

Serum Levels of Adiponectin, C-Reactive Protein and Tumor Necrosis Factor-alpha in Patients with Obstructive Sleep Apnea Syndrome: Effect of Nasal Continuous Positive Airway Pressure

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Abstract

Objectives: The aim of this study was to evaluate the influence of Continuous Positive Airway Pressure (CPAP) on serum adiponectin, high sensitivity C-Reactive Protein (hs-CRP) and Tumor Necrosis Factor -alpha (TNF- α) levels in patients with Obstructive Sleep Apnea Syndrome (OSAS). We also investigated the association between serum adiponectin, TNF- α , hs-CRP with body mass index, waist circumference, metabolic disorders, Cardiovascular Disease (CVD) and OSAS.

Methods: There were 50 subjects, control group (n=20) and patients with OSAS (n=30). Serum adiponectin, TNF- α , and hs-CRP levels were measured in both groups.

Results: Serum adiponectin levels were negatively correlated with Respiratory Disturbance Index (RDI), body mass index (BMI) and desaturation index, while it was positively correlated with minimum oxygen saturation. The Serum levels of TNF-alpha, hs-CRP were positively correlated with desaturation index, BMI and fasting plasma glucose levels. In addition, there was significant negative correlation between Serum TNF- α and adiponectin levels in the OSAS group. Obese OSAS patients had lower Serum adiponectin levels when compared with obese control subjects. CPAP improved all parameters.

Conclusion: Serum adiponectin is significantly lower in patients with OSAS and it is independent of obesity. Higher TNF- α and hs-CRP levels might explain the persistent inflammation and the high incidence of CVD and metabolic syndrome in patients with OSAS.

Keywords: Obstructive sleep apnea syndrome; OSAS; Adiponectin; TNF- α ; High sensitivity C-reactive protein; Continuous positive airway pressure.

Introduction

Obstructive Sleep Apnea (OSA) is a chronic condition characterized by repetitive episodes of upper airway collapse during sleep. The effects of intermittent hypoxia and re-oxygenation may provoke a number of pathological cascades which involve sympathetic over-activity, systemic inflammation, oxidative stress and endothelial dysfunction. These are believed to be the underlying mechanisms of OSA increased cardio-metabolic risk [1]. Untreated OSA subjects have been shown to suffer significantly increased risk of both fatal and non fatal cardiovascular events by 3-folds, when compared to healthy subjects [2] and treatment with nasal Continuous Positive Airway Pressure (CPAP) is effective in decreasing such risk, thus suggesting a causal relationship between OSAS and atherosclerosis [3]. It is well known that OSAS and metabolic syndrome diseases are strongly related to obesity; however, a recent study has suggested that OSAS is associated with atherosclerotic risk factors independent of obesity [4].

Adipocytokines, adipocyte-specific secreted proteins, were considered to be involved in the progression of these atherosclerotic diseases. Of all adipokines, adiponectin have received the most attention. Adiponectin is an adipocyte-derived molecule consisting of a 30 kDa (244 amino acids). It plays a very important role among fat-derived hormones due to its putative insulin-sensitising and anti-atherogenic properties. A negative correlation between obesity and serum adiponectin was established, and decreased adiponectin levels in obese individuals as well as increased adiponectin levels concomitant with weight loss have been shown. Furthermore, reduced serum adiponectin

levels are associated with insulin resistance and hyperinsulinemia, and many investigations have shown a relationship between adiponectin and type 2 diabetes mellitus. In OSAS patients, previous studies have shown a relationship between OSAS and adiponectin levels; however, the relationship between adiponectin OSAS remains controversial [4].

The Tumor Necrosis Factor-alpha (TNF- α) is a homotrimer of 157 amino acid residues. It is a pleiotropic cytokine that is produced by a variety of cell types. It signals through two distinct cell surface receptors i. e. TNF-RI (p55/p60) and TNF-RII (p75/p80). It is the most commonly studied pro-inflammatory cytokines in OSAS. Data from human and animal studies suggest that TNF- α may induce insulin resistance, and metabolic syndrome [5,6]. They are also postulated to be mediators of sleepiness and fatigue in OSA [7]. Significant elevation of TNF- α level in OSA compared with BMI-matched control subjects were recorded [3,8]. Observational studies of CPAP treatment reported a decrease in these pro-inflammatory activities [9,10].

C- reactive protein (CRP) is one of the major acute phase proteins

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and is a marker of systemic inflammation has been of particular interest to clinicians due to its clinical utility in CVD risk stratification. In contrast to regular CRP assays, a high-sensitivity CRP (hs-CRP) assay enables the diagnosis of even low grade inflammation. Elevated CRP levels are associated with metabolic syndrome [11,12]. Data on the association between OSA and CRP have been conflicting. Several groups have studied CRP in obese men with no prevalent medical conditions and identified an independent correlation between severity of OSA and CRP, controlled for BMI [8,13] as well as waist, percentage of body fat and total sleep time [14]. On the other hand, several studies reported negative results [15-17]. Two studies have shown a decrease in Hs-CRP levels in obese subjects with OSA after treatment with CPAP [8,18], whereas another found no change in either obese or non obese subjects with OSA [16].

However, the complexity of OSAS pathophysiology makes it very difficult to assess its precise mechanism (s), but an increasing number of studies suggest that OSAS, inflammatory activation and metabolic disturbances are closely linked. Understanding the pathogenesis of OSAS is of great importance in ultimately finding a treatment, cure or means of prevention of this disease. Therefore, the aim of this study was done to 1) Throw light upon the role of adiponectin, TNF- α and hs-CRP in OSAS development by delineating the changes in their serum levels before and after treatment with CPAP. 2) To correlate them with different clinical and anthropometric variables.

Patients and Methods

The study population consisted of patients recruited from the Sleep Lab. Chest Department, Assiut University Hospital, between January 2008 and January 2010, who were referred for clinically indicated sleep study. Thirty men and 20 women were included in this study. The subjects were classified as controls or OSAS patients according to the respiratory disturbance index (RDI). Subjects with an RDI <5 constituted the control group (20 subjects) and patients with an RDI \geq 5 constituted the OSAS group (30 patients). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters measured by a scale, and BMI >30 kg/m² was defined as obese (ref). Exclusion criteria were: patients with central sleep apnea, upper airway resistance and narcolepsy. Patients with cerebrovascular diseases or lung diseases with hypoxemia, e. g. chronic obstructive pulmonary disease, were also not included. Demographic characteristics, sleep and medical history, including CVD and metabolic diseases, medication use and habits, were obtained with the use of a standardized questionnaire before the sleep study. CVD was defined if patients had heart failure, coronary artery disease or arrhythmia. The demographic characteristics and laboratory evaluation comprised a routine blood examination (fasting glucose and lipid profile), pulmonary function tests and electrocardiogram.

The study was approved by the Ethics Committee of the Faculty of Medicine, Assiut University, and all patients gave written informed consent.

Polysomnography

Overnight polysomnography was performed in all subjects by a computerized system (Somnostar alpha; Sensormedics, Yorba Linda, Calif., USA) at the Sleep Lab, Chest department, Assiut University, and included the following: electro-oculogram (2 channels), electroencephalogram (4 channels), electromyogram of the submental muscles (2 channels), electromyogram of the anterior tibialis muscle

of both legs (2 channels), electrocardiogram and airflow (with an oronasal thermistor). Chest and abdominal efforts (2 channels) were recorded and arterial oxyhemoglobin saturation (SaO₂; 1 channel) was recorded by pulse oximetry with a finger probe. Apnea was defined as complete cessation of airflow \geq 10 s. Hypopnea was defined as a reduction of >50% in one of three respiratory signals, the airflow signal or either the respiratory or abdominal signals of respiratory inductance plethysmography, with an associated fall \geq 3% in oxygen saturation or arousal. Respiratory disturbance index RDI was calculated as the number of apneas plus hypopneas per hour of sleep. Patients with RDI \geq 5 events/h were diagnosed as having OSAS. The excessive daytime sleepiness of the patients was assessed according to the Epworth Sleepiness Scale (ESS) and values >10 were regarded as pathological. Patients diagnosed with OSA received Continuous Positive Pressure Ventilation (CPAP) for one night.

Assessment of Adiponectin, TNF- α , and Hs-C-reactive protein levels:

Peripheral venous blood samples were drawn at 07:00 and 08:00 hours after performing polysomnography to all subjects and a second sample was drawn at 07:00 and 08:00 hours after one night treatment with CPAP in patients with OSAS. The samples were allowed to clot for 30 min at room temperature and centrifuged at 3000 g for five min. The separated serum was stored into aliquots at -20°C until biochemical analyses.

Serum levels of adiponectin were determined using AviBion human adiponectin (Acrp 30) ELISA kit ref. no. ADIPO 25 (Orgenium Laboratories, Finland) according to Hu *et al.* [19]. Serum TNF- α level was determined using an ELISA kit (Cat No. KAC 1751, Biosource Europe S. A., Belgium) according to the method of Leroux-Roels *et al.*, [20]. The levels of serum hs-CRP were determined by Accu-Bind ELISA Kit code no. 3125-300 (Monobind Inc, CA 92630, USA) according to Kimberly *et al.* [21].

Statistical Analyses

SPSS software (Statistical Package for the Social Sciences, version 14.0, SSPS, Chicago, Ill, USA) was used for statistical analyses. The results are expressed as means \pm SD. For comparison of non-parametric

OSAS patients (n=30)	Controls (n=20)	Variables
46.2 \pm 2.3*** 21-67	38 \pm 2.2 23-55	Age (years) Mean \pm SD Range
20(67)*** 10(33)	10 (50) 10(50)	Male, n (%) Female, n (%)
37.3 \pm 3.3*** 30-45	28.1 \pm 3.5 21-29	BMI (Kg/m ²) Mean \pm SD Range
107 \pm 3.1*** 73-150	99.5 \pm 2.6 83-127	Waist circumference(cm) Mean \pm SD Range
7(23.3)* 7(23.3)*	2(10) 2(10)	Co-morbidities, n (%) Hypertensive Coronary heart disease Arrhythmias
3 (10)*** 1 (3)*** 5 (16)* 5 (16)*	0 0 2 (10) 2 (10)	Heart failure Diabetes Hyperlipidemia

BMI = body mass index

*= p<0.01 ***= p<0.001

Table 1: Demographic characteristics of the studied groups.

Variables		Controls	OSAS Before CPAP	OSAS after CPAP
RDI (events/hour)	Mean ± SD Range	2.4 ± 0.1 1-4	29.7 ± 3.9 12-83 a***	6.4 ± 0.9 1-19 a*** b**
Minimum O ₂ saturation, (mmHg)	Mean ± SD Range	90.7 ± 3.7 77-99	71.7 ± 3.1 30-90 a**	87.0 ± 1.8 61-98 a* b**
Desaturation index (PaO ₂ <90%)	Mean ± SD Range	13.9 ± 5.9 1-23	35.8 ± 4.8 13-43 a***	14.2 ± 3.6 4-25 a b**
Sleep efficiency (%)	Mean ± SD Range	89.32 ± 6.1 86.2-92.7	71.62 ± 1.5 68.3-74.1 a**	76.9 ± 13.4 75.1-89.9 a* b*
Number of arousals	Mean ± SD Range	1.3 ± 0.9 1-3	12.8 ± 5.3 8-14 a***	3.7 ± 2.1 2-5 a* b**
Adiponectin, (pg/ml)	Mean ± SD Range	7.6 ± 2.1 4.0-12.0	3.9 ± 1.1 2.0-6.0 a**	5.4 ± 1.5 2.8-9.0 a* b**
TNF-α (pg/ml)	Mean ± SD Range	8.7 ± 1.8 5.0-12.5	22.0 ± 5.4 15-32 a***	16.1 ± 4.6 10-26 a** b**
Hs-CRP (mg/l)	Mean ± SD Range	1.5 ± 0.4 0.9-2.5	3.8 ± 0.9 2.0-5.5 a***	2.8 ± 0.9 1.1-4.5 a** b*

OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; RDI, respiratory disturbance index; PaO₂ partial pressure of Oxygen; TNF-α, tumor necrosis factor –alpha; Hs-CRP, high sensitivity-C reactive protein
a: compared with controls, b: compared with group before CPAP
*:p<0.05; **:p<0.01; ***: p<0.001

Table 2: Polysomnographic and biochemical parameters in controls and patients before and after CPAP.

Variables	Non obese controls	Obese controls	Non –obese OSA patients	Obese OSA patients
RDI(events/hour)	1.4 ± 0.5	2.7 ± 0.3 a*	19.7 ± 2.8 a*** b**	54.9 ± 3.8 b*** c***
Minimum O ₂ saturation, (mmHg)	96.0 ± 7.7	90.5 ± 6.3 a*	81.7 ± 2.5 a** b**	67.1 ± 4.2 a*** b*** c**
Desaturation index (PaO ₂ <90%)	12.8 ± 3.5	13.9 ± 5.9 a	14.7 ± 4.8 b*	35.2 ± 4.2 a*** b*** c***
Sleep efficiency (%)	88.9 ± 6.5	89.32 ± 6.1 a	74.2 ± 3.5 a** b**	76.1 ± 3.0 a** b** c
Number of arousals	1.2 ± 0.5	1.3 ± 0.9	12.8 ± 5.3 b**	3.7 ± 2.1 c**
Adiponectin (pg/ml)	11.7 ± 0.6	4.7 ± 3.5 a**	3.1 ± 1.2 a** b*	2.9 ± 1.5 a** b* c*
TNF-α (pg/ml)	6.7 ± 2.9	8.7 ± 1.8 a	21.4 ± 2.4 a** b**	26.1 ± 4.6 a*** b*** c*
Hs-CRP (mg/l)	1.2 ± 0.5	1.5 ± 1.2 a	2.7 ± 0.8 a* b*	2.8 ± 2.4 a* b* c

OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; RDI, respiratory disturbance index; PaO₂ partial pressure of Oxygen; TNF-α, tumor necrosis factor –alpha; Hs-CRP, high sensitivity-C reactive protein
a: compared with non obese controls; b: compared with obese controls; c: compared with non- obese OSA
*:p<0.05; **:p<0.01; ***: p<0.001

Table 3: The polysomnographic and biochemical parameters in the obese and non-obese controls and patients before CPAP.

values between OSAS patients and controls, the Mann-Whitney test was used. The paired Student's t test was performed within groups to show significant differences. The Pearson correlation test was used to assess the strength of association between serum adiponectin, TNF-α, hs-CRP and sleep parameters, before and after CPAP. Significant determinants identified from these analyses were studied in a stepwise multiple regression. P value <0.05 was considered statistically significant.

Results

The demographic, clinical and biochemical data of both studied groups are shown in tables 1 and 2. Twenty men as well 10 women have OSAS (RDI>5), with mean age 46.2 ± 2.3, range 21-67 years old. The BMI of OSAS group is 37.3 ± 3.3, range 30-45 with significant difference from the control group (p<0.00), and waist circumference 107 ± 3.1 cm is significantly higher than controls (p<0.00). Also presence of co-morbidities was significantly higher in OSAS patients. Table 2 shows the polysomnographic values of controls and OSAS patients before and after treatment with CPAP. As expected all parameters were significantly different in OSA patients compared to controls and improved significantly after CPAP treatment. The adiponectin level was significantly lower in OSA patients compared to controls (3.9 ± 1.1 vs. 7.6 ± 2.1, p<0.001) and significantly increased but doesn't reach the normal level after CPAP (5.4 ± 1.5, p<0.01). The level of TNF- α is significantly higher in patients group (22.0 ± 5.4) compared to controls (8.7 ± 1.8), P<0.001, and significantly improved after CPAP. Same finding was observed in hs-CRP (3.8 ± 0.9 in OSAS before CPAP, vs. 1.5 ± 0.4 in controls, and 2.8 ± 0.9 after CPAP).

Table 3 shows that obese patients with OSAS have significantly higher RDI, desaturation index, higher level of TNF- α, hs-CRP but have lower minimum O2 saturation, and adiponectin level. All obese OSAS patients have CVS co-morbidities.

The BMI, waist circumference, DM, hyperlipidemia, TNF-α and adiponectin are independent risk factors for OSAS as shown in the stepwise multiple regression analysis in table 4. Finally, table 5 shows that adiponectin correlated negatively with BMI, waist circumference, RDI and desaturation index, while positive correlation between these parameters, fasting plasma glucose level and TNF-α, hs-CRP are present.

Finally, significant negative correlation was recorded between adiponectin, TNF-α and hs-CRP (table 6).

Variables	Odds ratio	95% confidence interval (CI)	P value
Age	2.7	0.76-2.33	NS
Sex	4.9	1.8-5.66	NS
BMI	3.3	2.1-3.9	0.05
Waist circumference	7.8	2.5-8.1	0.01
Hypertension	2.0	1.5-2.2	NS
DM	5.2	3.5-3.8	0.05
Hyperlipidemia	3.9	1.9-3.4	0.05
Adeponectin	0.9	0.21-1.43	0.01
TNF-α	2.4	0.95- 2.1	0.02
Hs-CRP	1.1	0.54-0.97	NS

OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; RDI, respiratory disturbance index; PaO₂ partial pressure of Oxygen; TNF-α, tumor necrosis factor –alpha; hs-CRP, high sensitivity-C- reactive protein

Table 4: Multivariate regression analysis of risk factors of OSA in the studied group.

Variables	BMI	Waist	RDI	Minimum O ₂ level	S PaO ₂ <90%	Fasting plasma glucose level
Adiponectin	-0.769**	-0.322*	-0.711**	0.511**	-0.335*	NS
TNF-α	0.346*	0.306*	0.766**	-0.534**	0.422*	0.289*
HS-CRP	0.325*	0.329*	0.826**	-0.611**	0.361*	0.401**

OSA, obstructive sleep apnea; RDI, respiratory disturbance index; SpaO₂ Oxygen saturation partial pressure of Oxygen; TNF-α, tumor necrosis factor –alpha; Hs-CRP, high sensitivity-C reactive protein

* P value significant at level <0.05; ** P value significant at level <0.01; NS: not significant

Table 5: Correlation coefficient (r) of the studied variables in OSA patients.

Variable	TNF- α	Hs-CRP	Adiponectin
Adiponectin	-0.916***	-0.946***	1.000
TNF- α	1.000	0.867**	-0.916***
hs-CRP	0.867***	1.000	-0.946***

TNF- α , tumor necrosis factor-alpha; Hs-CR, high sensitivity-C reactive protein
 *=P value <0.05, **=P<0.01

Table 6: Correlations between the studied biochemical indices in OSAS patients.

Discussion

The present study demonstrated that patients with OSAS had significantly lower level of serum adiponectin, higher level of serum TNF- α and hs-CRP, these parameters correlated to the severity of OSAS, BMI, waist circumference and improved after one night treatment with CPAP. These findings confirm the close association between the presence of OSAS specially with obesity, the low adiponectin and persistent inflammation causing increase TNF- α and hs-CRP.

It is known that OSAS causes repetitive episodes of airway occlusion with hypoxia, hypercapnea and change in intrathoracic pressure resulting in diverse autonomic, humeral, neurohumoral and hemodynamic responses [1]. Also, it is now generally accepted that white adipose tissue is a key endocrine and secretory organ which releases a large number of adipokines with a major link to inflammation and immunity. The majority of these adipokines are linked to inflammation and their production is increased in obesity. To date, the only known exception is adiponectin, which exerts anti-inflammatory and anti-diabetic activity and is reduced in obesity and type 2 diabetes [22]. Although the effects of hypoxia on the adipose tissue are still incompletely defined, adipose tissue hypoxia was shown to occur in obesity [23]. Adipocytes exposed to hypoxia *in vitro* produced less adiponectin [24]. Therefore, hypoxia may be a patho-physiologically important link between OSAS and obesity, but, to date, no study has assessed the response of adipocytes to intermittent hypoxia, which represents the main feature of OSAS.

The present study reported reduced level of serum adiponectin in OSAS patients especially in patients with more BMI and waist circumference but not correlated to fasting blood glucose level. This is similar to the results of Kanbay et al. , [25]. They reported that compared to non-obese OSAS group, subjects with obesity and OSAS had lower adiponectin levels and higher TNF- α levels [25]. Other studies reported that OSAS might decrease plasma adiponectin levels with increasing sympathetic activity [26-27]. Masserini and colleagues added that this reduced levels of adiponectin is independent of insulin-resistance and BMI [28].

This study also showed that treatment with CPAP increased adiponectin levels in OSAS patients. Similarly, Harsh et al. , (no) 2004 found that 2 days of CPAP rapidly improved insulin sensitivity and adiponectin levels in OSAS patients (AHI>20). The improved insulin sensitivity remained stable after 3 months but adiponectin levels were not, suggesting the lack of long lasting change in adiponectin can be affected by the overwhelming influence of body mass on adiponectin [29]. Makino et al. [30], added that a combination of CPAP treatment and weight loss in patients with OSAS should be strongly recommended for amelioration of metabolic dysfunction in OSAS. On the other hand, Masserini et al. [28] reported no difference in adiponectin level after a whole night control by Auto- CPAP. The difference between this study and other studies may be explained by the recruitment of only obese OSAS patients in their study with BMI = 38.9 (6.5), while the current study included obese and non-obese subjects [28-30].

This current study confirmed the significant inverse correlation

between adiponectin and TNF- α . Recently, it has been reported that adiponectin significantly inhibited macrophage phagocytic activity and suppressed lipopolysaccharide-induced production of tumor necrosis factor- alpha (TNF- α) and played an important role in the inhibitory effects of TNF- α [31]. The negative correlation between adiponectin and TNF- α level were in support of a previous suggestion that hypo adiponectinemia is a causal factor for cardiovascular morbidity in OSAS patients [27].

The increased levels of TNF- α in patients with OSAS in this study is similar to those previously recorded by many authors. It was reported that patients with OSAS have elevated levels of IL-6 and TNF- α [32]. Although sympathetic hyperactivity in OSAS patients is generally considered a major consequence of intermittent hypoxia, it could be potentiated by sleep disruption and contribute to inflammatory activation. Partial sleep deprivation induced a pro-inflammatory state, with increased release of IL-6 and TNF- α [33-34].

Finally this study added that OSAS patients have significantly higher level of hs-CRP. C- reactive protein levels have been reported to be increased in adults [8,13,14,35] and in children [36] with OSA. Punjabi and Beamer, reported that a strong association was found between the degree of sleep-disordered breathing and serum levels of CRP, with or without adjustment for age and several measures of adiposity [37].

As reported in this study many authors agreed that Nasal continuous positive airway pressure (nCPAP) therapy decreased levels of CRP and interleukin-6 in patients with OSA [38-40]. In contrast, Akashiba and colleagues, showed that > 6 months of nCPAP therapy did not decrease CRP levels in patients with OSA [41]. Whether short-term or long-term nCPAP therapy decreases CRP levels in patients with OSA is still controversial, and adherence to nCPAP therapy may be an important determinant. This is especially relevant to studies of the longer-term use of nCPAP when compliance may decrease over time [38,42]. It is possible that the improvement of apnea-related hypoxemia by nCPAP may decrease neurohumoral activation and cytokines and systemic inflammation, leading to decreased cardiovascular morbidity and mortality. Also, the hs-CRP used in this study may have more sensitive and earlier indication of improvement.

In conclusion, Serum adiponectin is significantly lower in patients with OSAS and it is independent of obesity. Higher TNF- α and hs-CRP levels might explain the persistent inflammation and the high incidence of CVD and metabolic syndrome in patients with OSAS. The use of CPAP improves these parameters and may decrease the OSAS associated inflammation and co-morbidities.

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