ORIGINAL ARTICLE

Choroidal Thickening in Patients with Sleep Apnea Syndrome

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ABSTRACT

Sleep apnoea syndrome (SAS) is characterised by repetitive episodes of cessation of breathing during sleep, resulting in hypoxaemia and hypercapnia. Ophthalmological consequences such as glaucoma, non-arteritic anterior ischaemic neuropathy and papilloedema are relevant to hypoxaemia. The choroid is a vascular structure that performs several regulatory functions for the retina. Defects in this structure contribute to degenerative, inflammatory, and neovascular changes in the retina. The authors examined the choroidal thickness (CT) in sleep apnoea patients using optical coherence tomography (OCT). The sleep apnoea patients were divided into subgroups according to their apnoea-hypopnoea index (AHI) scores, and statistical analysis was performed using the AHI and minimal arterial oxygen saturation (min. SpO₂) values. There was a medium-high negative correlation between CT and AHI (Spearman rho: $r = -0.744$, $p = 0.000$), and a positive correlation between CT and min. SpO₂ values (Pearson correlation: $r = 0.308$, $p = 0.000$).

Keywords: Choroidal thickness, hypoxia, optical coherence tomography, sleep apnoea syndrome

INTRODUCTION

Sleep apnoea syndrome (SAS), a common disorder, is characterised by repetitive episodes of cessation of breathing during sleep, resulting in hypoxaemia and sleep disruption.¹ Obstructive SAS is associated with multisystemic pathologies, involving cardiovascular, respiratory, neurological, haematological, psychiatric, and ophthalmological systems.¹ The effects of SAS and associated pathologies in ophthalmology are glaucoma, non-arteritic anterior ischaemic neuropathy, papilloedema, and floppy eyelid syndrome.² The common pathophysiologies in these conditions are, after intermittent apneic episodes, hypoxia and hypercapnia, sympathetic activity that causes increases in vasospasm, decreases in serum nitric oxide (NO), elevated intracranial pressure, and at the end of these processes optic nerve damage.^{2–4}

The choroid is a vascular compartment that provides oxygen and nourishment to the outer retina, has the main role in the thermoregulation of the retina, secretes growth factors, and adjusts the position of the retina by changing its thickness.^{5,6} Choroidal defects can cause degenerative changes and neovascularisation. The choroid seems to play a pathophysiological role in many disorders affecting the retina, such as age-related macular degeneration (AMD), central serous chorioretinopathy, polypoidal choroidal vasculopathy, and Vogt-Koyanagi-Harada disease.⁵

In the literature it has been reported that retinal blood flow decreases in hypertensive retinopathy, age-related macular degeneration, anterior ischaemic optic neuropathy, and smoking.⁷ It has also been reported that choroidal thickness (CT) is significantly lower in patients with chronic central

serous chorioretinopathy,^{8,9} Vogt-Koyanagi-Harada disease,^{10,11} pathological myopia,¹² AMD,¹³ age-related choroidal atrophy,¹⁴ glaucoma,¹⁵ and diabetic retinopathy,¹⁶ and in hypoxic conditions such as cigarette smoking,⁷ than it is in the normal population.

There are no published studies on the relationship between SAS and CT. Therefore, in the present study, we examined choroidal thickness in SAS patients with enhanced-depth image spectral-domain optical coherence tomography (OCT), which enables cross-sectional imaging of the retina and choroids.⁵

MATERIALS AND METHODS

The study adhered to the tenets of the Declaration of Helsinki. It was approved by the local ethics committee (Meeting: 2011/1; Document No: 10) and written informed consent was obtained from all patients before they had been recruited into the study.

Two hundred and forty-six eyes of 123 patients (68 males, 55 females) who were diagnosed with SAS after full-night polysomnography between January 2011 and June 2013 were included in the study. Eighty eyes of 40 subjects (19 males, 21 females) recruited from the patients' healthy relatives with no history of ophthalmological diseases constituted the control group. The control group was examined to exclude the possibility of SAS by inquiring about snoring, daytime sleepiness, and witnessed apnoea. Daytime sleepiness was established by the Epworth Sleepiness Scale. Participants with scores of 9 and above were considered to have excessive daytime sleepiness. Family members or bed partners of the controls were interviewed about their snoring and apnoea, and subjects with these symptoms were excluded from the study. The apnoea-hypopnoea index (AHI) is defined as the total number of apnoeas and hypopnoeas divided by the hours of sleep.

Patient Selection

Between January 2011 and June 2013, 1000 patients were assessed for breathing function disorders during sleep in the Sleep Disorders Clinic and 740 patients were evaluated as SAS. One hundred and seventy patients were not screened. One hundred and twenty-three of these patients were included in the study. Three hundred and ninety of the patients were excluded from the study because of their comorbidities such as diabetes mellitus, hypertension (either untreated or on hypertension medication), and smoking tobacco. Fifty-two of the patients were excluded from the study because of their ocular pathologies such as myopia, central serous chorioretinopathy, retinitis

pigmentosa, angioid streaks, primary angle-closure glaucoma, and choroidal neovascularization.

Polysomnography

Full-night polysomnographic parameters (Embla N7000; Medcare, Reykjavik, Iceland) were recorded as follows: electroencephalography, electrocardiography, electrooculography, sub-mental and anterior tibialis muscle electromyography, nasal pressure, oronasal airflow by thermal sensor, snoring, oxygen saturation by finger oximeter, and respiratory effort by thoracic and abdominal inductance plethysmography. Breathing function disorders during sleep were scored manually by the same investigator (N.H.), according to the American Academy of Sleep Medicine criteria.¹⁷ Obstructive apnoea was defined as a drop in the peak oronasal thermal sensor excursion by $\geq 90\%$ of baseline for at least 10 seconds. Hypopnoea was defined as at least a 50% drop in airflow for at least 10 seconds despite respiratory efforts and at least a 3% drop in oxyhaemoglobin saturation. Patients were diagnosed as having SAS if their AHI score was ≥ 5 . Patients with AHI values between 5 and 15, 16 and 30, and >30 were graded as mild, moderate, and severe, respectively, as defined in the report of the American Academy of Sleep Medicine Task Force, 1999.¹⁸ The minimal arterial oxygen saturation (min. SpO₂) value was measured throughout the night for each patient. Using the AHI values, the study group was separated into subgroups prior to the study.

Ophthalmological Examination

Full ophthalmological evaluations, including best-correct visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy with a three-mirror contact lens, and funduscopy were performed. CT was measured using OCT RTVue version 4.0 (Optovue, Fremont, CA, USA). OCT was performed through non-dilated pupils. Only scans that reached a signal strength of at least ≥ 6 , which indicates a high-quality scan, were accepted for analysis. Choroidal thickness measurements were taken perpendicularly from the outer edge of the retinal pigment epithelium to the choroid sclera boundary at the fovea, and at five more points that are located, respectively, 500 μm nasal to the fovea, 1000 μm nasal to the fovea, 500 μm temporal to the fovea, 1000 μm temporal to the fovea, and 1500 μm temporal to the fovea. Choroidal thickness measurements were made by two masked physicians (M.E. and H.Ç.). The average of the two measurements was used; differences between the readings of the masked physicians were found to be within 10% of the mean.

Statistical Analysis

Statistical analyses were performed with SPSS 20 (IBM, Somers, NY, USA). Analyses included an independent-samples *t* test; Kruskal-Wallis test and for post hoc comparison, a Mann-Whitney *U* test; and an analysis of variance and for post hoc comparison, a Dunnett *C* test. The degree of association between the variables AHI and CT was calculated with Spearman rho correlation coefficients. The degree of association between the variables min. SpO₂ and CT was calculated with Pearson correlation coefficients; *p* values <0.05 were considered statistically significant.

RESULTS

Two hundred and forty-six eyes of 123 patients (68 males, 55 females) were examined in the study group and 80 eyes of 40 patients in the control group. In the study group there were 21 (11 male, 10 female) patients in subgroup 1, 35 (19 male, 16 female) in subgroup 2, and 67 (38 male, 29 female) in subgroup 3.

Mean age was 53.86 ± 9.05 , 51.34 ± 11.58 , 54.24 ± 10.46 , and 50.40 ± 8.98 in subgroups 1, 2, and 3 and the control group, respectively. The mean ages of patients and controls were not significantly different from one another ($F = 1.479$, $p = 0.222$). Characteristics of the groups are presented in Table 1.

Mean CT values were 216.09 ± 44.17 and 293.51 ± 19.48 for the study and control groups, respectively. An independent-samples *t* test found a significant difference these means ($t = 9.923$, $p = 0.000$) (Table 2).

Mean CT values were 283.07 ± 26.23 , 236.04 ± 24.22 , 184.67 ± 21.35 , and 293.51 ± 19.48 for subgroups 1, 2, and 3 and the control group, respectively (Table 2). The Dunnett *C* test found significantly lower mean CT values for subgroups 2 and 3 than for the control group. The mean CT value for subgroup 1 was not significantly different than that for the control group ($p > 0.05$).

Mean AHI values for the overall study group and subgroups 1, 2, and 3 were 36.85 ± 22.87 , 11.15 ± 2.83 , 21.99 ± 3.76 , and 52.66 ± 19.38 , respectively. For the

study group, there was a significant medium-high negative correlation between CT and AHI values (Spearman rho correlation coefficient, $r = -0.744$, $p = 0.000$). As AHI values increased, the CT values decreased. Mean min. SpO₂ values (%) were recorded as 79.73 ± 8.92 , 84.70 ± 4.88 , 82.46 ± 6.72 , and 76.74 ± 8.92 in the overall study group, and subgroups 1, 2, and 3, respectively. For the study group, there was a weak but significant positive correlation between CT and min. SpO₂ values (Pearson correlation coefficient test, $r = 0.308$, $p = 0.000$). As min. SpO₂ values decreased, CT values also decreased (Table 3).

DISCUSSION

We investigated the correlation between CT values and SAS. There was a significant medium-strong negative correlation between CT and AHI values and a significant weak positive correlation between CT

TABLE 2 Mean CT values in subgroups and control group.

	<i>n</i>	CT mean value (μm)	SD	<i>p</i>
Overall study group	246	216.09	44.17	$t = -21.750$; $p = 0.000$
Control	80	293.51	19.48	$F = 478.690$; $p = 0.000$
Subgroup 1	42	283.07	26.23	
Subgroup 2	70	236.04	24.22	
Subgroup 3	134	184.67	21.35	
Control	80	293.51	19.48	

Control = subgroup 1 > subgroup 2 > subgroup 3. CT = choroidal thickness; SD = standard deviation.

TABLE 3 Correlation coefficients and *p* values for variables (AHI and CT, minimal O₂ saturation, and CT) in the SAS patients.

Variable	CT	<i>p</i>
AHI	$r = -0.744$	$p = 0.000$
Min. O ₂ saturation	$r = 0.308$	$p = 0.000$

AHI = apnoea-hypopnoea index; CT = choroidal thickness.

TABLE 1 Descriptive features of all groups.

Features	Study group			Control group
	Subgroup 1	Subgroup 2	Subgroup 3	
Number of cases	21	35	67	40
Age (mean ± SD)	53.86 ± 9.05	51.34 ± 11.58	54.24 ± 10.46	50.40 ± 8.98
Male/Female	11/10	19/16	38/29	19/21
AHI mean value	11.15 ± 2.83	21.99 ± 3.76	52.66 ± 19.38	–
Min. SpO ₂ value	84.70 ± 4.88	82.46 ± 6.72	76.74 ± 8.92	–

AHI = Apnoea-hypopnoea index (the number of apnoeic/hypopnoeic events occurring during 1 hour of sleep); CT= choroidal thickness (μm); min. SpO₂ = minimal arterial oxygen saturation.

and min. SpO₂ values. To the best of our knowledge, this is the first study investigating the relationship between CT and SAS.

The choroid is the vascular compartment of the eye and its main function is to supply oxygen and nutrients to the outer retina. Other functions include thermoregulation via heat dissipation, and modulation of intraocular pressure by adjusting the drainage of the aqueous humour from the anterior chamber, via the uveoscleral pathway. The major blood supply to the retina is the choroid, especially in darkness, where 90% of the oxygen comes from choroidal circulation.¹⁹ Because photoreceptors are extremely metabolically active, especially in darkness when the light-gated ion channels are open and active transport of ions is required to maintain ion homeostasis, over 90% of the oxygen delivered to the retina is consumed by the photoreceptors. Choroidal blood flow is regulated by parasympathetic innervation, with fibres rich in the vasodilators vasoactive intestinal polypeptide (VIP) and NO.^{20,21} Parasympathetic fibres terminate on vessels in the perivascular plexuses and mediate increases in blood flow by vasodilation. It is obvious that if choroidal blood flow decreases, clearance of debris from the retinal pigment epithelium (RPE) cells decreases and pathological changes such as degeneration and atrophy in Bruch's membrane, RPE, and the retina can occur. As a result, a structurally and functionally normal choroidal vasculature is essential for the function of the retina: abnormal choroidal blood volume and/or compromised flow can result in photoreceptor dysfunction and death.²²

Bourke et al. found that untreated systemic hypertension was associated with choroidopathy, which occurs later than the retinal vascular changes of arteriolar narrowing and arteriovenous crossing changes.²³ Regatieri et al. investigated CT in diabetic patients and observed that choroidal thinning was correlated with the severity of diabetic retinopathy. They suggested that CT was associated with retinal tissue hypoxia.²⁴ Steigerwalt et al. found a reduction in blood flow in the posterior ciliary artery following smoking, which is a good indicator of peripapillary choroidal blood flow; they proposed that this decrease was due to the increase in the vascular resistance of the vessels.²⁵ In other studies, Tamaki et al. and Sızmaz et al. reported a decrease in choroidal blood flow and choroidal thickness after cigarette smoking.^{7,26}

SAS is characterised by repeated episodes of obstruction of the airway, resulting in cessation of breathing for 10 seconds or longer during sleep.² Clinical findings of the relationship between SAS and oculo-vascular health include glaucoma, non-arteritic anterior optic neuropathy, papilloedema, and floppy eyelid syndrome.² The immediate physiological effects of sleep apnoea involve hypoxia, hypercapnia, and inspiratory effort. It is hypothesised that hypoxia and hypercapnia lead to damage of the optic nerve.²⁷

Narkiewicz and Somers reported that hypercapnia is circumvented during sleep because chemoreceptor sensitivity is decreased nocturnally,²⁸ and hypoxia, detected by carotid chemoreceptors, leads to an increase in blood pressure. Additionally, Berry and Gleeson and Smith et al. reported a sympathetic activation after inspiratory effort, sleep arousal, and sleep disturbance.^{29,30} Intermittent sympathetic activity and sleep disturbance results in vasoconstriction and in transient elevations in blood pressure.^{31,32} Phillips et al. observed that the stress caused by recurrent episodes of apnoea results in increased levels of endogenous endothelin, a long-lasting vasoconstrictor, and they also observed increased blood pressure and endothelin-1 concentrations after 4 hours of untreated obstructive apnoeas.³³ Additionally, Schulz et al. reported a reduction in level of NO, which is a known vasodilator, in SAS patients.³

In accord with the above-mentioned studies and the results of our study, we suggest that choroidal blood flow decreases in SAS because of increased sympathetic activity, increased endothelin-1 concentrations, reduced NO levels, and consequently elevated blood pressure.

Manjunath et al.¹³ found the mean subfoveal CT to be $272 \pm 81 \mu\text{m}$ in England, Li et al.³⁴ found the mean subfoveal CT to be $342 \pm 118 \mu\text{m}$ in Denmark, Karaca et al.³⁵ found the mean subfoveal CT to be $315.5 \pm 78.6 \mu\text{m}$ in Turkey, and our study found the mean subfoveal CT to be 216.09 ± 44.17 and 293.51 ± 19.48 in the study and control groups, respectively. In our opinion, CT can be affected by ethnicity.

In the literature, it has been reported that choroidal thickness decreases with age.¹³ On the other hand, Shin et al. have declared that age is not a factor independently related to choroidal thickness.³⁶ In our study, mean age was 53.86 ± 9.05 , 51.34 ± 11.58 , 54.24 ± 10.46 , and 50.40 ± 8.98 in subgroups 1, 2, and 3 and the control group, respectively. The ages of patients and controls were not significantly different from one another.

Our prospective study has some limitations. We did not evaluate the results according to gender, body mass index (BMI), and we did not obtain the OCT results at the same time; however, Tan et al. have reported diurnal variation in CT.³⁷ The association between obesity and SAS is well known.³⁸ We found a negative correlation between SAS and CT. Thus, there may be an association between obesity and CT. To the best of our knowledge, this topic has not been studied in the medical literature. For this reason, this issue should be addressed in future research. Also, we did not evaluate our patients for chronic hepatitis C virus infection, chronic renal failure and haemodialysis, and systemic sildenafil drug use; these three factors have been reported to act on CT.^{39–41}

In conclusion, there is choroidal thinning in SAS patients, with a negative correlation between CT and AHI values and a positive correlation between CT and min. SpO₂ values. The thickness of the choriocapillaris and the capillary lumen diameters also decrease with age and age-related macular degeneration (AMD).⁴² If a decrease in choroidal blood flow results in decreased clearance of debris from the RPE cells, this might contribute to the pathological changes in Bruch's membrane that accompany AMD.⁶ In clinical evaluation of an SAS patient this must be considered, and pathologies such as age-related macular degeneration, which is closely related to choroidal pathology and which can develop early, must be taken into consideration. Further investigation with SAS patients could examine their CT, as measured by spectral-domain OCT, to correlate choroidal blood flow, CT, and SAS.

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

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