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ORIGINAL PAPER

Effect of obstructive sleep apnea syndrome on corneal thickness

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Abstract Obstructive sleep apnea syndrome (OSAS) might be a risk factor for the development of eye disorders. The aim of the study was to evaluate the effect of OSAS on central corneal thickness (CCT). A total of 195 patients were enrolled in the study, and underwent polysomnography. Patients were divided according to their apnea-hypopnea index (AHI) scores into control group (AHI < 5), mild (AHI, 5–15), moderate (AHI, 15–30), and severe OSAS (AHI > 30) groups. In ophthalmological examinations, CCT, auto refractometer measurement, tear break-up time, and Schrimer's test results were evaluated. Central corneal thickness was significantly decreased in patients with OSAS compared to the control group (542.14 ± 31.21 vs. 569.92 ± 13.46, $p < 0.001$). As the severity of OSAS increased, CCT decreased (mild OSAS $= 567.48 \pm 23$ mm, moderate OSAS $= 530.21 \pm 30.2$ mm, and severe OSAS $= 557.97 \pm 16.52$ mm, respectively, $p < 0.001$). The mean values of auto refractometer, tear break-up time, and Schrimer's test were similar between the groups ($p > 0.05$). CCT was negatively correlated with AHI, oxygen desaturation index, desaturation percentages, and positively correlated with minimum oxygen saturation values ($p < 0.05$). This study showed that central corneal thickness is inversely correlated with the severity of OSAS. OSAS affects all organ systems particularly cardiovascular and neurological mechanisms. Further studies are warranted to evaluate the effect of OSAS treatment on CCT.

Keywords Obstructive sleep apnea syndrome · Central corneal thickness · Hypoxia · Polysomnography · Ophthalmic changes

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of complete or partial

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upper airway obstruction during sleep. The repetitive airway obstruction leads to increasing respiratory efforts, intermittent arterial oxygen desaturation, systemic and pulmonary arterial blood pressure surges, and sleep disorders [1]. The association between OSAS and ophthalmic pathologies including floppy eyelid syndrome, glaucoma, keratoconus, papilledema, optic neuropathy, and non-arteritic ischemic optic neuropathy have been reported in the literature [2–4]. It has been postulated that during respiratory events in the sleep, recurrent episodes of hypoxemia and hypercapnia may increase the intracranial pressure and sympathetic activation which contribute to the development of ocular pathology.

The cornea is the transparent part of the eye and contributes nearly 60 % of the eye's focusing power, and accounts for the two-thirds of the eye's total optical power. Measurement of central corneal thickness (CCT) is clinically very important in ophthalmology in terms of preoperative evaluation of the patients before refractive surgery [5, 6]. Ophthalmologists currently use ultrasound pachymetry (UP) to measure corneal thickness. The advantages of UP are its easy availability, portability, besides it has higher degrees of intra-examiner, inter-examiner, and inter-instrument reproducibility in the evaluation of normal corneas [7–9].

With this background in mind, we designed this large-scale study to evaluate the association of CCT with the severity of OSAS assessed by apnea-hypopnea index (AHI) and arterial oxygen saturation in patients with OSAS.

Materials and methods

Subjects and study design

Three hundred and ninety eyes of 195 patients who were diagnosed as OSAS after full-night polysomnography (PSG) performed between May 2013 and June 2014 were included in the study. Based on their AHI scores, patients were categorized in control group (AHI < 5), mild (AHI $= 5$–15), moderate (AHI $= 15$–30), and severe OSAS (AHI > 30) groups according to American Academy of Sleep Medicine (AASM) Task Force criteria [10]. Patients with central sleep apnea syndrome, upper airway resistant syndrome, narcolepsy and movement disorders were excluded from the study. We also excluded patients with a history of eye surgery, refractive laser treatment, contact lens implantation, corneal disease, ocular trauma, diabetes mellitus, vasculitis, dry eye syndrome, keratoconus, floppy eyelid syndrome, anti-glaucoma drug use, and ocular hypertension from the study in order to evaluate isolated effect of OSAS on CCT. Data related to demographic characteristics, sleep patterns, medical history, medication use, and habits were retrieved using a standardized questionnaire survey applied before the sleep study. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all of the subjects. The study protocol was reviewed and approved by the local Institutional Review Board and Ethics Committee of Gaziosmanpaşa University Faculty of Medicine.

Polysomnographic evaluation

Using a 55-channel polysomnograph (Alice® Sleepware, Philips Respironics, USA) overnight PSG, and the following examinations were performed in all patients: electrooculograms (two channels), electroencephalograms (four channels), electromyograms of the submental muscles (one channel), and anterior tibialis muscle of both legs (two channels); electrocardiograms, airflow measurements (with oro-nasal thermistor and nasal cannula pressure transducer), body position sensor which discerns changes in the body position during sleep, and a snore sensor for the detection of snoring vibrations. Respiratory efforts of chest and abdominal muscles (two channels) were recorded using piezo-electric belts, and arterial oxyhemoglobin saturation (SaO2: one channel) by pulse oximetry with a finger probe. The recordings were scored according to the standard criteria of AASM. Apnea was defined as $\geq$90 % decrease in the air flow amplitude persisting for at least 10 s relative to the baseline amplitude. Hypopnea was defined as $\geq$30 % decrease in the air flow amplitude relative to the baseline values associated with $\geq$3 % oxygen desaturation, all sustaining for at least 10 s [11]. AHI was calculated as the number of apneic plus hypopneic episodes per hour of sleep. Patients with AHI $\geq$5 events/h were diagnosed as having OSAS. Oxygen desaturation index (ODI) was defined as the total number of measurements of oxyhemoglobin

desaturation of ≥4 % within ≥10 s to <3 min from the baseline, divided by the total sleep time.

Ophthalmologic examination

Corneal thickness measurements and detection of dry eye

The cornea was anesthetized with topical proparacaine hydrochloride 0.5 % (Alcon-Couvreur; Puurs, Belgium), and CCT measurements were obtained three times using an ultrasonic pachymeter (Optikon 2000 SPA; Pacline, Rome, Italy). The subject was seated on a chair and asked to fix his/her gaze on a distant target, while the ultrasound probe was aligned perpendicular to the mid-pupillary axis of the cornea of the undilated eye and gently placed in contact with the cornea. The CCT was measured by an ophthalmologist. Measurement results of one eye from each subject were randomly used for the statistical analyses.

The tear break-up test was carried out with a sterile fluorescein strip placed in the fornix of the lower eyelid. The patient was asked to blink twice and then look straight ahead, without blinking. The time elapsed to the appearance of the first defect in the stained tear film was measured as the tear film break-up time (TBUT). The mean of three consecutive tear break-up (TBU) test results was calculated.

The Schirmer test was carried out under anesthesia. Three minutes after instillation of two proparacaine hydrochloride 0.5 % eye drops, the lid margin was dried with cotton. The Schirmer test strip was placed in the lower temporal fornix in the junction of the middle and lateral one-third of the eyelid. The patient was asked to keep both eyes fixed, and 5 min later the strip was removed and the amount of wetting in millimeters was recorded from the strips. The dry eye tests were performed within the same time interval (from 10.00 to 14.00 h) at a temperature of 20–25 °C and relative humidity of 35–45 %.

Statistical analysis

Continuous data were presented as the mean ± standard deviation. χ^2 test was used to compare the categorical data among groups. Categorical variables were presented as a numbers and percentages. One-way analysis of variance was used to compare continuous data with normal distribution among groups. In one-way analysis of variance (ANOVA), for multiple comparisons, Tukey HSD post hoc test was used. Kruskal–Wallis analysis of variance was used to compare the continuous data with non-normal distribution among groups. In Kruskal–Wallis analysis of variance, for multiple comparisons, Bonferroni Correction-Mann–Whitney *U* test was used. Relationships between the variables of simple correlation analysis were examined using Pearson's correlation coefficient. Statistical significance level of p was 0.05. Statistical analysis was performed by using commercial software (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Results

The clinical characteristics and polysomnographic parameters of the study population are presented in Table 1. Study population consisted of 128 (65.6 %) men and 67 (34.4 %) women. Mean age and body mass index (BMI) of the patients were 50.02 ± 11.97 years, and 32.60 ± 6.33 kg/m^2, respectively. A total of 169 (86.7 %) patients were classified as having OSAS, while 26 (13.3 %) patients with an AHI < 5 constituted the control group. Thirty-one (15.9 %), 31 (15.9 %), and 107 (54 %) study participants were categorized as the mild ($n = 31$; 15.9 %), moderate ($n = 31$; 15.9 %), and severe OSAS ($n = 107$; 54 %) groups, respectively. As expected, AHI, ODI, minimum oxygen saturation, and desaturation index (%), distribution of sleep stages were significantly different between groups ($p < 0.05$; Table 1).

Ophthalmologic evaluation findings of the study groups are presented in Table 2. Central corneal thickness was significantly decreased in patients with OSAS compared with the control group (542.14 ± 31.21 and 569.92 ± 13.46, $p < 0.001$). Also CCT values were different between patients with mild, moderate, and severe OSAS ($p < 0.001$). As severity of OSAS increases, CCT significantly decreases ($p < 0.05$; Table 2), whereas autorefractometer measurements, Schrimer test results, and tear break-up time measurements were similar in all groups ($p > 0.05$; Table 2).

Correlations between polysomnographic and ophthalmologic parameters were evaluated. CCT was

Table 1 Demographic and polysomnographic findings of the study population

	Control group ($n = 26$)	Mild OSAS ($n = 31$)	Moderate OSAS ($n = 31$)	Severe OSAS ($n = 107$)	*P* value
Age (year)	42.5 ± 15.3	49.16 ± 10.62	48.58 ± 8.31	52.5 ± 11.61[a]	**0.001***
Gender, male *n* (%)	11 (42.3)	24 (77.4)	25 (80.6)	68 (63.6)	**0.009**
BMI (kg/m^2)	30.83 ± 6.71	30.28 ± 4.95	31.22 ± 4.61	34.01 ± 6.66[b]	**0.005***
Polysomnographic findings					
Stage 1 (%)	9.16 ± 9.26	5.99 ± 3.96	9.14 ± 11.83	8.08 ± 7.81	0.828**
	5.15 [3.1–13.1]	5.3 [2.9–7.9]	5.5 [3.5–10]	6.5 [2.7–10.6]	
Stage 2 (%)	56.47 ± 16.55	53.96 ± 17.39	54.7 ± 18.24	62.87 ± 15.79[b]	**0.011***
Stage 3 (%)	24.99 ± 16.01	27.71 ± 12.5	22.21 ± 12.77	19.01 ± 11.66[b]	**0.004***
REM (%)	9.84 ± 8.28	14.83 ± 7.5	13.04 ± 8.29	10.45 ± 6.74[b]	**0.012***
SE (%)	76.5 ± 21.58	79.78 ± 10.74	80.79 ± 13.74	81.85 ± 10.11	0.782**
	81.55 [75–89.1]	81.9 [72.1–88.9]	85.2 [77.9–90.9]	83.2 [74.9–89.4]	
AHI	4.07 ± 8.25	9.72 ± 2.73	21.79 ± 4.13	55.13 ± 20.06	**<0.001****
	2.35 [1.3–4][c]	9.6 [7.2–12.1]	21.6 [18.3–25.3]	51.7 [39.3–71.9][d]	
Average O_2 sat (%)	94.54 ± 7.75	95.42 ± 1.57	92.1 ± 15.48	92.76 ± 3.18	0.178*
Minimum O_2 sat (%)	88.62 ± 13.78	88.58 ± 2.51	84.74 ± 4.6	72.21 ± 12.78	**<0.001****
	91 [89–92]	89 [87–90]	85 [81–89][a]	75 [64–83][e]	
Desaturation (%)	0.26 ± 0.5	1.19 ± 1.73	3.82 ± 18.97	13.85 ± 18.12[e]	**<0.001***
ODI	5.1 ± 10.43	6.28 ± 3.99	19.84 ± 25.04	53.43 ± 24.39	**<0.001****
	1.75 [0.9–3.8]	5.6 [3.3–8.5]	15.9 [11.4–21.9][a]	47.9 [34.2–71.2][e]	

Statistically significant results were written as bold

BMI body mass index, sleep stages are given as % of total sleep time, *Desaturation* (%) sleep time of SpO_2 <90 %, *REM* rapid eye movement, *SE* sleep efficiency, *AHI* Apnea-Hypopnea Index, *sat* saturation, *ODI* oxygen desaturation index

* ANOVA test was used. Tukey HSD test was used for multiple comparisons

** Kruskal–Wallis test was used. Bonferroni correction was used for multiple comparisons

[a] There is significant difference with group 1

[b] There is significant difference with group 2

[c] There is significant difference with group 3,4

[d] There is significant difference with group 2,3

[e] There is significant difference with group 1,2,3

Table 2 Ophthalmologic evaluation findings of study groups

	Control group ($n = 26$)	Mild OSAS ($n = 31$)	Moderate OSAS ($n = 31$)	Severe OSAS ($n = 107$)	*P* value
Central corneal thickness millimeters (mm)	569.92 ± 13.46	567.48 ± 23	557.97 ± 16.52	530.21 ± 30.21[a]	**<0.001****
	571 [561–577]	570 [556–584]	561 [547–570]	534 [505–558]	
Auto refractometer (diopter)	0.65 ± 0.99	0.44 ± 1.19	0.57 ± 1.07	0.88 ± 1.4	0.293
Tear break-up time (seconds)	9.88 ± 4.84	10.9 ± 4.87	11.52 ± 4.57	9.79 ± 4.28	0.226
Schirmer's test millimeters (mm)	10.29 ± 4.46	12.64 ± 5.72	13.82 ± 5.54	11.7 ± 5.4	0.100

Statistically significant results were written as bold

** Kruskal–Wallis test was used. Bonferroni correction was used for multiple comparisons

[a] There is significant difference with group 1,2,3

negatively correlated with AHI, ODI values, desaturation percentages, and positively correlated with minimum O_2 saturation values ($p < 0.05$; Figs. 1, 2; Table 3).

Discussion

The salient findings of the present study are as follows: firstly, CCT was found significantly lower in patients with OSAS than control group. Secondly, CCT decreases as the severity of OSAS and degree of hypoxemia increases.

Intermittent episodes of hypoxia are major physiologic characteristics of OSAS which resemble symptoms of ischemia–reperfusion injury [12]. Intermittent hypoxia and arousals from sleep can lead to increases in sympathetic activity [13]. Ocular pathologies such as retinal vascular tortuosity, floppy eyelid syndrome, glaucoma, keratoconus, papilledema, optic neuropathy, non-arteritic ischemic optic neuropathy, retinal vein occlusion, and central serous chorioretinopathy have been described in patients with OSAS [2–4, 14–18]. The pathogenesis of ocular complications in OSAS is likely to have a multifactorial origin that includes ischemia–reperfusion injury, hypercoagulability, production of free radicals, increased oxidative stress, endothelial dysfunction, direct anoxic damage to the optic nerve, indirect optic nerve damage due to blood pressure variations and sympathetic overactivity [19, 20]. Chronic hypoxia reduced cell viability which accompanied by lactate dehydrogenase release, increased mitochondrial reactive oxygen species, intracellular nitric oxide and calcium levels; and decreased superoxide dismutase activity, and cellular ATP contents [21]. Another reason to corneal thinning is hypoxia-induced stromal acidosis. This is mainly caused by anaerobic glycolysis under the hypoxic conditions [22]. Acute hypoxia can cause increase to central corneal thickness with swelling [23], while corneal swelling diminishes over time. It was documented that keratocyte loss may be observed due to chronic hypoxia in patient with extended contact lens wearer and this situation may cause reduction of corneal thickness [24]. Moreover, the exposure to hypoxia promotes several transcription factors, including nuclear factor-κB (NF-κB), which plays a central role in stimulating the proinflammatory cytokines TNF-α and IL-6 [25]. These cytokines are overexpressed in the tears of subclinical and

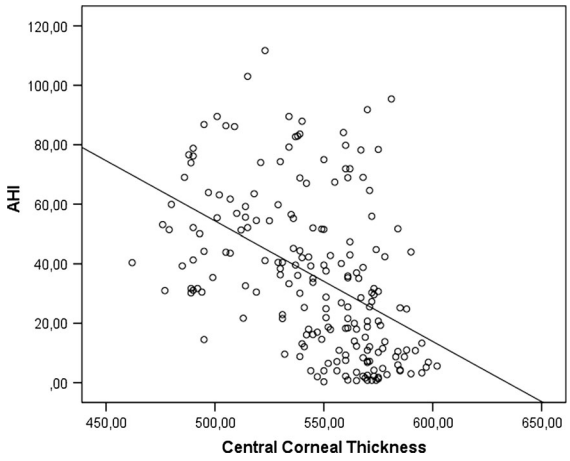

Fig. 1 Correlation between CCT and AHI

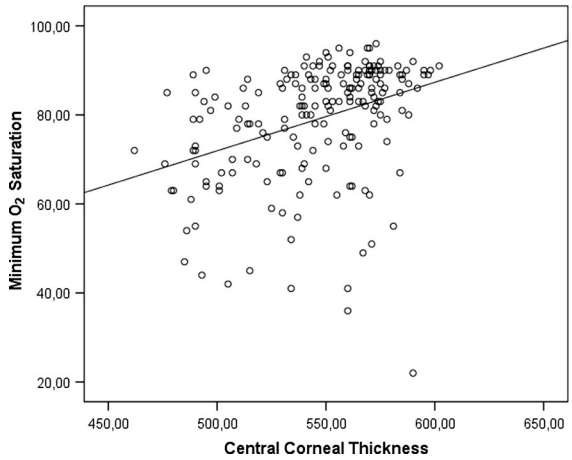

Fig. 2 Correlation between CCT and minimum O_2 saturation

Table 3 Correlations between polysomnographic parameters and central corneal thickness

	Central corneal thickness	
	*r**	*p* value
Apnea-hypopnea index	−0.469	<0.001
Minimum O_2 saturation (%)	0.359	<0.001
Desaturation (%)	−0.206	0.004
Oxygen desatüration index	−0.443	<0.001

* Pearson correlation coefficient was used

keratoconic eyes that characterized by progressive corneal thinning [26].

Hypoxia and hypercapnia cause significant changes in the corneal epithelium, stroma, and endothelium. Stromal changes include stromal edema, and acidosis, neovascularization, changes in corneal shape, and ultimately, corneal thinning. Central corneal thickness was significantly decreased in patients with OSAS compared with the control group in our study. Another important finding is that CCT decreases as the severity of OSAS increases. Furthermore, we also found that CCT was negatively correlated with ODI values, desaturation rates, and positively correlated with minimum O_2 saturation values. In other words, the depth of hypoxemia and hypoxia time in sleep is also associated with decrease in the corneal thickness. Hypoxemia might be triggering factor for development of ocular pathology in OSAS patients as it is caused cardiovascular disease. Indeed, results of many studies have supported this hypothesis. Purvin et al. suggested that intracranial pressure increases as a result of episodic nocturnal hypoxemia, thereby leading to papilledema and increased risk of visual loss in OSAS [27]. Karakucuk et al. showed visual field defects in OSAS patients despite normal ophthalmological examination. The main postulated mechanism of visual problem is optic nerve damage caused by cerebral ischemia in OSAS patients [14].

Our study yielded important outcomes in that it was conducted in a relatively larger patient population and also emphasized the importance of severity of OSAS and degree of hypoxemia as for CCT in cases with OSAS. However, the limitations of our study have to be mentioned. Firstly, our OSAS patients were older than the control group which may have an additional effect on the intergroup difference regarding CCT values. However, we showed that CCT decreases as the severity of OSAS increases. This negative correlation between OSAS and CCT, might be independent from age effect. We did not follow the patients prospectively and did not investigate the effect of continuous positive airway pressure treatment on CCT.

As a result, it should be noted that OSAS may cause ophthalmic pathologies like other systemic complications. Eye conditions are associated with a number of other risk factors, but OSAS is an important and treatable additional risk factor, therefore ophthalmologists should be alert to the possibility of sleep disorders in their patients, and sleep physicians should similarly be alert to the possibility of eye disorders in their patients with OSAS. The contribution of changes in ocular findings in the gold standard treatment of OSAS with continuous positive airway pressure therapy should be investigated in patients with ophthalmic pathologies.

Compliance with ethical standards

Conflict of Interest None of the authors has conflict of interest with this submission.

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