GLÁUCIA CARNEIRO

EFEITO DO TRATAMENTO DA APNÉIA DO SONO COM CPAP SOBRE A ATIVIDADE DO EIXO HIPOTÁLAMO-HIPÓFISE-ADRENAL, RESISTÊNCIA À INSULINA, MARCADORES INFLAMATÓRIOS E PERFIL HEMODINÂMICO

Tese apresentada à Universidade Federal de São Paulo – Escola Paulista de Medicina para obtenção do Título de Doutor em Ciências.

São Paulo
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3. marcadores inflamatórios 4. perfil hemodinâmico 5. resistência à insulina

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O mérito do homem não reside apenas no conhecimento que tem, mas no esforço que despendeu para alcançá-lo.

Gotthold Ephraim Lessing

Esta tese é dedicada

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SUMÁRIO

1. Introdução

A apnéia obstrutiva do sono (AOS) é uma síndrome caracterizada por eventos recorrentes de obstrução parcial (hipopnéias) ou total (apnéias) das vias aéreas superiores durante o sono, geralmente resultando em dessaturação da oxihemoglobina e despertares noturnos freqüentes com conseqüente sonolência diurna. Estima-se que 4% dos homens e 2 % das mulheres entre 30 e 60 anos têm apnéia do sono sintomática, entretanto, essa condição clínica é ainda pouco diagnosticada [(1)].

O não reconhecimento dos indivíduos com AOS é preocupante devido à forte associação com diversas patologias, incluindo hipertensão arterial sistêmica, hipertensão pulmonar, insuficiência cardíaca e coronariana, arritmia, acidente vascular cerebral e, principalmente, por contribuir de forma independente no aumento da mortalidade, especialmente em decorrência de eventos cardiovasculares e acidentes automobilísticos. Tais complicações parecem ser reversíveis após o tratamento da apnéia do sono com uso do CPAP (pressão positiva das vias aéreas superiores) [(2,3)]. Esse fato justifica a importância em identificar os indivíduos de risco para que seja instituída uma intervenção precoce com recursos terapêuticos que possam minimizar a gravidade dos casos e diminuir a intensidade das complicações, em especial no que diz respeito à redução dos riscos cardiovasculares.

Além do impacto sobre a morbi-mortalidade por doenças cardiovasculares, esta síndrome também tem sido alvo de atenção crescente já que sua presença parece contribuir para evolução desfavorável do perfil metabólico dos indivíduos [(4)]. Observações iniciais de que os indivíduos com apnéia do sono apresentam características clínicas similares aos indivíduos com síndrome metabólica, como obesidade principalmente visceral, maior prevalência na pós menopausa e no sexo masculino e efeitos sistêmicos como hipertensão arterial, resistência à insulina, diabetes mellitus tipo 2 e dislipidemia, levaram alguns pesquisadores a estabelecerem uma estreita relação entre apnéia obstrutiva do sono e síndrome metabólica [(5,6)]. Entretanto, os mecanismos através dos quais esta ligação se estabelece ainda não estão completamente esclarecidos.

Acredita-se que algumas co-morbidades associadas à AOS sejam decorrentes da hipóxia intermitente com despertares subseqüentes, da fragmentação do sono e tempo diminuído do sono, que desencadeiam uma resposta ao estresse com aumento da atividade simpática e da inflamação, além de provocar disfunção endotelial, aumento de espécies reativas de oxigênio e resistência à insulina [7,8].

Estudos recentes questionam se a apnéia do sono é um fator de risco independente para o surgimento das anormalidades metabólicas ou se, ao contrário, os componentes da síndrome metabólica, particularmente obesidade e resistência à insulina, podem influenciar no aparecimento da apnéia do sono [9]. Esta suposição pode ter grande impacto na conduta terapêutica e é baseada nas seguintes premissas [10-13]:

- pacientes com AOS nem sempre apresentam lesões estruturais nas vias aéreas e vice-versa, pacientes com estreitamento das vias aéreas nem sempre apresentam apnéia do sono;
- possível insucesso na terapêutica cirúrgica da apnéia do sono e a presença de melhora dos sintomas até mesmo com pequena perda de peso;
- nem todos os estudos mostram os benefícios do CPAP nas anormalidades metabólicas;
- apnéia do sono é freqüente nas condições em que a resistência à insulina é a anormalidade primária, como síndrome dos ovários policísticos;
- intervenções anti-inflamatórias têm a capacidade de diminuir a sonolência e os episódios de apnéia e/ou hipopnéia por hora de sono.

Diante dos aspectos apresentados, sentimo-nos motivados a realizar uma breve revisão da literatura dos trabalhos que analisaram os possíveis mecanismos envolvidos na interação entre resistência à insulina e apnéia do sono

(artigo 1). Em seguida elaboramos dois artigos relatando as alterações metabólicas, inflamatórias, endócrinas e hemodinâmicas encontradas em indivíduos obesos portadores de AOS, além dos possíveis benefícios do tratamento com CPAP nesses pacientes.

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2. Artigo 1

3. Artigo 2

Effect of Continuous Positive Airway Pressure Therapy on Hypothalamic-Pituitary-Adrenal Axis function and 24-hour Blood Pressure profile in Obese Men with Obstructive Sleep Apnea Syndrome

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Running head: HPA, 24-hour blood pressure profile, sleep apnea syndrome and nCPAP therapy

ABSTRACT

Obstructive sleep apnea syndrome (OSAS) increases the risk of cardiovascular events. Sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis activation may be the mechanism of this relationship. The aim of this study was to evaluate HPA axis and ambulatory blood pressure monitoring (ABPM) in obese men with and without OSAS and to determine whether nasal continuous positive airway pressure therapy (nCPAP) influenced responses. Twenty-four-hour ambulatory blood pressure monitoring and overnight cortisol suppression test with 0.25 mg of dexamethasone were performed in 16 obese men with OSAS and 13 obese men controls. Nine men with severe apnea were reevaluated three months after nCPAP therapy. Body mass index and blood pressure of OSAS patients and obese controls were similar. In OSAS patients, the percentage of fall in systolic blood pressure at night (p=0.010) and salivary cortisol suppression post DEX (p=0.029) were lower, while heart rate (p=0.009) was higher compared with obese controls. After nCPAP therapy, patients showed a reduction in heart rate (p=0.036) and a greater cortisol suppression after dexamethasone (p=0.001). No difference in arterial blood pressure (p=0.183) was observed after 3 months of nCPAP therapy. Improvement in cortisol suppression was positively correlated with an improvement in apnea-hypopnea index during nCPAP therapy (r= 0.817; p=0.007). In conclusion, men with OSAS present increased post dexamethasone cortisol levels and heart rate which were recovered by nCPAP.

Keywords: sleep disorders, low dose dexamethasone test, 24 hour blood pressure profile

INTRODUCTION

Obstructive Sleep Apnea Syndrome (OSAS) is receiving increased attention because it seems to be associated with a variety of long term consequences such as high rates of morbidity and mortality, mostly due to cardiovascular disease [23]. Although obesity is the main risk factor for OSAS [39], it has been demonstrated that OSAS may increase the risk for hypertension, myocardial infarction, congestive heart failure and stroke independently of obesity. Continuous positive airway pressure (CPAP) therapy is the treatment of choice for patients with moderate-to-severe OSAS, since it is highly effective in improving nocturnal hypoxia and sleep fragmentation, enhancing the quality of life and reducing many cardiovascular complications related to OSAS. However, the lack of acceptance and inadequate adherence to CPAP therapy remain the major cause of sleep apnea treatment failure [10, 20, 21,31,32].

The mechanisms proposed to explain the increased cardiovascular disease in obstructive sleep apnea are under assessment. It is speculated that recurrent episodes of upper airways constriction, progressive hypoxemia and sleep fragmentation may result in neural and metabolic changes, including activation of peripheral sympathetic activity, inflammatory pathways and hypothalamic-pituitary-adrenal (HPA) axis, impairment of insulin sensitivity and generation of reactive oxygen species (ROS), which could predispose to vascular damage [16,26,27, 34].

Sympathetic nervous system has been well demonstrated to be activated in sleep apnea patients by investigating muscle sympathetic nerve activity, heart rate variability, blood and urinary catecholamine levels [2]. In contrast, there are a limited number of studies which assess the effects of obstructive sleep apnea on cortisol secretion [9,12,13,18,35]. Some studies show an elevation of cortisol levels [13,18,35] in patients with OSAS while others do not [9,12].

The aim of the present study was to evaluate HPA axis, 24-hour heart rate and blood pressure values in severe obese patients with and without OSAS, and to assess if OSAS treatment with nasal CPAP influenced responses.

MATERIALS AND METHODS

Twenty-nine obese men, who were on the waiting list for bariatric surgery, were recruited from the Obesity Outpatient Clinic and Sleep Disorders Center of the Federal University of Sao Paulo. These patients, aged from 18 to 65 years and body mass index between 35-60 kg/m2 were submitted to polysomnography recordings (PSG) and classified according to their apnea/hypopnea index (AHI) in two different groups: AHI < 05 events/h: obese controls (n=13) or AHI ≥ 10 events/h: OSAS patients (n= 16).

Exclusion criteria included history of smoking, sleep apnea treatment, cardiovascular disease, malignant tumors, thyroid disorders, severe depression, subjects with diabetes mellitus, chronic renal or hepatic failure, on pharmacological obesity treatment, use of medication that could potentially affect sympathetic nervous system or steroid hormone secretion (alcohol, psychotropics, steroids, sympathomimetics, beta-blockers) and hepatic enzyme inducers such as carbamazepine, phenytoin, phenobarbitone, and rifampicin which reduce plasma dexamethasone concentrations [17]. Antihypertensive medications remained unchanged during the study period.

A questionnaire included demographic data, sleep symptoms, medical history and medications in use was enrolled. Physical examinations and anthropometric measurements were recorded including weight (in kilograms) and height (in meters). Body mass index (BMI) was calculated as the weight divided by the height squared.

Polysomnograms were recorded by the Sleep Analyser Computer (Alice 3 Diagnostics system) including one for OSAS diagnosis and other for positive airway pressure titration. An experienced sleep physician scored all sleep stages [28], arousals and respiratory events according to American Sleep Disorders Association criteria[11,30].

In healthy individuals, glucocorticoids synthesis and secretion follow a circadian rhythm with the highest levels in the morning and the nadir at around midnight. Overnight administration of dexamethasone (DEX), a potent exogenous glucocorticoid, suppresses the nocturnal surge in ACTH production and cortisol levels when measured the next morning [22]. Dexamethasone test is the most commonly used method to evaluate the sensitivity of the HPA axis to negative feedback. However, the conventional dose of 1-mg completely suppresses cortisol secretion in normal people. For this reason, low-dose DEX test (< 1 mg) has been used by some authors to induce a more modest suppression enabling the detection of subtle differences in feedback sensitivity of glucocorticoid on the HPA axis [7, 15,19,25,29, 33].

The assessment of the HPA axis function in this study included low-dose (0.25 mg) dexamethasone suppression test and the circadian rhythm of cortisol secretion. Salivary cortisol measurement reflects the free fraction of cortisol in plasma. Advantages are the easy and noninvasive collection procedure and its stability at room temperature for at least 7 days [5, 36, 37]. The subjects were given three Salivettes (Sarstedt, Rommelsdorf, Germany), which consist of a small cotton swab inside a centrifugation tube used to collect saliva, and a half tablet of 0.5 mg DEX (Decadron, Aché, Brazil). Salivary sample was obtained in the morning (8:00 am) and at bed time around 11:00 pm for all patients just before the administration of DEX. The next morning another salivary and blood samples were collected at 8:00 am to measure cortisol and dexamethasone concentrations by RIA to confirm the ingestion of the drug. To analyse the results we used an index of percentage of salivary cortisol suppression (% cortisol suppression) calculated as the difference between the post DEX cortisol levels and baseline cortisol levels at 8:00 am divided by baseline cortisol levels at 8:00 am.

Twenty-four-hour ambulatory blood pressure monitoring (24h ABPM) was recorded with a SpaceLabs model 90202 Ambulatory BP Monitor (Redmond, WA, USA). An appropriate sized cuff was applied. Blood pressure was registered every 15 minutes during daytime (awake) and every 20 minutes during nighttime

(asleep), based on the patient's reports on their activities during day and night. The percentage of fall in systolic blood pressure at night (Δ BP) was calculated by dividing the difference between mean daytime and mean nighttime systolic blood pressure by the mean daytime systolic blood pressure [24]. Blood pressure was considered to be controlled in those patients with 24h- mean blood pressure values < 135/85 mmHg [6].

Six patients with mild or moderate OSAS immediately underwent bariatric surgery and ten patients with severe OSAS (AHI of more than 30 events per hour of sleep) were advised to follow nasal continuous positive airway pressure (nCPAP) therapy before bariatric surgery (mean nCPAP pressure of 11.2 ± 0.7 cm of H_2O) in order to avoid surgery complications related with sleep apnea. One man who failed to use the device was excluded from the study before the follow-up analysis. Therefore, after three months of nCPAP therapy, nine patients with severe OSAS were reassessed and all measurements were repeated. The average nightly use of nCPAP was measured with a run-time course which ran when the patient is breathing through the machine and not just when the machine is switched on.

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

Statistical Analysis

Normally distributed variables are expressed as means ± SE or percentiles when appropriate. Continuous variables comparisons between OSAS and control obese groups were performed using unpaired Student's t test. ANCOVA test were used to adjust comparisons for body mass index. To assess differences between categorical variables were used chi-square statistics. The results before and after nCPAP therapy were compared using paired t-test. Correlations between variables were assessed by Pearson coefficient.

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

RESULTS

As shown in Table 1, no differences were observed between groups for age, body mass index and prevalence of hypertension. In OSAS men, the mean 24-hour heart rate was higher (p= 0.009) and the percentage fall in blood pressure during sleep time was lower compared with obese men controls (p=0.010). Mean 24-hour systolic and diastolic blood pressure values were similar in the two groups.

Although basal salivary cortisol values at 8:00h am (p=0.663) and at bedtime (p=0.498) were not different between groups, a smaller cortisol suppression post DEX (% cortisol suppression) was evident in OSAS patients compared with obese controls (p=0.010) (Figure 1). As a consequence, salivary cortisol post DEX was significantly higher in OSAS patients than in obese control (p= 0.029). The differences remained significant after adjustment for BMI (Table1).

All patients had detectable circulating plasma DEX level, indicating that all participants had ingested the DEX tablets (Table 1). DEX levels did not differ between OSAS patients and obese controls (84.5 ± 9.3 vs 101 ± 10.5; p=0.271) and in the total group, DEX levels did not correlate to plasma cortisol levels post DEX (r=-0.219; p=0.328).

Three months of nCPAP therapy was associated with a significant reduction in salivary cortisol after dexamethasone (p= 0.009) and heart rate (p= 0.036) compared with baseline. Also, a greater cortisol suppression (% cortisol suppression) post DEX was evident in apneic patients following the use of nCPAP (p=0.001). This was similar to the levels of obese controls (Figure 1). Average body mass index (p= 0.913) did not change and no differences in sleep blood pressure fall and blood pressure values were observed (Table 2). Six patients (67%) took anti-hypertensive drugs and blood pressure was controlled at entry.

Improvement of AHI in response to nCPAP were positively correlated with the improvement of cortisol suppression after oral dexamethasone (r= 0.817; p=0.007) and negatively correlated with cortisol suppression before nCPAP (r=-0.883; p=0.002). (Figure 2)

DISCUSSION

In the present study, we demonstrated a blunted response of cortisol suppression after dexamethasone and a higher 24-hour heart rate in obese men with obstuctive sleep apnea syndrome compared with obese male controls. These findings may reflect activation of sympathetic nervous and stress system in apneic patients, which could be due to nocturnal hypoxia and sleep fragmentation with several awakening and arousal episodes. In addition, we showed a significant reduction in heart rate and a marked improvement in dexamethasone induced salivary cortisol suppression in patients with OSAS after 3 months of nCPAP therapy. The reduction of apnea-hypopnea-index after nCPAP therapy was positively correlated with the improvement of cortisol suppression in response to low dose oral dexamethasone.

Stress related disorders such as depression, anorexia, alcoholism, excessive exercising, malnutrition, premenstrual tension syndrome may be associated with increase CRH activity and ACTH secretion, resulting in chronic exposure to circulating cortisol levels and loss of the normal negative feedback of the HPA axis by glucocorticoids [8]. In accordance with this hypothesis, it was expected that OSAS patients would be associated with an activation of HPA axis in response to stress caused by recurrent intermittent hypoxia, sleep fragmentation and frequent cerebral arousals during apneic events. However, only a few studies have assessed the relationship between sleep apnea and HPA axis and results are still controversial [9, 12, 13,18,35]. In the majority of these studies, the HPA axis was assessed by a single morning plasma cortisol measurement, which might not reflect the episodic nature of cortisol secretion and its appropriate elevations during the hypoxemia stress [8]. Two recent studies [9,35] have evaluated the 24-hour circadian

secretory pattern of cortisol in obese patients with and without sleep apnea. In agreement with our results, both studies have demonstrated that salivary and plasma cortisol secretion was circadian in OSAS patients and obese control. However, Dadoun et al [9] failed to find any significant differences for overnight cortisol secretion between obese patients with or without sleep apnea syndrome. Our results match those who have demonstrated that sleep apnea in obese men is associated with increased cortisol level during the nighttime period (11pm-07am) compared to obese controls, which is recovered after the use of nCPAP for 3 months [35]. Hence, we hypothesize that obstructive sleep apnea should be recognized by clinician and corrected before further clinical investigations for endocrine causes of hypercortisolemia.

Long-term mild activation of HPA axis has been shown to altering important functions in patients with some evidence of hypercortisolism, i.e., adrenal incidentalomas, depression or alcoholism, increasing the risk for chronic conditions such weight gain, lethargy, weakness, loss of libido, diabetes mellitus, hypertension and osteoporosis [22]. Thus, further prospective studies should explore these clinical manifestations in patients with OSAS and increased cortisol levels.

A positive and well established relationship between sleep apnea and the prevalence and severity of hypertension has been reported [4,14,26,38]. Nevertheless, we did not find any differences in 24-hour blood pressure values between patients with or without sleep apnea. Blood pressure fall during sleep, however, was smaller in OSAS patients than in obese controls. The reasons for these discrepancies might be the fact that, in our study, more than half of patients were on hypertensive medication, although none received beta blocker therapy.

Therapy with nCPAP is the most effective treatment for sleep apnea, preventing recurrent occlusion of upper airway during sleep [32]. However, the effects of nCPAP on blood pressure have shown conflicting results [1,3,21]. We did not find significant changes in blood pressure levels and blood pressure fall during sleep after nCPAP therapy in severe obese patients with OSAS. As our patients were

under antihypertensive therapy and blood pressure levels were controlled at baseline, this may be the reason for negative results. Consistent with our findings Campos-Rodriguez et al [3] have reported that 24 months of therapeutic nCPAP reduced 24-hour ambulatory blood pressure measurements only in a subgroup of patients with incompletely controlled hypertension at baseline. They suggest that in a group of controlled hypertensive patients nCPAP therapy failed to reduce blood pressure.

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 OSAS untreated before bariatric surgery was not forthcoming from university ethics committee.

In conclusion, our findings demonstrate that obstructive sleep apnea syndrome is associated with increased 24-hour heart rate, decreased percentage of fall in systolic blood pressure at night and lower cortisol suppression after low dose dexamethasone, suggesting that there is an activation of sympathetic nervous system and hypothalamic-pituitary-adrenal axis. Our results also show the beneficial effects of nCPAP on 24-hour heart rate and salivary cortisol levels after low dose dexamethasone test, which may contribute to reducing cardiovascular and metabolic complications related to OSAS.

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DISCLOSURES

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TABLES

Table 1: Clinical and laboratorial characteristics of obese men with and without sleep apnea.

	OSAS		*p*	*p**
	No (n=13)	Yes (n=16)		
AHI, events/hr	3.2 ± 0.5	65.7 ± 9.9	<0.001	<0.001
Age, years	38.8 ± 3.3	40.1 ± 2.8	0.771	0.378
BMI, kg/m^2	42.8 ± 1.3	46.9 ± 2.0	0.116	
24h SBP, mmHg	127.6 ± 2.3	133.1 ± 3.3	0.207	0.492
24h DBP, mmHg	76.1 ± 1.9	79.6 ± 2.3	0.282	0.349
24h Heart rate, beats/min	76.3 ± 2.8	89.3 ± 3.4	0.009	0.022
Δ BP, %	11.5 ± 1.8	5.5 ± 1.2	0.010	0.027
Hypertension , n (%)	07 (53.8)	11 (68.8)	0.466	
S Cortisol basal, ng/dL	483.9 ± 77.5	442.2 ± 57.5	0.663	0.715
S Cortisol 11h pm, ng/dL	177.8 ± 53.5	233.1 ± 56.3	0.498	0.388
S Cortisol post DEX, ng/dL	233.2 ± 65.6	445.4 ± 61.6	0.029	0.038
% cortisol suppression	-48.8 ± 10.5	-16.6 ± 6.1	0.010	0.012
Dexamethasone, ng/dL	101 ± 10.5	84.5 ± 9.3	0.271	0.241
Plasma cortisol, μg/dL	3.6 ± 1.0	6.9 ± 1.0	0.042	0.059

Abbreviations: AHI, apnea-hypopnea index; BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Δ BP, percentage of fall in systolic blood pressure at night; S Cortisol, salivary cortisol ; % cortisol suppression, cortisol post DEX minus cortisol basal at 8:00 am / cortisol basal at 8:00 am. Data are expressed by mean ± SE or n (%). p*: significance after adjustment for BMI.

Table 2: Characteristics of men with sleep apnea before and after three months of nCPAP therapy.

	CPAP		change from baseline	*p*
	Pre (n=09)	Post (n=09)		
AHI, events/hr	92 ± 7.6	19.1 ± 10.0	-72.8 ± 6.2	<0.001
BMI, kg/m^2	44.3 ± 2.4	44.4 ± 2.5	0.07 ± 0.70	0.913
24h SBP, mmHg	131.5 ± 3.7	125.7 ± 1.9	- 5.7 ± 3.9	0.183
24h DBP, mmHg	77.3 ± 2.5	76.0 ± 2.7	-1.3 ± 2.9	0.665
24h Heart rate, beats/min	82.1 ± 3.8	74.3 ± 3.5	- 7.7 ± 3.08	0.036
ΔBP, %	6.2 ± 1.9	7.3 ± 1.5	1.2 ± 2.1	0.603
S Cortisol basal, ng/dL	501.1 ± 89.0	521.2 ± 58.6	20.1 ± 89	0.827
S Cortisol post DEX, ng/dL	438.6 ± 70.4	168.1 ± 41.4	-270 ± 78.4	0.009
% cortisol suppression	-21.8 ± 8.5	-69.4 ± 6.2	-47.5 ± 8.6	0.001

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ΔBP, percentage of fall in systolic blood pressure at night; S Cortisol, salivary cortisol; % cortisol suppression, cortisol post DEX minus cortisol basal at 8:00 am / cortisol basal at 8:00. Data are expressed by mean ± SE.

FIGURES

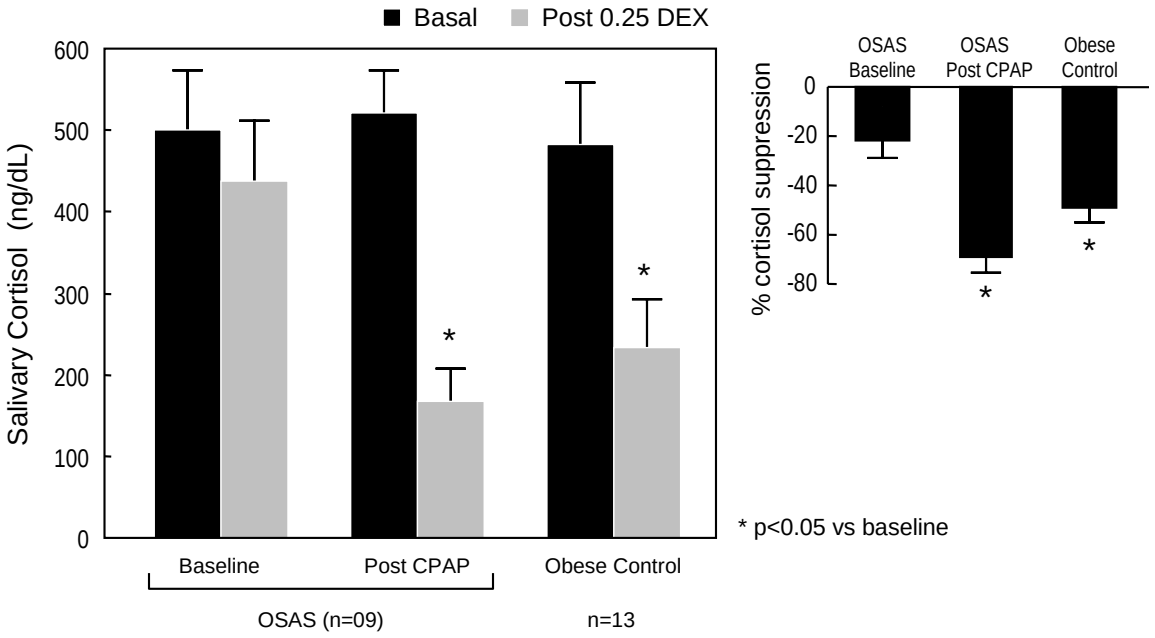

Figure 1: Salivary cortisol response to 0.25 mg dexamethasone and % cortisol suppression in obese men with and without OSAS.

Abbreviations: DEX, Dexamethasone; OSAS, obstructive sleep apnea syndrome; CPAP, continuous positive airway pressure. Data are expressed by mean ± SE.

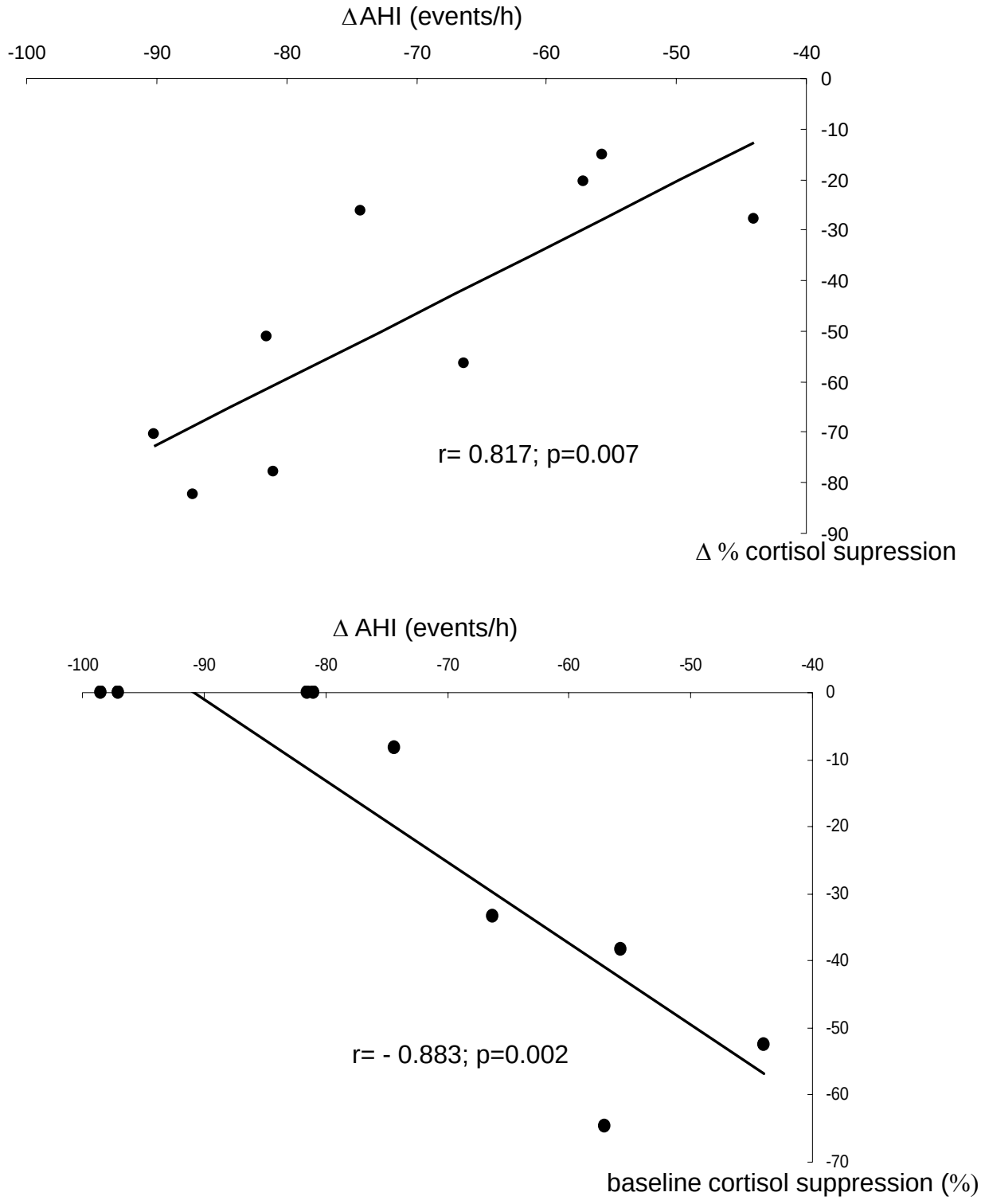

Figure 2: Correlations among cortisol suppression at baseline, changes (Δ) in cortisol suppression and changes (Δ) in apnea-hypopnea index (AHI) following nCPAP therapy.

4. Artigo 3

Continuous Positive Airway Pressure Therapy Improves Hypoadiponectinemia in Severe Obese Men with Obstructive Sleep Apnea: Influence of hypoxic stress.

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Abbreviated Title:

Insulin resistance, cytokines, sleep apnea syndrome and nCPAP therapy

Key words:

sleep apnea, adiponectin, inflammatory cytokines, hypoxia, nCPAP

ABSTRACT

Obstructive sleep apnea syndrome (OSAS) 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 OSAS, but the mechanisms underlying this association are not fully understood. The aim of the present study was to evaluate whether sleep apnea contributes to insulin resistance and alterations of inflammatory markers as well as to evaluate nasal CPAP benefits on these parameters in severe obese patients with OSAS. Plasma inflammatory cytokines and insulin resistance index (HOMA-IR, ISI) were measured in severe obese male with OSAS (n=16) and compared with body mass index (BMI)-matched male controls without OSAS (n=13). Seven patients with severe sleep apnea (apnea-hypopnea index > 30 events /hour) were reevaluated after three months of nasal CPAP therapy. OSAS 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) while HOMA-IR, ISI, TNF-α, CRP and IL-6 levels were not different between groups. Although insulin resistance index and body mass index did not change after three 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 was 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). In conclusion, nCPAP therapy reverses hypoadiponectinemia levels present in obese men with OSAS probably through reductions in hypoxia and inflammation activity.

INTRODUCTION

Previous studies have demonstrated that obstructive sleep apnea syndrome (OSAS) is associated with many cardiovascular and metabolic complications, such as hypertension, abdominal obesity, insulin resistance and dyslipidemia [1,2,3]. Treatment with continuous positive airway pressure (CPAP) reduces many cardiovascular morbidity and mortality related to OSAS [4,5]. In these regard, some authors have been suggested that OSAS is a manifestation of metabolic syndrome rather than a local anatomic abnormality.

Given that central obesity is a common risk factor for several diseases [6], it remains to be determined whether central obesity per se could be a confounding factor for the abnormalities present in OSAS. Adipose tissue, specifically visceral abdominal fat, is a rich source of inflammatory cytokines (TNF-α and IL-6). Some authors have been found that plasma circulating levels of TNF-α and IL-6 are elevated in sleep apneic patients independent of obesity, and their increased secretion are associated with sleepiness, fatigue and the development of a variety of metabolic and cardiovascular diseases [7,8]. Adiponectin is a protein secreted exclusively by white adipose tissue with an anti-inflammatory, anti-atherosclerosis and insulin sensitizing effects. Previous studies on the relationship between adiponectin and OSAS have yielded conflicting results [9-14].

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 [15]. Recently, epidemiologic and observational studies have suggested that OSAS is an independent risk factor for insulin resistance [16,17], but the effects of CPAP on insulin resistance remain controversial [18, 19].

Based on these findings, the aim of this study was to evaluate insulin resistance and adipocytokines in severe obese patients with and without OSAS and to assess the effects of nasal continuous positive airway pressure (nCPAP) treatment on these parameters.

PATIENTS AND METHODS

Sixteen severe obese men with documented OSAS, defined by 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 Sao Paulo and compared with thirteen men without OSAS (AHI < 5 events per hour of sleep) matched for age and body mass index (BMI). All patients were in the waiting list for bariatric surgery.

Subjects with history of smoking, alcohol abuse, a diagnosis of diabetes, on pharmacological obesity treatment, cardiovascular disease, malignancies tumor, thyroid disorders, 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 body mass index (BMI, in kg/m^2).

Polysomnograms were recorded by the Sleep Analyser Computer (Alice 3 Diagnostics system) including one for OSAS diagnosis and other 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 [20], arousals and respiratory events according to American Sleep Disorders Association criteria [21,22].

After 12-h overnight fasting, baseline blood samples were obtained for measurements of plasma glucose, insulin and adipocytokines. Thereafter, an oral glucose load (75 g) was given and plasma glucose (glucose oxidase method) and insulin (monoclonal antibody based immunofluorimetric assay) were measured after 2 hour. Hepatic insulin resistance index was assessed by the homeostasis model

assessement Program (HOMA-IR) calculated as fasting serum insulin (μU/ mL) x fasting plasma glucose (mmol /L) /22.5 [23]. 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 F et al: 2/[(INSp x 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 hour 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 body mass index [24].

TNF-α and IL-6 were measured using the immunometric kit (Immulite - DPC- Diagnostic Products Corporation- Los Angeles/USA) with sensitivities of 1.7 pg/mL and 2 pg/mL, an intra-assay coefficient of variation (CV) of 2.6%- 3.6% and 3.5%-6.2%, and an inter-assay 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, intra-assay CV of 1.8%-6.2% and inter-assay CV 6.9%-9.2%. High sensitive C reative protein (CRP) was measured using the chemiluminescent immunometric assay (Immulite- DPC, Los Angeles, CA, USA) with limit of detection 0.01 mg/dL and intra- and inter-assay 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 in order to avoid surgery complications related with sleep apnea. These patients were reassessed after three months of nCPAP use and all measurements were repeated. One man who failed to use the device and two men who failed to collect blood sample were excluded from the follow-up analysis. To assure nCPAP adherence, a follow-up in the out-patient clinic were performed monthly and the average nightly use of nCPAP was analyzed with a run-time course which ran when the patient is breathing through the machine and not just when the machine is switched on. The criteria for good compliance was the usage of the device for more than 5 hours/night during the study [25]. A self-

reported sleepiness was measured using the Epworth Sleepiness Scale (ESS) [26]. 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 ± SE or percentiles when appropriate. Data were analyzed using unpaired Student's t tests or paired t-test where appropriate. To assess differences between categorical variables were used qui-square 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 severe obese male, including 16 patients with OSAS and 13 patients without OSAS. The mean ± SE age of the apneics and obese control were 40.1 ± 2.8 and 38.8 ± 3.3 years, whereas their BMI were 46.9 ± 2.0 and 42.8 ± 1.3 kg/m^2, respectively (p=NS). The demographic and clinical characteristics of these two groups are shown in table 1. All patients had very high insulin resistance index and no significant differences were found in age, waist circumference, body mass, HOMA-IR and ISI index between groups. Plasma adiponectin levels were significantly lower in OSAS patients than in obese controls (8.7 ± 1.18 ng/mL vs 15.0 ± 2.55 ng/mL, p=0.025). With regard to cytokines, no differences in TNF-α, CRP and IL-6 levels were observed between groups (Table 1).

After an interval of three months, seven patients with severe OSAS treated with a mean nCPAP pressure of 11.5 ± 2.0 cm of H_2O were reassessed. Daytime sleepiness, analyzed by Epworth sleepiness scale, improved in all patients (score 10.5 ± 1.0 vs score 1.5 ± 0.71). Treatment with nCPAP improved 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 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 body mass index 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 them closer to the levels of obese controls (Figure 1). No significant differences in CRP, IL-6 levels, 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 male with OSAS compared with BMI-matched obese controls. Furthermore, the findings demonstrate marked improvement in adiponectin levels following nCPAP therapy for three months in patients with obstructive sleep apnea syndrome while no changes in body fat mass and insulin resistance index were observed.

Reduced plasma adiponectin concentration is a risk factor for cardiovascular and metabolic disorder [8]. It has been hypothesized that decreased adiponectin levels in patients with OSAS could partly explain the association between OSAS and cardiovascular disease. However, there have been conflicting reports regarding the relationship between adiponectin levels and OSAS [9-14].

Contrasting with our finding, one previous study has demonstrated that plasma adiponectin levels are elevated in OSAS patients compared with control [10]. Makino et al [11] have shown that plasma adiponectin levels did not differ between severe, moderate and mild OSAS patients. Consistent with our results, some authors have demonstrated reduced levels of adiponectin in OSAS patients compared with control [9,13]. Moreover, recently, Zhang et al have demonstrated that adiponectin levels did not change in OSAS patients on day 3 and day 7 of nCPAP treatment, but a significant elevation in adiponectin levels were observed on day 14 of nCPAP treatment, suggesting an independent effect of OSAS on adiponectin levels [14]. The mechanisms downregulating adiponectin levels in OSAS patients remain unknown. Some authors have pointed out that low plasma adiponectin levels in OSAS patients may be related with insulin resistance. To our knowledge, only four studies have assessed the relationship among sleep apnea, adiponectin levels and insulin sensitivity. Two of them [11,12], in which only OSAS patients were enrolled without an appropriate control group, have found that insulin sensitivity index was positively related to adiponectin levels. Conversely, in agreement with our results, Masserini B et al [13] and Zhang et al [14] have shown that hypoadiponectinemia in sleep apnea patients was not associated with insulin sensitivity and BMI.

In 2002, two independent investigators, in a larger well-controlled study, simultaneously demonstrated that AHI was associated with glucose intolerance and insulin resistance independent of obesity [16,17]. On the other hand some authors have showed that the relationship between insulin resistance and sleep-disordered breathing was entirely dependent on body mass [27-29]. The effect of nCPAP on glucose metabolism also have been shown in several studies and the results are mixed [19,30]. In our study participants, we did not find differences in whole body and hepatic insulin sensitivity indexes in severe obese patients with OSAS compared with severe obese controls and the intervention treatment did not change insulin resistance in apneic patients. However, it is interesting to note that all subjects enrolled in this study present marked elevated HOMA-IR level at baseline (7.4 ± 1.1 mmol•μU •mL^2), which reflect higher degree of insulin resistance. In our

general brazilian population Geloneze B et al [31] have reported the threshold value for insulin resistance (HOMA-IR) of 2.71 mmol•μU •mL^2.

It has been proposed that OSAS modulates the expression and secretion of inflammatory cytokines from fat and other tissues [32,33]. Some clinical data indicate that both IL-6 and TNF-α are elevated in obese patients with sleep apnea [7,34,35]. Vgontzas et al [7] have shown that these cytokines are the mediators of daytime sleepiness and are elevated in OSAS patients independently of obesity. Also, Carpagnano et al have reported a significant increase in interleukin-6 levels in exhaled breath condensate of obstructive sleep apneic patients compared with that of obese subjects [35]. However, in our study we found elevated levels of IL-6, TNF-α and CRP in severe obese patients, but the mean levels did not differ between OSAS 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 establish. During nCPAP therapy, plasma adiponectin levels were significantly increased and TNF-α levels tended to decrease from baseline levels, while no changes in BMI and others inflammatory markers were observed. 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.

Multiple others factors besides BMI and insulin sensitivity may influenced adiponectin levels, such as gender, smoking behavior, hypoxemia, hyperactivity of sympathetic nervous system, high levels of interleukin-6, TNF-α and increased glucocorticoid activity [8,36-42]. Recently, Ye J et al have demonstrated in an experimental study a potential role of adipose hypoxia in the inhibition of adiponectin in obese mice[43]. Also, Nakagawa Y et al have provided experimental evidence that exposure to hypoxic in mice and 3T3-L1 adipocytes decreased adiponectin concentrations by inhibiting adiponectin regulatory mechanisms at secretion and transcriptional levels[44]. The relationship between adiponectin levels and hypoxia in OSAS patients has not been previously reported. In our study we

demonstrated that improvement in minimum oxygen saturation after sleep apnea treatment were correlated with changes in adiponectin levels, suggesting that hypoxemia contributes, at least partly, to adiponectin levels in OSAS patients.

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 OSAS 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 body mass index-matched controls, and that it increases significantly during nasal continuous positive airways pressure treatment probably related to improvement of hypoxemia. Given that adiponectin is a hormone with anti-inflammatory and anti-atherosclerosis properties, theoretically, the improvement in adiponectinemia after nCPAP therapy may be beneficial to decrease cardiovascular complications associated with OSAS.

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TABLES

Table 1: Clinical and laboratorial characteristics of obese men with and without sleep apnea.

	OSAS		*p*
	No (n=13)	Yes (n=16)	
AHI, events/hr	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, $mmol \cdot \mu U \cdot mL^2$	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

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; HOMA and ISI, insulin sensitivity index; Data are expressed by mean ± SE n (%).

Table 2: Characteristics of obese men with sleep apnea before and after three months of nCPAP therapy.

	CPAP		change from baseline	*p*
	Pre (n=07)	Post (n=07)		
AHI, events/hr	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/ hr	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

Abbreviations: AHI, apnea-hypopnea index; HOMA and ISI, insulin sensitivity index. Data are expressed by mean ± SE.

FIGURE

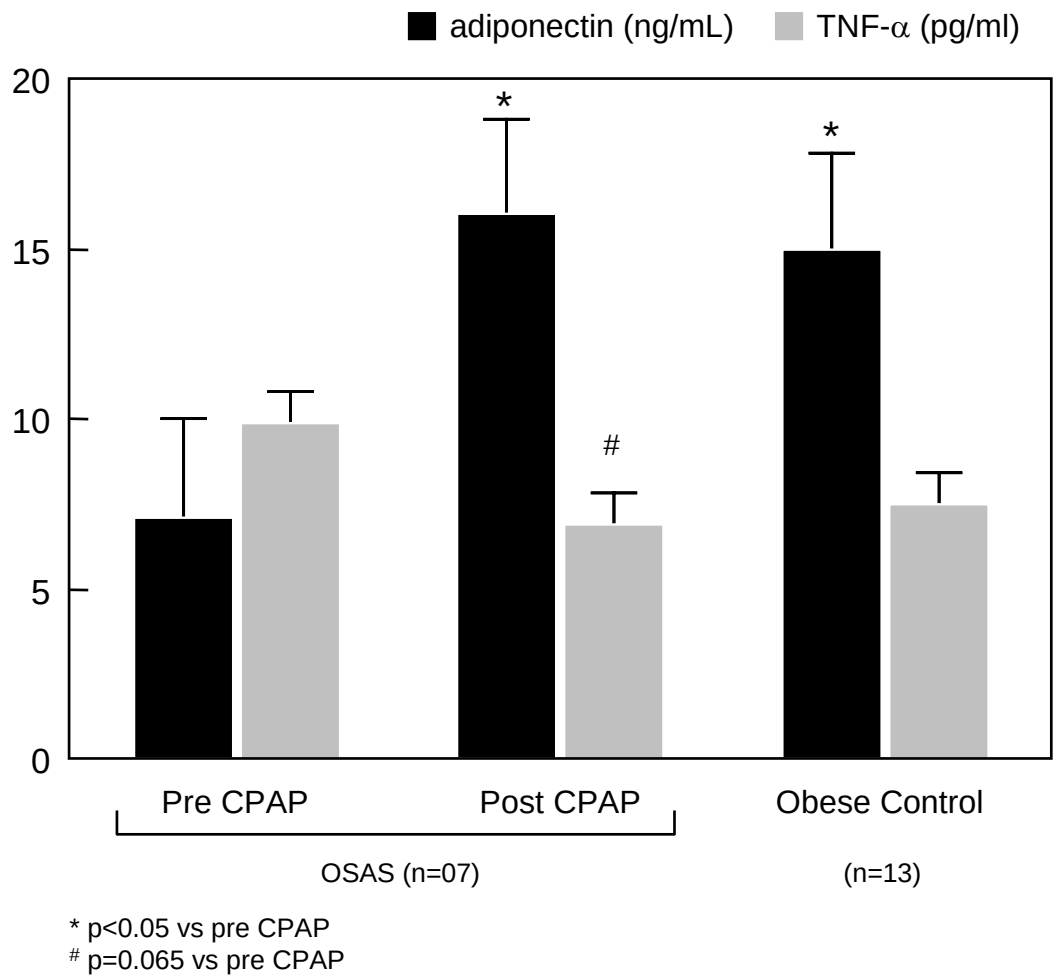

Figure. 1: Plasma Adiponectin and TNF-α levels in obese men with and without OSAS. Abbreviations: OSAS, obstructive sleep apnea syndrome; CPAP, continuous positive airway pressure. Data are expressed by mean ± SE.

5. Principais Achados e Conclusões

PRINCIPAIS ACHADOS

Nos indivíduos obesos com apnéia obstrutiva do sono em comparação aos indivíduos controle sem apnéia pareados pelo IMC evidenciamos:

- Menor supressão de cortisol no teste com baixa dose de dexametasona, sugerindo ativação do eixo hipotálamo-hipófise-adrenal;
- Aumento da freqüência cardíaca e menor descenso noturno da pressão arterial, sugerindo ativação do sistema nervoso simpático;
- Menores níveis de adiponectina predispondo à maior atividade inflamatória e aterogênica;
- Similaridade no grau de resistência à insulina, nos níveis pressóricos e nos marcadores inflamatórios.

Após o uso do CPAP nos indivíduos obesos com apnéia do sono houve:

- Melhora da supressão do cortisol após baixas doses de dexametasona, sugerindo normalização da atividade do eixo hipotálamo-hipófise-adrenal;
- Diminuição da freqüência cardíaca, sem melhora da pressão arterial nas 24 horas e do descenso noturno;
- Elevação dos níveis de adiponectina e uma tendência à diminuição nos níveis de TNF-α , sem alterações do peso corporal e do grau de resistência à insulina.
- A melhora da supressão do cortisol após uso do CPAP se correlacionou com a melhora do índice apnéia-hipopnéia e a melhora nos níveis de adiponectina se correlacionou com a melhora da saturação mínima de O_2 e dos níveis de TNF-α, sugerindo um efeito independente da apnéia do sono nesses parâmetros .

CONCLUSÕES

A partir desses resultados podemos concluir que:

- Os indivíduos com AOS apresentam alterações hormonais, inflamatórias e hemodinâmicas desfavoráveis que podem estar envolvidas na fisiopatogenia das complicações cardiovasculares e metabólicas associadas à AOS, independente da presença da obesidade.

- O tratamento com CPAP é benéfico pois contribui para atenuar o processo inflamatório, a ativação do sistema nervoso simpático e do eixo hipotálamo-hipófise-adrenal nos pacientes com apnéia obstrutiva do sono, independente da perda de peso ou alteração da resistência à insulina. É possível que estes benefícios no longo prazo, constituam alguns dos mecanismos cardioprotetores decorrentes do uso do CPAP.

6. *Anexos*

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