Effects of continuous positive airway pressure treatment on glycaemic control and insulin sensitivity in patients with obstructive sleep apnoea and type 2 diabetes: a meta-analysis

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Abstract

Introduction: Obstructive sleep apnoea (OSA) is a prevalent disorder characterised by repetitive upper-airway obstruction during sleep, and it is associated with type 2 diabetes. Continuous positive airway pressure (CPAP) is the primary treatment for OSA. Prior studies investigating whether CPAP can improve insulin resistance or glucose control in OSA patients have resulted in conflicting findings. This meta-analysis investigated whether CPAP treatment could improve glucose metabolism and insulin resistance in patients with OSA and type 2 diabetes.

Material and methods: We performed a systematic literature search using Medline, Cochrane, EMBASE, and Google Scholar databases for randomised controlled prospective studies that investigated the effect of CPAP on glycaemic control or insulin sensitivity in subjects with type 2 diabetes.

Results: The combined standard (STD) paired difference in mean change in the levels of glycated haemoglobin (HbA_{1c}) was –0.073% (standard error (SE): 0.126), indicating that CPAP treatment did not alter HbA_{1c} levels. The combined STD paired difference in mean change of insulin sensitivity was observed as 0.552 μmol/kg • min (SE = 0.196) and indicated insulin sensitivity significantly increased with CPAP treatment (p = 0.005).

Conclusions: We found that the CPAP treatment did not alter HbA_{1c} levels but did significantly improve insulin resistance, indicating treating OSA can positively impact the symptoms of type 2 diabetes.

Key words: obstructive airway apnoea, insulin resistance, glycaemic control, positive airway pressure.

Introduction

Obstructive sleep apnoea (OSA) is a prevalent disorder characterised by repetitive upper-airway obstruction during sleep resulting in intermittent hypoxia and fragmentation of sleep. In the adult population, OSA is an independent risk factor for the development of diabetes mellitus [1–4]. Cross-sectional epidemiological studies found an association between OSA and deterioration in glycaemic control [5–10]. Obstructive sleep apnoea is present in about 73% of patients with type 2 diabetes [11]. However, it is currently unclear if this results from a connection between the two diseases or if it is just that both diseases are associated with obesity.

Continuous positive airway pressure (CPAP) is the primary treatment for OSA. Prior studies investigating whether CPAP can improve insulin resistance of glucose control in OSA patients have resulted in conflicting findings. Some prior work found CPAP treatment resulted in a significant reduction in glycated haemoglobin (HbA_{1c}) [10, 12, 13], while other studies found no change [14–18]. Similarly, some but not all studies found CPAP therapy improved insulin sensitivity [12, 14, 15, 18–20]. Consequently, it is currently unclear if CPAP-therapy can have therapeutic benefit for type 2 diabetes in patients with OSA.

Three meta-analyses have investigated the effect of CPAP on measures of glycaemic control and insulin resistance [20–22]. Two of these studies evaluated patients with OSA but did not require patients to have type 2 diabetes [20–22], and the other included retrospective studies and did not evaluate changes in insulin resistance. In this study, we included prospective studies in patients with both OSA and diabetes, which measured HbA_{1c} or insulin resistance to assess whether CPAP treatment in these patients was of benefit for diabetics.

Material and methods

Search strategy

We performed a systematic literature search using Medline, Cochrane, EMBASE, and Google Scholar (up to March 31, 2013) databases for randomised controlled prospective studies that investigated the effect of CPAP on glycaemic control or insulin sensitivity in subjects with type 2 diabetes. All relevant studies published prior to March 31, 2013 were included. All included studies had to be published in English and had to have investigated human subjects with stable, controlled type 2 diabetes, who received CPAP treatment for obstructive sleep apnoea. Retrospective or cohort studies and studies that did not report numerical results on HbA_{1c} or insulin sensitivity (as evaluated by euglycaemic hyperinsulinaemic clamp) were excluded from the analysis. The overall search strategy combined search terms of diabetes mellitus, glycaemic control, insulin sensitivity, risk factors, sleep apnoea, obstructive sleep apnoea, and continuous positive airway pressure. Identified potential references were screened by two independent investigators. Disagreements were resolved by a third reviewer.

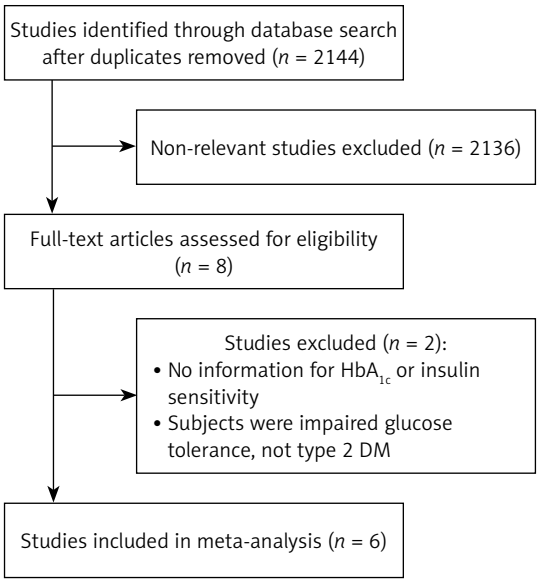


Figure 1. Flow chart for study selection

Data extraction

For studies that met the inclusion criteria (Figure 1), data was extracted into a standardised worksheet. Extracted data included the name of the first author, year of publication, study design, number of study subjects in each treatment group, the age and gender of subjects, the description of the CPAP protocol, and the results. We used a Delphi list to assess the included studies [23].

Statistical analysis

The primary efficacy outcome was HbA_{1c} levels following CPAP treatment. The secondary outcome was insulin sensitivity following CPAP therapy. The HbA_{1c} and insulin sensitivity before and after CPAP treatment were used to evaluate treatment efficacy. Means with standard deviations (SD) were summarised for the major outcome, and the change before and after CPAP was evaluated as for the treatment effect. Combined summary statistics of the standardised (STD) paired difference in mean for the individual studies are shown. Combined STD paired differences in means were calculated and a 2-sided p-value < 0.05 was considered to indicate statistical significance. An χ^2-based test of homogeneity was performed and the inconsistency index (I^2) statistic was determined. If I^2 was > 50% or > 75%, the studies were considered to be heterogeneous or highly heterogeneous, respectively. If I^2 was below 25%, the studies were considered to be homogeneous. If the I^2 statistic (> 50%) indicated that heterogeneity existed between studies, a random-effects model was calculated. Otherwise, fixed-effect models were calculated. Moreover, sensitivity analysis was performed based on the leave-one-out approach, and a funnel plot and the fail-safe N (which indicates whether the observed significance is spurious or not) were used to assess possible publication bias. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

The database search identified eight studies potentially eligible for analysis (Figure 1). Two studies were excluded, because one of them had no information regarding HbA_{1c} or insulin sensitivity and the subjects in the other did not have type 2 diabetes. Hence, a total of six studies met the inclusion criteria [12, 14, 15, 18, 19, 24]. The characteristics of the six studies included in the meta-analysis are summarised in Table I.

Four of the six included studies presented complete mean HbA_{1c} levels before and after CPAP treatment. A fixed-effect model was used to evaluate this data according to the heterogonous test ($Q = 0.148$, $I^2 = 0\%$, $p = 0.700$) [12, 14, 15, 19]. The combined STD paired difference in mean change in the levels of HbA_{1c} was –0.073% (standard error (SE): 0.126), indicating that CPAP treatment did not alter HbA_{1c} levels (Figure 2 A).

Two of the six studies reported changes in mean insulin sensitivity with CPAP therapy. A fixed-effect model was used according to the heterogeneous test ($Q = 0.148$, $I^2 = 0\%$, $p = 0.700$). The combined STD paired difference in mean changes of insulin sensitivity was observed as 0.552 µmol/kg • min (SE = 0.196), and indicated insulin sensitivity significantly increased with CPAP treatment ($p = 0.005$) (Figure 2 B).

Sensitivity analysis of our HbA_{1c} outcome indicated that removal of each study, one at a time, did not influence the direction or magnitude of the pooled estimate (Figure 3), indicating that no one study dominated the findings. In addition, funnel plot analysis demonstrated marked symmetry, indicating that there was no publication bias (Z value = –0.54; $p = 0.587$) (Figure 4). The quality assessment findings are summarised in Table II.

Discussion

This meta-analysis was designed to evaluate the effect of treatment of OSA with CPAP on glycaemic control in patients with type 2 diabetes. We found that CPAP treatment did not alter HbA_{1c} levels but significantly improved insulin resistance, indicating treating OSA can positively impact the symptoms of type 2 diabetes in patients with OSA. Additional analysis supports our findings; we found no significant evidence of heterogeneity among the studies, funnel plot analysis showed there was no substantial publication bias, and the baseline characteristics were similar across the studies.

Our meta-analysis has some similarities and differences with prior meta-analyses that also evaluated CPAP effect on diabetes [20–22]. Two meta-analyses in patients with OSA, but who were

Table I. Subject demographics and clinical outcomes for the 6 studies

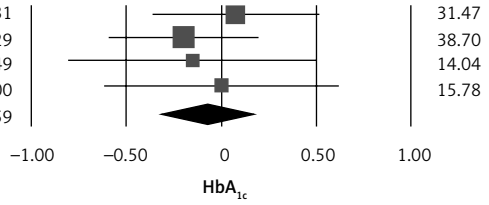
1st AU (year)	Treatment	Randomisation	Comparison	Patient number	Age [years]	Male (%)	HbA_{1c} [%]		Insulin sensitivity [µmol/kg · min]	
							Before	After	Before	After
Myhill (2012)	CAPA for 3 months	Randomised	CAPA initiated early (1 week) vs. CAPA initiated late (1–2 months)	44	66.1 ±8.8	61.4	Median = 6.9 (IQR = 6.1–7.3)	Median = 6.9 (IQR = 6.1–7.4)	N/A	N/A
Dawson (2008)	CAPA for 3 months	Non-randomised	Before CAPA vs. after CAPA	20	59.8 ±10.2	60	7.1 ±1.3	7.2 ±1.3	N/A	N/A
West (2007)	CAPA for 3 months	Randomised	CAPA for 3 months vs. placebo	20	57.8 ±10.4	100	8.5 ±1.8	N/A	26.5 ±14.4	N/A
Babu (2005)	CAPA for 1–3 months	Non-randomised	Before CAPA vs. after CAPA	25	50.7 ±9	64	8.3 ±2.2	7.9 ±1.8	N/A	N/A
Harsch (2004)	CAPA for about 3 months	Non-randomised	Before CAPA vs. after CAPA	9	56.3 ±8.2	77.8	6.4 ±0.7	6.3 ±0.6	2.98 ±2.62	4.38 ±2.94
Brooks (1994)	CAPA for 4 months	Non-randomised	Before CAPA vs. after CAPA	10	50.8 ±9.6	70	8.9 ±1.5	8.9 ±1.2	11.4 ±6.2	15.1 ±4.6

N/A – not available

A

Study name	Std paired difference	Standard error	Variance	Lower limit	Upper limit	Value of *Z*	Value of *p*	Relative weight
Dawson (2008)	0.077	0.224	0.050	–0.362	0.516	0.344	0.731	31.47
Babu (2005)	–0.197	0.202	0.041	–0.593	0.199	–0.976	0.329	38.70
Harsch (2004)	–0.152	0.335	0.112	–0.810	0.505	–0.455	0.649	14.04
Brooks (1994)	0.000	0.316	0.100	–0.620	0.620	0.000	1.000	15.78
Overall	–0.073	0.126	0.016	–0.320	0.173	–0.585	0.559	

Heterogeneity: *Q*-value = 0.935, $p = 0.817$, $I^2 = 0\%$



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Study name	Std paired difference	Standard error	Variance	Lower limit	Upper limit	Value of *Z*	Value of *p*	Relative weight
Harsch (2004)	0.501	0.237	0.056	0.360	0.966	2.112	0.035	68.44
Brooks (1994)	0.664	0.349	0.122	–0.021	1.348	1.900	0.057	31.56
Overall	0.552	0.196	0.039	0.168	0.937	2.815	0.005	

Heterogeneity: *Q*-value = 0.148, $p = 0.700$, $I^2 = 0\%$

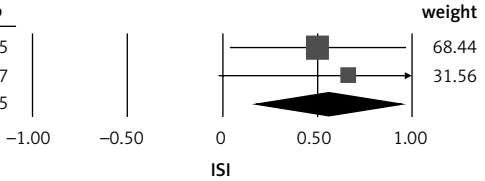

Figure 2. Forest plot of major outcomes, (**A**) HbA_{1c} level and (**B**) insulin sensitivity before and after CPAP treatment

Std – standardised, 95% CI – 95% confidence interval, ISI – insulin sensitivity

Study name	Std paired difference	Standard error	Variance	Lower limit	Upper limit	Value of *Z*	Value of *p*
Babu (2005)	0.005	0.160	0.026	–0.310	0.319	0.028	0.977
Brooks (1994)	–0.087	0.137	0.019	–0.356	0.181	–0.637	0.524
Dawson (2008)	–0.143	0.152	0.023	–0.440	0.155	–0.939	0.348
Harsch (2004)	–0.061	0.136	0.018	–0.326	0.205	–0.447	0.655
Overall	–0.0736	0.126	0.016	–0.320	0.173	–0.585	0.559

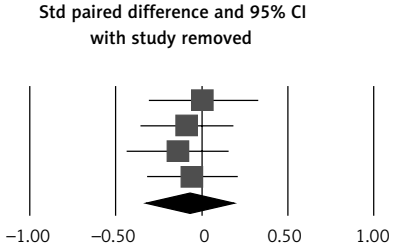

Figure 3. Sensitivity analysis for the influence of individual studies on pooled estimate by means of leave-one-out for HbA_{1c} level before and after CPAP treatment

Std – standardised, 95% CI – 95% confidence interval, ISI – insulin sensitivity

not selected for having type 2 diabetes, also found that CPAP treatment had no significant impact on HbA_{1c} [20, 22]. Subgroup analysis in one study also found no change in HbA_{1c} levels in patients with type 2 diabetes following CPAP therapy [22]. A meta-analysis by Yang *et al.* evaluated glycaemic control by assessing fasting blood glucose data and found that CPAP treatment did not alter control [21]. In two meta-analyses that assessed insulin sensitivity, one found a significant decrease in insulin resistance as evaluated using homeostasis model assessment insulin resistance (HOMA-IR) ([fasting insulin] × [fasting glucose]/22.5]), which correlates well with glucose disposal rates derived from hyperinsulinaemic euglycaemic clamp [21, 25, 26]. In contrast to our findings, the other meta-analysis, which evaluated only randomised controlled trials in patients with OSA, found no change in insulin resistance following CPAP therapy [20]. The difference in findings between ours and this latter meta-analysis may reflect the types of studies included in the analyses. The study by Hecht *et al.* included trials that measured insulin resistance by HOMA-index, adiponectin, or Kitt-insulin-sensitivity index [20], and some studies excluded patients with type 2 diabetes [20]. In contrast, we only included studies that measured

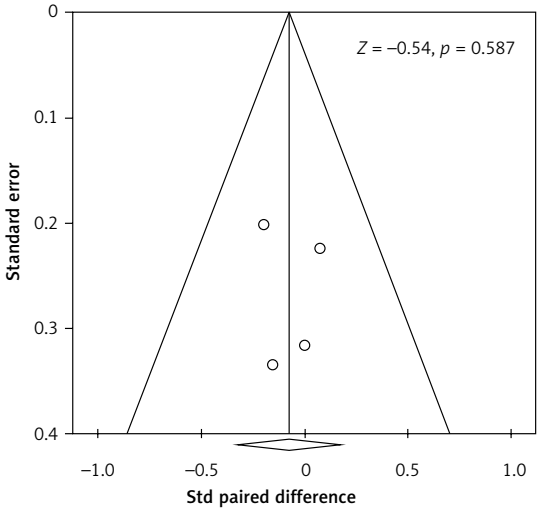

Figure 4. Funnel plot of HbA_{1c} level

Table II. Summary of data collected

First author (year)	Was a method of randomisation used?	Were the groups similar at baseline regarding the most important prognostic indicators?	Were the eligibility criteria specified?	Was the outcome assessor blinded?	Was the care provider blinded?	Was the patient blinded?	Were point estimates and measures of variability presented for the primary outcome measures?	Did the analysis include an intention-to-treat analysis?
Myhill (2012)	Yes	Yes	Yes	NA	NA	NA	Yes	NA
Dawson (2008)	No	Yes	Yes	NA	NA	NA	Yes	NA
West (2007)	Yes	Yes	Yes	Yes	NA	NA	Yes	NA
Babu (2005)	No	Yes	Yes	NA	NA	NA	Yes	NA
Harsch (2004)	No	Yes	Yes	NA	NA	NA	Yes	NA
Brooks (1994)	No	Yes	Yes	NA	NA	NA	Yes	NA

NA – information not available or not applicable

insulin resistance using the euglycaemic hyperinsulinaemic glucose clamp, which is a very sensitive measurement for this outcome. Moreover, our analysis was focused on trials with patients who had type 2 diabetes.

There are several limitations to our analysis that should be considered when interpreting the findings. Only a small number of studies qualified to be included in the meta-analysis. However, OSA is known to be an independent risk factor for diabetes mellitus, there are currently a limited number of studies that have evaluated the effect of CPAP treatment for OSA on symptoms of diabetes, in this case glucose metabolism. The fact that there are so few studies highlights the need for additional research into such a medically important question. In addition, heterogeneity existed among the included studies, and the length of CPAP therapy in these studies ranged from 41 days to 3 months, which may not be sufficient time to detect changes in HbA_{1c} [20]. None of the included studies had a CPAP sham control group. A prior study by West *et al.* [18] that randomised male patients with type 2 diabetes and OSA to either CPAP (n = 20) or sham CPAP (placebo) (n = 22) found that CPAP did not significantly improve insulin resistance or glycaemic control. We did not include this study because the data presented in the manuscript could not be incorporated into our quantitative analysis. The study did not provide the numerical data for post-treatment insulin sensitivity and glycaemic control findings, but only the difference from pre-treatment. Based on statistical theory, it is incorrect to calculate the post-treatment values from pre-treatment and the difference between pre- and post-treatment values. The inconsistency of the results of West *et al.* and our own results further indicates the need for additional studies to investigate this question. Our study also had a number of strengths, including the fact that it was the first meta-analysis to evaluate the effect of CPAP on insulin sensitivity and HbA_{1c} in patients with type 2 diabetes.

In conclusion, CPAP therapy in patients with type 2 diabetes and OSA improved insulin resistance without significant changes in glucose metabolism. The CPAP has also shown benefit for diseases associated with OSA, such as cardiovascular disease [27, 28]. It is possible that other biological markers, such as fetuin-A and leptin, in addition to HbA_{1c} and insulin resistance, may be useful in monitoring the effect of CPAP on symptoms of diabetes in patients with OSA [29, 30]. Larger randomised controlled studies with greater treatment times from diverse geographical areas are needed to further investigate this question.

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