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Effect of continuous positive airway pressure (CPAP) on glycemic control and variability in type 2 diabetes

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Dear Editor,

Obstructive sleep apnea (OSA) has been reported as a comorbidity of type 2 diabetes (T2D) in up to 80 % of patients, depending on the population studied [1]. Correlations between OSA severity and glycemic control have been reported [1]; however, studies investigating the effect of treatment with continuous positive airway pressure (CPAP) on glycemic control have demonstrated conflicting results [2]. A meta-analysis of six prospective observational studies and randomized controlled trials showed an improvement in insulin sensitivity with CPAP treatment in subjects with T2D, but no effect on HbA1c [2]. Studies using continuous glucose monitoring (CGM) before and during CPAP therapy demonstrated improvements in glycemic control [3, 4]. The few prospective trials investigating glycemic control with CPAP, however, have been limited by small sample sizes, short durations of treatment, variable adherence among participants, or absence of a control group [2].

The purpose of this pilot study was to investigate the effect of active versus sham CPAP therapy on glycemic control and variability (GV) using CGM in patients with T2D and previously untreated OSA.

This prospective study was approved by the Institutional Review Board at the University of Pittsburgh. All patients provided written informed consent prior to participation. Consented subjects (n = 23) with T2D, not on insulin, with HbA1c < 9 % (75 mmol/mol), with an apnea hypopnea index (AHI) ≥ 10 were randomly assigned to receive active (n = 12) or sham (n = 11) CPAP for 30 days. Body mass index (BMI) was obtained as weight in kilogram divided by the height in meters squared. Baseline measures of insulin sensitivity were calculated using homeostasis model assessment of insulin resistance (HOMA-IR). Changes in glycemic control were determined using the following measures performed at baseline and days 27–30 of assigned CPAP therapy: serum fructosamine, home blood glucose monitoring (BGM) performed four times per day before meals and bedtime, and 3 days of CGM (Medtronic; Minneapolis, MN). GV was determined as standard deviation (SD) and BG range during CGM.

The clinical characteristics of participants grouped according to CPAP assignment are summarized in the table. There were no group differences for age, gender, BMI (kg/m^2), HbA1c, fructosamine, or HOMA-IR (Table 1). Despite higher baseline AHI in the active CPAP group (p = 0.04), adherence to assigned therapy was similar. Subjects were effectively blinded to the therapy they received, with 58 % of active and 46 % of sham participants indicating that they were receiving real CPAP (p = 0.54). Serum fructosamine decreased with active (264.5 ± 36.9 umol/L vs. 253 ± 42 umol/L, p = 0.01), but not sham CPAP (265.2 ± 46.5 umol/L vs. 270 ± 47.8 umol/L), p = 0.88). A moderate effect size was observed for the reduction in fructosamine with active CPAP compared to

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Table 1 Baseline characteristics and CGM measures before and after active and sham CPAP

	Active CPAP			Sham CPAP			*p*
Age (year)	58 ± 12			53 ± 11			0.5
Gender (% male)	46 %			57 %			0.6
BMI (kg/m^2)	35.5 ± 6.3			34.9 ± 4.3			0.8
HbA1c % mmol/mol	6.6 ± 0.5 48 ± 5.5			6.9 ± 1 52 ± 10.9			0.3
HOMA-IR	3.8 ± 3			4.8 ± 4.5			0.9
Adherence (h)	4.1 ± 2.9			4.5 ± 2.7			0.8
	Pre	Post	Mean difference	Pre	Post	Mean difference	*p**
AHI	56.6 ± 29.8	7.0 ± 6.2	−49.1 ± 26.3	25.6 ± 11.4	21.3 ± 15.4	−4.3 ± 15.8	<0.001
CGM mean BG (mmol/L)	8.1 ± 1.5	8.5 ± 2.2	0.4 ± 2.1	7.4 ± 2	7.9 ± 1.5	0.5 ± 0.7	0.7
SD (mmol/L)	1.7 ± 0.7	1.8 ± 0.9	0.2 ± 0.4	1.6 ± 0.6	1.7 ± 0.7	0.2 ± 0.6	0.9
CGM BG range (mmol/L)	8.5 ± 3.2	9.3 ± 4	0.7 ± 2.4	8.0 ± 2.8	8 ± 3.1	0.1 ± 3.7	0.7
% time BG 3.9–10 mmol/L	80.6 ± 20.3	76 ± 24.5	−5 ± 22	80.1 ± 16.3	85.1 ± 19.5	5 ± 16.7	0.4
% time BG > 10 mmol/L	18.1 ± 20.8	23.1 ± 24.5	4.5 ± 19.6	13.1 ± 15.7	14.9 ± 19.5	1.7 ± 6.7	0.7

*Refers to group differences in pre vs. post data

sham CPAP (Cohen's D = −0.74). There was a larger effect size for the observed improvement in AHI with active vs. sham CPAP (Cohen's D = −1.67) (Table 1). No differences were observed in CGM mean BG 6a-6p with active CPAP (before vs. after: 8.2 ± 1.3 vs. 8.5 ± 2 mmol/L, $p = 0.6$) which differed from sham treatment where an increase in mean BG was observed (7.3 ± 2 vs. 8.4 ± 1.9 mmol/L, $p = 0.018$). Similar results were observed for home BGM (active CPAP: 8.2 ± 1.7 vs. 8.1 ± 1.4 mmol/L, $p = 0.84$) and (sham CPAP: 7.2 ± 1.7 vs. 8.4 ± 1.9, mmol/L, $p = 0.018$), respectively. No group differences were observed for any other CGM measures or GV (Table 1).

We observed subtle improvements in glycemic measures in subjects with T2D and OSA treated with active versus sham CPAP for 30 days as determined using serum fructosamine but not CGM. This discrepancy is likely due in part to the fact that fructosamine is a measure of glycemia over a 30-day period while CGM reflects only a 72-h period of time. The absence of any improvement in glycemic measures using BGM or CGM may also have been due in part to the fact that participants were under good glycemic control on oral agents alone at baseline as measured by HbA1c. Participants were effectively blinded to assigned therapies, demonstrating the feasibility of randomly assigning subjects to sham CPAP. The observed deterioration in glycemic measures in those receiving sham CPAP supports earlier findings demonstrating that active CPAP improves compliance with diabetes self-management practices which contributes to maintaining overall metabolic control [5]. The results of this pilot study need to be interpreted with caution given the small sample size and the group differences in baseline AHI measures. A larger randomized controlled clinical trial is currently being conducted.

Author contributions E.M. was involved in statistical analysis, interpretation of data, and wrote the manuscript. P.J. was involved in conception and design and reviewed the manuscript. E.C. was involved in conception and design, statistical analysis and interpretation of data, and reviewed the manuscript. M.K. was involved in conception and design, interpretation of data, and writing and editing the manuscript.

Compliance with ethical standards

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Conflict of interest Patrick Strollo has received grant support from and has been a consultant for Inspire Medical Systems, ResMed, Jazz Pharmaceuticals, and Philips Respironics. Philips Respironics provided equipment for the study, as disclosed by Eileen Chasens. Authors Elena Morariu and Mary Korytkowski have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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