Retinal vascular impairment in patients newly diagnosed with obstructive sleep apnea syndrome

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Background: To evaluate retinal morphological and vascular parameters in patients recently diagnosed with obstructive sleep apnea syndrome (OSAS) and determine the correlation between retinal vascular density and the severity of OSAS.

Methods: We performed a retrospective study on the retinal vasculature of patients with OSAS and age-match healthy controls. OSAS was confirmed by full-night cardiorespiratory polygraphy. Patients were divided into three groups according to disease severity given by apnea-hypopnea index (AHI) i.e., mild, moderate or severe. Retinal thicknesses and vascular density were compared among groups, for both the macula and optic disc. Correlation between vascular density and clinical features were also assessed.

Results: The study included 30 eyes of patients with OSAS and 12 controls. No differences were found regarding retinal thickness in both the macula and the optic disc between OSAS patients and controls. In contrast, significant differences were found in the peripapillary vessel density between groups versus control patients. The greatest difference being between severe OSAS and controls (49.4% ± 2.1 versus 40.4% ± 4.2 respectively, p=0.01). Peripapillary vessel density was found to significantly and negatively correlate with AHI (p=0.02; r= -0.74) and directly correlate with the lowest percutaneous oxygen saturation (p=0.02; r= 0.58).

Conclusions: This study indicates that OSAS is associated with retinal microvasculature impairment, that seems to mainly affect the optic disc. This suggests that microvascular damage increases with the increasing severity of OSAS. As such, prospective trials are needed to clarify if this vascular peripapillary damage precedes glaucomatous optic neuropathy in OSAS patients.

Key words: OSAS; glaucoma; oct-a; retinal density.
Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAS) is a potentially serious condition and is the most common sleep breathing disorder with almost one billion people affected [1]. It is characterized by repetitive nocturnal oxygen desaturation [2]. OSAS has been revealed as a leading cause of several cardiovascular disorders. Accumulating evidence has linked OSAS to hypertension, type 2 diabetes mellitus, coronary artery disease, heart failure, and cardiac arrhythmias [3].

OSAS has also been linked to some ophthalmological conditions. Specifically, studies have suggested that OSAS is a risk factor for anterior ischemic optic neuropathy, central serous retinopathy, retinal vein occlusion and both normal tension glaucoma (NTG) and open angle glaucoma (OAG) [4,5]. However, the specific mechanism for glaucomatous optic neuropathy in OSAS has not been established yet [6]. Some theories have suggested a vascular mechanism, with susceptible optic nerves being damaged due to poor blood flow. Some current studies have reported lower saturations were taken into account. Oxygen desaturation index (ODI) represents the complete vessels density of the superficial capillary plexus (SCP) in the parafovea. The vascular density is the percentage of signal positive pixels per total pixels in an area of 6x6mm retinal thickness macular and optic disc diameter of 2.5 mm centered on the FAZ. The parafovea was defined as an annular region extending from the outer edge of the parafovea to an outer diameter of 5.5 mm. Foveal avascular zone (FAZ), peripapillary and parafoveal superficial vascular density were automatically evaluated. Radial peripapillary capillary density (RPCD) concerns to the radial peripapillary plexus that runs superficially in the NFL. Superficial parafoveal vascular density (SVD) represents the complete vessels density of the superficial capillary plexus (SCP) in the parafovea. The vascular density is the percentage of signal positive pixels per total pixels in an area of interest. Only automatic superficial vascular densities were considered by the software. Perifoveal and deep plexus vascular densities required subjective measurements and for that reason, we chose to exclude them from this study.

Methods

This is a single center retrospective study including patients above 18 years recently diagnosed with OSAS. Exclusion criteria were systemic conditions such as: hypertension, diabetes mellitus (DM), atherosclerosis and ophthalmological morbidities such as: refractive errors >3 diopters, media opacities, known history of glaucoma, age related macular degeneration, retinal vascular disease, optic neuropathy, and previous retinal surgery. All patients were assessed at the same week of diagnosis i.e., just before starting nocturnal CPAP therapy. The study was conducted by the principles of the Declaration of Helsinki and approval was obtained by institutional Research Committee of Hospital Garcia de Orta (Almada, Portugal). Written consent was not required due to retrospective nature of this study. Demographic and clinical data were collected, including age, gender, body mass index (BMI), and disease duration.

Polygraphic parameters were collected from a full-night cardiorespiratory polygraphy performed with portable Embletta MPR Sleep System device (Embletta, Broomfield, CO, USA). The apnea-hypopnea index (AHI, times/h) was calculated as the average number of apneas and hypopneas per hour of sleep. Apnea was defined as cessation of airflow for at least 10 s with effort to breathe. Hypopnea was a ≥30% reduction of airflow compared to the baseline for at least 10 s accompanied by an oxygen desaturation > 3% or a “micro-arousal” [9]. OSAS severity was classified according to AHI. Mild OSAS for an AHI between 5-15, moderate for AHI 15-29 and severe for AHI ≥30. Oxygen saturation (SpO2) was measured by pulse oximetry and the lowest and mean oxygen saturations were taken into account. Oxygen desaturation index (ODI, episodes/h) was defined as the average number of desaturation episodes per hour of sleep. Desaturation episodes were described as a decrease in the mean oxygen saturation ≥4% for at least 10 s. Patients with ODI less than 20/h was considered “non-desaturating” and patients with ODI ≥20/h as desaturating. Cumulative time percentage with SpO2 <90% (CT90), defined as the cumulative time spent with SpO2 <90% during sleep, was also evaluated.

Results

Our study included a total of 42 eyes from 21 patients: 12 control, 8 in the mild disease group, 10 in the moderate and 12 in the severe. Demographic and clinical data are presented in Table 1. There were 13 males (62%) and 8 (38%) females. Six patients had history of smoking.
among groups (age: 66.4±5.2 vs 70.5±9.9 vs 68±7.6 vs 65.9±3.9 years; p=0.3 and BMI: 27.1±2.6 vs 27±1.7 vs 27.5±3.6 vs 28.8±5.8 Kg/m²; p=0.8). We also found no significant difference among groups of the mean best corrected visual acuity (p=0.81). All eyes were found to have a intraocular pressure within the ranges of normality and no difference was observed among groups (p=0.47). Furthermore, all patients were found to have an iridocorneal angle grade as 3 or 4 (Schafer’s classification).

No statistically significant difference was found among groups when assessing central corneal thickness (p=0.31). In fact, all visual field examinations were found to be reliable. No visual defects were reported, and the mean defect (p=0.21) and loss of variance did not differ among groups (p=0.41).

The polygraphy data is presented in Table 2. In the control group polygraphy data was not collected. The mean AHI data for OSAS was found to be 12±2.6 episodes/hour in the mild group, 21.8±2.5 in the moderate and 51.7±19.1 in the severe. We found a correlation between severity of disease and the reduced levels of lowest oxygen saturation with the severe group showing the lowest values for lowest oxygen saturation i.e., 72±8.9 %. These differences were found to be statistically significant when compared to the moderate (p<0.01) and to mild (p<0.01) groups. Moreover, CT90% decreased with increasing severity of disease (p=0.02). The ODI was higher in the severe group (42±25 episodes/hour) than in moderate (p=0.04) and mild (p=0.03) groups. Nine patients were considered as “desaturating” and six patients as “non-desaturating”. The macular OCT and OCTA data are shown in Table 3.

Table 1. Demographic and clinical data (n=21).

|               | Controls | Mild | Moderate | Severe | p* | p° |
|---------------|----------|------|----------|--------|----|----|
| Number of patients | 6        | 4    | 5        | 6      | -  | -  |
| Gender, n     |          |      |          |        |    |    |
| Male          | 3        | 3    | 3        | 4      | -  | -  |
| Female        | 3        | 1    | 2        | 2      | -  | -  |
| Age, years    | 66.4±5.2 | 70.5±9.9 | 68±7.6 | 65.9±3.9 | 0.3 | -  |
| BMI (kg/m²)   | 27.1±2.6 | 27±1.7 | 27.5±3.6 | 28.8±5.8 | 0.81| -  |

*p Results of comparison of means among three groups with Kruskal-Wallis’ corrected by Bonferroni; °Results of comparison of means between two groups with Mann-Whitney’s test; this test was performed when p-value was inferior to 0.05 on Kruskal-Wallis’ corrected by Bonferroni; BMI, body mass index.

Table 2. Polygraphy data (n=15).

|               | Mild | Moderate | Severe | p* | p° |
|---------------|-----|----------|--------|----|----|
| AHI, /h       | 12±2.6 | 21.8±2.5 | 51.7±19.1 | -  | -  |
| Mean O₂ saturation, % | 95.1±0.9 | 93.7±1.3 | 91.5±2.7 | 0.32 | -  |
| Lowest O₂ saturation, % | 89.3±2.7 | 84.3±0.9 | 72.1±8.9 | 0.03 | -  |
| CT90 (%)      | 0.51±0.12 | 42±0.6 | 21.2±4.1 | 0.02 | -  |
| ODI, /h       | 11±4 | 16.5±1.3 | 42±25 | 0.03 | -  |

*p Results of comparison of means among three groups with Kruskal-Wallis’ corrected by Bonferroni; °Results of comparison of means between two groups with Mann-Whitney’s test; this test was performed when p was inferior to 0.05 on Kruskal-Wallis’ corrected by Bonferroni; AHI, apnea-hypopnea index; CT90, cumulative time percentage with SpO₂ <90%; O₂, oxygen; ODI, oxygen desaturation index.

Discussion

Obstructive sleep apnea syndrome is a leading cause of several cardiovascular and ophthalmological diseases caused by
microvascular impairment. Walsh and Montplaisir initially described the association between OSAS and glaucoma in 1982 and Mojon et al. published the first article reporting higher glaucoma prevalence amongst OSAS patients [10,11]. Accumulating evidence indicates that the prevalence of glaucoma and its progression are higher in OSAS patients [6]. Although the underlying mechanism of glaucomatous damage in OSAS patients is unclear, there are several potential explanations.

The mechanical theory suggests that IOP compresses the optic nerve causing glaucomatous damage. Indeed, some studies have revealed higher IOP in OSAS patients compared to controls [12-14]. However, the literature contains conflicting data regarding changes in IOP in cases of OSAS. Some studies reported that the prevalence of glaucoma in OSAS is independent of IOP [15]. Bilgin et al. found an association between normal tension glaucoma and OSAS [16]. Shinmei et al. monitored IOP during sleep with wireless contact lens sensors and found a decrease in IOP during hypopneic and apneic events [17]. These studies suggest that elevated IOP might not be the only causative factor involved in the development of glaucomatous optic neuropathy, at least in the observed patients. In our study, we found that all patients had normal IOP values and there was no difference among groups.

In contrast to the mechanical theory the vascular theory proposes that neuropathy develops as a result of vascular dysregulation, ischemia and abnormal perfusion pressure of optic nerve which may become sensitized and then damaged in these patients even with normal IOP values [18]. Abegão Pinto et al. was one of the first groups that tried to integrate vascular findings into glaucoma practice [19]. Using colour doppler they found that glaucoma patients had higher mean ocular perfusion pressures and lower retrobulbar velocities than controls. Later, Breda et al. reported that they found RPCD to be the best factor discriminating among different severities of glaucoma. Here, lower vascular densities accompanied the severity of disease, emphasizing the importance of vascular integrity in this disease [20]. The vascular impairment in OSAS was first studied in cerebral vessels [21]. Some studies showed that impairment of brain vascular system was correlated in AH1 and oxygen saturation [22]. Coloma et al. reported a positive correlation between cerebral mean flow density and mean nocturnal oxygen saturation [23]. Considering these

| Table 3. Macular OCT and OCTA data (n=42). |
|-------------------------------------------|
| **Controls**                              | **Mild** | **Moderate** | **Severe** | **p*** | **p°** |
|-------------------------------------------|----------|--------------|------------|--------|--------|
| Fovea, µm                                  | 263.1±10.2 | 267.1±5.1    | 255.5±9.8  | 267.6±30.7 | 0.17   |
| Parafovea, µm                              | 321.1±6.9 | 318.3±7.1    | 300±4.2    | 329.5±27.2 | 0.37   |
| Superior                                  | 324.3±6.9 | 324.1±10     | 333±4.9    | 334±26.9  | 0.5    |
| Nasal                                     | 331.9±10.7 | 330.1±5.5    | 329±3.9    | 325.1±26.8 | 0.67   |
| Temporal                                  | 318.4±9.2 | 315.7±10.8   | 324.7±2.4  | 315±35.3  | 0.68   |
| Perifovea, µm                              | 267.2±8.1 | 269.1±8.5    | 276±7.5    | 269.7±15.7 | 0.34   |
| Superior                                  | 280.1±7.3 | 296.6±23.3   | 309.7±21.3 | 291.2±25.8 | 0.14   |
| Nasal                                     | 283.4±6.2 | 287.4±11.7   | 300±5      | 298.5±21.1 | 0.22   |
| Temporal                                  | 262.5±4.3 | 260.1±8      | 262.7±3    | 270.1±24.1 | 0.39   |
| GCC, µm                                    | 81±4.8   | 81±4.8       | 78.4±9.7   | 79±3.8   | 0.47   |
| SVD, %                                     | 38±3.2   | 37±8.2       | 35±2.5     | 34±2.1   | 0.34   |

*Results of comparison of means among three groups with Kruskal-Wallis’ corrected by Bonferroni; results of comparison of means between two groups with Mann-Whitney’s test; this test was performed when p was inferior to 0.05 on Kruskal-Wallis’ corrected by Bonferroni; GCC, ganglion cell complex; SVD, parafoveal superficial vascular density.

| Table 4. Optic disc OCT and OCTA data (n=42). |
|-----------------------------------------------|
| **Controls**                                  | **Mild** | **Moderate** | **Severe** | **p*** | **p°** |
|-----------------------------------------------|----------|--------------|------------|--------|--------|
| RPNL, µm                                     | 90.1±8.1 | 89.7±1       | 99±13.1    | 89.3±7.1 | 0.47   |
| Inferior                                     | 109.2±8.2 | 103.3±15.3  | 111.3±21.9 | 111.6±14.1 | 0.42   |
| Superior                                     | 116.3±11.2 | 112±7.1    | 105.5±7.1  | 115±14.4 | 0.23   |
| Nasal                                        | 90±12.7  | 92±18.1      | 83±8.2     | 84±8.2  | 0.27   |
| Temporal                                     | 60.1±11.7 | 60.2±13.6   | 55±13.3    | 56.9±8.2 | 0.69   |
| Area, mm²                                    | 1.6±0.2  | 1.7±0.2      | 1.8±0.1    | 1.6±0.1 | 0.32   |
| Neuroretinal rim, mm²                        | 1.3±0.3  | 1.3±0.1      | 1±0.1      | 1.3±0.1 | 0.34   |
| C/D                                          | 0.46±0.3 | 0.45±0.2     | 0.47±0.1   | 0.43±0.1 | 0.94   |
| RPCD, %                                      | 49.4±2.1 | 46±1.1       | 45.3±1.8   | 40.4±4.2 | 0.01   |

*Results of comparison of means among three groups with Kruskal-Wallis’ corrected by Bonferroni; results of comparison of means between two groups with Mann-Whitney’s test; this test was performed when p was inferior to 0.05 on Kruskal-Wallis’ corrected by Bonferroni; RPNL, retinal nerve fiber layer; C/D, cup to disc ratio; RPCD, radial peripapillary capillary density.
findings, it is possible that the cerebral vascular impairment that occurs in OSAS, may also occur at the level of the microcirculation of the optic nerve. To our knowledge, there are few studies regarding retinal microvasculature in patients with OSAS, especially those at the earliest stages of disease.

In our study, we observed a significant decrease in RPCD with increasing severity of OSAS. RPCD was higher in controls than in moderate and severe groups, suggesting a vascular impairment in these patients. Although there was no statistically significant difference, the RPCD seemed to be lower in the mild group compared to controls (p=0.06) and this lack of difference could be due to the small sample size. No significant differences were found in the parafoveal SVD. Yu et al. reported that retinal vessel densities in the parafoveal and peripapillary areas decreased with greater severity of OSAS, with more prominent decrease in the peripapillary area [7]. The vessels in the peripapillary area originate from central retinal artery (CRA) and also from short posterior ciliary arteries (SPCA) and are the source of nutrition to retinal ganglion cells. In macula the vessels originate only from CRA. Hayreh et al. reported that posterior ciliary arteries were more susceptible to high IOP effects than CRA, in patients with glaucoma [24]. Hosking et al. found an abnormal response to hypocapnia in SPCA but not in CRA [25]. These findings, taken together, suggest that ciliary vascular system may experience more damage in OSAS and supports the notion that the RPC is more prone to injury, corroborating our results.

Hypoxia is considered the trigger for microvascular disorders in OSAS patients. Potentially leading to ischemia around the optic nerve via several mechanisms as it promotes platelet activation and aggregation, hypercoagulability and decreases the synthesis of nitric oxide (NO) [26]. The most approximate scenario to study the impact of hypoxia was to compare the “desaturating” and “non-desaturating” patients. Moyal et al. [27] showed differences in RPCD between control and OSAS groups. Although our results showed a trend toward to be inferior in “non-desaturating” patients, it was not significant. However, we found a positive correlation between the lowest nocturnal oxygen saturation and RPCD what seems to support the role of hypoxia in optic nerve damage. Moreover, the inverse correlation between CT90 and OSAS severity could also highlight the role of chronic intermittent hypoxia and consequent vascular endothelial damage. CT90 was found to be positively correlated with serum NO concentration and with plasma endothelin-1 (ET-1). ET-1 contributes to endothelial dysfunction and enhances vasoconstriction which is the most probable mechanism of peripapillary vascular damage and further glaucoma development [28].

There is no consensus regarding RNFL damage in OSAS. Shiba et al. showed an inverse correlation between RNFL thickness and OSAS severity and Yu et al. showed that both moderate and severe OSAS were associated with a significant decrease in average RNFL thickness [29]. However, both Yu et al. and Moyal et al. found no differences in RNFL and macular thickness in OSAS patients [27]. Our study supports the findings of Yu et al. and Moyal et al. in that we too observed no significant differences between OSAS patients and controls. These findings suggest that in OSAS, as in other vascular retinopathies, vascular changes precede RNFL changes. As we only included newly diagnosed patients, that one would assume have only had a short duration of disease, we believe that morphological alterations may just become apparent later. We would also postulate that the conflicting data in the literature might be explained by the studies covering a wide range of disease duration and stages.

Functionally, we found no significant difference in visual field parameters (MD and sLV) between groups. Moyal et al. [27] found a negative correlation between AHI and visual field parameters. However, it did not seem to be reliable, and the authors believed it could be an incidental finding, due to lack of concentration or just the learning-curve phenomenon.

Our study is limited by the small sample, which reduces the significance of statistical analysis and also by the fact that we did not study the deep vascular plexus. However, others have shown that the deep vasculature is structurally normal in glaucoma [30]. In any case, our study differs from others, in regards to the inclusion of newly diagnosed patients which were not on CPAP therapy yet. A treatment that could mask any structural damage or vascular features was induced by disease or modified by oxygen therapy. At the same time, we only included patients with normal IOP, which could help to isolate the vascular damage in the role of glaucomatous damage in OSAS.

This study clearly suggests that the vascular peripapillary damage is seen in OSAS patients from the earliest stages. Despite our patients were recently diagnosed with OSAS, which may have precluded the observation of mounting vascular compromise, this could enhance the observation of the beginning of injury cycle. Moreover, we provide the basis for our ongoing long-term prospective clinical trial to understand the development of vascular damage preceding glaucomatous optic neuropathy in these patients.

**Conclusion**

Our study demonstrates that radial peripapillary capillary density is lower in newly diagnosed OSAS patients compared to controls and decreases as disease severity increases. The apnea-hypopnea index (AHI) and the lowest percutaneous oxygen saturation correlate the radial peripapillary capillary density.

As no morphological damage was observed in RNFL, a close follow up of these patients would help to understand the pathogenesis of this disease and the potential role of OCTA screening in the clinical care of OSAS patients.

**Abbreviations**

AHI: apnea-hypopnea index;
BVCA: best corrected visual acuity;
BMI: body mass index;
CCT: central corneal thickness;
CPAP: continuous positive airway pressure;
CT90: cumulative time percentage with SpO₂ <90%;
DM: diabetes mellitus;
IOP: intraocular pressure;
OSAS: obstructive sleep apnea syndrome;
OAG: open angle glaucoma;
OCT: optical coherence tomography;
OCTA: optical coherence tomography angiography;
ODI: oxygen desaturation index;
NTG: normal tension glaucoma;
RNFL: retinal nerve fiber layer;
RPCD: radial peripapillary capillary density;
SCP: superficial capillary plexus;
SpO₂: oxygen saturation;
SVD: superficial parafoveal vascular density.
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