Study of Insulin Resistance, Inflammatory Cytokines and Adhesive Molecules in Obese Subjects with Obstructive Sleep Apnea

Abstract

Background: Obstructive sleep apnea (OSA) is recognized as a major public health issue, as it has a significant influence on the incidence and prognosis of cardiovascular diseases.

Objective: This study was designed to detect the association between OSA and biomarkers of inflammation and adhesion molecules that may be useful in medical screening for OSA.

Methods: Sixty-five volunteer subjects were interviewed. However, only 64 of them met eligibility criteria. Their age ranged from 28-53 years and their body mass index (BMI) ranged from 30 to 40 kg/m². All participants who were enrolled into two groups according to value of Apnea–hypopnea index (AHI) into two groups: Group (A) consisted of 27 obese subjects with AHI ≥5 events/hour and group (B) consisted of 38 obese subjects with AHI <5 events/hour.

Results: The mean values of Tumor necrosis factor -alpha (TNF-α), Interleukin-6 (IL-6), C-reactive protein (CRP), Apnea–hypopnea index (AHI), Oxygen desaturation index (ODI), glucose, insulin, Homeostasis Model Assessment-Insulin Resistance Index (HOMA-IR), Inter-Cellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1) and E-selectin were significantly higher in group (A) than in group (B). However, the AHI and ODI showed a strong direct relationship with TNF-α, IL-6, CRP, glucose, insulin, HOMA-IR, ICAM-1, VCAM-1 and E-selectin in group (A).

Conclusion: Obese subjects with OSA are associated with systemic inflammation, insulin resistance and elevated values of adhesive molecules.

Keywords: Obstructive Sleep Apnea; Obesity; Adhesive Molecules; Cytokines; Insulin Resistance

Introduction

Obstructive sleep apnea is common and affects 2 to 26% in women and 4 to 49 % in men worldwide [1]. Several factors have been proposed to address these sex-differences, such as upper airway anatomy, fat distribution and testosterone levels [2]. Diagnosis of OSA is made when AHI is >5 events/hour of sleep and OSA severity is classified upon AHI value into mild (>5 and ≤15 events/hour), moderate (≥15 and ≤30 events/hour) and severe (>30 events/hour) [3]. However, OSA is a modifiable CVD risk factor [4].

Obstructive sleep apnea is closely associated to obesity [5] and systemic inflammation and oxidative stress markers are closely related to incidence of cardiovascular diseases [6,7]. In addition, there is an association between increased risk of cardiovascular disorders and OSA [8-11].

Abnormal levels of inflammatory cytokines include C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor a (TNF-α) in obesity are related to increased cardiovascular risk [12-14]. In addition, increased levels of adhesive molecules include intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), E-selectin and P-selectin are associated with cardiovascular disease and obesity [15,16].

The aim of this study was to detect the association between OSA and biomarkers of inflammation and adhesion molecules that may be useful in medical screening for OSA.

Patients and Methods

Subjects

Sixty-five volunteer subjects were interviewed; only 64 of them met eligibility criteria, signed the consent form to participate in the study and completed the detailed evaluation at the Sleep Unit of the Internal Medicine Department at King Abdul Aziz University Hospital. Participants were enrolled between May 2016 and September 2016. Scientific research ethical committee of the Faculty of Applied Medical Sciences, King Abdulaziz University approved this study. Their age ranged from 28-53 years and their body mass index (BMI) ranged from 30 to 40 kg/m². While, the
exclusion criteria were pregnant women, liver disease, smoking, diabetes mellitus, renal disease, respiratory infection, endocrine disease, thyroid diseases, patients with body mass index ≥40 kg/m² and subjects taking any medications or herbal supplements. A cardiologist conducted an initial clinical examination for all participants who were enrolled into two groups according to value of AHI into two groups: Group (A) consisted of 27 obese subjects with AHI ≥5 events/hour and group (B) consisted of 38 obese subjects with AHI <5 events/hour.

**Measurements**

For all subjects, independent assessors who were blinded to group assignment and not involved in the routine treatment of the patients performed clinical evaluations and laboratory analysis. Body mass index (BMI) was calculated on the basis of weight (kilograms) and height (meters), and subjects were classified as normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25-29.9 kg/m²), and obese (BMI ≥30 kg/m²). In addition, between 07:30 and 09:00, after an overnight fast of 12 h fasting blood sample was drawn. Plasma glucose concentration and insulin were determined (Roche Diagnostics GmbH, Mannheim, Germany) using commercially available assay kits. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR). HOMA-IR = [fasting blood glucose (mmol/l) - fasting insulin (mIU/ml)]/22.5 [17].

**Sleep recordings and daytime sleepiness (Polysomnography):**

Embletta system (Flaga, Reykjavik, Iceland) of the Sleep Unit of the Internal Medicine Department at King Abdul Aziz University Hospital was the polysomnography that was used as sleep recording system. Finger pulse oximetry was used to have recordings of oxygen saturation continuously overnight. Both apnea and hypopnea were recorded to calculate apnea hypopnea index (AHI). In addition, the number of dips 4% of basal SaO₂%/hour (oxygen desaturation index [ODI]) was measured [18].

**Measurement of biomarkers of endothelial function:**

Biomarkers of endothelial function includes inter-cellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and E-selectin that were measured from frozen serum samples stored at -80°C. Enzyme-linked immunosorbent assays (ELISAs) were used to measure soluble levels of E-selectin, ICAM-1 and VCAM-1 (R&D Systems, France).

**Measurement of inflammatory cytokines:**

Venous blood samples after a 12-hours fasting were centrifuged at + 4 °C (1000 × g for 10 min). Interleukin-6 (IL-6) levels were analyzed by "Immulite 2000" immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). However, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) levels were measured by ELISA kits (ELX 50) in addition to ELISA microplate reader (ELX 808; BioTek Instruments, USA).

**Statistical analysis**

Independent “t” test was used to compare the investigated parameters between both groups (P<0.05). However, the degree of correlation between AHI, ODI,TNF-α,IL-6, CRP, glucose, insulin, HOMA-IR, ICAM-1,VCAM-1 and E-selectin was calculated with Pearson’s correlation coefficients (r).

**Results**

Detailed baseline characteristics of all participants were presented in Table 1. There was no significant difference for all characteristics in both groups (Table 1).

The mean values of TNF-α, IL-6, CRP, AHI,ODI, glucose, insulin, HOMA-IR, ICAM-1,VCAM-1 and E-selectin were significantly higher in group (A) than in group (B) (Table 2). However, the AHI and ODI showed a strong direct relationship with TNF-α, IL-6, CRP, glucose, insulin, HOMA-IR, ICAM-1,VCAM-1 and E-selectin in group (A) (Table 3) (P < 0.05).

### Table 1: Characteristics of all participants according to OSA diagnosis.

|                | Group (A) (no=27) | Group(B) (no=38) | Significance |
|----------------|-------------------|------------------|--------------|
| Age (year)     | 42.75 ± 4.32      | 44.61 ± 4.28     | P>0.05       |
| Gender (male/female) | 20/17            | 23/15            | P>0.05       |
| BMI (kg/m²)    | 35.74 ± 2.81      | 35.65 ± 3.16     | P>0.05       |
| Neck circumference (cm) | 41.21 ± 3.21 | 39.88 ± 2.72     | P>0.05       |
| Waist circumference (cm) | 110.35 ± 9.37   | 108.92 ± 9.25    | P>0.05       |
| Waist-to-hip ratio | 0.92±0.05        | 0.84±0.04        | P>0.05       |
| SBP (mmHg)     | 133.16 ± 9.18     | 130.14 ± 8.95    | P>0.05       |
| DBP (mmHg)     | 86.63 ± 5.47      | 84.26 ± 5.13     | P>0.05       |

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

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Table 2: The mean value and the significance values of different parameters in both groups.

|                  | Mean ±SD       | T-Value | Significance |
|------------------|----------------|---------|--------------|
|                  | Group (A) (n=27) |         |              |
|                  | Group (B) (n=38) |         |              |
| TNF-α (pg/mL)    | 4.74 ± 1.47    | 5.22    | P<0.05       |
| IL-6 (pg/mL)     | 2.58 ± 0.96    | 5.75    | P<0.05       |
| CRP (pg/mL)      | 4.37 ± 1.25    | 5.17    | P<0.05       |
| Apnea Hypopnea Index (events/h) | 20.76 ± 3.58 | 6.25    | P<0.05       |
| Oxygen Desaturation Index (events/h) | 12.78 ± 3.27 | 6.22    | P<0.05       |
| Glucose (mg/dL)  | 91.73 ± 5.16   | 7.18    | P<0.05       |
| Insulin (mU/mL)  | 13.81 ± 1.43   | 6.31    | P<0.05       |
| HOMA-IR          | 3.72 ± 0.68    | 5.34    | P<0.05       |
| ICAM-1 (ng/ml)   | 94.17 ± 9.26   | 8.23    | P<0.05       |
| VCAM-1 (ng/ml)   | 811.45 ± 28.42 | 12.18   | P<0.05       |
| E-selectin (ng/ml) | 16.87 ± 3.57 | 6.14    | P<0.05       |

TNF-α: Tumor Necrosis Factor-Alpha; IL-6: Interleukin-6; CRP: C-Reactive Protein; AHI: Apnea-Hypopnea Index; ODI: Oxygen Desaturation Index; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; (*) indicates a significant difference, P < 0.05.

Table 3: Correlation coefficient (r) of AHI, ODI, TNF-α, IL-6, CRP, glucose, insulin, HOMA-IR, ICAM-1, VCAM-1 and E-selectin in group (A).

|                  | Apnea Hypopnea Index (events/h) | Oxygen desaturation Index (events/h) |
|------------------|---------------------------------|-------------------------------------|
| TNF-α (pg/mL)    | 0.625*                          | 0.743**                             |
| IL-6 (pg/mL)     | 0.712**                         | 0.522*                              |
| CRP (pg/mL)      | 0.618**                         | 0.547*                              |
| Glucose (mg/dL)  | 0.524*                          | 0.646**                             |
| Insulin (mU/mL)  | 0.512**                         | 0.611**                             |
| HOMA-IR          | 0.571*                          | 0.719**                             |
| ICAM-1 (ng/ml)   | 0.514*                          | 0.657**                             |
| VCAM-1 (ng/ml)   | 0.723**                         | 0.642**                             |
| E-selectin (ng/ml) | 0.517*                          | 0.618*                              |

Spearman's correlation was used *: P < 0.05 **: P < 0.01

Discussion

Circulating abnormal levels of inflammatory markers and adhesive molecules have been associated with future cardiovascular risk [19,20]. However, high risk of mortality and cardiovascular morbidity is associated with OSA [21-23]. The principal findings of this study were that participants with OSA exhibited higher values of AHI, ODI, TNF-α, IL-6, CRP, glucose, insulin, HOMA-IR, ICAM-1, VCAM-1 and E-selectin compared with those without OSA. However, in correlation analysis, AHI and ODI...
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were positively and significantly associated with TNF-α, IL-6, CRP, glucose, insulin, HOMA-IR, ICAM-1, VCAM-1 and E-selectin, these findings are in line with many previous researches.

Concerning inflammatory markers, the results of the present study showed significantly higher values of TNF-α, IL-6 and CRP in group (A) than in group (B). In correlation analysis, TNF-α, IL-6 and CRP were significantly and directly associated with the AHI and ODI. Our findings are similar to many case-controlled researches demonstrated increased level of TNF-α in patient with OSA in comparison to controls, along with significant reduction in TNF-α value with CPAP therapy [24-26]. Further studies proved that TNF-α level was increased in OSA [27-29]. In addition, Dyugovskaya et al. [30] stated that T-lymphocytes expressed isolated higher levels of TNF-α than control cells in OSA patients [30]. However, Ohga et al. [31] & Ryan et al. [32] reported that both TNF-α and IL-8 increased in patients with OSAS which were reduced following CPAP [31,32]. Similarly, Devouassoux et al. [33] proved that OSAS led to excessive airway expression of IL-8 that potentially increased bronchial hyper-responsiveness in OSA subjects [33]. In addition, several studies found positive associations between IL-6 levels and OSA [34-36]. Moreover, Montesi et al. [37] reported that the levels of the inflammatory markers include CRP, IL-8, TNF-α and IL-6 were higher in OSA patients [37]. However, Reyad et al. [38] reported that there was a statistical positive correlation between TNF-α and AHI that measure the severity of OSA [38]. Similarly, Minoguchi et al. [39] stated that levels of IL-6 and IL-18 are greater in OSA patients than controls which are correlated with severity of OSA [39]. In addition, Yokoe et al. [40] mentioned that among 22 subjects with OSA, where the magnitude of CRP elevation was directly related to AHI in these patients [40].

Regarding the values of adhesive molecules, the results of the present study showed significantly higher values of ICAM-1, VCAM-1 and E-selectin in in group (A) than in group (B). In correlation analysis, ICAM-1, VCAM-1 and E-selectin were significantly and directly associated with the AHI and ODI. Our findings agreed with Zamarrón-Sanz [41] reported that adhesive molecules were higher among 41 patients with OSA 82 male subjects than control group with the same sample size [41]. In addition, Korch et al. [42] stated that the levels of VCAM-1, E-selectin, P-selectin, CRP, WBC count were higher in OSA patients than in control subjects [42]. Similarly, several studies found direct significant relationship between adhesive molecules and severity of OSA measured by ODI and AHI [43-46].

Finally, results of the present study found significantly higher values of serum insulin, glucose and HOMA-IR in group (A) than in group (B). Moreover, OSA severity measured with AHI and ODI were directly and significant associated with insulin resistance, our results agreed with Ip et al. [47] reported similar findings [47]. However, Fleming et al. [48] reported that 73 male subjects were enrolled; 26 had moderate/severe OSA and concluded that elevated HbA1c, CRP have an even greater association with OSA severity [48]. Moreover, Araújo Lda et al. [10] conducted a cross-sectional study included 53 obese adults and reported that values of glucose, neck circumference and CRP were higher in OSA patients than control group, and in addition, insulin, neck circumference and HOMA-IR were positively and significantly associated with ODI in patients with OSA [10].

Conclusion

The present study suggests that in obese subjects with OSA are associated with systemic inflammation, insulin resistance and elevated values of adhesive molecules.

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References

1. Heinzner R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, et al. (2015) Prevalence of sleep-disordered breathing in the general population: the HypoNoLa study. Lancet Respir Med 3(4): 310-318.
2. Wittert G (2014) The relationship between sleep disorders and testosterone in men. Asian J Androl 16(2): 262-265.
3. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, et al. (2013) Recommendations for the management of patients with obstructive sleep apnoea and hypertension. Eur Respir J 41(3): 523-538.
4. Javaheri S, Bare F, Campos-Rodriguez F, Dempsey JA, Khayat R, et al. (2017) Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardiol 69(7): 841-858.
5. Young T, Palta M, Dempsey J, Skatrud J, Weber S, et al. (1993) The occurrence of sleep-disordered breathing among middle-aged adults. The New England Journal of Medicine 328(17): 1230-1235.
6. Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AL (2009) Molecular signatures of obstructive sleep apnea in adults: a review and perspective. Sleep 32(4): 447-470.
7. Hajer GR, van Haeften TW, Visseren FL (2008) Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. European heart journal 29(24): 2959-2971.
8. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G (2013) Obstructive sleep apnea. A cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol 62(7): 569-576.
9. Loke YK, Brown JW, Kwock CS, Niruban A, Myint PK (2012) Association of obstructive sleep apnea with risk of serious cardiovascular events a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 5(5): 720-728.
10. Araújo Lda S, Fernandes JF, Klein MR, Sanjuliani AF (2015) Obstructive sleep apnea is independently associated with inflammation and insulin resistance, but not with blood pressure, plasma catecholamines, and endothelial function in obese subjects. Nutrition 31(11-12): 1351-1357.
11. Ali SS, Oni ET, Warriaeh HJ, Blaha MJ, Blumenthal RS, Karim A, et al. (2014) Systematic review on noninvasive assessment of subclinical cardiovascular disease in obstructive sleep apnea: new kid on the block. Sleep Med Rev 18(5): 379-391.
12. Gopalakrishnan P, Tak T (2011) Obstructive sleep apnea and cardiovascular disease. Cardiol Rev 19(6): 279-290.
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13. Almendros I, Farre R, Torres M, Bonsignore MR, Dalmases M, Ramirez J, et al. (2011) Early and mid-term effects of obestatic apneas in myocardial injury and inflammation. Sleep Med 12(10): 1037-1040.

14. Montesi S, Bajwa E, Malhotra A (2012) Biomarkers of sleep apnea. Chest 142(1): 239-245.

15. Pak VM, Kean BT, Jackson N, Grandner MA, Maislin G, et al. (2015) Adhesion molecule increases in sleep apnea: beneficial effect of positive airway pressure and moderation by obesity. Int J Obes (Lond) 39(3): 472-479.

16. Pak VM, Grandner MA, Pack AI (2014) Circulating Adhesion Molecules in Sleep Apnea and Cardiovascular Disease. Sleep Med Rev 18(1): 25-34.

17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and beta cell function from plasma FBS and insulin concentrations in man. Diabetologia 28(7): 412-419.

18. Carriagnano GE, Spanello A, Sabato R, Depalo A, Palladino GP, et al. (2010) Systemic and airway inflammation in sleep apnea and obesity: the role of ICAM-1 and IL-8. Transl Res 155(1): 35-43.

19. Aukrust P, Yndestad A, Smith C, Ueland T, Gullesdal L, et al. (2007) Chemokines in cardiovascular risk prediction. Thromb Haemost 97(5): 748-754.

20. Charakida M, Masi S, Lüscher TF, Kastelein JJ, Deanfield JE (2010) Assessment of atherosclerosis: the role of flow-mediated dilatation. Eur Heart J 31 (23): 2854-2861.

21. VK Vijayan (2012) Morbidities associated with obstructive sleep apnea. Expert Rev Respir Med 6(5): 557-566.

22. Morgenstern M, Wang J, Beatty N, Batemarco T, Sica AL, et al. (2014) Greenbrown, Obstructive sleep apnea: an unexpected cause of insulin resistance and diabetes. Endocrinol Metab Clin N Am 43 (1): 187-204.

23. Hirotsu C, Albuquerque RG, Nogueira H, Hachul H, Bittencourt L, et al. (2017) The relationship between sleep apnea, metabolic dysfunction and inflammation: The gender influence. Brain Behav Immun 59: 211-218.

24. Ryan S, Taylor CT, Mch Nicholas WT (2006) Predictors of elevated nuclear factor kappa B–dependent genes in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 174(7): 824-830.

25. Ciftci TU, Korkturk O, Bukan N, Bilgihan A (2004) The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. Cytokine 28(2): 87-91.

26. Minoguchi K, Tazaki T, Yokoe T, Minoguchi H, Watanabe Y, et al. (2004) Elevated production of tumor necrosis factor-alpha by monocytes in patients with obstructive sleep apnea syndrome. Chest 126(5): 1473-1479.

27. Bhushan B, Guleria R, Misra A, Luthra K, Vikram NK (2009) TNF-alpha gene polymorphism and TNF-alpha levels in obese Asian Indians with obstructive sleep apnea. Respir Med 103(3): 386-392.

28. Dorkova Z, Petrascova D, Molcanyiova A, Popovnakova M, Tkacova R (2008) Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. Chest 134(4): 686-692.

29. Arias MA, Garcia-Rio F, Alonso-Fernández A, Hernanz A, Hidalgo R, et al. (2008) CPAP decreases plasma levels of soluble tumour necrosis factor-alpha receptor 1 in obstructive sleep apnoea. Eur Respir J 32(4): 1009-1015.

30. Dyugovskaya L, Lecie J, Lave I (2003) Phenotypic and functional characterization of blood gamma delta T cells in sleep apnea. Am J Respir Crit Care Med 168(2): 242-249.

31. Oghe E, Tomita T, Wada H, Yamamoto H, Nagase T, et al. (2003) Effects of obstructive sleep apnea on circulating ICAM-1 IL-8, and MCP-1. J Appl Physiol 94(1): 179-184.

32. Ryan S, Taylor CT, McNicholas WT (2006) Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 174(7): 824-830.

33. Devouassoux S, Lévy P, Rossini E, Pin I, Flor-Gozlan M (2007) Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure-induced airway hyperresponsiveness. J Allergy Clin Immunol 119(3): 597-605.

34. Arnaudtottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI (2009) Molecular signatures of obstructive sleep apnea in adults: a review and perspective. Sleep 32(4): 447-470.

35. Arnaudtottir ES, Maislin G, Schwab RJ, Staley B, Benediksdottir B, et al. (2012) The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic sleep apnea cohort. Sleep 35(7): 921-932.

36. Vgontzas AN, Papanicolaou DA, Bider EO, Hopper K, Lotsikas A, et al. (2000) Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercycotymia. J Clin Endocrinol Metab 85(3): 1151-1158.

37. Montesi S, Bajwa E, Malhotra A (2012) Biomarkers of sleep apnea. Chest 142(1): 239-245.

38. Reyad E, Abdelaty N, ElPrince M, Farid A, El-Serougy M (2012) Plasma levels of TNF in obstructive sleep apnea syndrome (OSA) before and after surgical intervention. Egyptian Journal of Chest Diseases and Tuberculosis 61: s179-s185.

39. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, et al. (2005) Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med 172(5): 625-630.

40. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, et al. (2003) Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 107(8): 1129-1134.

41. Zamarron-Sanz C, Rico-Galbaldon J, Gude-Sampedro F, Riveiro-Riveiro A (2006) Plasma levels of vascular endothelial markers in obstructive sleep apnea. Arch Med Res 37(4): 552-555.

42. O Korzh, S Krasnokutskiy, E Lavrova (2007) Role of low-grade inflammation markers and soluble cell adhesion molecules in patients with obstructive sleep apnea syndrome. Sleep Medicine 8(Suppl 1): S69-S114.

43. Priou P, Gagnadoux F, Tese A, Mastronardi ML, Agouni A, et al. (2011) Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. Am J Pathol 177(2): 974-983.
44. Ohga E, Nagase T, Tomita T, Teramoto S, Matsuse T, et al. (1999) Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. J Appl Physiol 87(1):10-14.

45. El-Solh AA, Mador MJ, Sikka P, Dhillon RS, Amsterdam D, et al. (2002) Adhesion molecules in patients with coronary artery disease and moderate-to-severe obstructive sleep apnea. Chest 121(5): 1541-1547.

46. Ursavaş A, Karadağ M, Rodoplu E, Yılmaztepe A, Oral HB, et al. (2007) Circulating ICAM-1 and VCAM-1 levels in patients with obstructive sleep apnea syndrome. Respiration 74(5): 525-532.

47. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, et al. (2002) Obstructive sleep apnoea is independently associated with insulin resistance. Am J Respir Crit Care Med 165(5): 670-671.

48. Fleming WE, Ferouz-Colborn A, Samoszuk MK3 Azad A, Lu J, et al. (2016) Blood biomarkers of endocrine, immune, inflammatory, and metabolic systems in obstructive sleep apnea. Clin Biochem 49(12): 854-861.