Journal of Lung Diseases & Treatment

Review Article Open Access

A Narrative Review of Obstructive Sleep Apnea in Relation to the Associated Biomarkers and the Impact of CPAP Treatment on them

Protas M[1,2,3]*, Dana O[1], Diyar O[1], Murray IJV[1], Ogedegbe C[4] and Ashtyani H[2]

[1]Department of Physiology, Neuroscience, and Behavioral Sciences, St. George's University, Grenada, West Indies
[2]Department of Pulmonology and Critical Care, Hackensack University Medical Center, 30 Prospect Ave, Hackensack, NJ, USA
[3]SUNY Upstate College of Medicine, School of Medicine, Syracuse, NY, USA
[4]Emergency Trauma Center, Hackensack University Medical Center, 30 Prospect Ave, Hackensack, NJ, USA

Abstract

Obstructive sleep apnea (OSA) is a sleep disorder characterized by intermittent cessations of breathing due to obstruction of the upper respiratory tract. Obesity and OSA often coexist and obesity may be a major risk factor for worsening OSA. Both are associated with several comorbidities such as hypertension, cardiovascular disease and cerebrovascular accidents. There are biomarkers that are shared between both obesity and OSA with some being more sensitive for OSA. To better understand the relationship of the biomarkers associated specifically with OSA, a more comprehensive review of OSA biomarkers compared to previous literature was conducted with the goal of determining whether OSA is an individual risk factor. Specifically, OSA patients were matched based on BMI to controls with no comorbidities to rule out confounders. Furthermore, it was investigated if continuous positive airway pressure (CPAP) therapy was effective in reducing these biomarkers. OSA was shown to be an individual associated risk factor, compared to obesity, for further changes in biomarkers related to inflammatory changes (Il-8, TNF- a, IL-6, INF-y), epithelial and cellular receptor regulation (ICAM-1, VCAM-1, P-Selectin, TLR-2 and TLR-4), atherosclerosis biomarkers and anatomical changes (increased CIMT, pulse wave velocity, catecholamines, aortic pulse velocity index), diabetes (HbA1c, insulin resistance) and hypertension (sFLT-1, sEng, YKL-40). This review revealed that biomarkers are significantly associated with OSA independent from obesity. CPAP treatment resulted in a reduction of these biomarkers.

Keywords: Obstructive sleep apnea; Sleep disorders; Obesity; Biomarkers; Diabetes; Continuous positive airway pressure

Introduction

Obstructive sleep apnea (OSA) is a disorder defined by intermittent cessations of breathing during sleep. OSA is most often caused by obesity and affects a large population of the United States [1]. Common symptoms include snoring, hypersomnia and nighttime awakening [2,3]. It has been associated with serious comorbidities such as coronary artery disease, cerebrovascular accidents, and arrhythmias. The proposed mechanisms in which OSA is thought to be pathogenic is through hypoxia, hypercapnia, negative intrathoracic pressure, sympathetic hyperactivity, hypercoagulability, endothelial dysfunction, oxidative stress, microarousal, metabolic and hormonal changes [4]. Often, patients with both OSA and obesity share many of the same biomarkers [2,5,6]. CPAP is the gold standard therapy for treating patients with OSA. It is effective at reducing the AHI (Apnea Hypopnea Index) [7,8] and is indicated for treatment in patients with mild to severe OSA (AHI of 5-30 and >30, respectively) [8,9]. Imaging such as MRI is unnecessary in the diagnosis in OSA however it has been shown to play a role in predicting treatment outcome and for monitoring disease progression [10,11].

To better understand the association of OSA and biomarkers, a comprehensive review was conducted to explore whether OSA may be an individual risk factor for biomarker elevation compared to healthy obese controls and to examine if CPAP treatment is able to reduce them. The review adds a more complete and up to date database of the inflammatory biomarkers compared to previous literature as well as examines only the adult population [12]. This paper also eliminates confounding bias seen in previous work by comparing the OSA patients with strict BMI matched controls with no comorbidities.

Methods

Search method

This review analyzed all pertinent data on all the available literature from 1997-2018 regarding OSA biomarkers. Two individual investigators accessed PubMed, Google Scholar, and Ovid Medline from January 2017 to June 2018 to find literature associated with biomarkers associated with OSA in comparison to obese controls. The following strategy was used for searching articles: "obstructive sleep apnea" or "obstructive sleep aponea" [All Fields] AND "*The biomarker in question*". These markers included receptors, cytokines, serum lipid levels. Other categories included endothelial damage and biomarkers involved in changes in sympathetic nervous system tone. Search yielded 359 results before exclusion (Figure 1).

Inclusion and exclusion criteria

Studies were excluded if they did not appropriately BMI match OSA patients with an obese control group. Patients with underlying comorbidities were excluded. Patients with underlying genetic disorders or those that did not confirm a diagnosis of OSA were excluded. Papers were also excluded if they were not either written in English or if a clear translation was not provided. Full articles must have been available for search. Abstracts and other editorials were excluded. The senior author had final decision on whether an article was included when ambiguity arose.

***Corresponding author:** Dr. Matthew Protas, Department of Pulmonology and Critical Care, Hackensack University Medical Center, 30 Prospect Ave, Hackensack NJ, 07601, USA, Tel: 551-427-8516; E-mail: matthew.protas@gmail.com

Received November 12, 2018; **Accepted** January 15, 2019; **Published** January 23, 2019

Citation: Protas M, Dana O, Diyar O, Murray IJV, Ogedegbe C, et al. (2019) A Narrative Review of Obstructive Sleep Apnea in Relation to the Associated Biomarkers and the Impact of CPAP Treatment on them. Lung Dis Treat 5: 131.

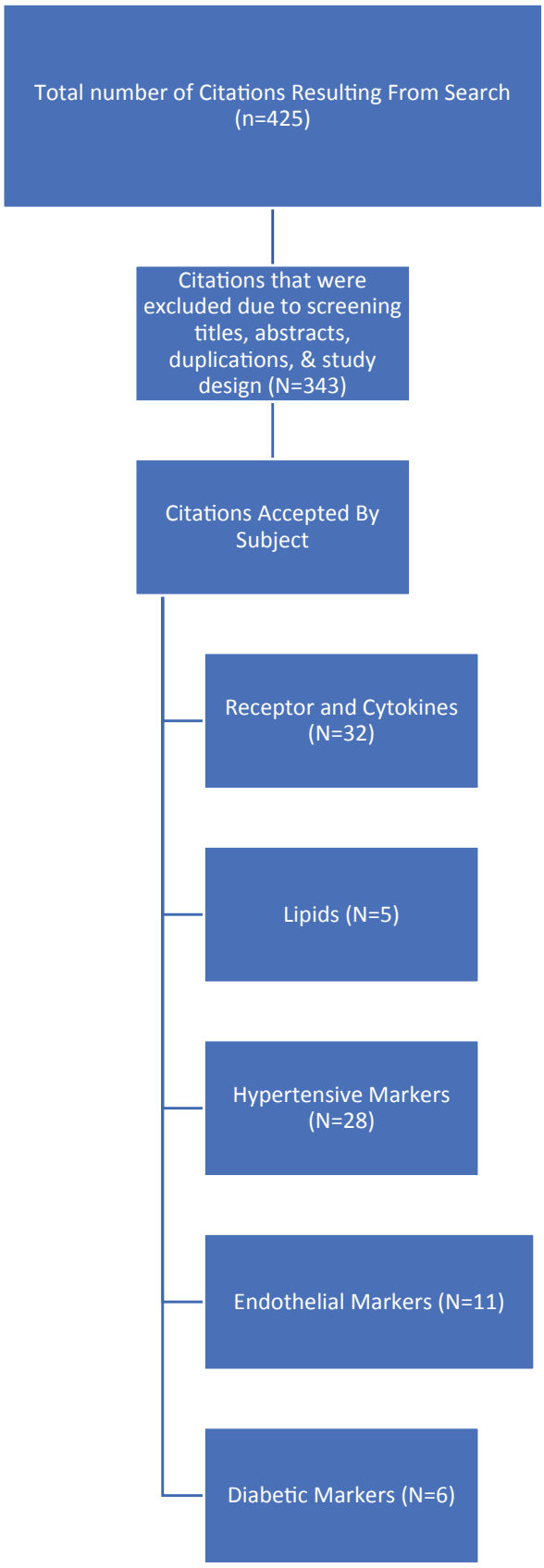

Figure 1: Flow chart of data collection.

Category of biomarkers within associated Sub-Groups

Receptor and cytokine elevation in obstructive sleep apnea: Expression of toll-like receptors (TLR) and inflammatory cytokines are responsible for the inflammatory response. When upregulated or over secreted, they can lead to atherosclerosis and further progression of cardiovascular disease [13,14]. TLR-2 and TLR-4 are associated with both human metabolic syndrome, obesity, and have been demonstrated to contribute to atherosclerosis [15,16]. Increased levels of TLR-2 and TLR-4 in serum [17-21], mRNA expression on circulating monocytes, serum proinflammatory proteins such as interleukin-6 (IL-6) [22-32], interferon gamma (INF-γ) [17], and tumor necrosis factor alpha (TNF-α) [17] have also been shown to be significantly increased in patients with OSA compared to obese controls. After CPAP treatment, there is a significant decrease in the release of inflammatory cytokines, IL-6 and INF-γ, and a downregulation of both TLR2 and TLR4 regardless of body weight. These changes lead to a subsequent decrease in NF-kB, which is part of the TLR cascade, demonstrating a decrease in inflammation. There is a positive correlation between NF-kB concentrations and OSA disease severity [33-36] which can be a useful biomarker for disease progression [37]. Elevated IL-6 and TNF-α are also prominent in obesity [17-37,38]. Increased levels of IL-8 [28] as well as TNF-α [39] have also been shown to be significantly elevated in patients with OSA compared to obese controls.

Changes in serum lipid levels in obstructive sleep apnea: Feres et al. demonstrated that OSA was not associated with changes in cholesterol, HDL, LDL, and triglycerides and that CPAP treatment did not cause a decrease in these [29,40]. However, Feres et al. showed that patients with OSA had increased serum oxLDL. Lee et al. and Svatikova et al. both suggest that oxLDL is not associated with OSA as there was no differences between the control and OSA group [41,42]. Saarelainen et al. stated that oxLDL was not appropriate for screening or an applicable biomarker for OSA [43].

Hypertension, sympathetic nervous system activation and catecholamines release in patients with obstructive sleep apnea: Previous studies have all indicated that OSA raises blood pressure while CPAP treatment will lower blood pressure [44-48]. OSA increases blood pressure through sympathetic nervous system activation, endothelial dysfunction, and vasoactive agents. Studies show that there is an elevation of sFlt-1 and sEng in OSA patients with hypertension compared to those without [49]. Another study comparing normotensive OSA patients and hypertensive OSA patients revealed an increase in plasma levels of YKL-40, an emerging biomarker for heart disease. An elevation of YKL-40 has been shown to be a poor prognostic indicator for hypertensive patients with OSA compared to controls [46]. This signaling pathway has been proposed to contribute to endothelial dysfunction by the disruption of VEGF signaling, leading to hypertension. Plasma levels of YKL-40 are decreased significantly after CPAP therapy [44].

Catecholamines have also been shown to be significantly elevated in patients with OSA [46-63] while CPAP treatment has been shown to be at significantly decreasing their levels [46-54,60,61]. There were several papers that disagreed that CPAP treatment decreased levels of catecholamines in patients [56-59,61,62]. One papers only viewed acute treatment only [59].

Pentraxin-3, an inflammatory signal independently linked to increases in cardio-ankle vascular index (CAVI), has been shown to be significantly elevated in patients who have moderate-to-severe OSA [64-67]. A decrease in pentraxin-3 is stated to be a useful marker for improvement in patients with OSA [58]. After CPAP treatment, both

CAVI and Pentraxin-3 levels decreased [65-67]. CPAP compliance in the study by Kasai et al. was measured by objective evaluation of compliance based on the downloaded data stored in the CPAP device [66]. However, other studies have not demonstrated CAVI to be a useful marker as there was no relationship between arterial stiffness and the presence of OSA [68]. CAVI in the elderly can be confounded by other comorbidities, as well as a ceiling effect [69]. Kumagai et al. however agreed with the study by Kasai et al. by saying that CAVI is a good index for progressive vascular damage in patients with OSA, however it is not a good biomarker [70].

Carotid intima-media thickness (CIMT) can also be a useful tool for the assessment of atherosclerosis and CVD risk in patients with OSA [51,71-75]. Increased CIMT is significantly associated with an increasing severity of OSA [76-79]. Drager et al. reported that as the pulse wave velocity increased, there was a significant proportionate decrease in carotid diameter demonstrating increasing severity of the vascular disease [51,80].

Endothelial dysfunction in obstructive sleep apnea: Active endothelial molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, L-selectin, interleukin-8 (IL-8), and myocyte chemoattractant protein-1 (MCP-1) are significantly increased in the serum of OSA patients and decrease significantly with CPAP treatment [75-81]. Other studies have shown significant elevation of leptin in OSA patient without significant elevations in endothelin-1(ET-1) and von willebrand factor [82]. Endothelin is produced by endothelial cells and is a potent vasoconstrictive and mitogenic peptide [83]. Saarelainen et al. saw a significant increase in ET-1 levels in patients with OSA compared to controls; however, there was not a significant decrease after three months of CPAP treatment [83]. Chen et al. contradicted this by reporting that TNF-α and ET-1 were reducible in OSA patient through CPAP treatment. It is important to note that Saarelainen et al. did not mention whether or not the CPAP usage was measured objectively or subjectively. Araújo et al. found that ICAM-1, VCAM-1 and P-selectin were not significantly difference which is contrary to the results of previous literature [84]. CD15+ and CD11c+ monocytes are significantly elevated in OSA patients compared to obese controls and decrease with CPAP treatment, while CD64+ monocytes were significantly decreased with no change after treatment [85]. CD expression on monocytes are all associated with atherosclerosis pathogenesis and further progression of cardiovascular disease.

Related or relative risk factors

The role of obstructive sleep apnea in insulin resistance: Hemoglobin A1c (HbA1c) levels have been shown to be elevated in patients with diabetes mellitus type 2 (DM2) and OSA compared to those with just OSA [85]. The mechanism is suspected to be impaired insulin receptor activation or insulin resistance which is positively correlated with the severity of OSA [84]. Insulin resistance has been shown to be significantly elevated in OSA patients [86-88] while insulin sensitivity increases after CPAP treatment [89,90]. Adiponectin levels were also significantly lower in patients with OSA and increased after CPAP treatment [91]. Conversely, Carneiro et al. stated that there was no difference in the insulin resistance index and insulin sensitivity index in patients with OSA compared to obese controls. Apnoeic males have been shown to have significantly higher levels of highly sensitive C-Reactive Protein, IL-6, leptin and insulin resistance than controls while females were shown to only have significantly higher hsCRP [89]. CPAP treatment has been shown to decrease the HbA1c levels in mild, moderate, and severe patients with both OSA and DM2 compared to those with just DM2 alone. HbA1c however has been used only as a prognostic and diagnostic tool for DM2 and is not directly correlated to the pathogenesis of this disease [86]. Araújo et al. found no significant changes in insulin effectiveness in patients with OSA compared to obese patients. However, they did find that frequent O_2 desaturation was also correlated with increased insulin levels. Homeostatic model assessment insulin resistance (HOMA-IR) was not significantly different between OSA and obese patients (Supplemental Table 1).

Discussion

Obstructive sleep apnea has been shown to be a definitive and individual risk factor for multiple morbidities such as systemic hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular accidents, arrhythmias and sudden cardiac death (SCD). The pathogenesis of OSA has been assumed to be related to hypoxia, hypercapnia, negative intrathoracic pressure, sympathetic hyperactivity, hypercoagulability, endothelial dysfunction, oxidative stress, micro-arousal, and metabolic and hormonal changes. OSA has been shown to be individually associated with inflammatory biomarkers (Il-8, TNF-a, NO, IL-6, INF-y), epithelial and cellular receptors (ICAM-1, VCAM-1, P-Selectin, TLR-2 & TLR-4), atherosclerotic changes (increased CMIT, pulse wave velocity), and hypertension (sFLT 1, sEng, YKL-40). Treatment with CPAP results in decreasing the intermittent hypoxia/reoxygenation which is believed to be responsible for the underlying pathogenesis. Compared to obese controls, CPAP usage in OSA patients significantly decreases the biomarkers mentioned previously suggesting that OSA is independently associated with these biomarkers. CPAP is preventative of these comorbidities. CPAP usage in this study was reported with objective reading from the built-in device.

Limitations of this narrative review include the typical problems inherent to retrospective studies, as well as specifically, CPAP usage was defined differently between investigators. Although most studies used objective measurement of the built-in devices, some studies relied on patient self-report.

Conclusion

This review revealed that these biomarkers are associated with OSA independent of obesity. These results further suggest the role of OSA in the pathogenesis of the comorbidities may be linked to OSA's association with these biomarkers.

Compliance with Ethical Standards

This study received no funding. None of the authors have any conflict of interest to disclose. No animals were used in this study. This article does not contain any studies with human participants performed by any of the authors.

References

1. Peppard P, Young T, Barnet J, Palta M, Hagen E, et al. (2013) Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 117: 1006-1014.

2. Pi-Sunyer FX (1999) Comorbidities of overweight and obesity: current evidence and research issues. Med Sci Sports Exerc 31: 602-608.

3. Genta PR, Schorr F, Eckert DJ, Gebrim E, Kayamori F, et al. (2014) Upper Airway Collapsibility is Associated with Obesity and Hyoid Position. Sleep 37:1673-1678.

4. Fava C, Montagnana M, Favaloro EJ, Guidi GC, Lippi G (2011) Obstructive sleep apnea syndrome and cardiovascular diseases. Semin Thromb Hemost 37: 280-297.

5. Toraldo D, Nuccio F, Benedetto M, Scoditti E (2015) Obstructive sleep apnoea

syndrome: a new paradigm by chronic nocturnal intermittent hypoxia and sleep disruption. Acta Otorhinolaryngol Ital 35: 69-74.

6. Dyugovskaya L, Lavie P, Lavie L (2002) Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Am J Respir Crit Care Med 165: 934-939.
7. Gay P, Weaver T, Loube D, Iber C (2006) Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep 29: 375-380.
8. Golbidi S, Badran M, Ayas N, Laher I (2012) Cardiovascular consequences of sleep apnea. Lung 190: 113-132.
9. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, et al. (2008) Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 4: 157-171.
10. Abdel Razek AA (2015) Diagnostic role of magnetic resonance imaging in obstructive sleep apnea syndrome. J Comput Assist Tomogr 39: 565-571.
11. Abdel Razek AA (2012) Imaging of scleroma in the head and neck. Br J Radiol 85: 1551-1555.
12. De Luca Canto G, Pachêco-Pereira C, Aydinoz S, Major PW, Flores-Mir C, et al. (2015) Biomarkers associated with obstructive sleep apnea: a scoping review. Sleep Med Rev 23: 28-45.
13. Li H, Sun B (2007) Toll-like receptor 4 in atherosclerosis. J Cell Mol Med 11: 88-95.
14. Mullick A, Tobias P, Curtiss L (2006) Toll-like receptors and atherosclerosis: key contributors in disease and health. Immunol Res 34: 193-209.
15. Hardy O, Kim A, Ciccarelli C, Hayman L, Wiecha J (2013) Increased Toll-like receptor (TLR) mRNA expression in monocytes is a feature of metabolic syndrome in adolescents. Pediatr Obes 8: 19-23.
16. Jialala I, Devaraj S, Bettaieb A, Haj F, Adams-Huet B (2015) Increased adipose tissue secretion of Fetuin-A, lipopolysaccharide-binding protein and high-mobility group box protein 1 in metabolic syndrome. Atherosclerosis 241: 130-137.
17. Akinnusi M, Jaoude P, Kufel T, El-Solh Ali (2013) Toll-Like receptor activity in patients with obstructive sleep apnea. Sleep Breath 17: 1009-1016.
18. Weinstock LB, Myers TL, Walters AS, Schwartz OA, Younger JW, et al. (2016) Identification and treatment of new inflammatory triggers for complex regional pain syndrome: small intestinal bacterial overgrowth and obstructive sleep apnea. A Case Rep 6: 272-276.
19. Polotsky VY, Bevans-Fonti S, Grigoryev DN, Punjabi NM (2015) Intermittent hypoxia alters gene expression in peripheral blood mononuclear cells of healthy volunteers. PLoS One 10: e0144725.
20. Chen YC, Su MC, Liou CW, Liu SF, Chen CJ, et al. (2015) Co-upregulation of Toll-like receptors 2 and 6 on peripheral blood cells in patients with obstructive sleep apnea. Sleep Breath 19: 873-882.
21. Jialal I, Kaur H, Devaraj S (2014) Toll-like receptor status in obesity and metabolic syndrome: a translational perspective. J Clin Endocrinol Metab 99: 39-48.
22. Abdel-Fadeil MR, Abedelhaffez AS, Makhlouf HA, Al Qirshi GA (2017) Obstructive sleep apnea: influence of hypertension on adiponectin, inflammatory markers and dyslipidemia. Pathophysiology 24: 305-315.
23. Perrini S, Cignarelli A, Quaranta VN, Falcone VA, Kounaki S, et al. (2017) Correction of intermittent hypoxia reduces inflammation in obese subjects with obstructive sleep apnea. JCI Insight 2.
24. Weingarten JA, Bellner L, Peterson SJ, Zaw M, Chadha P, et al. (2017) The association of NOV/CCN3 with obstructive sleep apnea (OSA): preliminary evidence of a novel biomarker in OSA. Horm Mol Biol Clin Investig 31.
25. Said EA, Al-Abri MA, Al-Saidi I, Al-Balushi MS, Al-Busaidi JZ, et al. (2017) Altered blood cytokines, CD4 T cells, NK and neutrophils in patients with obstructive sleep apnea. Immunol Lett 190: 272-278.
26. Li Y, Vgontzas AN, Fernandez-Mendoza J, Kritikou I, Basta M, et al. (2017) Objective, but not subjective, sleepiness is associated with inflammation in sleep apnea. Sleep P: 40.
27. Thorn CE, Knight B, Pastel E, McCulloch LJ, Patel B, et al. (2017) Adipose tissue is influenced by hypoxia of obstructive sleep apnea syndrome independent of obesity. Diabetes Metab 43: 240-247.
28. Vicente E, Marin JM, Carrizo SJ, Osuna CS, Gonzalez R, et al. (2016) Upper airway and systemic inflammation in obstructive sleep apnoea. Eur Respir J 48: 1108-1117.
29. De Luca Canto G, Pacheco-Pereira C, Aydinoz S, Major PW, Flores-Mir C, et al. (2015) Diagnostic capability of biological markers in assessment of obstructive sleep apnea: a systematic review and meta-analysis. J Clin Sleep Med 11: 27-36.
30. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, et al. (2013) Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J Clin Sleep Med 9: 1003-1012.
31. Kimoff RJ, Hamid Q, Divangahi M, Hussain S, Bao W, et al. (2011) Increased upper airway cytokines and oxidative stress in severe obstructive sleep apnoea. Eur Respir J 38: 89-97.
32. Zhong A, Xiong X, Shi M, Xu H (2016) Roles of interleukin (IL)-6 gene polymorphisms, serum IL-6 levels, and treatment in obstructive sleep apnea: a meta-analysis. Sleep Breath 20: 719-731.
33. Lu D, Li N, Yao X, Zhou L (2017) Potential inflammatory markers in obstructive sleep apnea-hypopnea syndrome. Bosn J Basic Med Sci 17: 47-53.
34. Gharib SA, Hayes AL, Rosen MJ, Patel SR (2013) A pathway-based analysis on the effects of obstructive sleep apnea in modulating visceral fat transcriptome. Sleep 36: 23-30.
35. Yamauchi M, Tamaki S, Tomoda K, Yoshikawa M, Fukuoka A, et al. (2006) Evidence for activation of nuclear factor kappaB in obstructive sleep apnea. Sleep Breath 10: 189-193.
36. Htoo AK, Greenberg H, Tongia S, Chen G, Henderson T, et al. (2006) Activation of nuclear factor kappaB in obstructive sleep apnea: a pathway leading to systemic inflammation. Sleep Breath 10: 43-50.
37. Arner P (2001) Regional differences in protein production by human adipose tissue. Biochem Soc Trans 29: 72-75.
38. Dusserre E, Moulin P, Vidal H (2000) Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. Biochim Biophys Acta 1500: 88-96.
39. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, et al. (2013) Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J Clin Sleep Med 9: 1003-1012.
40. Feres MC, Fonseca FA, Cintra FD, Mello-Fujita L, deSouza AL, et al. (2015) An assessment of oxidized LDL in the lipid profiles of patients with obstructive sleep apnea and its association with both hypertension and dyslipidemia, and the impact of treatment with CPAP. Atherosclerosis 241: 342-349.
41. Lee SD, Ju G, Choi JA, Kim JW, Yoon IY (2012) The association of oxidative stress with central obesity in obstructive sleep apnea. Sleep Breath 16: 511-517.
42. Svatikova A, Wolk R, Lerman LO, Juncos LA, Greene EL, et al. (2005) Oxidative stress in obstructive sleep apnoea. Eur Heart J 26: 2435-2439.
43. Saarelainen S, Lehtimaki T, Jaak-kola O, Poussa T, Nikkila M, et al. (1999) Autoantibodies against oxidised low-density lipoprotein in patients with obstructive sleep apnoea. Clin Chem Lab Med 37: 517-520.
44. Pujante P, Abreu C, Moreno J (2013) Obstructive sleep apnea severity is associated with left ventricular mass independent of other cardiovascular risk factors in morbid obesity. J Clin Sleep Med 9: 1165-1171.
45. Marin J, Carrizo S, Vicente E, Agusti A (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 365: 1046-1053.
46. Bisogni V, Pengo MF, Maiolino G, Rossi GP (2016) The sympathetic nervous system and catecholamines metabolism in obstructive sleep apnoea. J Thorac Dis 8: 243-254.
47. Pinto P, Barbara C, Montserrat JM, Patarrao RS, Guarino MP, et al. (2013) Effects of CPAP on nitrateand norepinephrine levels in severe and mild-moderate sleep apnea. BMC Pulm Med 13: 13.
48. Kohler M, Stoewhas AC, Ayers L, Senn O, Bloch KE, et al. (2011) Effects of continuous positive airwaypressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 184: 1192-1199.
49. Marrone O, Salvaggio A, Bue AL, Bonanno A, Riccobono L, et al. (2011) Blood pressure changes after automatic and fixed CPAP in obstructive sleep apnea: relationship with nocturnal sympathetic activity. Clin Exp Hypertens 33: 373-380.

50. Comondore VR, Cheema R, Fox J, Butt A, John Mancini GB, et al. (2009) The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial. Lung 187: 17-22.

51. Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF (2007) Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 176: 706-712.

52. Phillips CL, Yang Q, Williams A, Roth M, Yee BJ, et al. (2007) The effect of short-term withdrawal from continuous positive airway pressure therapy on sympathetic activity and markers of vascular inflammation in subjects with obstructive sleep apnoea. J Sleep Res 16: 217-225.

53. Sukegawa M, Noda A, Sugiura T, Nakata S, Yoshizaki S, et al. (2005) Assessment of continuous positiveairway pressure treatment in obstructive sleep apnea syndrome using 24-hour urinary catecholamines. Clin Cardiol 28: 519-522.

54. Mills PJ, Kennedy BP, Loredo JS, Dimsdale JE, Ziegler MG (2006) Effects of nasal continuous positive airway pressure and oxygen supplementation on norepinephrine kinetics and cardiovascular responses in obstructive sleep apnea. J Appl Physiol 100: 343-348.

55. Fletcher EC (2003) Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. Sleep 26: 15-19.

56. Bao X, Nelesen RA, Loredo JS, Dimsdale JE, Ziegler MG (2002) Blood pressure variability in obstructive sleep apnea: role of sympathetic nervous activity and effect of continuous positive airway pressure. Blood Press Monit 7: 301-307.

57. Bratel T, Wennlund A, Carlstrom K (1999) Pituitary reactivity, androgens and catecholamines in obstructive sleep apnoea. Effects of continuous positive airway pressure treatment (CPAP). Respir Med 93: 1-7.

58. Minemura H, Akashiba T, Yamamoto H, Akahoshi T, Kosaka N, et al. (1998) Acute effects of nasal continuous positive airway pressure on 24-hour blood pressure and catecholamines in patients with obstructive sleep apnea. Intern Med 37: 1009-1013.

59. Grunstein RR, Stewart DA, Lloyd H, Akinci M, Cheng N, et al. (1996) Acute withdrawal of nasal CPAP in obstructive sleep apnea does not cause a rise in stress hormones. Sleep 19: 774-782.

60. Stenlof K, Grunstein R, Hedner J, Sjostrom L (1996) Energy expenditure in obstructive sleep apnea: effects of treatment with continuous positive airway pressure. Am J Physiol 271: E1036-1043.

61. Hedner J, Darpo B, Ejnell H, Carlson J, Caidahl K (1995) Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: cardiovascular implications. Eur Respir J 8: 222-229.

62. Fernandez Pinilla C, Martin P, Espinar J, Ruiz MC, Martell N, et al. (1994) Effect of suppression of apnea on arterial pressure and plasma catecholamines in normotensive patients with sleep apnea. Med Clin (Barc) 103: 165-168.

63. Marrone O, Riccobono L, Salvaggio A, Mirabella A, Bonanno A, et al. (1993) Catecholamines and blood pressure in obstructive sleep apnea syndrome. Chest 103: 722-727.

64. Kohler M, Pepperell JC, Casadei B, Craig S, Crosthwaite N, et al. (2008) CPAP and measures of cardiovascular risk in males with OSAS. Eur Respir J 32: 1488-1496.

65. Kobukai Y, Koyama T, Watanabe H, Ito H (2014) Morning pentraxin3 levels reflect obstructive sleep apnea-related acute inflammation. J Appl Physiol 117: 1141-1148.

66. Kasai T, Inoue K, Kumagai T, Kato M, Kawana F, et al. (2011) Plasma pentraxin3 and arterial stiffness in men with obstructive sleep apnea. Am J Hypertens 24: 401-407.

67. Damiani MF, Zito A, Carratù P, Falcone VA, Bega E, et al. (2015) Obstructive sleep apnea, hypertension, and their additive effects on atherosclerosis. Biochem Res Int 150: 495-505.

68. Romsaiyut S, Chotnaiyawattrakul W, Boonyasirinant T (2015) Relationship between Cardio-Ankle Vascular Index (CAVI) and Obstructive Sleep Apnea (OSA). J Med Assoc Thai 98: 156-162.

69. Kim T, Lee CS, Lee SD, Kang SH, Han JW, et al. (2015) Impacts of comorbidities on the association between arterial stiffness and obstructive sleep apnea in the elderly. Respiration 89: 304-311.

70. Kumagai T, Kasai T, Kato M, Naito R, Maeno KI, et al. (2009) Establishment of the cardio-ankle vascular index in patients with obstructive sleep apnea. Chest 136: 779-786.

71. Liao LJ, Cho TY, Huang TW (2017) Assessment of carotid artery intima-media thickness in patients with obstructive sleep apnoea. Clin Otolaryngol 42: 974-978.

72. Kong D, Qin Z, Wang W, Kang J (2017) Effect of obstructive sleep apnea on carotid artery intima media thickness related to inflammation. Clin Invest Med 40: E25-E33.

73. Ciccone MM, Scicchitano P, Zito A, Cortese F, Boninfante B, et al. (2014) Correlation between inflammatory markers of atherosclerosis and carotid intima-media thickness in Obstructive Sleep Apnea. Molecules 19: 1651-162.

74. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, et al. (2005) Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 172: 613-618.

75. 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: 10-14.

76. Ohga 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: 179-184.

77. Chin K, Nakamura T, Shimizu K, Mishima M, Nakamura T, et al. (2000) Effects of nasal continuous positive airway pressure on soluble cell adhesion molecules in patients with obstructive sleep apnea syndrome. Am J Med 109: 562-567.

78. Jeon MS, Lim HJ, Yi TG, Im MW, Yoo HS, et al. (2010) Xenoreactivity of human clonal mesenchymal stem cells in a major histocompatibility complex-matched allogeneic graft-versus-host disease mouse model. Cell Immunol 261: 57-63.

79. Al Lawati N, Mulgrew A, Cheema R, vanEeden S, Butt A, et al. (2009) Pro-atherogenic cytokine profile of patients with suspected obstructive sleep apnea. Sleep Breath 13: 391-395.

80. Ertekin V, Selimoglu MA, Gursan N, Ozturk CF (2005) Image and diagnosis. Intracranial haemorrhage due to vitamin K deficiency, as the first symptom of extrahepatic biliary atresia. West Indian Med J 54: 392-397.

81. Ursavas A, Karadag M, Rodoplu E, Yilmaztepe A, Oral HB, et al. (2007) Circulating ICAM-1 and VCAM-1 levels in patients with obstructive sleep apnea syndrome. Respiration 74: 525-532.

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

83. Saarelainen S, Seppala E, Laasonen K, Hasan J (1997) Circulating endothelin-1 in obstructive sleep apnoea. Endothelium 5: 115-118.

84. Araújo LD, Fernandes JF, Klein MR, Sanjuliani AF (2015) Obstructive sleep apnea is independently associated with inflammation and insulin resistance, but not with blood pressure, catecholamines, and endothelial function in obese subjects. Nutrition 31: 1351-1357.

85. Chen BB (2015) Association of obstructive sleep apnea hypopnea syndrome with carotid atherosclerosis and the efficacy of continuous positive airway pressure treatment. Zhonghua Yi Xue Za Zhi 95: 2791-2795.

86. Aronsohn RS, Whitmore H, Van Cauter E, Tasali E (2010) Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. Am J Respir Crit Care Med 181: 507-513.

87. Papanas N, Steiropoulos P, Nena E, Tzouvelekis A, Maltezos E, et al. (2009) HbA1c is associated with severity of obstructive sleep apnea hypopnea syndrome in nondiabetic men. Vasc Health Risk Manag 5: 751-756.

88. Kritikou I, Basta M, Vgontzas AN, Pejovic S, Liao D, et al. (2014) Sleep apnoea, sleepiness, inflammation and insulin resistance in middle-aged males and females. Eur Respir J 43: 145-155.

89. Qian X, Yin T, Li T, Kang C, Guo R, et al. (2012) High levels of inflammation and insulin resistance in obstructive sleep apnea patients with hypertension. Inflammation 35: 1507-1511.

90. Lam JC, Lam B, Yao TJ, Lai AY, Ooi CG, et al. (2010) A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea. Eur Respir J 35: 138-145.

91. Carneiro G, Togeiro SM, Ribeiro-Filho FF, Truksinas E, Ribeiro AB, et al. (2009) Continuous positive airway pressure therapy improves hypoadiponectinemia in severe obese men with obstructive sleep apnea without changes in insulin resistance. Metab Syndr Relat Disord 7: 537-542.