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The effects of obstructive sleep apnea and continuous positive airway pressure on diabetic retinopathy and maculopathy: A review and meta-analysis

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ABSTRACT

Obstructive sleep apnea syndrome (OSA) is a common morbid disease, its association with diabetic retinopathy, this meta-analysis aimed to assess the relationship between OSA, and continuous positive airway pressure and diabetic retinopathy/maculopathy. We systematically searched PubMed, Medline, and Google Scholar with interest in articles reporting the relationship between obstructive sleep apnea and continuous positive airway pressure on diabetic retinopathy/maculopathy. The terms "obstructive sleep apnea", "continuous positive airway pressure", "diabetic retinopathy/maculopathy "were used. No limitation was set for the study period (from the first published article until November 2021). A pre-determined table was used to collect study information including author name, year of publication, patients number in the intervention and control groups, the study duration. Out of the 201 studies retrieved, 25 full articles were approached and nine cohorts fulfilled the inclusion and exclusion criteria. we pooled six studies (16-21); three were case-control, one prospective, a retrospective, and a cross-sectional study. Three were from Europe, one from Australia, one published in Asia, and one from Tunesei (15152 patients and 382 events). No association was found between obstructive sleep apnea and diabetic retinopathy progression, odd ratio, 1.27, 95% *CI*, 0.79-2.04, P-value, 0.33. Three studies (two from Europe and one from the USA, 361 patients, and 286 events) assessed the effect of CPAP on diabetic retinopathy and maculopathy with no significant effect, odd ratio, 1.15, 95% *CI*, 0.41-3.23, P-value, 0.79. No association was found between OSA, CPAP, and diabetic retinopathy.

1. INTRODUCTION

Obstructive sleep apnea (OSA) is associated with various morbid disorders including cardiovascular diseases, diabetes mellitus, hypertension, and impotence. OSA is also associated with increased healthcare utilization mainly from cardiovascular and all-cause mortality, in some countries, 8.8% (12.8% in men and 5.1% in women) were suffering from the disease [1].

Worldwide, 93 patients are suffering from diabetic retinopathy, of them; 28 million are vision-threatening diabetic retinopathy. Hypertension, diabetes duration, and poorly controlled diabetes are modifiable risk factors. Diabetic retinopathy is the leading cause of blindness with a great economic burden on the healthcare system [2].

Apnea/hypopnea index was not associated with diabetic retinopathy which was associated with a lower level of education [4], a study conducted in Singapore reported the association of apnea/hypopnea index with diabetic retinopathy and vision-threatening retinopathy [5], [6] found an association between obstructive sleep apnea and diabetic retinopathy. [7] in their retrospective study found that adherence to continuous positive airway pressure is beneficial in retinopathy reduction. Furthermore, apnea-hypopnea index during rapid eye movement was shown to be associated with diabetic retinopathy in both home sleep apnea testing and all-night polysomnography [8]. High prevalence microangiopathy was reported among patients with diabetes mellitus and OSA [9], Wong B and Fraser CL [10] in their narrative review showed that OSA was associated with diabetes mellitus, diabetic retinopathy, and hypertension. [11] thought that the link between OSA and diabetic retinopathy might be related to hypertension. A meta-analysis conducted in the year 2017 [12] pooled results from only six cohorts and showed the association of OSA and diabetic analysis. However, the limited databases included, the significant heterogeneity, and the methods and number of included studies (six case-control studies) limit its power to inform diabetes and ophthalmology communities regarding this important issue. The effects of CPAP on macular edema among patients with OSA are conflicting [13], [14]. The association between OSA and diabetic retinopathy is controversial [3]. Thus, we conducted this research to assess the relationship between OSA and diabetic retinopathy.

2. Subjects and Methods

2.1 Eligibility Criteria according to PICOS

We included Randomized controlled studies (RCTs), retrospective and prospective cohorts, and case-control studies published in English and containing information on the effects of obstructive sleep apnea and continuous positive airway pressure on diabetic retinopathy/maculopathy, case reports, animal studies, or otherwise published in a language other than English were not included.

2.2 Outcome measures

The primary outcomes were the effects of obstructive sleep apnea and continuous positive airway pressure on diabetic retinopathy/maculopathy.

2.3 Information sources and search

Two researchers systematically searched PubMed, Medline, and Google Scholar with interest in articles reporting the relationship between obstructive sleep apnea and continuous positive airway pressure on diabetic retinopathy/maculopathy. Besides, the references list was searched for additional studies. The terms "obstructive sleep apnea", "continuous positive airway pressure", "diabetic retinopathy/maculopathy "were used. No limitation was set for the study period (from the first published article until November 2021).

A pre-determined table was used to collect study information including author name, year of publication, patients number in the intervention and control groups, the study duration. Data were cross-checked and discrepancies were solved by agreement between the two authors. Figure 1, Table 1 &2.

2.4 Data analysis

The RevMan system for meta-analysis was used, the data were all dichotomous. The random effect was used

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because of the substantial heterogeneity observed. Funnel plots were used to assess lateralization. A P-value of <0.05 was considered significant.

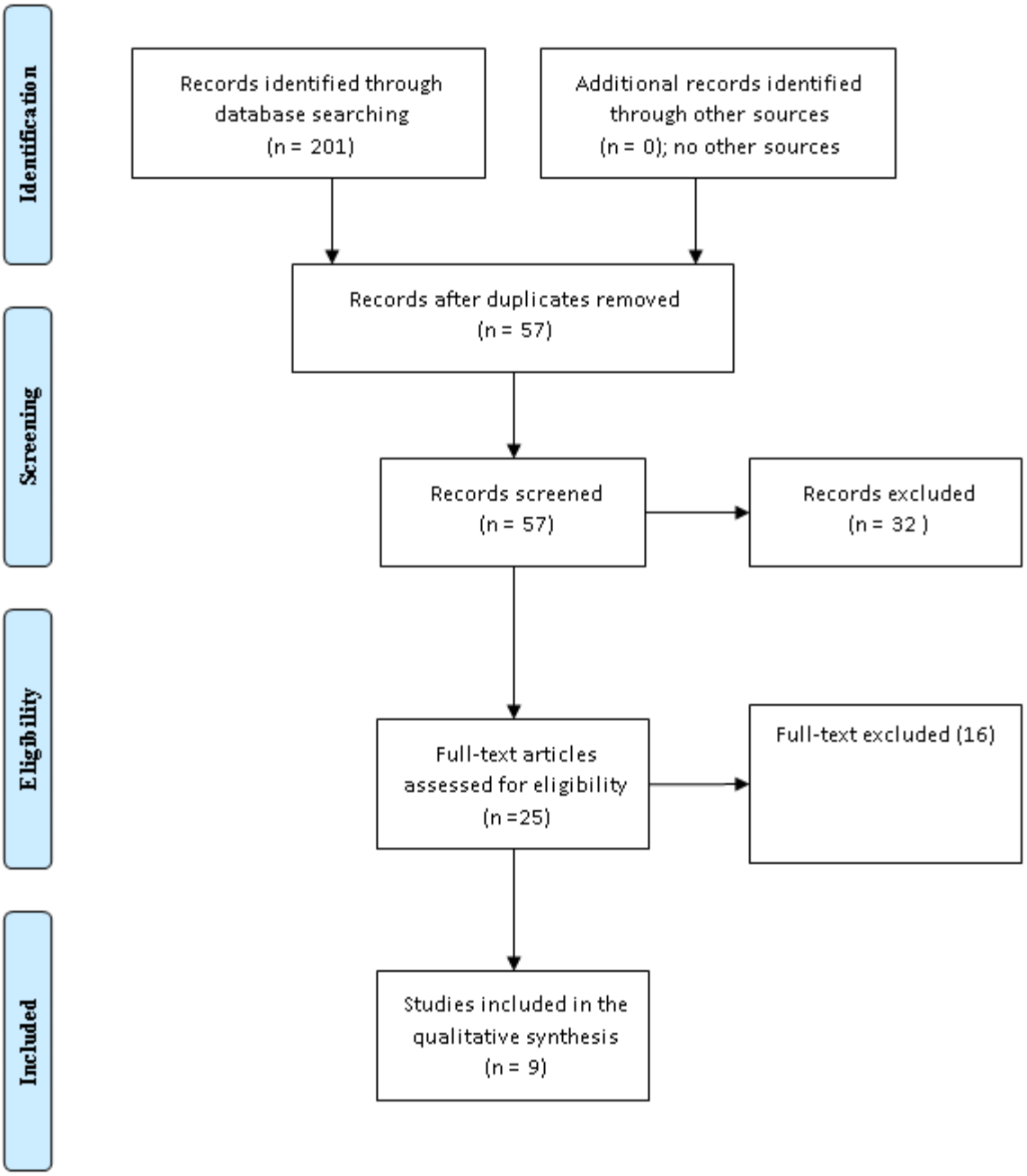

Figure 1. The effects of obstructive sleep apnea and continuous airway pressure on diabetic retinopathy and maculopathy.

Table 1. Obstructive sleep apnea and diabetic retinopathy.

Author	Year	Country	Study type	Intervention	Control
[15]	2020	UK	Retrospective	37/3667	105/10450
[16]	2017	UK	Case-control	29/147	26/83
[17]	2016	Tunesei	Case-control	11/20	6/40
[18]	2013	Australia	Case-control	18/46	18/47

[19]	2014	Denmark	Cross-sectional	19/72	21/108
[20]	2015	China	Prospective	68/310	24/162

Table 2. The effect of continuous positive airway pressure on macular edema and diabetic retinopathy progression.

Author	Year	Country	Study type	Intervention	Control
[21]	2012	UK	Case-control	10/13	5/15 mac
[22]	2019	USA	Retrospective	34/63	177/258
[23]	2018	UK	Case-control	21/40 31/58	23/43 29/54 mac

3. Results

Out of the 201 studies retrieved, 25 full articles were approached and nine cohorts fulfilled the inclusion and exclusion criteria., we pooled six studies (16-21); three were case-control, one prospective, a retrospective, and a cross-sectional study. Three were from Europe, one from Australia, one published in Asia, and one from Tunesei (15152 patients and 382 events). No association was found between obstructive sleep apnea and diabetic retinopathy progression, odd ratio, 1.27, 95% *CI*, 0.79-2.04, P-value, 0.33. Substantial heterogeneity was found, $I^{2,}$ 70%, chi-square, 18.68, and P-value for heterogeneity, 0.005. Figure 2. Three studies (two from Europe and one from the USA, 361 patients, and 286 events) assessed the effect of CPAP on diabetic retinopathy and maculopathy with no significant effect, odd ratio, 1.15, 95% *CI*, 0.41-3.23, P-value, 0.79, and significant heterogeneity, $I^{2,}$ 76%, chi-square, 8.41, and P-value for heterogeneity, 0.01. Figure 3.

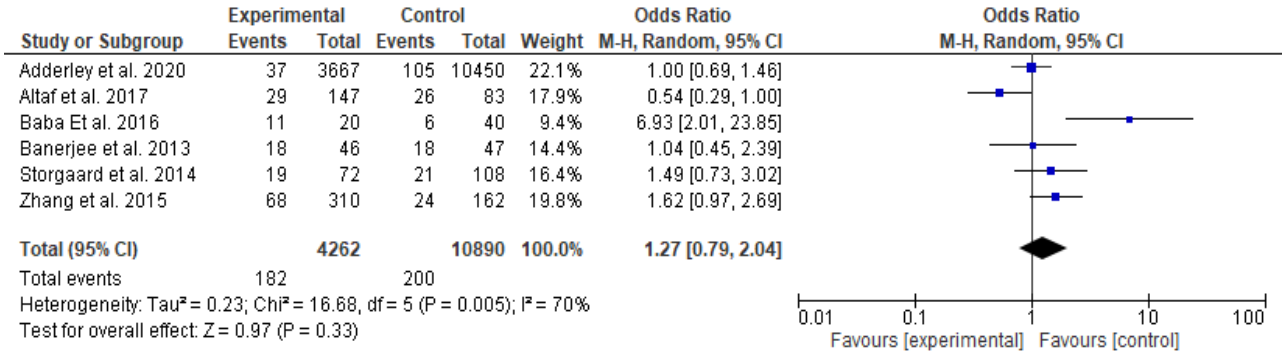

Figure 2. Obstructive sleep apnea and diabetic retinopathy.

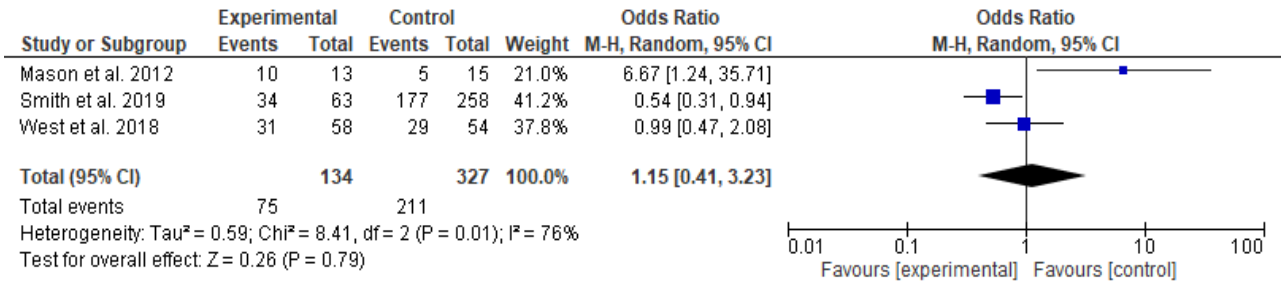

Figure 3. Continuous positive airway pressure on diabetic retinopathy.

4. Discussion

The association of obstructive sleep apnea and diabetic retinopathy was discussed controversially with some meta-analyses with limited studies showed no association [24], while others showed significant association [25]. The present meta-analysis showed no association of OSA and diabetic retinopathy, neither continuous positive airway pressure was beneficial, odd ratios, 1.27, 95% *CI*, 0.79-2.04 and1.15, 95% *CI*, 0.41-3.23 respectively. The effects of CPAP on diabetes retinopathy may be mediated by body mass index, the severity of OSA, and ethnicity [26]. Plausible explanations for the failure of CPAP might be that already the patients had advanced irreversible retinopathy or lack of adherence to its use. In addition, treatments for maculopathy and retinopathy may affect the outcomes [22]. There is a piece of evidence that OSA is associated with diabetic retinopathy severity and advanced retinopathy, also, minimum oxygen saturation is to blame [3]. Further possible explanations are the effects of intermittent hypoxia and hypercapnia on oxidative stress and endothelial dysfunction [27]. CPAP is indicated in moderate/severe OSA with a positive impact on hypoxia, endothelial dysfunction, and hypertension. In addition, there is some growing evidence in glycemic control. However, compliance to CPA is a big matter (83% are not compliant) [28], [29]. Hypertension, a major predictor of OSA and a major risk factor for diabetic retinopathy [30]. It is interesting to note that CPAP is more effective in controlling resistant hypertension among patients with OSA [31]. Thus, CPAP might be an effective measure in diabetic retinopathy prevention through its effects on the major risk factors of retinopathy.

5. Conclusion

Obstructive sleep apnea and continuous positive airway pressure showed no impact on diabetic retinopathy and maculopathy. The stage of retinopathy in the included studies, the lack of well-randomized control studies, and non-compliance to CPAP might affect the conclusion. In addition, other treatments for diabetic retinopathy/maculopathy may be confounders that affect the conclusion. Further well-controlled studies controlling for diabetic retinopathy/maculopathy with strict follow-up for CPAP compliance are needed.

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