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Brief report

Beneficial effects of severe sleep apnea therapy on nocturnal glucose control in persons with type 2 diabetes mellitus☆

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SUMMARY

Given the consequences of sleep apnea and coexisting diabetes, satisfactory treatment of both diseases is required. Our results of continuous glucose monitoring in severe sleep apnea diabetic patients before and during continuous positive airway pressure/CPAP therapy showed significant reduction of nocturnal glucose variability and improved overnight glucose control on CPAP.

1. Introduction

Severe sleep apnea-hypopnea syndrome (SAHS) and coexisting diabetes significantly increase cardiovascular morbidity and mortality. Therefore, the need exists for a multidisciplinary approach to improve clinical practice and coordinate research efforts to minimise the impact of the condition.

Nowadays, continuous positive airway pressure (CPAP) is the most effective treatment for moderate–severe SAHS. CPAP has also been shown to reduce mean arterial ambulatory blood pressure [1] and sympathetic drive [2], and rapidly improve insulin sensitivity in SAHS [3]. To date, there have been no reports on immediate glycemic response to sleep apnea in diabetic state. Current data on CPAP effects on glycemia are conflicting and often lacking in proper investigational methods [4–7]. Our previous study indicated that SAHS was associated with an increase in nocturnal glucose variability related to severity of sleep-disordered breathing in persons with type 2 diabetes (PWD2) [8]. We hypothesize that CPAP might prevent apnea-related glucose fluctuations. We sought to assess the immediate CPAP effects on overnight glucose control in PWD2.

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Abbreviations: AHI, apnea-hypopnea index; $AUC_{>7.8(0\text{–}480\ min)}$, hyperglycemic area under the interstitial glucose concentration curve for 8-h period of night; BMI, body mass index; CGMS, continuous glucose monitoring system; CPAP, continuous positive airway pressure; CV, coefficient of variance; HbA1c, glycosylated hemoglobin; $MeanSatO_2$, mean oxygen saturation; $MinSatO_2$, minimum oxygen saturation; MOND, mean of nocturnal glucose differences; ODI, oxygen desaturation index; PSG, polysomnography; PWD2, persons with type 2 diabetes; SAHS, sleep apnea-hypopnea syndrome; S.D., standard deviation; S.D. overnight, overnight glucose standard deviation.

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2. Subjects and methods

2.1. Study design and setting

This was a single-centre, single-arm, non-randomized, prospective study approved by the local Ethics Committee and performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

2.2. Patients

Inclusion criteria included adults with severe SAHS, type 2 diabetes controlled by diet alone or on stable oral hypoglycemic therapy, and ability to perform continuous glucose monitoring. Exclusion criteria included type 1 diabetes and the use of insulin. From 44 PWD2 screened for sleep apnea, 14 Caucasian subjects entered and completed the study (Table 1).

Table 1 – Demographic and metabolic characteristics

	All subjects (n = 14)
Age (years)	54 ± 6
Male: female (n)	12: 2
BMI (kg/m^2)	37.4 ± 6.3
Duration of diabetes (years)	3.7 ± 1.5
HbA1c (%)[a]	7.48 ± 0.92
Fasting C-peptide (nmol/l)[b]	1.37 ± 0.31
Diabetes treatment – diet only (n)	3
Diabetes treatment – oral hypoglycemic agents (n)	11

Data are mean ± S.D.
[a] Normal range: 4.5–6.2%.
[b] Normal range: 0.26–1.39 nmol/l.

2.3. Continuous glucose monitoring

All patients underwent continuous glucose monitoring (CGMS; Medtronic MiniMed; Northridge, CA) [9,10] for several days. Sensor calibration was accomplished by entering self-monitored blood glucose values measured by MediSense Optium glucometer (Abbott Laboratories; Bedford, MA) ≥4 times/day. Participants were each asked to follow a protocol regarding diet and physical activity, and return to the Sleep Laboratory on assigned dates for diagnostic- and CPAP titration sleep studies performed simultaneously with CGMS.

2.4. Polysomnography

Healthdyne computerized polysomnography (PSG) systems (Alice 3; Respironics Inc; Murrysville, PA) were used for overnight recordings of the biophysiological changes during sleep. Each recording and associated events were scored manually according to standard criteria [11–13]. RemstarPro nasal CPAP machines (Respironics Inc; Murrysville, PA) were used for the CPAP titration and home CPAP treatment.

2.5. Data analyses

At the end of the study period, CGMS data were downloaded for analysis. The primary endpoint was nocturnal glucose variability as indicated by overnight glucose standard deviation (S.D.), coefficient of variance (CV), and mean of nocturnal glucose differences (MOND). The secondary parameters assessed included mean nocturnal glucose values and hyperglycemic area under the interstitial glucose concentration curve for 8-h period of night $AUC_{>7.8(0–480\ min)}$.

2.6. Statistical analyses

Statistical calculations were performed using NCSS 2007 software (NCSS; Kaysville, UT). Student's t-test was used to compare pretreatment (without CPAP) and posttreatment (on CPAP) measurements. Correlations between indices of nocturnal glucose control and parallel PSG data were analyzed using Spearman rank correlation coefficients. p-values < 0.05 were considered significant.

3. Results

Table 2 shows sleep and respiratory characteristics of the participants. Severe SAHS was confirmed by diagnostic PSG showing frequent episodes of sleep apnea/hypopnea with oxygen desaturations. CPAP significantly decreased AHI and improved oxygen saturation parameters.

25,304 CGMS glucose values obtained from 16 glucose sensors correlated well with 473 paired capillary glucose measurements (mean duration of continuous glucose monitoring 150.5 ± 46.1 h/patient; correlation coefficient 0.85 ± 0.08; mean of absolute glucose differences 11.29 ± 3.13%). Table 3 shows the results of nocturnal glucose control during the nights without CPAP and on CPAP, using a separate evaluation of the parameters during the nights in the sleep lab, when diagnostic-

Table 2 – Sleep and respiratory characteristics

	Diagnostic PSG (n = 14)	CPAP titration PSG (n = 14)	p-value
Epworth sleepiness score	13 ± 5	–	–
Effective CPAP pressure (cm H_2O)	–	12 ± 2	–
AHI (episodes/h)	49 ± 20	7 ± 5	<0.001
MeanSatO_2 (%)	88 ± 5	91 ± 4	0.002
MinSatO_2 (%)	78 ± 8	87 ± 4	<0.001
ODI (episodes/h)	50 ± 33	19 ± 14	<0.001
Arousal index (episodes/h)	51 ± 16	28 ± 17	<0.001

Data are mean ± S.D.

Table 3 – Changes in nocturnal glucose control on CPAP therapy

Parameters	Diagnostic PSG ($n = 14$)	CPAP titration PSG ($n = 14$)	p-value	All nights without CPAP ($n = 44$)	All nights on CPAP ($n = 40$)	p-value
S.D. overnight	1.17 ± 0.45	0.6 ± 0.19	0.001	1.16 ± 0.27	0.55 ± 0.17	<0.001
CV (%)	14.16 ± 5.9	9.0 ± 3.65	0.011	13.68 ± 3.82	7.79 ± 3.15	<0.001
MOND (mmol/l)	4.59 ± 2.0	2.59 ± 0.86	0.002	4.5 ± 1.43	2.23 ± 0.67	<0.001
Ø nocturnal glycemia (mmol/l)	8.53 ± 1.92	7.04 ± 1.98	0.007	8.75 ± 1.73	7.45 ± 2.07	0.011
$AUC_{>7.8(0\text{–}480\ min)}$ (mmol/l night)	1.18 ± 1.3	0.58 ± 1.05	0.005	1.35 ± 1.29	0.78 ± 1.24	0.014

Data are mean ± S.D.

and CPAP titration sleep studies were performed. Eighty-four nocturnal CGMS profiles available for final analysis showed significant reduction of nocturnal glucose variability on CPAP. In addition, when overnight CPAP therapy was administered, there was a significant reduction in mean nocturnal glycemia and $AUC_{>7.8(0\text{–}480\ min)}$. The results showed greater improvement of glucose control during the CPAP nights in the sleep lab as compared to CPAP nights at home after partaking of a more substantial dinner, suggesting that diet remains an integral part of effective diabetes management. Evaluation of CGMS- and

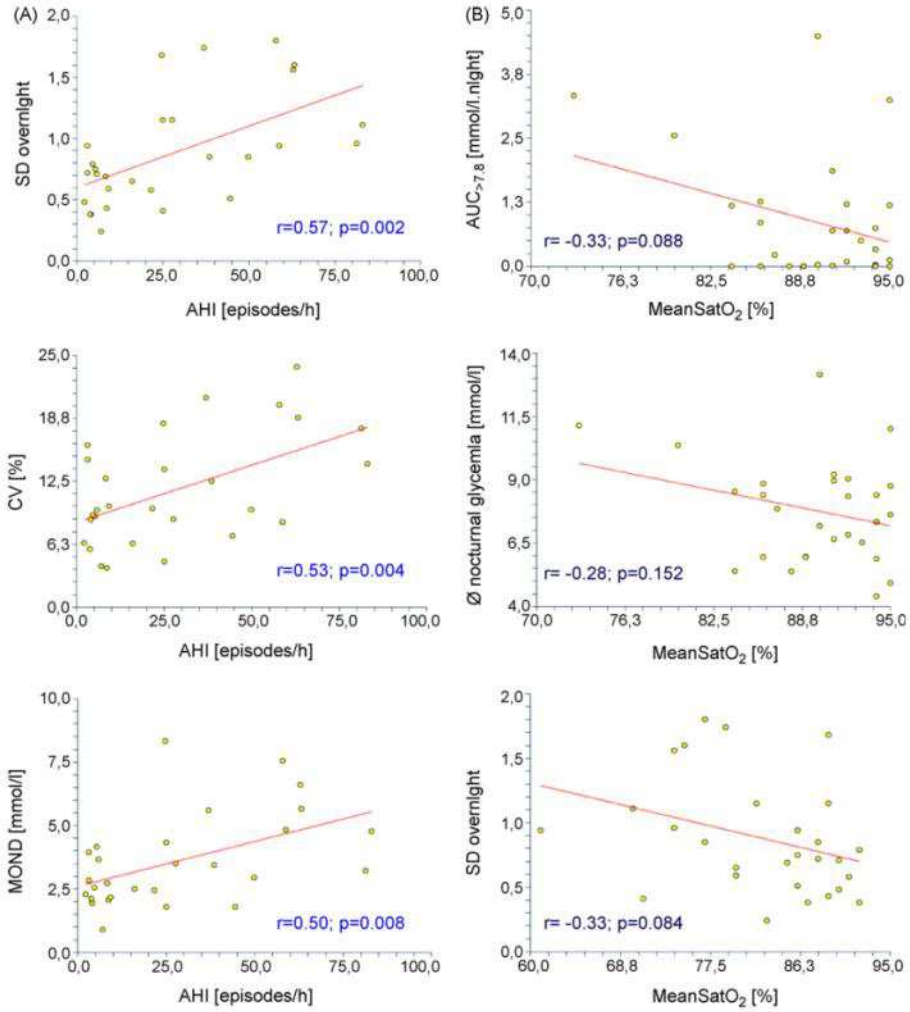

Fig. 1 – Correlations of AHI with parameters of nocturnal glucose variability (A, left panel). The trend of increasing mean nocturnal glycemia and $AUC_{>7.8(0\text{–}480\ min)}$ with decreasing mean oxygen saturation, and increasing nocturnal glucose variability with decreasing minimum oxygen saturation levels (B, right panel).

parallel PSG data showed strong positive correlations between AHI and parameters of nocturnal glucose variability (Fig. 1A). We observed a trend of increasing mean nocturnal glycemia and $AUC_{>7.8(0-480\ min)}$ with decreasing mean oxygen saturation, and increasing nocturnal glucose variability with decreasing minimum oxygen saturation levels (Fig. 1B).

No significant CGMS adverse events were reported. However, two sensors were unintentionally pulled out of the body in two subjects during the second and third day and were replaced.

4. Discussion

The primary finding is a significant reduction of nocturnal glucose variability and improved overnight glucose control during the ventilatory treatment of severe SAHS, which were observed in this cohort of predominantly male population with type 2 diabetes. To our knowledge, this is the first study to assess the immediate effects of CPAP on nocturnal glucose control in PWD2 with severe SAHS.

The underlying mechanism whereby SAHS affects glucose metabolism is likely repetitive hypoxemia and sleep fragmentation, which can trigger a cascade of pathophysiological events, including alterations in neuroendocrine function [14,15].

Glucose variability has already been shown to be a risk factor for complications independent of HbA1c in type 2 diabetes [16,17]. In order to reduce the burden of diabetes, there is an increasing need for early diagnosis and treatment of comorbidities, which might aggravate glucose control.

Our findings suggest that CPAP as an effective tool for restoring normal breathing in severe SAHS may prevent apnea-related glucose fluctuations and contribute to a more stable and improved overnight glucose control in patients with concomitant type 2 diabetes.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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