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Continuous Positive Airway Pressure Therapy Improves Hypoadiponectinemia in Severe Obese Men With Obstructive Sleep Apnea Without Changes in Insulin Resistance

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Abstract

Background: Obstructive sleep apnea (OSA) is associated with several conditions that could facilitate the onset of cardiovascular and metabolic dysfunctions. Continuous positive airway pressure (CPAP) therapy has been shown to improve cardiovascular morbidity and mortality related to OSA, but the mechanisms underlying this association are not fully understood.
Objective: The aim of the present study was to evaluate whether sleep apnea contributes to insulin resistance and inflammatory marker alterations and to evaluate the benefits of nasal CPAP therapy in severe obese patients with OSA.
Methods: Plasma inflammatory cytokines and the homeostasis model assessment of insulin resistance index (HOMA-IR, Insulin Sensitivity Index [ISI]) were measured in severe obese male with OSA ($n = 16$) and compared with body mass index (BMI)-matched male controls without OSA ($n = 13$). Seven patients with severe sleep apnea (apnea–hypopnea index >30 events/h) were reevaluated after 3 months of nasal CPAP therapy.
Results: OSA patients had a significantly lower adiponectin levels than obese controls (8.7 ± 1.18 ng/mL vs. 15.0 ± 2.55 ng/mL, $P = 0.025$). HOMA-IR, ISI, tumor necrosis factor-α (TNF-α, C-reactive protein (CRP), and interleukin-6 (IL-6) levels were not different between groups. Although insulin resistance index and BMI values did not change after 3 months of nCPAP therapy, adiponectin levels increased ($P = 0.036$) and the levels of TNF-α tended to decrease ($P = 0.065$). Changes in adiponectin levels during nCPAP therapy were positively correlated with an improvement in minimum oxygen saturation ($r = 0.773$; $P = 0.041$) and negatively correlated with changes in TNF-α levels ($r = -0.885$; $P = 0.008$).
Conclusions: nCPAP therapy reverses hypoadiponectinemia levels present in obese men with OSA, probably through reductions in hypoxia and inflammation activity.

Introduction

Obstructive sleep apnea (OSA) affects 2–4% of middle-aged adults, and a significant percentage of patients with this respiratory disturbance are obese men with central adiposity.[1] Despite the problems with hypersomnolence, decreased cognitive functions, and motor vehicle crashes, the strong association between OSA and cardiovascular diseases has led some authors to suggest that OSA is a manifestation of metabolic syndrome rather than a local anatomic abnormality.[2] Evidence indicates that treatment with nasal continuous positive airway pressure (nCPAP) reduces hypersomnolence and improves quality of life, in addition to decreasing many cardiovascular morbidity and mortality related to OSA.[3]

Given that central obesity is a common risk factor for several diseases, it remains to be determined whether central obesity *per se* could be a confounding factor for the abnormalities present in OSA.[4] Adipose tissue, specifically visceral abdominal fat, is a rich source of inflammatory cytokines such

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as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Some authors have been found elevated levels of TNF-αF and IL-6 in sleep apneic patients independent of obesity, and their increased secretion is associated with sleepiness, fatigue, and the development of a variety of metabolic and cardiovascular diseases.[5] Adiponectin is a protein secreted exclusively by white adipose tissue with antiinflammatory, antiatherosclerosis, and insulin-sensitizing effects. It has been suggested that reduced plasma adiponectin levels could partly explain increased cardiovascular disease in obstructive sleep apnea patients. However, previous studies on the relationship between adiponectin and OSA have yielded conflicting results.[6–12] Some studies have shown a decrease of adiponectin levels[6,10,11] in patients with OSA whereas others do not.[7–9,12]

Insulin resistance has been long considered to have a central role in the development of a range of metabolic abnormalities, which are known to increase cardiovascular risk. Recently, epidemiologic and observational studies have suggested that OSA is an independent risk factor for insulin resistance, but the effects of CPAP on insulin resistance remain controversial.[13,14]

On the basis of these findings, the aim of this study was to evaluate insulin resistance and adiponectin in severe obese patients with and without OSA and to assess the effects of nCPAP treatment on these parameters.

Patients and Methods

Sixteen severely obese men (defined as BMI ≥40 kg/m^2) with documented OSA, defined by an apnea–hypopnea index (AHI) ≥10 events per hour of sleep and symptoms of excessive daytime sleepiness, were recruited from the Obesity Outpatient Clinic and Sleep Disorders Center of the Universidade Federal de São Paulo and compared with 13 men without OSA (AHI <5 events per h of sleep) matched for age and body mass index (BMI). All patients were on the waiting list for bariatric surgery.

Subjects with a history of smoking, alcohol abuse, diagnosis of diabetes, pharmacological obesity treatment, cardiovascular disease, malignancies, thyroid disorders, or chronic renal or hepatic failure or who were receiving sleep apnea treatment with nCPAP were excluded from the study.

Physical examinations and anthropometric measurements were recorded, including weight (in kilograms), height (in meters), waist circumference (in centimeters), and BMI (in kg/m^2). Polysomnograms were recorded by the Sleep Analyser Computer (Alice 3 Diagnostics system, Respironics, Murrysville, PA), including one for OSA diagnosis and another for positive airway pressure titration. The following channels were included: 3 for electroencephalography, 2 for oculogram channels, 2 for chin and tibial electromyography, 1 for electrocardiography, 1 for airflow (nasal pressure), 2 for thoracic-abdominal movements (calibrated inductance plethismography), 1 for tracheal sound (snoring), 1 for pulse oxymetry, and 1 for recording of body position. An experienced sleep physician scored the sleep stages,[15] arousals, and respiratory events according to American Sleep Disorders Association criteria.[16,17]

After 12 hours of overnight fasting, baseline blood samples were obtained for measurements of plasma glucose, insulin, and adiponectin. Thereafter, an oral glucose load (75 grams) was given and, after 2 hours, plasma glucose and insulin were measured. Glucose was determined by hexokinase method (Hitachi 912 analyzer, Roche Diagnostics) and insulin was measured by commercialized two-site sandwich immunoassay using direct chemiluminescent technology (ADVIA Centaur Insulin Assay; Bayer Diagnostics). The lower detection limit of this assay was 0.1 μU/mL. The inter- and intraassay coefficients of variation (CV) for glucose and insulin were <10%. Hepatic insulin resistance index was assessed by the homeostasis model assesement of insulin resistance (HOMA-IR) calculated as fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5. The Insulin Sensitivity Index for glycemia, or ISI(gly), is a suitable tool to assess whole-body insulin sensitivity in the clinical setting. It was calculated according to the formula developed by Belfiore et al.[18]: $2/[(INSp \times GLYp) + 1]$, where INSp and GLYp are obtained by dividing the sum of plasma insulin (μU/mL) and glycemia (mmol/L), measured at 0 and 2 hours after oral glucose load, by the sum of the respective values for a normal population. These normal reference values were obtained in 35 normotensive subjects with normal BMI.[18]

TNF-α and IL-6 were measured using the immunometric kit (Immulite-DPC, Diagnostic Products Corporation, Los Angeles, CA) with sensitivities of 1.7 pg/mL and 2 pg/mL, an intraassay coefficient of variation (CV) of 2.6–3.6% and 3.5–6.2%, and an interassay CV of 4.0–6.5% and 5.1–7.5%, respectively. Adiponectin was determined by radioimmunoassay (LINCO Research, Inc., St. Charles, MO) with sensitivity of 1.0 ng/mL, intraassay CV of 1.8–6.2%, and interassay CV 6.9–9.2%. High-sensitivity C-reactive protein (CRP) was measured using the chemiluminescent immunometric assay (Immulite-DPC, Los Angeles, CA) with limit of detection 0.01 mg/dL and intra- and interassay coefficients of variation of 4.2–6.4 % and 4.8–10%, respectively.

Six patients with mild or moderate sleep apnea immediately underwent bariatric surgery. Subjects with severe sleep apnea (n = 10) were advised to follow nCPAP therapy before bariatric surgery to avoid surgery complications related with sleep apnea. These patients were reassessed after 3 months of nCPAP use, and all measurements were repeated. One man who failed to use the device and 2 men who failed to collect blood sample were excluded from the follow-up analysis. To assure nCPAP adherence, a follow-up in the outpatient clinic was performed monthly and the average nightly use of nCPAP was analyzed with a run-time course that ran when the patient was breathing through the machine and not just when the machine was switched on. The criteria for good compliance was the use of the device for more than 5 hours per night during the study. A self-reported sleepiness was measured using the Epworth Sleepiness Scale (ESS).[19] During the treatment period, no changes were made in the prescribed medications.

The study was approved by the UNIFESP Ethics Committee, and written informed consent was obtained from all subjects.

Statistical analysis

Normally distributed variables are expressed as means ± standard error (SE) or percentiles when appropriate. Data were analyzed using unpaired Student t-tests or paired t-test where appropriate. To assess differences between categorical variables were used chi-squared statistics. Correlations between variables were performed using Pearson coefficient.

A P value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 13.0.

Results

The final study participants consisted of 29 severely obese males, including 16 patients with OSA and 13 patients without OSA. The mean ± SE ages of the apneics and obese control were 40.1 ± 2.8 and 38.8 ± 3.3 years, whereas their BMIs were 46.9 ± 2.0 and 42.8 ± 1.3 kg/m^2, respectively (P = not significant [N.S.]). The demographic and clinical characteristics of these 2 groups are shown in Table 1. All patients had a very high insulin resistance index, and no significant differences were found in age, waist circumference, body mass, HOMA-IR, and ISI between groups. Plasma adiponectin levels were significantly lower in OSA patients than in obese controls (8.7 ± 1.18 ng/mL vs. 15.0 ± 2.55 ng/mL, P = 0.025). No differences in TNF-α, CRP, and IL-6 levels were observed between groups (Table 1).

After an interval of 3 months, 7 patients with severe OSA treated with a mean nCPAP pressure of 11.5 ± 2.0 cm of H_2O were reassessed. Daytime sleepiness, analyzed by the ESS, improved in all patients (score 10.5 ± 1.0 vs. score 1.5 ± 0.71). Treatment with nCPAP reduced AHI from 91.0 ± 9.7 to 15.3 ± 11.1 events per hour ($P < 0.001$), the arousal index from 52.6 ± 12.0 to 11.2 ± 5.1 arousals per hour ($P = 0.006$), and elevated minimum oxygen saturation from 71.2% ± 2.0 to 86.7% ± 0.99 ($P = 0.001$). The compliance of nCPAP was at an average of 6.6 ± 0.4 hours per night. Although average BMI did not change (46.1 ± 2.8 kg/m^2 vs. 46.8 ± 2.6 Kg/m^2, $P = 0.429$) during follow up, adiponectin levels significantly increased (7.1 ± 1.5 ng/mL vs. 16.0 ± 4.3 ng/mL, $P = 0.036$) and the levels of TNF-α showed a tendency to decrease (9.9 ± 1.8 pg/mL vs. 6.9 ± 1.6 pg/mL, $P = 0.065$), bringing it closer to the levels of obese controls (Fig. 1). No significant differences in CRP, IL-6 levels, and insulin resistance index were observed after nCPAP therapy (Table 2). Correlation analysis showed that changes in adiponectin levels after nCPAP therapy were positively correlated with the improvement of minimum oxygen saturation ($r = 0.773$; $P = 0.041$) and negatively correlated with changes in TNF-α levels ($r = -0.885$; $P = 0.008$).

Discussion

This study shows that plasma adiponectin levels are decreased in severe obese males with OSA compared with BMI-matched obese controls. Furthermore, the findings demonstrate marked improvement in adiponectin levels following nCPAP therapy for 3 months in patients with obstructive sleep apnea. Changes in BMI and insulin resistance index were not observed during nCPAP treatment; therefore, the elevation in adiponectin levels during nCPAP treatment could not be explained by changes in BMI and insulin resistance.

Reduced plasma adiponectin concentration is a risk factor for cardiovascular and metabolic disorder.[5] It has been hypothesized that decreased adiponectin levels in patients with OSA could partly explain the association between OSA and cardiovascular disease. However, there have been conflicting reports regarding the relationship between adiponectin levels and OSA.[6–11,12] Contrasting with our findings, 1 previous study has demonstrated that plasma adiponectin levels are elevated in OSA patients compared with control.[7] Makino et al.[8] have shown that plasma adiponectin levels did not differ between severe, moderate, and mild OSA patients. Consistent with our results, some authors have demonstrated reduced levels of adiponectin in OSA patients compared with controls.[6,10]

After CPAP therapy, Zhang et al. have demonstrated that adiponectin levels did not change in OSA patients on day 3 and day 7 of nCPAP treatment, but a significant elevation in adiponectin levels was observed on day 14 of nCPAP treatment, suggesting an independent effect of OSA on adiponectin levels.[11] On the other hand, Kohler et al.[12] did not demonstrate elevation in adiponectin levels following 4 weeks of CPAP treatment in patients with moderate to severe OSA. This paper was the first and largest double-blind randomized controlled trial that evaluated the beneficial effects of CPAP on adiponectin levels of OSA patients. The reasons for this discrepant finding might be the fact that in our study we enrolled only patients with severe OSA and hypoxemia

Table 1. Clinical and Laboratory Characteristics of Obese Men With and Without Obstructive Sleep Apnea

	OSA		
	No (n = 13)	*Yes (n = 16)*	*P*
AHI, events/h	3.2 ± 0.5	65.7 ± 9.9	<0.001
Age, years	38.8 ± 3.3	40.1 ± 2.8	0.771
Waist, cm	134.1 ± 4.1	137.6 ± 4.6	0.591
BMI, kg/m^2	42.8 ± 1.3	46.9 ± 2.0	0.116
HOMA-IR, mmol • μU • mL^2	8.6 ± 1.3	6.2 ± 0.9	0.129
ISI	0.47 ± 0.10	0.49 ±0.06	0.864
Adiponectin, ng/mL	15.0 ± 2.55	8.7 ± 1.18	0.025
CRP, mg/dL	0.91 ± 0.34	0.83 ± 0.14	0.812
TNF-α, pg/mL	7.5 ± 0.44	10.7 ± 1.66	0.084
IL-6, pg/mL	4.2 ± 1.18	4.9 ± 0.83	0.633
Hypertension , *n* (%)	7 (53.8)	11 (68.8)	0.466

Data are expressed by mean ± standard error (SE) *n* (%).

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

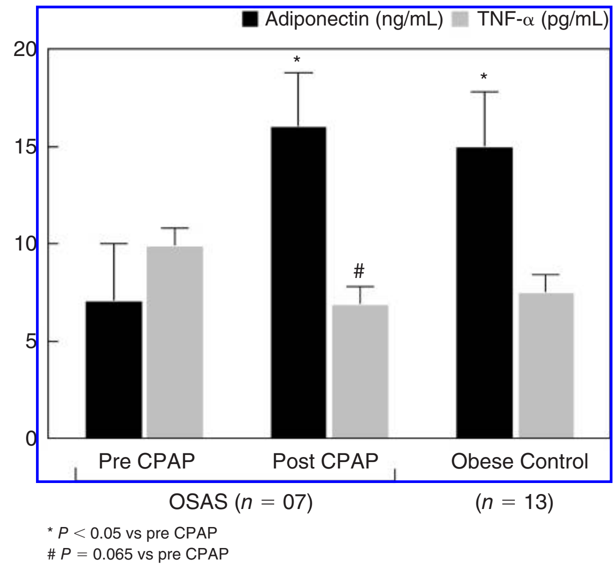

FIG. 1. Plasma adiponectin and TNF-α levels in obese men with and without OSA. Data are expressed by mean ± standard error. Abbreviations: OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; TNF-α, tumor necrosis factor-α.

(minimum oxygen saturation from 71.2% ± 2.0). Recently, Ye et al. have demonstrated in an experimental study that adipose hypoxia inhibits adiponectin in adipose tissue in obese mice.[20] Also, Nakagawa et al. have provided evidence *in vitro* and *in vivo* that sustained exposure to hypoxia decreased adiponectin concentrations by inhibiting adiponectin regulatory mechanisms at secretion and transcriptional levels.[21]

In concordance with this hypothesis, after CPAP therapy, we found that improvement in minimum oxygen saturation was associated with the improvement in adiponectin levels, suggesting that hypoxemia contributes, at least partly, to adiponectin levels in severe OSA patients. Other reasons for the differences found between ours and Kohler's would be the short duration of CPAP treatment (4 weeks) and the presence of other co-morbidities (such as diabetes) that could be contributing to the negative results reported by Kohler.

It is known that adiponectin levels are influenced by many others factors besides hypoxemia, such as BMI, insulin sensitivity, gender, smoking behavior, hyperactivity of sympathetic nervous system, high levels of IL-6 and TNF-α, and increased glucocorticoid activity.[22–25] Some authors have pointed out that low plasma adiponectin levels in OSA patients may be related to insulin resistance, because the strong positive correlation between both parameters is well known.[22] To our knowledge, only 4 studies have assessed the relationship among sleep apnea, adiponectin levels, and insulin sensitivity. Two of them,[8,9] in which only OSA patients were enrolled without an appropriate control group, have found that the ISI was positively related to adiponectin levels. Conversely, in agreement with our results, Masserini et al.[10] and Zhang et al.[11] have shown that hypoadiponectinemia in sleep apnea patients was not associated with insulin sensitivity and BMI.

Two independent investigators, in larger well-controlled studies, simultaneously demonstrated that AHI was associated with glucose intolerance and insulin resistance independent of obesity.[12,13] Carpagnano et al. have reported a significant increase in IL-6 levels in the exhaled breath condensate of obstructive sleep apneic patients compared with that of obese subjects.[26] However, in our study we found elevated levels of insulin sensitivity indexes (HOMA), IL-6, TNF-α, and CRP in severe obese patients, but the mean levels did not differ between OSA and obese controls. We speculate that this discrepancy could be explained by the fact that only severe obese patients were enrolled in this study, which could account for the high IL-6, TNF-α, CRP values, and HOMA-IR index in both severe obese groups, so that differences among them would be more difficult to

TABLE 2. CHARACTERISTICS OF OBESE MEN WITH SLEEP APNEA BEFORE AND AFTER 3 MONTHS OF nCPAP THERAPY

	CPAP		*Change from baseline*	*P*
	Pre (n = 07)	*Post (n = 07)*		
AHI, events/h	91.0 ± 9.7	15.3 ± 11.1	−75.7 ± 6.6	<0.001
Minimum oxygen saturation, %	71.2 ± 2.0	86.7 ± 0.99	15.4 ± 2.6	0.001
Arousal index, events/h	52.6 ± 12.0	11.2 ± 5.1	−41.3 ± 10.0	0.006
BMI, kg/m2	46.1 ± 2.8	46.8 ± 2.6	0.64 ± 0.76	0.429
HOMA-IR, mmol • μU • mL[2]	7.6 ± 1.7	5.9 ± 1.5	−1.7 ± 1.2	0.287
ISI	0.52 ± 0.08	0.58 ± 0.14	0.06 ± 0.14	0.664
Adiponectin, ng/mL	7.1 ± 1.5	16.0 ± 4.3	8.9 ± 3.3	0.036
CRP, mg/dL	0.85 ± 0.29	0.72 ± 0.34	−0.13 ± 0.06	0.109
TNF-α, pg/mL	9.9 ± 1.8	6.9 ± 1.6	−2.9 ± 1.3	0.065
IL-6, pg/mL	3.5 ± 0.65	2.8 ± 0.72	−0.70 ± 0.65	0.329

Data are expressed by mean ± standard error (SE).

Abbreviations: nCPAP, nasal continuous positive airway pressure; AHI, apnea–hypopnea index; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

establish. It is interesting to note that all subjects enrolled in this study present a markedly elevated HOMA-IR level at baseline (7.4 ± 1.1 mmol • µU • mL^2), which reflects a higher degree of insulin resistance. In our general Brazilian population, Geloneze et al.[27] have reported the threshold value for insulin resistance (HOMA-IR) of 2.71 mmol • µU • mL^2. During nCPAP therapy, plasma adiponectin levels increased significantly and TNF-α levels tended to decrease from baseline levels, whereas no changes were observed in insulin resistance, BMI, and other inflammatory markers. Therefore, the elevation in adiponectin levels during nCPAP treatment could not be explained by changes in BMI and was not associated with insulin resistance changes.

Some limitations of the current study include the small sample size and lack of a post-nCPAP treatment control group. However at the time of the study, sham-CPAP machines capable of use in a double-blinded setting were not available. Moreover, ethical approval to leave patients with severe symptomatic OSA untreated before bariatric surgery was not forthcoming from the university ethics committee.

In summary, our study shows that plasma adiponectin levels are lower in men with obstructive sleep apnea compared to BMI-matched controls and elevated significantly during nasal continuous positive airways pressure treatment, probably related to improvement of hypoxemia. Given that adiponectin is a hormone with antiinflammatory and antiatherosclerosis properties, theoretically, this improvement in adiponectinemia after nCPAP therapy may be beneficial in decreasing cardiovascular complications associated with OSA.

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Author Disclosure Statement

There are no financial or other potential conflicts of interest for all of the authors.

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