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REVIEW

Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis

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Abstract
Background Previous studies addressing the question of whether continuous positive airway pressure (CPAP) could improve the insulin resistance and glucose control in patients with obstructive sleep apnea (OSA) have led to conflicting results. Therefore, we conducted the meta-analysis to evaluate the effects of CPAP on glycemic control and insulin resistance in OSA patients.
Methods We searched PubMed, HighWire Press, Ovid Medline (R), Cochrane library, and EMBASE before December 2011 on original English language studies. The meta-analysis was conducted using Review Manager Version 5.
Results The summary estimate for mean difference of homeostasis model assessment insulin resistance (HOMA) from 12 non-diabetic studies was −0.55 (95 % CI, −0.91 to −0.20; P=0.002). When compared with fasting blood glucose at baseline, 3 to 24 weeks of CPAP treatment did not improve glycemic control in non-diabetic subjects (−0.12; 95 % CI, −0.3 to 0.06; P=0.20), as well as in diabetic subjects (−0.71; 95 % CI, −2.24 to 0.83; P=0.37). There were no intervention-related changes in body mass index.
Conclusions Our analysis showed that CPAP significantly improved insulin resistance in non-diabetic patients with moderate to severe OSA, while no significant change in body mass index was detected. Compared with fasting blood glucose at baseline, there was no change in glycemic control with CPAP. Further large-scale, randomized, and controlled studies are needed to evaluate the longer treatment and its possible effects on weight loss and glycemic homeostasis.

Keywords OSA · CPAP · HOMA-IR · BMI · Glucose · Meta-analysis

Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep, leading to intermittent hypoxia and sleep fragmentation. It is estimated that 24 % of men and 9 % of women in the middle-aged individuals meet the minimal diagnostic criteria for OSA (≥5 apnea–hypopnea events per hour of sleep) [1]. Accumulating evidence implicates that OSA may be associated with insulin resistance, glucose intolerance, and metabolic syndrome, but independent of obesity. Obesity, specifically central obesity, is very common in patients with OSA who may gain weight more easily than the equally obese without OSA [2].

The primary treatment for OSA is continuous positive airway pressure (CPAP), which benefits the patients by maintaining upper airway patency. Previous studies addressing the question of whether CPAP could improve the insulin resistance and glucose control in these OSA patients have led to conflicting results. Some investigations demonstrate that adherence to CPAP treatment plays an important role in ameliorating insulin resistance or glucose intolerance, without significant changes in body weight [3–5]. However, other studies reported that the relationship between insulin resistance

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and OSA was entirely dependent on body mass and failed to show any improvement with CPAP therapy [6, 7].

To update the state of knowledge in this area, we conducted a meta-analysis of the effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with OSA. Given the potential role of obesity in the prevalence of insulin resistance or glucose intolerance, we also evaluated the changes of body mass index (BMI) before and after CPAP intervention.

Methods

Literature search

We searched PubMed, HighWire Press, Ovid Medline (R), Cochrane library, and EMBASE before December 2011 on original English language studies, using the following search terms: "sleep disordered breathing" or "obstructive sleep apnea" and "CPAP" and "insulin resistance". Although other methods had been developed and validated to evaluate insulin resistance, such as quantitative insulin sensitivity check index and fasting plasma glucose-to-insulin ratio, homeostasis model assessment insulin resistance (HOMA-IR) calculated by a mathematical model (fasting insulin (microunits per milliliter)×fasting glucose (millimoles per liter)/22.5), correlates well with the glucose disposal rate derived from the hyperinsulinemic euglycemic clamp [8, 9] and is universally used in non-diabetic populations [10, 11]. After review the titles and abstracts of retrieved articles, 390 duplicate and unrelated searches were first removed; then, 40 were identified for additional scrutiny. Further exclusions (23 papers) were made through perusal of full texts and two studies were subsequently excluded from the meta-analysis. Finally, 15 were eligible for the meta-analysis.

Selection criteria

Studies that met the following criteria were included: (1) prospective observational studies; (2)the study populations were limited to adults with newly diagnosed moderate to severe OSA receiving CPAP therapy; (3) duration of CPAP intervention was >2 weeks; (4) HOMA-IR, fasting glucose, and BMI were measured before and after CPAP. All the selected articles were independently reviewed by two investigators (DY and HY) to determine whether they could be included in this meta-analysis.

Data collection and analysis

The longitudinal data extracted from each paper included first author, year of publication, study design, sample size, mean age, mean BMI, AHI, duration of CPAP intervention, adherence with CPAP, fasting glucose, and HOMA-IR before and after therapy. The articles with overlapping data sets or the same study subjects were excluded.

The meta-analysis was conducted using Review Manager Version 5. Estimates of summary statistics on BMI, fasting glucose, and HOMA-IR in humans at baseline and post-treatment of CPAP, were calculated as mean differences (MD) and corresponding 95 % confidence intervals (95 % CI). To calculate pooled results, studies were weighted by inverse variance method with a random-effects or a fixed-effects model. The I^2 index and corresponding 95 % CI were used to summarize variability of outcomes derived from heterogeneity between the trials [12, 13]. If I^2 is <50 %, a fixed-effects model was used; otherwise, the random-effects model was adopted. All the papers that resulted in significant heterogeneity of the studies in the meta-analysis were removed from the meta-analysis. Potential publication bias was observed using a funnel plot.

Results

Study characteristics

A total of 430 papers that fitted our criteria for inclusion were retrieved from PubMed, HighWire Press, Ovid Medline (R), and EMBASE before December 2011. Three hundred ninety papers were excluded because they were duplicate articles or otherwise did not meet our inclusion criteria, or requisite data were not available. Thus, 40 were identified for additional scrutiny. Of the 40 studies, 23 papers were subsequently dropped from the review after further exclusions were made through review of full texts, and two studies (Garcia et al. [14] and Henley et al. [15]) were excluded from the meta-analysis for significant heterogeneity or too much weight (>60 %) on the meta-analyses of fasting blood glucose, HOMA-IR, and BMI. Finally, 15 were eligible for the meta-analysis (Table 1).

Quantitative synthesis

Meta-analysis of fasting blood glucose in OSA with CPAP

Eleven of the 15 studies reviewed in this section were qualified for inclusion. Of these 11studies, 9 studies provided glycemic data for non-diabetic OSA while 2 studies for those with diabetes. The analysis showed that compared with fasting blood glucose at baseline, 3 to 24 weeks of CPAP treatment did not improve glycemic control in non-diabetic subjects (−0.12; 95 % CI, −0.3 to 0.06; P=0.20;

Table 1 General baseline characteristics of 15 studies of CPAP included in the meta-analysis

Study	Design	Sample size	Age, year	Baseline BMI, kg/m^2	AHI,events per h	CPAP use, h/day	Follow-up mean, week	Baseline	
								FBG (mmol/l)	HOMA-IR
Barcelo A et al. 2008 [26]	O	20	49 (6)	32 (3)	52 (19)	>4	12	6.3 (1.05)	4.4 (2.4)
Carneiro G et al. 2009 [27]	O	7	40 (3)	46.1 (2.8)	91 (9.7)	>5	12	–	7.6 (1.7)
Chung S et al. 2011 [28]	O	25	51 (11)	27.7 (3.7)	>15	>4	20	6.13 (2.03)	3.5 (1.9)
Cuhadaroğlu C et al. 2009 [29]	O	31	54 (10)	32.3 (4.7)	43 (21)	>4	8	5.42 (1.01)	3.65 (1.91)
Dawson A et al. 2008 [30]	O	20	60 (10)	39.6 (8)	63 (30.4)	5.8 (1.0)	6	6.77 (3.43)	–
De Lima AM et al. 2010 [31]	O, C	9	56 (10)	37.3 (4.9)	29.9 (8.6)	5.3 (1.7)	8	–	4.99 (1.51)
Dorkova Z et al. 2008 [32]	O	16	51 (10)	32.8 (4.4)	64.7 (23.3)	>4	8	6.78 (2.78)	4.73 (3.18)
Lindberg E et al. 2006 [33]	O	28	64 (8)	29.4 (4.2)	23 (13)	5.1 (1.9)	3	5.7 (2.2)	3.9 (4.0)
Murri M et al. 2009 [34]	O	78	52 (11)	32.2 (5.2)	54.7 (19.3)	–	4	5.8 (1.05)	4.51 (3.13)
Nena E et al. 2010 [35]	O	47	45 (11)	33.1 (7.4)	55.9 (30)	4.72 (0.66)	24	5.23 (0.5)	2.8 (2)
Nguyen PK et al. 2010 [36]	R, C	10	53 (11)	30.1 (4.7)	38.8 (21.38)	5.1 (1.9)	12	5.53 (0.95)	–
Patruno V et al. 2007 [37]	O	16	47 (11)	35.2 (4.0)	46 (14.6)	6 (1)	12	–	5.2 (1.7)
Steiropoulos P et al. 2009 [38]	O, C	21	46 (10)	35.9 (9.78)	>15	>4	24	5.7 (0.8)	3.48 (4.15)
Trenell MI et al. 2007 [39]	O	19	49 (12)	36 (8)	64 (30)	>4	12	5.6 (0.7)	5.3 (3.4)
West SD et al. 2007 [40]	R, C	20	57 (11)	36.6 (4.9)	33.1 (21.6)	4.4 (2.0)	12	10.1 (3.6)	47.9 (1.6)

Values are presented as mean (SD)

O observational study design, *R* randomized study design, *C* controlled study design, *CPAP* continuous positive airway pressure, *OSA* obstructive sleep apnea, *FBG* fasting blood glucose, *HOMA-IR* homeostasis model assessment insulin resistance (calculated as fasting serum insulin (micro-units per milliliter)×fasting plasma glucose (millimoles per liter)/22.5), *BMI* body mass index (calculated as weight in kilograms divided by the square of height in meters), *AHI* apnea–hypopnea index

Fig. 1). For diabetic subjects, there was also no change in glycemic control with CPAP (−0.71; 95 % CI, −2.24 to 0.83; P=0.37) and insufficient data could be extracted to make conclusive statement.

Meta-analysis of effects of CPAP on HOMA-IR

To estimate the pooled mean difference of HOMA-IR from 12 non-diabetic studies, a meta-analysis was performed. No significant heterogeneity was observed among these studies (I^2=28, P>0.10).The summary estimate for mean HOMA-IR difference was −0.55 (95 % CI, −0.91to −0.20; P=0.002; Fig. 2). That is to say, CPAP therapy led to an improvement in non-diabetic HOMR-IR of 0.55 points lower than pre-treatment. As for diabetic subjects, West et al. reported that CPAP might have a trend in decrease of mean HOMA-IR value in comparison with pre-CPAP (−1.5; 95 % CI, −3.39 to o.39).

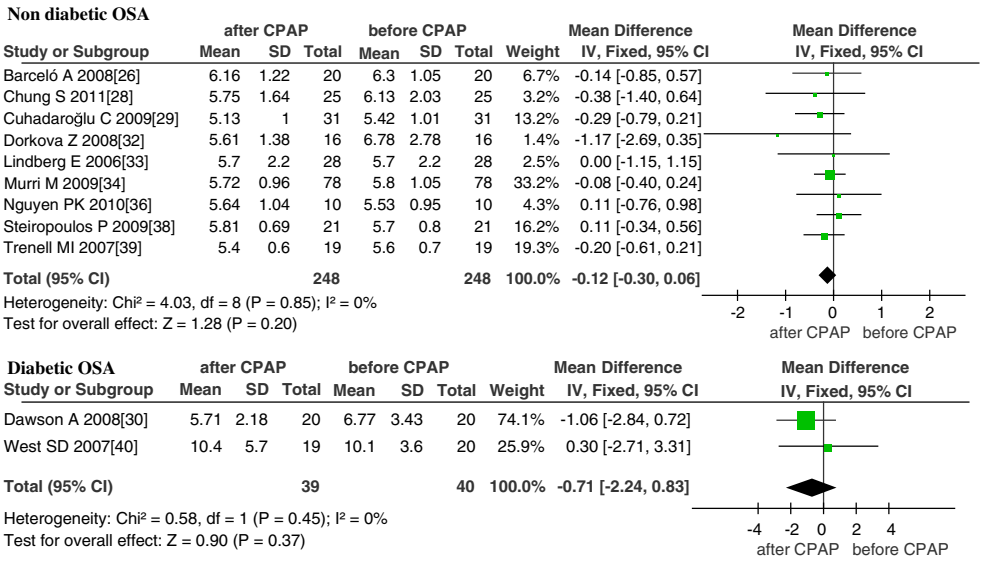

Fig. 1 Forest plot of mean difference and 95 % CI in fasting blood glucose before and after CPAP. The *top forest plot* represents the analysis on non-diabetic OSA. The *bottom forest plot* represents the analysis on diabetic OSA

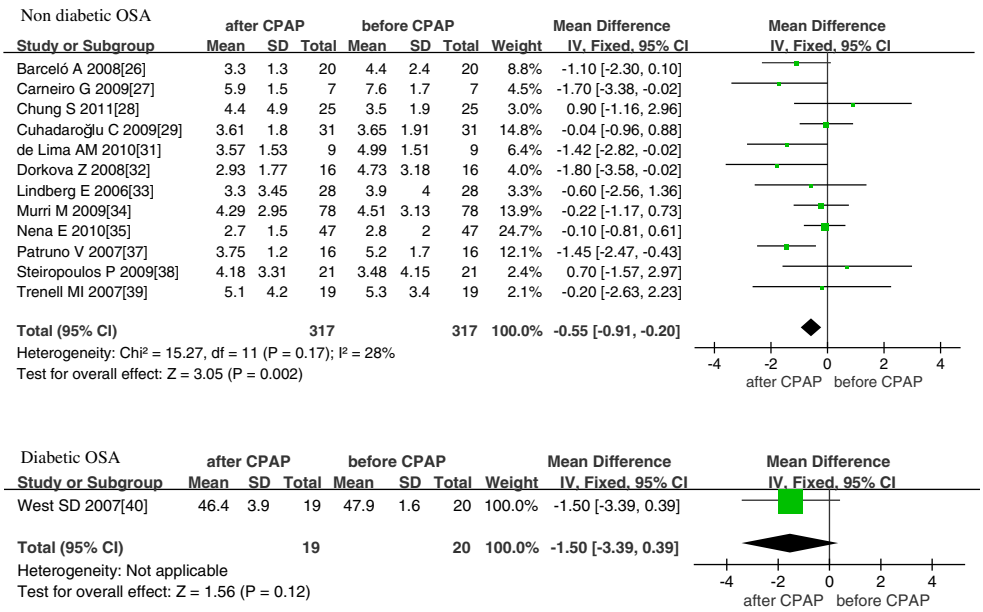

Fig. 2 Forest plot of mean difference and 95 % CI in HOMA-IR before and after CPAP therapy. The *top forest plot* represents the analysis on non-diabetic OSA. The *lower forest plot* represents the analysis on diabetic OSA

Meta-analysis of BMI for OSA with CPAP

There were no intervention-related changes in BMI in six non-diabetic studies (0.22, 95 % CI, −0.96 to 1.40, P=0.72) and two diabetic studies (−0.03, 95 % CI, −2.84 to 2.78, P= 0.98; Fig. 3).

No evidence of publication biases was observed in the graphed funnel plots of the above meta-analysis.

Discussion

In our meta-analysis, therapeutic CPAP in non-diabetic subjects with moderate to severe OSA resulted in a significant decrease in HOMA-IR. However, there was no intervention-related reduction in BMI. The analysis also indicated that compared with fasting blood glucose at baseline, 3 to 24 weeks of CPAP treatment did not have different effects on glucose levels.

This meta-analysis has a number of strengths that increase confidence to our findings. Firstly, after removing the individual high heterogeneity, there was no significant evidence of heterogeneity across the studies. Secondly, we constructed a funnel plot that did not suggest a substantial effect of publication bias. Thirdly, the compliance of CPAP use, AHI, and other baseline characteristics were comparable among studies.

Nevertheless, the review also has several limitations. Firstly, small sample population with overweight to obese may limit the generalizability of the results. So, additional large scale, different demography, and randomized controlled trials are needed to confirm these results. Secondly, the use of only English language papers only may cause some publication biases. Thirdly, the duration of CPAP

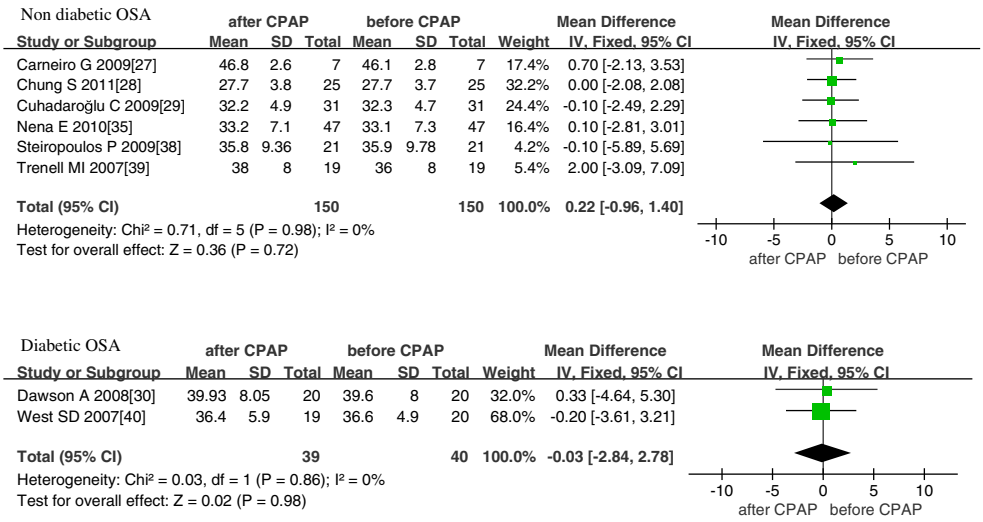

Fig. 3 Forest plot of mean difference and 95 % CI in BMI before and after CPAP. The *top forest plot* represents the analysis on non-diabetic OSA; the *lower forest plot* represents the analysis on diabetic OSA

therapy, ranging from 3 to 24 weeks, may be relatively shorter, which could not exert ameliorative effects on weight loss and glycemic homeostasis. Further studies are required to evaluate longer treatment and its possible effects.

Despite of these limitations, our data showed that insulin resistance could be improved after CPAP treatment without significant alteration of BMI and thereby indirectly demonstrated that OSA may induce insulin resistance independent of obesity [3–5]. It is well-established that insulin resistance is essential to the development of multiple metabolic disorders, including prediabetes or type 2 diabetes and lipid abnormalities, which are known to increase cardiovascular risk. Several population-based prospective studies demonstrated that insulin resistance was significantly related to coronary heart disease and stroke [16, 17]. Furthermore, the Insulin Resistance Atherosclerosis Study showed insulin resistance was positively associated with intimal medial thickness of the carotid artery [18]. Therefore, the earlier the CPAP is instituted as a treatment for moderate to severe OSA, the greater it will bring the benefits to cardiovascular protection.

HOMA-IR is regarded as a simple, inexpensive, and reliable surrogate measure of insulin resistance [19], predicting both diabetes and cardiovascular disease outcomes in many epidemiological studies [11, 20–22]. In the Women's Health Initiative Observational Study [22], with a median follow-up period of 5.9 years, the estimated relative risk of diabetes per SD increment in HOMA-IR were 3.40 (2.95–3.92), adjusting for matching factors and diabetes risk factors. Additionally, prospective data from the Verona Diabetes Complications Study [21] showed that a 1-unit increase in HOMA-IR value was associated with an odds ratio for incident CVD of 1.56, after a mean follow-up of 4.5 years. Thus, in our meta-analysis, the measured change of HOMA-IR index (−0.55) might have beneficial effects not only on risk of diabetes but also on prevalence of CVD in patients with type 2 diabetes.

For the evaluation of fasting blood glucose, the result indicated that 3 to 24 weeks of CPAP treatment did not improve glycemic control in non-diabetic subjects compared with pre-CPAP. Possible reason may be explained by the reported increase in plasma growth hormone during CPAP treatment [23, 24]. Growth hormone causes strong lipolytic effect, increase in the supply of free fatty acids, decrease in glucose utilization by skeletal muscles and thus leads to hyperglycemia [25].

In conclusion, CPAP significantly improves insulin resistance in non-diabetic patients with moderate to severe OSA, without significant changes in BMI. Compared with fasting blood glucose at baseline, there was no change in glycemic control with CPAP. Further large-scale, randomized, and controlled studies are needed to evaluate the longer treatment and its possible effects on weight loss and glycemic homeostasis.

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