Original Research

Insulin Resistance and Leptin Levels in Patients with Obstructive Sleep Apnea

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

[1.] *Occupational Sleep Research Center, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[2.] *Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[3.] *Occupational Sleep Research Center, Baharloo Hospital AND Department of Internal Medicine, School of Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran*

Received: 24 Jun. 2016 Accepted: 20 Aug. 2016

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 participants 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 and mild OSA. Leptin level was significantly correlated with age (r = 33, P = 0.020), apnea–hypopnea index (AHI) (r = 0.41, P = 0.004), and oxygen desaturation index (r = 46, P = 0.030). HOMA was insignificant positive correlation only with triglyceride level (P = 0.010). Stepwise multiple regression analysis showed that AHI, body mass index, and gender were determinants of leptin levels, however, no variable was found for predicting HOMA.

Conclusion: Present 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 patients with OSA.

Keywords: Insulin; Leptin; Obstructive sleep apnea

Citation: Sadeghniiat-Haghighi K, Mohajeri-Tehrani MR, Khajeh-Mehrizi A, Banafsheh Alemohammad Z, Rahimi-Golkhandan A, Hafizi S, et al. **Insulin Resistance and Leptin Levels in Patients with Obstructive Sleep Apnea.** J Sleep Sci 2017; 2(1-2): 7-12.

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 between OSA and insulin resistance (10-14).

Leptin is a single-chain proteohormone produced by adipocytes that play a key role in the

*** *Corresponding author***: *A. Khajeh-Mehrizi, Occupational Sleep Research Center, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*
Tel: +982155677333, Fax: +982155677333
Email: khmehrizi.a@gmail.com

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 a 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 demographic characteristics, 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.

PSG: 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 the patient had AHI > 5. Mild, moderate, or severe OSA were classified if the patient had $5 \leq AHI < 15$, $15 \leq AHI < 30$, or $AHI \geq 30$, 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-cholesterol (HDL), low-density lipoprotein-cholesterol (LDL), 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 (BioVendor, Germany).

Statistical analysis: Continuous variables were presented as the mean ± standard deviation (SD) and categorical variables as a percentage of subjects. χ^2 test or one-way analysis of variance with the post-hoc Scheffe test was 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, sex, and body mass index (BMI) was performed to identify variables which independently are associated with the levels of leptin, HOMA, insulin, and FBG. $P < 0.050$ was considered statistically significant. SPSS for Windows (version 21, IBM Corporation, Armonk, NY, USA) 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.

Table 1. Demographic and anthropometric characteristics of the participants

Variable	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)	0.910
	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)	0.050
BMI (kg/m^2)	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)	0.030
Systolic blood pressure (mmHg)	113.3 (5.7)	116.6 (13.6)	117.5 (9.5)	125 (18.7)	0.630
Diastolic blood pressure (mmHg)	73.3 (11.5)	71.6 (7.5)	77.5 (5)	83.3 (10.3)	0.160
ISI score	15.2 (8.2)	11.1 (5)	17.1 (8.6)	16 (4.4)	0.390
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; SD: Standard deviation

Significant differences in age, weight, BMI, and neck circumference were found 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 was found regarding AHI, oxygen saturation index (ODI), minimum O_2 saturation, 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.

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 = 0.020), AHI (r = 41, P = 0.004), and ODI (r = 46, P = 0.030); 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 = 0.020), and TG level (r = 40, P = 0.002) while insulin level was only significantly correlated with AHI (r = 23, P < 0.050). Although HOMA was not significantly correlated with polysomnographic variables, a significant positive correlation was found between HOMA and TG level (r = 31, P = 0.010).

In multiple regression analysis, after adjusting for age, sex, and BMI, the leptin level was independently associated with AHI (β = 0.52, P < 0.010) and ODI (β = 0.42, P < 0.010). 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 = 0.020) (Table 4).

Table 2. Polysomnographic and laboratory variables of the participants

Variable	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
SaO_2 < 90% (minute)	0.2 (0.1)	2.2 (3.1)	8.4 (10.1)	27.2 (32)	0.050
Mean SaO_2 (%)	94.5 (1.9)	93.2 (2.8)	90.7 (11.1)	89.3 (11)	0.150
Minimum SaO_2 (%)	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)	0.630
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)	0.050
HOMA	2.9 (2.2)	2.5 (1.9)	5.2 (4.7)	4 (3.1)	0.110
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)	0.460
HDL (mg/dl)	51.7 (40.2)	51.6 (31.7)	39.6 (12.4)	46.3 (21.4)	0.630
LDL (mg/dl)	119.6 (30.3)	113 (32.6)	104.9 (34)	125.9 (50.7)	0.500
TC (mg/dl)	189.6 (24.9)	205.1 (28.20	178.9 (36.9)	210.1 (70.4)	0.260

OSA: Obstructive sleep apnea; AHI: Apnea–hypopnea index; ODI: Oxygen desaturation index; SaO_2: Oxygen saturation; TST: Total sleep time; FBG: Fasting blood glucose; HOMA: Homeostasis assessment method for insulin resistance; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; SD: Standard deviation

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

Variable	Leptin	HOMA	Insulin	FBG
Age (year)	0.33*	0.04	0.08	0.24
BMI (kg/m^2)	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
SaO_2 < 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; SaO_2: Oxygen saturation; TST: Total sleep time; TG: triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; *P < 0.050; **P < 0.010

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 4. Multiple regression analysis for independent association of leptin, HOMA, insulin, and glucose levels

Variable	FBG			
	Leptin	HOMA	Insulin	FBG
AHI	0.52	0.29	0.28	0.02
	(0.010)	(0.080)	(0.020)	(0.850)
ODI	0.42	0.14	0.26	−0.02
	(0.010)	(0.450)	(0.090)	(0.910)
TG	−0.002	0.18	0.13	0.24
	(0.990)	(0.220)	(0.370)	(0.060)

Results are presented as β (P value). Adjustments were made for age, sex, and BMI; HOMA: Homeostasis assessment method for insulin resistance; FBG: Fasting blood glucose; AHI: Apnea–hypopnea index; ODI: Oxygen desaturation index; TG: Triglyceride; BMI: Body mass index

Discussion

In this study, we assessed the association between insulin resistance and leptin levels with the severity of symptoms in OSA patients. In the current study, the leptin level was independently associated with OSA severity determined by AHI and ODI after adjustment for age, sex, and BMI. Insulin resistance estimated by HOMA method was not correlated with OSA severity as well as 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 et al. found that both FBG and plasma insulin levels were higher in the patients with sleep apnea than obese controls (10) and Ip et al. showed that OSA patients were more insulin resistant than non-apneic patients as indicated by higher levels of fasting serum insulin, and HOMA-IR (13). Moreover, Gruber et al. found greater levels of insulin resistance in patients with OSA, but after adjustment for age, BMI, and smoking history, no independent association was found between OSA and insulin resistance state. They reported that levels of FBG and TG, and the ESS score were independently associated with OSA (14).

Similarly, Kapsimalis et al. in a study on 67 referred men to sleep laboratory reported that insulin resistance was not significantly correlated with OSA severity (18). In this study, we did not find an independent association between insulin resistance and OSA severity. Population differences may explain the contradictory results of relevant studies (18).

Chronic sleep loss due to a sleep disorder or behavioral disorders 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 PSG 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 PSG and ISI score are not entirely representatives of the chronic sleep loss.

Leptin is a protein of 167 amino acids secreted by adipocytes which are involved in the pathogenesis of obesity and cardiovascular diseases. Obesity plays 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 et al., BMI, percentage of sleep time with SaO_2 < 90%, and AHI were determinants of serum leptin levels (17). Kapsimalis et al. reported that waist-to-hip ratio and percentage of sleep time with SaO_2 < 90% were significant variables predicting leptin levels (18). Furthermore, Ulukavak Ciftci et al. showed that AHI and BMI had an independent association with leptin levels (19). In contrast, Ursavas et al. reported no significant difference of leptin level between patients with

OSA and controls (21) and Sharma et al. in a study on 40 apneic obese patients and 40 non-apneic obese subjects reported no significant difference in levels of insulin resistance and leptin (27). In the current study, we showed that leptin was significantly correlated with AHI and ODI and the association remained after adjustment for age, sex, and obesity. Finally, stepwise multiple regression demonstrated that AHI, BMI, and sex 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. Present 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.

This 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 sex 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. Current 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.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

The authors wish to thank the staff of Baharloo sleep disorders clinic for their support.

References

1. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis 2015; 7: 1311-22.
2. Qian Y, Xu H, Wang Y, et al. Obstructive sleep apnea predicts risk of metabolic syndrome independently of obesity: A meta-analysis. Arch Med Sci 2016; 12: 1077-87.
3. Rajan P, Greenberg H. Obstructive sleep apnea as a risk factor for type 2 diabetes mellitus. Nat Sci Sleep 2015; 7: 113-25.
4. Sadeghniiat-Haghighi K, Mohajeri-Tehrani MR, Khajeh-Mehrizi A, et al. Obstructive sleep apnea and excessive daytime sleepiness among patients with type 2 diabetes mellitus: A single-center study from Iran. Int J Diabetes Dev Ctries 2015; 35: 189-93.
5. Uyar M, Davutoglu V. An update on cardiovascular effects of obstructive sleep apnoea syndrome. Postgrad Med J 2016; 92: 540-4.
6. Khajeh-Mehrizi A, Rahimi-Golkhandan A, Sedaghat M. Obstructive sleep apnea among individuals admitted for myocardial infarction. J Sleep Sci 2016; 1: 23-7.
7. Xu S, Wan Y, Xu M, et al. The association between obstructive sleep apnea and metabolic syndrome: A systematic review and meta-analysis. BMC Pulm Med 2015; 15: 105.
8. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-607.
9. Haffner SM, Miettinen H. Insulin resistance implications for type II diabetes mellitus and coronary heart disease. Am J Med 1997; 103: 152-62.
10. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: Relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000; 85: 1151-8.
11. Tassone F, Lanfranco F, Gianotti L, et al. Obstructive sleep apnoea syndrome impairs insulin sensitivity independently of anthropometric variables. Clin Endocrinol (Oxf) 2003; 59: 374-9.
12. Zahin M, Bercik Ynal B, Ögeden S, et al. Metabolic profile and insulin resistance in patients with obstructive sleep apnea syndrome. Turk J Med Sci 2011; 41: 443-54.
13. Ip MS, Lam B, Ng MM, et al. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165: 670-6.
14. Gruber A, Horwood F, Sithole J, et al. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovasc Diabetol 2006; 5: 22.
15. Mark AL, Correia ML, Rahmouni K, et al. Selective leptin resistance: A new concept in leptin physiology with cardiovascular implications. J Hypertens 2002; 20: 1245-50.
16. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in nor-

mal-weight and obese humans. N Engl J Med 1996; 334: 292-5.

17. Tokuda F, Sando Y, Matsui H, et al. Serum levels of adipocytokines, adiponectin and leptin, in patients with obstructive sleep apnea syndrome. Intern Med 2008; 47: 1843-9.

18. Kapsimalis F, Varouchakis G, Manousaki A, et al. Association of sleep apnea severity and obesity with insulin resistance, C-reactive protein, and leptin levels in male patients with obstructive sleep apnea. Lung 2008; 186: 209-17.

19. Ulukavak Ciftci T, Kokturk O, Bukan N, et al. Leptin and ghrelin levels in patients with obstructive sleep apnea syndrome. Respiration 2005; 72: 395-401.

20. Ozturk L, Unal M, Tamer L, et al. The association of the severity of obstructive sleep apnea with plasma leptin levels. Arch Otolaryngol Head Neck Surg 2003; 129: 538-40.

21. Ursavas A, Ilcol YO, Nalci N, et al. Ghrelin, leptin, adiponectin, and resistin levels in sleep apnea syndrome: Role of obesity. Ann Thorac Med 2010; 5: 161-5.

22. Sadeghniiat Haghighi K, Montazeri A, Khajeh Mehrizi A, et al. The Epworth Sleepiness Scale: Translation and validation study of the Iranian version. Sleep Breath 2013; 17: 419-26.

23. Sadeghniiat-Haghighi K, Montazeri A, Khajeh-Mehrizi A, et al. The Insomnia Severity Index: Cross-cultural adaptation and psychometric evaluation of a Persian version. Qual Life Res 2014; 23: 533-7.

24. American Academy of Sleep Medicine. The international classification of sleep disorders: Diagnostic and coding manual. 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.

25. Spiegel K, Knutson K, Leproult R, et al. Sleep loss: A novel risk factor for insulin resistance and Type 2 diabetes. J Appl Physiol (1985) 2005; 99: 2008-19.

26. Barcelo A, Barbe F, Llompart E, et al. Neuropeptide Y and leptin in patients with obstructive sleep apnea syndrome: Role of obesity. Am J Respir Crit Care Med 2005; 171: 183-7.

27. Sharma SK, Kumpawat S, Goel A, et al. Obesity, and not obstructive sleep apnea, is responsible for metabolic abnormalities in a cohort with sleep-disordered breathing. Sleep Med 2007; 8: 12-7.

28. Harsch IA, Konturek PC, Koebnick C, et al. Leptin and ghrelin levels in patients with obstructive sleep apnoea: Effect of CPAP treatment. Eur Respir J 2003; 22: 251-7.

29. Schafer H, Pauleit D, Sudhop T, et al. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. Chest 2002; 122: 829-39.