Meta-analysis: Continuous Positive Airway Pressure Improves Insulin Resistance in Patients with Sleep Apnea without Diabetes

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Abstract

Rationale: Obstructive sleep apnea (OSA) is an independent risk factor for the development of insulin resistance (IR). Treatment with continuous positive airway pressure (CPAP) for OSA has shown conflicting results on IR.

Objectives: To conduct a meta-analysis of randomized controlled trials (RCTs) that have evaluated the effect of CPAP on a validated index of IR, the homeostasis model assessment of insulin resistance (HOMA-IR).

Methods: PubMed and Embase were searched through August 10, 2012. Two independent reviewers screened citations to identify trials of the effect of CPAP on HOMA-IR. Data were extracted for postintervention HOMA-IR values.

Measurements and Main Results: A total of five studies that enrolled 244 subjects (83% male) met the inclusion criteria. None of

the subjects in the included studies had diabetes. The pooled estimate of the difference in means in HOMA-IR between the CPAP and sham CPAP/control groups was -0.44 (95% confidence interval, -0.82 to -0.06 ; $P = 0.02$). The funnel plot does not suggest the presence of any publication bias. The I-squared index for the data on difference in means in HOMA-IR between the CPAP and sham CPAP/control groups was 0.00 ($P = 0.61$).

Conclusions: The pooled estimate of RCTs shows a favorable effect of CPAP on insulin resistance as measured by HOMA-IR in patients with OSA without diabetes. The effect size on HOMA-IR is modest, but not insignificant, when compared with the effects of thiazolidinedione in nondiabetic patients with metabolic syndrome. Further research and RCTs are warranted involving a larger number of patients and longer treatment periods to determine the beneficial effects of CPAP on IR.

Keywords: obstructive sleep apnea; CPAP; insulin resistance

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Obstructive sleep apnea (OSA) is a highly prevalent condition (1) that is characterized by repetitive upper airway obstruction resulting in cyclic intermittent hypoxia during sleep in affected individuals. OSA has been shown to be an independent risk factor for the occurrence of insulin resistance (IR) and diabetes mellitus (DM) in the adult population (2–5). Most of the cross-sectional epidemiologic studies performed in the general or in clinic-based populations show an association between OSA and IR. However, these association studies do not offer definitive proof that OSA leads to IR (6).

IR is characterized by an impaired response in glucose metabolism to a given level of insulin and is considered to contribute to the development of DM and to be a major risk factor for cardiovascular disease (7–11). The assessment of IR ranges from simple measurements of fasting insulin and glucose to complex procedures, such as the frequently sampled intravenous glucose tolerance test and the hyperinsulinemic euglycemic clamp (12, 13), the latter being considered the “gold standard” of IR measurement (14–16). However, the more complex procedures are

technically demanding, costly, and time consuming. On the other hand, mathematical derivations of the fasting insulin and glucose values, such as the homeostasis model assessment of insulin resistance (HOMA-IR), defined by the product of fasting glucose and fasting insulin divided by a constant, are very simple to use and have been shown to have a reasonable linear correlation with the hyperinsulinemic euglycemic clamp procedure (17, 18). As a result, the HOMA-IR has been used more frequently in clinical trials (16, 19). Not surprisingly, studies

examining the effects of OSA treatment on IR have used the HOMA-IR more frequently, and very few studies have used the more complex procedures.

In OSA, intermittent hypoxia during sleep is thought to be an important stimulus that leads to insulin resistance (20). Although the exact mechanism remains to be elucidated, preclinical studies in animals show that exposure to intermittent hypoxia that mimics the hypoxic stress seen in patients with OSA results in the development of IR, thereby offering support to the concept that OSA causes IR (21, 22). The first-line treatment for OSA is continuous positive airway pressure (CPAP) therapy, which alleviates hypoxic stress during sleep (23), and, presumably, this should also improve IR.

Two previous meta-analyses have studied the effect of CPAP on HOMA-IR with conflicting results (24, 25). Since the publication of these two meta-analyses, two additional randomized control trials

(RCTs) (26, 27) that reported the effect of CPAP on HOMA-IR were completed that enrolled more OSA subjects than the prior studies combined. Therefore, we performed a meta-analysis to analyze the pooled estimate of all such studies examining the effect of CPAP on HOMA-IR.

Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for analysis of postintervention data obtained from RCTs (28). We adhered to all stages of the design, implementation, and reporting of this meta-analysis using these guidelines.

Search Strategy and Selection Criteria

We conducted a search, using PubMed and Embase, for RCTs that studied the effects of

CPAP on HOMA-IR. We used Boolean Operator terms (AND, OR) to pair Medical Subject Heading (MeSH) text terms. All relevant published studies were included. We did not contact the authors of the studies that were published in foreign language. Reference lists of the available articles were also hand searched. A final screening was performed once potentially relevant articles were identified by the initial search. We used the following criteria: (1) the published article had to be written in the English language, (2) the study had to include only adult human subjects (age ≥ 18 yr), (3) duration of CPAP therapy in the study had to be ≥ 1 week, and (4) HOMA-IR measurements from either the differences between CPAP intervention and control groups were to be reported or individual values from each group were mentioned after intervention. Two investigators (I.I. and U.J.M.) performed the final screening using the above-mentioned criteria.

Figure 1. Flow diagram of articles identified and evaluated during the study selection process. CPAP = continuous positive airway pressure; HOMA-IR = homeostasis model assessment of insulin resistance; RCTs = randomized controlled trials.

Table 1. Characteristics of studies

Author	Year	Study Design	Duration of CPAP Treatment	Patient Population	Number of Participants	Percentage of Male Participants	Mean Age (SD)	Mean BMI (SD)	AHI (events/h)	CPAP Adherence (hours of use)
Coughlin (30)	2007	RCT Crossover design	6 wk	OSAS	34	100%	49 (8.3)	36.1 (7.6)	39.7 (13.8)	3.9 (0.7.4)
Comondore (31)	2009	RCT Crossover design	4 wk	OSAS	13	69%	55.5 (7.07)	31.1	27.9	5.53
Lam (32)	2010	RCT	1 wk	OSAS	61 CPAP (31); sham (30)	100%	46.3 (10.2)	27.5 (3.7)	39.7 (22.1)	4.9 (1.4)
Sharma (26)	2011	RCT Crossover design	12 wk	OSAS	(Seq 1) 43 (Seq 2) 43	(Seq 1)* 84% (Seq 2) [†] 95%	45 (8) 45 (8)	33.8 (4.7) 31.8 (5.2)	47.9 (19.6) 47.8 (17.3)	5.1 (1.0) 5.2 (1.1)
Weinstock (27)	2012	RCT	8 wk	OSAS and impaired glucose tolerance	(Seq 1) [‡] 25	(Seq 1) 44%	54 (10)	39 (8)	44 (27)	5.3 (1.7)
		Crossover design			(Seq 2) [‡] 25	(Seq 2) 40%	53 (8)	38 (8)	32 (20)	4.3 (2.1)

Definition of abbreviations: AHI = apnea hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; OSAS = obstructive sleep apnea syndrome; RCT = randomized controlled trial.

*Seq 1 indicates the group that was treated with CPAP first in the crossover study.

[†]Seq 2 indicates the group that was treated with sham CPAP first in the crossover study.

[‡]Only the data from the period before the crossover were provided.

Data Abstraction

For studies that met the inclusion criteria, data were extracted to a standardized data collection worksheet. The data included first author's name, year of publication, number of subjects, postintervention HOMA-IR data for CPAP and the sham CPAP/control groups, and data on the mean HOMA-IR difference between CPAP and the sham CPAP/control groups (where available).

In our final analysis of postintervention HOMA-IR data from RCTs, we used the difference in means between the CPAP and the sham CPAP/control group along with their confidence intervals (CIs). The difference in means was calculated if the data were not directly provided.

Quantitative Data Synthesis

The data for HOMA-IR were analyzed using the pooled estimate of the difference in means between the CPAP and the sham CPAP/control groups along with their CIs. Because the included studies used different methods of measurements and involved different study participants and different study durations, we have reported results from the random effects models.

Publication bias was assessed with funnel plots of standard error and difference in means. We also used the Begg and Mazumdar rank correlation test (29) to check for publication bias. Heterogeneity

was assessed with the I-squared index. The Comprehensive Meta Analysis version 2.2.064 software was used to analyze the data.

Results

A total of five studies (26, 27, 30–32) that enrolled 244 subjects (83% male) met the inclusion criteria. Figure 1 describes our search for these studies. Except for one (32), all studies used a randomized crossover design. None of the patients included in the analysis had DM, and one study included subjects specifically with OSA and impaired glucose tolerance based on a 2-hour oral glucose tolerance test (27). We did not include one RCT (33) in the final analysis because it specifically enrolled patients with type 2 DM and because the HOMA-insulin sensitivity (HOMA-%S) was reported instead of HOMA-IR (the reciprocal of HOMA-%S). Study participants in all of the included studies were 27 years of age and older and had a body mass index (BMI) of 26 kg/m² or greater. The duration of effective CPAP treatment ranged from 1 to 12 weeks (Table 1).

The pooled estimate of the difference in means in HOMA-IR between the CPAP and the sham CPAP/control groups was

−0.44 (95% CI, −0.82 to −0.06; $P = 0.02$), indicating an overall favorable effect of CPAP on HOMA-IR values (Figure 2).

Assessment of Heterogeneity and Publication Bias

The I-squared index was used to account for variability in effect size estimates across the studies. The I-squared index for the data on difference in means in HOMA-IR between the CPAP and the sham CPAP/control groups was 0.00 ($P = 0.61$), indicating that the included studies were homogeneous. Figure 3 shows the funnel plot of the data analyzed, which does not suggest the presence of publication bias. The Begg and Mazumdar rank correlation test also does not suggest the presence of publication bias (Figure 3).

Discussion

Our meta-analysis shows that CPAP treatment in subjects with OSA without diabetes improves insulin resistance as measured by the difference in means in HOMA-IR between the CPAP and the sham CPAP/control groups. A majority of cross-sectional studies involving patients recruited from the clinics and from the general population showed a positive association between the presence of OSA and worsening

Figure 2. Forest plot for differences in means in homeostasis model assessment of insulin resistance (HOMA-IR) and corresponding 95% confidence intervals (CIs). The pooled estimate of the difference in means in HOMA-IR between the continuous positive airway pressure (CPAP) and sham CPAP/control groups was -0.44 (95% CI, -0.82 to -0.06 ; $P = 0.02$).

IR (2–5). However, these association studies do not prove causality, and interventional studies using an effective treatment for OSA (such as CPAP) are needed to support this concept. The effect size of CPAP treatment on HOMA-IR is modest (-0.44) when compared with the effect of the thiazolidinedione rosiglitazone, which has been reported to improve the HOMA-IR by -0.9 in nondiabetic obese patients or in those with the metabolic syndrome (34, 35).

Our study does not address whether OSA and the development of diabetes are causally linked. It also does not address whether OSA worsens glucose control or IR in patients with diabetes. Nonetheless, the development of IR is important because it is a known risk factor for the future occurrence of cardiovascular disease and diabetes (8–11). OSA is a highly prevalent condition that is associated with an increased incidence of cardiovascular disease (36), and recent studies show that treatment of OSA with CPAP reduces cardiovascular morbidity and mortality (37). Therefore, showing an independent link between OSA and IR adds to the growing body of evidence regarding the health outcomes related to sleep apnea.

There were two previous meta-analyses examining the effects of CPAP on IR. In the meta-analysis by Yang and colleagues (24), the authors based their results on pre- and postintervention data obtained mostly from observational studies. Their study showed a statistically significant effect of CPAP on HOMA-IR. The meta-analysis by Hecht and colleagues (25) included randomized and nonrandomized controlled trials that examined the effects of CPAP on measures of glucose metabolism. Their study did not

show any significant effect of CPAP on HOMA-IR. Our current study included results from two additional RCTs (26, 27) that examined the effect of CPAP on HOMA-IR that were completed after these two meta-analyses were published.

That adiposity is not the sole factor contributing to IR in patients with OSA has been suggested by cross-sectional epidemiologic studies (2–5). In addition, intermittent hypoxia during sleep, a major pathophysiologic phenomenon in patients with OSA that is thought to be the stimulus responsible for the metabolic consequences of this condition, has been shown to induce IR in lean and obese animals (21, 22). More importantly, normal human subjects exposed to intermittent hypoxia that simulates the hypoxic stress in OSA have been shown to develop IR (38). These findings are consistent with the results of our meta-analysis.

The exact mechanisms involved in the development of IR in patients with OSA are unclear. Although some investigators believe that this relationship is entirely dependent on central adiposity (39), others argue that OSA is a major independent factor (2). A heightened sympathetic nerve activity, a hallmark of patients with OSA, has been documented to influence insulin metabolism (40). However, recent animal studies do not support the involvement of an increased sympathetic nerve activity as the mechanism for the IR related to intermittent hypoxia (22). This suggests that other pathways may be involved. It has been observed that sleep disruption and hypoxemia may produce alterations in the hypothalamic–pituitary–adrenal axis, which could be another factor in the

causation of IR (41). Similarly, an increase in circulating free fatty acids (42) and a reduction in adiponectin secretion by adipocytes have been implicated (43).

There are limitations to our study. First, we did not include one RCT that specifically enrolled patients with type 2 DM (33) in the final analysis because the HOMA-insulin sensitivity (HOMA-%S) was reported instead of HOMA-IR. Although HOMA-IR is simply the reciprocal of HOMA-%S, the standard errors of the transformed values of the HOMA-IR were not available. This parallel design RCT study enrolled a total of 42 subjects with known diabetes and did not show any significant effect of CPAP therapy after 3 months on glycemic control and insulin sensitivity as measured by the hyperinsulinemic euglycemic clamp. None of the subjects in the studies included in our analysis had diabetes, and therefore we were able to assess the effects of CPAP treatment in a relatively homogeneous population who are not using any antidiabetic medications. Hence, the exclusion of the study by West and colleagues (33) strengthens our findings in patients without DM. Second, we used the HOMA-IR as an index of IR rather than the hyperinsulinemic euglycemic clamp procedure. The more complex procedures of assessing IR are technically demanding and costly. In addition, the HOMA-IR has been shown to have a reasonable correlation with the IR indices derived from the hyperinsulinemic euglycemic clamp procedure (17). The few studies that used the hyperinsulinemic euglycemic clamp procedure (41, 44, 45), except for the study by West and colleagues (33), were not RCTs and reported different derived

Figure 3. Funnel plot for data analyzed. In this case, Kendall's tau b (corrected for ties, if any) is -0.10000 , with a one-tailed P value (recommended) of 0.40325 or a two-tailed P value of 0.80650 (based on continuity-corrected normal approximation). The funnel plot of the data analyzed does not suggest the presence of publication bias.

indices, preventing the use of meta-analysis. Third, body weight and fat distribution were not controlled for in our meta-analysis, and these could have been confounding variables in CPAP treatment and its effect on IR. Indeed, there is a suggestion that IR improves in patients with OSA who are not obese (41). Only two studies included in our

meta-analysis provided relevant information on the impact of BMI on IR in the population studied (26, 27). The study by Weinstock and colleagues showed no association of BMI with IR (27). Similarly, in the study by Sharma and colleagues, although the weight and BMI changed with CPAP, the correlation of change in HOMA-

IR with the change in weight was only -0.05 and was not statistically significant ($p = 0.67$) (26). Fourth, confounding by genetic differences may have affected our analysis because the studies included in our analysis involved different ethnic groups, and diabetes risk may manifest itself in subtle differences in different ethnic populations (46). Despite these limitations, we believe that the results of our meta-analysis remain valuable in that they support the concept that OSA may be causally related to the development of IR, at least in patients with OSA without overt diabetes.

In conclusion, although the mechanism of IR in patients with OSA is not fully understood, the pooled estimate from our meta-analysis of these studies demonstrates a favorable effect of CPAP on one of the measures of IR (HOMA-IR) in patients with OSA without DM. We believe that this meta-analysis adds to the therapeutic profile of CPAP in patients with OSA. Further research and RCTs are warranted involving a larger number of patients and longer treatment periods to determine if the beneficial effects of CPAP on IR can be sustained over prolonged periods of time. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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