Original Article

Reversibility of retinochoroidal vascular alteration in patients with obstructive sleep apnea after continuous positive air pressure and surgical intervention

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Purpose: The aim of this work was to study various retinochoroidal parameters in patients with obstructive sleep apnea syndrome (OSAS) and the effect of interventions on these parameters at 6 months follow-up. **Methods:** A total of 36 patients were recruited prospectively from the otorhinolaryngology clinics of a large tertiary center between September 2018 to March 2020. The subjects were divided into three groups depending upon intervention chosen for OSAS: Group A (surgery, i.e., uvulopalatopharyngoplasty), group B (medical therapy, i.e., continuous positive air pressure) and group C (no intervention). Various retinochoroidal parameters which were studied included retinal thickness (RT), choroidal thickness (CT), choroidal vascularity index (CVI), arteriovenous ratio (AVR), capillary density index (CDI) in superficial and deep retina, at baseline and 6 months of follow-up after the intervention. **Results:** In group A, CT increased significantly at 6 months (332.76 ± 86.41 um) compared to baseline (306.28 ± 78.19) (P = 0.0004). Similarly, CDI at both superficial and deep capillary plexus increased significantly at 6 months (superficial CDI: 0.65 ± 0.04, deep CDI: 0.38 ± 0.01) compared to baseline (superficial CDI: 0.62 ± 0.03, deep CDI: 0.36 ± 0.02) (P = 0.004 and 0.002 respectively). In group B, CT increased significantly at 6 months (361.38 ± 78.63 um) compared to baseline (324.21 ± 76.97 um) (P = 0.008). Also, CVI showed a significant decrease at 6 months (65.74 ± 1.84%) compared to baseline (67.36 ± 1.57%) (P = 0.019). In group C, all except CDI in deep capillary plexus showed a significant decrease at 6 months (0.35 ± 0.01) compared to baseline (0.36 ± 0.02) (P = 0.003). **Conclusion:** OSAS alters various retinochoroidal parameters and timely intervention in patients with OSAS can prevent these alterations. Also, these retinochoroidal parameters could serve as one of the markers to monitor the disease progression.

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Obstructive sleep apnea syndrome (OSAS) is the most common form of sleep-associated breathing disorder characterized by repetitive episodes of apnea and hypopnea that may occur several times during sleep.[1] Repetitive cycles of desaturation and reoxygenation in OSAS leads to hypoxia, hypercapnia, and a sympathetic overdrive.[2] OSAS has been linked to various cardiovascular abnormalities like hypertension, atherosclerosis and stroke, neurocognitive disorders, diabetes mellitus, gastroesophageal reflux disease, and myocardial infarction.[3,4] Patients with OSAS have been shown to have autonomic dysfunction, increase in baseline heart rate, elevated plasma catecholamine levels, reduced adrenergic vascular responses, and endothelial dysfunction.[5] Management of OSAS involves either nasal continuous positive airway pressure (CPAP) or surgical intervention that is done in adults not complaint to CPAP, those with narrow airway (macroglossia, retrognathia, tonsillar hypertrophy) or improper CPAP mask fit.[6-8]

The mechanisms of choroidal autoregulation are not clearly understood, but certain neurogenic and myogenic factors may play a role. Such factors may adversely affect the choroidal perfusion due to increased vessel wall tension and derangements such as hypercapnia that can occur in OSAS. In addition, vasodilators such as nitric oxide and vasoconstrictors such as endothelin-1 (ET-1) play a role in maintaining the perfusion of the ocular structures. In OSAS, an imbalance of these mediators or blunted response may adversely affect ocular perfusion.[9] Previous studies have reported associations between OSAS and some ocular disorders including primary open-angle glaucoma, non-arteritic anterior ischemic optic neuropathy, retinal vein occlusion, papilledema and central

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serous chorioretinopathy.[10-14] The ocular changes may result from vascular alterations in the choroidal and retinal structure which were documented using optical coherence tomography (OCT)[15,16] and OCT angiography (OCTA).[17] Though there are few studies indicating the causal effect of OSAS on retinochoroidal vasculature, there is no study evaluating the longitudinal follow-up in these eyes and documenting the effect of therapeutic intervention, if any, on retinochoroidal parameters.

The present study was aimed to evaluate angio-architectural changes in retina and choroid in patients with OSAS and the impact of therapeutic interventions (either medical or surgical) on these retino-choroidal parameters at a longitudinal follow-up of 6 months.

Methods

The index study was prospective, non-randomized including 36 eyes of 36 patients of either gender with OSAS, who presented to a tertiary referral otorhinolaryngology care center in North India. Patients were prospectively categorized into 3 groups based on the treatment chosen and compliance. Group A had 14 patients who underwent surgical correction for OSAS, Group B included 11 patients who obtained CPAP therapy and Group C, 11 patients who did not undergo any intervention. The study was approved by the Institute Ethics Committee (IEC) and was conducted in accordance with the declaration of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study.

The inclusion criteria were: a) Patients diagnosed as OSAS based on polysomnography findings b) age 18-70 years of either gender and c) patients consented to undergo treatment for OSAS (either medical or surgical measures). Patients where media clarity was obscured by the presence of cataract, vitreous haze, or any other such co-existent pathology that does not allow the acquisition of good images; patients with refractive errors more than +3D or -3D (high hyperopia and myopia, patients with any ocular pathology that can affect the retinal/choroidal thickness or vascularity such as diabetic retinopathy, macular degeneration, central serous chorioretinopathy, optic atrophy, glaucoma and uveitis and patients who do not agree to come for follow-up visits were excluded from the study. Detailed history regarding associated comorbidities including diabetes mellitus, hypertension, and breathing disorder were recorded. A detailed treatment history regarding concomitant medications being taken by the patient for several associated co-morbidities were recorded. A general physical examination was done and parameters including height, weight, BMI and AHI were measured. OSAS was graded according to the following apnea-hypopnea index (AHI) values: mild: 5–15; moderate: 15–30, and severe: AHI ≥ 30.[18]

All enrolled patients underwent complete ocular examination for best-corrected visual acuity (BCVA) by Snellen's chart (converted to LogMAR units for statistical analysis), intraocular pressure (IOP) measured by non-contact tonometer, slit-lamp biomicroscopy for anterior segment and posterior segment examination.

Pupils of the patients were dilated by instilling tropicamide 0.8%. 55-degree color fundus photographs acquired on the digital fundus camera (DRI Triton, Topcon®) with images focused on disc and macula. SS-OCT 3D and 5-Line raster scan of the macula were obtained. OCTA (DRI Triton, Topcon) using 3 × 3 mm scanning protocol at macula was performed. The acquisition was repeated multiple times and the images with the least amount of motion artifacts were selected for further analysis. The acquired images were analyzed by three independent observers (V.G., R.A., A.A. – Vitreoretina consultants). Retinal thickness, choroidal thickness, choroidal vascularity index, arteriovenous ratio and capillary density index were measured.

Retinal thickness (RT) was assessed using a central 1 mm subfield RT analyzed by a built-in software in Triton OCT. Choroidal thickness (CT) was measured by two independent graders vertically from the outer border of the retinal pigment epithelium to the inner border of the sclera. The upper border was marked at the retinal pigment epithelium and the lower border area was below the line of light pixels at the choroidal-scleral junction. The average of the two graders' measurements was used for analysis. The arteriovenous ratio (AVR) was calculated from optic disc centered digital color fundus photographs. Venular and arteriolar vessel tree extraction using VAMPIRE annotation tool (Vessel Assessment and Measurement Platform for Images of the Retina). It is equipped with semiautomated tool for Vessel segmentation and extraction. The software is available from the website: http://vampire.computing.dundee.ac.uk/tools.html. After extraction of venular and arteriolar vascular network from each fundus photograph, their diameters were assessed using ARIA (Automated Retinal Image Analyzer v1.0 software) developed at Centre for Vision and Vascular Science, Queen's University of Belfast, UK. This open-source software uses MATLAB Programming to automatically detect vessel diameter. For retinal capillary density index (CDI), all OCTA images were analyzed using Image J. A circle with a radius of 1.5 mm was centered at the subfoveal region and it was divided into 4 quadrants – superonasal, superotemporal, inferonasal and inferotemporal quadrants. Using the Niblack thresholding and ROI manager, all images were binarized and converted to 8-bits with a mean pixel value and standard deviation of all points. Subsequently, LA was highlighted within the circle with the brightness set to 0 and 254. The LA in the individual quadrant was merged with the corresponding threshold area and measured using ROI manager. The CDI of each quadrant was defined as the percentage of capillary density over the stromal area at the macula region. The global CDI was the average CDI value within the 1.5 mm-radius circle centering on the subfoveal region [Fig. 1]. CDI was obtained at both, superficial and deep retinal capillary plexus.

In order to measure the Choroidal vascularity index (CVI) central B-scan was chosen for image analyses and after performing image binarization, the image was processed on public domain software ImageJ (National Institutes of Health, Bethesda, USA). Polygon tool was used to select the total choroid area (TCA), which was added in the region of interest (ROI) manager. After converting the image into 8 bit, Niblack auto local thresholding was subsequently applied which gives the mean pixel value with standard deviation for all the points. On the SS-OCT scans, the Luminal Area (LA) was highlighted by applying the color threshold. In order to determine the LA within the selected polygon, both the areas

in ROI manager were selected and merged by 'AND' operation of ImageJ. The composite third area was added to the ROI manager. The first area represented the total of the choroid selected, and the third composite area was the vascular or LA. The CVI was calculated by dividing LA by TCA.

All participants underwent the above mentioned complete ocular examination and imaging at the initial presentation before any interventions had been started and at follow-up visits at 6 months.

The continuous parameters such as age, BMI and AHI were summarized in terms of mean and standard deviation, while other categorical parameters like gender and comorbidities were expressed in terms of frequencies and percentages. The parameter description was obtained according to study groups. The parameters age as well as AHI were compared across three groups using one-way analysis of variance, while gender distribution was compared using Pearson's Chi-square test. The mean retinochoroidal parameters were compared between baseline and 6 months. Since there was statistically significant difference in the mean age of patients in three groups, all the retinochoroidal parameters were adjusted with age in three study groups using analysis of covariance (ANCOVA). For each parameter, the adjusted mean values of three groups were compared using one-way analysis of variance, while the adjusted mean difference between baseline and 6 months for each parameter was compared using paired *t* test. All the analyses were performed using SPSS version 20.0 (IBM-SPSS Statistics, Inc, Chicago, IL) and the statistical significance was tested at 5% level.

Results

Thirty six patients diagnosed as OSAS based on polysomnography study and fulfilling the inclusion criteria were recruited. Patients were divided into three groups depending upon the intervention chosen. Table 1 summarizes the demographic details, clinical characteristics and AHI score and stage of patients. Mean age of study population was 43.47 ± 9.17 years. Patients in group C were significantly younger than group A and group B (p value = 0.005). Thirty one (86.11%) patients did not have any comorbidity, while 4 (11.11%) had hypertension and 1 (2.78%) had diabetes. The patients with comorbidities had a good systemic control and had no features of hypertensive or diabetic retinopathy. All

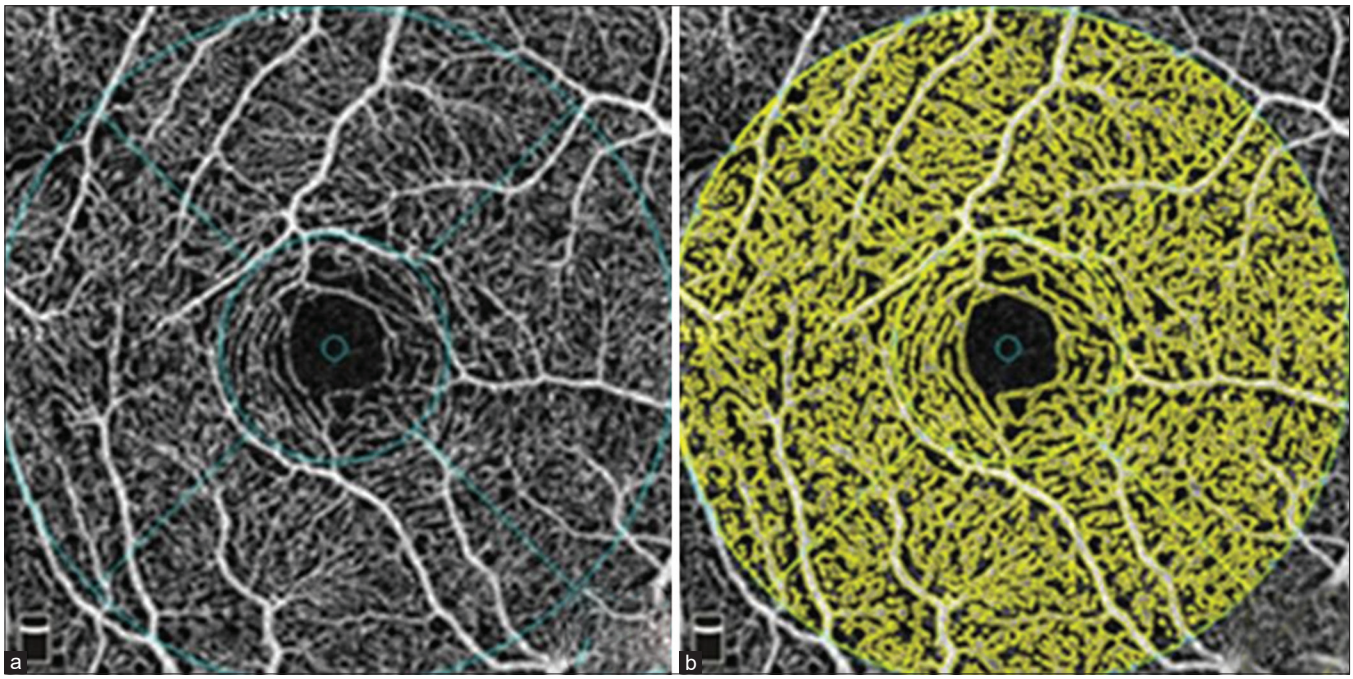

Figure 1: (a) OCTA image of superficial retinal capillary layer. (b) Binarized photograph of OCTA image

Table 1: The demographic details, clinical characteristics and AHI score and stage of patients

	Group A (*n*=14)	Group B (*n*=11)	Group C (*n*=11)	*P*
Age	45.14±7.39	48.27±8.76	36.55±8.03	0.005
BMI	28.32±3.06	30.30±4.55	29.23±2.84	0.386
Male	12 (85.71%)	10 (90.90%)	11 (100%)	0.437
Mean AHI	35.83±15.92	44.36±21.01	47.35±22.51	0.321
Moderate AHI (15-30)	6 (42.85%)	3 (27.27%)	1 (9.09%)	0.174
Severe AHI (>30)	8 (57.15%)	8 (72.73%)	10 (90.91%)	

BMI=Body mass index, AHI: Apnea Hypopnea index

Table 2: Comparison of age-adjusted retinochoroidal parameters at baseline and at 6 months follow-up within and across groups

Parameters	Baseline				6 months				$P^{\ddagger}$ (Group A)	$P^{\ddagger}$ (Group B)	$P^{\ddagger}$ (Group C)
	Group A	Group B	Group C	P^{*}	Group A	Group B	Group C	P^{*}			
RT (μm)	230.41±22.72	219.35±14.86	216.37±17.76	0.164	230.09±25.42	221.72±14.29	216.88±17.32	0.266	0.881	0.339	0.856
CT (μm)	306.28±78.19	324.21±76.97	219.69±72.98	**0.006**	332.76±86.41	361.38±78.63	235.46±78.95	**0.002**	**0.0004**	**0.008**	0.223
CVI (%)	67.37±2.51	67.36±1.57	66.22±3.22	0.245	65.99±2.20	65.74±1.84	67.32±1.01	0.985	0.096	**0.019**	0.696
AVR	0.69±0.03	0.67±0.03	0.68±0.02	0.311	0.69±0.02	0.68±0.02	0.68±0.02	0.051	0.285	0.361	0.748
CDI-superficial	0.62±0.03	0.62±0.02	0.63±0.03	0.699	0.65±0.04	0.64±0.04	0.63±0.04	0.673	**0.004**	0.127	0.597
CDI-Deep	0.36±0.02	0.37±0.01	0.36±0.02	0.747	0.38±0.02	0.37±0.01	0.35±0.01	**<0.0001**	**0.0002**	0.248	**0.003**

P-values in bold indicate statistical significance; *Obtained using one-way ANOVA; ‡Obtained using paired t-test. The mean values of parameters were obtained after adjusting with age by using analysis of covariance (ANCOVA). The comparison of parameters across groups at baseline and 6 months was carried out using one-way ANOVA, while the comparison of parameters between baseline and 6 months was performed using paired t-test. RT: Retinal thickness, CT: Choroidal thickness, CVI: Choroidal vascularity index, AVR: Arterovenous ratio, CDI: Capillary density index

patients had moderate to severe stages of OSAS. All the three groups were comparable in terms of AHI score. The distribution of cases in two groups viz., AHI: 15–30 (moderate OSAS) and AHI: >30 (severe) was statistically insignificant.

All patients had a BCVA of 20/20 (log MAR 0) in the eye included in the study. The mean IOP in Group A was 17.5 ± 2.5 mm Hg, Group B was 17.5 ± 2.9 mm Hg and in Group C was 19.1 ± 2.6 mm Hg. Mean IOP in the 3 groups was statistically insignificant ($p > 0.05$). Anterior segment and posterior segment examination were within normal limits among three groups.

Table 2 shows various age-adjusted retinochoroidal parameters at baseline and at 6 months follow-up, with intragroup and intergroup analysis. The overall mean retinal and choroidal thickness in the study population at baseline was 222.72 ± 19.62 μm and 285.31 ± 86.55 μm respectively. At 6 months follow-up the mean retinal and choroidal thickness was 223.50 ± 20.40 μm and 311.78 ± 95.40 μm respectively.

Table 2 shows that at baseline, among all parameters, the mean age-adjusted choroidal thickness differed significantly across groups ($P = 0.006$) and further continued to differ at 6 months ($P = 0.002$). The paired analysis using Tukey's test revealed a significantly low mean value for group C as compared to group A and B at both baseline and 6 months. At 6 months, the adjusted mean CDI-Deep also showed statistically significant difference across groups ($p < 0.0001$), with group C showing significantly low value as compared to other groups.

In study group A, there was a significant increase in the adjusted mean choroidal thickness from baseline (306.28 ± 78.19 μm) to 6 months (332.76 ± 86.41 μm) as indicated by a *P* value of 0.0004. Moreover, the adjusted mean CDI in superficial and deep retina increased significantly from baseline (0.62 ± 0.03 μm and 0.36 ± 0.02 μm) to 6 months (0.65 ± 0.04 μm and 0.38 ± 0.02 μm) [$P = 0.004$ and 0.0002, respectively]. The other parameters showed insignificant difference between two time points.

In study group B, the baseline mean choroidal thickness (324.21 ± 76.97 μm) increased significantly at 6 months (361.38 ± 78.63 μm) [p value = 0.008]. The mean CVI showed a significant reduction from baseline (67.36 ± 1.57) to 6 months (65.74 ± 1.84) [p value = 0.019]. The remaining parameters showed insignificant change after intervention.

In study group C, only the mean CDI in deep retina showed a significant decrease from baseline (0.36 ± 0.02) to 6 months (0.35 ± 0.01) [p value = 0.003], while rest of the parameters differed insignificantly at 6 months when compared with their respective baseline.

Discussion

Management of OSAS involves nasal CPAP or surgical intervention. CPAP is considered the gold standard for treatment of OSAS. CPAP machine by delivering a constant flow of air through the tube, creates enough pressure in the airway to prevent tissue from collapsing. Patients who are non-compliant or have difficulty using CPAP are suitable candidates for surgery.

Choroid is the most vascular layer of the eye and normal choroid is essential for the proper functioning of retina and

retinal pigment epithelium (RPE). Choroidal circulation has one of the highest rates of blood flow in the body.[19] Being such a vascular tissue, choroid is amenable to fluctuating microvascular alterations as seen in OSAS. With the introduction of OCT and OCTA, some studies have shown structural and vascular alterations in retina and choroid in OSAS patients indicating an indirect correlation between the severity of OSAS and various retinochoroidal parameters like choroidal thickness, retinal vessel density and AVR.[15-17,20] Thus these alterations may be considered as a marker for determining the vascular effects of OSAS in the retina and choroid. However, there is no study indicating the longitudinal changes and effect of intervention for correlating OSAS. We used swept-source OCT, OCTA to study several imaging markers including CVI to monitor response to therapy.

The mean choroidal thickness in our study population at baseline was 285.31 ± 86.55 μm which is less than what has been reported previously.[15,16] There was an increase in choroidal thickness following therapeutic intervention for OSAS. Choroidal thickness is considered as an indirect biomarker of choroidal circulation as both vascular and non-vascular smooth muscles in the choroid are under autonomic control.[19] Sympathetic stimulation in the eye causes vasoconstriction of uveal blood vessels and increases its vascular resistance.[21,22] Multiple factors like oxidative stress, endothelial dysfunction, unresponsiveness to various vasodilator circulating molecules, and vasoconstriction due to increased sympathetic activity may be responsible for thinner choroid.[23] Extravascular (stroma) tissue of choroid contains collagen, fibroblasts, melanocytes, and non-vascular smooth muscles. Contraction of these non-vascular smooth muscles too has been shown to decrease the choroidal thickness.[18] Both medical and surgical intervention in OSAS effectively decreases sympathetic overactivity and improves the hemodynamics that could have accounted for increased choroidal thickness post-intervention at 6 months.[24,25]

The central foveal thickness in our patients with OSAS at baseline was 222.72 ± 19.62 μm that is in contrast to report by Xin *et al.* that showed an increased foveal thickness in patients with severe OSAS.[16] The near-normal retinal thickness in our patients could be attributed to the fact that the majority of our patients had moderate OSAS patients and were comparatively younger; thus, we believe they had a shorter duration of the disease. Both the factors could account for a normal retinal thickness in our patients.

OSAS is associated with a decreased AVR in response to chronic retinal hypoxia.[20] Contrary to this, our study population had a normal AVR at baseline. This could be attributed to fact that majority of our patients had moderate OSAS.

As far as retinal capillary density index was concerned, our study showed that CDI improved in patients with intervention than patients where no intervention was done. Though CDI increased in both surgical and CPAP group, it increased significantly in surgical group. This again is attributed to improved hemodynamics and decreased sympathetic stimulation after treatment of OSAS, as described earlier.[24,25] Patients with no intervention showed a decrease in CDI, indicating increased disease severity with time. The decrease in CDI was significant in deeper layers suggesting that capillary dropout starts to happen in deeper layers first as the disease progresses.

Our study also highlighted the effect of OSAS and its intervention on CVI, a newly described parameter to measure vascular status of choroid. CVI is believed to be a relatively stable index and less influenced by physiological factors.[26] CVI is defined as vessel lumen area divided by total choroidal area. CVI thus takes into account both vascular and stromal components of the choroid. CPAP therapy significantly reduced the CVI. Though the intervention increased the total choroidal thickness, a decreasing CVI suggests that increase in stromal area is much more than vascular area. Hemodynamic changes dues to CPAP therapy are complex.[27] CPAP therapy helps in recruitment of collapsed alveoli and causes chest inflation, thus increasing intrathoracic pressure.[28] Increased intrathoracic pressure causes decrease in both preload and afterload to heart.[29,30] CPAP has also been shown to redistribute extracellular water in pharyngeal soft tissue.[31] We believe that these complex hemodynamic changes might cause expansion of choroidal stromal tissue. This increase in stromal area is more than vascular luminal area. This disproportionate increase in vascular and stromal components of choroid results in a significant decrease in CVI post CPAP therapy.

Unaltered CVI and significant increase in CDI in surgical group points to the fact that surgical group might be better than CPAP therapy for OSAS patients, as far as retinochoroidal parameters are concerned. Further studies with a longer follow-up are required to compare the two treatment modalities. A potential limitation of our study is the presence of a selection bias given the retrospective nature and allocation of the patients into 3 groups without randomization. However, as shown in Table 1, the mean AHI values were not significantly different between the groups. Hence, more severe patients did not preferentially undergo surgical interventions in our cohort. A prospective study design can eliminate the selection bias and further refine the results. We measured CDI in the macular region using 3 × 3 mm scans. On the other hand, the measurement of CVI was done by using a single subfoveal OCT line scan. Thus, it may be argued that CVI may not represent the macular choriocapillaris perfusion. The utility of a single-line scan in measuring CVI has been previously assessed by our group. It has been shown that CVI obtained using a subfoveal scan adequately represents the total macular choriocapillaris perfusion.[32]

Conclusion

In short, both medical and surgical intervention in patients with OSAS is beneficial in improving the structural and microvascular alterations at the level of retina and choroid. Not only does it improve the choroidal thickness, it also improves the retinal vessel density. Disease progression in the form of decreased retinal vessel density has been shown in patients with no intervention. We believe that timely intervention in patients with OSAS can prevent microvascular alterations at retinochoroidal level. Also the retinochoroidal parameters could also serve as one of the markers to determine response to therapeutic intervention or monitor disease progression in OSAS.

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Conflicts of interest

There are no conflicts of interest.

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