



# Insulin Resistance and Serum Leptin Levels in Men with Obstructive Sleep Apnea Syndrome

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## ABSTRACT

**Aim:** The aim of this study was to assess the insulin resistance and serum leptin levels in patients with obstructive sleep apnea syndrome (OSAS), and to compare body mass indexes (BMI) of OSAS patients with matched controls without OSAS.

**Method:** Twenty eight patients having apnea-hypopnea index (AHI)  $\geq 5$  included in the study. Thirty two healthy subjects assumed as a control group. Venous blood was obtained in the fasting state for the measurement of glucose, insulin and leptin levels. Insulin resistance index was based on the homeostasis model assesment method (HOMA-IR).

**Result:** There was no significant difference in the serum leptin levels (control group,  $32.88 \pm 24.22$  ng/ml, OSAS group,  $24.93 \pm 25.84$  ng/ml) and HOMA-IR (control group,  $3.01 \pm 1.81$ , OSAS group,  $2.58 \pm 1.21$ ) between control group and OSAS patients. Insulin resistance and circulating plasma leptin concentrations in OSAS patients were independent of the AHI and were not different from the control group.

**Conclusion:** We concluded that insulin resistance and plasma leptin concentrations are mostly associated with the degree of obesity and BMI. Those parameters seem not to be related with the AHI in OSAS patients.

**Key words:** Apnea hypopnea index, insulin resistance, leptin, OSAS

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## Obstrüktif Uyku Apne Sendromu Olan Erkek Hastalarda İnsülin Rezistansı ve Serum Leptin Seviyeleri

**Amaç:** Bu çalışmanın amacı obstrüktif uyku apne sendromu (OUAS) olan hastalarda insülin rezistansı ve serum leptin seviyelerini incelemek ve OUAS olan hastaların vücut kitle indeksini (VCI) kontrol grubuyla karşılaştırmaktır.

**Metod:** Apne hipopne indeksi (AHI)  $\geq 5$  olan 28 hasta çalışmaya dahil edildi. Sağlıklı 32 birey kontrol grubu olarak kullanıldı. Çalışmaya katılan bireylerden glukoz, insülin ve leptin seviyelerini ölçmek için açlık durumunda venöz kan elde edildi. İnsülin rezistans indeksinde, hemostaz modeli analiz methodu (HOMA-IR) temel alındı.

**Bulgular:** OUAS grubu ile kontrol grubu arasında serum leptin seviyeleri (kontrol grubu,  $32.88 \pm 24.22$  ng/ml, OUAS grubu,  $24.93 \pm 25.84$  ng/ml) ve HOMA-IR (kontrol grubu,  $3.01 \pm 1.81$ , OUAS grubu,  $2.58 \pm 1.21$ ) açısından anlamlı bir fark yoktu. OUAS olan hastalarda insülin rezistansı ve plazma leptin konsantrasyonları AHI'den bağımsızdı ve kontrol grubundan farklı değildi.

**Sonuç:** İnsülin rezistansı ve plazma leptin konsantrasyonları sıklıkla VKI ve obesitenin derecesiyle ilişkili olduğunu düşünüyoruz. Bu parametreler OUAS olan hastalarda AHI ile ilişkili olmadığı gözükmemektedir.

**Anahtar kelimeler:** Apne hipopne indeksi, insülin rezistansı, leptin, OUAS

### INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated collapse of the pharynx during sleep, which leads to oxygen desaturation, fragmentation of sleep, and often daytime sleepiness (1). A high prevalence of the condition, affecting approximately 2 to 4% of middle-aged adults, was found in an epidemiologic study (2). OSAS is well defined syndrome that includes one or two of the following symptoms: severe snoring, nocturnal respiratory arrest, repeated nocturnal awakening, non-recuperative sleep, diurnal fatigue, and altered concentration. The respiratory responses are related to the extent of hypoxemia and hypercapnia that develop as a result of the disordered breathing (3). The diagnosis of this syndrome should be suspected on clinical evaluation and is confirmed by polysomnography. Extensive research related with obesity has shown that the location of body fat deposits rather than their size is more important in determining the risk of developing of obesity-linked disorders (4). It is well known that excess weight in adults is associated with increased incidence of hypertension, cardiovascular disease, stroke, insulin resistance and type 2 diabetes mellitus (5,6). Leptin is a circulating hormone that is expressed abundantly throughout the body specifically in adipose tissue (7-9), although it is also secreted from other tissues including human placenta and stomach (10,11). Plasma leptin concentrations are increased in people who are obese in direct proportion to body fat mass (12). It has been reported that circulating plasma leptin levels are raised in men with newly diagnosed untreated OSAS (13-14).

We have therefore aimed to evaluate the insulin resistance and serum leptin levels in patients with OSAS.

### MATERIALS AND METHODS

#### Subjects

Sixty male patients who had been referred to our hospital, for suspected OSAS were evaluated. After an overnight sleep study 28 patients having apnea-hypopnea index (AHI)  $\geq 5$  included in the study as obstructive sleep apnea group. Thirty two healthy subjects assumed as a control group. Exclusion criteria included the followings: cardiopulmonary or vascular disease, hypertension (140/90 mmHg or on medication), chronic renal disease and diabetes mellitus. Subjects who smoked or had systemic infections at the time of the study were also excluded. The following parameters were evaluated; age, body mass index (BMI), leptin, fasting glucose, insulin, insulin resistance and AHI. The average of two weight and height measurements were used to calculate BMI as  $\text{weight (kg)} / [\text{height (m)}]^2$ . Leptin was determined in plasma using the DSL-10-23100 ACTIVE Human Leptin ELISA-kit (Diagnostic System Laboratories; Webster, TX). The sensitivity of this assay was 0.5ng/mL, and the inter-assay coefficient of variation was 4.6%. HOMA of insulin resistance; plasma glucose was measured by the glucose-oxidase method on a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Serum insulin was measured by a double-antibody radioimmunoassay. The estimate of insulin resistance by HOMA (HOMA-IR) was calculated with the formula  $\text{fasting serum insulin } (\mu\text{U/ml}) \times \text{fasting plasma glucose (mmol/l)} / 22.5$ .

#### Study Procedures

All patients gave written informed consent to participate in the trial. The study protocol was approved by the university ethics committee, and the study was performed in accordance with the guidelines of the Declaration

**Table 1.** Comparison of sample characteristics in those control and OSAS group

	Control (n:32)	OSAS (n:28)	p value
Age (year)	45.31±6.86	47.14±8.57	ns
BMI (kg/m) <sup>2</sup>	31.12±4.33	29.63±3.55	ns
Systolic BP mmHG	125±12.93	124.4±12.12	ns
Diastolic BPmmHG	76.88±7.37	76.43±6.21	ns
AHI	2.72±1.61	25.04±18.50	<0.05
Low O2 saturation	89.52±7.13	73.60±13.40	<0.05
Mean saturation	95.90±4.79	88.60±5.58	<0.05

ns: nonsignificant

of Helsinki and its current revision. An overnight polysomnography in the sleep laboratory was performed. Blood was drawn at 8 am after an overnight fast for the determination of multiple clinical chemistry parameters. Polysomnography (Somnostar alpha) was started at 21.00 hours and ended at 06.30 hours. Surface electrodes were applied using standard techniques to obtain an electroencephalogram, an electromyogram of the chin, an electrocardiogram, and an electrooculogram. Ventilation was monitored by inductive plethysmography. Airflow was monitored by thermistors placed at the nose and mouth, while arterial oxygen saturation (SaO<sub>2</sub>) was monitored continuously with a pulse oximeter. A polygraph was run continuously at 10 mm/s to record all of the above physiological data simultaneously throughout the course of the experiment. All parameters were stored in a data recorder for subsequent analysis. Apnea was defined as the cessation of airflow at the nose and mouth lasting for more than 10 seconds. Hypopnoea was defined as a decrease of 50% or more in thoracoabdominal motion associated with a fall in the baseline oxygen saturation of 4% or more. All AHI values were calculated to express the number of episodes of apnoea and hypopnoea per hour of total sleep time. AHI<5 were excluded from study. Patients with sleep disorders, except OSAS, such as upper airway resistance syndrome, periodic leg movements or narcolepsy were excluded. OSAS was defined as the combination of an AHI of 5 or more events/h with daytime sleepiness.

### Statistical Analysis

Results are expressed as mean ± standard error. We used an unpaired two-sided Student's t-test to analyse any differences in demographic and haemodynamic characteristics between these two groups. In correlation analysis Pearson correlation was used. All statistical analysis performed with SPSS 11.0 programme. Statistical significance was defined as  $p < 0.05$ .

### RESULTS

Table 1 shows the main clinical characteristics and polysomnographic data of all subjects. There was no significant differences between control and OSAS group with respect to age, BMI, blood pressure. Fasting glucose, insulin, leptin levels and HOMA-IR were examined in whole groups. There was no significant differences between control and OSAS group with respect to fasting glucose, insulin, leptin levels and HOMA-IR (Table 2). To examine the relationship between apne-hipopnea index, serum leptin levels and HOMA-IR, OSAS group were divided into two subgroups; AHI 5-20, AHI ≥ 20. Table 3 shows the comparison of fasting glucose, insulin, leptin levels, HOMA-IR and the main clinical characteristics in those control and OSAS subgroups. There was no significant differences between OSAS subgroup1 and OSAS subgroup 2 with respect to HOMA-IR, serum leptin, insulin and fasting glucose expect AHI index.

**Table 2.** Comparison of fasting glucose, insulin, leptin levels and HOMA-IR in those control and OSAS group

	Control (n:32)	OSAS (n:28)	p value
Fasting glucose (mg/dl)	101.75±11.92	96.72±14.25	ns
Insulin (uIU/ml)	10.36±4.35	12.59±7.56	ns
Leptin (ng/ml)	24.93±25.84	32.88±24.22	ns
HOMA-IR	2.58±1.21	3.01±1.81	ns

**Table 3.** Comparison of fasting glucose, insulin, leptin levels, HOMA-IR and clinical characteristics in those control and OSAS subgroups.

	Control (n :32)	Subgroup 1 AHI 5-20 (n:15)	Subgroup 2 AHI ≥20 (n:13)	p value
Age (year)	45.31±6.86	48.0±7.99	46.0±8.23	ns
BMI (kg/m) <sup>2</sup>	31.12±4.33	30.48±4.42	29.85±2.74	ns
AHI	2.72±1.61	12.4±5.48	41.83±21.07	<0.05
Insulin (uIU/ml)	12.59±1.33	9.04±2.70	12.11±5.76	ns
Fasting glucose (mg/dl)	98.72±14.25	101.88±11.50	101.58±12.15	ns
Leptin ( ng/ml)	32.88±24.22	21.34±18.91	29.7±33.88	ns
HOMA-IR	3.01±1.81	2.21±0.67	3.07±0.47	ns

To determine whether the degree of BMI was related to serum leptin levels and HOMA-IR, the subjects were separated into two groups with respect to BMI; BMI < 30 (kg/m)<sup>2</sup> ( group 1), BMI ≥ 30 (kg/m)<sup>2</sup> (group 2). Serum leptin levels and HOMA-IR were higher in group 2. Table 4 shows the comparison of fasting glucose, insulin, leptin levels, HOMA-IR and the main clinical characteristics in those group 1 and group 2.

**DISCUSSION**

In the present study we found that serum leptin levels and insulin resistance in male patients with OSAS are not associated with AHI. Furthermore, as expected serum leptin levels and insulin resistance were showed significant correlation with obesity. The results of published data on the relationship between OSAS, insulin resistance and leptin levels are conflicting.

Leptin is a hormone that reduce food receiving and raise consumption of energy by inhibiting hypothalamic NPY synthesis. Serum leptin levels were increased because of the leptin resistance in obese individuals (15,16). And also previous reports had shown that serum leptin lev-

els are higher in patients with OSAS than simple obese patients (17,18). TNF-α and IL-6 levels in patients with OSAS were significantly higher because of high levels of serum leptin and it has been suggested that high levels of these inflammatory markers were contributed to inflammation in the upper airway (19). Ozturk et al was found that there was a significant relationship between serum leptin levels and degree of OSAS. And they also showed that this relationship was independent from age and BMI (20). In patients with OSAS serum leptin levels are decreasing distinctly after the CPAP treatment with a correlation of improvement in AHI levels (21,22). Nonetheless Schafer et al was showed that leptin concentrations when controlled for body fat are not related to the degree of OSAS (23). In Barcelo’s study serum leptin levels in patients with OSAS was related to obesity (24). Recently Kapsimalis et al suggested that central obesity, which reflects visceral obesity has a major effect on leptin levels and the effect of apne -related hypoxemia maybe smaller (25). In our study we found no correlation between serum leptin levels and AHI.

Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral

**Table 4.** Comparison of fasting glucose, insulin, leptin levels, HOMA-IR and clinical characteristics in those group 1 and group 2.

	BMI<30kg/m <sup>2</sup> group 1 (n:28 )	BMI ≥30kg/m <sup>2</sup> group 2 (n:32)	p value
Insulin (uIU/ml)	9.1±4.96	13.6±6.69	<0.05
Leptin ( ng/ml)	21.95±19.83	35.49±27.71	<0.05
HOMA-IR	2.28±1.31	3.27±1.64	<0.05
Fasting glucose (mg/dl)	102.25±15.87	96,28±10.12	ns
Age (year)	44.5±8.0 4	7.5±7.24	ns
BMI (kg/m <sup>2</sup> )	27.31±1.80	33.16±3.40	<0.05
AHI	13.25±20.14	13.03±15.83	ns

glucose and fatty acid utilization, often leading to type 2 diabetes mellitus. The syndromes of insulin resistance actually make up a broad clinical spectrum, which includes obesity, glucose intolerance, diabetes, and the metabolic syndrome, as well as an extreme insulin-resistant state. In obese patients, down regulation of insulin receptor leads to insulin resistance and hyperinsulinemia (26). And previous reports have shown a linked relationship between OSAS and obesity (27). Conflicting results have been reported on the potential link between OSAS and insulin resistance. According to some studies including obese patients with OSAS, significant insulin resistance was determined (28,29). And also significant relationship between nocturnal hypoxemia, AHI and insulin resistance regardless of age and BMI have been reported in OSAS patients (29,30).

In patients with OSAS, it has been suggested that the presence of other mechanisms might be lead to insulin resistance with regardless of BMI and body fat. A lot of mechanisms that support the relationship between OSAS and insulin resistance have been considered but the investigators were focused on three important reasons. Firstly, in OSAS patients, hypoxia continued throughout the night was lead to elevated blood catecholamine levels and activated sympathetic system (31). Second, hypoxia occurred during the night as a stress factor was lead to an increase of glucocorticoid secretion (32). Third, it has been shown that hypoxia alone contributes insulin resistance in patients with chronic pulmonary disease (33).

In Rajala's study increasing per unit of BMI leads four times respiratory impairment (34). In many studies, the prevalence of respiratory impairment reached about 40% in exceedingly obese patients (35,36). In a study which performed by Stoohs and colleagues, there was a significant relationship with insulin resistance and respiratory impairment in sleep but they also suggested that this relationship was entirely dependent on body mass (36). A similar study, Somers and colleagues didn't find any relationship between insulin resistance and sleep disorders (37). On the contrary in another study which enrolled 261 male patient, was showed a significant relationship between sleep apnea and insulin levels with regardless of BMI (38).

Up to date, reviewing the literature, conflicting results have been reported between leptin levels, insulin resistance and OSAS. Some deficiencies and limitations

are observed in these studies which include followings; small number of patients, no gender discrimination, the patients which had systemic disease such as DM, hypertension were comprised the study, no assessment of ratio of body fat. For this reason in the present study we enrolled only male individuals to standardize the differences of results and also we excluded the patients who have systemic diseases.

In the present study, we evaluated the association between serum leptin levels, insulin resistance and apnea-hypopnea index; however no correlation was found. So that in order to prove the accuracy of serum leptin levels and insulin resistance, the subjects were separated into two groups with respect to BMI. As expected insulin resistance and plasma leptin concentrations are mostly associated with the degree of obesity.

In the literature different results had been reported. What is the potential mechanism which lead to different results between OSAS, leptin levels and insulin resistance? The distribution of fat to the upper body does seem to be more specific marker of the health hazards of obesity than overweight alone. Lara et al showed that different fat patterns for each sex, changes with age in body fat distribution, and different usefulness of external anthropometric measures in males and females to predict fat deposits and their distribution at the abdominal level (39). Furthermore Jensen et al concluded that a single-slice CT scan (or other imaging technique) with or without DXA is required for accurate predictions of intraabdominal fat (40). These conflicting results appear to suggest that BMI alone is a poor marker of body fat deposits and it seems that BMI alone did not correctly reflect the amount of visceral obesity.

In conclusion, in this study we found that in OSAS patients serum leptin levels and insulin resistance was associated with BMI but rather not associated with apnea-hypopnea index. To analyse the relationship with OSAS, insulin resistance and serum leptin levels, further investigations are needed. Future studies should be included larger population and the factors which affect the body fat deposits should be evaluated both invasive and non-invasive methods.

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