Original Article

Efficacy of continuous positive airway pressure for obstructive sleep apnea in overweight patients with type 2 diabetes mellitus

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Abstract: Although the association between obstructive sleep apnea (OSA) and type 2 diabetes mellitus (T2DM) is well-established, the impact of continuous positive airway pressure (CPAP) therapy on glycemic control or metabolic profiles in T2DM patients with OSA is unclear. The objective of this study was to investigate metabolism-related parameters and diabetes treatment satisfaction following CPAP therapy for OSA in overweight patients with T2DM or impaired glycemic tolerance. This retrospective study included 16 overweight patients treated with CPAP for OSA by comparison of laboratory and anthropometric data between baseline (3 months before initiation of CPAP treatment) and at 3- and 6-months post-treatment, and by psychometric scores of DM treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Significant reductions in body weight and waist circumference were observed after initiating CPAP therapy (both \( P < 0.001 \)). Mean glycosylated hemoglobin (HbA1c) level measured at 3 months after CPAP therapy was lower than the baseline assessment, and the mean HbA1c level at 6 months post-treatment was lower than that at 3 months post-treatment (both \( P < 0.05 \)). In addition, fasting and postprandial plasma glucose levels decreased significantly at 3 months after CPAP therapy, remaining stable at 6 months (\( P < 0.009 \)). Furthermore, significant decreases in fasting insulin level (\( P = 0.037 \)), postprandial insulin level (\( P < 0.001 \)), and triglyceride level (\( P = 0.002 \)) were observed following CPAP. Finally, satisfaction with diabetes treatment improved significantly following initiation of CPAP therapy (\( P < 0.001 \)). CPAP for OSA improved anthropomorphic measures as well as glycemic control, insulin sensitivity and diabetes treatment satisfaction in overweight patients with T2DM or abnormal glucose metabolism.

Keywords: Continuous positive airway pressure, obstructive sleep apnea, overweight, type 2 diabetes mellitus

Introduction

Obstructive sleep apnea (OSA) is characterized by repeated episodes of complete (apnea) or partial (hypoeapnea) upper airway blockage during sleep that can interrupt sleep and result in intermittent hypoxia [1]. Obesity is a risk factor for developing OSA due to upper airway narrowing and reduced lung volume as a result of soft tissue enlargement [2]. Thus, the prevalence of OSA has increased in recent decades due to the epidemic of obesity. Approximately 50%-60% of obese patients or those with metabolic syndrome have OSA [3, 4]. Furthermore, analysis of obese patients with type 2 diabetes mellitus (T2DM) revealed that 86% had OSA [5], and it is reported that 15%-30% of individuals with OSA have T2DM [6].

Cross-sectional, observational, and population-based studies have shown a consistent link between OSA and insulin resistance (IR), glucose intolerance and T2DM [7-10]. In addition, analysis of 475 patients with suspected OSA revealed that concomitant OSA and metabolic syndrome (MS) frequency was 70.52% in those who were obese [11]. Furthermore, OSA is an independent risk factor for T2DM [6]. Studies in animals [12] and healthy volunteers [13] have also shown that acute intermittent hypoxia can induce IR, and chronic intermittent hypoxia altered fasting hyperglycemia and induced glucose intolerance and IR in obese mice [14, 15].
The apparent association of OSA and T2DM suggests that OSA treatment, which primarily consists of continuous positive airway pressure (CPAP) therapy, may improve glycemic control or metabolic profiles in T2DM patients with OSA [16]. However, results of studies analyzing the effects of CPAP on glycemic dysregulation have been inconsistent [17-19]. In a systematic review of 22 studies examining the impact of CPAP for OSA in T2DM patients, improvements in HbA1c, postprandial and nocturnal glucose, and insulin sensitivity were observed following CPAP therapy, with greater improvement after its long-term use [19]. In contrast, another recent systematic review and meta-analysis that included six randomized, controlled studies or prospective observational studies showed that CPAP had no impact on HbA1c or body mass index (BMI) but did improve insulin sensitivity [18].

This retrospective, observational small-scale study aimed to ascertain whether OSA treatment by CPAP improves glycemic control and diabetes treatment satisfaction in overweight OSA patients with T2DM or impaired glucose tolerance. The results showed that several diabetic markers and anthropometric parameters were all improved significantly after CPAP treatment. In addition, satisfaction with diabetes treatment as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) improved significantly following initiation of CPAP therapy.

Table 1. Baseline characteristics of overweight patients treated with CPAP for OSA (n=16)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>49.5 ± 6.7</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.4 ± 1.9</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>13 (81.3%)</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>3 (18.8%)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Oral agents</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>Lifestyle intervention</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Duration of OSA (y)</td>
<td>3.8 ± 2.2</td>
</tr>
</tbody>
</table>

Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; SD, standard deviation. *Values represent either n (%) or mean ± SD.

Material and methods

Study design and patients

This retrospective study included 16 overweight patients (eight males and eight females) with OSA who had a complete medical record and were treated from January 2013 to November 2014. Thirteen patients were diagnosed with T2DM and three with impaired glucose tolerance using the World Health Organization (WHO) criteria [20]. Anthropometric and laboratory data of candidate patients who had received CPAP treatment were retrieved from medical charts. The therapeutic protocol for T2DM or impaired glucose tolerance remained unchanged. This study was approved by the Institutional Review Board of the Guangdong General Hospital. Due to the retrospective nature of this study, informed consent was waived.

OSA diagnosis and treatment

OSA was diagnosed by real-time monitoring of sleep using standard 12-channel polysomnography (PSG) and mobile monitoring and using the definitions of the American Academy of Sleep Medicine (AASM) Manual for Scoring of Sleep and Associated Events. For each patient, CPAP was performed for >4 h daily for >5 times weekly. PSG was also used to confirm a diagnosis of OSA. In addition, OSA duration was determined by medical record review.

Laboratory analyses

Blood samples were collected from each participant, and metabolism-related parameters were measured before initiation of CPAP (baseline) as well as at 3 and 6 months following treatment initiation. The following parameters were assessed using the manufacturers’ protocols: glycosylated hemoglobin (cation-exchange high-performance liquid chromatography; BioRad, Hercules, CA, USA), cholesterol (colorimetry; Beckmann Coulter, Brea, CA, USA), blood glucose (Beckmann Coulter), and insulin (electrochemiluminescence; Roche Diagnostics, Rotkreuz, Switzerland).

Analysis of treatment satisfaction

The DTSQ was employed to evaluate patients’ quality of life before and after initiation of CPAP,
Effects of CPAP for OSA

Table 2. Effects of CPAP therapy on the clinical characteristics of overweight patients with OSA (n=16)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-CPAP</th>
<th>3 months</th>
<th>6 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>78.4 ± 10.0</td>
<td>75.4 ± 9.7</td>
<td>73.7 ± 8.6</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.9 ± 9.6</td>
<td>86.4 ± 8.5</td>
<td>84.0 ± 7.3</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137.0 ± 7.7</td>
<td>136.9 ± 6.5</td>
<td>0.841b</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86.0 ± 6.8</td>
<td>85.7 ± 6.1</td>
<td>0.715b</td>
<td></td>
</tr>
<tr>
<td>DTSQ score</td>
<td>23.7 ± 1.6</td>
<td>28.1 ± 2.4</td>
<td>&lt;0.001b</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; DTSQ, diabetes treatment satisfaction questionnaire. aAnalyzed using repeated-measures analysis of variance. Pair-wise comparisons between any two time points were performed with Bonferroni correction. bAnalyzed using a paired t-test. P<0.05, compared with the baseline measurement. P<0.05, compared with measurements at 3 months after CPAP treatment.

Discussion

Although links between OSA and T2DM have been observed consistently [7-10], the effects of CPAP therapy on the metabolic profiles of T2DM patients with OSA are inconsistent [17-19]. In the present retrospective study, significant reductions in body weight and waist circumference, as well as improvements in glycemnic control, insulin sensitivity and triglyceride levels, were observed 3 months after initiation of CPAP therapy and were maintained at 6 months. In addition, satisfaction with diabetes treatment improved significantly following initiation of CPAP therapy (P<0.001). CPAP therapy did not alter blood pressure levels (P=0.841 for systolic blood pressure and P=0.715 for diastolic blood pressure).
Effects of CPAP for OSA

With the exception of blood pressure, which was not affected, the improved metabolic parameters observed in the present study are consistent with previous reports [23, 24]. Specifically, in patients with metabolic syndrome, CPAP therapy for >4 h/night for 8 weeks improved blood pressure, triglyceride levels and glucose levels to a greater extent than in those using CPAP for <4 h/night [23]. In a randomized, double-blind, crossover study, Sharma et al. [24] observed decreases in blood pressure as well as cholesterol, triglyceride, and Hba1c levels with CPAP therapy. However, other studies did not observe an improvement in glucose metabolism with CPAP treatment in obese patients with [25] and without [26] T2DM, which may be due to lower compliance (use of an average of 3.9 h/night vs. >4 h/night in the present study). Thus, further studies are required to examine the extent to which CPAP duration impacts metabolic parameters.

Previous studies have shown that CPAP therapy reduces OSA-associated IR and diabetic inflammation, which may reduce pancreatic β cell damage [16]. Furthermore, reduced metabolic hormone levels, including adiponectin and leptin, were observed after 3 months of CPAP in obese individuals [27]. As observed previously with the application of CPAP and left ventricular remodeling in patients with abdominal obesity [28], the metabolic improvements observed in the present study may be due at least in part to the accompanying reductions in weight and waist circumference following CPAP therapy, which continued to improve at 6 months post-treatment. Similarly, Sharma et al. [24] reported that BMI and visceral adiposity were reduced after CPAP. However, not all studies noted such changes in anthropomorphic indices [29, 30], and a recent meta-analysis of randomized trials showed that CPAP may actually increase BMI and body weight [31]. These inconsistencies may be due to differences in the duration and frequency of the CPAP therapy as well as CPAP compliance, which may be different for obese and non-obese individuals [32]. Because the patients in the present study only received CPAP and were not participating in a diet or exercise program simultane-

**Figure 1.** Changes in biochemical measures for overweight patients with OSA before and after CPAP therapy (n=16). Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea. HbA1c and triglyceride were analyzed by paired t-test. Plasma glucose and insulin were analyzed by repeated-measures analysis of variance; pair-wise comparisons between any two time points were performed with Bonferroni correction. *P*<0.05, compared with the baseline measurement. †*P*<0.05, compared with measurements at 3 months after CPAP treatment.
ously, their weight loss appears to be a consequence of the CPAP therapy and parallel to the improvement of other parameters, including blood glucose. However, further analyses are required to fully elucidate the effects of CPAP on body weight and BMI.

Although it is known that obesity is a risk factor for developing OSA [2], and that OSA is highly prevalent in obese patients with T2DM (up to 86%) [5], the relationship between OSA and the occurrence of metabolic syndrome is not well-characterized. OSA may increase the risk of developing T2DM [33]; thus, it is possible that OSA and T2DM coexist due to shared risk factors, including obesity [34]. Additionally, studies showing altered glucose metabolism in non-diabetic individuals with OSA independent of obesity [7, 35, 36] suggest that OSA and T2DM may be linked by an underlying metabolic disorder. Analysis of patients with suspected OSA revealed that those with metabolic syndrome had significantly lower levels of nesfatin-1, a neuropeptide that regulates food ingestion as well as paradoxical sleep [37]. Because the level of nocturnal hypoxia is related to IR [38], OSA-associated hypoxia may induce concomitant metabolic dysfunction [39]. This is consistent with the results of our study as well as those of another study involving 31 nondiabetic obese adolescents in whom hypercapnia was associated with carotid narrowing [40].

A relationship between intermittent hypoxia and IR has been shown in both animals [12] and healthy volunteers [13]. Analysis of the effects of intermittent hypoxia have shown increased hepatic inflammation, oxidative stress, and steatosis as well as increased pancreatic β cell death and decreased glucose-induced insulin secretion [39]. In skeletal muscle, decreased glucose metabolism and GLUT4 translocation was observed with intermittent hypoxia [39]. In addition, impaired sympathetic nervous system activation that has been observed in patients with OSA can be induced with intermittent hypoxia [41, 42], which has the potential to impact lipid and glucose metabolism [39]. Given the beneficial effects of CPAP treatment on glycemic control and insulin sensitivity observed in the present study, we propose that OSA may cause secondary diabetes that develops independent of insulin-dependent, non-insulin-dependent, or gestational diabetes mellitus, and this underlying mechanism may be ameliorated by CPAP. However, further studies are necessary to explore this hypothesis.

The present study is limited by its retrospective nature. In addition, we did not examine the effects of sleep improvement with CPAP on the metabolic parameters assessed. Finally, the present study focused on overweight patients with OSA who also had T2DM or impaired glucose control; therefore, further studies are needed to determine the impact of CPAP therapy in otherwise healthy adults with OSA.

In conclusion, glycemic control and insulin sensitivity improved significantly after CPAP treatment. In addition, patients' satisfaction with diabetes treatment improved significantly following initiation of CPAP therapy.

Disclosure of conflict of interest

None.

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Effects of CPAP for OSA


