ORIGINAL ARTICLE

The Association of the Severity of Obstructive Sleep Apnea With Plasma Leptin Levels

Levent Öztürk, MD; Murat Ünal, MD; Lülüfer Tamer, PhD; Firuz Çelikoğlu, MD

Objective: To examine whether circulating leptin levels correlate with the severity of disease in patients with obstructive sleep apnea.

Design: Prospective nonrandomized study.

Setting: Referral sleep laboratory for patients with sleep-disordered breathing and biochemistry laboratory.

Patients: Thirty-two subjects (mean±SD age, 47±12 years) who were referred for suspected sleep apnea underwent an overnight sleep study and fasting morning venous blood sampling. Patients were divided into 3 groups with respect to apnea-hypopnea index: (1) severe sleep apnea (n=8), apnea-hypopnea index greater than 20; (2) mild sleep apnea (n=12), apnea-hypopnea index between 5 and 20; and (3) nonapneic control (n=12), apnea-hypopnea index less than 5.

Results: Leptin levels (mean±SD) were 21.2±8.6, 16.2±5.2, and 10.6±7.5 ng/mL (P=.005) in patients with severe and mild obstructive sleep apnea and nonapneic controls, respectively. Plasma leptin levels correlated positively with the degree of sleep-disordered breathing as recorded by the apnea-hypopnea index (r=0.54, P=.001) and percentage of sleep time spent with oxygen saturation below 90% (r=0.39, P=.02).

Conclusions: Circulating leptin concentrations in patients with obstructive sleep apnea, independent of body mass index and age, are significantly higher than levels in nonapneic controls and there is a positive relationship between leptin concentrations and the severity of sleep apnea. Hyperleptinemia may be a prognostic marker of obstructive sleep apnea syndrome.

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From the Departments of Physiology (Dr Öztürk) and Pneumology (Dr Çelikoğlu), School of Medicine, Kadir Has University; and the Departments of Otorhinolaryngology (Dr Ünal) and Biochemistry (Dr Tamer), School of Medicine, Mersin University, Istanbul, Turkey. *The authors have no relevant financial interest in this article.*

LEPTIN, THE hormone secreted by adipocytes, acts on hypothalamus producing a satiety signal.[1,2] It also induces a complex response involving control of body weight and energy expenditure.[3] Despite the weight-reducing effects of leptin, obese patients have a marked increase in leptin levels in proportion to body fat content.[4] It is thought that obesity is a result of leptin resistance in these patients.[5]

Obstructive sleep apnea (OSA) is a common disorder in which obesity plays an important role in the pathophysiology of the disease. Two thirds of middle-aged apneic men are obese, with particularly the central obesity type, and one third have hypertension.[6,7] Although the certain mechanisms of obesity remain unknown, theoretical constructs[8] and experimental data[9,10] suggest that hypoxia or sleep interruption, as occurs in OSA, may contribute to the changes in body fat accumulation and deposition. Furthermore, altered glucose metabolism[11] or leptin resistance[12] in OSA could promote development of obesity. Recent investigations have established that patients with OSA develop increased blood leptin levels[13,14] that decrease significantly following both short-term[14] and long-term[14,15] nasal continuous positive airway pressure treatment without any change in body weight, fasting insulin levels, and cortisol levels.

The purpose of this study was to determine whether blood leptin levels correlate with the severity of sleep apnea and to examine the respiratory parameters as well as blood leptin levels in patients with OSA.

METHODS

SUBJECTS

Thirty-two subjects (mean±SD age, 47±12 years) were recruited from those who were referred for suspected sleep apnea to our sleep laboratory. The study was approved by the local ethics committee and patients gave written informed consent. All subjects underwent an overnight sleep study to diagnose sleep apnea. Patients were divided into 3 groups with respect to the apnea-hypopnea index (AHI): (1) severe OSA (n=8), AHI greater than 20; (2) mild OSA (n=12), AHI between 5 and 20; and (3) non-OSA control (n=12), AHI less than 5.

Demographic, Anthropometric, and Respiratory Characteristics of Study Groups*

Variable	Severe OSA (n = 8)	Mild OSA (n = 12)	Non-OSA Controls (n = 12)
M/F, No.	8/0	11/1	10/2
Age, y	47 ± 12	49 ± 11	45 ± 14
BMI	30.8 ± 2.7	31.0 ± 3.7	28.5 ± 4.5
AHI	43 ± 12	12 ± 5	2 ± 1
Min O_2	75.7 ± 6.9	83.9 ± 5.6	85.4 ± 9.4
TST <90, %	15.8 ± 12.2	2.0 ± 3.1	0.8 ± 0.9
TST <90, min	62.8 ± 44.3	9.1 ± 12.2	3.3 ± 3.6

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); Min O_2, lowest value of oxyhemoglobin saturation; OSA, obstructive sleep apnea; TST <90, total sleep time spent with oxyhemoglobin saturation below 90%.

*Values are mean ± SD unless otherwise noted.

Consistent with earlier studies,[11,16] the cutoff point for AHI was selected as 20 to divide the OSA group into 2 subgroups of severe and mild. The body mass index (BMI; defined as weight in kilograms divided by the square of the height in meters), was calculated from body weight and height measured by a scale. Fasting venous blood samples were taken between 7 AM and 8 AM, after completion of the nocturnal polysomnographic recording. Plasma samples were stored at –20°C until leptin analysis. All samples were processed in the same manner.

SLEEP STUDY

The polygraphic sleep study was performed by using a computerized polysomnography system (Alice 3; Healthdyne/Respironics, Pittsburgh, Pa). To determine the stages of sleep, 2-channel electroencephalogram (C4-A1, C3-A2), chin electromyogram, and left and right electrooculograms were obtained. Thoracoabdominal movements were monitored with thoracic and abdominal strain gauges. Airflow was monitored with an oronasal thermistor. Arterial oxyhemoglobin saturation was recorded with the use of a pulse oxymeter. Electrocardiogram, snoring, and body position were also recorded. Recordings were manually scored according to standard criteria.[17] An episode of obstructive apnea was defined as the absence of airflow for at least 10 seconds, in the presence of rib cage and abdominal excursions. Hypopnea was defined as a discernible reduction in airflow lasting 10 seconds or longer and associated with at least a 4% decrease in arterial oxyhemoglobin saturation, an electroencephalographic arousal,[18] or both. The number of episodes of apnea and hypopnea per hour is referred to as the AHI.

LEPTIN ANALYSIS

Plasma leptin levels were measured using an enzyme-linked immunosorbent assay kit (DSL-10.23100; Diagnostic Systems Laboratories, Webster, Tex). The assay range was 0.5 to 100 ng/mL. The intra-assay coefficient of variation for the quality control values was 6.3%.

STATISTICAL ANALYSIS

Results are expressed as mean ± SD. The nonparametric Kruskal-Wallis test was used to assess differences of severe OSA, mild OSA, and non-OSA control groups, and intergroup differences among the 3 groups were evaluated with the Mann-Whitney *U* test. Correlation between plasma leptin concentration and other parameters was evaluated with the Spearman rank correlation test. Partial correlation was also performed to control the effects of BMI and age on the relation between leptin and AHI. $P<.05$ was considered to indicate statistical significance.

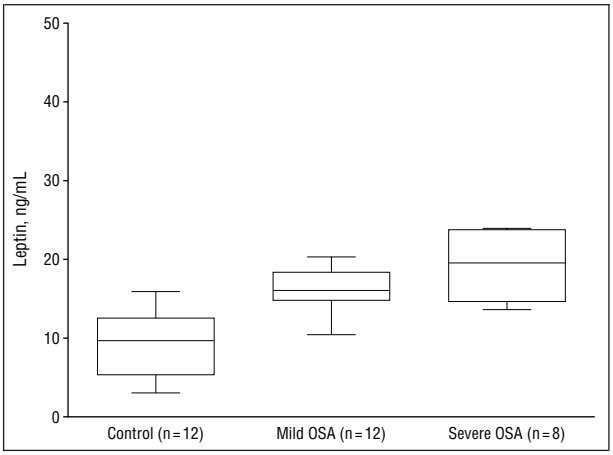

Figure 1. Leptin levels in the 3 study groups. OSA indicates obstructive sleep apnea.

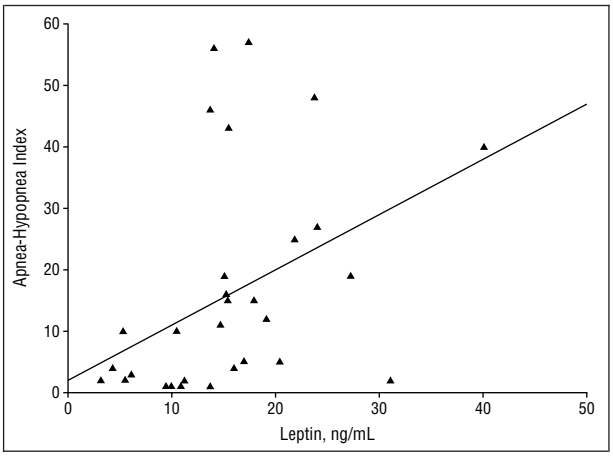

Figure 2. Positive correlation of plasma leptin levels with apnea-hypopnea index.

RESULTS

Demographic and anthropometric characteristics of the study groups are shown in the **Table**. The study groups were matched in terms of age and BMI. Leptin levels were 21.2±8.6, 16.2±5.2, and 10.6±7.5 ng/mL in patients with severe OSA and mild OSA, and non-OSA controls ($P=.005$), respectively (**Figure 1**).

In the entire study group, plasma leptin levels correlated positively with the degree of OSA as recorded by AHI ($r=0.54$, $P=.001$) (**Figure 2**) and percentage of sleep time spent with oxygen saturation below 90% ($r=0.39$, $P=.02$). Controlled for BMI, leptin levels were still in correlation with AHI ($r=0.38$, $P=.04$).

COMMENT

The important, novel finding of this study is that the patients with severe OSA have higher circulating leptin levels than do patients with mild OSA, and the severity of OSA is associated with increasing leptin levels. We also

found that patients with OSA have higher leptin levels than age- and BMI-matched nonapneic control subjects. Leptin levels were about 70% higher in the OSA group compared with the non-OSA group.

Increased plasma leptin levels may have implications for understanding the pathophysiology of obesity in OSA. Obesity, as defined by BMI greater than 28, is present in 60% to 90% of patients with OSA.[11] Particularly, measures of central obesity (hip-waist ratio or neck circumference) exhibit strong correlation with OSA.[7] It is believed that increased deposition of fat in the neck and upper airway region predisposes the individual to upper airway collapse and apnea during sleep. Even nonobese patients with OSA have more total body fat than do age- and BMI-matched control subjects and they have substantially greater deposits of fat anterolateral to the upper airway.[19] It may be suggested that circulating leptin's action may determine the type of obesity (ie, central vs peripheral type) or the region of fat accumulation (ie, upper airway or abdominal viscera). Thus, it may predispose some patients to sleep apnea. Consistent with this suggestion, in a recent study, leptin levels were found in correlation with visceral fat accumulation, and both leptin and visceral fat accumulation decreased in patients with OSA following the nasal continuous positive airway pressure treatment.[14] The patients in this study had BMIs in the overweight and obese range. However, BMIs of patients with OSA tend to be greater than those of patients who do not have OSA, although there was no statistically significant difference.

Recent observations suggest that leptin has a much broader physiological role than the regulation of body weight and energy metabolism. For instance, leptin was reported to regulate fertility,[20] angiogenesis,[21] and immune function.[22] Interestingly, leptin promotes platelet aggregation in vitro and is necessary for the formation of stable thrombi in vivo.[23] These effects are mediated by leptin receptors on platelets. On the other hand, it is now known that chronic hyperleptinemia may play a role in the pathogenesis of some forms of obesity-related hypertension.[24] These latter observations, together with the results of the present study, raise the possibility that leptin may promote, or at least in part have a role in the development of, hypertension and cardiovascular disease in patients with OSA.

There are some additional intriguing physiologic implications from previous studies. Leptin deficiency in the presence of obesity is associated with an elevated Pa_{CO_2} and hypoventilation.[25] It is demonstrated that impaired ventilatory responses in leptin-deficient ob/ob mice improves after infusion of leptin into these animals.[25-27] The stimulating effect of leptin on ventilation is independent of weight, carbon dioxide production, and food intake, consistent with a direct effect of leptin on respiratory control centers in the brain.[25] It is also suggested that the effect of leptin on baseline ventilation is not likely coupled with a restoration of metabolism or temperature regulation.[27] In the light of all these data, it is speculated that the concentration of leptin in the cerebrospinal fluid, or the sensitivity of leptin receptors in the brain, is the factor that determines whether respiration in an obese human is normal or depressed.[25] Future studies are required to assess cerebrospinal fluid leptin concentrations and central regulatory effects of leptin on breathing.

We conclude that patients with severe OSA have higher levels of plasma leptin than patients with mild OSA and there is a positive correlation, independent of age and BMI, between the plasma leptin levels and the severity of disease in OSA. These results suggest that hyperleptinemia may be a prognostic marker of OSA.

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Corresponding author and reprints: Levent Öztürk, MD, Fizyoloji ABD, Kadir Has Üniveritesi Týp Fakültesi, Vefabey Sk. No: 5 Gayrettepe, Istanbul, Turkey 80810 (e-mail: leventrk@hotmail.com).

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