Original Article

Effect of Continuous Positive Airway Pressure Therapy on Glycemic Excursions and Insulin Sensitivity in Patients with Obstructive Sleep Apnea-hypopnea Syndrome and Type 2 Diabetes

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Abstract

Background: For patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) and type 2 diabetes mellitus (T2DM), the night sleep interruption and intermittent hypoxia due to apnea or hypopnea may induce glycemic excursions and reduce insulin sensitivity. This study aimed to investigate the effect of continuous positive airway pressure (CPAP) therapy in patients with OSAHS and T2DM.

Methods: Continuous glucose monitoring system (CGMS) was used in 40 patients with T2DM and newly diagnosed OSAHS. The measurements were repeated after 30 days of CPAP treatment. Subsequently, insulin sensitivity and glycohemoglobin (HbA1c) were measured and compared to the pretreatment data.

Results: After CPAP therapy, the CGMS indicators showed that the 24-h mean blood glucose (MBG) and the night time MBG were significantly reduced ($P < 0.05$ and $P = 0.03$, respectively). The mean ambulatory glucose excursions (MAGEs) and the mean of daily differences were also significantly reduced ($P < 0.05$ and $P = 0.002$, respectively) compared to pretreatment levels. During the night, MAGE also significantly decreased ($P = 0.049$). The differences between the highest and lowest levels of blood glucose over 24 h and during the night were significantly lower than prior to CPAP treatment ($P < 0.05$ and $P = 0.024$, respectively). The 24 h and night time durations of high blood glucose (>7.8 mmol/L and > 11.1 mmol/L) decreased ($P < 0.05$ and $P < 0.05$, respectively) after the treatment. In addition, HbA1c levels were also lower than those before treatment ($P < 0.05$), and the homeostasis model assessment index of insulin resistance was also significantly lower than before CPAP treatment ($P = 0.034$).

Conclusions: CPAP therapy may have a beneficial effect on improving not only blood glucose but also upon insulin sensitivity in T2DM patients with OSAHS. This suggests that CPAP may be an effective treatment for T2DM in addition to intensive diabetes management.

Key words: Continuous Glucose Monitoring System; Continuous Positive Airway Pressure; Obstructive Sleep Apnea-hypopnea Syndrome; Type 2 Diabetes Mellitus

Introduction

It is estimated that the prevalence of obstructive sleep apnea-hypopnea syndrome (OSAHS) among adults ranges from 2% to 4%, with a higher prevalence among men. With an increasing understanding of factors causing type 2 diabetes mellitus (T2DM) and influencing its control, numerous studies have demonstrated that sleep disordered breathing (SDB), especially OSAHS, and T2DM are frequently comorbid conditions. The Sleep Heart Health Study[1] in 2003 reported that patients with diabetes had a higher prevalence of sleep disorders. On the other hand, several studies based on outpatient and the general population indicate that the prevalence of OSAHS in patients with T2DM

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.163382

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Received: 13-02-2015 **Edited by:** Li-Min Chen

How to cite this article: Guo LX, Zhao X, Pan Q, Sun X, Li H, Wang XX, Zhang LN, Wang Y. Effect of Continuous Positive Airway Pressure Therapy on Glycemic Excursions and Insulin Sensitivity in Patients with Obstructive Sleep Apnea-hypopnea Syndrome and Type 2 Diabetes. Chin Med J 2015;128:2301-6.

ranges from 18% to as high as 36%,[2,3] while the prevalence of T2DM in patients with OSAHS is even higher.[3,4]

Recent studies have revealed the association of SDB with glycemic excursions and insulin resistance (IR). For patients with OSAHS and T2DM, the night sleep interruption and intermittent hypoxia due to apnea or hypopnea may induce glycemic excursions and reduce insulin sensitivity. Therefore, this study was designed to observe the effect of continuous positive airway pressure (CPAP) treatment on glycemic excursions and insulin sensitivity in patients with OSAHS and T2DM. Furthermore, we investigated the therapeutic effect on the stabilization of blood glucose and elevation of insulin sensitivity.

Methods

Subjects

Consecutive subjects with type 2 diabetes admitted to the Ministry of Health, Beijing Hospital from July 2008 to November 2009. Forty-three patients who were newly diagnosed with OSAHS and did not have CPAP treatment or any other surgical interventions were recruited. They were instructed to maintain a constant diet, lifestyle, and antidiabetic regimen for 3 months, and then started the CPAP therapy. All of the patients satisfied the *2003 Diagnostic Criteria of T2DM by American Diabetes Association*. Exclusion criteria were an inability to follow instructions: The existence of sinusitis, nasal polyps, nasal septum deviation, hypertrophy of tongue or tonsil, lymphoid hyperplasia at the base of the tongue or any other respiratory anatomical stenosis; hypothyroidism, acromegaly, adrenal cortical hyperplasia or any other endocrine diseases; taking drugs which affect insulin sensitivity, such as steroids, and application of biguanides, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers within 4 weeks before enrollment. The study was approved by the Ethics Commission of the Institutional Review Board of the Beijing Hospital, and all the patients gave written informed consent to participate.

General data

The data of all subjects including age, gender, height, and weight were recorded in detail. The height of the patients was measured barefoot standing before and after the experiment, and the weight was measured by emptying the bladder, fasting, and single underwear. Body mass index (BMI, kg/m^2) = $weight/height^2$.

Polysomnography monitoring

The patients were subjected to nocturnal sleep polysomnography monitoring for at least 7 h at the sleep center with an Alice 4 Polysomnography Device that simultaneously recorded the following: (1) Oronasal airflow, (2) snoring, (3) percutaneous oxygen saturation (mean SaO_2 and minimum SaO_2), and (4) chest and abdominal breathing movements. These measurements were recorded and automatically calculated by a computer. Apnea was scored when cessation of airflow for 10 s or longer was observed, while hypopnea was defined as 50% or greater reduction of air flow from the normal range accompanied by a 4% or greater decline of SaO_2. An apnea or hypopnea event occurs when a paradoxical thoracoabdominal motion is defined as obstructive.

According to international standards,[5] the average number of apnea and hypopnea events during at least 7 h of sleep was defined as the apnea-hypopnea index (AHI). Patients with an AHI ≥5 and mainly obstructive apnea were diagnosed with OSAHS.

Continuous glucose monitoring system

Interstitial glucose levels were monitored using the continuous glucose monitoring system (CGMS; San Meditech Co. Ltd., China) for up to 72 h. The measurement principle is as follows: (1) The glucose-sensing probe is a glucose oxidase platinum electrode that contains a layer of semi-permeable membrane; (2) the sensing probe is implanted subcutaneously; (3) the interstitial glucose penetrates through the semi-permeable membrane and reacts with glucose oxidase in a redox reaction; (4) electrical signals proportional to the glucose concentration are generated; (5) the signals are transferred through the cables and converted to blood glucose values by a glucose recorder, downloaded to a computer by an information extractor, and finally analyzed by software. In this study, electrical signals were recorded every 11 s, and the average 3-m signals were saved, providing 480 glucose level readings per day, and 1440 data points for 3 consecutive days. Meanwhile, finger blood glucose levels were monitored at seven time points each day, including before breakfast, 2 h after breakfast, before lunch, 2 h after lunch, before supper, 2 h after supper, and at bedtime.

According to the CGMS results of a day before and after therapy, the following parameters were calculated: (1) Mean blood glucose (MBG) level (MBG^1): The average value and standard deviation (SD) of the 480 data points recorded during the 24-h of CGMS. (2) Mean ambulatory glucose excursions ($MAGE^1$): Ambulatory glucose excursions (AGE^1) that were calculated as the absolute distance from the summit to the valley. When AGE^1 was greater than the SD of MBG^1, an effective glucose excursion was counted, and the average number of all effective glucose excursions (NGE^1) was then recorded. (3) Absolute mean of daily differences (MODDs): The mean absolute deviation of matched values between two consecutive 24-h periods of CGMS monitoring. (4) The difference between the highest and lowest level of blood glucose (BG_{diff}^1): Calculated as the difference between the highest and lowest blood glucose values during 24 h of continuous glucose monitoring. (5) T_{BG} >7.8 mmol/L and T_{BG} >11.1 mmol/L: Recorded as the proportion of time that the blood glucose value was >7.8 mmol/L and 11.1 mmol/L, respectively. (6) T_{BG} <3.9 mmol/L: Recorded as the proportion of time that the blood glucose value was <3.9 mmol/L. (7) MBG level at night: The average value and SD of the 120 data points recorded from midnight to 6:00 a.m of CGMS (8) MAGEs

at night ($MAGE^2$): AGEs at night (AGE^2) were calculated as the absolute distance from the summit to the valley from midnight to 6:00 a.m. When AGE^2 was greater than the SD of MBG^2, an effective glucose excursion was counted, and the average and NGE^2 were then recorded. (9) The difference between the highest and lowest level of blood glucose at night (BG_{diff}^2): Calculated as the difference between the highest and lowest blood glucose values from midnight to 6:00 a.m. (10) postprandial blood glucose (PBG) (PBG_1: The blood glucose after breakfast; PBG_2: The blood glucose after lunch; PBG_3: The blood glucose after supper): Calculated as the average glucose levels of the interstitial fluid glucose from 120 m to 135 m after meals.

Blood biochemical examination

Subjects fasted overnight for 10 h, and blood samples were drawn at 6:00 a.m. from the median cubital vein to measure fasting blood glucose (FBG), glycohemoglobin (HbA1c), and fasting insulin (FINS). FBG levels were measured in a local clinical biochemical laboratory using an Imx Analyzer Biochemical Analyzer (Abbott Inc., USA) with intra-batch and inter-batch coefficients of variation (CVs) <5%. HbA1c levels were tested by HPLC with intra-batch and inter-batch CVs <3%. FINS levels were tested by radioimmunoassay. IR was evaluated by the homeostasis model assessment of IR (HOMA-IR) index with the following formula: FINS (in mIU/L) × FBG (in mmol/L)/22.5.

Intervention

After the completion of baseline CGMS monitoring, 43 subjects were treated with a CPAP automatic single-level ventilator (ResMed Inc., USA). The CPAP treatment were adjusted according to the situation of patients who using ventilator after 1-3 days for trying. The CPAP treatment lasted 4 h per night for at least 4 weeks. All the subjects were instructed to maintain a constant lifestyle and antidiabetic regimen.

Statistical analysis

The normal distribution test was conducted in the variables, and the abnormal distribution test was applied to analyze the data after logarithm transition or nonparametric-test (the rank sum test). The normal distribution parameters are represented as mean ± standard deviation (SD) while abnormal distribution parameters are represented as medians and quartiles. All statistics were analyzed with SPSS 11.5 (SPSS Inc., USA). Comparisons of pre- and post-treatment values were performed by paired *t*-tests, with a $P < 0.05$ being statistically significant.

Results

Three patients quit from the study because they could not tolerate the CPAP therapy. The average age of the other 40 subjects was 54.8 ± 9.8 years, 28 males and 12 females, their mean BMI was 29.80 ± 3.50 kg/m^2, and AHI was 30.65 ± 18.56. The mean mechanical ventilation time was 57.03 ± 24.85 d, with an average daily ventilation time of 5.57 ± 1.19 h/d. The average continuous glucose monitoring time was 70.61 ± 9.19 h. There was a good correlation between the subcutaneous interstitial glucose concentration and reference fingertip blood glucose. While the mean absolute difference was 3.15%, the correlation coefficient was 0.937.

Biomedical parameters

We found that the BMIs of the patients did not significantly change after at least 30 days of CPAP treatment. However, HbA1c and FBG were significantly reduced compared with pretreatment levels ($P < 0.05$). Furthermore, HOMA-IR was also significantly reduced ($P = 0.034$) [Table 1].

Continuous glucose monitoring

MBG values were significantly reduced after at least 30 days of CPAP treatment. Moreover, the indicators that reflect the stabilization of blood glucose, such as SD, MAGE, MODD, and BG_{diff}, were significantly reduced compared with pretreatment values ($P < 0.05$). Furthermore, the time percentage of hyperglycemia and PBG was significantly decreased ($P < 0.05$). In our study, however, the NGE and time percentage of hypoglycemia did not significantly change after treatment with CPAP ($P > 0.05$) [Table 2].

Discussion

T2DM is characterized as IR and dysfunction of pancreatic β-cells. Studies have shown that IR is a common phenomenon in OSAHS patients by using either the HOMA index[6] or the hyperinsulinemic-euglycemic clamp test.[7] Previous studies have suggested that SDB due to OSAHS and IR are independent factors, while obesity might link them. Recent findings suggest that glycemic excursions due to IR may be directly worsened by the physiological stress caused by intermittent hypoxia[8] and sleep disruption,[9] and OSAHS

Table 1: HbA1c, FBG, FINS, and HOMA-IR and its comparison pre- and post-treatment

Characteristics	*n*	Pretreatment	Posttreatment	*P*
BMI (kg/m^2, mean±SD)	40	29.80 ± 3.50	29.72 ± 3.55	0.191
HbA1c (%, mean (range))	40	8.70 (7.40, 10.40)	6.95 (6.38, 7.52)	<0.001
FBG (mmol/L, mean±SD)	40	9.35 ± 2.89	6.68 ± 1.19	<0.001
AHI, mean±SD	40	30.66 ± 2.79	3.95 ± 0.35	<0.001
SBP (mmHg, mean±SD)	40	129.53 ± 3.75	129.19 ± 3.77	0.83
DBP (mmHg, mean±SD)	40	86.51 ± 7.44	86.16 ± 7.78	0.83
TC (mmol/L)	40	6.07 ± 2.31	4.82 ± 1.09	0.219
TG (mmol/L)	40	2.64 ± 2.03	2.26 ± 1.43	0.307
LDL-C (mmol/L)	40	3.28 ± 1.10	2.64 ± 0.68	0.001
FINS (μU/ml)	40	8.06 (5.19, 13.70)	8.30 (5.09, 11.30)	0.442
HOMA-IR	40	3.57 (1.95, 5.08)	2.48 (1.38, 3.90)	0.013

BMI: Body mass index; HbA1c: Glycated hemoglobin; FBG: Fasten blood glucose; HOMA-IR: Homeostasis model assessment insulin resistance; AHI: Apnea-hypopnea index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglyceride; FINS: Fasting insulin; LDL-C: Low density lipoprotein-cholesterol.

Table 2: The change of continuous glucose monitoring pre- and post-CPAP treatment

Items	*n*	Pretreatment	Posttreatment	*P*
MBG^1 (mmol/L, mean (range))	40	7.85 (6.80, 9.85)	6.75 (5.92, 7.68)	<0.001
SD^1 (mmol/L, mean (range))	40	1.84 (1.35, 2.52)	1.12 (0.86, 1.46)	<0.001
$MAGE^1$ (mmol/L, mean (range))	40	4.06 (2.98, 5.54)	2.68 (1.97, 3.28)	<0.001
NGE^1 (times/d, mean±SD)	40	6.00 ± 1.91	6.68 ± 1.90	0.060
MODD (mmol/L, mean (range))	40	1.76 (1.16, 2.87)	1.29 (0.85, 1.81)	0.001
BG_{diff}^1 (mmol/L)	40	8.46 ± 3.32	5.24 ± 1.76	<0.001
MBG^2 (mmol/L, mean (range))	40	6.35 (5.50, 7.90)	6.00 (5.13, 6.55)	0.030
SD^2 (mmol/L)	40	0.73 ± 0.51	0.53 ± 0.38	0.012
$MAGE^2$ (mmol/L, mean (range))	40	1.29 (1.05, 2.38)	0.91 (0.59, 1.83)	0.008
NGE^2 (times/day, mean±SD)	40	3.55 ± 1.75	3.83 ± 1.85	0.456
BG_{diff}^2 (mmol/L, mean (range))	40	2.25 (1.52, 3.85)	1.60 (1.13, 3.05)	0.029
T_{BG} >7.8 (mmol/L) (%, mean (range))	40	37.5 (27.5, 75.3)	19.25 (5.28, 42.43)	<0.001
T_{BG} >11.1 (mmol/L) (%, mean (range))	40	11.80 (0.00, 31.63)	0.00 (0.00, 0.45)	<0.001
T_{BG} <3.9 (mmol/L) (%, mean (range))	40	0.00 (0.00, 0.60)	0.00 (0.00, 0.00)	0.522
PBS_1 (mmol/L, mean±SD)	40	9.77 ± 3.00	7.77 ± 2.08	<0.001
PBS_2 (mmol/L, mean±SD)	40	9.82 ± 3.48	7.58 ± 1.87	<0.001
PBS_3 (mmol/L, mean±SD)	40	9.93 ± 3.06	7.63 ± 1.48	<0.001

MBG^1: Mean blood glucose level; $MAGE^1$: Mean ambulatory glucose excursions; MODD: Absolute means of daily differences; NGE^1: Numbers of glucose excursions; BG_{diff}^1: The difference between the highest and lowest blood glucose values of 24 h of continuous glucose monitoring; MBG^2: MBG level at night; NGE^2: Numbers of glucose excursions at night; BG_{diff}^2: The difference between the highest and lowest blood glucose values at night; T_{BG} > 7.8 (mmol/L): The time span percentage when blood glucose value >7.8 mmol/L; T_{BG} > 11.1 (mmol/L) refers to time span percentage when blood glucose value <3.9 mmol/L; PBS_1: Postprandial blood glucose (after breakfast); PBS_2: Postprandial blood glucose (after lunch); PBS_3: Postprandial blood glucose (after supper); SD: Standard deviation.

might be an independent risk factor for blood glucose disturbances among patients with diabetes.[10]

The principle of CPAP treatment for OSAHS is to enforce positive airway pressure throughout the entire exhalation and inhalation process during spontaneous breathing, which prevents airway contraction, increases pulmonary functional residual capacity, improves pulmonary compliance, reduces breathing consumption, and lessens the severity of airway resistance. Moreover, upper airway muscle function is enhanced through the afferent inputs and feedbacks from the chest wall and vagus nerve, which keeps the upper respiratory tract open. Researchers have studied whether CPAP therapy for OSAHS improves glucose and lipid metabolism, but the limitation in the number of subjects and controls in most of those studies may have been insufficient to demonstrate an effect of CPAP therapy in obese or nondiabetic patients. Our study demonstrated that there was a decrease in HOMA-IR that insulin sensitivity improved and that FPG levels significantly decreased after at least 30 days of CPAP treatment. These findings were consistent with the report from Pamidi *et al*.[11] and Iftikhar *et al*.[12] In contrast, another recent randomized controlled trial[13] reported that CPAP did not improve HbA1c levels. Generally, CPAP therapy takes effect only after treatment of 4 h or more per night, implying that the benefit of treatment would not be obvious when patients receive a shorter treatment time.[14]

The previous results show that changes in HbA1c may be related to changes in sleep quality and sleep fragmentation.[15] Whether CPAP therapy is beneficial to reduce the HbA1c levels in patients with T2DM is still controversial. Shpirer *et al*.[16] found that HbA1c levels were significantly reduced after 3–5 months of CPAP treatment in 30 patients with OSAHS in diabetes and prediabetes. While a recent systematic review suggested that CPAP therapy dose not lower the HbA1c level in patients with OSAHS and T2DM.[17] In our study, CPAP can effectively reduce the HbA1c level of the patients ($P < 0.001$).

Current considerations of the functional impairments caused by the dysfunction of glycemic excursions and exacerbated IR due to OSAHS might include the following components: (1) Activation of the sympathetic nervous system: OSAHS patients have high sympathetic nervous activity whether they are asleep or awake, which induces IR by increasing glycogenolysis and triggering gluconeogenesis. The increased sympathetic activity is likely to be related to nocturnal hypoxia, and sympathetic activity may also be boosted by repeated awakening during obstructive sleep apnea. (2) Direct effects hypoxia: Hypoxia due to OSAHS may increase anaerobic glycolysis, resulting in pyruvate being partially reduced to lactic acid without oxidation and then converted to heparin in the liver. Intermittent hypoxia in the general population may decrease insulin sensitivity and increase IR and has a strong independent association with poorer glycemic control.[18] (3) Hypothalamic–pituitary–adrenal (HPA) dysfunction: Hypoxia and sleep pattern disorders may lead to dysfunction of the HPA axis, abnormal elevation of glucocorticoid levels, and worsening of IR. (4) Systemic inflammatory response: Studies have shown that all OSAHS patients with or without obesity have elevated inflammatory markers (interleukin-6 [IL-6], IL-10, and tumor necrosis factor-α).[19] These inflammatory factors may affect glucose metabolism by inhibiting glucose uptake in fat and muscle and increasing the levels of hormones that counteract insulin. (5) Adipocytokines: Elevated leptin levels with decreased adiponectin levels occur in patients with OSAHS.[20] In addition, the reduction of patients' physical activities or increased sedentary behavior caused by fatigue

and somnolence due to OSAHS may also be a risk factor of diabetes.

Daily glycemic excursions in patients with T2DM have the following characteristics: (1) high PBG levels, and (2) the blood glucose nadir appears at a period between 1:00 a.m. and 6:00 a.m. Nocturnal severe hypoxemia has a direct impact on the amplitude of glycemic excursions in patients with T2DM and OSAHS. The results of this study also demonstrate that the MAGE and MODD levels of the patients were significantly lower ($P < 0.05$ and $P = 0.002$), as was the hyperglycemia time percentage, after CPAP treatment. Dawson *et al*.[21] found that CPAP treatment did not significantly improve PBG in patients with OSAHS and T2DM. They speculated that PBG was mostly affected by mealtime and food type, which could not be regulated by CPAP treatment. In contrast, the results of Babu *et al*.[22] support the idea that CPAP treatment significantly improved PBG levels. In this study, all the interstitial PBG levels (PBG_1, PBG_2, and PBG_3) monitored by CGMS were significantly different when pre- and post-treatment levels were compared ($P < 0.05$ for each). Indicating that CPAP therapy may have a beneficial effect on improving not only blood glucose but also upon insulin sensitivity in T2DM patients with OSAHS, due to improved sleep quality and decreased IR.

This study also compared nocturnal glycemic excursions before and after CPAP treatment, showing significant differences in nocturnal MBG and glycemic excursions. Compared to pretreatment, the posttreatment MAGE, and BG_{diff} levels significantly decreased ($P = 0.049$ and $P = 0.024$, respectively) during the time between midnight and 6:00 a.m. Pamidi *et al*.[13] reached the same conclusion. In the latter study, the CPAP treatment efficacy for improving interstitial MBG and glycemic excursions in the treatment of patients with T2DM and OSAHS occurred at the beginning of CPAP application. In this study, the nocturnal MBG and glycemic excursions after CPAP treatment were significantly decreased, suggesting that CPAP treatment may have improved the intermittent night time hypoxia in OSAHS patients. Once the hypoxia state was corrected, the overall nocturnal MBG decreased compared to the pretreatment MBG levels, similar to the decrease in MAGE levels, which reflect the glycemic excursions.

In this study, only 3 of 43 subjects (7.0%) were excluded because of nonadherence to the CPAP therapy. The major limitation of our study was the lack of a control group. The study conducted by West *et al*.[23] suggested that study results might be influenced if subjects modified their behaviors, including diet and exercise, because they knew they were being monitored. In this study group, BMI did not significantly decrease, which suggests that their diet and exercise did not substantially change, at least during the CPAP treatment period.

Our findings need to be confirmed by a larger study that randomly assigns subjects to sham-CPAP and effective-CPAP groups. CPAP treatment not only improves sleep quality in patients with T2DM but also significantly improves insulin sensitivity and reduces the HbA1c level in patients with OSAHS and T2DM. In addition to lifestyle intervention and drug treatment, CPAP treatment might be an effective treatment for T2DM patients, particularly in poorly controlled subjects on maximum therapeutic regimens.

Financial support and sponsorship

This study was supported by the grant from the Foundation of Beijing Municipal Science and Technology Commission (No.B141107005314005).

Conflicts of interest

There are no conflicts of interest.

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