Early Corneal and Optic Nerve Changes In Paediatric Population Affected By Obstructive Sleep Apnea Syndrome

Erika Bonacci (bonaccierika89@gmail.com)
University of Verona: Universita degli Studi di Verona https://orcid.org/0000-0002-3184-3444
Adriano Fasolo
University of Verona: Universita degli Studi di Verona
Marco Zaffanello
University of Verona: Universita degli Studi di Verona
Tommaso Merz
University of Verona: Universita degli Studi di Verona
Giacomo Brocoli
University of Rome: Universita degli Studi di Roma La Sapienza
Angelo Pietrobelli
University of Verona: Universita degli Studi di Verona
Maria Clemente
University of Verona: Universita degli Studi di Verona
Alessandra De Gregorio
Azienda ULSS 3 Bassano del Grappa: Azienda ULSS 7 Pedemontana
Rosa Longo
University of Verona: Universita degli Studi di Verona
Francesca Bosello
University of Verona: Universita degli Studi di Verona
Giorgio Marchini
University of Verona: Universita degli Studi di Verona
Emilio Pedrotti
University of Verona: Universita degli Studi di Verona

Research Article

Keywords: Obstructive sleep apnea syndrome, OSAS, Sleep respiratory disorders, Keratoconus, Pediatric Ophthalmology, RNFL.

Posted Date: June 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-522563/v1

Version of Record: A version of this preprint was published at International Ophthalmology on November 5th, 2021. See the published version at https://doi.org/10.1007/s10792-021-02115-2.

Abstract

PURPOSE: The relation between OSAS and eye diseases is well-known in adults, while very few and contradictory data can be found regarding paediatric ages. The aim of this study is to explore the early corneal, macular and optic nerve changes in paediatric patients with OSAS.

METHODS**:** prospective study that enrolled children aged ≥ 4 years referred to the Paediatric Pneumology Clinic in Verona for suspected obstructive sleep apnea syndrome (OSAS) and investigated with the overnight respiratory polygraphy. Patients with apnea-hypopnea index (AHI)>1 were classified as OSAS, those with AHI<1 were classified non-OSAS. All patients underwent comprehensive eye examination including slit lamp, refraction, intraocular pression (Goldman applanation tonometry), corneal tomography (corneal astigmatism, corneal keratometry at the apex, Surface Asymmetry Index, Central corneal Thickness and Thinnest corneal Thickness), optical coherence tomography (central macular thickness, macular volume, and retinal nerve fiber layer).

RESULTS**:** 72 children were enrolled in the study. The overall prevalence of OSAS was 48.6%. Statistically significant differences were found between OSAS and non-OSAS group for corneal asymmetry (0.9 ± 0.5 and 0.6 ±0.3, respectively; p=0.02), thinnest corneal thickness (551.8 ± 33.9 and 563.7 ±32.5; p= 0.04), average retinal nerve fiber layer (102.8 µm ± 10.5 and 98.1 µm ±12.3; p=0.012) and in nasal quadrant (76.2±15.4 µm and 66.5 ±12.6 µm; p= 0.0002).

CONCLUSIONS**:** comprehensive eye examination with corneal and optic nerve imaging showed early corneal and optic nerve changes in children newly diagnosed with OSAS. These could be prelude of the known ocular manifestations associated with OSAS in adult patients.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a respiratory disorder characterized by repetitive collapse of the upper airway during sleep [1–2] reported in 1–3% of the general paediatric population.[3]

The most frequent causes of OSAS are adenotonsillar hypertrophy and regional deposition of fat in the neck [3–6]. Anyway, the result of airway collapse is the reduction of the inspiratory flow leading to hypoxemia and hypercapnia which cause injury of blood vessels and organ involvement, [6, 7] including the eyes.

The association between OSAS and eye diseases is well-known in adults. Several studies have linked OSAS with glaucoma, keratoconus, papilloedema, nonarteritic ischemic optic neuropathy, age-related maculopathy and floppy eyelid syndrome (8–9); while very few and contradictory data can be found regarding paediatric ages.(10–11)

Aim of this study is to explore the early corneal, macular and optic nerve changes in paediatric patients with OSAS.

Methods

This is a single-centre prospective study conducted in paediatric patients investigated for OSAS (ICD-9-CM 307.4x, 327.23, and 780.5x) by the overnight respiratory polygraphy (RP) between June and December 2020 at the Paediatric Pneumology Clinic in Verona.

The study was performed in accordance with the tenets of the Declaration of Helsinki. Approval of the local Institutional Ethics Committee was obtained.

Patients aged ≥ 4 years, whose parents agreed to participate in the study by signing informed consent, were included. Patients with comorbidities (pulmonary, cardiac, facial dysmorphism and other) were excluded from the study. Patients affected by congenital or acquired ocular abnormalities not-related to OSAS (congenital cataract, amblyopia, trauma, etc).

Children underwent in-laboratory overnight RP in a dedicated room at the Pediatric Pneumology Clinic, and performed a comprehensive ophthalmic examination with corneal and optic nerve imaging at the Eye Clinic of Verona University.

The collected medical clinical data included age, sex and body growth parameters. Trained personnel using standardized techniques measured height and weight. Body mass index [BMI, weight (kg) / height (m2)], BMI percentiles, and BMI z-scores were calculated according to age and sex following the calculator tool for children aged 2 through 19 years old provided by the Centres for Disease Control and Prevention [12].

RP was performed using a portable ambulatory device (SOMNOscreenTM PSG, SOMNOmedics GmbH, Randersacker, Germany) following the indications of 2007 American Academy of Sleep Medicine (AASM) manual for the Scoring of Sleep and Associated Events[13].

The analysis of the entire recording session was done automatically (DOMINO software, Somnomedics v.2.6.0), and accurately manually checked for artefactual or non-interpretable periods of nasal flow, thoracic effort, abdominal effort or oximetry channel. Periods with artificial data were withdrawn by the estimated total sleep time (TST), and movement periods excluded. TST was calculated according to published criteria[13].

Respiratory events were scored accordingly to the AASM manual[13]. The number of apneas (apnea for the duration of at least 2 breaths during baseline breathing associated with the presence of respiratory effort throughout the entire period of absent airflow) and hypopneas (reduction in airflow > 50% for 10 seconds or greater, with a decrease of oxygen saturation of ≥ 3%) was divided by the hours of TST and expressed as apnea-hypopnea index (AHI).

Desaturation was defined a drop of ≥ 3% of oxygen saturation. The oxygen desaturation index (ODI) was calculated as the total number of desaturations per hour divided by the TST.

Patients with AHI > 1 were classified as OSAS, those with AHI < 1 were classified as non-OSAS.

Comprehensive ophthalmology examination

After family ocular history had been recorded, all children underwent comprehensive ophthalmological examination within 1 month from RP. Visual Acuity was assessed using age-appropriate tests (Albini chart for preschool children and Snellen Acuity charts for literate ones), mean spherical equivalent (SE) after cycloplegic refraction (Autoref/Ker Canon RK-F2, Canon, Japan), slit lamp examination, corneal tomography to assess corneal astigmatism (cyl), corneal keratometry at the apex (AK), Surface Asymmetry Index (SAI), Central corneal Thickness (CCT) and Thinnest corneal Thickness (TCT) (Galilei G4 v.6.1.4, Ziemer Ophthalmic Systems AG, Switzerland), intraocular pressure (IOP) (Goldman applanation tonometry).

Dilated fundus examination was performed with indirect ophthalmoscopy. The central macular thickness (CMT), macular volume (MV) and peripapillary retinal nerve fiber layer (RNFL) thickness were assessed by spectral domain optical coherence tomography (SD-OCT Spectralis, Heidelberg Engineering, Heidelberg, Germany; software version 6.0), adjusted for corneal curvature, fixation and patient positioning for patient-age and level of co-operation.

The CMT, MV, and RNFL values were generated automatically by the instrument and scans taken following the sequence published by Turk et al.[14] All instrumental acquisitions have been performed by two trained examinators who did not know the overnight RP result. All accepted SD-OCT images showed Q-score ≧ 20 and those of poor quality or with segmentation errors were excluded from this analysis. For corneal tomography, only measurements with quality rate higher than 70%, were accepted and examinations repeated until the achievement of this target.

Statistical analyses

Both eyes were examined and included in the analysis.

The prevalence for stratified clinical and demographic characteristics and calculated confidence interval through the normal approximation interval were evaluated. For the quantitative variables, results of descriptive analyses were expressed as mean and standard deviation in the case of normal distribution (according to the Kolmogorov–Smirnov normality test), median and interquartile range (IQR) otherwise and as a count and percentage for categorical variables.

In dummy variables (sex, ODI) the chi-square test was used to assess differences between groups, and the t-test was used to assess differences between continuous variables (BMI, age). Statistical analyses were performed using the STATA 13.0 statistical package (Stata Corp. LP, College Station, TX). The significance level was set at 0.05.

Results

A total of 72 consecutive children were included in the study, 30 (41.66%) females and 42 (58.33%) males, mean aged 9.20 ± 3.70 years (range 4.13–15.91) and BMI 21.93 ± 5.82 Kg•m-2 (range 12.91–40.64) with 51% having BMI ≥ 95th percentile. All children were born at term and no perinatal morbidities were reported.

The overall prevalence of OSAS was 48.61%, and in the 57% of the cases it was a mild (Table 1).

Table 1
Demographic and anthropometric distribution in OSAS (AHI ≥ 1) and non-OSAS (AHI < 1) groups

	AHI < 1 (%)	AHI ≥ 1 (%)	P
	(N = 37)	(N = 35)	
Demography and anthropometry			
Sex			
female	15 (40.55)	15 (42.86)	0.71
male	22 (59.45)	20 (57.14)	
Age, *y*	11.10 ± 3.41	10.31 ± 3.60	0.43
median	10.72	9.02	
range	4-15	4-16	
BMI, $Kg \bullet m^{-2}$	24.81 ± 5.90	20.41 ± 5.91	-
median	20.71	20.92	
range	17 - 31	12 – 41	
Comorbidities*			-
Adenotonsillar hypertrophy	-	14 (40.00)	
Obesity	13 (35.14)	8 (22.86)	
Environmental allergy	3 (8.10)	5 (14.29)	
Previous adenotonsillectomy	4 (10.81)	15 (42.86)	
Severity of OSAS			
AHI, events/h			
1 - 5, *mild*	-	20 (57.14)	
5 - 10, *moderate*	-	7 (20.00)	
> 10, *severe*	-	8 (22.86)	
ODI, events/h			0.00*
< 1	36	11	

≥ 1	1	23

** p< 0.05*

Family history of eye disease was positive in one child for glaucoma and in another one for keratoconus and high myopia. Both patients were classified in OSAS group. No differences were found between OSAS and non-OSAS groups regarding visual acuity (all children achieved 0.0 logMar), SE (-0.08 D ± 2.76 and – 0.03D ± 2.50, respectively; p = 0.54). None required lenses modifications. No corneal or lens opacities and no ophthalmoscopic retina or optic nerve abnormalities were found.

Corneal tomography examination showed no difference for cyl (p = 0.89), AK (p = 0.42) and CCT (p = 0.19) between groups. However, significant differences were found for SAI (p = 0.02) and TCT (p = 0.04) (Table 2). One child with moderate OSAS was diagnosed with early corneal ectasia and was referred to the cornea service for follow-up/management.

Table 2
Tomographic corneal evaluation: corneal astigmatism (cyl), corneal keratometry at the apex (AK), Surface Asymmetry Index (SAI), Central corneal Thickness (CCT) and Thinnest corneal Thickness (TCT)

	OSAS	NON OSAS	P
CYL	0.63 D ± 0.71	0.45 D ± 0.39	0.89
AK	45.30 D ± 2.70	44.97 D ± 1.45	0.42
SAI	0.86 ± 0.49	0.61 ± 0.35	0.02*
CCT	567.31 µm ± 26.91	574.46 µm ± 33.93	0.19
TCT	551.81 µm ± 33.97	563.68 µm ± 32.50	0.04*
** p < 0.05*			

All children showed IOP in normal range (12 mmHg ± 0.54), without difference between groups (p = 0.73).

SD-OCT examination showed no significant difference between OSAS and non-OSAS group regarding CMT (277 µm ± 23.50 and 273 µm ± 35.60, respectively) (p = 0.61) and MV (8.80 µm ± 0.60 and 8.70 µm ± 1.00, respectively) (p = 0.17).

The average RNFL thickness was significantly higher in OSAS group (102.80 µm ± 10.50) than in non-OSAS one (98.10 µm ± 12.30) (p = 0.01).

The analysis of the RNFL thickness in 4 segments (superior, nasal, temporal and inferior) showed higher values in the OSAS group in all quadrants (table 3), however statistically significant difference was found only in the nasal one (76.20 ± 15.40 µm and 66.50 ± 12.60 µm) (p = 0.00) (Table 3).

Table 3 Analysis of the Retinal Nerve Fiber Layer (RNFL)thickness at four segments and average.

RNFL	OSAS	NON OSAS	P
AVERAGE	102.80 ± 10.50	98.10 ± 12.30	0.01*
SUPERIOR	128.30 ± 17.10	122.90 ± 17.80	0.06
NASAL	76.20 ± 15.40	66.50 ± 12.60	0.00*
TEMPORAL	74.80 ± 10.40	72.60 ± 14.80	0.10
INFERIOR	132.40 ± 16.90	129.30 ± 22.70	0.14
** p < 0.05*			

Discussion

We examined children assessed for OSAS by overnight RP, to investigate for early signs of ocular changes related to airway obstruction during sleep, poorly documented and understood in the previous literature[10–11].

Retina and optic nerve have been examined in OSAS paediatric patients with adenotonsillar hypertrophy with controversial results. Cinici and Tatar[10] found no significant alterations of RNFL thickness, while Simsek *et al*[11] showed that OSAS seems to influence RNFL and IOP parameters. Both studies highlighted the potential risk of long-term optic injury due to blood intermittent hypoxia and recommend prompt treatment of OSAS in young people. None evaluated corneal alterations in OSAS paediatric patients.

The major limitation of these studies was the assessment of OSAS diagnosis by questionnaire, contrasting with AAMS recommendations [15]. The questionnaires, indeed, are sensitive just for severe grades of apnoea so they are not suitable for children and could under-diagnose the disease.

Despite the gold standard for diagnosis of OSAS is the polysomnography, it is an expensive test, the setup can be challenging, and the placement of numerous electrodes can be difficult in children.

In our study, we investigated the OSAS using RP in a dedicate room, according with J. Corral et al. that found RP management was similarly effective to polysomnography, with a substantially lower cost [16].

None of the children enrolled in the study had visual impairment and all reached 0.00 logMar, with or without optical correction, without anomalies during ophthalmological examination.

However, although corneal parameters were within normal range in both OSAS and non-OSAS group, statistically significant differences were found for SAI and TCT values ($p = 0.02$ and $p = 0.04$, respectively).

SAI is the index of asymmetry of the corneal surface and is based on the specular correspondence between the two hemicorneas (superior and inferior), which normally does not exceed small physiological differences (< 0.5). Values greater than 1, result in a notable corneal asymmetry which is suggestive for ectasia[17–18].

Our results suggest that OSAS children have a higher corneal asymmetry than non-OSAS. This finding, added to the detection of a lower TCT, leads to suspect a possible evolution towards ectasias. In fact, we found one OSAS patient with suspect corneal ectasia. This would be in keeping with the previous literature on the correlation between OSAS and keratoconus in adult patients[8, 9]. The SAI values within the normal range, found in this study, could be explained by the shorter period of exposure to OSAS in children patients compared to adult ones. Indeed, the latter have generally several years of exposure to OSAS when a diagnosis of keratoconus is made. Therefore, a possible evolution towards ectasia in young patients should be suspected.

Similar behaviour has been found in RNFL parameters, whose values were found within the normal range in all patients [14]. However, the OSAS group showed higher RNFL thickness in all quadrants, reaching statistically significant difference in the average values and in the nasal quadrant values.

The relation between OSAS and optic injury is well known in middle-aged adults and the elderly and most of the studies reported reduction in RNFL thickness [8, 9]. Recently, Lee *et al* confirmed this relation also in young OSAS patients (aged 19–22 years) reporting RNFL thinning in inferotemporal and superotemporal segments [19].

This study shows that a correlation between OSAS and optic nerve fibers is already detectable also in very young patients, but not in terms of a reduced RNFL thickness when compared with non-OSAS group. On the opposite, our data showed increased RNFL in OSAS patients. These changes could reflect a mild swelling of the optic nerve fibres secondary to capillaries dilatation, due to hypoxic condition, or to a possibly increased intracranial pressure, which are common conditions in OSAS patients [20–22].

The peripapillary and retinal capillary tone, indeed, is under local vascular control and it responds to O2 and CO2 concentration in the blood. Moreover, Jaki Mekjavic et al. [23] described in patients under experimental condition that hypoxia and acute hypercapnia induce dilation of retinal vessels and radial peripapillary capillary network, causing the increasing of RNFL thickness, as compensatory response.

As know, in adults with moderate-severe OSAS, RNFL thickness is significantly reduced compared to healthy subjects and is associated with macular retinal thinning due to ganglion cells loss [24]. However, already other authors have noted that probably the optic nerve head changes through the stage of subtle edema in the mild and moderate OSAS groups and pass to a secondary phase of reduction in RNFL thickness in patients with long-standing severe OSAS [20].

The fact that in our study a mild increase in RNFL thickness was not associated to any visual disturbances and CMT and RV appeared within normal limits could be a sign of very early and potentially

reversible change.

Most of our patients were newly diagnosed with a mild stage of OSAS, with a disease duration likely to be relatively short due to the young age of the patients. We cannot exclude that, in case of OSAS is left untreated and progress with time to more severe disease stages, optic nerve head changes could evolve over the years to chronic nerve fibres distress with reduction of RNFL thickness.

In this study, OSAS children show higher RNFL thickness in all quadrants, reaching statistically significant difference in the average and in the nasal one. Furthermore, the significant increase in RNFL only in the nasal sector could be explained by the swelling disc scheme proposed by Frisen [25], which showed that edema begins precisely in the nasal part of the disc.

In our study, the correlation between OSAS and increased RNFL thickness could represent an early modification of the peripapillary nerve fiber layers, due to apneas and desaturation events. A limitation of this study is the lack of measurement of retinal ganglion cell layer values.

No significant differences were found in CMT and MV, however higher values were found in the OSAS group. These findings could be due to the vascular response of retinal capillary network in OSAS group.

Further investigations with larger populations in paediatric patients with OSAS are needed to confirm our hypotheses.

This is the first study that found a correlation between OSAS and corneal alterations in childhood, contributing to the knowledge of the ocular implications related to OSAS.

Ocular damages in children are completely asymptomatic and these early signs could give insight on pathogenesis of corneal and optic disc changes that appear clinically evident in the adult population. So, based on our evidence, we suggest to plan earlier ophthalmological examination including evaluation of corneal asymmetry and RNFL thickness in paediatric patients affected by OSAS.

Declarations

ACKNOWLEDGEMENTS

The corresponding author affirms that are listed all everyone who contributed significantly to the work

Eye Clinic, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

Pz.Le LA Scuro 10, 37100, Verona (VR), Italy.

Erika Bonacci, MD, FEBO, Adriano Fasolo, MSc, Tommaso Merz, MD, FEBO, Giacomo Brocoli, MD, Rosa Longo, MD, Francesca Bosello, MD Giorgio Marchini, MD, Emilio Pedrotti, MD, FEBO

Eye Clinic, Department of Sense Organs, Sapienza University of Rome, Rome, Italy

Pz.Le A Moro 5, 00185, Rome (RM), Italy.

Giacomo Brocoli, MD

Ophthalmic Unit, San Bassiano Hospital, Bassano del Grappa, Italy

Via dei Lotti, 40, 36061 Bassano del Grappa (VI). Italy.

Alessandra De Gregorio, MD

Pediatric Division, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy.

Piazzale Stefani, 1 - 37126 Verona (VR), Italy.

Angelo Pietrobelli, MD, Marco Zaffanello, MD, Maria Clemente, MD

Corresponding author

Correspondence to Francesca Bosello, Policlinico G.B. Rossi, P.le L.A. Scuro 10, 37100 Verona, Italy. +390458126115;

francesca.bosello87@gmail.com

Funding

No financial assistance was received in support of the study.

Informed consent

Informed consent was obtained from the parents of all individual participants included in the study.

Ethics approval

All procedures performed in the study were in accordance with the ethical standards of the institutional and national ethic committee.

References

1. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K et al (2016) Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J 47:69–94
2. Cohen-Gogo S, Do NT, Levy D, Metreau J, Mornand P, Parisot P et al (2009) Sleep-disordered breathing in children. Arch Pediatr 16:123–131

3. Katz ES, D'Ambrosio CM (2008) Pathophysiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 5:253–262
4. Shott SR (2011) Evaluation and management of pediatric obstructive sleep apnea beyond tonsillectomy and adenoidectomy. Curr Opin Otolaryngol Head Neck Surg 19:449–454
5. Nandalike K, Shifteh K, Sin S, Strauss T, Stakofsky A, Gonik N et al (2013) Adenotonsillectomy in obese children with obstructive sleep apnea syndrome: magnetic resonance imaging findings and considerations. Sleep 36:841–847
6. Tagetti A, Bonafini S, Zaffanello M, Benetti MV, Vedove FD, Gasperi E et al (2017) Sleep disordered breathing is associated with blood pressure and carotid arterial stiffness in a sample of obese children. J Hypertens 35:125–131
7. Somers VK, Mark AL, Zavala DC, Abboud FM (1989) Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. J Appl Physiol 67:2101–2106
8. McNab AA (2007) The eye and sleep apnea. Sleep Med Rev 11:269–276
9. Pedrotti E, Demasi CL, Bruni E, Bosello F, Di Sarro PP, Passilongo M et al (2017) Prevalence and risk factors of eye diseases in adult patients with obstructive sleep apnoea: results from the SLE.E.P.Y cohort study. BMJ Open 7:e016142
10. Cinici E, Tatar A (2015) Thickness alterations of retinal nerve fiber layer in children with sleep-disordered breathing due to adenotonsillar hypertrophy. Int J Pediatr Otorhinolaryngol 79:1218–1223
11. Simsek A, Bayraktar C, Dogan S, Uckrdes F, Reyhan AH, Sarikaya Y et al (2016) Retinal nerve fiber layer thickness alteration in apneic children. Optom Vis Sci 93:63–69
12. BMI Percentile Calculator for Child and Teen English Version. Available from https://www.cdc.gov/healthyweight/bmi/calculator.html. (accessed 17 Feb 2019)
13. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK et al (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 8:597–619
14. Turk A, Ceylan OM, Arici C, Keskin S, Erdurman C, Durukan AH et al (2012) Evaluation of the nerve fiber layer and macula in the eyes of healthy children using spectral-domain optical coherence tomography. Am J Ophthalmol 153:552–559
15. Kirk V, Baughn J, D'Andrea L, Friedman N, Galion A, Garetz S et al (2017) American Academy of Sleep Medicine Position Paper for the Use of a Home Sleep Apnea Test for the Diagnosis of OSA in Children. J Clin Sleep Med 13(10):1199–1203
16. Corral J, Sanchez-Quiroga MA, Carmona-Bernal C, Sánchez-Armengol Á, de la Torre AS, Durán-Cantolla J et al (2017) Conventional Polysomnography Is Not Necessary for the Management of Most Patients with Suspected Obstructive Sleep Apnea Non inferiority, Randomized Controlled Trial. Am J Respir Crit Care Med 196(9):1181–1190
17. Reddy SP, Bansal R, Vaddavalli PK (2013) Corneal topography and corneal thickness in children. J Pediatr Ophthalmol Strabismus 50:304–310

18. Burns DM, Johnston FM, Frazer DG, Patterson C, Jackson AJ (2004) Keratoconus: an analysis of corneal asymmetry. Br J Ophthalmol 88:1252–1255. doi:10.1136/bjo.2003.033670
19. Lee S, McArdle N, Sanfilippo PG, Yazar S, Eastwood PR, Hewitt AW, Li Q, Mackey DA (2019) Associations between Optic Disc Measures and Obstructive Sleep Apnea in Young Adults. Ophthalmology 126(10):1372–1384. https://doi.org/10.1016/j.ophtha.2019.04.041
20. Huseyinoglu N, Ekinci M, Ozben S, Buyukuysal C, Kale MY, Sanivar HS (2014) Optic disc and retinal nerve fiber layer parameters as indicators of neurodegenerative brain changes in patients with obstructive sleep apnea syndrome. Sleep Breath 18(1):95–102. doi: 10.1007/s11325-013-0854-z. Epub 2013 May 1. PMID: 23636560
21. Dhillon S, Shapiro CM, Flanagan J (2007) Sleep-disordered breathing and effects on ocular health. Can J Ophthalmol 42:238–243
22. Stein JD, Kim DS, Mundy KM, Talwar N, Nan B, Chervin RD, Musch DC (2011) The association between glaucomatous and other causes of optic neuropathy and sleep apnea. Am J Ophthalmol 152:989–998
23. Jaki Mekjavic P, Lenassi E, Eiken O, Mekjavic JB (2016) Effect of acute hypercapnia during 10-day hypoxic bed rest on posterior eye structures. J Appl Physiol 120:1241–1248
24. Wang JS, Xie HT, Jia Y, Zhang MC (2016) Retinal nerve fiber layer thickness changes in obstructive sleep apnea syndrome: a systematic review and meta-analysis. Int J Ophthalmol 9:1651–1656
25. Frisen L (1982) Swelling of the optic nerve head: A staging scheme. J Neurol Neurosurg Psychiatry 45:13–18