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REVIEW ARTICLES

Sleep apnea and eye diseases: evidence of association and potential pathogenic mechanisms

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Eye diseases are an important group of increasingly prevalent disorders that contribute very significantly to disability and represent a considerable health burden. Some data suggest that several of these diseases may be associated with sleep-disordered breathing, mainly obstructive sleep apnea (OSA), due to intermediate mechanisms, such as intermittent hypoxia or sleep fragmentation. The aims of this systematic review were to identify and critically evaluate the current evidence supporting the existence of a possible relationship between OSA and the more relevant eye diseases as well as to evaluate the potential pathogenic mechanisms. There is a body of largely low-level evidence for the association of OSA with glaucoma, nonarteritic ischemic optic neuropathy, central serous chorioretinopathy, and diabetic retinopathy. Meta-analysis of available case-control studies shows that OSA increases the risk of glaucoma (pooled odds ratio: 1.50; 95% confidence interval: 1.25 to 1.80; $P < .001$), nonarteritic ischemic optic neuropathy (3.62; 1.94 to 6.76; $P < .001$), and diabetic retinopathy (1.57; 1.09 to 2.27; $P = .02$). Moreover, several pathogenic pathways have been identified, mainly related to hypoxic damage, mechanical stress, systemic inflammation, oxidative stress, sympathetic tone, and endothelial dysfunction. In contrast, information about the effect of apnea-hypopnea suppression on the development and progression of eye damage is either nonexistent or of a very low level of evidence. In conclusion, OSA has emerged as an additional potential risk factor for many eye diseases, although their link is weak and contradictory, so further examination is required.

Keywords: sleep apnea, eye, glaucoma, retinopathy, intermittent hypoxia, oxidative stress, diabetes

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INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disorder, characterized by repeated episodes of partial or complete collapse of the upper airway during sleep, leading to intermittent hypoxemia and sleep fragmentation.[1,2] Current evidence has demonstrated that OSA is strongly associated with cardiovascular and metabolic diseases[3–5] through several pathways, including increased sympathetic activity, oxidative stress, systemic inflammation, insulin resistance, or endothelial dysfunction.[6–8] Many of these disorders are also recognized risk factors for the development and progression of different eye diseases.[9–12] In fact, over the last few years, an increasing number of publications have reported on a potential association between OSA and several ophthalmic diseases (**Table 1**).[13–17]

Although it is estimated that 936 million adults have OSA worldwide,[1] the prevalence of some eye diseases is experiencing a notable increase. In 2020, the number of adults worldwide with diabetic retinopathy (DR) was estimated to be 103.12 million and by 2045 is projected to increase to 160.50 million.[18] In turn, from 2010 to 2050, the number of people in the United States with glaucoma is expected to increase by more than double, from 2.7 million to 6.3 million.[19] Moreover, and despite the existence of increasing therapeutic options, the socio-sanitary impact of many of these disorders is still excessive. Globally, in 2020, glaucoma and DR were responsible for 3.6 and 0.86 million cases of blindness, respectively, in individuals aged 50 years and older.[20] Consequently, it seems necessary to explore the contribution of other possible risk factors both for the development and progression of ocular disorders, particularly if they are as prevalent as OSA.

The aim of this review is to identify and critically evaluate the current evidence that supports the existence of a possible association between OSA and glaucoma, nonarteritic ischemic optic neuropathy (NAION), central serous retinopathy (CSR), and DR. The paper discusses the current evidence supporting the association between OSA and the more prevalent eye diseases as well as their potential pathogenic mechanisms.

METHODS

Literature search and study selection

In June 2020, we conducted a literature search on PubMed and Web of Science databases, focused on the identification of clinical series about the OSA–eye disease association, descriptions of potential pathogenic mechanisms, and evaluations of the effect of apnea suppression on eye pathology. The keywords and Boolean operators were as follows: ("sleep apnea" OR "sleep apnoea" OR "obstructive apnea" OR "sleep breathing

Table 1—Characteristics of the case-control studies included in meta-analysis.

Study	Country/ Ethnicity	Participants	Total Number	Mean Age y	Sex	Evaluated Eye Disease	OSA Diagnosis	Adjustment for Covariates	Significant Association between OSA and Eye Disorder
Altaf, 2017	UK, White and Asian	Outpatient diabetes unit	230	57	Mixed	Diabetic retinopathy	Polygraphy,* AHI ≥ 5 events/h	Yes	Yes
Aptel, 2014	France, White	Medical database	9,580	63	Mixed	Nonspecific glaucoma	Research database, AHI ≥ 15 events/h	Yes	No
Arda, 2013	Turkey, White	Clinic-based	40	64	Mixed	NAION	PSG, AHI > 5 events/h	Yes	No
Banerjee, 2013	UK, White	Weight-management clinic	93	52	Mixed	Diabetic retinopathy	Polygraphy, AHI ≥ 15 events/h	Yes	No
Bilgin, 2013	Turkey, White	Clinic-based study	54	64	Mixed	NAION	PSG, AHI > 20 events/h	Yes	Yes
Bogabas, 2019	Arabia Saudi, Arab	Suspected OSA	84	44	Mixed	Nonspecific glaucoma	PSG, AHI ≥ 15 events/h	No	No
Boonyaleephan, 2008	Thailand, Asian	Suspected OSA	86	75	Mixed	OAG, NTG	PSG, AHI ≥ 10 events/h	No	No
Boyle, 2011	USA, NA	Medical database	71,960	NA	Mixed	Nonspecific glaucoma	Database record; ICD-9 codes	No	Yes
Chen, 2014	China, Asian	Medical database	12,640	45	Mixed	Nonspecific glaucoma	Database record; ICD-9 codes	No	Yes
Furukawa, 2013	Japan, Asian	Diabetes outpatients	513	62	Mixed	Diabetic retinopathy	Oximetry, ODI-3% ≥ 5	Yes	N0
Kadyan, 2010	UK, White	Suspected OSA	115	55	Mixed	OAG, NTG	Oximetry, ODI-4% > 10	No	No
Karakucuk, 2008	Turkey, White	Suspected OSA	56	52	Mixed	OAG, NTG	PSG, AHI > 5 events/h	No	No
Keenan, 2017	UK, NA	Hospital database	2,751,917	> 55	Mixed	OAG	Database record; ICD-10 codes	No	No
Laaban, 2009	France, White	Hospital inpatient	303	61	Mixed	Diabetic retinopathy	Polygraphy, RDI > 5	No	Yes
Li, 2007	USA, NA	Clinic-based study	146	64	Mixed	NAION	SA-SDQ	Yes	No
Lin, 2011	China, Asian	Suspected OSA	247	56	Mixed	NTG	PSG, AHI ≥ 5 events/h	No	No
Lin, 2013	Taiwan, Asian	Clinical database	6,072	67	Mixed	OAG	Database record; ICD-9 codes	Yes	Yes
Manin, 2015	France, White	Diabetes outpatients	67	54	Mixed	Diabetic retinopathy	PSG, AHI > 10 events/h	Yes	Yes

(continued on following page)

Table 1—Characteristics of the case-control studies included in meta-analysis. (*Continued*)

Study	Country/ Ethnicity	Participants	Total Number	Mean Age y	Sex	Evaluated Eye Disease	OSA Diagnosis	Adjustment for Covariates	Significant Association between OSA and Eye Disorder
Moghimi, 2013	Iran, Arab	Suspected OSA	106	47	Mixed	OAG, NTG	PSG, AHI ≥ 5 events/h	No	No
Mojon, 2002	Switzerland and USA, White	Clinic-based study	34	64	Mixed	NAION	PSG, RDI > 10	Yes	Yes
Morsy, 2019	Egypt, Arab	Diagnosed OSA patients and control participants	100	NA	Mixed	NTG	PSG, AHI > 5 events/h	Yes	Yes
Muniesa, 2014	Spain, White	Suspected OSA	227	54	Mixed	OAG, NTG	PSG, AHI ≥ 10 events/h	No	No
Nowak, 2011	Poland, White	Suspected OSA	52	50	Mixed	OAG, NTG	PSG, AHI ≥ 5 events/h	No	No
Palombi, 2006	France, White	Clinic-based study	27	64	Mixed	NAION	PSG, AHI > 15 events/h	Yes	Yes
Schober, 2011	Germany, White	Primary care centers	556	60	Mixed	Diabetic retinopathy	ApneaLink, AHI ≥ 15 events/h	No	No
Sergi, 2007	Italy, White	Diagnosed OSA patients and controls	91	64	Mixed	NTG	PSG, AHI ≥ 10 events/h	No	No
Stein, 2011	USA, NA	Medical database	2,181,315	> 40	NA	OAG	Database record, ICD-9 codes	Yes	Yes
Storgaard, 2014	Denmark, White	Diabetes outpatients	180	59	Mixed	Diabetic retinopathy	Berlin questionnaire + ApneaLink, AHI ≥ 5 events/h	NA	No
Sun, 2019	Taiwan, Asian	Health insurance database	42,440	48	Mixed	NAION	Database record, ICD-9 codes	Yes	Yes
West, 2010	UK, White	Diabetes outpatient and primary care centers	118	67	Males	Diabetic retinopathy	Oximetry, ODI-4% > 10	Yes	Yes
Yang, 2019	Korea, Asian	Health insurance database	10,109	> 40	Mixed	NAION	Database record, ICD-10 codes	Yes	Yes
Zhang, 2015	China, Asian	Hospitalized patients	472	55	Mixed	Diabetic retinopathy	ApneaLink, AHI ≥ 5 events/h	No	Yes
Zhang, 2016	China, Asian	Hospitalized patients	162	56	Mixed	Diabetic retinopathy	ApneaLink, AHI ≥ 5 events/h	No	Yes

*Polygraphy is unattended multi-channel testing without electroencephalography sensor use. AHI = apnea-hypopnea index, ICD-9 = *International Classification of Diseases, Ninth Revision*, ICD-10 = *International Classification of Diseases, Tenth Revision*, NAION = nonarteritic anterior ischemic optic neuropathy, NTG = normal-tension glaucoma, OAG = open-angle glaucoma, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, PSG = polysomnography, RDI = respiratory disturbance index, SA-SDQ = Sleep Apnea Scale of the Sleep Disorders Questionnaire, NA = not available.

disorder" OR "apnea-hypopnea") AND ("eye diseases" OR "glaucoma" OR "nonarteritic ischemic optic neuropathy" OR "central serous retinopathy" OR "diabetic retinopathy"). No restriction of year or language of publication was used.

The search included articles that met the following criteria: study that reports prevalence or proportion of OSA in patients with some of the 4 evaluated eye diseases or, vice versa, study that reports risk factors for this association; or study that evaluates the effect of sleep apnea suppression (by continuous positive airway pressure [CPAP] or other procedures) on evaluated eye diseases. The exclusion criteria were as follows: overlapping databases, publications not available as full texts, absence of specific data about sleep apnea–eye disease association, no description of the design used, lack of definition of diagnostic criteria for the eye diseases evaluated, and lack of information on sleep parameters or evidence of a previous diagnosis of OSA. For the narrative review, no limitations were established regarding the study design, selecting both clinical case series, cohort and case-control studies, longitudinal observational studies, and randomized clinical trials. Systematic reviews and meta-analyses were also included.

Two authors performed the literature search and reviewed each study individually. Duplicate studies were removed, and titles and abstracts were screened to decide whether selected manuscripts should be included or not based on the predetermined inclusion and exclusion criteria. Disagreements between 2 authors were resolved by discussion. In case disagreement persisted, another author was involved in the final decision.

Data extraction and quality assessment

Two reviewers (A.G.-S. and F.G.-R.) independently abstracted recorded data from full versions of selected manuscripts using a standardized Excel table (Microsoft Corporation, Redmond, WA). The table includes 5 parts: (1) study details (such as authors, year of publication, country, region, and blinding); (2) characteristics of the included population (such as diagnosis, age, and sex); (3) prevalence, association, or risk factors data; (4) treatment protocols including CPAP or other procedures, when therapeutic response was evaluated; and (5) efficacy and safety outcomes, when available as in the previous case.

We used the following criteria to appraise cross-sectional studies: (1) representativeness of the sample; (2) nonrespondents; (3) ascertainment of the exposure (risk factor); (4) whether the participants in different outcome groups are comparable, based on the study design or analysis, and confounding factors are controlled; (5) assessment of the outcome; and (6) statistical test. For case-control studies we used the following criteria: (1) adequate case definition, (2) representativeness of the cases, (3) selection of controls, (4) definition of controls, (5) comparability of cases and controls based on the design or analysis, (6) ascertainment of exposure, (7) same method of ascertainment for cases and controls, and (8) nonresponse rate.

Statistical analysis

The meta-analysis of extracted data was conducted using Cochrane Review Manager 5.3 (Cochrane Collaboration, London, UK). To evaluate associations between sleep apnea and analyzed eye diseases only case-control studies were used to calculate the odds ratio (OR) with the 95% confidence interval (CI). Heterogeneity was calculated using the Higgins χ^2 test, and inconsistency was quantified by I^2. A χ^2 test with a P value < .10 was considered to indicate the presence of heterogeneity, and an $I^2 > 50\%$ was considered to suggest marked inconsistency in effect between studies. As heterogeneity was higher than 50%, a random-effects model with the Mantel-Haenszel method was used.

RESULTS

Our literature search revealed a total of 737 articles. After excluding duplicates, there were 681 articles. Subsequently, 538 were removed after title and abstract screening, leaving 143 full-text articles to be assessed for eligibility. From this total, 36 were excluded: 11 studies did not include information about sleep parameters, 16 did not include participants/models with OSA, 5 studies included patients with hypoxemia secondary to other respiratory disorders, and 4 studies were guidelines/consensus statements (**Figure 1**). Finally, 107 studies were included in our narrative synthesis, 17 of which were clinical case series, 23 cohort studies, 33 case-control studies, 7 longitudinal observational studies, 3 randomized clinical trials, 8 retrospective analyses, 7 reviews, and 8 meta-analyses. Of these, only 33 case-control studies were included for quantitative analysis of associations between OSA and eye disorders. The characteristics of the studies included in meta-analysis are represented in **Table 1**.

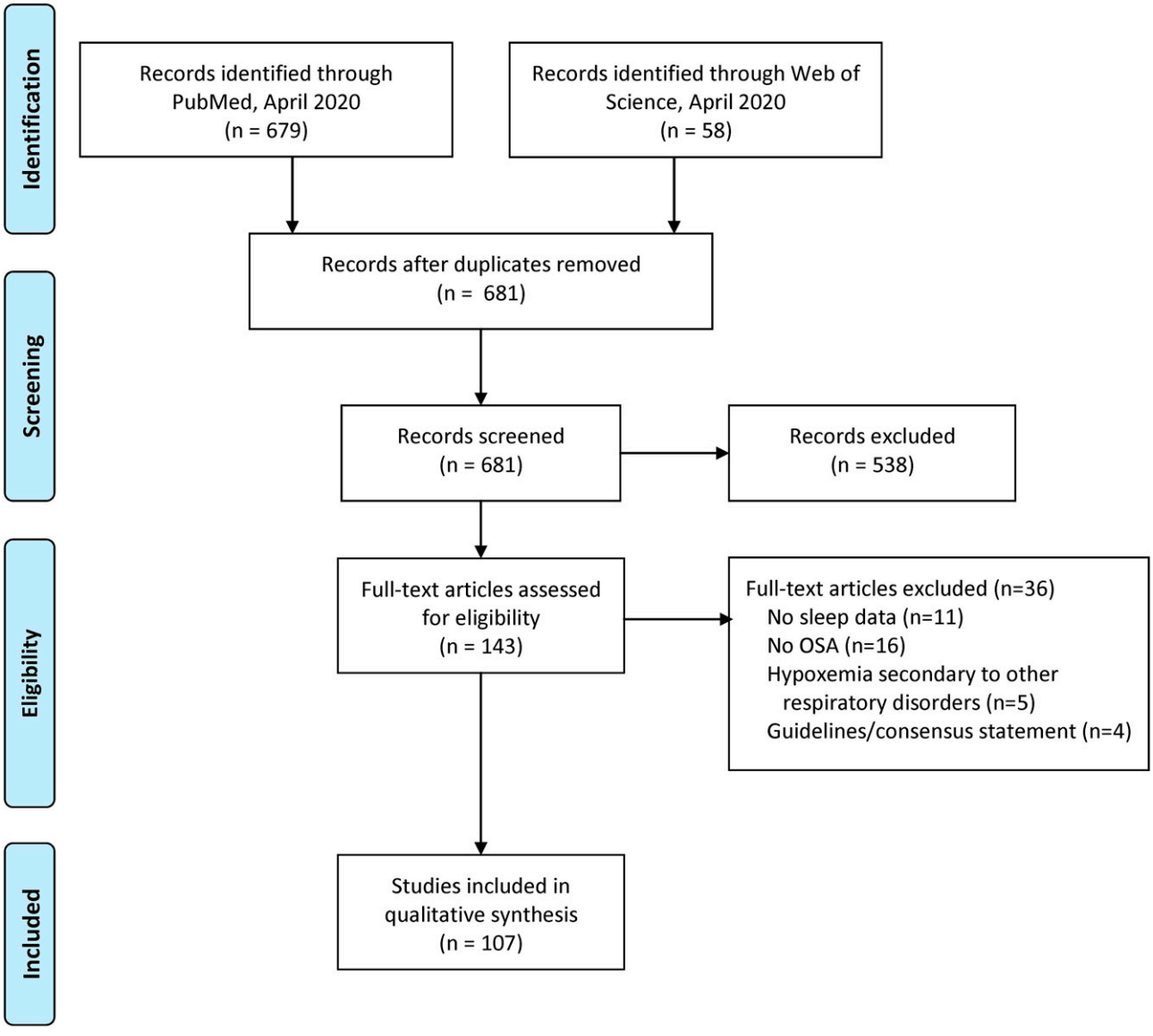
Glaucoma

Glaucoma is a progressive optic neurodegenerative disease characterized by loss of ganglion cells and damage of the optic nerve causing visual field disturbances. It is the second leading cause of blindness worldwide. Variations of glaucoma include open-angle glaucoma (OAG), normal-tension glaucoma (NTG), and angle-closure glaucoma. In OAG and angle-closure glaucoma, high intraocular pressure causes compressive neuropathy and visual field defects.[21]

Evidence of association with OSA

In 1999, Mojon et al[15] published the first paper describing an increased prevalence of glaucoma in patients with OSA, and a number of subsequent case reports have also suggested the association of OSA with both OAG and NTG.[22] Although several studies have described an increased prevalence of glaucoma in patients with OSA,[23–27] they failed to identify a relationship between apnea-hypopnea index (AHI) and intraocular pressure (IOP). In contrast, other authors[27] have not found an increased prevalence of glaucoma in patients with OSA or an association between AHI and the presence of glaucoma or the IOP level. These discrepancies may be partially explained by differences in age, body mass index, OSA diagnosis method, or delay time between sleep study and IOP measurement, factors that are known to influence glaucoma progression.[21] Another important aspect to consider is the severity of OSA,

Figure 1—Flow diagram for identification of relevant studies.



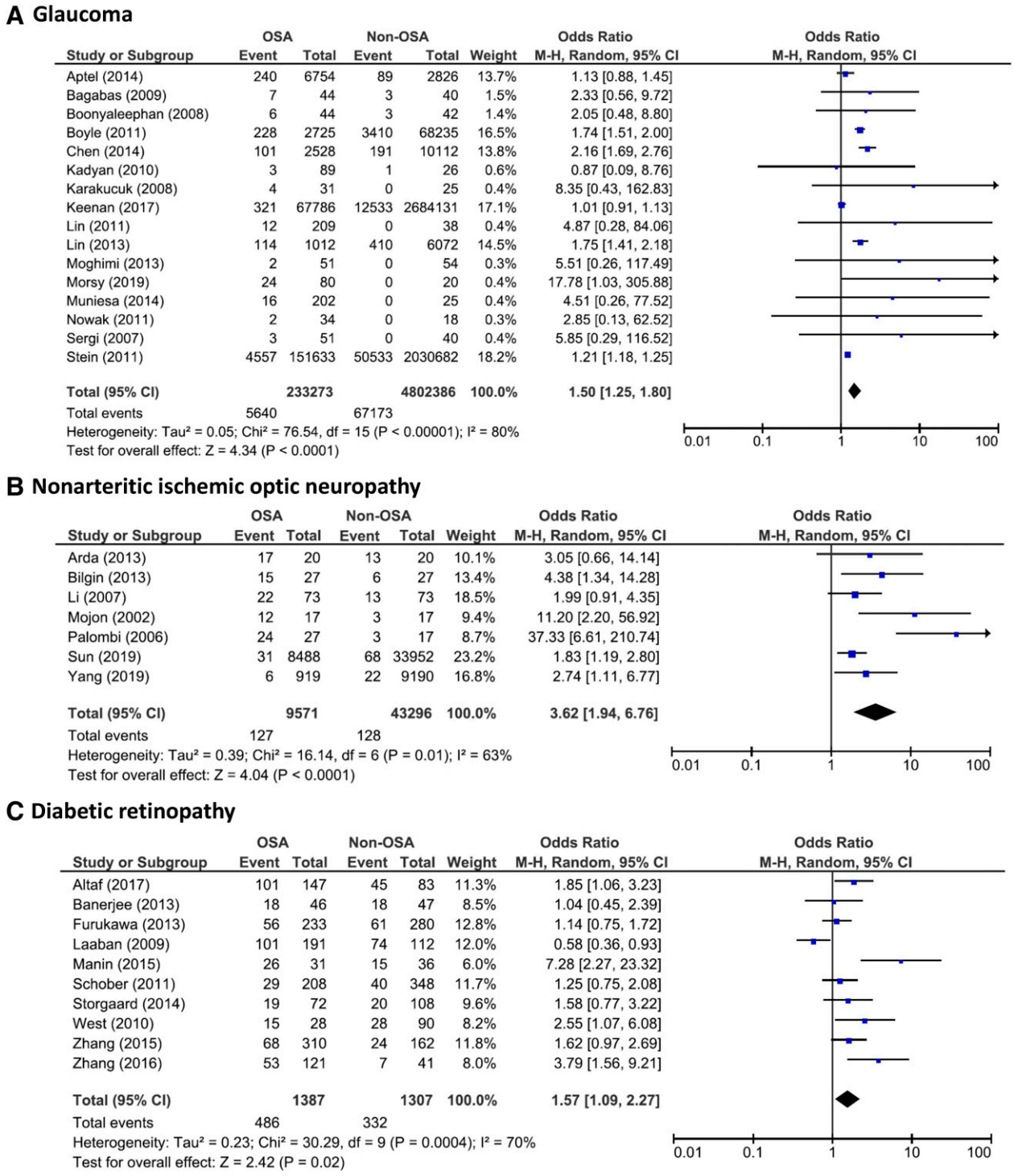
OSA = obstructive sleep apnea.

since a recent cohort study has reported that patients with severe OSA have glaucoma more frequently than patients with mild OSA (OR: 2.50; 95% CI: 1.05–5.93).[28]

Three meta-analyses performed several years ago support the evidence for the association between OSA and glaucoma. A meta-analysis of 6 case-control studies found a pooled OR of 1.96 (95% CI: 1.37–2.8) for the presence of glaucoma in patients with OSA,[29] whereas the subanalysis of cross-sectional studies provided an OR of 1.41 (95% CI: 1.11–1.79).[29] In another meta-analysis of 12 international studies, Wu et al[30] obtained a similar increase of glaucoma risk (OR: 1.65; 95% CI: 1.44–1.88) and verified that only patients with severe OSA had increased risk for glaucoma compared with nonapneic participants (OR: 5.49; 95% CI: 1.04–33.83). The reciprocal glaucoma–OSA association was evaluated in a meta-analysis by Huon et al,[31] which also found a higher risk of OSA in patients with glaucoma (OR: 1.75; 95% CI: 1.23–2.48).

Taking into account the studies included in these meta-analyses and others published to date, we carried out a meta-analysis of 16 case-control studies, including 233,273 patients with OSA and 4,802,386 individuals without OSA.[25,32–46] The results obtained confirm that OSA is associated with a significantly increased risk of glaucoma, with a pooled OR of 1.50 (95% CI: 1.25–1.80; $P < .001$) (**Figure 2A**). However, it should be noted that all of these results are based on unadjusted ORs, without controlling for all possible confounders. Therefore, a causal relationship still cannot be confirmed.

Figure 2—Forest plots of cross-sectional studies showing the odds ratios of eye diseases in participants with and without OSA.



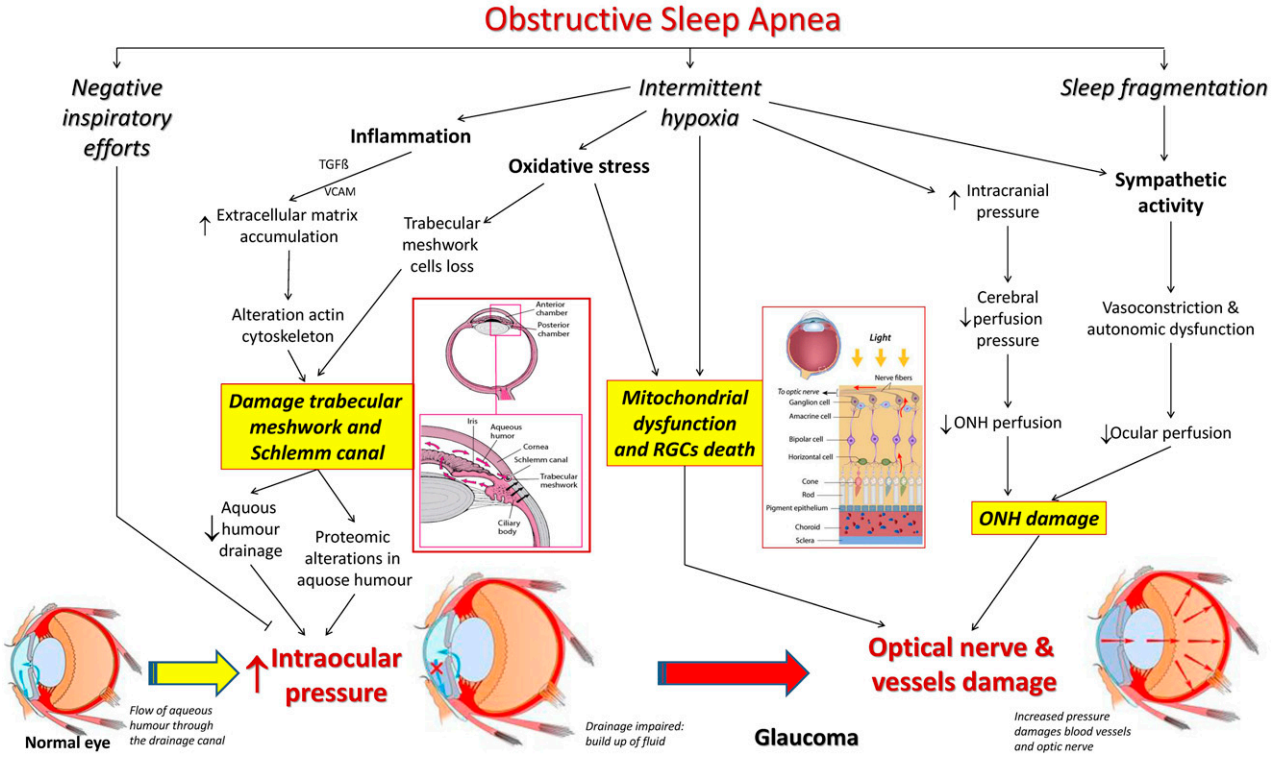
Forest plots of cross-sectional studies showing the odds ratios with 95% confidence intervals (95% CI) of glaucoma (**A**), nonarteritic ischemic optic neuropathy (**B**), or diabetic retinopathy (**C**) for participants with and without OSA. The squares and horizontal lines represent the study-specific OR and 95% CI. The sizes of the squares reflect the statistical weights of the studies. The pooled OR is indicated by a diamond (random-effect model). CI = confidence interval, OR = odds ratio, OSA = obstructive sleep apnea, M-H: Mantel-Haenszel analysis.

Potential pathogenic mechanisms

Several pathways have been proposed to explain the association between OSA and glaucoma, through mechanisms that facilitate both increased IOP and damage to the vessels and optic nerve that determine disease progression (**Figure 3**).

In normal conditions, the aqueous humor produced by the ciliary body is absorbed in the anterior chamber of the eye

Figure 3—Diagram illustrating pathophysiological hypotheses relating obstructive sleep apnea to glaucoma development and progression.



ONH = optic nerve head, RGC = retinal ganglion cell, TGFβ = transforming growth factor-β, VCAM = vascular cell adhesion molecule.

through the trabecular meshwork and Schlemm's canal. However, it has been described that both inflammation and oxidative stress induced by OSA might damage these structures, compromising the drainage capacity of the aqueous humor. In fact, it has been reported that cultured human anterior segments perfused with high levels of transforming growth factor (TGF)-β2 have significantly less outflow facility, which correlates with fine fibrillar extracellular matrix accumulation and altered actin cytoskeleton in the trabecular meshwork—Schlemm's canal region.[47] On the other hand, in vivo human studies have demonstrated that markers of oxidative damage in trabeculectomy specimens are elevated 5-fold,[48] suggesting that oxidative stress induces trabecular meshwork cell loss. As a consequence of both alterations, the drainage capacity of the aqueous humor is reduced and, consequently, the IOP increases. Moreover, oxidation-induced trabecular damage has been related to proteomic alterations of the aqueous humor.[49] All of these alterations, which can be potentiated through the inflammatory response and the increased oxidative stress induced by intermittent hypoxia, establish a connection between OSA and primary OAG.

There is more controversy about the effect of negative inspiratory effort due to apneas-hypopneas on the circadian IOP course. In healthy young adults, Lundmark et al[50] investigated the effect of negative inspiratory efforts generated by the Mueller maneuver on IOP and pulsatile ocular blood flow, finding that negative pressure was surprisingly associated with a decrease in IOP. Similar results were reported by Shinmei et al[51] in patients with OSA. Using a contact lens sensor, they identified a statistically significant decrease in IOP during hypopneic and apneic events. The authors explained that the decrease in IOP during apneic events likely resulted from negative intrathoracic pressure created by attempted inspiration against a blocked airway. Along the same line, Pépin et al[52] demonstrated that normal IOP nycthemeral rhythm is lost in most patients with severe OSA and that the IOP profile is restored after respiratory event suppression by CPAP. In fact, it has been proposed that CPAP-induced elevation in intrathoracic pressure might increase venous pressure, reducing the aqueous humor outflow through the episcleral veins, and contribute to IOP increase.[53] All of these data suggest that OSA-induced mechanical changes would have an inhibitory effect on IOP increase, which is outweighed by the compromise to aqueous humor drainage.

Current evidence shows that OSA also predisposes patients to optic nerve head ischemia and damage through episodes of hypoxia, oxidative stress, mitochondrial dysregulation, and hemodynamic changes to retinal blood vessels,[29] leading to nerve fiber dysfunction and degeneration seen in glaucoma. Successive hypoxia episodes directly damage the optic nerve head, retinal ganglion cells, and their axons. Moreover, mitochondrial dysfunction of retinal ganglion cells has been related

to the hypoxia-induced increase in reactive oxygen species. In fact, it has been reported that patients with glaucoma with OSA have higher reactive oxygen metabolites than patients without OSA, suggesting that systemic oxidative stress secondary to OSA may promote glaucomatous visual field defect progression.[54] Hypoxia is also known to increase intracranial pressure, which is one of the most important risk factors for developing glaucoma. This leads to decreased cerebral perfusion pressure and may disturb the blood flow to optic nerve head, especially during nocturnal systemic hypotension.[55] Finally, intermittent hypoxia also causes sympathetic activation, which leads to vasoconstriction and autonomic dysfunction that may alter nocturnal ocular perfusion pressure.

In short, the optic nerve heads of patients with OSA may be more sensitive to mechanical damage given their poor perfusion and potential for ischemic changes.[29] Consequently, OSA has also been proposed as a risk factor for NTG. Although the pathogenesis of this disorder remains uncertain, it is believed that chronic progressive ischemia with hypoperfusion of the optic nerve contributes to the development of NTG. In fact, several authors have reported an association between OSA and NTG through the hypoxia-induced compromise on optic nerve perfusion.[45,56,57] However, studies on the association between OSA and glaucomatous optic neuropathy have reported conflicting results.[58] While Lin et al[39] reported a higher proportion of NTG between patients with OSA and control participants, Stein et al[46] did not find a significant relationship in a large retrospective cohort study. This discrepancy is probably because the association between OSA and NTG remains subject to potential confounding factors, such as conditions associated with poor blood supply to the optic nerve head, including obesity, hypertension, and diabetes.

Nonarteritic ischemic optic neuropathy

NAION is an ischemic disorder of the anterior portion of the optic nerve, characterized by sudden and painless unilateral visual loss, altitudinal visual field defects, and optic disc swelling.[59] It is the most frequent acute optical neuropathy after the age of 50, with an incidence of 2–10 per 100,000 people per year. It is classically associated with several risk factors, particularly cardiovascular, such as hypertension, diabetes, dyslipidemia, ischemic heart disease, or cerebrovascular disease.[60] Moreover, patients with NAION have a 15% risk of contralateral eye involvement within 5 years.[59]

Evidence of association with OSA

A large cohort study by Stein et al[46] found a 16% increase in the risk of developing NAION in patients with untreated OSA compared with patients without OSA. In several case-control studies,[13,16,61] the prevalence of OSA in patients with NAION varied from 55.6% to 59%, which means that the risk ratio for a patient with NAION to have OSA is 2.6–4.9 compared with the general population.[16,61]

Although there are also some contradictory results,[62,63] a meta-analysis including 4 prospective cohort studies and 1 case-control study found that the pooled OR of developing NAION in patients with OSA was 6.18 (95% CI: 2.00–19.11) vs non-OSA controls.[64] However, in this same analysis, potential confounders were not adjusted for in all the studies, which may have affected the results. Two large retrospective studies have recently suggested that the OSA and NAION association may be independent of confounding factors. In a retrospective, longitudinal cohort study of the national health insurance database of Taiwan, the patients with OSA showed a higher risk of NAION after multivariate analysis with an adjusted hazard ratio (HR) of 1.66 (95% CI: 1.08–2.55).[65] Simultaneously, a 12-year nationwide, population-based, retrospective cohort study from the Korean National Health Insurance Service database showed that patients with OSA had an increased risk of developing NAION compared with the non-OSA group (HR: 3.80; 95% CI: 1.46–9.90) after adjusting for demographic characteristics, comorbidities, and medication.[66]

We also performed a meta-analysis including all case-control studies published to date about the association between NAION and OSA. The evaluation of 7 studies, including 9,571 patients with OSA and 43,296 participants without OSA,[13,16,61,62,65–67] showed that patients with OSA are more at risk of NAION than nonapneic individuals, with a pooled OR of 3.62 (95% CI: 1.94–6,76; $P < .001$) (**Figure 2B**).

Finally, it is interesting to consider that OSA may also have a prognostic impact on the evolution of patients with established NAION. A 3-year follow-up study of patients with NAION showed that those with severe OSA who did not adhere to CPAP treatment had 5.5 times more risk of NAION in the contralateral eye than patients without OSA or those with mild–moderate OSA.[68] Although the noncompliant group could be biased toward being noncompliant with other therapeutic measures, these data suggest that OSA may be a risk factor for developing NAION in the other eye.

Potential pathogenic mechanisms

It is not yet clear whether OSA contributes directly to the development of NAION or whether the association is a mere consequence of certain comorbidities, such as obesity, hypertension, or diabetes.[59] Nevertheless, evidence suggests that OSA might contribute to optical nerve damage through direct exposure to hypoxia. Patients with NAION often report experiencing symptoms upon waking,[69] suggesting a contribution of sleep events. In this sense, intermittent hypoxia could impair optic nerve perfusion and, moreover, increase intracranial pressure during apneic episodes, limiting perfusion of the optic nerve head.[69] In turn, blood flow autoregulation is impaired in patients with OSA due to an imbalance of vasoactive substances exacerbating the hypoxic hypoperfusion of tissues. Also, hypoxia-induced cerebral vasodilation may further impair optic nerve perfusion due to decreased cerebral perfusion pressure. Therefore, these variations in arterial blood pressure could also contribute to optic nerve vascular dysregulation.[13]

It has also been proposed that increased intracranial pressure during apneic episodes might directly contribute to optic nerve damage[69] and that increased sympathetic tone and oxidative stress generated by hypoxia-reoxygenation episodes favors endothelial damage and the development of atherosclerosis, which could also compromise the vascular autoregulation of the optic nerve.

Central serous retinopathy

CSR or chorioretinopathy is characterized by an idiopathic serous detachment of the neurosensory retina secondary to serous fluid collection beneath the retina. This condition, which may be caused by increased permeability in the choriocapillaris and subsequent damage to the retinal pigment epithelium, has been associated with increased endogenous or exogenous cortisol, which occurs with stress, pregnancy, corticosteroid therapy, or Cushing syndrome.[70]

Evidence of association with OSA

Several studies have shown that between 22% and 61% of patients with CSR have OSA,[71,72] which is a higher prevalence than in the general population. The increased risk of OSA in patients with CSR has been confirmed by a meta-analysis, which obtained an OR of 2.02 (95% CI: 1.08–3.78).[31] Another more recent meta-analysis also confirms that patients with CSR have more risk of having OSA than controls (OR: 1.56; 95% CI: 1.16–2.10).[73] Moreover, it reported that only patients with moderate and severe OSA had thinner choroidal thickness measurements than controls. However, it is important to consider that 1 study found that, when controlling for obesity, prevalence of OSA in patients with CSR was similar to the general population.[74] This finding suggests that the strong link between CSR and OSA might result from the common factor of obesity.

In turn, there is also evidence that CSR is more frequent in patients with OSA. An analysis of the Taiwan National Health Insurance Database showed that, after adjusting for age, sex, residence, income level, and comorbidities, the incidence rate of CSR was significantly higher in patients with OSA than in control participants (adjusted incidence rate: 1.2; 95% CI: 1.1–1.4).[75] In patients with OSA, risk factors for CSR included male sex, age less than 50 years, increased income, presence of heart or liver disease, and absence of chronic lung disease. Furthermore, the meta-analysis showed that patients with OSA treated with CPAP had a significantly lower incidence rate of CSR than untreated patients.[75] This latter finding coincides with a previous case report that described the first bilateral CSR in a man with OSA that was resolved after 1 week of CPAP treatment.[76] However, large prospective longitudinal studies are still needed to definitively answer the question about the association between CSR and OSA.

Potential pathogenic mechanisms

In patients with OSA, several pathways have been proposed to justify the increased risk of CSR. Oxidative stress can cause endothelial cell damage and vasoconstriction, both of which may be related to CSR pathogenesis.[72] Ischemia can also increase permeability of the choriocapillaris.[70] Furthermore, an association between CSR and increased sympathetic activity has been reported.[77] In fact, the sympathetic overactivity produces endothelial dysfunction on the retinal blood barrier, which can lead to accumulation of subretinal serous fluid.[78] Last, blood coagulation abnormalities have also been proposed as a pathogenic mechanism.

Diabetic retinopathy

DR, the most frequent microvascular complication of diabetes and a major cause of vision loss, can be nonproliferative, with dilated retinal veins and microaneurysms causing hemorrhage or edema, or proliferative DR (PDR), with new vessels forming near the optic disc. In individuals with diabetes, the prevalence of DR is 34.6% and of PDR is 7%.[79]

Evidence of association with OSA

Classically, diabetes duration, hypertension, and dyslipidemia are recognized risk factors for DR. However, growing evidence shows that OSA is a risk factor for the development of type 2 diabetes (T2D), poor glycemic control, and microvascular complications, especially DR.

Evidence published until now suggests the existence of a relationship between OSA and T2D. OSA-induced intermittent hypoxia and sleep fragmentation might promote the development of insulin resistance and progression to T2D by increasing sympathetic tone, oxidative stress, and systemic inflammation as well as appetite-regulating hormones.[80–82] Some data support the fact that OSA can alter glucose metabolism, progressing to insulin resistance and finally to T2D. It has been reported that AHI is related to glycosylated hemoglobin (HbA1c) levels.[5] Moreover, patients with OSA have increased insulin resistance, assessed by the homeostatic model assessment (HOMA) index,[83] which is independent of sex and obesity.[84,85] As a result, some data show a higher OSA prevalence in patients with T2D than in the general population.[86–89] Conversely, there is still little information about the CPAP effect on patients with OSA with T2D, and it is partially contradictory. However, some studies reported that good CPAP compliance can cause a decrease in insulin resistance and HbA1c, especially in patients with more severe OSA and poor metabolic control.[90–92]

OSA has also been related to the development of microvascular complications of T2D, including nephropathy, neuropathy, and retinopathy. Several common mechanisms have been proposed as causes of endothelial dysfunction and microvascular alterations, such as disorders of protein kinase C signaling, reduced nitric oxide synthase, or increased endothelin-1.[93–95]

Several epidemiological studies suggest that OSA is associated with a greater frequency of microvascular anomalies,[96,97] DR,[17,97,98] or macular edema.[97] Moreover, 2 studies showed that the frequency of DR increases with the severity of OSA.[96,99] Reciprocally, it has been found that 29% of patients with nonproliferative DR and 48% of those with PDR had OSA.[100] Moreover, patients with OSA with PDR had a lower minimum oxygen saturation and a higher time spent with oxygen saturation levels below 90% ($tSaO_2 < 90$) than patients with OSA with nonproliferative DR, suggesting that nocturnal intermittent hypoxia and reoxygenation might play a role in the progression of DR.[101]

In any case, the degree of evidence for the association between OSA and DR is still weak. A meta-analysis of 3 studies failed to detect a significant association, although OSA was associated with a more advanced stage of DR and the lower oxygen saturation was associated with diabetic macular edema (adjusted OR: 0.79; 95% CI: 0.65–0.95) and retinopathy (OR: 0.91; 95% CI: 0.87–0.95).[102] In contrast, a later meta-analysis including 6 eligible studies found that OSA was significantly associated with an increased risk of DR (2.01; 95% CI: 1.49–2.72).[103]

The relationship between OSA and DR was longitudinally evaluated by Altaf et al[104] using the clinical data resource from the diabetic eye screening program established within the UK National Health Service. They found that the prevalence of baseline sight-threatening DR was higher in patients with OSA than in nonapneic individuals (43% vs 24%) and that after a 43-month follow-up, patients with OSA were more likely to develop DR than non-OSA patients (18% vs 6%). After adjusting for confounders, OSA remained an independent predictor of progression to DR (OR: 5.2; 95% CI: 1.2–23.0). Although it is a secondary result, it is also interesting to note that the patients with OSA treated with CPAP were significantly less likely to develop DR.[104]

To update information, we also performed a meta-analysis including all case-control studies published to date about the association between OSA and DR. In this case, the evaluation of 10 studies,[88,97–99,104–109] including 1,387 patients with OSA and 1,307 participants without OSA, shows that patients with OSA are more at risk of DR than nonapneic individuals, with a pooled OR of 1.57 (95% CI: 1.09–2.27; $P = .02$) (**Figure 2C**).

Another way to assess the association between OSA and DR is to analyze the effect of apnea-hypopnea suppression by specific treatment. A retrospective cohort study assessed the impact of bariatric surgery on DR, finding that progression to maculopathy was significantly less in patients who underwent surgery than in those who received routine care, although progression to sight-threatening DR was not statistically significant between the 2 groups.[110] However, OSA was not evaluated in this study, so the results might not be able to be extrapolated to patients with OSA with DR.

Until now, only 2 studies have evaluated the CPAP effect on DR progression in patients with OSA. In an observational nonrandomized study, good adherence to CPAP treatment was associated with a greater improvement in the visual field within 6 months.[111] However, a randomized clinical trial performed by West et al[112] in 131 patients with severe OSA with T2D and diabetic macular edema causing visual impairment did not detect a significant difference in visual acuity after 12 months between the CPAP and the control groups. CPAP use time was also not able to detect differences, so the authors concluded that CPAP therapy for OSA did not improve visual acuity in patients with T2D with diabetic macular edema compared with standard care alone over 12 months. Undoubtedly, more randomized trials are still needed to assess the CPAP effect on variables related to the severity or progression of DR.

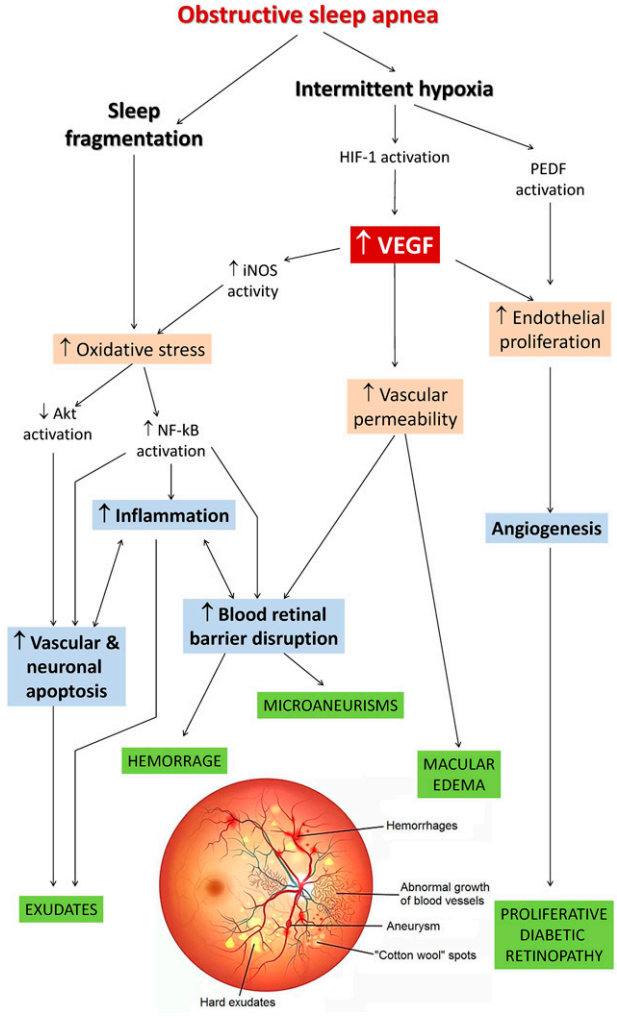
Potential pathogenic mechanisms

Although it is evident that the development of DR depends on the time of progression and the control of diabetes, OSA could be an associated factor that contributes to its development or progression through several intermediate mechanisms (**Figure 4**).

It is known that the retina is very vulnerable to hypoxia,[113] and it is believed that intermittent hypoxia in patients with OSA with DR is more severe and occurs earlier than in control groups matched for other variables.[114] Until now, several pathogenic pathways triggered by hypoxia have been proposed. In diabetic patients, retinal ischemia results in the stimulation of transcriptional hypoxia-inducible factor-1 (HIF-1), which promotes the expression of multiple gene products, including vascular endothelial growth factor (VEGF).[115] VEGF stimulates endothelial proliferation and leads to angiogenesis, which characterizes the development of proliferative DR. In addition, VEGF promotes vascular permeability, which plays an important role in the development of maculopathy. This result is especially relevant because the retina is particularly prone to hypoxic damage during the night,[116] which is the same time in which OSA-associated hypoxemia occurs. This pathway is supported by the demonstration that OSA-induced hypoxemia is associated with increased VEGF, whose levels decrease after CPAP treatment.[117]

Furthermore, in patients with OSA, intermittent hypoxia and sleep fragmentation promote the activation of Poly ADP ribose polymerase, protein kinase C, and the polyol pathway while

Figure 4—Potential pathways implicated in the development of diabetic retinopathy in patients with obstructive sleep apnea.



Akt = protein kinase B, HIF-1 = hypoxia-induced factor-1, iNOS = inducible nitric oxide synthase, NF-κB = nuclear factor kappa light-chain-enhancer of activated B cells, PEDF = pigment epithelium-derived factor, VEGF = vascular endothelial growth factor.

increasing the production of advanced glycation end products, all of which can lead to inflammation and oxidative and nitrosative stress.[95,118] Increased circulating levels of VEGF, along with oxidative stress and systemic inflammation, facilitate the blood retinal barrier disruption, which leads to the development of microaneurysms and retinal hemorrhages. Last, both oxidative stress and the inflammatory response itself might also potentiate vascular and neuronal apoptosis,[95] completing the set of alterations showed by patients with DR.

CONCLUSIONS

OSA is a major public health problem, while eye diseases cause a significant health burden and are a leading cause of disability. There is a body of largely low-level evidence for the association of OSA with glaucoma, NAION, CSR, and DR. The systematic analysis of the available evidence confirms the existence of a weak, and at times contradictory, association between sleep apnea and glaucoma, NAION, CSR, or DR. The information provided by several studies enables us to begin to understand how the alterations generated by intermittent hypoxia or sleep fragmentation contribute to the pathogenesis of ocular damage, favoring its development or contributing to its progression. In the absence of high-quality evidence on the effect of apnea-hypopnea suppression on the described ocular disorders, further studies should be performed.

ABBREVIATIONS

AHI, apnea-hypopnea index
CPAP, continuous positive airway pressure
CSR, central serous retinopathy
DR, diabetic retinopathy
IOP, intraocular pressure
NAION, nonarteritic anterior ischemic optic neuropathy
NTG, normal-tension glaucoma
OAG, open-angle glaucoma
OR, odds ratio
OSA, obstructive sleep apnea
PDR, proliferative diabetic retinopathy
T2D, type 2 diabetes
VEGF, vascular endothelial growth factor

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