J. Endocrinol. Invest. 29: 700-705, 2006

Reduced levels of adiponectin in sleep apnea syndrome

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ABSTRACT. ***Background:*** **To investigate adiponectin levels in an obese population with and without obstructive sleep apnea syndrome (OSAS) and the acute modifications in adiponectin after a whole-night control by auto continuous positive air pressure (CPAP).** ***Methods:*** **46 obese subjects [22 males, 24 females, age 55.1±11.4 yr, body mass index (BMI) 38.9±6.5 kg/m^2]: 11 OSAS with apnea/hypopnea index (AHI) from 10/h to 30/h, 14 OSAS with AHI >30/h and 21 without OSAS. Thirty-seven normal weight healthy subjects (20 males, 17 females, age 31.3±9.5 yr, BMI 21.5±1.8 kg/m^2). Serum adiponectin levels, biochemical parameters, anthropometric measurements, pulmonary function, pulse-oxymetry and polisomnography.** ***Results:*** **The 3 groups of obese patients were comparable for gender, BMI, age, fat mass, fat free mass, hip and waist circumference, waist-to-hip ratio (WHR), systolic and diastolic blood pressure and glycometabolic parameters. Adiponectin levels were significantly reduced in obese patients compared to healthy normal weight subjects (8.1±3.5** ***vs*** **11.3±4.8 µg/ml** ***p*****<0.001) In particular, adiponectin showed a trend to decrease according to the severity of OSAS. No differences in adiponectin levels were found after a whole-night control by Auto CPAP.** ***Conclusions:*** **OSAS is associated with reduced levels of adiponectin independently of insulin-resistance and BMI. These low adiponectin levels may contribute to the increased mortality seen in such patients.**

(J. Endocrinol. Invest. 29: 700-705, 2006)

INTRODUCTION

The prevalence of obesity is rapidly increasing all over the world, particularly in the USA (1). The obstructive sleep apnea syndrome (OSAS) affects up to 5% of adults in Western countries (2). In obese population, the prevalence of OSAS reaches 40-50% (3). This syndrome is characterized by the presence of repetitive apnea and hypopnea during sleep (>10 episodes/h). Consequently these patients report snoring, daytime sleepiness and fatigue, morning headache and cognitive impairment (4, 5). Interestingly, many subjects with OSAS have central obesity and other features of metabolic syndrome which have been established as independent risk factors for cardiovascular disease (6). OSAS carries an increased risk of myocardial infarction, stroke and mortality (7) compared with simple obesity, which *per se* is an established marker of cardiovascular risk (8). Moreover, OSAS is associated with insulin resistance (IR) independent of obesity which can account for a further increase in cerebro-cardiovascular risk in these patients. The impairment of the metabolic function is associated with the degree of nocturnal hypoxemia, probably due to alterations in sympathetic system and hypothalamic-pituitary-adrenal axis caused by microawakening and hypoxia (8-10). This hypothesis is supported by the fact that nasal continuous positive airway pressure (CPAP) treatment ameliorates insulin sensitivity without modification in body mass index (BMI) (11). Another hypothesis to justify the increased insulin resistance is the alteration in adipokine secretion by adipose tissue, in particular leptin pathways (12).

It is known that adipose tissue is an important endocrine organ secreting a number of biologically active adipokines such as leptin, adiponectin, tumor necrosis factor α (TNF-α) and plasminogen activator inhibitor-1. Previous studies have found high levels of leptin in OSAS patients, consistent with the observation that the *in vitro* expression of human leptin gene is greatly enhanced by hypoxia (13) or, alternatively, is the consequence of heightened neuroex-

Key-words: Adiponectin, sleep apnea syndrome, obesity, insulin resistance, apnea hypopnea index.

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Accepted March 29, 2006.

citation and sympathetic activity (14). An additional hypothesis to explain the link between OSAS, insulin resistance and increased cardiovascular risk is the impaired secretion of adiponectin in this syndrome. Adiponectin has insulin-sensitizing actions, antiatherogenic and anti-inflammatory effects. Reduced levels of adiponectin are commonly observed in a variety of states frequently associated with insulin resistance, such as obesity and diabetes (15-18) with the exception of anorexia nervosa (19). However, there are controversial results in previous studies that analysed adiponectin levels in OSAS patients. Wolk et al. (20) found that adiponectin in OSAS patients was higher than that in non-OSAS group, while Zhang et al. (21) found lower levels of adiponectin in the OSAS patients. A recent study by Makino et al. (22) found no differences in adiponectin levels between mild, moderate and severe OSAS groups. The present study investigated adiponectin levels in an obese population with and without OSAS, as well as the acute modifications in adiponectin levels after a whole-night control by auto CPAP.

MATERIALS AND METHODS

Subjects

The study included 46 subjects (22 males, 24 females) belonging to a cohort of outpatients with obesity who were consecutively admitted to obesity service of our institute, reporting symptoms such as a daytime sleepiness and nocturnal snoring, suggesting possible OSAS. Exclusion criteria included already diagnosed sleep-disordered breathing, known or newly diagnosed diabetes mellitus, thyroid disorders, acromegaly or recent surgery of the upper airways and eating disorders (DSM IV). Written informed consent was obtained by all subjects and the study was approved by the institutional Ethics Committee.

All patients were evaluated by physical examination, medical history, eating behavior (performed by an operator well trained in obesity), biochemical parameters, Epworth Sleepiness Scale (23-25), an in-house questionnaire for OSAS risk, and nocturnal oxygen saturation. All the patients who showed repeated desaturation episodes during the night were studied with a complete polysomnography. Alcohol consumption was investigated as standard drinks per day. Smoking habit was defined by number of smoked cigarettes per day and years of smoking. Physical activity was defined by metabolic equivalent (MET)-h/week.

All subjects had fasting blood samples taken between 08:00 and 09:00 h. Blood samples were stored on ice, immediately separated by centrifugation at 3000 rpm for 10 min at 4 C and stored at –80 C until assay.

After pulse-oxymetry and/or polysomnographic study the patients were divided into three groups depending on apnea/hypopnea-severity score: A=non OSAS: apnea/hypopnea index (AHI) <10/h; B=OSAS with AHI from 10/h to 30/h; C=OSAS with AHI >30/h. Group A was represented by 21 patients characterized by age 55.4±9.6 yr and BMI 37.5±4.7 kg/m^2; Group B: 11 patients with age 57.6±13.5 yr and BMI 36.9±6.5 kg/m^2; and Group C: 14 patients with age 52.8±12.6 yr and BMI 42.3±7.8 kg/m^2.

The study also included 37 non-obese healthy subjects (20 males and 17 females, BMI 21.5±1.8 kg/m^2, age 31±9.5 yr). The healthy subjects took no medication, had normal physical examination and blood tests and did not show sleep-disordered breathing.

In a little randomized group of 13 patients positive for OSAS (7 males, 6 females, BMI 40.3±5.1 kg/m^2, age 53.5±13.5 yr, waist circumference 120.3±12.6 cm, hip circumference 125.2±9.9 cm) blood samples were taken before and after a whole-night control by auto CPAP.

METHODS

Anthropometric measurements

In all subjects anthropometric measurements were performed including weight, height, waist and hip circumferences. Then BMI and WHR were calculated. Waist circumference was taken at the level of umbilicus and hip circumference at trochanter level. Blood pressure was also measured using a sphygmomanometer after a 10 min rest in supine position. Fat mass and fat free mass were measured using impedance method (Maltron BioScan®).

Pulmonary function

For every patient a pulmonary respiratory test (PFT) was evaluated with a plethysmographic method using a Jaeger Plethysmograph (German) and recorded forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1) as principal parameters. All values were expressed as percentages of predicted values.

Pulse oxymetry

All patients were submitted to a nocturnal pulse-oxymetry with a Nonin 3100; the pulse oxymetry continuously records the variation of SaO_2 and heart beats with an infra-red finger sensor.

Polisomnography

Overnight sleep studies were performed with a full polysomnography with 20 channels (P Series Compumedics, Sydney) recording the sleep stage, Nadir SaO_2 (the lower level of SaO_2 measured during the night), the respiratory disturbances index (RDI) and the apnea/hypopnea index (AHI), electroencephalography (C3, C4, A1, A2), electrooculogram (EOGR, EOGL), electromyogram (EMG), ECG, thorax and abdominal motion (piezo electrodes), nasal and oral airflow were measured by a thermistor, bilateral tibialis electomyogram, the body position and the snoring by a microphone.

Scoring

The polysomnography recording was scored manually for sleep stages and respiratory events (apnea/hypopnea). According to the international standards definition, apnoea was defined as complete cessation of airflow lasting 10 sec or more together with a dip in the SaO_2 ≥4%. Hypopnoea was defined as a reduction in airflow of at least 40% in relation to the immediately preceding baseline combined with a dip in SaO_2 ≥4%.

AHI

Number of episodes of A/H/h during sleep (normal value <10/h). The severity of OSAS was defined on the basis of AHI: mild if AHI ranged between 10 and 30 episodes/h and severe if AHI was higher than 30 episodes/h (26). Sleep stage evaluation was performed according to Retcshaffer and Kales (27).

Each patient positive for OSAS underwent a whole-night control by Auto CPAP (Autoset Sullivan Res Med Sidney) (28) with soft nasal mask

Mirage, for titration of nCPAP pressure level; titration was started at a pressure of 4 cmH_2O and progressively increased by 1 cmH_2Ox10 min until apnoeas; hypopnoeas and snoring were eliminated (29-32).

Assay

Serum adiponectin levels were measured by human adiponectin ELISA kit (B-Bridge International, Inc., San Jose, CA, USA). The sensitivity of the assay was 0.23 mg/l and the intra-interassay coefficient of variation (CV) are 3.5 and 5%, respectively.
Insulin was measured by an immunoenzymetric one-step assay (Medgenics Diagnostics, Belgium) and fasting glucose was measured with standard enzymatic methods. HbA_{1c} was measured by HPLC.
The investigators were not aware of the results of polisomnography when performing the assays.
IR was evaluated by the homeostatic model assessment IR (HOMA-IR), a computer-solved model used to predict the degree of IR starting from fasting plasma insulin (FI) and glucose concentrations (FG):

IR=FI (mU/l)xFG (mmol/l)/22.5 (33)

Statistics

All results are expressed as mean±SD. Differences between groups were analyzed using one-way analysis of variance or Kruskal-Wallis test for multiple comparisons whenever appropriate. The relation between the severity of OSAS and adiponectin was analyzed with the test for linear trend between means. Differences in qualitative parameters were analysed with χ-square test. Correlations were made using linear regression.
Values of $p<0.05$ were considered statistically significant.

RESULTS

As shown in Table 1, the three groups were comparable for gender, BMI, age, fat mass, fat free mass, hip and waist circumferences, WHR and systolic and diastolic blood pressure.

Moreover, the three groups were similar for alcohol consumption (28.6 *vs* 27 and 43%, *p*=ns), smoking (19 *vs* 30 and 45%, *p*=ns), and eating behavior, while OSAS patients showed a more sedentary lifestyle (94 *vs* 67 and 65%, $p<0.05$).
Table 2 shows results of PFT that were comparable in the three groups, with the exception of the AHI that was significantly higher in both OSAS positive groups (60.2±19.2 and 20.4±4.2 *vs* 1.71±1.88 episodes/h, $p<0.05$). The patients with or without OSAS didn't show any differences in fasting glucose, fasting insulin and HbA_{1c} levels (Table 3). Glucose and insulin levels 120 min after oral glucose tolerance test (OGTT) were not statistically different in the three groups as HOMA-IR. Finally, the three groups did not show any difference in the prevalence of hypertension (68.4, 76.2 and 73.1%, *p*=ns) and IGT (44.0, 36.0 and 23.8%, *p*=ns).
The obese group of patients as a whole, as expected, showed reduced adiponectin levels compared to normal weight subjects (8.1±3.5 *vs* 11.3±4.8 µg/ml, respectively; $p<0.001$). When analyzing the three groups of obese patients adiponectin showed a trend to decrease according to the severity of OSAS (Fig. 1, test for linear trend between means, $p<0.05$).
Adiponectin serum levels were measured before and after a whole-night control by auto CPAP, and no difference was found (7.4±2.6 *vs* 6.7±2.8 µg/ml *p*=ns. Data not shown).

DISCUSSION

In the present study we evaluated adiponectin levels in a cohort of morbidly obese patients with and with-

Table 1 - *Demographic, clinical and anthropometric characteristics of patients with mild and severe obstructive sleep apnea syndrome (OSAS) and non-OSAS subjects.*

	Group A	Group B	Group C	*p*
No.	21	11	14	
Age (yr)	55.4±9.6	57.6±13.5	52.8±12.6	ns
Male/female (no.)	7/14	6/5	9/5	ns
BMI (kg/m^2)	37.5±4.7	36.9±6.5	42.3±7.8	ns
WHR	0.95±0.08	0.94±0.09	1.0±0.1	ns
Waist circumference (cm)	113.3±10.3	114.1±12.0	127.6±13.9	ns
Hip circumference (cm)	118.8±10.7	121.7±13.7	126.2±17.0	ns
Fat mass (%)	43.5±8.5	38.6±8.4	40.0±4.4	ns
FFM (%)	56.7±8.5	61.4±8.4	60.0±4.4	ns
SBP (mmHg)	140.2±15.5	124.2±16.9	133.6±16.5	ns
DBP (mmHg)	84.7±7.7	79.2±12.8	85.4±12.3	ns

BMI: body mass index; WHR: waist-to-hip ratio; FFM: fat free mass; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2 - *Pulmonary respiratory test (PFT) and apnea/hypopnea index (AHI) in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS subjects.*

	Group A	Group B	Group C	*p*
AHI (episodes/h)	1.71±1.88	20.4±4.2	60.2±19.2	<0.0001
FEV_1 (%)	79.9±49.5	107.0±32.7	88.0±14.8	ns
FVC (%)	100.0±22.9	107.0±27.6	89.0±12.4	ns
PEF (%)	81.0±28.5	87.1±17.7	76.3±15.3	ns

FEV_1: forced expiratory volume in 1 sec; FVC: forced vital capacity; PEF: peak expiratory flow.

out OSAS and in the subgroup with OSAS before and after a whole-night control by auto CPAP, in order to evaluate possible acute modification in adiponectin levels induced by normalization of oxygen saturation. We chose to evaluate the modification of this hormone after one-night control by auto CPAP for two reasons: first because its plasma halflife is known to be 2.5 h (34), and second in order to avoid the bias of changed BMI because our patients are withdrawn with appropriate diet therapy.

As expected, adiponectin levels were reduced in our obese population compared to normal weight population (35). Interestingly, we found lower serum levels of adiponectin in patients positive for OSAS, according to one study (21) and in contrast with another (20) where increased levels of adiponectin in OSAS were found. However, it is important to note that this last study evaluated only a male population with a moderate degree of obesity (mean BMI 31 kg/m^2). This population was profoundly different from ours which is made up by both male and female subjects with a mean BMI of 37 kg/m^2. Our population was instead similar to that investigated by Zhang et al. (21), who studied an overweight Chinese population of both genders with and without OSAS.

It is known that adiponectin levels are influenced by multiple factors, such as BMI, insulin sensitivity (35), gender (36) and smoking behavior (37). In order to evaluate only OSAS effect on adiponectin levels, we balanced the two groups of patients for all these parameters and surprisingly adiponectin levels fall concurring with severity of OSAS.

One can speculate that the elevated inflammatory response is responsible for reduced levels of adiponectin. In fact, higher levels of IL6 and TNF-α, which are present in OSAS patients, can inhibit the expression

Table 3 - *Metabolic and hormonal parameters in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS subjects.*

	Group A	Group B	Group C	*p*
Adiponectin (µg/ml)[1]	9.3±3.9	7.5±3.6	6.9±2.5	<0.05
Insulin 0 OGTT (UI/ml)	21.7±13.7	17.2±15.2	28.7±22.3	ns
Insulin 120 OGTT (UI/ml)	186.2±208.3	162.9±188.8	117.0±81.3	ns
Glucose 0 (mg/dl)	100.0±10.6	95.0±28.9	99.9±15.6	ns
Glucose 120 OGTT (mg/dl)[2]	128.3±34.8	142.3±52.5	136.7±44.6	ns
HOMA-IR	5.0±3.0	6.8±7.1	6.9±5.1	ns
HbA_{1c} (%)	5.6±0.4	5.7±0.7	6.1±0.6	ns
Total cholesterol (mg/dl)	231.3±36.9	224.1±29.1	180.8±43.0	<0.05
HDL cholesterol (mg/dl)	60.0±9.3	53.2±15.1	46.4±12.09	ns
Triglycerides (mg/dl)	152.4±59.5	126.6±51.9	125.4±38.8	ns
Uric acid (mg/dl)	5.9±1.8	6.1±1.4	5.8±1.3	ns
TSH (mU/l)	1.6±1.3	1.9±0.5	1.3±0.9	ns
FT_4 (pmol/l)	15.6±4.6	12.6±0.6	13.2±2.2	ns

[1]In healthy normal weight subjects [20 males, 17 females, body mass index (BMI) 21.5±1.8 kg/m^2, age 31.3±9.5 yr] adiponectin levels were: mean±SD 11.3±4.8, range 3.5-20.9 µg/ml; [2]5 patients with mild OSAS (AHI >10 <30 events/h), 6 patients with severe OSAS (AHI> 30 events/h) and 5 without OSAS were diagnosed for impaired glucose tolerance (IGT) (*p*=ns). OGTT: oral glucose tolerance test; HOMA-IR: homeostasis model assessment-insulin resistance; FT_4: free T_4.

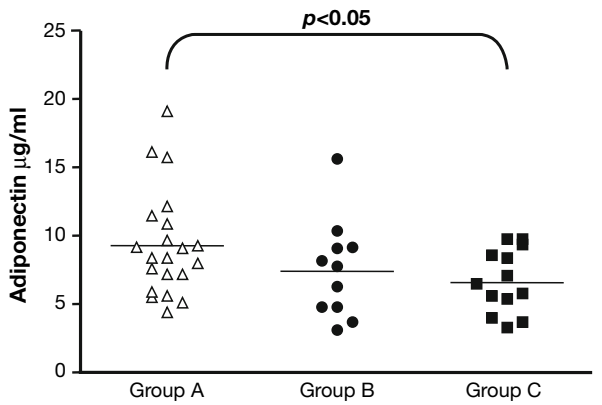

Fig. 1 - *Adiponectin levels are reduced by the severity of obstructive sleep apnea syndrome (OSAS) (*test for linear trend between means, p<0.05). Non OSAS= Group A: AHI <10 episodes/h; OSAS= Group B: AHI >10 and <30 episodes/h; OSAS= Group C: AHI >30 episodes/h. AHI: apnea/hypoapnea index.*

of adiponectin (38-40). Alternatively, a role of the increased sympathetic activity present in OSAS patients is possible (41) because studies *in vitro* showed that β-adrenergic agonists inhibited adiponectin gene expression in human visceral adipose tissue (42).
Another hypothesis to explain lower levels of serum adiponectin is a direct effect of hypoxia on mRNA transcription of adiponectin gene. It is known that the hypoxia due to OSAS induces expression of leptin as demonstrated *in vivo* and *in vitro* studies (8, 13), and increases IR by multiple mechanism (8, 12). We postulate an opposite effect of hypoxia caused by OSAS on adiponectin gene transcription. Moreover, we report in our subjects a negative trend of adiponectin levels according to the severity of OSAS expressed by AHI and this data can suggest a direct effect of hypoxia on adiponectin secretion. This observation is in contrast with the study of Makino et al. (22) who did not find any difference in adiponectin levels in three groups of patients with mild, moderate and severe OSAS. However, it is important to note that the population of this last study is different from ours because: a) it is made up of overweight subjects, b) the groups are not comparable for HOMA-IR and c) the division based on AHI also differs from ours.
We evaluated adiponectin levels after a whole-night control by auto CPAP, which can modify IR, inducing a normalization of oxygen saturation (43). The gold treatment of OSAS with CPAP did not acutely modify adiponectin levels as shown by the absence of modification of adiponectin levels after a whole night control by auto CPAP. However the design of this study does not allow one to evaluate the chronic effect of normal SaO_2 on adiponectin. In fact, it is known that leptin levels fall, without modification of BMI, after 6 months of CPAP therapy in obese patients. On the other hand, Harsch et al. (44) investigated serum adiponectin levels after 3 months of CPAP treatment. They found similar baseline levels of adiponectin after 3 months of therapy. They analyzed a profoundly different population from ours (mean BMI 32.2 kg/m^2 and 86.7% males). A treatment period of 3 months is probably too short to have significant modification in adiponectin levels as seen for leptin (14). Alternatively, CPAP treatment ameliorates insulin sensitivity and OSAS symptoms but does not modify adiponectin, and this can be explained by the overwhelming influence of BMI on levels of this adipokine.
In conclusion, OSAS is associated with lower levels of adiponectin independently of IR, BMI and gender, and can at least partially explain the increased mortality seen in OSAS patients.
Further studies are required to understand the mechanisms involved in the decreased adiponectin levels in this pathological condition and above all if the specific therapy of OSAS can revert this phenomenon.

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