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CLINICAL REVIEW

Diseases of the retina and the optic nerve associated with obstructive sleep apnea

Marielle Mentek [a], Florent Aptel [a, b], Diane Godin-Ribuot [a], Renaud Tamisier [a, c], Jean-Louis Pepin [a, c], Christophe Chiquet [a, b, *]

[a] Grenoble Alpes University, HP2 Laboratory, INSERM U1042, Grenoble, France
[b] Department of Ophthalmology, University Hospital of Grenoble, Grenoble, France
[c] Pôle Thorax et Vaisseaux, University Hospital of Grenoble, Grenoble, France

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SUMMARY

Many associations between ocular disorders and obstructive sleep apnea (OSA) have been studied, such as nonarteritic anterior ischemic optic neuropathy, glaucoma, papilledema, retinal vein occlusion, eyelid hyperlaxity, lower-eyelid ectropion and recurrent corneal erosions. The objective of this review is to synthetize the possible vascular disorders of the retina and the optic nerve associated with sleep apnea patients and to discuss the underlying pathophysiological hypotheses. Main mechanisms involved in the ocular complications of OSA are related to intermittent hypoxia, sympathetic system activation, oxidant stress, and deleterious effects of endothelin 1. The main evidence-based medicine data suggest that OSA should be screened in patients with ischemic optic neuropathy and diabetic retinopathy. The effect of OSA treatment and emerging therapies are discussed.

Introduction

Ocular diseases potentially associated with obstructive sleep apnea (OSA) include nonarteritic anterior ischemic optic neuropathy (NAION), glaucoma, papilledema, and retinal vein occlusion (RVO), eyelid hyperlaxity, lower-eyelid ectropion, blepharochalasis, keratoconus, xerophthalmia, and recurrent erosions of the corneal epithelium [1]. The pathophysiological mechanism related to OSA that causes these disorders, notably in the retina and optic nerve, are uncompletely known. By contrast, many recent prospective studies reported the incidence and prevalence of ocular diseases in OSA patients. Due to the frequency of OSA in the elderly population, there is a need to understand and evaluate the impact of OSA on the eye physiology. This could help the non-ophthalmologist clinician to know which ocular screening should be performed in OSA patients and guide the ophthalmologist when screening of OSA is important.

The objective of this review is to describe vascular disorders of the retina and the optic nerve in sleep apnea patients and to discuss the underlying pathophysiological mechanisms.

Methods

We conducted a systematic literature search of the NIH database (https://www.ncbi.nlm.nih.gov/pubmed) for all papers published before May 2016, using the following search terms: “obstructive sleep apnea”, “retina”, “optic nerve”, “glaucoma”, “primary open angle glaucoma”, “non-arteritic/nonarteritic anterior ischemic optic neuropathy”, “retinal nerve fiber layer”, “papilledema”, “diabetic retinopathy”, “retinal vein occlusions”, “central serous chorioretinopathy”, “retinal arteries”, “retinal vasculature”, “retinal diameter”, “ocular blood flow”, and “intraocular pressure”. Articles

* Corresponding author. Department of Ophthalmology, Grenoble University Hospital, Grenoble Alpes University, 38000 Grenoble, France. Fax: +33 4 76765757.
E-mail address: christophe.chiquet@inserm.fr (C. Chiquet).

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Abbreviations

AHI	apnea hypopnea index
AHT	arterial hypertension
BF	blood flow
BP	blood pressure
CRA	central retinal artery
CSCR	central serous chorioretinopathy
CI	confidence interval
CPAP	continuous positive airway pressure
DR	diabetic retinopathy
ET-1	endothelin 1
HIF1	hypoxia inducible factor 1
HR	hazard ratio
ICH	intracranial hypertension
ICP	intracranial pressure
IH	intermittent hypoxia
IL	interleukin
IOP	intraocular pressure
NO	nitric oxide
NAION	nonarteritic anterior ischemic optic neuropathy
NTG	normal tension glaucoma
OA	ophthalmic artery
ONH	optic nerve head
OPP	ocular perfusion pressure
OR	odds ratio
OSA	obstructive sleep apnea
PCAs	posterior ciliary arteries
PDR	proliferative diabetic retinopathy
POAG	primary open-angle glaucoma
RDI	respiratory disturbance index
RNFL	retinal nerve fiber layer
RVO	retinal vein occlusion
T2D	type 2 diabetes
VEGF	vascular endothelial growth factor

Glossary of terms

Retinal nerve fiber layer: this layer is composed of retinal ganglion cell axons and represents the innermost layer of the retina (adjacent to the internal limiting membrane and vitreous body). These axons, after crossing the sclera through the lamina cribrosa, give rise to the optic nerve

Optic nerve cupping: the term “cup” refers to the central portion of the optic disk. During glaucoma progression, death of retinal ganglion cells lead to the loss of axons and then to an enlargement of the optic nerve cupping

Papilledema: optic disc swelling

published before May 2016, in English or French, were considered for review.

The results were first reviewed by analyzing the abstract, and case-reports, reviews, duplicates and irrelevant topics were excluded from further analysis (Fig. 1).

All remaining studies related to the subject were downloaded in full-text format for detailed analysis. Studies were included in this review if they met the following criteria: 1) the population of interest consists of OSA patients, 2) the endpoint is the prevalence of OSA in the corresponding population with the targeted retinal/optic nerve affection, or the prevalence of these affections in an OSA population, or 3) a report of the relation between OSA and/or continuous positive airway pressure (CPAP) and ocular parameters: intraocular pressure (IOP) and retinal nerve fiber layer (RNFL) thickness.

We extracted data using a data-collection form relevant for each retinal/optic nerve disease studied. The main information recorded was: names of the authors, publication year, study type, number of patients in each group, inclusion and exclusion criteria, general methodology for retinal/optic nerve and OSA evaluation, OSA and retinal/optic nerve diagnosis criteria, method used for RNFL measurement, statistical methodology and statistical results (prevalence, odds or risk ratio).

Pathophysiological hypotheses relating OSA to retinal and optic nerve disorders

The deleterious mechanisms activated during the nocturnal sequences of apneas/hypopneas are well described [2], and contribute to the increased risk of cardiovascular events in OSA patients. These mechanisms, among which sympathoactivation, oxydative species and pro-inflammatory mediators release and their consequences in vascular endothelial function, represent potentially harmful effects for the optic nerve and retina.

The blood flow (BF) self-regulation mechanisms, most particularly in the retina and optic nerve head (ONH), pursue the objective of maintaining constant delivery of oxygen, despite variations in ocular perfusion pressure (OPP) or blood saturation in oxygen. Several factors associated with OSA may alter ocular BF regulation:

1) Hypoxia: leads to a vasodilation ranging from +5 to +9% in the retinal capillaries [3] and a +15 to +38% increase in ONH BF [4,5] permitting to maintain tissue oxygenation.
2) BP and OPP variations: OPP depends on systemic BP and IOP, according to the formula OPP = BP − IOP. Retinal BF remains constant for up to 40% increase in BP in human [6], whereas ONH blood flow is ensured up to a 34% increase in OPP [7]. Moreover, an increase in IOP up to 30–45 mmHg, leading to OPP decrease, is also associated with regulation of ONH and retinal BF [8]. Thus, AHT associated with OSA and BP variations during apneas activate chronically and acutely the OPP self-regulation mechanisms, and could have deleterious effects for retinal and ONH vasculature.
3) Alteration in the vasoconstrictive/vasodilatory balance: the main vasoactive agents altered during OSA, ET-1 and NO, are involved in ocular BF self-regulation mechanisms [9] and are potentially associated with ocular vascular self-regulation modifications, in particular during apneas. Additionally, ET-1 plays a role in the proliferation of ONH astrocytes and the death of retinal ganglion cells and the disruption of axonal transport within the optic nerve [10]. Thus, activation of the hypoxia–tumor necrosis factor α–ET-1 axis could play a major role by this way in the pathophysiology of optical neuropathies in OSA patients.

The main pathophysiological mechanisms associated with OSA and their potential effect at the ocular level are summarized in Fig. 2.

Nonarteritic anterior ischemic optic neuropathy

Nonarteritic anterior ischemic optic neuropathy is an ischemic disorder of the anterior portion of the optic nerve, clinically

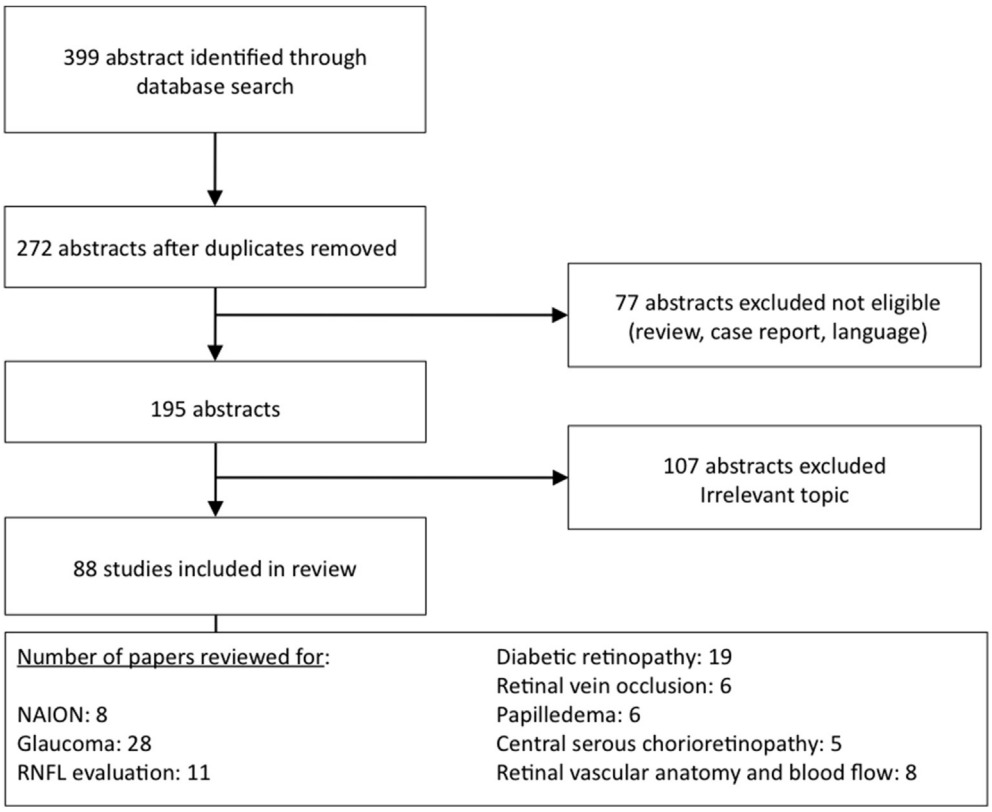

Fig. 1. Modified PRISM study inclusion flowchart. RNFL, retinal nerve fiber layer; NAION, nonarteritic anterior ischemic optic neuropathy; RNFL, retinal nerve fiber layer.

characterized by constant impairment of the visual field and often a reduction in central vision, associated with papilledema observed in the fundus. Initial visual acuity is greater than 20/60 in 35% of cases, between 20/200 and 20/60 in 29% of cases, and less than 20/200 in 23–36% of cases [11,12]. Automated visual field data show that perimetric defect is constant and that the mean defect at 6 months is often severe, between −10.3 and −28 dB in cases of inferior scotoma and between −16.4 and −27 dB in cases of diffuse defect [12] (Fig. 3).

Definition, epidemiology, and risk factors

Two clinical forms of anterior ischemic optic neuropathy have been defined: the arteritic form (giant cell arteritis) and the nonarteritic form (NAION). Nonarteritic anterior ischemic optic neuropathy is the most frequent acute optical neuropathy after the age of 50 y, with an incidence of 2–10 for 100,000 people per year (in the United Sates) [13]. Nonarteritic anterior ischemic optic neuropathy is a disease of the elderly with a mean age at onset of 61 years. Men are slightly more affected than women (58% vs 41%) [14].

Several risk factors, in particular cardiovascular, have been described: OSA (found in 70–90%) (odds ratio [OR] = 2.82; 95% Confidence Interval [CI]: 0.62–12.94 [15]; OR = 4.9; 95% CI: 4.2–5.7 [16]), AHT [17], diabetes [18], a history of ischemic stroke, coronary ischemia [11], and dyslipidemia, notably in patients under 50 y of age [19].

Other risk factors remain controversial such as nocturnal hypoperfusion of the ONH related to a nocturnal drop in BP [20], elevation of plasma homocysteine [21], smoking [11], treatment with 5′phosphodiesterase inhibitors (sildenafil, tadalafil), notably in patients presenting AHT or myocardial infarction [22], and cataract surgery [23].

NAION and obstructive sleep apnea syndrome: epidemiological studies

In 1998, Mojon et al. reported an alteration in the visual field compatible with neuropathy in seven OSA patients as well as a significant correlation between the respiratory disturbance index (RDI, in events/h) and the mean visual field defect [24]. Thereafter, several prospective studies reported the OSA prevalence in NAION patients. The main characteristics of these studies are summarized in Table 1. The prevalence of OSA in NAION patients ranges from 55.6% [25] to 89% [15]. It is significantly higher than in the general population (18% [26]) or in a control group (18–22%) [16,25]. Of five prospective studies using polysomnography, only the study reported by Arda et al. [27], with a small number of subjects (20 patients), did not show a significant difference in the prevalence of OSA in NAION patients and healthy subjects (85 vs 65%, respectively).

The eyes of OSA patients without NAION present perimetric involvement: 30% of these eyes present perimetric defects according to the ischemic optic neuropathy decompression trial classification [28]. We recently demonstrated that the visual field defects found on the contralateral eye of OSA patients with NAION in one eye were significantly more affected than visual field of OSA patients without NAION. This suggests that these perimetric anomalies could be explained by subclinical episodes of NAION on the contralateral eye [29].

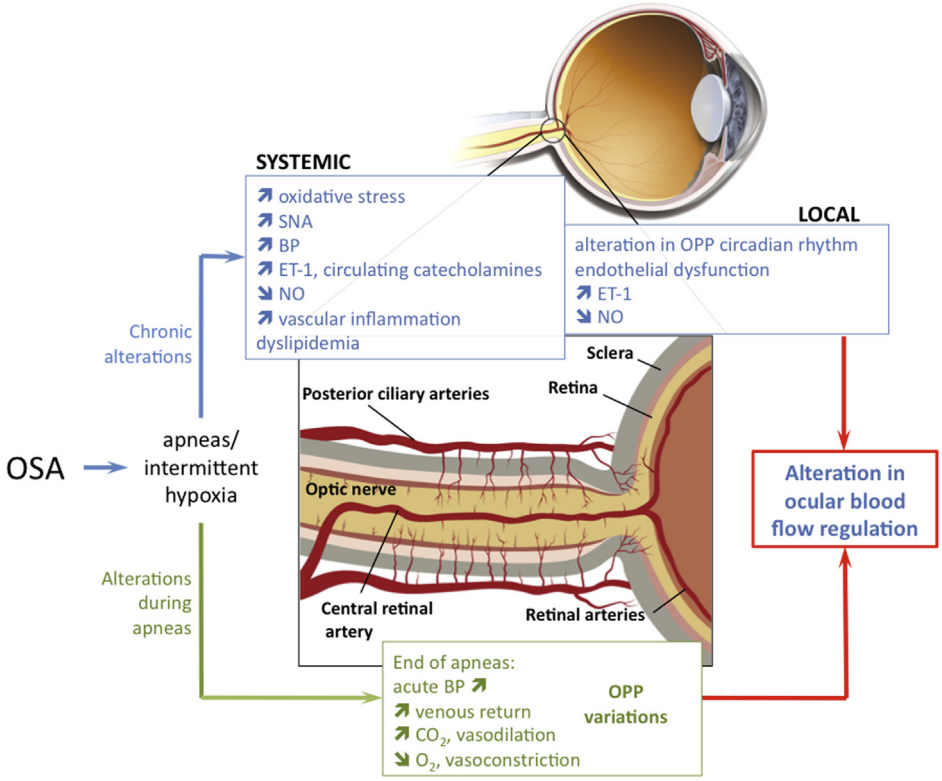

Fig. 2. Diagram illustrating pathophysiological hypotheses relating obstructive sleep apnea syndrome to retina and optic nerve disorders. BP, blood pressure; ET-1, endothelin 1; NO, nitric oxide; OPP, ocular perfusion pressure; OSA, obstructive sleep apnea; SNA, sympathetic nerve activity.

NAION and obstructive sleep apnea syndrome: pathophysiological aspects

Several factors influencing ocular blood flow could play a crucial role in the onset of the ischemic event initiating NAION. The presence of nocturnal hypotension has been reported as a potential trigger of NAION. The arguments in favor of this hypothesis were: 1) a high prevalence of patients (75%) presenting the first symptoms upon awakening in the morning [34], 2) a greater decrease in systolic BP (25%) compared to the usual reduction observed (13–17%) in a healthy control population [35], 3) a more pronounced deterioration of the visual field in patients treated for AHT presenting a nocturnal reduction in systolic and diastolic BP [36].

These results are challenged because they were not found in two other studies. The first study [37] did not show a difference in the nocturnal diastolic pressure bathyphase between 24 patients with NAION and 24 matched controls but reported a smaller increase in BP upon wakening in NAION patients, followed during the day by lower systolic and diastolic BP in sleep apnea patients. A more recent study evaluating the nyctohemeral rhythm of OPP [20] showed that 45% of the NAION patients presented a nocturnal acrophase of the OPP. Ocular perfusion pressure was not significantly lower during the night, because of a low rate of patients presenting nocturnal hypotension (5%).

Treatments and effect of continuous positive airway pressure

There currently exists no validated curative or preventive treatment for NAION [38]. The association of NAION with OSA raises many questions on the potential role of OSA treatment on the risk of NAION in the contralateral eye. Continuous positive airway pressure cancels the respiratory abnormalities, restores physiological sleep, and totally or partially improves the acute or chronic cardiovascular complications associated with OSA, notably vascular reactivity [39]. A 3-year follow-up of NAION patients showed that NAION patients with severe OSA non compliant to CPAP treatment have a risk of NAION in the contralateral eye multiplied by 5.5 compared to non-OSA patients and those with moderate OSA with no indication for CPAP [33]. This original study suggests that the specific treatment of OSA with CPAP could be considered as a therapeutic strategy in severe OSA to reduce the risk of bilateralization of NAION.

Practice points

Polysomnography should be performed in all patients with NAION. However the prevalence of NAION in OSA patients is not known, thus ocular fundus examination should not be systematically performed in OSA patient. OSA patients with acute visual loss require as early as possible a fundus imaging and visual field examination. The benefit of continuous positive airway pressure in patients with NAION for reducing the risk of second eye involvement has been shown in one study.

Research agenda

Further work on the pathophysiology of nonarteritic ischemic optic neuropathy is required to understand the link with OSA and to set up specific treatment. A multicentric randomized clinical trial is underway to evaluate the effect of ET-1 antagonist in OSA and non-OSA patients at the acute phase of NAION (NCT 2014-000848-14).

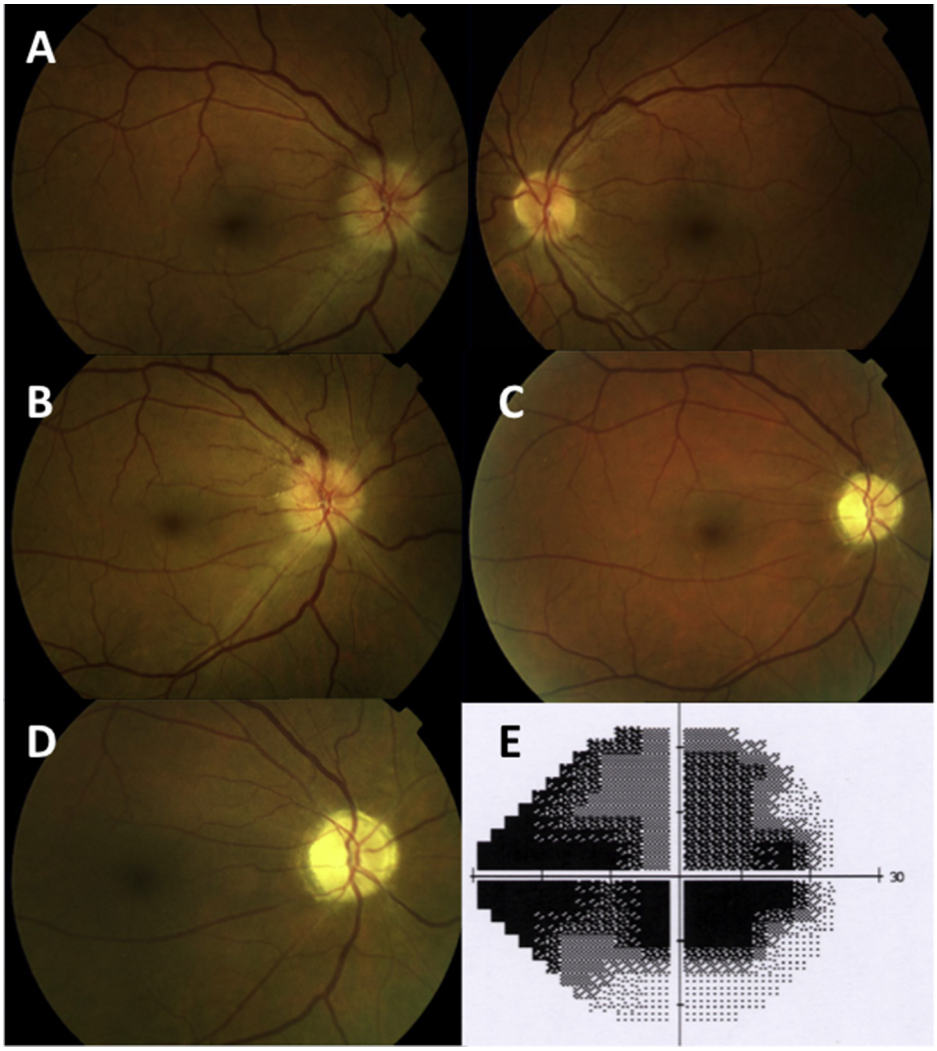

Fig. 3. Representative ocular fundus evolution in NAION patient. **A**: edema of the optic disc at the first visit (left), and undamaged left eye, note the small optic disc cup (right). **B**: evolution at 7 days, note the peripapillary hemorrhage. **C**: evolution at 1 month, with a white aspect due to the atrophy of the neural tissue. **D**: evolution at 6 months, with a complete atrophy of the optic nerve. **E**: visual field at 6 months, with large defects due to the episode of NAION (grey and black parts indicate areas of the visual field poorly seen or not seen by the patient).

Primary open-angle glaucoma

Definition, epidemiology, and risk factors

Glaucoma is a progressive optic neuropathy comprising accelerated apoptosis of retinal ganglion cells, manifesting structurally by pathological excavation of the optic disc (or disc cupping) and functionally by visual field alteration that can lead to blindness at a late stage [40]. The classifications of the different forms of glaucoma depends on the anatomical condition of the iridocorneal angle and on the etiology of glaucoma (primary glaucoma or secondary to another ocular or general disease). Primary open-angle glaucoma (POAG) is associated with a wide angle formed by the iris and the cornea, allowing an easy access of aqueous humor to the trabecular meshwork, whereas closed-angle glaucoma results from iris apposition against the trabecular meshwork and the cornea, preventing access of aqueous humor to the trabecular meshwork. POAG, the most frequent form of glaucoma in the West and Africa, will be detailed below.

Glaucoma is the second leading cause of blindness in the world, with approximately 80–110 million people affected, of whom approximately three million are blind [41]. The prevalence of glaucoma is approximately 0.5–1% of an adult population over 40 years of age in Europe and North America, and increases with age.

The pathophysiological mechanisms of glaucoma are not yet perfectly known; however, a number of factors associated with a high risk of appearance or progression of glaucoma have been identified. The most frequently found risk factor and the only accessible to treatment is high IOP [40]. High IOP increases the risk of glaucoma onset, and the risk and rate of glaucoma progression in cases of proven glaucoma. Vice versa, reduction of IOP reduces the risk of glaucoma development in a hypertensive patient and reduces the risk and rate of progression in a subject with proven glaucoma, whatever treatment method is used to lower IOP. It should be noted that a subject may develop glaucoma when IOP is within normal statistical limits (10–21 mmHg). This form of glaucoma is called normal tension glaucoma (NTG). Vascular factors could be important in the pathophysiology of this form of glaucoma.

Risk factors such as age, ethnicity, family history, myopia, and a thin cornea are not accessible to therapeutic intervention. Other risk factors are currently considered controversial, such as diabetes,

Table 1
Summary of the studies having investigated the association between nonarteritic anterior ischemic optic neuropathy and obstructive sleep apnea syndrome.

Study	Methodology Population	Methodology	Methodology OSA evaluation	Conclusion
Mojon et al., 1998 [24]	Prospective, control-case study 17 NAION patients 17 controls referred for polysomnography	Cases et controls unmatched for NAION risk factors (diabetes, arterial hypertension, atherosclerosis, smoking)	**Polysomnography** Normal (controls): RDI (events/h)<10 Mild OSA: 10 ≤ RDI<20 Moderate OSA: 20 ≤ RDI<40 Severe OSA: RDI ≥40	OSA prevalence: 71% of NAION patients and 18% of controls
Palombi et al., 2006 [15]	Prospective study 27 patients with suspected NAION	Adjusted for confounding factors	**Polysomnography** OSA: AHI >15 events/h	OSA prevalence: 89% of NAION patients vs 18% in general population OSA RR is multiplied by 4.9 in NAION patients (RR = 4.9; 95% CI 4.2–5.7)
Li et al., 2007 [30]	Prospective, control-case study 73 NAION patients 88 controls	Cases et controls matched for NAION risk factors (smoking, alcohol consumption, BMI)	SA-SDQ	30.1% of NAION patients et 17.8% of controls present AHI score compatible with OSA NAION patients have a risk multiplied by 2.62 to present AHI score compatible with OSA (OR = 2.62; 95% CI 1.03–6.6)
Stein et al., 2011 [31]	Retrospective study (database) 156 336 OSA patients	Adjusted for confounding factors	Diagnostic codes	Untreated OSA patients present a risk of developing NAION increased by 16% (HR = 1.16; 95% CI 1.01–1.33) No differences between OSA patients treated by CPAP and non-OSA controls
Arda et al., 2012 [27]	Prospective, control-case study 20 NAION patients 20 controls	Cases et controls matched for NAION risk factors (diabetes mellitus, arterial hypertension, atherosclerosis, smoking, BMI)	**Polysomnography** OSA: AHI >5 events/h	OSA prevalence: 85% in NAION patients vs 65% in controls (non significant difference)
Kolb et al., 2013 [32]	Prospective study 17 NAION patients	NA	**Polysomnography** Diagnostic criteria NA	OSA prevalence in NAION patients: 64.7%
Bilgin et al., 2013 [25]	Prospective control-case study 27 NAION patients 27 controls	Cases et controls matched for NAION risk factors (diabetes, arterial hypertension, atherosclerosis, smoking, BMI)	**Polysomnography** OSA: AHI >20 events/h	OSA prevalence: 55.6% in NAION patients vs 22.2% in controls Relative risk for OSA multiplied by 2.5 in NAION patients
Aptel et al., 2015 [33]	Prospective, cohort study 89 NAION patients	73 patients receiving CPAP treatment	**Polysomnography** OSA: AHI (events/h) >15 Severe OSA: AHI >30	OSA prevalence in NAION patients: 75% (36% moderate OSA and 64% severe OSA) After 3 years, NAION bilateralization is observed in 15.4% of OSA patients and 9.5% of non-OSA controls Patients with severe OSA who are non-compliant to CPAP treatment have an increased risk of bilateralization (RR 5.5, p = 0.035)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; NA, not available; NAION, nonarteritic anterior ischemic optic neuropathy; OR, odds ratio; OSA, obstructive sleep apnea; RDI, respiratory disturbance index; RR, relative risk; SA-SDQ, sleep apnea scale of sleep disorders questionnaire.

low or high BP, vasospasms, hypercoagulability, migraines, and OSA.

Glaucoma and obstructive sleep apnea syndrome: epidemiological studies

A summary of the epidemiological studies that have evaluated the prevalence of glaucoma in OSA subjects is proposed in Table 2, and a summary of the studies assessing the prevalence of OSA in glaucoma patients in Table S1. The epidemiological studies are not unanimous, and the existence of an increased risk of POAG or NTG in OSA patients remains controversial. Most of the studies that found a relation between OSA and glaucoma are small case series. Half of these studies did not include a control group, making it impossible to determine whether OSA is an independent risk factor. Finally, in some of these studies, diagnosis of OSA was based only on symptoms reported by the patients, with no objective sleep study.

In contrast, three of the four large case–control studies (>1000 subjects included) [31,42–44] conducted from databases and based on multivariate analysis taking into account possible confounding factors (age, ethnic origin, cardiovascular characteristics, etc.) did not find an increased risk of glaucoma in case of OSA.

Girkin et al.[42] analyzed the medical data of 667 veterans in whom glaucoma had been newly diagnosed. These data were compared to those from 6667 control subjects without glaucoma. In multivariate analysis, the risk of glaucoma was not significantly higher in OSA subjects (OR = 1.80; 95% CI: 0.76–4.23).

Stein et al. [31] analyzed the medical data of 2.3 million people aged 40 years or more based on a computerized insurance network database in the United States: 6.9% had a diagnosis of OSA. The risk of POAG did not differ significantly in untreated OSA patients (adjusted hazard ratio [HR] = 1.01; 95% CI: 0.98–1.05) or those who were treated with CPAP (HR = 0.99; 95% CI: 0.82–1.18) compared to subjects who did not have OSA. Similarly, the risk of NTG did not differ significantly in untreated OSA patients (HR = 0.98; 95% CI:

0.86–1.12) or those treated with CPAP (HR = 0.79; 95% CI: 0.38–1.67) compared to non-OSA subjects.

Lin et al. [43] did not assess the relation between the prevalence of glaucoma and the presence of OSA, but rather the risk of glaucoma development within a 5-year period after the first diagnosis of OSA. During a 5-year follow-up, the incidence of glaucoma per 1000 persons/year was 11.2 (95% CI: 8.6–14.4) and 6.7 (95% CI: 5.8–7.8) for subjects with and without OSA, respectively. After adjustment for confounding factors, the sleep apnea patients presented a higher relative risk of POAG development of 1.67 (95% CI: 1.30–2.17; $p < 0.001$).

Aptel et al. [44] analyzed the computerized medical data of 9580 subjects over 50 years of age who had undergone a polysomnographic sleep recording. The prevalence of glaucoma was 3.5% in subjects with OSA and 3.1% in control subjects. In multivariate analysis taking into account any confounding factors, the presence of OSA did not significantly increase the risk of glaucoma (OR = 1.13; 95% CI: 0.87–1.47).

Glaucoma and obstructive sleep apnea syndrome: pathophysiological aspects

Several hypotheses are currently being considered to study the role of OSA in the development of glaucomatous neuropathy:

- **Vascular disorders of the optic nerve**: as detailed above in "Pathophysiological hypotheses relating OSA to retinal and optic nerve disorders" Section, the relation between OSA and optic/glaucoma neuropathy could be explained by a dysregulation of optic nerve vascularization (autoregulation impairment) secondary to repeated apneas (prolonged and repeated hypoxia), AHT and atherosclerosis induced by OSA, the imbalance between vasodilator (NO) and vasoconstrictor (ET-1) stimuli, abnormal platelet aggregation, and the increase in ICP.
- **Role of IOP**: OSA as well as CPAP treatment seems able to modify IOP as well as nyctohemeral rhythms of IOP.

A summary of the studies assessing the potential effect of OSA on IOP or on nyctohemeral rhythms of IOP is provided in Table 3. The results of the study on IOP in sleep apnea patients are also contradictory. The three studies that excluded patients with IOP >21 mmHg are not in agreement: two studies reported a significant increase in IOP in OSA patients [47,57], whereas the last study showed no IOP difference [51]. Moreover, only one study showed a correlation between severity of OSA (AHI, in events/h) and IOP [47].

Of the studies that did not exclude patients with IOP >21 mmHg and that compared IOP between OSA patients and control subjects, two found a significant increase in IOP in sleep apnea patients [53,58], whereas the other two studies did not show a difference in IOP [49,50].

Concerning the nyctohemeral rhythms of IOP in OSA subjects, we analyzed the hourly variation in IOP over 24 h in 18 apnea patients (AHI ≥15 events/h) [60]. Only 28% of the OSA patients presented a normal circadian IOP rhythm (nocturnal acrophase); the other patients presented either absence of a circadian rhythm (50%) or an inversed rhythm (diurnal acrophase, 22%). As for OPP, a normal nocturnal rhythm was found most often (78%), whereas an absence of rhythm was found in 22% of the cases. CPAP treatment restored the circadian rhythm of IOP in 67% of apneic patients who presented an abnormal rhythm. Very recent data from our team underscore the role played by sleep cycles on IOP variation. During the nocturnal period, IOP is lower during awake periods than during the rapid eye movement sleep phase, and stages 1, 2, and 3 of non rapid eye movement sleep. During the different sleep phases, IOP is higher during rapid eye movement sleep and progressively decreases during slow sleep stages [61]. Other mechanisms have been advanced to explain these observations. Notably, dehydration associated with the increase in nocturnal diuresis in sleep apnea patients [62], could cause a decrease in IOP [63].

During obstructive apneas simulated in seven healthy volunteers [64], negative intrathoracic pressure associated with inspiratory efforts was reproduced with the Müller maneuver (apnea simulated with a −40 mmHg negative pressure). This study demonstrated a significant decrease in IOP during respiratory efforts miming apnea. The greater the negative pressure imposed, i.e., the respiratory effort, the greater the reduction in IOP was. The authors attributed this response to an increase in venous return toward the heart, which reduces episcleral venous pressure, thus decreases the resistance to flow of the aqueous humor exiting the eye and leading to a drop in IOP. Thus, the decrease in IOP observed during simulated inspiratory efforts could possibly be involved in the disappearance of the nocturnal acrophase of IOP observed in sleep apnea patients. This study shows that abrupt variations in IOP on the order of −4 to −33% exist during each apnea. Some studies have shown that these substantial fluctuations in IOP may be a risk factor for glaucoma worsening [65].

A number of studies have also reported the effect of CPAP on IOP or nyctohemeral rhythms of IOP. In contrast, no randomized longitudinal study has assessed the effect of CPAP on the progression of glaucoma in OSA patients. The effect of CPAP on daily variations in IOP was reported in two studies. The first study [66] showed in 21 OSA patients, that CPAP treatment leads to an overall increase in nocturnal IOP whereas the other study reported no effect of CPAP in nocturnal IOP variation in OSA patients treated (n = 31, first night of treatment) [67]. In our experience [60], CPAP increases the nocturnal IOP (from 14.8 to 18.3 mmHg) and normalizes the circadian rhythm of IOP. Restoration of the normal IOP rhythm after a single night of CPAP in this latter study suggests that there is a direct effect of nocturnal inspiratory efforts on the decrease in IOP observed in OSA patients.

Practice points

The relationship between OSA and glaucoma prevalence is still controversial. Polysomnography should not be systematically performed in all subjects with glaucoma. Continuous positive airway pressure increases the nocturnal IOP in OSA patients.

Other optic neuropathies

Evaluation of the thickness of the retinal nerve fiber layer in sleep apnea patients

Use of optical coherence tomography, a recent noninvasive ocular imaging technique, in glaucomatous patients demonstrates and quantifies the decrease in the thickness of the RNFL associated with enlargement of the optic nerve cupping. This decrease in the RNFL thickness corresponds to a loss in ganglion cells of the retina, notably their axons, and precedes detectable visual defects [68]. It has thus been shown that a glaucoma patient could lose 40% of his retinal ganglion cells before the appearance of visual field defects [69]. For this reason, evaluation of the RNFL thickness occupies an important place in the early diagnosis of glaucoma. Nevertheless, it should be noted that an isolated decrease in the thickness of the

Table 2
Prevalence of primary open angle glaucoma in OSA patients.

Study	Methodology Population	Methodology Glaucoma criteria	Methodology OSA evaluation	Conclusion
Mojon et al., 1999 [45]	Cross-sectional study 69 OSA patients Spearman correlation	Optic disk cupping Visual field defects characterizing glaucoma IOP >21 mmHg	**Polysomnography** Non-OSA: RDI (events/h) <10 Mild OSA: 10 ≤ RDI < 20 Moderate OSA: 20 ≤ RDI < 40 Severe OSA: RDI ≥40	Glaucoma prevalence in OSA patients (7.2%) > observed prevalence in caucasian population (2%) Positive correlation between RDI et IOP, visual field defects variance and glaucomatous optic disk presence
Tsang et al., 2006 [46]	Case-control study 66 patients 36 OSA patients 30 controls Spearman correlation, adjusted for age and BMI	Cup to disk ratio >0.5 IOP >21 mmHg without treatment Visual field defects	**Polysomnography** OSA: AHI ≥20 events/h	Significant difference between OSA and controls concerning visual field parameters, Glaucoma excavation of the optic disk: OSA 26.3% > controls 6.78% No correlation between visual field parameters and AHI and untreated OSA duration
Sergi et al., 2007 [47]	Case-control study 91 patients 51 OSA patients 40 controls Spearman correlation	Optic disk cupping Visual field defects IOP <21 mmHg without treatment (for NTG definition)	**Polysomnography** OSA: AHI ≥10 events/h	NTG prevalence in OSA patients (5.9%) > prevalence in control group (0%) Cup to disk ratio similar in both groups In OSA patients: AHI and IOP values higher than in control group, visual field and RNFL thickness values were lower than in control group Positive correlation between AHI and: IOP, visual field alterations, cup to disk ratio and mean RNFL thickness
Bendel et al., 2008 [48]	Cross-sectional study 115 OSA patients Kendall test	POAG: Preferred Practice Pattern's definition	**Polysomnography** OSA AHI ≥15 events/h	Glaucoma prevalence in OSA patients: 27% (95% CI 19–37) Positive correlation between IOP and BMI No correlation between AHI and glaucoma
Karakucuk et al., 2008 [49]	Case-control study 56 patients 31 OSA patients 25 controls ANOVA	Cup to disk ratio >0.5 + difference between 2 eyes >0.2 IOP > 21 mmHg for POAG and <21 mmHg for NTG	**Polysomnography** Mild OSA: 5 ≤ AHI (events/h) < 15 Moderate OSA: 15 ≤ AHI < 30 Severe OSA: AHI ≥30	Glaucoma prevalence in OSA patients: 12.9% Positive correlation between IOP and AHI (r = 0.43)
Nowak et al., 2009 [50]	Case-control study 34 OSA patients 18 controls	Intraocular hypertension Glaucoma diagnosis criteria from the Ocular Hypertension Treatment Study Group	**Polysomnography** OSA AHI >5 events/h	Glaucoma prevalence in OSA patients (5.9%) > prevalence in control group (0%)
Lin, 2011 [51]	Prospective study 285 patients 247 OSA patients 38 controls Pearson correlation	Optic disk cupping IOP <21 mmHg (NTG) Visual field defects OCT	**Polysomnography** Mild OSA: 5 ≤ AHI (events/h) < 15 Moderate OSA: 15 ≤ AHI < 30 Severe OSA: AHI ≥30	Glaucoma prevalence in OSA patients (5.7%) > prevalence in control group (0%) Glaucoma prevalence in severe OSA patients (7,1%) > prevalence in moderate OSA patients + controls (1.1%) Positive correlation between mean and minimal SaO_2 and mean RNFL thickness in OSA patients (r = 0.13)
Muniesa et al., 2013 [52]	Cross-sectional study 152 patients 75 OSA + FES patients 52 OSA without FES patients 25 controls Spearman correlation, adjusted for age and BMI	Asymetric optic disk cupping + neuroretinal rim thinning and/or optic disk hemorrhages and/or RNFL thinning Visual field defects POAG: IOP >21 mmHg NTG: IOP <21 mmHg	**Polysomnography** or cardiorespiratory night study Mild OSA: 10 ≤ AHI (events/h) < 20 Moderate OSA: 20 ≤ AHI < 30 Severe OSA: AHI ≥30	Glaucoma prevalence in OSA patients (12.9%) > prevalence in control group (0%) Glaucoma prevalence in OSA without FES patients (5.3%; 95% CI 1.5–13.1) < glaucoma prevalence in OSA + FES patients (23%; 95% CI 11.2–34.9), after adjustments No association between AHI and glaucoma after adjustments No correlation between AHI and IOP, visual field defects and mean RNFL thickness

Table 2 (*continued*)

Study	Methodology Population	Methodology Glaucoma criteria	Methodology OSA evaluation	Conclusion
Lin et al., 2013 [43]	Retrospective, cohort, case-control study 7084 patients 1012 OSA patients 6072 controls	Exclusion criteria: patients <40 y, no ophthalmologic follow-up, untreated glaucoma	**Polysomnography** Criteria NA	POAG incidence rate (per 1000 person-years) during 5 years after OSA diagnosis (11.2; 95% CI 8.6–14.4) > POAG incidence rate during same period in control group (6.7; 95% CI 5.8–7.8) POAG diagnosis risk in OSA patients is increased compared to controls (HR = 1.67; 95% CI 1.04–2.31)
Moghimi et al., 2013 [53]	Cross-sectional study 105 patients 51 OSA patients 54 matched controls Linear regression	ONH alterations: diffuse or focal narrowing or notching of the disk rim and/or nerve fiber layer hemorrhages RNFL defect in the presence of characteristic visual field defects	**Polysomnography** Mild OSA: 5 ≤ AHI (events/h) < 15 Moderate OSA: 15 ≤ AHI < 30 Severe OSA: AHI ≥30	Glaucoma prevalence in OSA patients (3.9%) > prevalence in control group (0%) Positive correlation between IOP and AHI (r = 0.33; p = 0.007)
Geyer et al., 2003 [54]	Cross-sectional study 228 OSA patients Multivariate regression Adjustment for BMI	Cup to disk ratio >0.6 Cup-disk asymmetry >0.3 Visual field defects IOP <21 mmHg without treatment	**Polysomnography** Mild OSA: 10 ≤ RDI (events/h) ≤ 19 Moderate OSA: 20 ≤ RDI ≤ 39 Severe OSA: RDI ≥40	POAG prevalence in OSA patients: 2% = prevalence in caucasian population No association between RDI and glaucoma or IOP
Kadyan et al., 2010 [55]	Case-control study 115 patients 89 OSA patients 26 controls	Cup to disk ratio ≥0.6 Difference between the 2 eyes ≥0.3 ± total or partial optic disk cupping ± peripapillary hemorrhages IOP >21 mmHg	Transcutaneous oxymetry Mild OSA: 5 ≤ ODI (events/h) < 15 Moderate OSA: 15 ≤ ODI < 30 Severe OSA: ODI ≥30	Glaucoma prevalence in OSA patients (3.%) similar to glaucoma prevalence in general population (1.7–3%)
Stein et al., 2011 [31]	Retrospective, longitudinal, cohort study 156,336 OSA patients Multivariate regression Adjustment for confounding factors	Diagnostic codes	NA	POAG prevalence similar in untreated OSA patients (0.94%), OSA patients treated by CPAP (0.83%) and non-OSA patients (0.93%) NTG prevalence in non-OSA patients (0.08%) > NTG prevalence in untreated OSA patients POAG and NTG risk is not increased in OSA patients, treated or not with CPAP
Aptel et al., 2014 [44]	Retrospective, longitudinal, cohort study 9580 patients 6754 OSA patients 330 glaucoma patients Uni/multivariate regression Adjustment for confounding factors	Diagnostic codes	**Polysomnography** OSA: AHI (events/h) ≥15 non-OSA: AHI <15	Glaucoma prevalence in OSA patients (3.5%) ≅ prevalence in control group (3.1%) OSA does not influence glaucoma risk (univariate analysis: OR = 1.1; 95% CI 0.8–1.4) No difference in glaucoma prevalence according to OSA severity (AHI): AHI 15–30/h (5%), AHI 30–50/h (3.8%), AHI >50/h (3.1%)
Ko et al., 2016 [56]	Retrospective cross-sectional study 172 glaucoma cases 5574 non glaucoma cases	Optic disk photography evaluation and grading by 3 glaucoma specialists	**Questionnaire based**	OSA prevalence in glaucoma patients (8.1 ± 2.1%) = OSA prevalence in non-glaucoma patients (6.5 ± 0.3%) OSA is not a risk factor for glaucoma development (multivariate analysis: OR = 1.37; 95% CI 0.6–2.9)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; CCT, central corneal thickness; FES, floppy eyelid syndrome; HR, hazard ratio; IOP, intraocular pressure; NA, non available; NTG, normal tension glaucoma; OCT, optical coherence tomography, ODI, oxygen desaturation index; ONH, optic nerve head; OR, odds ratio; OSA, obstructive sleep apnea syndrome; POAG, primary open-angle glaucoma; RDI, respiratory disturbance index; RNFL, retinal nerve fiber layer.

optical fiber layer is not sufficient to provide a diagnosis of glaucoma. The diagnosis of glaucoma is based on the association of characteristic alterations in the ONH observed during fundus examination and corresponding visual field abnormalities (Fig. 4).

The studies evaluating RNFL thickness in OSA patients are presented in Table S2. The results of these studies agree in that they show that OSA patients with no signs of optic neuropathy, notably glaucoma, often present a significant decrease in mean RNFL

Table 3
Study of intraocular pressure in OSA patients.

Study	Number of patients	Exclusion of IOP >21 mmHg	IOP OSA >IOP controls	Correlation
Mojon et al., 1999 [45]	69 OSA	No	NA	Positive between IOP and RDI (events/h)
Geyer et al., 2003 [54]	228 OSA	No	NA	No correlation between IOP and RDI
Sergi et al., 2007 [47]	51 OSA and 40 controls	Yes	Yes	Positive between IOP and AHI (events/h)
Karakucuk et al., 2008 [49]	31 OSA and 25 controls	No	No Moderate OSA > severe OSA	Positive between IOP and AHI
Bendel, 2008 [48]	100 SA0S	No	NA	No correlation between IOP and AHI
Nowak et al., 2011 [50]	34 OSA and 19 controls	No	No	NA
Lin et al., 2011 [51]	209 OSA and 38 controls	Yes	No	No correlation between IOP and AHI
Lin et al., 2011 [58]	105 OSA and 22 controls	No	Yes	No correlation between IOP and RNFL thickness
Moghimi et al., 2013 [53]	51 OSA	No	Yes	Positive between IOP and AHI
Huseyinoglu et al., 2014 [57]	101 OSA and 20 controls	Yes	Yes	No correlation between IOP and AHI or RNFL thickness
Shiba et al., 2014 [59]	214 OSA	No	NA	Positive between IOP and nasal RNFL thickness
Muniesa et al., 2014 [52]	127 OSA and 25 controls	No	NA	No correlation between IOP and AHI

Abbreviations: AHI, apnea-hypopnea index; IOP, intraocular pressure; NA, non available; OSA, obstructive sleep apnea syndrome; RDI, respiratory disturbance index; RNFL, retinal nerve fiber layer.

thickness or localized in certain retinal quadrants. The severity of OSA is predominantly correlated with a greater decrease in RNFL thickness [57–59,70]. Several studies have reported a negative correlation between RNFL thickness and AHI (events/h) [57–59,70] or minimum blood oxygen saturation [58]. There is no preferential involvement of one of the peripapillary retinal quadrants.

These results suggest an effect of OSA on RNFL thickness, as reported in a recent meta-analysis [71]. This reduction could be associated with preclinical optic neuropathy. Most particularly, the increase in ET-1 and oxidative stress associated with OSA could have an impact on the retinal ganglion cells. Endothelin 1 in particular promotes the development of the astroglial reaction and retinal ganglion cell death by direct stimulation or by disturbing axonal transport within the optic nerve [10].

Research agenda

Complementary studies are mandatory to understand the potential role of OSA in the reduction of RNFL. Long-term effect of OSA on the ocular hemodynamics should be studied.

Intracranial hypertension and papilledema

Loss of visual function related to papilledema is considered one of the most serious complications of intracranial hypertension (ICH). Currently, two theories are advanced to explain by which mechanism ICH leads to the appearance of papilledema. The mechanical theory postulates that high ICP directly compresses the optic nerve axons at the lamina cribrosa, a fibrous porous structure allowing the arrangement of optic nerve axons in the optic nerve at the back of the eye [72]. The ischemic theory postulates that high ICP causes a decrease in vascular perfusion of the optic nerve. The increase in pressure in the subarachnoid space compresses the ciliary circulation and reduces the blood supply toward the laminar region of the optic nerve, interfering with choroidal blood flow. This chronic ischemia alters the metabolism related to axoplasmic flow, with local accumulation of toxic metabolites [73]. It is highly probable that an association of these factors such as cerebrospinal fluid pressure, IOP, and systemic BP are involved.

A higher risk of papilledema in OSA patients could be suspected by the relation between papilledema and ICH, alterations in ICP, cerebrospinal fluid pressure, and systemic BP associated with OSA. Moreover, obesity, a known risk factor for papilledema, is one of the most frequently encountered conditions in OSA patients. Several clinical case studies have suggested the association of papilledema with OSA [74–76]. Measurement of nocturnal ICP reveals cyclic variations associated with apneas [76–78].

One retrospective study reports a high prevalence of OSA patients with papilledema among 18 cases of idiopathic intracranial hypertension [79]. Only two prospective studies have analyzed the prevalence of papilledema in OSA patients [80,81]. Out of 162 OSA patients included in these two studies, no papilledema was diagnosed after fundus examination. It should be noted that no case–control studies comparing OSA patients and subjects matched for confounding factors have yet proven that the risk of papilledema is increased in OSA cases.

Practice points

Given the absence of increased prevalence of papilledema, systematic visual field and fundus examinations are not required in patients with OSA.

Retinal disorders

Diabetic retinopathy

Diabetic retinopathy (DR) is the most frequent microvascular complication of diabetes and is a major cause of vision loss. The prevalence of DR, its proliferative form (PDR), and diabetic macular edema in the general population is today estimated at 34.6%, 7%, and 6.8%, respectively [82]. The risk factors of DR classically recognized are AHT, hyperglycemia, and diabetes duration. The molecular mechanisms involved in the appearance of DR include an increase in oxidative stress and inflammation associated with the activation of certain factors such as vascular endothelial growth factor, tumor necrosis factor α, and insulin-like growth factor. An overview of DR ocular fundus lesions is shown in Fig. S1.

Changes in glucose metabolism and the increased risk of developing type 2 diabetes (T2D) associated with OSA independently of obesity [83] have motivated several teams to study the

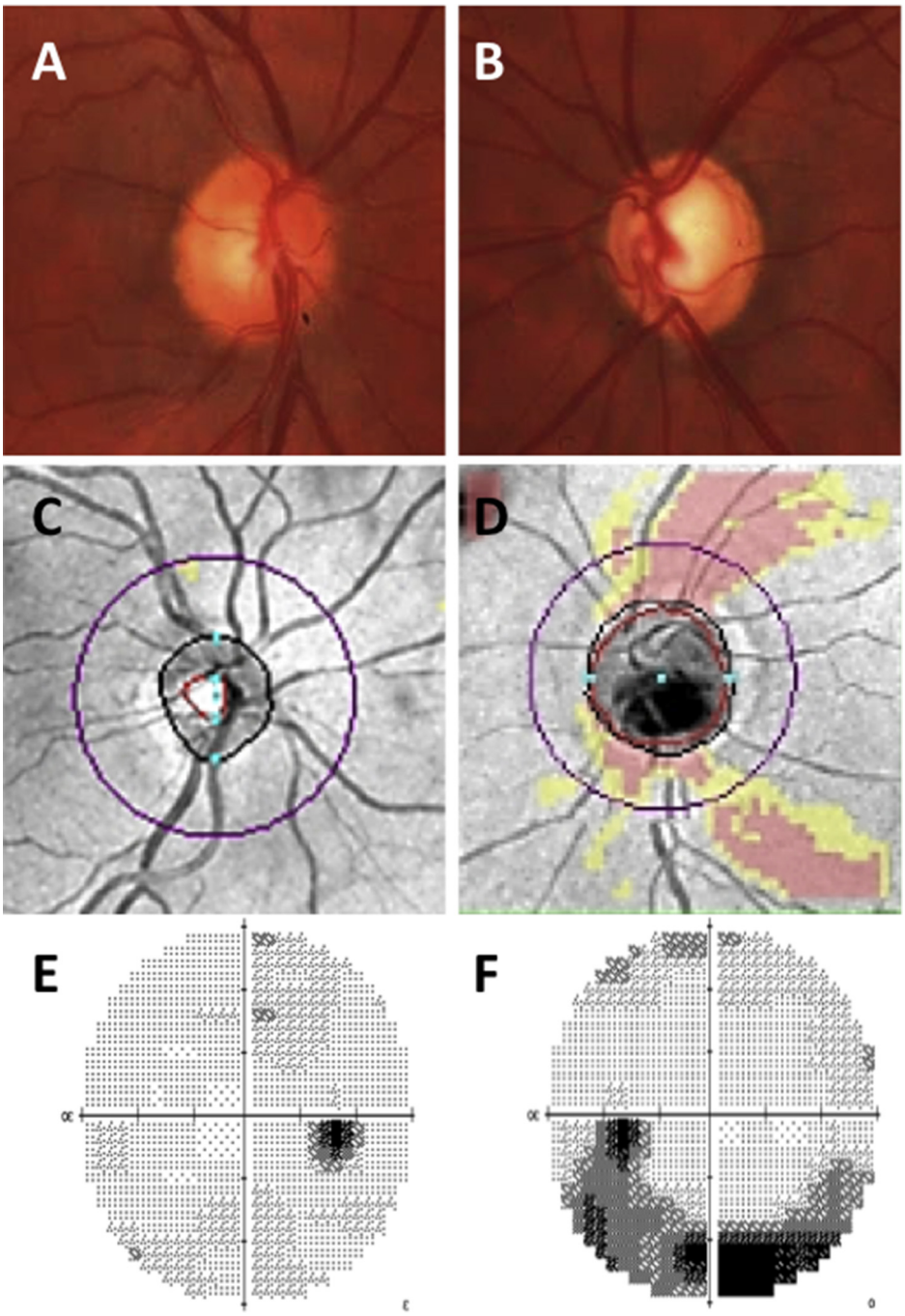

Fig. 4. Optic nerve head cupping, retinal nerve fiber layer thickness (RNFL) and visual field (VF) in normal and primary open angle glaucoma (POAG) eye. **A**: optic nerve head of a healthy subject. Note the small cup in the central part of the disc (white part). **B**: optic nerve head of a subject with POAG. Note the larger cup in the central part of the disc, indicating a loss of neuronal tissue. **C**: corresponding optical coherence tomography examination, with no decrease of the retinal nerve fiber layer thickness (normal). **D**: corresponding optical coherence tomography examination, with a large decrease of the retinal nerve fiber layer thickness in the superior and inferior area (POAG). The red rim delimits the deficit in retinal nerve fibers. **E**: corresponding visual field (normal). **F**: corresponding visual field, with a large inferior arcuate scotoma due to the loss of the retinal ganglion cells (POAG). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

potential impact of OSA on the progression of DR. A summary of the epidemiological studies having assessed the relation between OSA and DR is provided in Table 4.

Four types of studies suggest a relation between diabetic retinopathy and OSA.

1) **OSA prevalence studies in diabetic patients developing DR**: 11 epidemiological studies out of 15 suggest that OSA is associated with a greater frequency of microvascular anomalies [88,90], DR [90,92,95], or maculopathy (macular edema) [90]. Other studies show that blood oxygen desaturation due to OSA is

independently associated with the presence of DR [85,96]. The results therefore seem to show that DR is more frequently observed in OSA patients with T2D compared to non-sleep apnea patients with T2D [89,90,94].

Of the four studies that did not suggest association between OSA and DR, one reported no difference in DR prevalence between the sleep apnea group (39%) and the control group (38%) [100]. Another study did not demonstrate a difference in DR prevalence between patients with mild (48%), moderate (53%), severe (68%) OSA and control subjects (66%) [97]. Moreover, no relation between nocturnal apneas and the presence of DR was demonstrated in 219 patients with T2D [99]. Finally, the last study did not show a relation between central macular retinal thickness and the severity of OSA in patients with diabetic macular edema [98].

2) **A single longitudinal study** has examined the role played by OSA in the appearance and progression of DR [94]. This study reports a higher prevalence of severe DR threatening the visual prognosis in OSA patients with T2D (48.8%) compared to non-OSA patients (21.6%). The follow-up of patients over a 5-year period has also shown that OSA patients presented a more frequent progression toward more advanced stages of DR (15.3%) than the non-OSA group (3%).
3) **Studies reporting the effect of the severity of OSA on diabetic retinopathy**: three studies showed that the frequency of DR increases with the severity of OSA [88,91,93], whereas one study reported no correlation [97].
4) **One study reported the effect of CPAP treatment on the progression of DR in 35 sleep apnea and diabetic patients** [101]: good observance of CPAP treatment was associated with better improvement of the visual field after 6 months of treatment compared to the improvement in patients who showed little compliance. Nevertheless, no randomized longitudinal study has evaluated the effect of CPAP on the progression of DR in sleep apnea and diabetic patients.

A recent meta-analysis [102] suggests that OSA is associated with a more advanced stage of DR in patients with T2D and that minimal blood oxygen saturation is associated with diabetic macular edema (adjusted OR = 0.79; 95% CI: 0.65–0.95) and retinopathy (pooled OR = 0.91 (95% CI: 0.87–0.95; $I^2 = 0\%$). The analysis emphasizes the weaknesses of the above-cited studies, such as the heterogeneity of the diagnostic methods and the definition criteria for OSA, the variability of the diagnostic criteria and methods for DR, or the selection bias in the patients included. It is interesting to note that the only two studies obtaining a maximum overall quality grade do not agree on the relation between OSA and DR [90,100].

Practice points

Patients with diabetes and OSA should be closely monitored for retinopathy screening and follow-up. The frequency of DR increases with the severity of OSA.

Research agenda

In diabetic patients, the role of OSA treatment, especially CPAP, should be evaluated for the progression of DR and diabetic macular edema.

Retinal vein occlusion

The pathophysiology of retinal vein occlusion is complex and multifactorial. It is often simplified by Virchow's triad that includes changes in the vascular wall (endothelial dysfunction), changes in the constituents of blood (hypercoagulability), and hemodynamic changes. The currently recognized risk factors are age, AHT, hyperlipidemia, glaucoma, diabetes, and the risk factors associated with atherosclerosis [103]. Analysis of the Framingham score over 10 years in patients with RVO shows a greater risk in these patients of developing cardiovascular disease [104].

From the viewpoint of the cardiovascular and metabolic consequences of OSA and the pathophysiological hypotheses of RVO, it is legitimate to question the role of OSA in the onset of RVO. The pathophysiological factors associated with OSA potentially involved in the pathogenesis of RVO may be several: vasodilation and the slow-down of blood flow associated with repeated nocturnal hypercapnia, the decrease in venous return related to inspiratory efforts during the apnea phases, abrupt modifications in BP during micro-arousals, and the presence of a hypercoagulability state in response to systemic inflammation and oxidative stress. Locally, hypoxia and hypercapnia during apnea episodes can lead to vasodilation of the central artery of the retina, compressing the adjacent central vein located in the same adventitial sheath [105].

The first observations of RVO in OSA patients were reported in 2009 [106]. More recently, two cases of bilateral and simultaneous central RVO, a rare presentation of the disease, were described in patients with OSA [107,108], morbid obesity, and a high hematocrit level. One of the two cases also presented high blood levels of fibrogen and C-reactive protein, suggesting a chronic inflammatory state associated with dysregulation of the thrombogenic mechanisms [108].

From an epidemiological point of view, prevalence of OSA was estimated at 37% in samples of 40 and 63 patients with RVO [105], with a majority of mild or moderate OSA cases (AHI <30 events/h). In another study, OSA prevalence was estimated at 30.8% in a sample of 19 patients with newly diagnosed RVO and no other risk factors [109]. However, these studies present significant limitations (use of nocturnal oximetry, selection of patients referred for polysomnography, absence of a control group), but these preliminary results deserve being completed by larger studies. Systematic polysomnography has shown that sleep apnea patients had an independent relative risk of 1.94 (HR = 1.94; 95% CI: 1.03–3.65) of developing RVO [110].

Central serous chorioretinopathy

Central serous chorioretinopathy (CSCR) is characterized by the presence of serous retinal detachment, often localized within the central retina, especially the macula (Fig. S2). The risk factors of CSCR are currently male gender, a genetic predisposition (including polymorphisms on the factor H genes of the complement or cadherin 5), corticosteroid intake, sympathomimetic medications, and Cushing disease [111]. The cardiovascular risk factors associated with CSCR such as AHT, increased orthosympathetic activity and decreased parasympathetic activity, motivated the study of the relation between OSA and CSCR.

The role played by OSA in the appearance of CSCR is under debate. A study using the Berlin questionnaire (evaluating the functional signs of OSA, 86% sensitivity for diagnosis and 77% specificity) [112] suggests a higher prevalence of OSA in CSCR patients (58.6%) than in a control group (31%) paired for age and gender. These results were not confirmed in another study using the same questionnaire (46% vs 44%) [113]. In a sample of 113 CSCR

Table 4
Epidemiological studies having evaluated the relations between obstructive sleep apnea syndrome and diabetic retinopathy.

Study	Methodology Population	Methodology OSA and diabetes evaluation	Methodology Exclusion criteria	Ophthalmologic exam	Conclusion
Merritt et al., 2007 [84]	Prospective study 44 type 2 diabetes patients 23 DR patients 21 sight threatening DR patients	OSA: pulse oxymetry (ODI 4%, in events/h) Diabetes: Diabeta 3® database	NA	Ocular fundus exam and photography	ODI 4% is higher in sight threatening DR patients (13.5 ± 16.5) compared to no sight threatening DR patients (3.8 ± 3.1). Sight threatening DR patients spend more time at SaO_2 < 90% (12.6 ± 18% vs 1.8 ± 2.6%)
Shiba et al., 2009 [85]	Cross-sectional case-control study 166 type 2 diabetes patients 116 PDR patients 48 NPDR patients Multiple regression	OSA: pulse oxymetry Sleep-disordered breathing diagnosed if ODI4% >5 events/hour Diabetes: NA	NA	NA	ODI 4% is higher in PDR patients compared to NPDR patients OSA diagnosis is more frequent in PDR group: ODI 4% is an independent contributing factor to OSA diagnosis (standard regression coefficient = 0.2, *t* value = 2.15) No difference in mean SpO_2 between both groups
Unver et al., 2009 [86]	Cohort study 44 type 1 and 2 diabetes patients 22 OSA patients 22 non OSA patients Matched for age, weight, diabetes duration	OSA: questionnaire (Epworth score >10) + polygraphy Diabetes: NA	NA	Ocular fundus exam and photography + fluorescence angiography	DR is present in all OSA patients and only in 5 non OSA patients DME is present in 20 OSA patients and in 9 non OSA patients
Shiba et al., 2010 [87]	Cross-sectional comparative study 219 type 2 diabetes patients 151 PDR patients 68 NPDR patients Logistic regression	OSA: pulse oxymetry OSA: 4% ODI ≥ 5 events/h Diabetes: NA	NA	NA Medical record	In NPDR group, mean ODI 4% and cumulated time spent at SaO_2 <90% are lower, and mean minimal SpO_2 is higher compared to PDR group High minimal SpO2 value is a protective factor for PDR (OR = 0.93; 95% CI 0.88 −0.99)
Kosseifi et al., 2010 [88]	Retrospective study 98 OSA and type 2 diabetes patients	OSA: overnight home polygraphy Diabetes: NA Inclusion of patients with mean HbA1c ≤6,5%	NA	NA	Microvascular anomalies and retinopathy are associated with higher AHI and lower oxygen desaturation
Borel et al., 2010 [89]	Prospective study 37 type 1 diabetes patients Non-obese patients	OSA: pulse oxymetry ± **Polysomnography** (n = 18) Non OSA: AHI <15 events/h Nocturnal oxymetry: - Normal: absence of SaO_2 fluctuation - Pathological: repetitive desturation-reoxygenation sequences - Borderline: desturation-reoxygenation sequences limited in amplitude or time Diabetes: NA	NA	NA	DR is more frequent in patients with abnormal nocturnal oximetry (11 patients, 73%) compared to patients with normal to borderline nocturnal oximetry (5 patients, 44%)
West et al., 2010 [90]	Cohort study 118 type 2 diabetes patients 24% OSA 76% non OSA Multiple regression	OSA: pulse oxymetry ODI 4% > 10 events/h Diabetes: Oxford Center for Diabetes, endocrinology and Metabolism database	NA	Ocular fundus photography DR gradation by 2 independent examiners (English National Screening Program for Diabetic retinopathy)	DR (haemorrhages and hard exudates) is more frequent in OSA group: Grade 2 DR: 36% of OSA patients vs 4% of non OSA patients (p < 0.0001) DME: 29% of OSA patients vs 4% of non OSA patients (p < 0.0001) Retinal microaneuryms: 26% of OSA patients vs 8% of non OSA patients (p = 0.02)

(*continued on next page*)

Table 4 (*continued*)

Study	Methodology Population	Methodology OSA and diabetes evaluation	Methodology Exclusion criteria	Ophthalmologic exam	Conclusion
Schober et al., 2011 [91]	Cohort study 556 patients type 1 diabetes (58) type 2 diabetes (498)	OSA: pulse oxymetry Non OSA: AHI (events/h) <15 Moderate to severe OSA: AHI ≥15 Diabetes: NA	History of malignoma, liver or endocrine disease, treated mental disorders	NA Medical record	DR frequency increases with increasing AHI (15% for AHI <5, 25% for 5 < AHI < 14 and 29% for AHI ≥15) OSA prevalence among diabetes patients: 37%
Rudrappa et al., 2012 [92]	Cohort study 31 type 2 diabetes patients 17 OSA patients 16 non OSA patients Multiple regression	OSA: overnight home polygraphy Non OSA: AHI (events/h) <5 Mild OSA: 5 ≤ AHI < 15 Moderate OSA: 15 ≤ AHI < 30 Severe OSA: AHI ≥30 Diabetes: NA	NA	English National Screening Program for Diabetic retinopathy	Retinopathy score ($p = 0.04$) but not DME ($p = 0.15$) is higher in OSA group DME is not associated with OSA presence OSA is an independent significant predictor of the total retinopathy scores
Mehta et al., 2012 [93]	Prospective study 80 type 2 diabetes patients 50 DR patients (30 NPDR et 20 PDR) 30 Non DR patients Multivariate regression	OSA: Polysomnography (AHI classification NA) Diabetes: NA	Coronary disease, chronic or acute heart failure, hypothyroïdism, known OSA, known pulmonary disease	Ocular fundus exam + fluorescence angiography	OSA is found in 66% DR patients, of which 90% of PDR patients and 50% of NPDR OSA severity (AHI) is: - Higher in DR patients (AHI = 24.3 ± 28) with respect to non DR patients (13 ± 20) - Higher in PDR patients (35 ± 30) with respect to NPDR patients (17 ± 24)
Altaf et al., 2013 [94]	Longitudinal study 199 type 2 diabetes patients Multiple regression	OSA: overnight home polygraphy (AHI > 5 events/h) Diabetes: NA	Known OSA, severe renal dysfunction, non diabetic retinopathy	Ocular fundus photography Advanced DR: PDR or pre-proliferative DR Sight threatening DR: PDR ou pre-proliferative DR, maculopathy or photocoagulation scars	OSA prevalence among type 2 diabetes patients: 62.8% OSA is independently associated with: - Sight threatening DR (OR = 3.7; 95% CI 1.6–8.9) - DME (OR = 4.5; 95% CI 1.8–11.4) - Advanced DR (OR = 3.9; 95% CI 1.02–15.3) Over 4.4 ± 1 y, OSA patients presented increased risk of DR worsening (OR = 6.6; 95% CI 1.2–35.1) OSA did not predict the development of DME
Manin et al., 2015 [95]	Cross-sectional multicentric study 67 type 1 diabetes patients Logistic multivariate regression	OSA: Polysomnography or overnight home polygraphy (13 patients) Mild to moderate OSA: 10 < AHI (events/h) < 30 Severe OSA: AHI ≥30 Diabetes: blood parameters	NA	Ocular fundus exam and photography ± retinal laser surgery	DR was present in 84% of OSA patients vs 42% of non OSA patients DR was associated with OSA (OR = 4.5; 95% CI 1.1–18.8)
Nishimura et al., 2015 [96]	Prospective study 136 type 2 diabetes patients 37 DR patients 99 Non DR patients Logistic multivariate regression	OSA: polygraphy Comparison of AHI, 4% ODI and 3% ODI (in events/h) between DR and non-DR groups Diabetes: glycemia >126 mg/dl, oral glucose tolerance test (>200 mg/dl), hypoglycemic therapy	Heart failure, chronic obstructive pulmonary disease, hemodialysis, serum triglyceride > 400 mg/dl	Ocular fundus exam or photography Non-DR or DR (proliferative or no)	No difference in AHI, time spent at SaO_2 < 90%, ODI 4% or 3% between DR or non DR groups Minimal SaO_2 is correlated to DR (OR = 0.8; 95% CI 0.8–0.9)
Laaban et al., 2009 [97]	Prospective study 303 type 2 diabetes patients (poorly controlled)	OSA: polygraphy Mild OSA: 5 < AHI (events/h) ≤ 15 Moderate OSA: 16 ≤ AHI ≤ 29 Severe OSA: AHI ≥30 Diabetes: NA	Known OSA, heart failure, severe valvulopathy, severe renal dysfunction, instable heart or respiratory disease	NA Medical record	No difference in DR prevalence between mild, moderate, severe OSA patients and non OSA patients
Mason et al., 2012 [98]	Prospective study 80 type 2 diabetes patients DME (diagnosis by OCT) 1 laser treatment or more	OSA: overnight home polygraphy Non OSA: AHI (events/h) < 5 Mild OSA: 5 ≤ AHI < 15 Moderate OSA: 15 ≤ AHI < 30 Severe OSA: AHI ≥30	Known central apnea or OSA, heart failure, severe pulmonary disease	Ocular fundus photography Central macular thickness measurement (OCT)	High OSA prevalence in patients with DME: 54% with ODI 4% ≥10 and 31% with AHI ≥15 No relationship between macular retinal thickness and OSA characteristics (in particular time spent

					at $SaO_2 < 90\%$)
Furukawa et al., 2013 [99]	Prospective study 219 type 2 diabetes patients Logistic multivariate regression	OSA: pulse oxymetry ODI 3% > 5 events/h	NA	Ocular fundus exam and photography + fluorescence angiography	No differences in DR features between OSA and non OSA groups No association between nocturnal IH and neuropathy or DR presence
Banerjee et al., 2013 [100]	Cohort study 93 type 2 diabetes patients Logistic multivariate regression	OSA: overnight home polygraphy Non OSA: AHI (events/h) < 15 OSA: AHI ≥15 Diabetes: NA	NA	English National Screening Program for Diabetic retinopathy	No significant differences in OSA presence/absence in patients with DR and DME No association between DR or DME and AHI, mean SaO_2 and time spent at $SaO_2 < 90\%$ Minimal SaO_2 is a predictive factor for DME (OR = 0.79; 95% CI 0.65–0.95)

Abbreviations: AHI, apnea-hypopnea index (in events/h); CI, confidence interval; DME, diabetic macular edema; DR, diabetic retinopathy; HbA1c, glycated haemoglobin; IH, intermittent hypoxia; NA, non available; NPDR, nonproliferative diabetic retinopathy; O_2, oxygen; OCT, optical coherence tomography; ODI, oxygen desaturation index (in events/h); OR, odds ratio; OSA, obstructive sleep apnea syndrome; PDR, proliferative diabetic retinopathy; SaO_2, arterial oxygen saturation; SpO_2, pulsed oxygen saturation.

patients and 339 control subjects matched for age and gender [114], snoring (34.5%) and disturbed sleep were more often reported in CSCR patients. Nevertheless, using questionnaires to assess the risk of OSA remains a significant limitation in these studies.

Polysomnography screening was carried out in 14 of 36 CSCR patients [115] who had obtained an Epworth sleepiness scale score greater than 10. Finally, the diagnosis of OSA was made for eight patients (8/36), assessing the prevalence of OSA at 22%. This prevalence is close to the 17% prevalence in 50- to 70-year-old men [116]. In another study, the prevalence of OSA evaluated by polysomnography was 60% in a group of 23 CSCR patients [117]. However, other risk factors for CSCR were not reported in these patients. Larger-scale studies are therefore necessary to confirm these preliminary results.

Retinal vascular alterations in OSA patients

Anatomic alterations

Analysis of color retinal photographs in sleep apnea patients participating in the Wisconsin sleep cohort study [118] showed a positive association between the AHI and the diameter of the retinal veins (OR = 1.28; 95% CI: 1.07–1.53), independently of the effect attributed to age, gender, body mass index, diabetes, hypertension, and the lipid level in blood. The AHI (events/h) was not associated with arteriolar narrowing.

Prospective analysis of the fundus photographs of 215 sleep apnea patients showed that severe OSA (AHI ≥20 events/h) was associated with retinal arteriolar alterations (arteriolar narrowing, arteriolar sclerosis and arteriovenous nicking; OR = 1.09 for an increase of 5 AHI units), contrary to mild OSA (AHI <5 events/h) [81].

A third study did not show a significant association between retinal microvascular alterations (arteriole-to-venule ratio) and nocturnal respiratory disturbances after adjustment for age, body mass index, hypertension, and diabetes [119]. However, the arteriole-to-venule ratio can be unaltered in presence of dilation or contriction of both arteries and veins.

Blood flow modifications

Several studies have described vascular regulation and ocular blood flow in sleep apnea patients, notably in the retrobulbar vessels (the ophthalmic artery (OA), posterior ciliary arteries (PCAs), central retinal artery (CRA)) and the choroidal vessels.

Compared to the control group, a significant increase in the peak systolic velocity and the end-diastolic velocity was shown in the OA, CRA, and the lateral and medial PCAs in patients with severe OSA (AHI >20 events/h) [120]. In the same way, the velocities in the OA and the medial and lateral PCAs of severe apnea patients were significantly higher than in moderate OSA patients. On the other hand, the resistance index was not modified. In agreement with these data, another study did not demonstrate a modification of the resistance index in the OA and CRA between the sleep apnea group and the control group [49]. It is possible that small-caliber vessels are affected earlier by variations in CO_2 related to apneas [120].

Assessing the regulation of choroidal blood flow is an opportunity to study the regulation of a microvascular bed since the choroid, contrary to the vessels of the retina and the optic nerve head, is controlled by the autonomic nervous system. We have shown that sleep apnea patients with no cardiovascular comorbidities presented a normal response of choroidal blood flow to hypercapnia, hyperoxia [121], postural change, and isometric exercise (increase in OPP) [122], which did not differ from the response observed in the control group. These results suggest that in absence of cardiovascular comorbidities, the choroid is not

sensitive to IH. These results agree with a study using the pulsatile ocular blood flow technique [50].

Conclusion

OSA is a frequent disease, affecting 18% of the population over 50 y of age. OSA contributes to the appearance of hypertension, atherosclerosis, autonomic dysfunction, endothelial dysfunction, systemic inflammation, and metabolic modifications (notably insulin resistance), which may interact with the vascular regulation of the eye.

The strong relation between OSA and NAION is now well documented. Many questions persist nonetheless concerning the mechanisms involved in the appearance of this neuropathy and how OSA contributes to it. The role of CPAP in the progression of the disease remains much debated and large-scale studies are necessary to evaluate this question. The relation between OSA and other optical neuropathies (glaucoma, papilledema) has not been clearly defined to date. The impact of OSA on RNFL strongly suggests that physiopathological factors involved in OSA have an impact on retinal ganglion cells. Many studies suggest that the supervision of retinopathy should be cautiously considered in diabetic OSA patients.

Conflicts of interest

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2017.05.003

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