• Clinical Research •

Effects of obstructive sleep apnea on retinal microvasculature

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Abstract

● **AIM:** To detect retinal microvascular variations in obstructive sleep apnea syndrome patients.

● **METHODS:** This prospective, observational case-control study included healthy controls and patients with mild, moderate, and severe obstructive sleep apnea syndrome. Vascular parameters, foveal avascular area, and flow areas in macula-centered, 6.00×6.00 mm^2 scan size optical coherence tomography angiography images were compared.

● **RESULTS:** The control group had the highest whole image, parafoveal, and perifoveal vessel density among the groups in both superficial and the deep capillary plexus (all P<0.05). Rapid eye movement sleep apnoea-hypopnoea index was reversely correlated with whole (Rho=-0.195, P=0.034), parafoveal (Rho=-0.242, P=0.008), perifoveal (Rho=-0.187, P=0.045) vessel density in the superficial capillary plexus, and whole (Rho=-0.186, P=0.046), parafoveal (Rho=-0.260, P=0.004), perifoveal (Rho=-0.189, P=0.043) vessel density in the deep capillary plexus, though the mean and non-rapid eye movement sleep apnoea-hypopnoea index related with only parafoveal vessel density in the superficial capillary plexus (Rho=-0.213, P=0.020; Rho=-0.191, P=0.038) and the deep capillary plexus (Rho=-0.254, P=0.005; Rho=-0.194, P=0.035).

● **CONCLUSION:** This study shows decreased vessel density and its reverse correlation with the apnoea-hypopnoea index in patients with obstructive sleep apnea syndrome.

● **KEYWORDS:** apnoea-hypopnoea index; deep capillary plexus; obstructive sleep apnea; superficial capillary plexus; vessel density; retinal microvasculature

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a chronic sleep disorder designated nocturnal cessation (apnea) or reduction (hypopnea) in ventilation resulting in a significant decline in oxygen saturation due to upper respiratory system collapse. This condition is associated with many systemic disorders, including neurocognitive, cardiovascular, metabolic, and ocular pathologies[1-2]. An increased prevalence of central serous retinopathy, glaucoma, floppy eyelid syndrome, ischemic optic neuropathy, retinal and choroidal pathologies have been reported in OSAS[3-4].

Nocturnal cardiorespiratory monitoring of full night sleep in a polysomnography (PSG) unit is used to diagnose disease severity by calculating the apnoea-hypopnoea index (AHI), the number of apnoeas, and hypopnoeas per hour during sleeping. The severity of OSAS is classified depending on AHI (number/hour) as none (AHI<5/h), mild (5/h≤AHI<15/h), moderate (15/h≤AHI<30/h), and severe (AHI≥30/h)[5].

Optical coherence tomography angiography (OCTA) has been commonly used for imaging retinal and choroidal vessels without requiring any contrast agent or dye. Recently, studies with OCTA showed alterations in the retinal vessel density (VD) in patients with OSAS[6].

We aimed to detect retinal microvascular variations and define the effects of disease severity on retinal microvasculatures in patients with OSAS.

SUBJECTS AND METHODS

Ethical Approval Consent was obtained from all participants and this research took no specific donations from public, commercial, or not-for-profit funding agencies. Muğla Sıtkı Koçman University Clinical Research Ethics Committee approved this study with a 03/I decision number and 13.02.2020 date.

In this observational case-control study, we prospectively evaluated patients diagnosed with OSAS between February

2020 and December 2021 and compared them to healthy controls (patients having an AHI<5). We included patients suffering from daytime sleepiness, concentrating difficulty, snoring, morning headache, and episodic breathing cessation during asleep and attended Muğla Sıtkı Koçman University Training and Research Hospital, Neuropsychology Clinic for a routine examination. Exclusion criteria included history of ophthalmic pathologies and systemic diseases such as diabetes mellitus, arterial hypertension, vasculitis, rheumatologic and neurologic diseases. After diagnosing OSAS with PSG and defining disease severity, patients were informed and referred to Opthalmology Clinic for ocular examination and imaging.

Patients were monitored according to the American Academy of Sleep Medicine manual for the scoring of sleep and associated events: rules, terminology and technical specifications[7]. Electro-oculography electrodes for detecting eye movements, electroencephalography electrodes in 10-20 international systems, submental and bilateral anterior tibial electromyography electrodes, and electrocardiographic electrodes for cardiac monitoring were placed. Thoracal and abdominal respiratory movements were monitored, nasal air pressure sensors and oronasal thermistors were used for detecting airflow. A pulse oximeter was used to monitor oxygen saturation. Sleep efficiency of more than 70% was accepted as eligible. Embla RemLogic PSG Software was used. Sleep stages scoring as wake, N1 sleep, N2 sleep, N3 sleep, and rapid eye movement (REM) sleep and respiration scoring offline were conducted with two certified technicians and a sleep disorder specialist neurologist (Bek S and Kutlu G), respectively, according to the American Academy of Sleep Medicine manual[7].

All patients underwent a complete ocular examination in the ophthalmology clinic, including ocular history inquiry, visual acuity, refraction, intraocular pressure (IOP) measurements, anterior and posterior segment biomicroscopic checks. Axial length (AL) was automatically measured with an optical biometer (IOLMaster 700, Carl Zeiss Meditec AG, Jena, Germany). The device estimates the average of scans and offers a standard deviation (SD). The SD under 27 μm was accepted as reliable.

Macula-centered, 6.0×6.0 mm^2 sized OCTA images were automatically taken by an expert at the same period of time (9:00-12:00 *a.m.*) to lower the effect of diurnal variations using RTVue-XR Avanti (Optovue, CA, USA) device. The VD of both superficial and deep capillary plexus (SCP, DCP) in four segments (foveal, perifoveal, parafoveal, whole), the flow area of the outer retina and choriocapillaris, foveal avascular zone (FAZ) area, and foveal thickness were automatically explored and quantified by software available in the device with the segmentation of retinal layers (Figures 1-4).

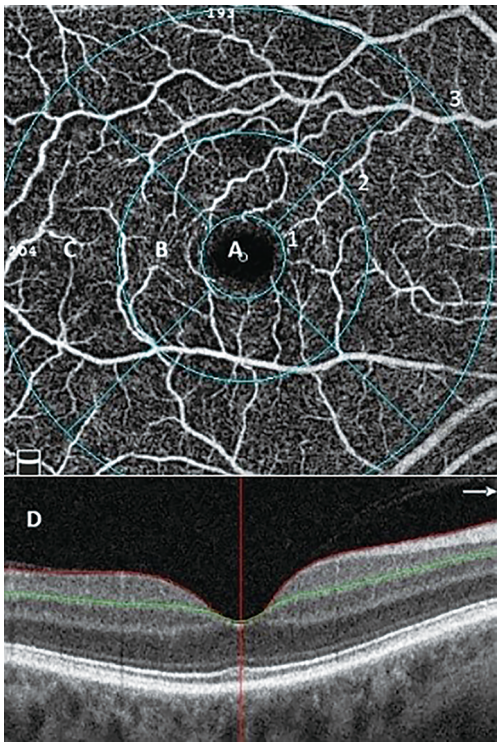

Figure 1 The whole image, foveal (A), parafoveal (B), and perifoveal (C) areas divided into 1 (1), 3 (2), and 6 (3) mm diameter rings in the superficial capillary plexus, which is located between the internal limiting membrane and the inner plexiform layer (D).

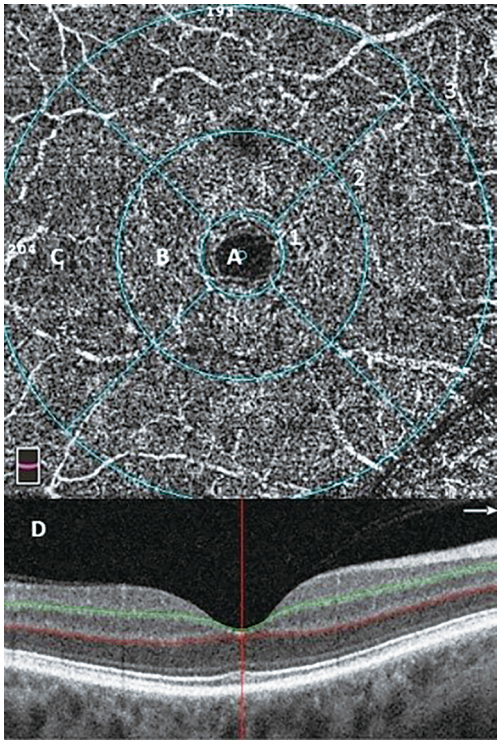

Figure 2 The whole image, foveal (A), parafoveal (B), and perifoveal (C) areas divided into 1 (1), 3 (2), and 6 (3) mm diameter rings in the deep capillary plexus, which is located between the inner plexiform layer and the outer plexiform layer (D).

The image quality was determined with the signal strength index.

Table 1 Demographic characteristics, ocular and polysomnographic findings of the groups mean±SD (range)

Parameters	Control (*n*=26)	Mild (*n*=30)	Moderate (*n*=26)	Severe (*n*=36)	*P*
Gender, *n* (%)					0.354
Female/male	7 (53.8)/6 (46.2)	9 (60.0)/6 (40.0)	6 (46.2)/7 (53.8)	7 (38.9)/11 (61.1)	
Age (y)	45.5±6.4 (36-60)	45.7±4.9 (39-58)	46.4±6.9 (36-59)	47.6±5.4 (35-57)	0.156
AL (mm)	23.26±1.35 (21.73-25.57)	23.35±1.11 (21.71-25.51)	23.88±0.62 (22.95-25.14)	23.01±0.56 (21.97-24.67)	0.462
SE (D)	-0.11±0.78 (-1.38-1.00)	0.13±0.84 (-1.75-2.00)	-0.21±0.59 (-0.88-1.00)	0.32±0.76 (-0.50-1.88)	0.738
IOP (mm Hg)	13.35±2.35 (8-18)	13.91±1.63 (11-17)	14.04±2.37 (9-19)	14.08±2.45 (10-19)	0.591
BMI (kg/m^2)	28.43±5.79 (19.1-38.4)	28.01±5.45 (20.9-39.1)	28.76±3.52 (23.5-36.3)	30.17±2.77 (29.75-39.1)	0.229
SpO_2 (%)					
Mean	94.3±1.5	93.8±1.9	93.3±1.2	91.6±1.9[a]	<0.001
Min	89.2±3.1	86.2±3.8[a]	83.7±4.5[a]	73.3±9.3[a,b]	<0.001
AHI					
Total sleep	2.29±1.31	9.71±2.29[a]	22.12±4.02[a,b]	59.43±18.86[a,b,c]	<0.001
Non-REM	1.89±1.11	8.37±2.47[a]	21.55±6.08[a,b]	58.07±23.02[a,b,c]	<0.001
REM	3.95±3.55	13.06±7.19[a]	24.47±15.45[a,b]	62.41±25.17[a,b,c]	<0.001

Kruskal-Wallis test and Chi-square test were applied to compare continuous and categorical parameters among the groups. Mann-Whitney *U* post-hoc test was performed to assess the differences between the groups. [a]*P*<0.05 *vs* control group, [b]*P*<0.05 *vs* mild group, [c]*P*<0.05 *vs* moderate group. AHI: Apnoea-hypopnoea index; AL: Axial length; BMI: Body mass index; IOP: Intraocular pressure; REM: Rapid eye movement; SD: Standard deviation; SE: Spherical equivalent; SpO_2: Peripheral oxygen saturation.

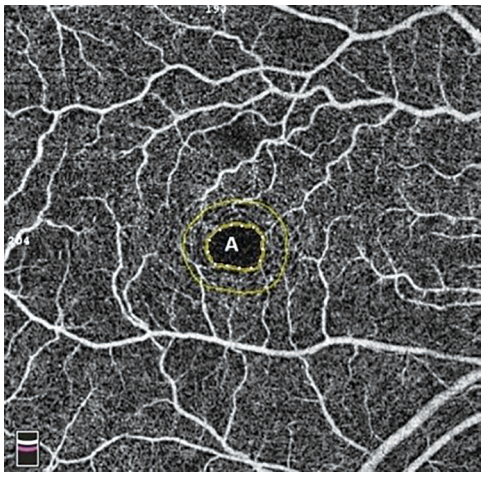

Figure 3 The foveal avascular zone automatically encircled by the device.

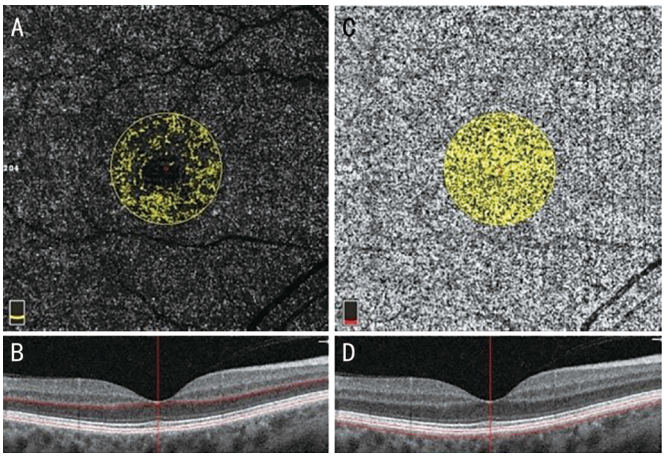

Figure 4 The 3.142 mm^2 flow area in the outer retina (A, B) and choriocapillaris (C) segmented 30 μm deep from Bruch's membrane (D).

We excluded patients with any corneal, lenticular, vascular, macular, and optic nerve pathology; amblyopia, nystagmus, glaucoma; history of previous ocular surgery; AL greater than 26 mm and less than 18 mm; spherical equivalent (SE) more than two diopters , and images with signal strength index less than 8/10.

The patients were divided into four groups for their AHI results as the control group (AHI<5), mild (5≤AHI<15), moderate (15≤AHI<30), and severe (AHI≥30) OSAS groups.

Statistical Analysis Data was recorded into the Statistical Package for the Social Sciences program, version 21.0.0.0 (IBM Corporation and other[s] 1989, 2012). Following the evaluation of normality with the Shapiro-Wilk test, Kruskal-Wallis and Chi-squared tests were applied to compare continuous and categorical variables among groups. Mann-Whitney *U* post-hoc test was performed to assess the differences between the groups. Spearman's rank correlation coefficient was used for assessing relations. Statistical significance was indicated as *P*<0.05.

RESULTS

One hundred and eighteen eyes of 59 patients were enrolled. Mild, moderate, severe OSAS and control groups had 30, 26, 36, and 26 eyes, respectively. The groups were similar for gender, age, AL, SE, IOP, and body mass index (BMI; *P*=0.354, 0.156, 0.462, 0.738, 0.591, 0.229, respectively). The mean best-corrected visual acuity was 0.0 logMAR in all groups. Pulse oximetry measurements (SpO_2) and AHI were significantly different among the groups (*P*<0.001; Table 1).

In the SCP and DCP, the control group had a significantly higher whole image, parafoveal, and perifoveal VD than the

Table 2 Comparison of the mean vessel density in SCP and DCP among the groups mean±SD

Parameters	Control (*n*=26)	Mild (*n*=30)	Moderate (*n*=26)	Severe (*n*=36)	*P*
SCP density (%)					
Whole image	53.39±1.96	51.93±2.72[a]	51.52±2.92[a]	51.85±3.29[a]	0.034
Parafovea	56.22±1.89	54.59±3.45[a]	54.30±6.53[a]	54.13±3.43[a]	0.036
Perifovea	54.05±1.83	52.58±2.94[a]	52.24±3.13[a]	52.51±3.45[a]	0.033
Fovea	22.97±7.52	21.04±7.43	21.72±8.59	21.72±6.17	0.341
DCP density (%)					
Whole image	59.41±4.12	57.06±6.09[a]	57.45±5.55[a]	57.51±4.85[a]	0.041
Parafovea	60.85±2.69	58.03±4.67[a]	57.85±4.76[a]	58.81±3.34[a]	0.032
Perifovea	61.42±4.24	59.85±6.54[a]	59.59±6.11[a]	59.44±4.96[a]	0.028
Fovea	42.11±8.27	39.93±7.52	39.15±6.37	39.67±6.43	0.141
Foveal thickness (μm)	249.88±19.42	251.01±26.83	252.70±44.34	252.91±14.05	0.858
FAZ (mm^2)	0.251±0.145	0.273±0.109	0.265±0.110	0.274±0.094	0.485
Flow area (mm^2)					
Outer retina	0.368±0.145	0.444±0.184	0.425±0.185	0.381±0.188	0.098
Choriocapillaris	2.138±0.112	2.153±0.96	2.149±0.110	2.159±0.89	0.532

The Kruskal-Wallis test was applied to compare continuous parameters among groups. Mann-Whitney *U* post-hoc test was performed to assess the differences between the groups. [a]*P*<0.05 *vs* control group. DCP: Deep capillary plexus; FAZ: Foveal avascular zone; SCP: Superficial capillary plexus; SD: Standard deviation.

Table 3 Relation between AHI, SpO_2, and the mean vessel density in SCP and DCP

Parameters	SCP density (%)			DCP density (%)		
	Whole	Parafovea	Perifovea	Whole	Parafovea	Perifovea
AHI						
Total sleep						
Rho	-0.137	-0.213	-0.112	-0.124	-0.254	-0.113
P	0.137	0.020	0.228	0.183	0.005	0.224
Non-REM						
Rho	-0.075	-0.191	-0.051	-0.064	-0.194	-0.057
P	0.418	0.038	0.585	0.489	0.035	0.542
REM						
Rho	-0.195	-0.242	-0.187	-0.186	-0.260	-0.189
P	0.034	0.008	0.045	0.046	0.004	0.043
Mean SpO_2 (%)						
Rho	-0.045	-0.021	-0.079	-0.127	-0.093	-0.139
P	0.626	0.817	0.397	0.169	0.316	0.132

Spearman's rank correlation coefficient was used for assessing relations. AHI: Apnoea-hypopnoea index; DCP: Deep capillary plexus; REM: Rapid eye movement; Rho: Spearman rank correlation coefficient; SCP: Superficial capillary plexus; SpO_2: Peripheral oxygen saturation.

VD of OSAS groups (*P*=0.034, 0.036, 0.033, 0.041, 0.032, 0.028, respectively). Foveal VD was not different among the groups (*P*=0.341, 0.141, respectively). Foveal thickness, FAZ area, outer retinal, and choriocapillaris flow area were also similar for the groups (*P*=0.858, 0.485, 0.098, 0.532, respectively; Table 2).

REM sleep AHI significantly and reversely correlated with whole (Rho=-0.195, *P*=0.034), parafoveal (Rho=-0.242, *P*=0.008), perifoveal (Rho=-0.187, *P*=0.045) VD in SCP, and whole (Rho=-0.186, *P*=0.046), parafoveal (Rho=-0.260, *P*=0.004), perifoveal (Rho=-0.189, *P*=0.043) VD in DCP, though the mean and non-REM AHI related with only parafoveal VD in SCP (Rho=-0.213, *P*=0.020; Rho=-0.191, *P*=0.038) and DCP (Rho=-0.254, *P*=0.005; Rho=-0.194, *P*=0.035). Moreover, whole, parafovea, and perifovea VD in SCP and DCP were not related to SpO_2 (Table 3).

DISCUSSION

Vascular diseases in patients with OSAS are considered to result from systemic inflammation due to intermittent hypoxia. Endothelial dysfunction and excessive platelet activation accelerate coagulation and atherosclerotic processes, leading to vascular complications[8]. Additionally, chronic hypoxemia

and hypercapnia induce some neuroendocrine, autonomic, and hemodynamic responses that result in endothelial dysfunction, endothelin production, peripheric vasoconstriction, and eventually peripheral vascular diseases[9].

The prevalence of retinal vascular diseases, such as retinal vein occlusion, diabetic retinopathy, hypertensive retinopathy, vascular sclerosis, narrowing, and nicking, also increased in patients with OSAS[10]. Some studies showed that diabetic retinopathy and maculopathy progression positively correlated with REM-AHI value[11]. Various methods can easily detect disease-related gross vascular findings after the onset of vasculopathy. However, it may be too late to treat these complications or slow down the progression after that moment. Therefore, detecting early changes in which obvious vasculopathy has not yet started may benefit for prevention of vascular complications.

This study aimed to determine the retinal microvascular changes in patients with OSAS whose eyes did not have detectable vasculopathy on fundus examination. Additionally, we planned to define the relationship between disease severity and retinal microvascular changes.

Since it was known that age, gender, best-corrected visual acuity, IOP, AL, SE, BMI, some ocular and systemic diseases could affect retinal microvascular structures, we equated the groups with seeing the pure effect of OSAS on retinal vasculature[12-13]. We found that the mean whole, parafoveal, and perifoveal VD in SCP and DCP were significantly decreased in patients with OSAS. Moreover, REM-AHI value was reversely correlated with VD in these sectors.

The mean and nonREM-AHI values were only related to parafoveal VD. Interestingly, there was no significant relation between SpO_2 and VD in these sectors. Foveal thickness, FAZ area, choriocapillaris, and outer retinal flow area did not differ among the groups.

Studies with OCTA showed decreased retinal vessel density in the eyes of patients with OSAS. Ucak and Unver[14] reported decreased VD in SCP and DCP. They also showed a significant reverse relation between the AHI value and VDs. Likewise, Yu *et al*[15] found a significant decrease in parafoveal and perifoveal VD in the eyes of patients with OSAS and reported that disease severity negatively affected these VDs.

The effects of OSAS on the FAZ area are still controversial. Some studies showed an enlarged FAZ area, while others reported reduced or unchanged FAZ area in the eyes of patients with OSAS[14,16]. In our study, the mean FAZ area was increased in OSAS groups, but the differences were insignificant compared among the groups.

Choroidal structural and vascular changes in patients with OSAS have been seen as an increased area of interest. Most case-control studies with optical coherence tomography have shown decreased choroidal thickness in patients with OSAS[17]. However, data on choroidal microvascular changes are limited. In a case-control study, Özcan *et al*[18] reported no significant change in the choroidal vascular index in patients with moderate OSAS compared to controls. Some studies suggested that patients with OSAS have an adaptive and protective mechanism, such as hypercapnia-induced vasodilatation in choroidal microcirculation[19].

Additionally, some animal studies showed an autoregulatory capacity in choroidal blood flow even though it had been known that the choroid was assumed to have no autoregulation[20]. We also found no significant differences in choriocapillaris flow area among the groups. It could be related to choroidal blood flow autoregulation.

This observational case-control study was unique in that the groups were equalized for gender, age, AL, SE, IOP, BMI, and systemic-ocular diseases were excluded to show the pure impact of OSAS on retinal and choroidal microvasculatures. However, the sample size was relatively small, and the effects of smoking, caffeine use, and OSAS treatment on these microvasculatures were not investigated.

Consequently, this novel and non-invasive technique could be used for determining OSAS-related microvascular changes and disease monitorization by imaging retinal and choroid vessels. Extensive sample-sized prospective cohort studies are required to highlight the impact of OSAS treatment on these microvasculatures.

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