (μm)	82.6 ± 9.7	77.6 ± 9.6	74.1 ± 7.6	72.3 ± 11.2	0.003
Inferior quadrant RNFL (μm)	140.4 ± 19.1	139.5 ± 14.9	137.8 ± 20.1	135.0 ± 22.5	0.774

OSA, obstructive sleep apnoea; RNFL, retinal nerve fibre layer.

central serous chorioretinopathy, and vascular eye diseases including non-arteritic ischemic optic neuropathy and glaucoma.[20–22]

OSAS is characterized by the recurrent complete or partial upper airway obstructions during sleep. Each episode of apnoea or hypopnea is associated with hypoxemia and hypercapnia.[23] It is well known that changes in arterial partial pressure of carbon dioxide regulate ocular blood flow and main regulator of the acute vasodilatory response to hypercapnia is the L-arginine-nitric oxide system, probably interacting with other mediators.[24] Unfortunately, in OSAS balance between vasodilators, such as nitric oxide, and vasoconstrictors, such as endothelin is disturbed.[10,25] In addition, the hypoxia re-oxygenation pattern and sleep fragmentation associated with OSAS contribute to the activation of sympathetic system.[6] The adaptation of choroidal vascular resistance is achieved through the sympathetic nervous system by the way of rich choroid innervation.[26] Thus, expecting choroidal structural changes in OSAS is reasonable.

Indeed, in the present study, we found that the CT decreases significantly at 1.5 mm and 3.0 mm nasal to the fovea in OSAS patients without known comorbidities. To the best of our knowledge, there is no study in the literature comparing the CT in eyes of the OSAS patients who do not have known systemic diseases and controls. Recently, Xin *et al.* studied a smaller sample and reported thinning of the subfoveal CT in addition to the nasal CT in OSAS patients.[27] However, in the mentioned study, the authors did not exclude the subjects having systemic diseases, and about 50% of the participants were indicated to have hypertension. The choroid is prone to suffer from microvascular atherosclerotic changes and changes inherent to other microvascular systems.[28] So, we think that including the patients having hypertension and diabetes may affect the conclusion of the CT studies.Though the number of the patients and controls having the systemic disease are matched, severity and duration of the systemic diseases could not be standardized. Therefore, the difference between our study and Xin *et al.*'s in terms

of the subfoveal CT alterations might be due to the underlying systemic diseases and concomitant treatment in Xin *et al*.'s study.

On the other hand, Tonini *et al*. showed unimpaired choroidal vascular reactivity in a population of 16 otherwise healthy men with sleep apnoea using laser Doppler flowmetry. The authors reported that their patients had only subclinical changes demonstrated by changes in pulse wave velocity. They also concluded that the absence of comorbidities may be the main reason of the intact choroidal vascular responses during hyperoxia and hypercapnia in obstructive sleep apnoea, and the choroid is protected against low or moderate OSAS by local adaptive mechanisms.[29]

Validation of a technique for the measurement of choroidal blood flow in humans is difficult because of the specific angioarchitecture of this vascular bed. Several limitations have to be considered when using laser Doppler flowmetry. First, only local measurements in the subfoveal choroid can be taken with the fundus camera-based system. Also, one needs to be careful to compare laser Doppler flowmetry readings between subjects because the absolute values are strongly influenced by the scattering properties of the tissues and morphological differences between groups may introduce measurement variability.[30] It is known that vascular responses to hypoxia or hypercapnia can occur either globally and locally, and this response is most pronounced in the smallest measurable arteries.[31] A previous study in monkeys indicates that after section of posterior ciliary arteries supplying the posterior part of the optic nerve head, blood flow as measured with the laser Doppler flowmetry does not change.[32] Thus, any change occurring in the choroidal circulation, reflected as nasal choroidal thinning in our study, may have been outside the detection limits of the subfoveal laser Doppler flowmetry technique. A further study evaluating the laser Doppler flowmetry and SD-OCT techniques together is needed to understand this.

The question why only the nasal CT, the portion of the macula closest to the optic nerve head, is affected in OSA remains open. However, a significant reduction of the peripapillary RNFL thickness was also reported in OSAS previously, and nonarteritic ischemic optic neuropathy and glaucoma are believed to occur at the optic nerve head.[33] In this study, we also found that the RNFL thickness was reduced in the severe OSAS group compared with those of the controls in the nasal and superior quadrants. Moreover, nasal RNFL thickness measurement of the moderate OSAS group was also thinner than that of the controls. Consistent with our findings, Shiba *et al*.[34] recently reported significantly thinner nasal RNFL thickness in OSAS patients. However, contrary to Casas *et al*.'s[33] and our findings, Shiba *et al*.[34] found that AHI index was correlated with the RNFL thickness. The subjects in our study and Casas *et al*.'s[33] were almost 10 years younger than those in Shiba *et al*.'s. Thus, it can be possible that patients in Shiba *et al*.'s study might have OSAS for a longer time. As Shiba *et al*. were also speculated, an extended disease duration may result in a continuous reduction of the RNFL thickness, and the differences in the thickness among the severities of sleep apnoea syndrome become obvious in the end.

The mechanisms how peripapillary RNFL thickness measurements are affected in OSAS were not clearly understood. Direct exposure of the optic nerve to OSAS induced hypoxia may be a contributory factor, but this could not rule out the potential choroidal disturbance. Also, both endothelin-1 and nitric oxide have been implicated in the pathogenesis of glaucoma, and considering this may provide a possible link between altered endothelin-1 system and nasal choroidal thinning in OSAS.[35]

Important strengths of our study are, first, all patients with OSAS were free of other known diseases, and had never been treated for sleep apnoea. Second, control subjects were matched for age, axial length and body mass index to rule out any potential confounding influence of these factors on our data. Third, to exclude any occult sleep apnoea in our obese control subjects, both study group and control group subjects completed overnight polysomnography.

The limitations of this study include its cross-sectional nature, so the results obtained do not allow us to draw any conclusions about direct causal relationships between choroidal structural changes and ophthalmic manifestations of OSAS. Also, we do not know how long our patients suffered from OSAS before their official diagnosis; choroidal alterations may occur gradually or intermittently over long periods of time with the disease. A prospective longitudinal evaluation of the CT in OSAS patients will help shed further light on the role of the choroid in OSA. Another limitation is that the current operating software of the RTVue OCT does not provide automatic segmentation of the choroid. Manual segmentation might introduce some inaccuracy and to decrease this, the measurements from the two independent observers were averaged in our study.

In conclusion, we observed that OSAS patients had thinner CT nasal to the fovea, and nasal CT of OSAS patients negatively correlate with AHI. This is especially important for the patients who have any additional systemic disease that could potentiate the deterioration of the choroid. This may have clinical implications in terms of the ophthalmological disease's progression and visual function.

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