ORIGINAL ARTICLE

Insulin resistance and Leptin levels in patients with Obstructive Sleep Apnea

Khosro Sadeghniiat-Haghighi[1], Mohammad Reza Mohajeri-Tehrani[2], Ahmad Khajeh-Mehrizi[1,3], Zahra Banafsheh Alemohammad[1], Ania Rahimi-Golkhandan[1,4], Sina Hafizi[1], Bagher Larijani[2]

[1.] *Occupational Sleep Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[2.] *Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[3.] *Department of Internal Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[4.] *Center for Research on Occupational Diseases, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract

Background and Objective: Obstructive sleep apnea (OSA) has been associated with metabolic syndrome, diabetes mellitus and cardiovascular diseases. Insulin resistance and increased leptin levels could explain the impaired metabolic conditions in patients with OSA. This study aimed to assess the association of OSA severity with insulin resistance and leptin levels in a group of patients referred to a sleep disorders clinic.

Materials and Methods: Seventeen patients without OSA and 28, 33 and 30 patients with mild, moderate and severe OSA; respectively, were included in this study. All subjects underwent full night polysomnography (PSG) and blood samples were collected in the morning after PSG. The insulin resistance index was estimated by homeostasis model assessment (HOMA).

Results: HOMA values were not significantly different among the study groups. Significant difference in leptin level was found between patients with severe OSA and mild OSA. Leptin level was significantly correlated with age (r=33, *P*=0.02), apnea-hypopnea index (r=0.41, *P*=0.004), and oxygen desaturation index (r=46, *P*=0.03). HOMA were in significant positive correlation only with triglyceride level (*P*=0.01). Stepwise multiple regression analysis showed that apnea-hypopnea index, body mass index and gender were determinants of leptin levels, however no variable was found for predicting HOMA.

Conclusion: Our findings suggest that leptin levels might be independently associated with severity of OSA. Other factors other than insulin resistance should be considered for increasing vascular diseases in OSA patients.

Keywords: Insulin, HOMA, leptin, obstructive sleep apnea

Introduction

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by excessive daytime sleepiness and frequent episodes of airway obstructions during sleep. The male gender, age and obesity are some of the known risk factors for this condition (1). OSA has been linked with metabolic syndrome, hypertension, diabetes mellitus and cardiovascular morbidities (2-7).

Insulin resistance, which is identified as an impaired biological response to insulin, has been shown to have a central role in the pathogenesis of the metabolic syndrome (8) and has been also recognized as an independent risk factor for vascular diseases (9). Several studies performed in the general or in clinic-based populations showed that OSA is an independent risk factor for the occurrence of insulin resistance. These studies, however, do not provide definitive evidence that OSA results in insulin resistance. On the other hand, there are studies reporting no independent association

Corresponding Author: A. Khajeh-Mehrizi, Occupational Sleep Research Center, Tehran University of Medical Sciences, Tehran, Iran.
E-mail address: khmehrizi.a@gmail.com,
Tel: +98 21 55677333, Fax: +98 21 55677333

between OSA and insulin resistance (10-14).

Leptin is a single-chain proteohormone produced by adipocytes that plays a key role in the regulation of food intake, energy expenditure, body weight, and glucose and lipid metabolism. Elevated leptin levels have been linked to increased risk of cardiovascular diseases (15). In spite of the anti-obesity effects of leptin, leptin levels are increased in obese individuals (16) and patients with OSA (17-21).

Obesity which is very common in patients with OSA is strongly associated with insulin resistance (8) and leptin levels (16) and may be the major confounding factor in the association of OSA with insulin resistance and cardiovascular disease. In this study, we aimed to assess the association of OSA with insulin resistance and leptin levels by controlling for obesity in the patients referring to the sleep clinic.

Materials and Methods

Patients

This study included OSA patients who were referred to Baharloo sleep disorders clinic in Tehran, Iran. Patients completed a questionnaire battery containing of demographic characteristics, past medical history, medications history, Persian version of the Epworth Sleepiness Scale (ESS) and Insomnia Severity Index (ISI) on the night of sleep study. ESS was used for the subjective assessment of daytime sleepiness (22) and ISI evaluated the daytime symptoms and nighttime severity of insomnia (23). Systolic and diastolic blood pressures, weight, height and neck circumference (directly below the laryngeal prominence) were measured. All patients underwent a full-night polysomnography (PSG). Patients were excluded if they had a metabolic disease (such as diabetes mellitus and thyroid dysfunction), cardiac, cerebral, renal, liver or pulmonary diseases (except for OSA) in addition to whom taking glucose-lowering agents. Written consents were obtained from all participants. The study was approved by the Institutional Review Board of Diabetes Research Center, and the research ethics board of Tehran University of Medical Sciences, Iran.

Polysomnography

We used Sandman Elite digital sleep software and Sandman SD32+amplifiers for running PSG. Electroencephalogram, electrocardiogram, submental and bilateral anterior tibialis electromyogram, right and left electrooculogram, snoring, respiratory airflow, arterial oxygen saturation, respiratory effort of abdomen and chest, and body position were monitored during sleep. All tests were analyzed according to the recommendation criteria by the American Academy of Sleep Medicine (24). Apnea–hypopnea index (AHI) was defined as the average number of apnea (complete cessation of airflow for at least 10 seconds) and hypopnea (the reduction of airflow for more than 30 % for at least 10 seconds with 3% reduction of arterial oxygen saturation or with arousal) per hour of sleep. OSA was diagnosed if patient had AHI greater than 5. Mild, moderate, or severe OSA were classified if patient had $5 \leq$ AHI <15, $15 \leq$ AHI <30, or AHI ≥ 30, respectively.

Laboratory tests

Blood samples were taken from all subjects in the morning of the day after PSG. A specimen of clotted blood was centrifuged and stored at -80 °C until subsequent analysis. The levels of total cholesterol, triglycerides (TG), high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and fasting blood glucose (FBG), were measured in plasma.

Insulin levels were measured by an Insulin AccuBind ELISA Kit, Monobind, USA. The insulin resistance index was estimated by homeostasis model assessment (HOMA-IR): (fasting serum glucose (mmol/L) * fasting serum insulin (lU/ml))/22.5. The serum leptin level was evaluated using a sandwich enzyme-linked immunosorbent assay kit (BioVender, Germany).

Statistical analysis

Continuous variables were presented as means± standard deviation (SD) and categorical variables as percentage of subjects. $\chi 2$ test or one-way analysis of variance (ANOVA) with the post-hoc Scheffe test were performed to establish the difference of categorical or continuous variables; respectively. Pearson correlation coefficients were used to test the association between variables. Multiple regression analysis with adjustment for age, gender and BMI was performed to identify variables which independently associated with the levels of leptin, HOMA, insulin and FBG. *P*.value<0.05 was considered statistically significant. SPSS version 21.0 for Windows (SPSS Inc, Chicago, IL) was used for the statistical analysis.

Results

Patients were divided into four groups based on their OSA severity as follow: (a) individuals without OSA

(n=17), (b) patients with mild OSA (n=28), (c) patients with moderate OSA (n=33), and (d) patients with severe OSA (n=30).

Demographic and anthropometric characteristics of the 108 enrolled participants (age 19-81 years) are presented in Table 1. There were a significant differences in age, weight, body mass index (BMI), and neck circumference showed between the four groups. Patients with OSA had significantly greater ESS score while there was no significant difference in ISI score. Among the polysomnographic and laboratory variables (Table 2), significant difference were found regarding AHI, oxygen saturation index (ODI), minimum O2 saturation, fasting blood glucose (FBG) and leptin levels among the four groups. In post-hoc scheffe test, the FBG was significantly higher in patients with moderate OSA than patients with mild OSA and subjects without OSA as well as in patients with severe OSA than those with mild OSA. Significant difference in leptin level was only found between patients with severe OSA and mild OSA.

Table 1. Demographic and anthropometric characteristics of the subjects

	No OSA (n=17)	Mild OSA (n=28)	Moderate OSA (n=33)	Severe OSA (n=30)	P. value
Female number (%)	5 (29.4)	9 (32.1)	8 (24.2)	9 (30)	0.91
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Age (years)	36.4 (12.2)	42.4 (15)	45.9 (9.9)	50.6 (9)	0.001
Weight (kg)	77.8 (11.8)	75.7 (15.5)	91.1(16.1)	89.3 (15.2)	0.001
Height (cm)	171.2 (9.3)	168.4 (14.7)	176.1 (7.3)	168.3 (10.6)	0.05
BMI (kg/m2)	26.5 (3.7)	26.5 (3.6)	29.4 (4.9)	31.6 (5.4)	<0.001
Neck circumference (cm)	38.5 (0.7)	39.9 (1.3)	41.5 (0.7)	42 (1.5)	0.03
Systolic blood pressure (mmHg)	113.3 (5.7)	116.6 (13.6)	117.5 (9.5)	125 (18.7)	0.63
Diastolic blood pressure (mmHg)	73.3 (11.5)	71.6 (7.5)	77.5 (5)	83.3 (10.3)	0.16
ISI score	15.2 (8.2)	11.1 (5)	17.1 (8.6)	16 (4.4)	0.39
ESS score	6 (5.2)	7.2 (3.9)	12.2 (1.3)	14.5 (5.3)	0.002

OSA obstructive sleep apnea, BMI body mass index, ISI insomnia severity index, ESS Epworth sleepiness scale

Table 2. Polysomnographic and laboratory variables of the subjects

	No OSA (n=17) Mean (SD)	Mild OSA (n=28) Mean (SD)	Moderate OSA (n=33) Mean (SD)	Severe OSA (n=30) Mean (SD)	*P*. value
AHI	3.1 (1.5)	9.1 (2.7)	21.2 (4.8)	55.1 (18.7)	<0.001
ODI	2.8 (2.2)	5.8 (3.7)	14.4 (4.6)	40.5 (27.8)	<0.001
Sao2<90 % (min)	0.2 (0.1)	2.2 (3.1)	8.4 (10.1)	27.2 (32)	0.05
Mean Sao2 (%)	94.5 (1.9)	93.2 (2.8)	90.7 (11.1)	89.3 (11)	0.15
Minimum Sao2 (%)	88.6 (3.2)	84.8 (6.1)	76.6 (21.4)	69.3 (23.5)	0.005
TST (hour)	6.3 (1.4)	6.5 (1.2)	6.8 (1.2)	6.7 (1.3)	0.63
FBG (mmol/L)	5.3 (0.5)	5.2 (0.6)	6.1 (0.6)	5.9 (0.6)	0.001
Insulin (µU/ml)	10.9 (7.8)	10 (8)	15.5 (14.6)	18.1 (14.7)	0.05
HOMA	2.9 (2.2)	2.5 (1.9)	5.2 (4.7)	4 (3.1)	0.11
Leptin (ng/ml)	14.7 (12.4)	11.8 (11.6)	24.1 (13.8)	31 (15.4)	0.007
TG (mg/dl)	144 (87.8)	170 (88.8)	186.8 (81.30	196.8 (106.7)	0.46
HDL (mg/dl)	51.7 (40.2)	51.6 (31.7)	39.6 (12.4)	46.3 (21.4)	0.63
LDL (mg/dl)	119.6 (30.3)	113 (32.6)	104.9 (34)	125.9 (50.7)	0.50
TC (mg/dl)	189.6 (24.9)	205.1 (28.20	178.9 (36.9)	210.1 (70.4)	0.26

OSA obstructive sleep apnea, AHI apnea hypopnea index, ODI oxygen desaturation index, Sao2 oxygen saturation, TST total sleep time, FBG fasting blood glucose, HOMA homeostasisassessment method forinsulinresistance, TG triglycerides, HDL high-density lipoprotein, LDL low-density lipoprotein, TCtotal cholesterol

The Pearson correlation coefficients between leptin, HOMA, insulin, glucose and measured variables are presented in Table 3. Leptin level was significantly correlated with age (r=33, *P*=0.02), AHI (r=41, *P*=0.004), and ODI (r=46, *P*=0.03), however, it was not correlated with HOMA, insulin and FBG levels. FBG was significantly correlated with BMI (r= 43, *P*=0.001), AHI (r=29, *P*=0.02) and TG level (r=40, *P*=0.002) while insulin level was only significantly correlated with AHI (r=23, *P*<0.05). Although HOMA was not significantly correlated with polysomnographic variables, a significant positive correlation was found between

HOMA and TG level (r=31, *P*= 0.01).

In multiple regression analysis, after adjusting for age, gender and BMI, the leptin level was independently associated with AHI (β=0.52, *P*<0.01) and ODI (β=0.42, *P*<0.01). HOMA and FBG were not independently associated with measured variables, whereas insulin level was found to be independently associated with AHI (β=0.28, *P*=0.02) (Table 4). Stepwise multiple regression analysis showed that AHI, BMI and gender were determinants of leptin levels (leptin= -28.77 + (0.44*AHI) + (0.36*BMI) + (0.33*gender), R^2=0.713). No determinant variable was found in the stepwise multiple regression for predicting HOMA.

Table 3. Pearson correlation coefficients of leptin, HOMA, insulin and glucose levels

	Leptin	HOMA	Insulin	FBG
Age	o.33*	0.04	0.08	0.24
BMI	0.22	0.07	0.07	0.43**
ISI score	0.70	-0.18	-0.07	-0.10
ESS score	0.62	0.01	0.14	0.47
AHI	0.41**	0.23	0.23*	0.29*
ODI	0.46*	0.07	0.20	0.10
Sao2<90 %	0.006	0.31	0.22	0.21
TST	-0.15	0.09	0.06	-0.05
TG	-0.09	0.31*	0.26	0.40**
HDL	0.27	-0.08	-0.09	-0.16
LDL	-0.10	-0.06	0.01	-0.01
TC	-0.14	0.20	0.19	0.11

HOMA homeostasis assessment method for insulin resistance, FBG fasting blood glucose, BMI body mass index, ISI insomnia severity index, ESS Epworth sleepiness scale AHI apnea hypopnea index, ODI oxygen desaturation index, Sao2 oxygen saturation, TST total sleep time, TG triglycerides, HDL high-density lipoprotein, LDL low-density lipoprotein, TCtotal cholesterol

**P*. value<0.05, ***P*. value<0.01

Table 4. Results of multiple regression analysis to find independent association of leptin, HOMA, insulin and FBG

	Leptin	HOMA	Insulin	FBG
AHI	0.52 (0.01)	0.29 (0.08)	0.28 (0.02)	0.02 (0.85)
ODI	0.42 (0.01)	0.14 (0.45)	0.26 (0.09)	-0.02 (0.91)
TG	-0.002 (0.99)	0.18 (0.22)	0.13 (0.37)	0.24 (0.06)

Results are presented as β (*P*. value).

Adjustments were made for age, gender and BMI.

HOMA homeostasisassessment method forinsulinresistance, FBG fasting blood glucose, AHI apnea hypopnea index, ODI oxygen desaturation index, TG triglycerides.

Discussion

In this study, we assessed the relationship between insulin resistance and leptin levels with the severity of symptoms in OSA patients. In our study the leptin level was independently associated with OSA severity determined by AHI and ODI after adjustment for age, gender and BMI. Insulin resistance estimated by HOMA method was not correlated with OSA severity as well as with BMI.

Conflicting results were established in the association of insulin resistance and OSA in previous studies. Some studies demonstrated an independent association between insulin resistance and OSA (10-13) whereas several studies did not find such a relationship (14, 18). Vgontzas and colleagues (10) found that both FBG and plasma insulin levels were higher in the apneics than in obese controls and Ip and colleagues (13) showed that OSA patients were more insulin resistant than nonapneic patients as indicated by higher levels of fasting serum insulin and HOMA-IR. On the other hand, Gruber et al (14) found a greater levels of insulin resistant in OSA patients but after adjustment for age, BMI and smoking history, no independent association were found between OSA and insulin resistance state. They reported that levels of FBG and triglyceride and the ESS score were independently associated with OSA. Similarly, Kapsimalis and colleagues (18) in a study on 67 referred men to sleep laboratory reported that insulin resistance was not

significantly correlated with OSA severity. In our study we did not find an independent association between insulin resistance and OSA severity. Population differences may be explained the contradictory results of relevant studies (18).

Chronic sleep loss, due to a sleep disorder or behavioral, is suggested as a risk factor for weight gain and insulin resistance (25). In this study we investigated the relationship of insulin resistance with total sleep time (TST) in polysomnography and ISI score as indicators for sleep insufficiency. HOMA was not significantly correlated with TST and ISI score, considering the fact that TST in one night polysomnography and ISI score are not entirely representatives of the chronic sleep loss.

Leptin is a protein of 167 amino acids secreted by adipocytes which is involved in the pathogenesis of obesity and cardiovascular diseases. Obesity plays as a strong confounding factor in the relationship of leptin and OSA. Several studies reported an independent association between leptin and OSA (17-20), whereas some did not (21, 26-29). These conflicting results are linked to the confounding effect of obesity. In the study of Tokuda and colleagues (17) BMI, percentage of sleep time with SaO2<90% and AHI were determinants of serum leptin levels. Kapsimalis and colleagues (18) reported that waist-to-hip ratio and percentage of sleep time with SaO2<90% were significant variables predicting leptin levels. Also, UlukavakCiftci et, al. (19) showed that AHI and BMI had an independent association with leptin levels. In contrast, Ursavas and colleagues (21) reported no significant difference of leptin level between patients with OSA and controls and Sharma and colleagues (27) in a study on 40 apneic obese patients and 40 nonapneic obese subjects reported no significant difference in levels of insulin resistance and leptin. In our study, we showed that leptin was significantly correlated with AHI and ODI and the association remained after adjustment for age, gender and obesity. Finally, stepwise multiple regression demonstrated that AHI, BMI and gender were significant determinants of leptin. The body fat ratio in women was greater than men and since leptin originates from adipose tissue, this was an expected result that leptin levels were higher in women than men. Our results are consistent with previous studies reporting obesity as a confounder on the association of leptin and OSA, however, we showed that AHI as a marker for OSA severity is a significant determinant of leptin level and this effect is a little greater than BMI in the prediction model developed by stepwise multiple regression.

Our study had several limitations. First, we did not measure the waist circumference and waist to hip ratio as indicators for central obesity. Some studies reported that central obesity is a determinant for insulin resistance and leptin levels. Second, in our sample we did not match the patients and controls for gender and BMI. However the gender ratio was relatively similar while BMI was associated with OSA severity.

Conclusion

This study showed that leptin levels in contrast to insulin resistance were elevated in OSA patients. Our findings indicated that insulin resistance was not associated with OSA severity. In contrast, the leptin levels were independently associated with severity of OSA and AHI plays as a significant determinant for prediction of leptin levels.

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Conflict of Interest

Authors declare no conflict of interest.

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