

# Eye Disorders Associated with Obstructive Sleep Apnoea

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## **Abstract**

Obstructive Sleep Apnoea (OSA) is increasing in prevalence due to rising obesity. Public awareness is also growing. Whilst OSA is a disorder primarily of the upper airway during sleep, its physiological impact on other parts of the body is now well recognised. There is increasing interest in the association of OSA with various eye disorders. Work in this field has been directed predominantly to OSA prevalence and association studies, but some authors have tried to elucidate the effect of OSA therapies on eye diseases, including continuous positive airway pressure, upper airway surgery or bariatric surgery. The purpose of this review is to discuss the publications in this area from the past year. The key ocular disorders featured include: glaucoma, floppy eyelid syndrome, nonarteritic ischaemic optic neuropathy, keratoconus, age-related macular degeneration and diabetic retinopathy. The published studies will be discussed and the remaining gaps in our knowledge and thus the direction of future research highlighted.

## **Introduction**

Obstructive Sleep Apnoea (OSA) continues to rise in prevalence due to obesity levels<sup>1</sup>. Increasing public and health care provider awareness of the disease has led to increasing numbers of people presenting to sleep clinics; symptoms typically include snoring, witnessed apnoeas, unrefreshing sleep and daytime somnolence. The cyclical desaturations, intermittent hypoxia, arousals and catecholamine surges of OSA have been well studied<sup>2</sup>. These pathophysiological features affect more than the sleep-wake cycle; impacts on hypertension, atherosclerosis, endothelial dysfunction, insulin resistance and autonomic

dysfunction have been found<sup>3,4</sup>. There is clear potential for OSA to cause or worsen ocular disease through these mechanisms and interest in this area is increasing.

Hypertension is the most robustly proven disease to be caused by OSA. Associations with OSA were found in epidemiological studies<sup>5</sup>, but confounders for both include male gender, weight, upper body obesity, type 2 diabetes. Randomised controlled trials of continuous positive airway pressure (CPAP) therapy established OSA as a cause of hypertension and meta-analyses of these trials have now been published<sup>6,7</sup>. There is interest in determining the association of OSA with eye disorders. We need well-matched control groups and robust randomised controlled trials to allow conclusions about possible associations; this is often not the case, but these studies can be regarded as hypothesis (and interest) generating. This review looks at work published in the last year, including meta-analyses, aiming to elucidate the associations between OSA and ocular disease.

## **Glaucoma**

Glaucoma is an optic neuropathy associated with damage to the head of the optic nerve, causing visual field disturbances. Glaucoma can be associated with increased intraocular pressure (IOP) or normal or reduced IOP (normal tension glaucoma). Previous studies of associations of OSA with glaucoma have shown variable results. A “vascular theory” suggests intermittent hypoxia affects the optic nerve, leading to optic neuropathy; a “mechanical theory” suggests OSA increases IOP through changes in sleep architecture and increased sympathetic tone, with raised IOP causing optic nerve damage. Inflammation, oxidative stress and hypercapnia are also implicated. Shi sought to further evaluate the

association between OSA and glaucoma with a meta-analysis of 16 studies with a massive 2, 278 832 individuals<sup>8</sup>. Glaucoma was diagnosed either by systematic eye examinations or by database or billing records, the latter two clearly being less robust. OSA was diagnosed mostly by polysomnography or overnight oximetry; one study used an unspecified questionnaire and some used database or billing records. Only four of the studies reported their results after adjusting for confounding factors. Using a fixed effects model, the pooled odds ratio (OR) of six case control studies was 1.96, 95% CI=1.37-2.8,  $p=0.0002$ . The meta-analysis of nine cross-sectional studies using a random effects model showed a pooled OR of 1.41, 95% CI= 1.11-1.79,  $p=0.006$ , but both results were based on unadjusted ORs (figure 1). There is a suggestion therefore of an association of OSA with the prevalence of glaucoma, but the authors express concerns about possible confounders and highlight causation cannot be confirmed. They state OSA could be a marker of poor vascular health and obesity, not necessarily an independent risk factor for glaucoma.

Another meta-analysis of 12 international studies of 36909 subjects found similar results, with OSA being associated with a significantly increased risk of glaucoma, OR 1.65; 95%CI 1.44-1.88,  $p<0.00001$ <sup>9</sup>. Asians and Caucasians had significantly increased glaucoma risk (OR 1.78; 95%CI 1.49-2.12,  $p<0.00001$  and 2.03; 95%CI 1.12-3.69,  $p=0.02$  respectively), along with women and men (OR 1.81; 95%CI 1.27-2.57,  $p=0.001$  and 1.62; 95%CI 1.29-2.03,  $p<0.00001$  respectively). In sub-group analysis, OSA patients showed increased primary open-angle glaucoma risk (OR 1.87; 95%CI 1.54-2.33,  $p<0.00001$ ) but not normal tension glaucoma risk (OR 3.57; 95%CI 0.89-14.43,  $p=0.07$ ). The authors comment the numbers were small for normal tension glaucoma studies and these results may lack validity. Patients

with severe OSA had an increased glaucoma risk (OR 5.49; 95%CI 1.04-33.83,  $p=0.04$ ), whilst those with mild and moderate OSA did not have increased glaucoma risk. From these two studies we can conclude there seems to be an association of OSA with glaucoma, and certainly Eye Hospitals would be well advised to consider OSA in their glaucoma patients.

### **CPAP and glaucoma**

Ulusoy et al<sup>10</sup> investigated the effect of using CPAP in patients with glaucoma. Consecutive patients with severe OSAS and 36 healthy controls with no OSA confirmed on polysomnography were studied with full ocular examination. The OSA group was divided into 38 who used CPAP and 32 who did not. There was no assessment of baseline pre-CPAP ocular values and the patients were not randomised to CPAP but elected to have it or not. All three groups were similar in terms of BMI and neck circumference. The apnoea-hypopnoea index (AHI) was comparable in the CPAP and no CPAP groups (mean AHI  $62.9 \pm 27.0$  vs.  $55.6 \pm 27.3$ /hour). IOP was significantly higher in the no CPAP group ( $16.7 \pm 3.1$  mmHg) than CPAP group ( $15.1 \pm 3.5$  mmHg) or control group ( $14.1 \pm 2.4$ ),  $p < 0.001$  (figure 2). Glaucoma prevalence was cited as 12.5% in the no CPAP group, 5.2% in the CPAP group and 0% in the control group. There are several issues with this study. There is no description of where the patients and controls were recruited from, and no comment on comorbid and potentially confounding disease. The control population was not matched in any way. There were meaningful differences in age (No CPAP 53.4 years, CPAP 49.1 years, Control 46.8 years) and percentage females (No CPAP 21.9%, CPAP 18.4% and Control 41.7%), even if these did not quite reach statistical significance ( $p=0.05$  and  $0.06$  respectively), which could affect the results. There were no baseline ocular measures before

CPAP. Subjects were not randomised to CPAP, but selected whether or not to use it. This may have reflected their other health usage behaviours, with CPAP users perhaps being less likely to smoke, more likely to take other medicines, and so on. None of this data is available, nor is it discussed. Although the study suggests CPAP can prevent development of glaucoma complications and this may be true, this study's weaknesses limit the conclusions that can be reached.

### **Floppy Eyelid Syndrome (FES)**

Floppy eyelid syndrome (FES) is characterised by easily turning and floppy eyelids, papillary conjunctivitis and corneal epithelial erosions. Associations with OSA have previously been shown, along with obesity, diabetes, hypertension and ischaemic heart disease. Anecdotally, FES patients in particular seem to be screened for OSA symptoms in the Eye Clinic and referred to the Sleep clinic.

Bayir sought to evaluate a surgical treatment for OSA, anterior palatoplasty, on FES patients with OSA<sup>11</sup>. Sixty two sleep clinic patients found to have mild or moderate OSA (AHI 5-15 or 16-30 per hour respectively) were recruited and screened for FES. Patients with previous eye surgery or with local anticholinergic therapy for eye examination in the preceding week were excluded. Patients could choose whether they had surgical treatment for OSA (n=35) and if they did not opt for this, they formed the control group (n=27). They were therefore not randomised, although the two groups appear to be well matched. Ophthalmic examinations were performed before polysomnography to look for FES, defined as whether

an upper eyelid could easily turn on itself while the patient looked downward, as well as when the eyelid skin was pulled upward. These examinations were repeated three months following palatal surgery. Polysomnography was repeated in the surgical group but not in the control group. Surgical success was defined as a fall in AHI of 50% or greater. At baseline, 60% of patients in the surgical group were diagnosed with FES and 56% in the control group. This percentage fell to 26% in the surgical group post-operatively. Surgery is said to have been successful in 57% of patients; the proportion of people with FES fell from 60% to 10%,  $p=0.02$ . The authors postulate that the correction of tissue hypoxia may be responsible for the improvement in FES. Again, patients were not randomised to their treatment arm, which introduces a selection bias. There are no comments on weight loss in either group, which would profoundly affect the severity of OSA. The success rate of the surgery on AHI seems very high and not in keeping with other literature on surgical therapies in OSA, which are generally not recommended as a single treatment<sup>12</sup>. Also there is no repeat three month polysomnogram in the control group, who may have lost weight or changed sleeping position after OSA diagnosis (having opted not to have palatal surgery) or whose sleep indices may have shown regression to the mean and improved. The improvements in FES seem impressive, but the initial prevalence is high and the total numbers of patients are small; the authors conclude larger studies are warranted.

### **Nonarteritic anterior ischaemic optic neuropathy (NAION)**

Nonarteritic anterior ischaemic optic neuropathy (NAION) is an acute optic neuropathy, characterised by sudden and painless unilateral visual loss, altitudinal visual field defects and optic disc swelling. A multifactorial cause is postulated, with vascular dysfunction,

crowded optic nerve, hypertension, hypercholesterolaemia and diabetes associated. OSA is also considered a potential risk factor, not least because many people discover this visual defect on waking. Wu et al performed a systematic review and meta-analysis to investigate the association between OSA and NAION<sup>13</sup>. They identified four prospective cohort studies and one case control study. The studies ranged in size from 17 to 73 in each group. OSA was diagnosed by sleep studies in four studies and Sleep Disorders Questionnaire in one. The pooled OR of developing NAION in subjects with OSA was 6.18, 95% CI 2-19.11 versus non-OSA controls,  $p=0.002$ . Sensitivity analyses showed the association between risk of NAION and OSA remained statistically significant no matter which study was excluded. Potential confounders were not adjusted for in all the studies, which may have affected the results.

Aptel published a cohort study looking at 89 patients diagnosed with NAION, who underwent polysomnography; 85 were followed for three years<sup>14</sup>. Of these patients, 75% had OSA at diagnosis; they were more likely to develop NAION in their other eye (15.4% vs. 9.5%, 95%CI 0.2% to 11.5%,  $p=0.04$ ). Patients with severe OSA who were non-adherent with CPAP therapy were at increased risk of developing involvement in the second eye when compared with those with no OSA or moderate OSA not requiring CPAP (HR 5.54, 95%CI 1.13 to 27.11,  $p=0.04$ ). This data once again shows the frequent coexistence of OSA and NAION and suggests OSA may be a risk factor for developing disease in the other eye in those already affected. The authors acknowledge that the group who are non-adherent with CPAP could be biased towards being non-compliant with other therapies.



## **Keratoconus**

Keratoconus is a chronic bilateral noninflammatory ectatic disorder of the cornea, with progressive frontal protrusion and thinning of the cornea. The role of hypoxia and reperfusion injury has been questioned in its development; hence the role of OSA in possible causation has been questioned. In this prospective case control study, 616 patients diagnosed with keratoconus were enrolled, along with 616 age, gender and BMI matched controls attending the cornea clinic for refractive errors, with no suspicion of keratoconus<sup>15</sup>. The mean BMI of the keratoconus group 24.4 kg/m<sup>2</sup> and mean age was 25.3 years. Patients had telephone interviews which included the Berlin questionnaire, a tool for assessing high or low risk of OSA, but no sleep studies. This tool does not allow any severity stratification of OSA and was originally reported to have a sensitivity of 86% and specificity of 77% for OSA diagnosis, but others have not obtained such results<sup>16,17</sup>. The keratoconus group had a significantly higher history of previously diagnosed OSA, 2.9% vs. 0.6%,  $p=0.004$  and were at higher risk of developing OSA, 12.3% vs. 6.5%,  $p=0.001$ . Those patients at high risk of OSA had more severe keratoconus than those at low risk of OSA,  $p<0.05$ . Unsurprisingly, higher BMI was an independent risk factor for increased Berlin score defined risk of OSA in patients with keratoconus in multivariate logistic regression, as was family history of OSA. In the control group, surprisingly only female gender was associated with a higher Berlin score defined risk of OSA. The number of patients with high risk of sleep apnoea in the control arm were relatively low ( $n=40$ ), OSA was not confirmed by sleep studies and in other prevalence studies, male gender has been found to be a risk factor for OSA<sup>18</sup>. This study raises interesting questions about associations between keratoconus and OSA and

hypothesises about related causes of both. Certainly the study makes a case for more research in this field, using sleep studies to stratify OSA severity.

### **Age related macular degeneration**

Age related macular degeneration (AMD) is one of the leading causes of blindness in the Western world. Anti-vascular endothelial growth factor injections (VEGF) are a common treatment for the exudative subtype of AMD, although non-response to therapy is common. A small study showed a better response to anti-VEGF treatment in patients with known OSA who used CPAP therapy compared with OSA patients who were non-compliant, with improved visual acuity, reduced central retinal thickness and fewer injections required <sup>19</sup>. However, the authors do not report whether there were between group differences in important confounders such as age, smoking or cardiovascular disease, or whether there were baseline differences in OSA severity. Furthermore, again with a non-randomised design there is a potential bias in comparing patients who accept and do not accept CPAP.

### **Diabetic retinopathy**

Diabetic retinopathy (DR) can be non-proliferative with dilated retinal veins and microaneurysms causing haemorrhage or oedema, or proliferative (PDR) with new vessels forming near the optic disc. OSA may make retinopathy worse through intermittent hypoxia, hypertension, sympathetic activation and insulin resistance. It is known that the retina is very vulnerable to hypoxia. Zhang explored the influence of OSA on diabetic complications in 880 hospitalised Chinese patients with type 2 diabetes across 12 hospitals in China<sup>20</sup>. Sixty

percent of the cohort was found to have OSA on sleep recordings, 30% had DR and 4% had PDR. There was no significant difference in the severity of OSA between those with and without DR or PDR in multivariate logistic regression, although the lowest oxygen saturation percentage in patients with PDR was lower than in those without PDR,  $p=0.04$ , in univariate analysis. The authors wondered whether the lowest oxygen saturation percentage was a more sensitive parameter than others, including AHI, as it was also independently associated with diabetic nephropathy and estimated Glomerular Filtration Rate (eGFR) in this study. They concluded they could not determine a causal relationship between diabetic complications and OSA.

Leong performed a systematic review and meta-analysis of the effect of OSA on diabetic retinopathy and maculopathy<sup>21</sup>. In the systematic review, they included 16 studies, one was longitudinal, the rest cross-sectional. Three studies were included in the meta-analysis. There were a total of 2731 participants, 2636 with type 2 diabetes. A range of diagnostic sleep tests were used, but OSA was diagnosed by sleep study rather than questionnaire in all studies. The definition of diabetic retinopathy was noted to be variable. There was no evidence that OSA was associated with diabetic retinopathy, but there was some evidence that OSA was associated with greater severity of diabetic retinopathy as well as advanced diabetic retinopathy in people with type 2 diabetes. Data on diabetic maculopathy were more limited and inconclusive. The level of hypoxaemia was again found to be associated with diabetic retinopathy (figure 3). The authors note it is difficult to infer causality in cross-sectional studies and comment that further studies are needed. They also conclude that the effect of CPAP on diabetic retinopathy and diabetic macular oedema needs assessment through randomised controlled trials.

## **ROSA trial**

The ROSA trial (Retinopathy and Obstructive Sleep Apnoea) has recruited patients with diabetic macular oedema and newly diagnosed severe OSA from 23 Eye Hospitals across the UK and randomised them to 1 year of CPAP plus best ophthalmic care versus best ophthalmic care only. Follow up completes in 2017 and this data will answer and whether CPAP is a potential therapy for the visual impairment found in people with diabetic macular oedema<sup>22</sup>.

## **Bariatric surgery**

Amin et al conducted a retrospective cohort study to assess the impact of bariatric surgery on retinopathy in patients with type 2 diabetes<sup>23</sup>. They compared the retinal images of 152 patients from the English National Diabetic Eye Screening Programme taken in the year before surgery to images taken a mean of  $3.0 \pm 1.9$  years after surgery. Sight threatening diabetic retinopathy (STDR) was defined as the presence of preproliferative or PDR, maculopathy, or laser treatment. The comparator group comprised patients with type 2 diabetes attending the same centre who had not undergone bariatric surgery. Compared with a group matched for age, glycated haemoglobin, and follow-up duration, only the progression to maculopathy was significantly less in patients who underwent surgery versus those who received routine care, 5.6% [8/143] versus 15.4% [16/104],  $p=0.01$ . The progression to STDR was not statistically significant between the two groups. Although OSA severity was likely to have decreased following bariatric surgery, they did not measure OSA,

so its role in this relationship is unclear. They concluded that after bariatric surgery, patients with T2DM remain at risk for developing STDR, even those who did not have evidence of retinopathy before surgery. Prospective randomized clinical trials are needed to ascertain the impact of bariatric surgery on retinopathy.

## **Conclusions**

The literature shows much interest in the field of eye disorders and OSA. Prospective studies are lacking, acknowledged by all the authors of retrospective studies and meta-analyses reviewed here; thus only limited conclusions can be drawn about associations between eye disorders and OSA. The evidence suggests associations between OSA and glaucoma, keratoconus, NAION and severity of diabetic retinopathy. Causality is not established and there are many common confounders for ocular disorders and OSA. It seems prudent however for ophthalmologists to ask their patients about OSA symptoms. Many authors acknowledge that randomised controlled trials of therapy may be the best way to establish a direct association and whether treatment is beneficial. One such trial is underway and may provide a model for future work.

## **Key Points**

- Two large meta-analyses have shown there seems to be an association of OSA with glaucoma; the odds ratio was statistically significant, at between 1.41 and 1.96 and up to 5.49 with severe OSA, but causation cannot be confirmed. Eye Hospitals should consider OSA in their glaucoma patients.

- Nonarteritic ischaemic optic neuropathy showed a significant association with OSA, OR 6.18. If OSA was present on diagnosis, the chances of NAION affecting the other eye were significantly increased.
- A meta-analysis found no evidence that OSA was associated with diabetic retinopathy, but some evidence that OSA was associated with greater severity of diabetic retinopathy as well as advanced diabetic retinopathy in people with type 2 diabetes.

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## Figures and Tables

Figure 1.

Forest plot of case-control studies showing the odds ratios (ORs) with 95% confidence intervals (95%CI) of OSAS for participants with and without glaucoma. The squares and horizontal lines represent the study specific ORs and 95%CIs. The sizes of the squares reflect the statistical weights of the studies. The pooled OR is indicated by a diamond (fixed effect model).

Shi Y, Liu P, Guan J et al. Association between glaucoma and obstructive sleep apnea syndrome: a meta-analysis and systematic review. PLoS One. 2015 Feb 23;10(2):e0115625.

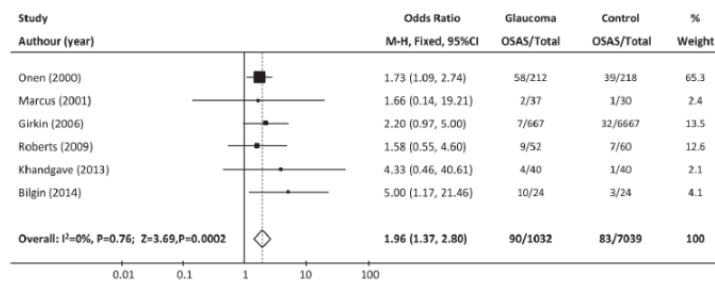
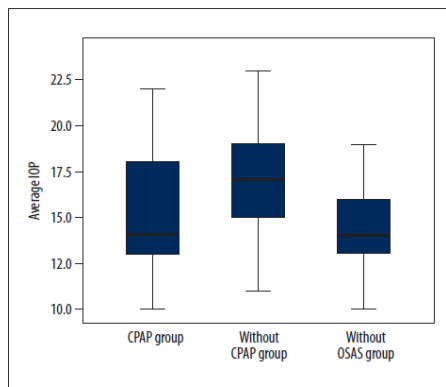


Figure 2. Comparison of patients with glaucoma: with OSA and choosing to use CPAP (n=38), with OSA and choosing not to use CPAP (n=32) and no OSA controls (n=36).

Ulusoy S, Erden M, Dinc ME et al. Effects of Use of a Continuous Positive Airway Pressure Device on Glaucoma. Med Sci Monit. 2015 Nov 8;21:3415-9



**Figure 3.**

Forest plot of the pooled estimate of the effects of minimum oxygen saturation (from sleep study) on diabetic retinopathy using a random effects model.

Leong WB, Jadhakhan F, Taheri S et al. Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: a systematic review and meta-analysis. Diabet Med. 2016 Feb;33(2):158-68.

