

## REVIEW ARTICLE

# Obstructive Sleep Apnea and Ophthalmic Disorders-Clinical Implications

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## Abstract

Sleep is essential for physical, mental and emotional well being. Body systems require sleep of good quality and quantity for their proper functioning. There are several sleep disorders. Obstructive sleep apnea hypopnea syndrome (OSAHS) is one of the most important disorders identified in the last 50 years. The disorder has systemic ill effects by virtue of cyclical hypoxia and sympathetic stimulation. It is a risk factor for the development of hypertension, ischemic heart disease, type 2 diabetes mellitus, stroke and dementia. Retina being the highest oxygen consuming part of the body, is particularly vulnerable to the effects of hypoxia. Several eye disorders have been identified to be associated with OSAHS. In clinical practice Identifying and treating sleep disorders have been rewarding.

Literature search done via [www.google.com](http://www.google.com).

## Introduction

Sleep is a basic biologic function and is essential for life. It is an active state that is critical for our physical, mental and emotional well being. The normal duration of adult sleep varies between 5-9 hours with an average of 7 hours. Sleep is not a protected state. Sleep disorders have the capacity induce stress in body systems and repeated nocturnal insults can therefore generate disorders eg. cardiometabolic disorders. There are nearly 88 disorders of sleep. Sleep disordered breathing (SDB) is one of the most common disorders of sleep. It encompasses a spectrum of disorders viz snoring, upper airway resistance syndrome, obstructive sleep apnea-hypopnea syndrome (OSAHS). OSAHS is one of the most important disorder identified in the last 50 years and has a high prevalence. It has deleterious systemic consequences like hypertension, diabetes, ischemic heart disease, stroke and dementia. Repetitive pharyngeal collapse and cyclical nocturnal hypoxemia are the hallmarks of OSAHS. Retina is the highest oxygen consuming part of the body and is therefore liable to get affected adversely by nocturnal events in patients with OSAHS. Also patients of non-arteritic anterior ischemic optic

neuropathy and retinal detachment often report visual loss on awakening from sleep.

## Sleep Disordered Breathing (SDB)

SDB basically means disordered breathing in sleep. SDB can be observed in any age and its prevalence increases with age.<sup>[1,2]</sup> In elderly subjects polysomnography shows predominance of obstructive events over central or mixed events. Therefore several elderly subjects suffer from OSAHS. It must also be remembered that there is also increased prevalence of hypertension, diabetes, several retinal diseases with advancing age. In India Udawadia et al<sup>[3]</sup> reported habitual snoring in 26 % of the study population (middle aged urban Indian men) and the estimated prevalence of SDB was 19.5% and that of OSAHS (SDB with daytime hypersomnolence) was 7.5%. In our study snoring in elderly was found to be 69.5%.<sup>[4]</sup> With advancing age there is reduction of lean tissue and increase in fat content. Central

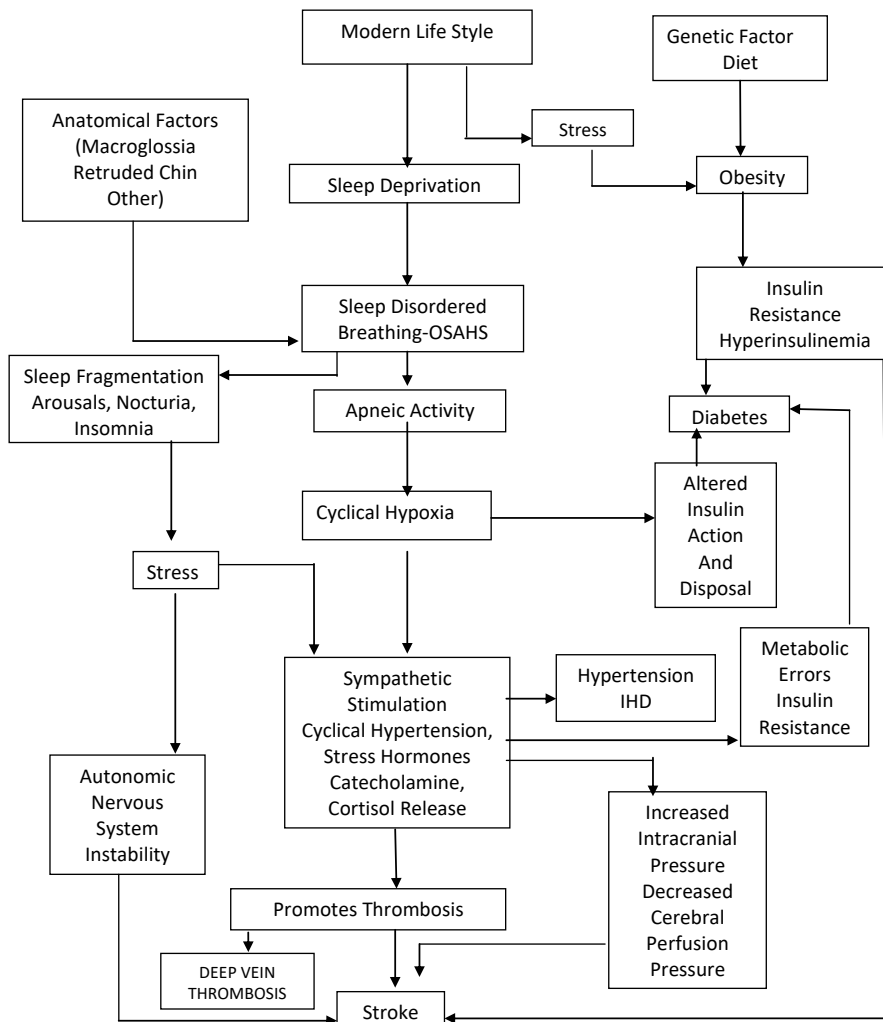
obesity is a common feature of ageing process. The fat of this central obesity is also metabolically active. It is also observed that blood glucose increases as age advances.<sup>5</sup> People over the age of 65 years constitute more than 40% of cases of diagnosed diabetes.<sup>6</sup>

## Obstructive Sleep Apnea Hypopnea Syndrome and its Consequences

In OSAHS there is repetitive pharyngeal collapse in sleep resulting in cyclical hypoxemia, cyclical hypertension and release of stress hormones and catecholamines. Habitual snoring and excessive daytime sleepiness are two prominent symptoms of OSAHS. Snoring in society is a common occurrence and is generally perceived as a sign of sound sleep. Snoring is usually evident when a group of subjects sleep together as in sleeper coaches of railway trains.

The other nocturnal symptoms include witnessed apneas, choking, dyspnea, restlessness, diaphoresis, acid reflux, drooling, somniloquy, frequent changes of posture in sleep, unable to sleep supine and bruxism. The daytime symptoms apart from sleepiness include fatigue, morning headache, poor concentration, decrease libido or impotence, decreased attention, depression, decreased dexterity and personality changes-mood swings and angry behavior. In OSAHS there is intermittent hypoxia, recurrent arousals from sleep and sleep fragmentation causing sympathetic stimulation. Sympathetic stimulation results in the release of stress hormones and catecholamines. Both these effects are known to decrease insulin sensitivity

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**Fig. 1: Highlighting the path taken by nocturnal events in sleep disordered breathing OSAHS culminating in stroke, cardiovascular and metabolic consequences<sup>16</sup>**

and worsen glucose tolerance. OSAHS conduces to myocardial ischemia and arrhythmias,<sup>7</sup> hypertension,<sup>8</sup> myocardial infarction,<sup>9</sup> increased severity of congestive heart failure<sup>10</sup> and cardiac death.<sup>11</sup> Habitual snoring predicts the onset of diabetes.<sup>12,13</sup> It must be appreciated that OSAHS is a risk factor for the development of diabetes and this has been reviewed recently.<sup>14</sup> OSAHS is a hypercoagulable state and can induce thrombosis in various sites of the vascular system. OSAHS is also a risk factor for stroke.<sup>15</sup> This association has been recently reviewed<sup>16</sup> (Figure 1). Sleep disordered breathing in pregnancy may have adverse effects on the mother and fetus (pregnancy induced hypertension and small for gestational age birth).<sup>17</sup> Approximately 28% of children born in India are of low birth weight and low birth weight is associated with elevated levels of glucocorticoids in later life<sup>18</sup>

(a story from womb to the tomb).

OSAHS can affect all age groups. Subjects with obesity, short neck, retruded chin, neck circumference  $\geq 43$  cms, macroglossia (both relative and absolute), narrow mandible, narrow maxilla are prone to develop OSAHS. Owing to anatomical reasons OSAHS can be seen in non-obese subjects also. Males are usually more affected than females but there is increased prevalence in post menopausal women. Polysomnography is essential to diagnose OSAHS.

Management of OSAHS chiefly rests on achieving optimal body weight and usage of Continuous Positive Airway Pressure (CPAP). CPAP is an established mode of treatment for OSAHS. This device has several systemic benefits. Several studies have documented improvement of insulin sensitivity also.<sup>19-21</sup> This has important

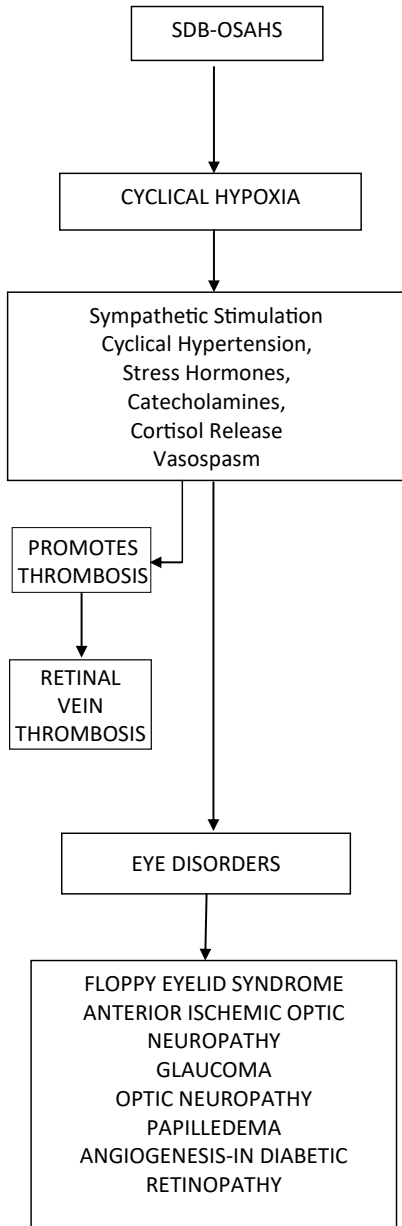
clinical implications. Insulin resistance is the core issue in type 2 diabetes mellitus.

## Retina, Oxygen and Sleep

Oxygen is essential for retinal function. It is known that retina has 2 domains - avascular retina and inner vascular retina. The retina is the most metabolically active tissues consuming oxygen more rapidly than many other tissues including brain. The difficulty of measuring oxygen intraretinally in humans or animal models of human diseases has prevented a more complete understanding of the role of oxygen in retinal diseases. It is known that inner and outer halves of retina are different domains in terms of oxygen and this has important therapeutic implications. Inner retinal PO<sub>2</sub> averages about 20 mm Hg and this dependent on an effective autoregulation of the retinal circulation. This mechanism protects it from effects of systemic hypoxia, hyperoxia and increased intraocular pressure in healthy animals. Failure of retinal circulation results in tissue hypoxia. This hypoxia underlies the vasoproliferation in diabetic retinopathy and retinopathy of prematurity. On the other hand, choroidal blood flow is not regulated metabolically so systemic hypoxia and elevated intraocular pressure lead to decreases in choroidal pO<sub>2</sub> and photoreceptor oxygen consumption. However this lack of regulation allows choroidal pO<sub>2</sub> to increase dramatically during hyperoxia. This phenomenon offers a chance to use oxygen therapeutically in retinal vascular diseases and retinal detachment.

## Linkages of SDB-OSAHS with Retina and Diabetic Retinopathy

The first author had proposed for the first time in 2003 that cyclical hypoxia of OSAHS can have deleterious effects on the retina.<sup>15</sup> Diabetic retinopathy is a known complication of diabetes mellitus. Cyclical hypoxia of OSAHS can stimulate angiogenesis in retina leading to progressive diabetic retinopathy.<sup>15</sup> Recently McNabb<sup>22</sup> has reported association of obstructive sleep apnea with several eye disorders, viz. floppy eyelid syndrome, anterior ischemic optic neuropathy, optic neuropathy,



**Fig. 2: Depicting the possible eye consequences of sleep disordered breathing-OSAHS**

glaucoma, papilloedema secondary to raised intracranial pressure (Figure 2).

Diabetic retinopathy is a disease predominantly of retinal vasculature. Initially there is capillary occlusion and then to vascular proliferation. Animal experiments have demonstrated that retina is hypoxic early in the disease. For many years tissue hypoxia has been suggested to be involved in the progression of diabetic retinopathy<sup>[23]</sup> and retinal neovascularization in general.<sup>[24]</sup> In fact there is a difference in the intensity of insult to body tissues due to continuous low grade hypoxia and cyclical hypoxia. Sympathetic

stimulation due to cyclical hypoxia is core feature of OSAHS, resulting in fluctuating blood pressure, insulin resistance and cardiovascular effects. Therefore retina suffers in cyclical hypoxia by dual mechanism-direct and via sympathetic system activation. Further sleep complaints are common in diabetic subjects. Gislason et al<sup>25</sup> reported that diabetes was associated with near frequent complaints of difficulty in initiating sleep (21.1%), difficulty in maintaining sleep (21.9%) and excessive daytime sleepiness (12.2%). The relation of type 2 diabetes mellitus and sleep has been reviewed recently.<sup>14</sup> Also there are several similarities between type 2 diabetes mellitus and obstructive sleep apnea.<sup>14</sup>

It is difficult to explain why the retina microvasculature is affected more than the brain in patients of diabetes. Arden et al<sup>26</sup> suggested that dark adaption aggravates hypoxia by depriving the inner retina of the small amount of oxygen that diffuses from the choroid during light adaption. Avoiding a long period of dark adaptation eg. sleeping during night could be a alternative therapy of diabetic retinopathy. However this is not practically useful. It must be remembered that it is the quality of sleep which is more important than quantity in terms of reference of hypoxia to retina. Hypoxia may induce the synthesis of Vascular Endothelial Growth Factor (VEGF). Also the concentration of VEGF is higher in proliferative diabetic retinopathy. It is known that no treatment stops retinopathy apart from panretinal photocoagulation. If early circulatory retinal changes preceding VEGF up regulation could be detected clinically, then interfering with leucocyte adhesion or using other pharmacological techniques to increase retinal blood flow might be effective. It must be remembered that treatment of SDB-OSAHS is highly rewarding.<sup>14</sup> Correction of hypoxia in sleep is expected to give favourable results in patients with diabetic retinopathy.

Meritt et al<sup>27</sup> conducted a limited channel sleep study on 44 adults with type 2 diabetes mellitus suffering from diabetic retinopathy. They stated that, the extra burden of hypoxia to an already ischemic retina along with recurrent activation of sympathetic nervous system and fluctuating blood pressure could play as contributory

factors. They concluded that SDB may play an aetiological role in the development and/or progression of diabetic retinopathy. Shiba T et al<sup>28</sup> in a study concluded that diabetic retinopathy patients with nocturnal desaturation, reoxygenation caused by SDB may relate to the development of progressive diabetic retinopathy. Mason RH et al<sup>29</sup> observed that individuals with clinically significant macular edema have high prevalence of SDB. Further, Mason RH et al<sup>30</sup> assessed whether treatment of obstructive sleep apnea (OSA) with CPAP will improve visual acuity in patients clinically significant macular oedema (CSMO). They concluded that usage of CPAP  $\geq$  2.5hr/night over six months in individuals with CSMO and OSA may be associated with improvement in visual acuity.

Based on these observations it therefore becomes imperative to screen patients of diabetes for SDB.

## Retinal Detachment

Retinal and vitreous degeneration are precursors to retinal detachment. OSAHS can be present since childhood due to anatomical factors like macroglossia, retruded chin etc. Snoring may not severe since subjects often sleep prone to enlarge the airway. Daytime sleepiness may be replaced by hyperactivity in children. OSAHS by virtue of effects viz hypoxia and oxidative stress can cause degenerations in retina paving the path for retinal holes and retinal detachment in adult life. The oxidative stress aggravates aging process. It is a matter of coincidence that patients of retinal detachment who are injected with silicone oil in the posterior chamber are advised to sleep prone to produce desired results. Recently Linsenmeier et al<sup>31</sup> have suggested that hyperoxia may be useful in preventing photoreceptor damage in patients with retinal detachment.

## Glaucoma

Glaucoma is a slowly progressive, insidious optic neuropathy. It is usually associated with chronic elevation of intraocular pressure. The mechanism by which raised intraocular pressure injures the optic nerve is not known. Recent evidence indicates reduced ocular blood flow and by implication reduced oxygen is contributing factor

in retinal damage.<sup>32,33</sup> Studies have shown that retinal oxygenation can be partially or completely restored during arterial occlusion by making animals hyperoxic<sup>34,35,36</sup> OSAHS has been found to be associated with glaucoma.<sup>22</sup> Margherita et al<sup>37</sup> have reported that the prevalence of normal tension glaucoma (NTG) in OSAHS patients is higher than expected in a white population of the same age and that OSAHS may be an important risk factor of NTG. Mojon et al<sup>38</sup> have reported high prevalence of glaucoma in patients with sleep apnea syndrome. As discussed above, these observations should compel the ophthalmologist to rule out OSAHS in patients with glaucoma. CPAP usage must be done under ophthalmological monitoring since CPAP can raise intraocular pressure.

### Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)

Non-Arteritic Anterior Ischemic Optic Neuropathy is a disease characterized by sudden painless mostly irreversible and generally non-progressive visual loss accompanied by nerve fibre bundle field defects, a relative afferent papillary defect and optic disc oedema. NAION by definition involves 1 mm segment of optic nerve head and results in visible disc swelling. The pathophysiological aspects of NAION remain unclear. Vast majority of the cases of NAION are idiopathic but some specific etiologies have been reported. The risk factors include i) aging ii) small optic nerve head iii) neurovascular changes associated with hypertension and diabetes. Many patients notice the symptoms of NAION early morning. Hayreh et al<sup>39</sup> observed in a prospective study that in at least 399 (73.3%) of 544 episodes of NAION patients discovered visual loss upon first awakening or at first opportunity to use vision critically after sleeping suggesting that nocturnal arterial hypertension may play an important role. Mojon et al<sup>40</sup> state that it is unclear as to how sleep apnea syndrome can cause NAION. However it is hypothesized that apneic spells of OSAHS might result in acute increases in blood pressure, intracranial pressure or nocturnal hypoxemia which could cause optic nerve oedema and ischemia. It must also be noted that systemic hypertension, arteriosclerosis,

vasospasm or medications may reduce the autoregulatory capacity of the optic disc.<sup>141</sup> Exaggerated decreases in nocturnal blood pressure eg. by aggressive antihypertensive therapy especially if drugs are taken late at night might also contribute to the development of NAION.<sup>42</sup> It must be remembered that OSAHS is a risk factor for both Type 2 diabetes and hypertension and OSAHS itself has been associated with NAION.<sup>22</sup> There have been case series that have demonstrated a possible association between sleep apnea syndrome and NAION.<sup>40</sup>

### Floppy Eyelid Syndrome (FES)

Floppy eyelid syndrome is characterized by the presence of an easily everted upper eyelid associated with keratoconjunctivitis.<sup>43</sup> Patients of FES are usually overweight and has been associated with obstructive sleep apnea. Patients usually have loose rubbery tarsus, spontaneous eyelid eversion, loss of lid to globe contact at night, chronic papillary conjunctivitis, meibobian gland dysfunction and loose and easily everted upper lids. Patients of OSAHS may also visit the ophthalmologist with complaints of unrefreshed feeling with heaviness and burning in eyes. Woog JJ reported 3 cases of obstructive sleep apnea with FES.<sup>44</sup> Recognition of OSAHS in patients with FES is important since management of OSAHS is highly rewarding not only for ophthalmic complaints but also for systemic well being.

### Papilledema

Association of sleep apnea syndrome and papilledema has been recognized. Purvin et al<sup>45</sup> have reported 4 cases of disc edema and sleep apnea syndrome. Owing to episodic nocturnal hypoxia and hypercarbia in OSA there is increased intracranial pressure secondary to cerebral vasodilation. Sustained raised intracranial pressure (ICP) causes papilledema due to obstruction of retrograde axonal transport at the level of optic disc. Continuous intracranial pressure monitoring has shown that although the daytime measurements of CSF pressure are within normal range, marked episodic nocturnal increases of ICP occur in patients with sleep

apnea syndrome. The rise in pressures range between 50-750 mm of H<sub>2</sub>O.<sup>46</sup> This can lead to persistent disc edema. Also these patients are at risk for visual loss secondary to papilledema (PE). Visual field defects can also occur. The diagnosis of OSAHS in PE may not be appreciated because daytime cerebrospinal pressure measurements are normal. Also patients tend to present with visual loss rather than with symptoms of increased intracranial pressure. Pseudotumor cerebri (PTC) is a syndrome of elevated ICP with a variety of causes including chronic obstructive pulmonary disease (COPD). Patients with underlying cause of COPD have persistently raised ICP as compared to patients with OSAHS. Also COPD can coexist with OSAHS (overlap syndrome). Therefore patients of PTC should be screened for OSAHS.

### Suggested Hypothesis

Based on the various facts stated above it is compelling to suggest that OSAHS should also be suspected in patients with age related macular degeneration, macular edema and vascular disorders of retina like branched retinal vein occlusion and retinal vein thrombosis.

### Conclusions

Sleep disorders have the potential to disturb body systems. OSAHS is a systemic disease. There is a close association of OSAHS with various retinal and visual tract diseases. Suspecting and treating OSAHS in a given patient is expected to give favourable results.

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