The Associations of Obstructive Sleep Apnea and Eye Disorders: Potential Insights into Pathogenesis and Treatment

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Abstract

Purpose of Review Obstructive sleep apnea (OSA) patients are at significantly increased risks for cardiovascular and cerebrovascular morbidities. Recently, there has been heightened interest in the association of OSA with numerous ocular diseases and possible improvement of these conditions with the initiation of OSA treatment. We reviewed the current evidence with an emphasis on the overlapping pathogeneses of both diseases.

Recent Findings Currently available literature points to a substantial association of OSA with ocular diseases, ranging from those involving the eyelid to optic neuropathies and retinal vascular diseases. Since the retina is one of the highest oxygen-consuming tissues in the body, the intermittent hypoxia and hypercapnia ensuing in OSA can have deleterious effects on ocular function and health. Tissue hypoxia, autonomic dysfunction, microvascular dysfunction, and inflammation all play important roles in the pathogenesis of both OSA and ocular diseases. Whether OSA treatment is capable of reversing the course of associated ocular diseases remains to be determined. It is anticipated that future therapeutic approaches will target the common underlying pathophysiologic mechanisms and promote favorable effects on the treatment of known associated ocular diseases.

Summary Emerging evidence supports the association of ocular diseases with untreated OSA. Future studies focusing on whether therapeutic approaches targeting the common pathophysiologic mechanisms will be beneficial for the course of both diseases are warranted.

Keywords Obstructive sleep apnea · Floppy eyelid syndrome · Optic neuropathy · Nonarteritic anterior ischemic optic neuropathy (NAION) · Retinal vascular disease

Introduction

Within the past 5 years, there have been several excellent published reviews addressing the relationship of obstructive sleep apnea (OSA) and ocular disorders [1, 2•, 3]. During this period, there has also been an intensification of the relationship of OSA with ocular disorders that has been inspired by new imaging technologies that can identify structural changes

in the eye that may shed light on the pathogenesis of ocular disorders in the context of OSA. As we better understand the metabolic, immune, and biological attributes of OSA, it is worthwhile to revisit these associations in order to better understand potential models for the pathogeneses of these ocular conditions and to potentially identify therapeutic interventions that might impact their management. This review will attempt to summarize the evidence for the associations of OSA and ocular disorders, the newer structural and functional parameters of eye disorders and vision that may be linked to OSA, and attempt to consider the underlying metabolic, genetic, and structural mechanisms that may inform our understanding of both OSA and ocular conditions (Table 1). In some instances, we will consider shared etiologies and risk factors, while for others, we will consider how the alterations caused by OSA may directly influence ocular function and disease. This third segment of the paper, based on peer-reviewed publications, is ultimately speculative but gives us some hints for future research directions and potential therapies.

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Table 1 Evidence for, or a lack of, associations with various ocular diseases and obstructive sleep apnea (OSA) and responses to OSA therapy

	Association with OSA		Response to OSA therapy	
	Yes	No	Yes	No
External and surface eye disease				
Floppy eyelid	[4–15]	[16]	[17–19]	
Keratoconus	[20, 21, 22–25]	[26]		
Dry eyes	[11, 27, 28]	[11]	[29]	[30]
Optic neuropathy				
Primary open-angle glaucoma	[31–40]	[5, 41–45]	[46]	[32]
Normal-tension glaucoma	[35–38, 40, 42, 47–50]	[39]	[50]	
Non-arteritic ischemic optic neuropathy	[51–58]			[59]
Retinal vascular disease				
Diabetic retinopathy	[60–82]	[74]	[60, 67, 83–85]	[85]
Retinal vein occlusion	[86–93]			
Central serous chorioretinopathy	[94–100]			
Age-related macular degeneration	[45, 101]		[102]	

Definition of OSA, Age-Dependent Differences, and Implications for Eye Disorders

Obstructive sleep apnea (OSA) is a subset of sleep-disordered breathing that is characterized by episodic sleep state-dependent upper airway collapse, resulting in periodic reductions or cessations in ventilation, with subsequent hypoxia, hypercapnia, or arousals from sleep [103]. Risk factors for OSA are conditions that reduce the size of the resting pharynx or increase airway collapsibility such as obesity, male sex, persons with hypothyroidism or acromegaly, increased tonsillar and adenoid tissue, and certain craniofacial abnormalities [104].

In terms of OSA prevalence and age, although there is a gradual increase, prevalence tends to level off after 65 years [105]. Geriatric patients exhibit more severe and deeper nocturnal intermittent hypoxia compared to young adults, independent of OSA severity which could be reflective of the already present chronic hypoxemic conditions, due to the physiologic aging process [106]. When we consider the association of OSA with ocular conditions, we have to consider if these relationships are due to pleiotropic effects of shared risk factors (such as anatomic features and common physiologic pathways) and/or if the metabolic and systemic effects of the OSA itself contributes as a risk factor for these conditions, as illustrated in Fig. 1.

Association of OSA with Specific Ocular Conditions

The association of OSA with microvascular eye diseases, including non-arteritic ischemic neuropathy, retinal vein occlusion, and diabetic retinopathy, seems to be strengthened by a

common disturbance in tissue perfusion and oxygenation as well as potential metabolic derangements that promote coagulation disorders. One can make a case that similar processes could underlie the association of OSA with both primary open-angle glaucoma and normal-tension glaucoma. However, it is certainly possible that structural changes in connective tissue that contribute to the intermittent loss of airway integrity could act as a shared risk factor for floppy eyelid syndrome (FES), and also result in increased optic nerve vulnerability to damage from elevated intraocular pressures or compression in high myopes [107, 108]. These mechanisms do not seem to offer a clear explanation for the associations of OSA with central serous chorioretinopathy (CSR). While CSR is also intimately related to abnormalities of the choroidal circulation and closely associated with choroidal thickening (known as pachychoroid), the distinct clinical features of CSR, the focal or multifocal character with considerable ocular asymmetry, its intermittent acute flares and spontaneous remissions, and associations with endogenous cortisol or exogenous steroid exposure seem to be outside of known OSA risk factors. Yet, the association of OSA with CSR is so clearly established that some clinicians have even suggested that every patient with CSR undergo testing for OSA regardless of clinical symptoms [94].

There is one study that indicates that the clinical response to anti-vascular endothelial growth factor (VEGF) injections for treating exudative age-related macular degeneration (AMD) is impacted by whether or not an OSA patient is treated with continuous positive airway pressure (CPAP) [101]. If such a finding were to be replicated, it would suggest a very dynamic relationship between the physiologic changes during sleep and potential exacerbations of retinal hypoxia and secondary elevations of VEGF in the retina/choroid. Given our lack of therapies to prevent or slow the progression of

Fig. 1 The pleiotropic effects of shared etiologies on both obstructive sleep apnea (OSA) and ocular diseases, and the acute/chronic effects of OSA on ocular blood flow. FES, floppy eyelid syndrome; POAG, primary open-angle glaucoma; PR, prelaminar region; LC, lamina cribrosa; R, retina; C, choroid; S, sclera; PCA, posterior ciliary artery;

CRV, central retinal vein; CRA, central retinal artery; NAION, non-arteritic ischemic optic neuropathy; RAO, retinal artery occlusion; RVO, retinal vein occlusion; DR, diabetic retinopathy; CSR, central serous chorioretinopathy; AMD, age-related macular degeneration

nonexudative AMD and the relatively high percentage of patients with exudative AMD who demonstrate only a partial response to anti-VEGF therapies, it would be invaluable to explore the potential impact of OSA treatment on this condition.

Figure 2 summarizes the effects of OSA on various ocular structures and associated ocular diseases.

The Association of OSA with Structural and Functional Changes of the Eye and Vision

Eyelid and Ocular Surface Morphology

Ever since Gonnering and Sonneland first reported a patient with both obstructive sleep apnea (OSA) and floppy eyelid syndrome (FES) in 1987 [7], there have been numerous papers looking at the association between the two diseases [4, 8–12, 14, 16] (Fig. 3). Lid laxity quantification is important in determining the presence or absence of structural eyelid change and there have been several methods suggested, such as measuring the “vertical lid pull,” “vertical hyperlaxity of the lid,” or simply “horizontal eyelid distraction distance” [10, 11, 13]. McNab measured the excursion of the upper lid margin from traction

applied to the pretarsal skin in a vertical direction and found a vertical lid pull of 15 to 25 mm for FES patients, 7 to 16 mm for OSA, and 5 to 10 mm for age- and gender-matched controls [10]. Robert et al. found increased eyelid hyperlaxity in OSA patients, and Mojon et al. found positive correlation between respiratory disturbance index (RDI) and eyelid distraction distance [11, 13]. However, Fox et al. recently performed a cross-sectional observational study with individuals referred for overnight polysomnography and found no association between the presence of OSA and eyelid laxity [16]. The authors enrolled a large number of patients (201 individuals, 402 eyes) and attempted to employ validated quantitative measurements to objectively determine the presence of eyelid laxity. The lack of a gold standard for assessing and the relatively subjective methods with which previous studies investigated structural eyelid change are all possible reasons for the discrepancy in these study results. Age and body mass index (BMI) are both important factors associated with increased eyelid laxity and OSA and may possibly act as a confounding factor, but previous studies controlling for these factors nonetheless found an association between FES and OSA [8, 10, 11].

The number of elastin fibers has been found to be markedly decreased in FES patients with increased expression of matrix metalloproteinases implicated as a possible cause [109, 110].

Fig. 2 Summary of the effects of OSA on various ocular structures and associated ocular diseases. Hypercapnia, hypoxemia, oxidative stress, and autonomic dysfunction, as a result of OSA, contribute to the pathogenesis of various retinal vascular diseases such as diabetic retinopathy, retinal vein occlusion, and age-related macular degeneration. Ocular structural changes arising in association with OSA result in various ocular diseases according to the different tissues affected. OSA, obstructive sleep apnea; DR, diabetic retinopathy; RVO, retinal vein occlusion; AMD, age-related macular degeneration; FES, floppy eyelid syndrome; RNFL, retinal nerve fiber layer; DED, dry eye disease; NAION, non-arteritic ischemic optic neuropathy; NTG, normal-tension glaucoma; POAG, primary open-angle glaucoma; CSR, central serous chorioretinopathy

Interestingly, elastin fiber network disorganization in the distal uvula was found to be associated with the apnea-hypopnea index (AHI) [111] and such pathologic tissue changes may be the common pathophysiology underlying both FES and OSA. Therapeutic approaches that could mitigate these structural changes to the tissues would potentially benefit patients with either FES or OSA. However, a more functional interrelationship between these two conditions has been suggested by several studies that reported that FES improved in a group of OSA patients with successful use of CPAP [18, 19]. The not-so-clear-cut effects of CPAP therapy and OSA-related surgery on FES suggest that both shared factors related to the structural integrity of the palate and lid tissues, as well as dynamic

Fig. 3 A patient with floppy eyelid syndrome. There is significant lid eversion (white arrow) with mild upward traction demonstrating extensive lid laxity. (Image credit: Dr. Robert A. Goldberg, UCLA Stein Eye Institute)

features of OSA, can impact FES directly. This may also be due to inflammatory factors that appear to improve with OSA therapy and may contribute to the OSA severity, as well as to the severity of the lid swelling and laxity.

Ocular surface changes have also been studied in conjunction with eyelid laxity in OSA patients. One study found that although 52% of OSA patients had abnormal eye findings and RDI correlated negatively with tear film break-up time (TBUT), corneal abnormalities were found in only 4.5%, with symptoms of ocular irritation being rare [11]. Another study conducted a more comprehensive study focusing specifically on ocular surface changes occurring in OSA patients and found that moderate and severe OSA is associated with lower Schirmer and TBUT, high scores on the ocular surface disease index questionnaire, and corneal staining pattern stage [112].

Corneal Hysteresis

Normal human corneal thickness is about 500 μm and diurnal variation is present with overnight swelling and resolution by early afternoon, possibly arising from hypoxia created by lid closure [113]. Both hypoxic and hypercapnic environments are known to affect corneal thickness with 7% swelling per hour observed in the normal human cornea [114]. One study analyzed changes in corneal thickness with/without CPAP application in OSA patients using an ultrasonic pachymeter and found a significant corneal thickness increase in only the without-CPAP group [115]. Another study looked at central corneal thickness (CCT), TBUT, and Schirmer's test in OSA patients according to severity defined by AHI scores [116]. CCT was significantly decreased in OSA patients compared to that in the control group, and as OSA severity increased, CCT decreased in a stepwise manner (mean CCT 570 μm , 561 μm , and 534 μm in mild, moderate, and severe OSA, respectively, $p < 0.05$). There were no significant differences in TBUT or Schirmer's test results among different OSA severity groups. Dikkaya et al. used an ocular response analyzer to

study corneal biochemical properties in OSA patients and showed significantly lower corneal hysteresis and resistance in the severe OSA group, which implies possible corneal biochemical changes in OSA, especially in the severe type [117].

Optic Disc

Retinal ganglion cells (RGCs) are responsible for conveying synaptic input initiated by a visual stimulus to the visual cortex within the brain. Ganglion cell axons converge at the optic disc and exit through the lamina cribrosa to form the optic nerve. Optic nerve examination, as well as examination of the peripapillary retinal nerve fiber layers (RNFL), consisting of ganglion cell axons, is useful for investigating the presence of neuroaxonal degeneration, either anterograde or retrograde. OSA has been reported to be associated with various optic nerve diseases, such as non-arteritic anterior ischemic optic neuropathy (NAION), primary open-angle glaucoma, normal-tension glaucoma, and papilledema [118, 119, 120, 121–123].

Huseyinoglu et al. looked specifically at changes in optic disc parameters in OSA patients, such as optic disc area, cup area, cup volume, cup/disc area ratio, and nerve head volume, using OCT to obtain 12 radial scans and 13 concentric rings, centered on the disc, but were unable to detect any significant differences [118].

Studies related to optic neuropathy/glaucoma and OSA have suggested that the negative effects of OSA on RNFL and nerve oxygenation may be reversed by CPAP. However, to date, IOP control is the only proven treatment for glaucoma and there is yet no evidence that IOP can be altered by CPAP therapy. Oxidative stress and lower oxygenation could also be contributing factors for ischemic optic neuropathy, which also has implications for diabetic retinopathy (which also seems to respond to CPAP therapy but not always consistently) [83], as well as complications of retinal vein occlusion (RVO).

Idiopathic intracranial hypertension (IIH), a syndrome of increased intracranial pressure (ICP) with unknown etiology, has also been reported to be associated with OSA [124–126]. Intermittent ICP elevation is not infrequently observed in OSA, and Sugita et al. hypothesized this to be due to a combination of factors such as increased central venous pressure and subsequent cerebrovascular volume increase, systemic arterial hypertension with secondary increased cerebral perfusion pressure and cerebral vasodilation due to hypoxia and hypercapnia, and resulting intracranial blood volume increase [127, 128]. Since IIH and OSA share a common risk factor of obesity, it remains to be determined whether OSA itself is a comorbidity or an independent risk factor for IIH. There was a report of IIH symptom resolution after surgery for OSA in a pediatric patient and optic disc swelling resolution was observed after CPAP, but as with the association between OSA and IIH, there is no consensus at this time as to whether OSA treatment affects IIH [126, 128, 129].

Optic Nerve Vasculature: Non-arteritic Ischemic Optic Neuropathy

The perfusion of the retina by the central retinal artery and its branches is crucial for the maintenance of the inner retinal neurons. The outer retinal layers, specifically the photoreceptor layer, derive their vascular and metabolic support from the choroidal circulation. Effective blood flow and oxygenation are achieved by having sufficient perfusion pressure of the retinal vasculature to overcome the resistance caused by the intraocular pressure. Reductions in nocturnal blood pressure, in conjunction with the impairment of central retinal artery blood flow and/or elevated intraocular pressures, can lead to acute ischemic events such as NAION (Fig. 4) and, more rarely, central retinal artery occlusions (CRAO) [130, 131]. Among 925 episodes of NAION, 73% of patients first reported visual symptoms after waking from sleep, and nocturnal arterial hypotension showed a significant correlation with progressive visual field deterioration in NAION, altogether implying that nocturnal blood pressure depression may precipitate NAION development in patients having additional risk factors [132, 133]. In OSA, the imbalance between nitric oxide and endothelin results in reduced autoregulatory ability of the optic nerve microcirculation to compensate for fluctuations in blood pressure and decreased blood oxygen saturation during apnea may cause direct injury to the optic nerve head [134, 135]. Such structural and functional changes occurring in OSA could act as the additional risk factor tipping the fine balance of perfusion towards ischemia for patients at risk for NAION. Prospective studies also reported the prevalence of OSA in NAION patients to be 55.6–89% in comparison to that of 18–22% in the general population or a control group, while a 12-year nationwide population-based retrospective cohort study found an increased risk of developing NAION in the OSA group compared to the non-OSA group (HR 3.80; 95% CI 1.46 to 9.90) even after adjusting for demographics, comorbidities, and comedications [136, 57, 53, 105, 119]. Hence, individuals who have experienced an episode of NAION or a CRAO should be carefully questioned regarding a history of OSA-related symptoms and a formal sleep study should be considered, even if other OSA comorbidities are not present. There is no evidence at this time that suggests that treatment of OSA will alter the recovery of the eye from one of these acute ischemic events [59] although nonadherence to CPAP treatment in patients with both OSA and unilateral NAION was found to increase the risk of fellow eye involvement [51].

Choroidal Layer

Choroidal circulation has autonomic regulation, sharing regulatory properties as that of cerebral blood flow [137]. Alternating hypoxia and arousal occurring in OSA is thought to stimulate the sympathetic nervous system leading to an

Fig. 4 A 66-year-old male non-arteritic ischemic optic neuropathy patient presenting with vision blurring in the right eye. Disc photograph of the right eye (a) showed blurring (white arrowheads) of the superotemporal optic disc margin compared to a normal-looking optic disc in the left eye

(b). Humphrey visual field testing showed inferior visual field defect (black arrows) in the right eye (c) corresponding to the area of optic disc swelling, while the left eye showed normal visual field (d)

increase in choroidal blood flow following hypercapnia and expression of hypoxia-inducible factor and vascular growth factors, resulting in vascular endothelium damage, changes

in vessel permeability, and choroidal thinning. One study used choroidal laser Doppler flowmetry to study choroidal vascular reactivity in OSA men with a mean age of 50.9 years, having

no cardiovascular comorbidities, and found no impairments, i.e., hypercapnia-induced blood flow increase and stable choroidal blood flow in hyperoxia, suggesting long-term adaptive mechanisms coming into play in the ocular microcirculation [138]. As with RNFL, numerous studies have found thinner choroidal thickness while others have found no difference in OSA patients compared to controls, although a meta-analysis was able to confirm significant choroidal thickness reduction, especially in severe OSA [94, 139–143]. In terms of reversal of choroidal thickness changes after treatment, one study reported significant increases in choroidal thickness after 12 months of CPAP institution with possible improvements in choroidal function [144]. Different modalities and analysis techniques used to assess choroidal blood flow may be one of the underlying reasons for varied results in previous studies.

The biological basis between CSR, in which a thickened choroid is the most distinct characteristic, and OSA is perhaps the most complicated and unclear (Fig. 5). CSR does not appear to be triggered by topical, periocular, or intravitreal exposures to steroids, even though there are multiple reports of activation associated with systemic steroids, as well as from intra-articular, intranasal, and inhalant exposures. This paradox highlights the fact that the underlying mechanism of CSR is poorly understood. The relationship of CSR and OSA becomes an even more intriguing target for study. There is no evidence that the choriocapillaris is thicker in OSA patients, suggesting that this “pachychoroid” feature is relatively independent of OSA. It is possible that the association of OSA and CSR is not with the underlying pathology that is required to develop CSR but may be related to factors that cause acute activation and/or persistence of active CSR [94, 139, 141, 145].

The initial activation and recurrences of CSR have suggested the possibility of an infectious and/or inflammatory etiology for this condition. There is an association of OSA with activation of herpes zoster in patients which has been suggested to be due to modulation of the immune system [146, 147]. An infectious etiology for CSR has been proposed with an association of *Helicobacter pylori* [148], though the natural history of recurrent episodes would require either reactivation of infection or sensitization of the choroid with inflammatory cells that continue to reside in the choroid, and which are vulnerable to sporadic activation. Other studies have shown that *H. pylori* can both promote the accumulation and degranulation of mast cells in different tissues [149–154]. There are even several studies that have focused on the association of *H. pylori* itself with OSA. Whether such infectious etiologies play an important role in the pathophysiology of OSA and its comorbidities is a topic that requires further investigations [155–162].

Some investigators have suggested that CSR activation may be due to the degranulation of mast cells that are resident in the choriocapillaris, and this could certainly be triggered by low-dose steroid exposure. Whether or not *H. pylori* plays a

role in CSR, the activation and degranulation of mast cells that are resident within the choriocapillaris may be a reasonable connection with other known associations of CSR such as stress or low-dose(not high-dose) steroid exposure and OSA, which can also modulate the immune system and trigger mast cell degranulation. This hypothesis that CSR may be driven and triggered by mast cell accumulation and degranulation, as well as local inflammation, would also be consistent with the purported role of mast cell accumulation and activation in floppy eyelid syndrome [163].

Retinal Nerve Fiber Layer and Ganglion Cell Layer

Numerous studies have reported significant reduction, while other studies have found no difference in RNFL thickness in OSA patients compared to normal controls [118, 121–123, 164–173]. Recently, numerous meta-analyses have been published, in which all found a significant reduction of average RNFL thickness in OSA patients [122, 123, 166, 167, 174]. Recurrent obstruction of airflow occurring in OSA, leading to repeated hypoxemia, hypercapnia, and reduced perfusion in the optic nerve, would most likely result in retinal ganglion cell apoptosis and subsequent retinal nerve fiber layer reduction [118, 121].

Sleep disturbance is one of the most prevalent non-motor symptoms in Parkinson’s disease (PD) [175]. Rapid eye movement sleep behavior disorder (RBD), characterized by the loss of normal atonia during rapid eye movement (REM) sleep, has been implicated as a precursor to α -synucleinopathies such as dementia with Lewy body (DLB) and PD [176]. Peripapillary RNFL thickness, as well as inner retinal thickness in the macular area, has been reported to be reduced in both PD and RBD [177–181]. Melanopsin-containing retinal ganglion cells (mRGCs) are a subset of RGCs that also participate in non-image-forming functions such as circadian rhythm regulation or pupillary light reflex activation [182, 183]. Their degeneration and impairment are one of the pathways in which sleep disturbance is hypothesized to occur in PD [184]. Neither PD nor RBD has any overlapping pathogenic mechanisms with OSA; however, both neurodegenerative diseases result in sleep disturbance and have ocular manifestations both functionally and anatomically, as in OSA, and are examples of a sleep-associated disease, such as OSA, in which ophthalmic examination may reveal more than meets the eye.

Metabolic, Structural, Genetic Correlates that May Underlie the Association of OSA with Ocular Disorders

Hypoxia

In vitro model of intermittent hypoxia (IH)/reoxygenation shows activation of the pro-inflammatory transcription factor NF κ B. Circulating tumor necrosis factor- α levels which were

Fig. 5 A patient with central serous chorioretinopathy. Subretinal fluid (arrowheads) is evident on fundus photograph (a) of the right eye and horizontal optical coherence tomography scan (b) shows subretinal fluid with elevated retina and thickened choroid (double head arrows)

significantly higher in OSA patients normalized after CPAP therapy, demonstrating that selective activation of inflammatory pathways as a result of intermittent hypoxia in OSA may be one of the molecular pathways underlying macro/microvascular diseases associated with OSA [185]. The pro-inflammatory nature of OSA could potentially play important roles in the pathophysiology of floppy eyelids, dry eyes, diabetic retinopathy, and age-related macular degeneration.

Autonomic Dysfunction

High sympathetic tone, increase in baseline heart rate, and elevated muscle sympathetic nerve activity are all commonly observed in OSA patients [186]. The following phenomena all come into play in OSA patients, and such changes may affect the choroidal vascular supply, which is mainly controlled by the autonomic nervous system, pathologic changes in which could have an impact on diabetic retinopathy, central serous

chorioretinopathy, and age-related macular degeneration. However, treatments that would alter these autonomic states have not been explored as potential treatments for these ocular conditions as of yet.

- 1) Elevated catecholamines and muscle sympathetic nerve activity during apnea as while awake
- 2) Activation of the renin-angiotensin-aldosterone system
- 3) Differing vascular reactivity between OSA and controls
- 4) Changes in sympathetic and vascular reactivity with OSA treatment
- 5) Animals exposed to intermittent hypoxia or apnea show the above observations.

Microvascular Changes

One study used OSA patient skin biopsies to identify molecular biomarkers involved in the vascular dysfunction of OSA and found endothelial nitric oxide synthase (eNOS), tumor

necrosis factor- α -induced protein 3, hypoxia-inducible factor 1 α , and vascular cell adhesion molecule 1 (VCAM-1) expressions to be significantly upregulated [187]. All of these factors have also been implicated in the pathogenesis of diabetic retinopathy, retinal vascular occlusive disease, and exudative forms of age-related macular degeneration [188–190]. However, there is yet no study that has considered the role of these factors in the combined context of OSA patients with any of these retinal diseases.

Oxidative Stress

When rats were exposed to 14 days of IH, superoxide ion expression in the ophthalmic artery (OA) wall and OA contractile response to endothelin-1 both increased, and nitric oxide-mediated relaxation was significantly delayed [191]. This shows the induction of oxidative stress in rat OA by chronic IH, combined with endothelial cell and nitric oxide synthase dysfunction. Given the known vulnerabilities of the optic nerve, as well as the retina, to damage from oxidative stress for many of the conditions that we know are associated with OSA, we need to consider if agents that reduce oxidative stress might be potentially useful in a subset of OSA patients and have a clinical impact on the ocular conditions in these individuals.

Conclusions and Future Directions

We can see that the ocular associations with OSA likely involve both structural comorbidities such as collagen mutations that affect the structural integrity of the airways and the eyelids, as well as the activation of mast cells that place a role in the atopic aspects of many cases of floppy eyelid syndrome as well as dry eye manifestations. At the same time, this modulation of mast cells and/or cortisol in patients with OSA may contribute to the risk of activation of CSR. Elevated inflammatory factors that have been reported in OSA may contribute to both AMD and diabetic retinopathy. Microvascular changes may also play a role in the severity and progression of diabetic retinopathy. The chronic, intermittent hypoxia of untreated OSA may play a role in patients' visual dysfunction and may offer a potential means of functionally monitoring these patients both before and in response to treatment. Central serous chorioretinopathy appears to be ameliorated by the treatment of OSA and may be related to either cortisol modulation and/or mast cell activation. These hypothetical connections offer new opportunities to better understand both OSA and the ocular conditions that are influenced by this disorder. They offer potential, testable interventions to limit the damage from a number of these eye conditions by either treating the underlying OSA or the shared pathways that may be contributory (even in individuals without clinical evidence of OSA). Using ocular imaging and visual function to assess

therapeutic interventions for OSA and the impact of those treatments on ocular anatomy and metabolic states can help us better understand how the amelioration of OSA in patients with these ocular conditions may offer an adjunct to our current therapies.

Compliance with Ethical Standards

Conflict of Interest The authors report no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. West SD, Turnbull C. Obstructive sleep apnoea. *Eye (Lond)*. 2018;32(5):889–903. <https://doi.org/10.1038/s41433-017-0006-y>.
- 2.•• Mentek M, Aptel F, Godin-Ribuot D, Tamisier R, Pepin JL, Chiquet C. Diseases of the retina and the optic nerve associated with obstructive sleep apnea. *Sleep Med Rev*. 2018;38:113–30. <https://doi.org/10.1016/j.smrv.2017.05.003> **Comprehensive review of the effect of obstructive sleep apnea on specifically the retina and optic disc.**
3. Grover DP. Obstructive sleep apnea and ocular disorders. *Curr Opin Ophthalmol*. 2010;21(6):454–8. <https://doi.org/10.1097/ICU.0b013e32833f00dc>.
4. Chambe J, Laib S, Hubbard J, Erhardt C, Ruppert E, Schroder C, et al. Floppy eyelid syndrome is associated with obstructive sleep apnoea: a prospective study on 127 patients. *J Sleep Res*. 2012;21(3):308–15. <https://doi.org/10.1111/j.1365-2869.2011.00968.x>.
5. Kadyan A, Asghar J, Dowson L, Sandramouli S. Ocular findings in sleep apnoea patients using continuous positive airway pressure. *Eye (Lond)*. 2010;24(5):843–50. <https://doi.org/10.1038/eye.2009.212>.
6. Ezra DG, Beaconsfield M, Sira M, Bunce C, Wormald R, Collin R. The associations of floppy eyelid syndrome: a case control study. *Ophthalmology*. 2010;117(4):831–8. <https://doi.org/10.1016/j.ophtha.2009.09.029>.
7. Gonnering RS, Sonneland PR. Meibomian gland dysfunction in floppy eyelid syndrome. *Ophthalmic Plast Reconstr Surg*.

- 1987;3(2):99–103. <https://doi.org/10.1097/00002341-198703020-00009>.
8. Karger RA, White WA, Park WC, Rosales AG, McLaren JW, Olson EJ, et al. Prevalence of floppy eyelid syndrome in obstructive sleep apnea-hypopnea syndrome. *Ophthalmology*. 2006;113(9):1669–74. <https://doi.org/10.1016/j.ophttha.2006.02.053>.
9. Leibovitch I, Selva D. Floppy eyelid syndrome: clinical features and the association with obstructive sleep apnea. *Sleep Med*. 2006;7(2):117–22. <https://doi.org/10.1016/j.sleep.2005.07.001>.
10. McNab AA. Floppy eyelid syndrome and obstructive sleep apnea. *Ophthalmic Plast Reconstr Surg*. 1997;13(2):98–114. <https://doi.org/10.1097/00002341-199706000-00005>.
11. Mojon DS, Goldblum D, Fleischhauer J, Chiou AG, Frueh BE, Hess CW, et al. Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. *Ophthalmology*. 1999;106(6):1182–5. [https://doi.org/10.1016/S0161-6420\(99\)90256-7](https://doi.org/10.1016/S0161-6420(99)90256-7).
12. Muniesa MJ, Huerva V, Sanchez-de-la-Torre M, Martinez M, Jurjo C, Barbe F. The relationship between floppy eyelid syndrome and obstructive sleep apnoea. *Br J Ophthalmol*. 2013;97(11):1387–90. <https://doi.org/10.1136/bjophthalmol-2012-303051>.
13. Robert PY, Adenis JP, Tapie P, Melloni B. Eyelid hyperlaxity and obstructive sleep apnea (O.S.A.) syndrome. *Eur J Ophthalmol*. 1997;7(3):211–5.
14. Woog JJ. Obstructive sleep apnea and the floppy eyelid syndrome. *Am J Ophthalmol*. 1990;110(3):314–5. [https://doi.org/10.1016/s0002-9394\(14\)76357-3](https://doi.org/10.1016/s0002-9394(14)76357-3).
15. Wang P, Yu DJ, Feng G, Long ZH, Liu CJ, Li H, et al. Is floppy eyelid syndrome more prevalent in obstructive sleep apnea syndrome patients? *J Ophthalmol*. 2016;2016:6980281. <https://doi.org/10.1155/2016/6980281>.
16. Fox TP, Schwartz JA, Chang AC, Parvin-Nejad FP, Yim CK, Feinsilver SH, et al. Association between eyelid laxity and obstructive sleep apnea. *JAMA Ophthalmol*. 2017;135(10):1055–61. <https://doi.org/10.1001/jamaophthalmol.2017.3263>.
17. Bayir O, Acar M, Yuksel E, Yuceege M, Saylam G, Tatar EC, et al. The effects of anterior palatoplasty on floppy eyelid syndrome patients with obstructive sleep apnea. *Laryngoscope*. 2016;126(9):2171–5. <https://doi.org/10.1002/lary.25905>.
18. McNab AA. Reversal of floppy eyelid syndrome with treatment of obstructive sleep apnoea. *Clin Exp Ophthalmol*. 2000;28(2):125–6. <https://doi.org/10.1046/j.1442-9071.2000.00278.x>.
19. Vieira MJ, Silva MJ, Lopes N, Moreira C, Carvalheira F, Sousa JP. Prospective evaluation of floppy eyelid syndrome at baseline and after CPAP therapy. *Curr Eye Res*. 2020;1–4. <https://doi.org/10.1080/02713683.2020.1776332>.
20. Gupta PK, Stinnett SS, Carlson AN. Prevalence of sleep apnea in patients with keratoconus. *Cornea*. 2012;31(6):595–9. <https://doi.org/10.1097/ICO.0b013e31823f8acd>.
21. Arriola-Villalobos P, Benito-Pascual B, Peraza-Nieves J, Peruchogonzalez L, Sastre-Ibanez M, Dupre-Pelaez MG, et al. Corneal topographic, anatomic, and biomechanical properties in severe obstructive sleep apnea-hypopnea syndrome. *Cornea*. 2020;39(1):88–91. <https://doi.org/10.1097/ICO.0000000000002102> **Comprehensive analysis of the corneal topographic, anatomic, and biomechanical properties in severe obstructive sleep apnea patients.**
22. Pedrotti E, Demasi CL, Fasolo A, Bonacci E, Brighenti T, Gennaro N, et al. Obstructive sleep apnea assessed by overnight polysomnography in patients with keratoconus. *Cornea*. 2018;37(4):470–3. <https://doi.org/10.1097/ICO.0000000000001509>.
23. Naderan M, Rezagholizadeh F, Zolfaghari M, Naderan M, Rajabi MT, Kamaledin MA. Association between the prevalence of obstructive sleep apnoea and the severity of keratoconus. *Br J Ophthalmol*. 2015;99(12):1675–9. <https://doi.org/10.1136/bjophthalmol-2015-306665>.
24. Pihlblad MS, Schaefer DP. Eyelid laxity, obesity, and obstructive sleep apnea in keratoconus. *Cornea*. 2013;32(9):1232–6. <https://doi.org/10.1097/ICO.0b013e318281e755>.
25. Saidel MA, Paik JY, Garcia C, Russo P, Cao D, Bouchard C. Prevalence of sleep apnea syndrome and high-risk characteristics among keratoconus patients. *Cornea*. 2012;31(6):600–3. <https://doi.org/10.1097/ICO.0b013e318243e446>.
26. Gencer B, Ozgurhan EB, Kara S, Tufan HA, Arikian S, Bozkurt E, et al. Obesity and obstructive sleep apnea in patients with keratoconus in a Turkish population. *Cornea*. 2014;33(2):137–40. <https://doi.org/10.1097/ICO.0000000000000024>.
27. Galor A, Feuer W, Lee DJ, Florez H, Carter D, Pouyeh B, et al. Prevalence and risk factors of dry eye syndrome in a United States veterans affairs population. *Am J Ophthalmol*. 2011;152(3):377–84 e2. <https://doi.org/10.1016/j.ajo.2011.02.026>.
28. Lim EWL, Chee ML, Sabanayagam C, Majithia S, Tao Y, Wong TY, et al. Relationship between sleep and symptoms of tear dysfunction in Singapore Malays and Indians. *Invest Ophthalmol Vis Sci*. 2019;60(6):1889–97. <https://doi.org/10.1167/iovs.19-26810>.
29. Acar M, Firat H, Yuceege M, Ardic S. Long-term effects of PAP on ocular surface in obstructive sleep apnea syndrome. *Can J Ophthalmol*. 2014;49(2):217–21. <https://doi.org/10.1016/j.cjco.2013.11.010>.
30. Hayirci E, Yagci A, Palamar M, Basoglu OK, Veral A. The effect of continuous positive airway pressure treatment for obstructive sleep apnea syndrome on the ocular surface. *Cornea*. 2012;31(6):604–8. <https://doi.org/10.1097/ICO.0b013e31824a2040>.
31. Muniesa M, Sanchez-de-la-Torre M, Huerva V, Lumbierres M, Barbe F. Floppy eyelid syndrome as an indicator of the presence of glaucoma in patients with obstructive sleep apnea. *J Glaucoma*. 2014;23(1):e81–5. <https://doi.org/10.1097/IJG.0b013e31829da19f>.
32. Cohen Y, Ben-Mair E, Rosenzweig E, Shechter-Amir D, Solomon AS. The effect of nocturnal CPAP therapy on the intraocular pressure of patients with sleep apnea syndrome. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(12):2263–71. <https://doi.org/10.1007/s00417-015-3153-5>.
33. Fan YY, Su WW, Liu CH, Chen HS, Wu SC, Chang SHL, et al. Correlation between structural progression in glaucoma and obstructive sleep apnea. *Eye (Lond)*. 2019;33(9):1459–65. <https://doi.org/10.1038/s41433-019-0430-2>.
34. Chen HY, Chang YC, Lin CC, Sung FC, Chen WC. Obstructive sleep apnea patients having surgery are less associated with glaucoma. *J Ophthalmol*. 2014;2014:838912. <https://doi.org/10.1155/2014/838912>.
35. Aptel F, Chiquet C, Tamisier R, Sapene M, Martin F, Stach B, et al. Association between glaucoma and sleep apnea in a large French multicenter prospective cohort. *Sleep Med*. 2014;15(5):576–81. <https://doi.org/10.1016/j.sleep.2013.11.790>.
36. Bendel RE, Kaplan J, Heckman M, Fredrickson PA, Lin SC. Prevalence of glaucoma in patients with obstructive sleep apnoea—across-sectional case-series. *Eye (Lond)*. 2008;22(9):1105–9. <https://doi.org/10.1038/sj.eye.6702846>.
37. Hashim SP, Al Mansouri FA, Farouk M, Al Hashemi AA, Singh R. Prevalence of glaucoma in patients with moderate to severe obstructive sleep apnea: ocular morbidity and outcomes in a 3 year follow-up study. *Eye (Lond)*. 2014;28(11):1304–9. <https://doi.org/10.1038/eye.2014.195>.
38. Lin CC, Hu CC, Ho JD, Chiu HW, Lin HC. Obstructive sleep apnea and increased risk of glaucoma: a population-based matched-cohort study. *Ophthalmology*. 2013;120(8):1559–64. <https://doi.org/10.1016/j.ophttha.2013.01.006>.
39. Wu X, Liu H. Obstructive sleep apnea/hypopnea syndrome increases glaucoma risk: evidence from a meta-analysis. *Int J Clin Exp Med*. 2015;8(1):297–303.

40. Perez-Rico C, Gutierrez-Diaz E, Mencia-Gutierrez E, Diaz-de-Atauri MJ, Blanco R. Obstructive sleep apnea-hypopnea syndrome (OSAHS) and glaucomatous optic neuropathy. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(9):1345–57. <https://doi.org/10.1007/s00417-014-2669-4>.
41. Cabrera M, Benavides AM, Hallaji NAE, Chung SA, Shapiro CM, Trope GE, et al. Risk of obstructive sleep apnea in open-angle glaucoma versus controls using the STOP-Bang questionnaire. *Can J Ophthalmol*. 2018;53(1):76–80. <https://doi.org/10.1016/j.jcjo.2017.07.008>.
42. Bagabas N, Ghazali W, Mukhtar M, AlQassas I, Merdad R, Maniyar A, et al. Prevalence of glaucoma in patients with obstructive sleep apnea. *J Epidemiol Glob Health*. 2019;9(3):198–203. <https://doi.org/10.2991/jegh.k.190816.001>.
43. Salzgeber R, Iliev ME, Mathis J. Do optic nerve head and visual field parameters in patients with obstructive sleep apnea syndrome differ from those in control individuals? *Klin Monatsbl Augenheilkd*. 2014;231(4):340–3. <https://doi.org/10.1055/s-0034-1368260>.
44. Wozniak D, Bourne R, Peretz G, Kean J, Willshire C, Harun S, et al. Obstructive sleep apnea in patients with primary-open angle glaucoma: no role for a screening program. *J Glaucoma*. 2019;28(8):668–75. <https://doi.org/10.1097/JG.0000000000001296>.
45. Keenan TD, Goldacre R, Goldacre MJ. Associations between obstructive sleep apnoea, primary open angle glaucoma and age-related macular degeneration: record linkage study. *Br J Ophthalmol*. 2017;101(2):155–9. <https://doi.org/10.1136/bjophthalmol-2015-308278>.
46. Himori N, Ogawa H, Ichinose M, Nakazawa T. CPAP therapy reduces oxidative stress in patients with glaucoma and OSAS and improves the visual field. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(4):939–41. <https://doi.org/10.1007/s00417-019-04483-z>.
47. Lin PW, Friedman M, Lin HC, Chang HW, Wilson M, Lin MC. Normal tension glaucoma in patients with obstructive sleep apnea/hypopnea syndrome. *J Glaucoma*. 2011;20(9):553–8. <https://doi.org/10.1097/IJG.0b013e3181f3eb81>.
48. Sergi M, Salerno DE, Rizzi M, Blini M, Andreoli A, Messenio D, et al. Prevalence of normal tension glaucoma in obstructive sleep apnea syndrome patients. *J Glaucoma*. 2007;16(1):42–6. <https://doi.org/10.1097/01.jig.0000243472.51461.24>.
49. Bilgin G. Normal-tension glaucoma and obstructive sleep apnea syndrome: a prospective study. *BMC Ophthalmol*. 2014;14:27. <https://doi.org/10.1186/1471-2415-14-27>.
50. Kremmer S, Selbach JM, Ayertey HD, Steuhl KP. Normal tension glaucoma, sleep apnea syndrome and nasal continuous positive airway pressure therapy—case report with a review of literature. *Klin Monatsbl Augenheilkd*. 2001;218(4):263–8. <https://doi.org/10.1055/s-2001-14923>.
51. Aptel F, Khayi H, Pepin JL, Tamisier R, Levy P, Romanet JP, et al. Association of nonarteritic ischemic optic neuropathy with obstructive sleep apnea syndrome: consequences for obstructive sleep apnea screening and treatment. *JAMA Ophthalmol*. 2015;133(7):797–804. <https://doi.org/10.1001/jamaophthalmol.2015.0893>.
52. Berry S, Lin WV, Sadaka A, Lee AG. Nonarteritic anterior ischemic optic neuropathy: cause, effect, and management. *Eye Brain*. 2017;9:23–8. <https://doi.org/10.2147/EB.S125311>.
53. Bilgin G, Koban Y, Arnold AC. Nonarteritic anterior ischemic optic neuropathy and obstructive sleep apnea. *J Neuroophthalmol*. 2013;33(3):232–4. <https://doi.org/10.1097/WNO.0b013e31828eeecbd>.
54. Chang MY, Keltner JL. Risk factors for fellow eye involvement in nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol*. 2019;39(2):147–52. <https://doi.org/10.1097/WNO.0000000000000715>.
55. Wu Y, Zhou LM, Lou H, Cheng JW, Wei RL. The association between obstructive sleep apnea and nonarteritic anterior ischemic optic neuropathy: a systematic review and meta-Analysis. *Curr Eye Res*. 2016;41(7):987–92. <https://doi.org/10.3109/02713683.2015.1075221>.
56. Stein JD, Kim DS, Mundy KM, Talwar N, Nan B, Chervin RD, et al. The association between glaucomatous and other causes of optic neuropathy and sleep apnea. *Am J Ophthalmol*. 2011;152(6):989–98 e3. <https://doi.org/10.1016/j.ajo.2011.04.030>.
57. Mojon DS, Hedges TR 3rd, Ehrenberg B, Karam EZ, Goldblum D, Abou-Chebl A, et al. Association between sleep apnea syndrome and nonarteritic anterior ischemic optic neuropathy. *Arch Ophthalmol*. 2002;120(5):601–5. <https://doi.org/10.1001/archophth.120.5.601>.
58. Sun MH, Lee CY, Liao YJ, Sun CC. Nonarteritic anterior ischaemic optic neuropathy and its association with obstructive sleep apnoea: a health insurance database study. *Acta Ophthalmol*. 2019;97(1):e64–70. <https://doi.org/10.1111/aos.13832>.
59. Behbehani R, Mathews MK, Sergott RC, Savino PJ. Nonarteritic anterior ischemic optic neuropathy in patients with sleep apnea while being treated with continuous positive airway pressure. *Am J Ophthalmol*. 2005;139(3):518–21. <https://doi.org/10.1016/j.ajo.2004.11.004>.
60. Altaf QA, Dodson P, Ali A, Raymond NT, Wharton H, Fellows H, et al. Obstructive sleep apnea and retinopathy in patients with type 2 diabetes. A Longitudinal Study. *Am J Respir Crit Care Med*. 2017;196(7):892–900. <https://doi.org/10.1164/rccm.201701-0175OC>.
61. Chang AC, Fox TP, Wang S, Wu AY. Relationship between obstructive sleep apnea and the presence and severity of diabetic retinopathy. *Retina*. 2018;38(11):2197–206. <https://doi.org/10.1097/IAE.0000000000001848>.
62. Chew M, Tan NYQ, Lamoureux E, Cheng CY, Wong TY, Sabanayagam C. The associations of objectively measured sleep duration and sleep disturbances with diabetic retinopathy. *Diabetes Res Clin Pract*. 2020;159:107967. <https://doi.org/10.1016/j.diabres.2019.107967>.
63. Du C, He C, Dong L, Zheng S, Wang W, Zheng C, et al. Associations of apnea hypopnea index and educational attainments with microvascular complications in patients with T2DM. *Endocrine*. 2020;67(2):363–73. <https://doi.org/10.1007/s12020-020-02192-w>.
64. Zhang R, Zhang P, Zhao F, Han X, Ji L. Association of diabetic microvascular complications and parameters of obstructive sleep apnea in patients with type 2 diabetes. *Diabetes Technol Ther*. 2016;18(7):415–20. <https://doi.org/10.1089/dia.2015.0433>.
65. Zhu Z, Zhang F, Liu Y, Yang S, Li C, Niu Q, et al. Relationship of obstructive sleep apnoea with diabetic retinopathy: a meta-analysis. *Biomed Res Int*. 2017;2017:4737064. <https://doi.org/10.1155/2017/4737064>.
66. Vie AL, Kodjikian L, Agard E, Voirin N, El Chehab H, Denis P, et al. Evaluation of obstructive sleep apnea syndrome as a risk factor for diabetic macular edema in patients with type II diabetes. *Retina*. 2019;39(2):274–80. <https://doi.org/10.1097/IAE.0000000000001954>.
67. Smith JP, Cyr LG, Dowd LK, Duchin KS, Lenihan PA, Sprague J. The Veterans Affairs continuous positive airway pressure use and diabetic retinopathy study. *Optom Vis Sci*. 2019;96(11):874–8. <https://doi.org/10.1097/OPX.0000000000001446>.
68. Shiba T, Takahashi M, Matsumoto T, Hori Y. Sleep-disordered breathing is a stronger risk factor for proliferative diabetic retinopathy than metabolic syndrome and the number of its individual components. *Semin Ophthalmol*. 2019;34(2):59–65. <https://doi.org/10.1080/08820538.2019.1569074>.
69. Tan NYQ, Chew M, Tham YC, Nguyen QD, Yasuda M, Cheng CY, et al. Associations between sleep duration, sleep quality and

- diabetic retinopathy. *PLoS One*. 2018;13(5):e0196399. <https://doi.org/10.1371/journal.pone.0196399>.
70. Leong WB, Jadhakhan F, Taheri S, Chen YF, Adab P, Thomas GN. Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: a systematic review and meta-analysis. *Diabet Med*. 2016;33(2):158–68. <https://doi.org/10.1111/dme.12817>.
 71. He M, Huang W. The role of choroidal thickness in diabetic retinopathy and obstructive sleep apnea syndrome. *Sleep Breath*. 2016;20(3):1009–10. <https://doi.org/10.1007/s11325-016-1343-y>.
 72. Baba A, Zbiba W, Bouayed E, Korbi M, Ghrairi H. Obstructive sleep apnea syndrome. Is it a risk factor for diabetic retinopathy? *J Fr Ophthalmol*. 2016;39(2):139–42. <https://doi.org/10.1016/j.jfo.2015.08.014>.
 73. Nishimura A, Kasai T, Tamura H, Yamato A, Yasuda D, Nagasawa K, et al. Relationship between sleep disordered breathing and diabetic retinopathy: analysis of 136 patients with diabetes. *Diabetes Res Clin Pract*. 2015;109(2):306–11. <https://doi.org/10.1016/j.diabres.2015.05.015>.
 74. Banerjee D, Leong WB, Arora T, Nolen M, Punamiya V, Grunstein R, et al. The potential association between obstructive sleep apnea and diabetic retinopathy in severe obesity—the role of hypoxemia. *PLoS One*. 2013;8(11):e79521. <https://doi.org/10.1371/journal.pone.0079521>.
 75. Rudrappa S, Warren G, Idris I. Obstructive sleep apnoea is associated with the development and progression of diabetic retinopathy, independent of conventional risk factors and novel biomarkers for diabetic retinopathy. *Br J Ophthalmol*. 2012;96(12):1535. <https://doi.org/10.1136/bjophthalmol-2012-301991>.
 76. Mason RH, West SD, Kiire CA, Groves DC, Lipinski HJ, Jaycock A, et al. High prevalence of sleep disordered breathing in patients with diabetic macular edema. *Retina*. 2012;32(9):1791–8. <https://doi.org/10.1097/IAE.0b013e318259568b>.
 77. Shiba T, Takahashi M, Hori Y, Saishin Y, Sato Y, Maeno T. Relationship between sleep-disordered breathing and iris and/or angle neovascularization in proliferative diabetic retinopathy cases. *Am J Ophthalmol*. 2011;151(4):604–9. <https://doi.org/10.1016/j.ajo.2010.10.002>.
 78. Shiba T, Takahashi M, Hori Y, Saishin Y, Sato Y, Maeno T. Evaluation of the relationship between background factors and sleep-disordered breathing in patients with proliferative diabetic retinopathy. *Jpn J Ophthalmol*. 2011;55(6):638–42. <https://doi.org/10.1007/s10384-011-0076-5>.
 79. West SD, Groves DC, Lipinski HJ, Nicoll DJ, Mason RH, Scanlon PH, et al. The prevalence of retinopathy in men with type 2 diabetes and obstructive sleep apnoea. *Diabet Med*. 2010;27(4):423–30. <https://doi.org/10.1111/j.1464-5491.2010.02962.x>.
 80. Shiba T, Maeno T, Saishin Y, Hori Y, Takahashi M. Nocturnal intermittent serious hypoxia and reoxygenation in proliferative diabetic retinopathy cases. *Am J Ophthalmol*. 2010;149(6):959–63. <https://doi.org/10.1016/j.ajo.2010.01.006>.
 81. Kasseifi S, Bailey B, Price R, Roy TM, Byrd RP Jr, Peiris AN. The association between obstructive sleep apnea syndrome and microvascular complications in well-controlled diabetic patients. *Mil Med*. 2010;175(11):913–6. <https://doi.org/10.7205/milmed-d-10-00131>.
 82. Shiba T, Sato Y, Takahashi M. Relationship between diabetic retinopathy and sleep-disordered breathing. *Am J Ophthalmol*. 2009;147(6):1017–21. <https://doi.org/10.1016/j.ajo.2008.12.027>.
 83. Mason RH, Kiire CA, Groves DC, Lipinski HJ, Jaycock A, Winter BC, et al. Visual improvement following continuous positive airway pressure therapy in diabetic subjects with clinically significant macular oedema and obstructive sleep apnoea: proof of principle study. *Respiration*. 2012;84(4):275–82. <https://doi.org/10.1159/000334090>.
 84. Raman R, Verma A, Srinivasan S, Bhojwani D. Partial reversal of color vision impairment in type 2 diabetes associated with obstructive sleep apnea. *GMS Ophthalmol Cases*. 2018;8:Doc05. <https://doi.org/10.3205/oc000087>.
 85. West SD, Prudon B, Hughes J, Gupta R, Mohammed SB, Gerry S, et al. Continuous positive airway pressure effect on visual acuity in patients with type 2 diabetes and obstructive sleep apnoea: a multicentre randomised controlled trial. *Eur Respir J*. 2018;52(4). <https://doi.org/10.1183/13993003.01177-2018>.
 86. Agard E, El Chehab H, Vie AL, Voirin N, Coste O, Dot C. Retinal vein occlusion and obstructive sleep apnea: a series of 114 patients. *Acta Ophthalmol*. 2018;96(8):e919–e25. <https://doi.org/10.1111/aos.13798>.
 87. Govetto A, Dominguez R, Rojas L, Pereiro M, Lorente R. Bilateral and simultaneous central retinal vein occlusion in a patient with obstructive sleep apnea syndrome. *Case Rep Ophthalmol*. 2014;5(2):150–6. <https://doi.org/10.1159/000363132>.
 88. Turati M, Velez-Montoya R, Gonzalez-Mijares CC, Perez-Montesinos A, Quiroz-Mercado H, Garcia-Aguirre G. Bilateral central retina vein occlusion associated with obesity-hypoventilation syndrome (pickwickian syndrome). *Retin Cases Brief Rep*. 2009;3(2):140–3. <https://doi.org/10.1097/ICB.0b013e31815e9919>.
 89. Kwon HJ, Kang EC, Lee J, Han J, Song WK. Obstructive sleep apnea in patients with branch retinal vein occlusion: a preliminary study. *Korean J Ophthalmol*. 2016;30(2):121–6. <https://doi.org/10.3341/kjo.2016.30.2.121>.
 90. Kanai H, Shiba T, Hori Y, Saishin Y, Maeno T, Takahashi M. Prevalence of sleep-disordered breathing in patients with retinal vein occlusion. *Nippon Ganka Gakkai Zasshi*. 2012;116(2):81–5.
 91. Chou KT, Huang CC, Tsai DC, Chen YM, Perng DW, Shiao GM, et al. Sleep apnea and risk of retinal vein occlusion: a nationwide population-based study of Taiwanese. *Am J Ophthalmol*. 2012;154(1):200–5 e1. <https://doi.org/10.1016/j.ajo.2012.01.011>.
 92. Glacet-Bernard A, Leroux les Jardins G, Lasry S, Coscas G, Soubrane G, Souied E et al. Obstructive sleep apnea among patients with retinal vein occlusion. *Arch Ophthalmol*. 2010;128(12):1533–8. <https://doi.org/10.1001/archophthalmol.2010.272>.
 93. Leroux les Jardins G, Glacet Bernard A, Lasry S, Housset B, Coscas G, Soubrane G. Retinal vein occlusion and obstructive sleep apnea syndrome. *J Fr Ophthalmol*. 2009;32(6):420–4. <https://doi.org/10.1016/j.jfo.2009.04.012>.
 94. Wu CY, Riangwiwat T, Rattanawong P, Nesmith BLW, Deobhakta A. Association of obstructive sleep apnea with central serous chorioretinopathy and choroidal thickness: a systematic review and meta-analysis. *Retina*. 2018;38(9):1642–51. <https://doi.org/10.1097/IAE.0000000000002117>.
 95. Brodie FL, Charlson ES, Aleman TS, Salvo RT, Gewaily DY, Lau MK, et al. Obstructive sleep apnea and central serous chorioretinopathy. *Retina*. 2015;35(2):238–43. <https://doi.org/10.1097/IAE.0000000000000326>.
 96. Chang YS, Weng SF, Wang JJ, Jan RL. Increased risk of central serous chorioretinopathy following end-stage renal disease: a nationwide population-based study. *Medicine (Baltimore)*. 2019;98(11):e14859. <https://doi.org/10.1097/MD.00000000000014859>.
 97. Chatziralli I, Kabanarou SA, Parikakis E, Chatzirallis A, Xirou T, Mitropoulos P. Risk factors for central serous chorioretinopathy: multivariate approach in a case-control study. *Curr Eye Res*. 2017;42(7):1069–73. <https://doi.org/10.1080/02713683.2016.1276196>.
 98. Kloos P, Laube I, Thoelen A. Obstructive sleep apnea in patients with central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(9):1225–8. <https://doi.org/10.1007/s00417-008-0837-0>.
 99. Leveque TK, Yu L, Musch DC, Chervin RD, Zacks DN. Central serous chorioretinopathy and risk for obstructive sleep apnea. *Sleep Breath*. 2007;11(4):253–7. <https://doi.org/10.1007/s11325-007-0112-3>.
 100. Yavas GF, Kusbeci T, Kasikci M, Gunay E, Dogan M, Unlu M, et al. Obstructive sleep apnea in patients with central serous

- chorioretinopathy. *Curr Eye Res.* 2014;39(1):88–92. <https://doi.org/10.3109/02713683.2013.824986>.
101. Nesmith BL, Ihnen M, Schaal S. Poor responders to bevacizumab pharmacotherapy in age-related macular degeneration and in diabetic macular edema demonstrate increased risk for obstructive sleep apnea. *Retina.* 2014;34(12):2423–30. <https://doi.org/10.1097/IAE.0000000000000247>.
 102. Schaal S, Sherman MP, Nesmith B, Barak Y. Untreated obstructive sleep apnea hinders response to bevacizumab in age-related macular degeneration. *Retina.* 2016;36(4):791–7. <https://doi.org/10.1097/IAE.0000000000000981>.
 103. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90(1):47–112. <https://doi.org/10.1152/physrev.00043.2008>.
 104. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med.* 2019;380(15):1442–9. <https://doi.org/10.1056/NEJMc1816152>.
 105. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med.* 2002;165(9):1217–39. <https://doi.org/10.1164/rccm.2109080>.
 106. Bostanci A, Bozkurt S, Turhan M. Impact of age on intermittent hypoxia in obstructive sleep apnea: a propensity-matched analysis. *Sleep Breath.* 2018;22(2):317–22. <https://doi.org/10.1007/s11325-017-1560-z>.
 107. Clark RA, Suh SY, Caprioli J, Giaconci JA, Nouri-Mahdavi K, Law SK, et al. Adduction-induced strain on the optic nerve in primary open angle glaucoma at normal intraocular pressure. *Curr Eye Res.* 2020;1–11. <https://doi.org/10.1080/02713683.2020.1817491>.
 108. Li Y, Wei Q, Le A, Gawargious BA, Demer JL. Rectus extraocular muscle paths and staphylomata in high myopia. *Am J Ophthalmol.* 2019;201:37–45. <https://doi.org/10.1016/j.ajo.2019.01.029>.
 109. Netland PA, Sugrue SP, Albert DM, Shore JW. Histopathologic features of the floppy eyelid syndrome. involvement of tarsal elastin. *Ophthalmology.* 1994;101(1):174–81. [https://doi.org/10.1016/s0161-6420\(94\)31368-6](https://doi.org/10.1016/s0161-6420(94)31368-6).
 110. Schlotzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, Cursiefen C, Kruse FE, Holbach LM. The pathogenesis of floppy eyelid syndrome: involvement of matrix metalloproteinases in elastic fiber degradation. *Ophthalmology.* 2005;112(4):694–704. <https://doi.org/10.1016/j.ophtha.2004.11.031>.
 111. Series F, Chakir J, Boivin D. Influence of weight and sleep apnea status on immunologic and structural features of the uvula. *Am J Respir Crit Care Med.* 2004;170(10):1114–9. <https://doi.org/10.1164/rccm.200404-458OC>.
 112. Acar M, Firat H, Acar U, Ardic S. Ocular surface assessment in patients with obstructive sleep apnea-hypopnea syndrome. *Sleep Breath.* 2013;17(2):583–8. <https://doi.org/10.1007/s11325-012-0724-0>.
 113. du Toit R, Vega JA, Fonn D, Simpson T. Diurnal variation of corneal sensitivity and thickness. *Cornea.* 2003;22(3):205–9. <https://doi.org/10.1097/00003226-200304000-00004>.
 114. Polse KA, Mandell RB. Critical oxygen tension at the corneal surface. *Arch Ophthalmol.* 1970;84(4):505–8. <https://doi.org/10.1001/archophth.1970.00990040507021>.
 115. Gelir E, Budak MT, Ardic S. The relationship between CPAP usage and corneal thickness. *PLoS One.* 2014;9(1):e87274. <https://doi.org/10.1371/journal.pone.0087274>.
 116. Koseoglu HI, Kanbay A, Ortak H, Karadag R, Demir O, Demir S, et al. Effect of obstructive sleep apnea syndrome on corneal thickness. *Int Ophthalmol.* 2016;36(3):327–33. <https://doi.org/10.1007/s10792-015-0122-2>.
 117. Dikkaya F, Yildirim R, Erdur SK, Benbir G, Aydin R, Karadeniz D. Corneal biomechanical properties in obstructive sleep apnea syndrome. *Eye Contact Lens.* 2018;44(Suppl 2):S361–S4. <https://doi.org/10.1097/ICL.0000000000000489>.
 118. Huseyinoglu N, Ekinci M, Ozben S, Buyukyuksal C, Kale MY, Sanivar HS. Optic disc and retinal nerve fiber layer parameters as indicators of neurodegenerative brain changes in patients with obstructive sleep apnea syndrome. *Sleep Breath.* 2014;18(1):95–102. <https://doi.org/10.1007/s11325-013-0854-z>.
 119. Yang HK, Park SJ, Byun SJ, Park KH, Kim JW, Hwang JM. Obstructive sleep apnoea and increased risk of non-arteritic anterior ischaemic optic neuropathy. *Br J Ophthalmol.* 2019;103(8):1123–8. <https://doi.org/10.1136/bjophthalmol-2018-312910> **A nationwide population-based, retrospective cohort study showing increased risk of NAION in the OSA group.**
 120. SSY L, McArdle N, Sanfilippo PG, Yazar S, Eastwood PR, Hewitt AW, et al. Associations between optic disc measures and obstructive sleep apnea in young adults. *Ophthalmology.* 2019;126(10):1372–84. <https://doi.org/10.1016/j.ophtha.2019.04.041> **Preclinical peripapillary RNFL thinning was present in young adults with obstructive sleep apnea suggesting possible increased glaucoma risk in these patients.**
 121. Shiba T, Takahashi M, Sato Y, Onoda Y, Hori Y, Sugiyama T, et al. Relationship between severity of obstructive sleep apnea syndrome and retinal nerve fiber layer thickness. *Am J Ophthalmol.* 2014;157(6):1202–8. <https://doi.org/10.1016/j.ajo.2014.01.028>.
 122. Wang W, He M, Huang W. Changes of retinal nerve fiber layer thickness in obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Curr Eye Res.* 2017;42(5):796–802. <https://doi.org/10.1080/02713683.2016.1238942>.
 123. Yu JG, Mei ZM, Ye T, Feng YF, Zhao F, Jia J, et al. Changes in retinal nerve fiber layer thickness in obstructive sleep apnea/hypopnea syndrome: a meta-analysis. *Ophthalmic Res.* 2016;56(2):57–67. <https://doi.org/10.1159/000444301>.
 124. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. *Neurology.* 2002;59(10):1492–5. <https://doi.org/10.1212/01.wnl.0000029570.69134.1b>.
 125. Wall M, Purvin V. Idiopathic intracranial hypertension in men and the relationship to sleep apnea. *Neurology.* 2009;72(4):300–1. <https://doi.org/10.1212/01.wnl.0000336338.97703.fb>.
 126. Lee AG, Golnik K, Kardon R, Wall M, Eggenberger E, Yedavally S. Sleep apnea and intracranial hypertension in men. *Ophthalmology.* 2002;109(3):482–5. [https://doi.org/10.1016/s0161-6420\(01\)00987-3](https://doi.org/10.1016/s0161-6420(01)00987-3).
 127. Sugita Y, Iijima S, Teshima Y, Shimizu T, Nishimura N, Tsutsumi T, et al. Marked episodic elevation of cerebrospinal fluid pressure during nocturnal sleep in patients with sleep apnea hypersomnia syndrome. *Electroencephalogr Clin Neurophysiol.* 1985;60(3):214–9. [https://doi.org/10.1016/0013-4694\(85\)90033-1](https://doi.org/10.1016/0013-4694(85)90033-1).
 128. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea syndrome. *Arch Ophthalmol.* 2000;118(12):1626–30. <https://doi.org/10.1001/archophth.118.12.1626>.
 129. Onder H, Aksoy M. Resolution of idiopathic intracranial hypertension symptoms by surgery for obstructive sleep apnea in a pediatric patient. *J Pediatr Neurosci.* 2019;14(2):110–2. https://doi.org/10.4103/jpn.JPN_30_19.
 130. Lacharme T, Alamanjourni A, Aptel F, Khayri H, Pepin JL, Baguet JP, et al. Twenty-four-hour rhythm of ocular perfusion pressure in non-arteritic anterior ischaemic optic neuropathy. *Acta Ophthalmol.* 2014;92(5):e346–52. <https://doi.org/10.1111/aos.12352>.
 131. Hayreh SS. Blood flow in the optic nerve head and factors that may influence it. *Prog Retin Eye Res.* 2001;20(5):595–624. [https://doi.org/10.1016/s1350-9462\(01\)00005-2](https://doi.org/10.1016/s1350-9462(01)00005-2).
 132. Hayreh SS, Podhajsky PA, Zimmerman B. Nonarteritic anterior ischemic optic neuropathy: time of onset of visual loss. *Am J*

- Ophthalmol. 1997;124(5):641–7. [https://doi.org/10.1016/s0002-9394\(14\)70902-x](https://doi.org/10.1016/s0002-9394(14)70902-x).
133. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *Am J Ophthalmol*. 1994;117(5):603–24. [https://doi.org/10.1016/s0002-9394\(14\)70067-4](https://doi.org/10.1016/s0002-9394(14)70067-4).
 134. Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK. Effects of obstructive sleep apnea on endothelin-1 and blood pressure. *J Hypertens*. 1999;17(1):61–6. <https://doi.org/10.1097/00004872-199917010-00010>.
 135. Hayreh SS. Ischemic optic neuropathy. *Prog Retin Eye Res*. 2009;28(1):34–62. <https://doi.org/10.1016/j.preteyeres.2008.11.002>.
 136. Palombi K, Renard E, Levy P, Chiquet C, Deschaux C, Romanet JP, et al. Non-arteritic anterior ischaemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea. *Br J Ophthalmol*. 2006;90(7):879–82. <https://doi.org/10.1136/bjo.2005.087452>.
 137. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res*. 2010;29(2):144–68. <https://doi.org/10.1016/j.preteyeres.2009.12.002>.
 138. Tonini M, Khayi H, Pepin JL, Renard E, Baguet JP, Levy P, et al. Choroidal blood-flow responses to hyperoxia and hypercapnia in men with obstructive sleep apnea. *Sleep*. 2010;33(6):811–8. <https://doi.org/10.1093/sleep/33.6.811>.
 139. Xin C, Wang J, Zhang W, Wang L, Peng X. Retinal and choroidal thickness evaluation by SD-OCT in adults with obstructive sleep apnea-hypopnea syndrome (OSAS). *Eye (Lond)*. 2014;28(4):415–21. <https://doi.org/10.1038/eye.2013.307>.
 140. Karaca EE, Ekici F, Yalcin NG, Ciftci TU, Ozdek S. Macular choroidal thickness measurements in patients with obstructive sleep apnea syndrome. *Sleep Breath*. 2015;19(1):335–41. <https://doi.org/10.1007/s11325-014-1025-6>.
 141. He M, Han X, Wu H, Huang W. Choroidal thickness changes in obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Sleep Breath*. 2016;20(1):369–78. <https://doi.org/10.1007/s11325-015-1306-8>.
 142. Zengin MO, Oz T, Baysak A, Cinar E, Kucukerdonmez C. Changes in choroidal thickness in patients with obstructive sleep apnea syndrome. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45(4):298–304. <https://doi.org/10.3928/23258160-20140624-02>.
 143. Karalezli A, Eroglu FC, Kivanc T, Dogan R. Evaluation of choroidal thickness using spectral-domain optical coherence tomography in patients with severe obstructive sleep apnea syndrome: a comparative study. *Int J Ophthalmol*. 2014;7(6):1030–4. <https://doi.org/10.3980/j.issn.2222-3959.2014.06.22>.
 144. Uslu H, Kanra AY, Cetintas G, Tatar MG. Effect of therapy on choroidal thickness in patients with obstructive sleep apnea syndrome. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(11):846–51. <https://doi.org/10.3928/23258160-20181101-05>.
 145. Cakabay T, Ustun Bezgin S, Bayramoglu SE, Sayin N, Kocyigit M. Evaluation of choroidal thickness in children with adenoid hypertrophy. *Eur Arch Otorhinolaryngol*. 2018;275(2):439–42. <https://doi.org/10.1007/s00405-017-4846-7>.
 146. Ghimire-Aryal P, Schwartz S, Sebastião YV, Anderson WM, Foulis PR. 0914 Association between obstructive sleep apnea, nightmare disorder and incident herpes zoster. *Sleep*. 2018;41(suppl_1):A339–A40. <https://doi.org/10.1093/sleep/zy061.913>.
 147. Chung WS, Lin HH, Cheng NC. The incidence and risk of herpes zoster in patients with sleep disorders: a population-based cohort study. *Medicine (Baltimore)*. 2016;95(11):e2195. <https://doi.org/10.1097/MD.0000000000002195>.
 148. Bagheri M, Rashe Z, Ahoor MH, Somi MH. Prevalence of *Helicobacter pylori* infection in patients with central serous chorioretinopathy: a review. *Med Hypothesis Discov Innov Ophthalmol*. 2017;6(4):118–24.
 149. Tsai CC, Kuo TY, Hong ZW, Yeh YC, Shih KS, Du SY, et al. *Helicobacter pylori* neutrophil-activating protein induces release of histamine and interleukin-6 through G protein-mediated MAPKs and PI3K/Akt pathways in HMC-1 cells. *Virulence*. 2015;6(8):755–65. <https://doi.org/10.1080/21505594.2015.1043505>.
 150. Caruso RA, Parisi A, Crisafulli C, Bonanno A, Lucian R, Branca G, et al. Intraepithelial infiltration by mast cells in human *Helicobacter pylori* active gastritis. *Ultrastruct Pathol*. 2011;35(6):251–5. <https://doi.org/10.3109/01913123.2011.606964>.
 151. Nakajima S, Bamba N, Hattori T. Histological aspects and role of mast cells in *Helicobacter pylori*-infected gastritis. *Aliment Pharmacol Ther*. 2004;20(Suppl 1):165–70. <https://doi.org/10.1111/j.1365-2036.2004.01974.x>.
 152. Yamamoto J, Watanabe S, Hirose M, Osada T, Ra C, Sato N. Role of mast cells as a trigger of inflammation in *Helicobacter pylori* infection. *J Physiol Pharmacol*. 1999;50(1):17–23.
 153. Nakajima S, Krishnan B, Ota H, Segura AM, Hattori T, Graham DY, et al. Mast cell involvement in gastritis with or without *Helicobacter pylori* infection. *Gastroenterology*. 1997;113(3):746–54. [https://doi.org/10.1016/s0016-5085\(97\)70167-7](https://doi.org/10.1016/s0016-5085(97)70167-7).
 154. Kurose I, Granger DN, Evans DJ Jr, Evans DG, Graham DY, Miyasaka M, et al. *Helicobacter pylori*-induced microvascular protein leakage in rats: role of neutrophils, mast cells, and platelets. *Gastroenterology*. 1994;107(1):70–9. [https://doi.org/10.1016/0016-5085\(94\)90062-0](https://doi.org/10.1016/0016-5085(94)90062-0).
 155. Kountouras C, Polyzos SA, Stergiopoulos C, Katsinelos P, Tzivras D, Zavos C, et al. A potential impact of *Helicobacter pylori* infection on both obstructive sleep apnea and atrial fibrillation-related stroke. *Sleep Med*. 2017;34:256. <https://doi.org/10.1016/j.sleep.2017.03.010>.
 156. Banawan LAH, Daabis RGA, Elsheikh WH, Tolba MM, Youssef AM. The prevalence of *Helicobacter pylori* infection in patients with obstructive sleep apnea having metabolic syndrome and its relation to both disorders. *Egyptian Journal of Bronchology*. 2017;11(3):268–75. https://doi.org/10.4103/ejb.ejb_54_16.
 157. Wasilewska J, Klukowski M, Debkowska K, Kilon J, Citko D, Flisiak M, et al. *Helicobacter pylori* seroprevalence in children with sleep-disordered breathing. *Int J Pediatr Otorhinolaryngol*. 2016;87:208–12. <https://doi.org/10.1016/j.ijporl.2016.06.024>.
 158. Kountouras J, Polyzos SA, Deretzi G. *Helicobacter pylori* associated with obstructive sleep apnea might contribute to sleep, cognition, and driving performance disturbances in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2015;13(8):1547. <https://doi.org/10.1016/j.cgh.2015.02.009>.
 159. Nartova E, Kraus J, Pavlik E, Lukes P, Kutra R, Plzak J, et al. Presence of different genotypes of *Helicobacter pylori* in patients with chronic tonsillitis and sleep apnoea syndrome. *Eur Arch Otorhinolaryngol*. 2014;271(3):607–13. <https://doi.org/10.1007/s00405-013-2607-9>.
 160. Stergiopoulos C, Kountouras J, Daskalopoulou-Vlachoyianni E, Polyzos SA, Zavos C, Vlachoyianni E, et al. *Helicobacter pylori* may play a role in both obstructive sleep apnea and metabolic syndrome. *Sleep Med*. 2012;13(2):212–3. <https://doi.org/10.1016/j.sleep.2011.04.016>.
 161. Ye XW, Xiao J, Qiu T, Tang YJ, Feng YL, Wang K, et al. *Helicobacter pylori* seroprevalence in patients with obstructive sleep apnea syndrome among a Chinese population. *Saudi Med J*. 2009;30(5):693–7.
 162. Unal M, Ozturk L, Ozturk C, Kabal A. The seroprevalence of *Helicobacter pylori* infection in patients with obstructive sleep apnoea: a preliminary study. *Clin Otolaryngol Allied Sci*.

- 2003;28(2):100–2. <https://doi.org/10.1046/j.1365-2273.2003.00672.x>.
163. Bousquet E, Zhao M, Thillaye-Goldenberg B, Lorena V, Castaneda B, Naud MC, et al. Choroidal mast cells in retinal pathology: a potential target for intervention. *Am J Pathol*. 2015;185(8):2083–95. <https://doi.org/10.1016/j.ajpath.2015.04.002>.
 164. Casas P, Ascaso FJ, Vicente E, Tejero-Garcés G, Adiego MI, Cristóbal JA. Visual field defects and retinal nerve fiber imaging in patients with obstructive sleep apnea syndrome and in healthy controls. *BMC Ophthalmol*. 2018;18(1):66. <https://doi.org/10.1186/s12886-018-0728-z>.
 165. Yazgan S, Erboy F, Celik HU, Ornek T, Ugurbas SH, Kokturk F, et al. Peripapillary choroidal thickness and retinal nerve fiber layer in untreated patients with obstructive sleep apnea-hypopnea syndrome: a case-control study. *Curr Eye Res*. 2017;42(11):1552–60. <https://doi.org/10.1080/02713683.2016.1266661>.
 166. Zhao XJ, Yang CC, Zhang JC, Zheng H, Liu PP, Li Q. Obstructive sleep apnea and retinal nerve fiber layer thickness: a meta-analysis. *J Glaucoma*. 2016;25(4):e413–8. <https://doi.org/10.1097/IJG.0000000000000349>.
 167. Sun CL, Zhou LX, Dang Y, Huo YP, Shi L, Chang YJ. Decreased retinal nerve fiber layer thickness in patients with obstructive sleep apnea syndrome: a meta-analysis. *Medicine (Baltimore)*. 2016;95(32):e4499. <https://doi.org/10.1097/MD.00000000000004499>.
 168. Ferrandez B, Ferreras A, Calvo P, Abadía B, Marin JM, Pajarin AB. Assessment of the retinal nerve fiber layer in individuals with obstructive sleep apnea. *BMC Ophthalmol*. 2016;16:40. <https://doi.org/10.1186/s12886-016-0216-2>.
 169. Cinici E, Tatar A. Thickness alterations of retinal nerve fiber layer in children with sleep-disordered breathing due to adenotonsillar hypertrophy. *Int J Pediatr Otorhinolaryngol*. 2015;79(8):1218–23. <https://doi.org/10.1016/j.ijporl.2015.05.017>.
 170. Moghimi S, Ahmadraji A, Sotoodeh H, Sadeghnia K, Maghsoudipour M, Fakhraie G, et al. Retinal nerve fiber thickness is reduced in sleep apnea syndrome. *Sleep Med*. 2013;14(1):53–7. <https://doi.org/10.1016/j.sleep.2012.07.004>.
 171. Adam M, Okka M, Yosunkaya S, Bozkurt B, Kerimoglu H, Turan M. The evaluation of retinal nerve fiber layer thickness in patients with obstructive sleep apnea syndrome. *J Ophthalmol*. 2013;2013:292158. <https://doi.org/10.1155/2013/292158>.
 172. Lin PW, Friedman M, Lin HC, Chang HW, Pulver TM, Chin CH. Decreased retinal nerve fiber layer thickness in patients with obstructive sleep apnea/hypopnea syndrome. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(4):585–93. <https://doi.org/10.1007/s00417-010-1544-1>.
 173. Kargi SH, Altin R, Koksall M, Kart L, Cinar F, Ugurbas SH, et al. Retinal nerve fibre layer measurements are reduced in patients with obstructive sleep apnoea syndrome. *Eye (Lond)*. 2005;19(5):575–9. <https://doi.org/10.1038/sj.eye.6701582>.
 174. Wang JS, Xie HT, Jia Y, Zhang MC. Retinal nerve fiber layer thickness changes in obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Int J Ophthalmol*. 2016;9(11):1651–6. <https://doi.org/10.18240/ijo.2016.11.19>.
 175. Comella CL. Sleep disorders in Parkinson's disease: an overview. *Mov Disord*. 2007;22(Suppl 17):S367–73. <https://doi.org/10.1002/mds.21682>.
 176. Nomura T, Inoue Y, Kagimura T, Nakashima K. Clinical significance of REM sleep behavior disorder in Parkinson's disease. *Sleep Med*. 2013;14(2):131–5. <https://doi.org/10.1016/j.sleep.2012.10.011>.
 177. Yu JG, Feng YF, Xiang Y, Huang JH, Savini G, Parisi V, et al. Retinal nerve fiber layer thickness changes in Parkinson disease: a meta-analysis. *PLoS One*. 2014;9(1):e85718. <https://doi.org/10.1371/journal.pone.0085718>.
 178. Lee JY, Ahn J, Oh S, Shin JY, Kim YK, Nam H, et al. Retinal thickness as a marker of neurodegeneration in prodromal lewy body disease. *Mov Disord*. 2020;35(2):349–54. <https://doi.org/10.1002/mds.27914>.
 179. Chrysou A, Jansson NM, van Laar T. Retinal layers in Parkinson's disease: a meta-analysis of spectral-domain optical coherence tomography studies. *Parkinsonism Relat Disord*. 2019;64:40–9. <https://doi.org/10.1016/j.parkreldis.2019.04.023>.
 180. Yang ZJ, Wei J, Mao CJ, Zhang JR, Chen J, Ji XY, et al. Retinal nerve fiber layer thinning: a window into rapid eye movement sleep behavior disorders in Parkinson's disease. *Sleep Breath*. 2016;20(4):1285–92. <https://doi.org/10.1007/s11325-016-1366-4>.
 181. Ahn J, Lee JY, Kim TW, Yoon EJ, Oh S, Kim YK, et al. Retinal thinning associates with nigral dopaminergic loss in de novo Parkinson disease. *Neurology*. 2018;91(11):e1003–e12. <https://doi.org/10.1212/WNL.0000000000006157>.
 182. Lax P, Ortuno-Lizaran I, Maneu V, Vidal-Sanz M, Cuenca N. Photosensitive melanopsin-containing retinal ganglion cells in health and disease: implications for circadian rhythms. *Int J Mol Sci*. 2019;20(13). <https://doi.org/10.3390/ijms2013164>.
 183. Do MTH. Melanopsin and the intrinsically photosensitive retinal ganglion cells: biophysics to behavior. *Neuron*. 2019;104(2):205–26. <https://doi.org/10.1016/j.neuron.2019.07.016>.
 184. Ortuno-Lizaran I, Esquivia G, Beach TG, Serrano GE, Adler CH, Lax P, et al. Degeneration of human photosensitive retinal ganglion cells may explain sleep and circadian rhythms disorders in Parkinson's disease. *Acta Neuropathol Commun*. 2018;6(1):90. <https://doi.org/10.1186/s40478-018-0596-z>.
 185. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation*. 2005;112(17):2660–7. <https://doi.org/10.1161/CIRCULATIONAHA.105.556746>.
 186. Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. *Sleep*. 2003;26(1):15–9. <https://doi.org/10.1093/sleep/26.1.15>.
 187. Kaczmarek E, Bakker JP, Clarke DN, Csizmadia E, Kocher O, Veves A, et al. Molecular biomarkers of vascular dysfunction in obstructive sleep apnea. *PLoS One*. 2013;8(7):e70559. <https://doi.org/10.1371/journal.pone.0070559>.
 188. Li Q, Verma A, Han PY, Nakagawa T, Johnson RJ, Grant MB, et al. Diabetic eNOS-knockout mice develop accelerated retinopathy. *Invest Ophthalmol Vis Sci*. 2010;51(10):5240–6. <https://doi.org/10.1167/iovs.09-5147>.
 189. Kida T, Flammer J, Oku H, Konieczka K, Morishita S, Horie T, et al. Vasoactivity of retinal veins: a potential involvement of endothelin-1 (ET-1) in the pathogenesis of retinal vein occlusion (RVO). *Exp Eye Res*. 2018;176:207–9. <https://doi.org/10.1016/j.exer.2018.07.016>.
 190. Totan Y, Koca C, Erdurmus M, Keskin U, Yigitoglu R. Endothelin-1 and Nitric oxide levels in exudative age-related macular degeneration. *J Ophthalmic Vis Res*. 2015;10(2):151–4. <https://doi.org/10.4103/2008-322X.163765>.
 191. Mentek M, Morand J, Baldazza M, Faury G, Aptel F, Pepin JL, et al. Chronic intermittent hypoxia alters rat ophthalmic artery reactivity through oxidative stress, endothelin and endothelium-derived hyperpolarizing pathways. *Invest Ophthalmol Vis Sci*. 2018;59(12):5256–65. <https://doi.org/10.1167/iovs.18-25151>.