International Journal of Recent Advances in Multidisciplinary Topics
Volume 4, Issue 4, April 2023
https://www.ijramt.com | ISSN (Online): 2582-7839

The Interplay Between Obstructive Sleep Apnea and Metabolic Syndrome Can Lead to Alteration in Metabolic and Inflammatory Markers

Akshay Surendra Raut[1*], Sanjay Gaikwad[2]
[1]Final Year Resident, MD Respiratory Medicine, Department of Respiratory Medicine, B.J. Government Medical College, Pune, India
[2]MD Respiratory Medicine, Department of Respiratory Medicine, B.J. Government Medical College, Pune, India

***Abstract*: This paper presents a study on the interplay between obstructive sleep apnea and metabolic syndrome.**

***Keywords*: metabolic syndrome, obstructive sleep apnoea, IL-6, CRP, lipid profile.**

1. Introduction

A person with central obesity, insulin resistance, dyslipidemia, and high blood pressure is said to have the "metabolic syndrome" (MetS), a group of metabolic and cardiovascular issues [1]. MetS is associated with a higher cardiovascular risk than would be predicted by adding merely its separate pieces, notwithstanding some controversy [2]-[4]. However, there may be other factors that have a role in the significant cardiovascular burden seen in MetS patients. Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete obstruction of the upper airway, intermittent hypoxia and frequent arousals from sleep [5]. Numerous human and animal studies have shown that OSA may have an effect on every facet of MetS, including obesity [6], hypertension [7], insulin resistance [8], dyslipidemia [9], [10] and obesity. Furthermore, previous studies [11]-[20] have shown that OSA and MetS can coexist.

It is unclear whether the overlap between OSA and MetS is solely due to the underlying obesity or if OSA adds an additional burden that exacerbates metabolic dysfunction and systemic inflammation in those who already have MetS. It is unknown how cardiovascular risk factors in persons with MetS are impacted by daytime drowsiness. Patients with OSA exhibit considerably higher plasma levels of interleukin-6 (IL-6), tumour necrosis factor alpha (TNF), and C-reactive protein (CRP) when compared to controls who are age- and BMI-matched [21], [22].

AHI, arousal index, and oxygen desaturation have all been linked favourably to CRP levels [23,] [24]. In people with and without type 2 diabetes, TNF levels have been linked to insulin resistance [25], [26]. Given the well-established links between obesity, inflammation, and insulin resistance, it is not unexpected that numerous studies have found links between OSA severity and insulin resistance levels [27]-[29], even in participants who are not fat [30], [31].

Hypoxic stress is linked to both short-term and long-term increases in glucose, insulin, and/or haemoglobin A1c (HbA1c) levels, according to a number of experimental [32], [33] and observational [34], [35] investigations in both humans and animals. However, despite the fact that the theory that OSA leads to chronic insulin resistance and diabetes has been the subject of numerous research, OSA alone does not contribute as much to these diseases as obesity and other metabolic variables do.

Recurrent hypoxia, which is linked to obstructive sleep apnea syndrome (OSAS), causes adenosine triphosphatase to degrade more quickly into xanthine, which raises uric acid levels [36]. These risk factors, which include obesity, high blood pressure, dyslipidemia, and hyperglycemia, group together in some people and are referred to as syndrome X, insulin resistance syndrome, or metabolic syndrome. Microalbuminuria, hypercoagulability, an increase in inflammatory mediators, and endothelial dysfunction are further characteristics of the metabolic syndrome [37], [38].

2. Materials and Methods

80 individuals with a recent diagnosis of MetS who were recruited from tertiary care hospitals were included in the study. Asymptomatic outpatients who were all admitted for regular check-up exams. At the time of hiring, no sleep questionnaire was used**.** The patients' written informed permission was obtained following ethical committee approval. Patients having a prior diagnosis of OSA as well as those with established cerebrovascular illness, coronary disease, heart failure, rheumatologic diseases, renal failure, hypothyroidism, pregnancy, a history of smoking, and regular exercisers were excluded from the study. Additionally, we disqualified individuals who were on steroids, insulin, fibrates, statins, uricosuric drugs (such allopurinol), hypoglycemic drugs, insulin, contraceptives, fibrates, or hypoglycemic medications. After volunteers in light clothing and without shoes had their body weight and height assessed, the body mass index was determined. On standing subjects, the distance around the waist

*Corresponding author: akshay136913@gmail.com

between the lowest rib and the iliac crest was measured using soft tape. After 15 minutes of rest, two blood pressure readings were taken from the right arm of patients sitting in a chair at 5-minute intervals, and their mean values were determined. On the basis of current recommendations, hypertension was diagnosed [39].

Enzymatic methods were used to analyse fasting blood samples to determine levels of glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and uric acid. Particle enhanced immunonephelometry was used to assess high-sensitivity C-reactive protein (Dade Behring, Inc. Deerfield, Illinois). The enzyme-linked immunosorbent assay was used to quantify IL-6 (R & D Systems, Minneapolis, MN) All samples were taken without any signs of clinically active inflammation or infection, including viral infections.

Within 1 month after blood sample collection, all participants underwent a standard overnight polysomnography as previously described [40]. A total halt of airflow for at least 10 seconds, accompanied by a 3% desaturation in oxygen, was referred to as an apnea. A decrease in respiratory signals for at least 10 seconds accompanied by a 3% desaturation in oxygen was deemed to be hypopnea. The total number of respiratory events (hypopneas plus apneas) per hour of sleep was used to construct the apnea-hypopnea index (AHI).

The AHI cut offs were 5 to 14.9, 15 to 29.9, and 30 occurrences per hour of sleep for mild, moderate, and severe OSA, respectively. The presence of OSA was also limited to the moderate to severe instances, i.e., AHI 15 events per hour of sleep, as previously described [41], due to the high expected prevalence of OSA in this cohort. The Epworth sleepiness scale[42] was used to measure daytime somnolence; a score of >10 was deemed severe daily somnolence.

A. Statistical Analyses

Version 18.0 of SPSS statistical software was used to examine the data (Chicago, Illinois, USA). When appropriate, the Student t test or Mann-Whitney test was used to compare continuous variables between patients with and without OSA. The Fisher exact test was used to compare categorical variables that were expressed using frequency distributions. Normal-distributed continuous variables were reported as mean SD. We used univariable and multivariable logistic regression analysis to examine the relative contribution of OSA as a categorical variable (presence or absence of OSA) or as a continuous variable (AHI, lowest oxygen saturation during sleep, and total sleep time below 90%).

3. Results

A total of 80 individuals with recently conformed diagnosis of metabolic syndrome were enrolled.The prevalence of OSA was 71.25%(57 patients). The prevalence of OSA (AHI >/15 events per hour of sleep) in patients with MetS was 60.5%. 15 patients (18.75%) presented with an AHI ,5 events per hour of sleep. 17 patients (21.2%) presented with an AHI from 5 to 14.9 events per hour of sleep. Moderate OSA (AHI 15–29.9 events per hour of sleep) and severe OSA (AHI >/30 events per hour of sleep) were observed in 18 patients (22.5%) and 30patients (38.1%), respectively. The demographic, anthropometric and sleep characteristics of the total population of patients studied, as well as comparisons of patients with or without OSA are shown in Table 1, The majority of participants were obese with high waist circumference measurements. There were no significant differences in sex, race, body mass index, waist circumference, hypertension, and diabetes status between patients with and without OSA.

MetS patients with OSA were older (Table 1). Patients with OSA met a higher number of MetS criteria due to the higher rate of hypertriglyceridemia and hyperglycemia than patients without OSA (Figure 2 and 3). Patients with OSA and MetS had significantly higher levels of MetS-defining parameters including blood pressure, fasting blood glucose and serum triglycerides compared to patients with MetS alone (Table 2). The levels of HDL were similar between patients with and without OSA. In contrast, the levels of several non-MetS parameters including serum total cholesterol, LDL, triglycerides/HDL ratio, cholesterol/HDL ratio, uric acid, IL-6 and C-reactive protein were also higher in patients with OSA.

Univariable and multivariable logistic regression analysis (Table 3) showed that the presence of OSA was independently associated with 2 of 5 criteria for MetS (triglycerides and glucose). Moreover, the presence of OSA was independently associated with abnormally elevated cholesterol/HDL ratio, uric acid and C-reactive protein. There was a strong trend for an independent association between the presence of OSA and triglycerides/HDL ratio. Multiple linear regression analysis showed that the AHI or minimum oxygen saturation during sleep were independently associated with serum levels of triglycerides and glucose as well as with several metabolic and inflammatory parameters not included in the MetS criteria (cholesterol/HDL ratio, uric acid, IL-6 and C-reactive protein – Table 4). Systolic and diastolic blood pressure were independently related only to age (data not shown; P <0.001 for both comparisons)

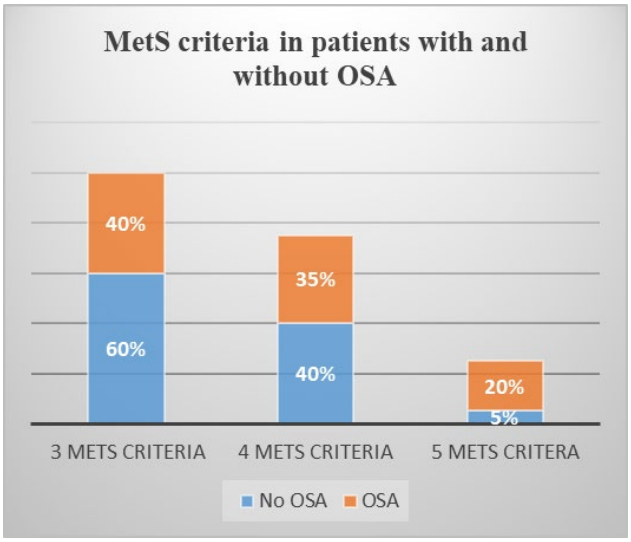

Fig. 1. MetS criteria in patients with and without OSA

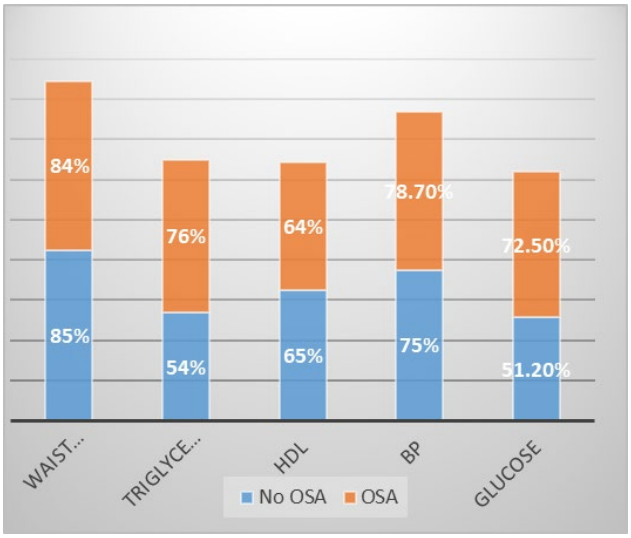

Fig. 2.

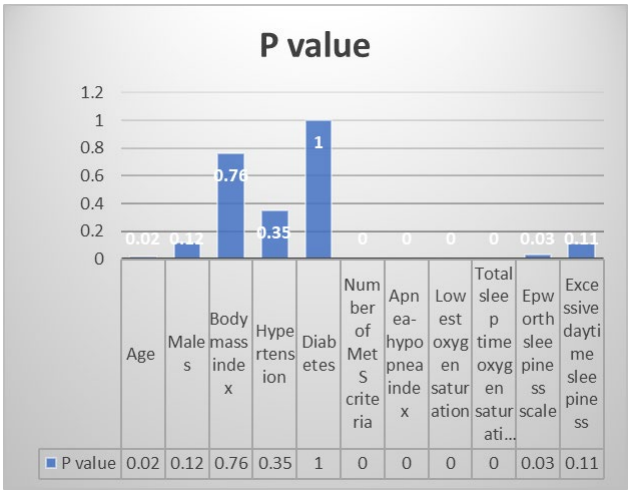

Fig. 3. P value

Table 1
Sociodemographic characteristics

	Total sample	No OSA	OSA	P value
Age	48±9	46±8	49±8	0.02
Males	42.6	30	50	0.12
Body mass index	31.5±3.9	31.3±3.8	31.4±3.4	0.76
Hypertension	66.4	61.7	69.6	0.35
Diabetes	7.6	9.3	8.4	1.00
Number of MetS criteria	3 (3-4)	3 (3-4)	4 (3-4)	<0.01
Apnea-hypopnea index	19.4 (7.8-38.9)	5.2 (2.4-8.7)	34.3(25.2-53.9)	<0.001
Lowest oxygen saturation	81 (73-86)	85 (83-90)	74(70-80)	<0.001
Total sleep time oxygen saturation <90%	3.1(0.3-10.1)	0.4(0.4-1.9)	8.7 (2.9-24.6)	<0.001
Epworth sleepiness scale	10 (7-11)	9(8-10)	10(8-11)	0.03
Excessive daytime sleepiness	46 (30.7)1	5 (23.7)	31(35.4)	0.11

Table 2
Quantitative values of metabolic and inflammatory profile in Metabolic Syndrome patients with and without Obstructive Sleep Apnea

	Total	No OSA	OSA	P value
Variables included in MetS criteria				
Waist circumference	107.2±8.3	105±8.71	106±7.8	0.14
Triglycerides	195±85	168±79	210±83	0.003
HDL cholesterol	37(35-45)	37(35-45)	35(36-45)	0.88
Systolic blood pressure	140±23	135±20	144±22	0.06
Diastolic blood pressure	83±12	80±12	85±13	0.04
Fasting glucose	103±10	99±9	106±11	<0.001
Variables not included in MetS criteria				
Total cholesterol	214±40	203±37	220±34	0.004
Total cholesterol/HDL ratio	5.6±1.3	5.3±1.3	5.8±1.5	0.02
Triglycerides/HDL ratio	5.2±3.0	4.5±29	5.7±30	0.008
Uric acid	6.7±1.5	5.9±13	7.0±13	<0.001
IL-6	35±5.1	7.8±0.2	23±5.1	<0.001
C-reactive protein	3.1(2.1-3.9)	2.7(1.4-3.1)	3.8(2.8-4.3)	<0.001

Table 3
Univariable and multivariable logistic regression analysis for the association between presence of OSA with variables included and not included in the MetS criteria

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	P value
Variables included in MetS criteria			
Waist circumference criteria	0.77(0.26-2.3)	0.75(0.23-2.7)	0.71
Triglycerides criteria	2.86(1.32-6.01)	3.26 (1.47–7.21)	0.005
HDL-C criteria	0.89(0.44-1.80)	0.85(0.41-1.79)	0.72
Arterial blood pressure criteria	1.19(0.58-2.7)	1.03(0.47-2.2)	0.95
Fasting glucose criteria	2.52(1.3-5.2)	2.31 (1.12–4.80)	0.03
Variables not included in MetS criteria			
Total cholesterol/HDL ratio ≥4.5	2.38(1.19-4.89)	2.38 (1.08–5.24)	0.04
Triglycerides/HDL ratio >3	2.23(1.07-4.8)	2.19(0.98-5.03)	0.06
Uric Acid >7 mg/Dl	4.16(1.8-9.7)	4.19 (1.70–10.35)	0.004
IL-6	6.9(2.12-12.1)	7.1 (2.11-13.4),	0.004
C-reactive protein >3 mg/L	4.89(2.39-9.9)	6.10 (2.64–14.11	<0.001

Table 4
Stepwise linear regression analysis for the association between markers of OSA severity and components of MetS and metabolic/inflammatory variables not included in the MetS criteria*

	Variables	Co-efficient(β)	95% CI	P value
Variables included in MetS criteria				
Triglycerides	Race	-14.432	-25.898 -1.178	*0.05*
	Body mass index	-5.541	-10.687-0.500	*0.05*
	Minimum O_2 saturation	-2.016	-3.891 -0.042	0.03
Glucose	Age	0.371	0.1010.517	0.002
	Apnea-hypopnea index	0.079	0.013 0.178	*0.03*
Variables not included in MetS criteria				
Cholesterol/HDL	Apnea-hypopnea index	0.012	0.003 0.019	0.007
Uric Acid	Sex	0.798	0.356 1.298	*0.001*
	Apnea-hypopnea index	0.012	0.002 0.019	*0.03*
C-reactive protein	Minimum O_2 saturation	-0.041	-0.069 -0.012	*0.005*
	Sex	-0.632	-1.215 -0.003	*0.05*
	Age	0.036	0.003 0.069	*0.04*
IL-6	Sex	*-0.675*	*-1.316-0.003*	*0.04*
	Age	*-0.032*	*0.004 0.059*	*0.03*

4. Discussion

According to the results of the current investigation, undiagnosed OSA is frequent in MetS patients and is independently correlated with indicators of metabolic dysfunction and systemic inflammation. In particular, triglycerides and glucose, two MetS criteria, as well as cholesterol/HDL ratio, uric acid, IL-6 and C-reactive protein, three non-MetS cardiovascular risk factors, were related with OSA. Our data as a whole imply that OSA may increase the metabolic and cardiovascular burden of MetS patients.

OSA was not taken into account in earlier clinical investigations of MetS as a potential confounding condition that raises the risk of cardiovascular disease [43], [44]. Accordingly, OSA was briefly covered in the American Heart Association Scientific statement on MetS and categorised as being relevant to "other fields of medicine," receiving the same consideration as cholesterol gallstones and lipodystrophies [1]. On the other hand, the majority of earlier studies coming from the sleep community focused exclusively on patients who had been referred for sleep testing [45]. With the help of our study's methodology, we were able to systematically assess the prevalence of undiagnosed OSA in a cohort of MetS patients.

We found a 60.5% prevalence of OSA in MetS, even using conservative diagnostic OSA criteria (AHI >/15 events per hour of sleep. The prevalence of OSA seen in this study is consistent with two earlier publications from separate groups that assessed individuals with MetS (ranging from 68 to 87.5%) [41]. A recent study indicated that obese patients with type 2 diabetes had a significant prevalence of OSA (,86%), which is consistent with our data [46]. The high prevalence of OSA among our MetS patients may be related to the fact that both disorders have visceral obesity as a common characteristic. Visceral fat, not subcutaneous or total body fat, is what actually predisposes to OSA development [47].

However, it has been demonstrated that the impact of OSA on MetS metabolic function, at least in terms of glucose regulation, occurs independently of waist size, a proxy indicator of visceral adiposity [41].

In the present larger study, which excluded patients treated with hypoglycemic and lipid-lowering medications, we show that the co-existence of OSA in patients with MetS is associated with increased glucose and triglycerides levels.

Additionally, we have demonstrated a relationship between OSA and non-MetS cardiovascular risk factors as the cholesterol/HDL ratio, uric acid, IL-6 and C-reactive protein. These biomarkers have been proven to be reliable indicators of cardiovascular risk. In comparison to total cholesterol, HDL cholesterol, and non-HDL cholesterol, a cholesterol/HDL ratio of 4.5 is a stronger predictor of ischemic heart disease 48. The catabolic end product of ATP, uric acid, has been linked to oxidative stress, inflammation, subclinical atherosclerosis, and a higher risk of cardiovascular events [49]. Independent research has demonstrated that individuals with MetS and OSA frequently have high plasma uric acid levels.

Our study suggests that OSA has an additive effect on uric acid levels in patients with MetS. Finally, pro-inflammatory effects of MetS and OSA were widely discussed in the literature and many independent studies reported that both MetS and OSA [50] are independently associated with high C-reactive protein levels, which is a marker of cardiovascular inflammation. C-reactive protein adds clinically important prognostic information to the MetS.

Our investigation found an independent relationship between OSA and dyslipidemia and systemic inflammation that has a biological foundation.

Through the upregulation of hepatic lipid production and lipoprotein release via hypoxia inducible factor 1 alpha, intermittent hypoxia, the characteristic of OSA, leads to dyslipidemia in mice [51]. Additionally, intermittent hypoxia stimulates the expression of pro-inflammatory mediators, which may impair endothelial function, by promoting the activation of a variety of inflammatory cells and pro-inflammatory transcription factors such nuclear factor kappa B [52].

In the current investigation, we showed that patients with and without excessive daytime sleepiness shared similar levels of various metabolic and inflammatory markers linked to OSA. Independent of daytime symptoms, other researchers have demonstrated that OSA is linked to atherosclerotic markers and mortality [53]. These findings cast doubt on the idea that OSA patients who are just drowsy are at higher cardiovascular risk.

OSA may not be recognised in those who don't sleep, which causes it to be disregarded as a possible cardiovascular risk factor. The cross -sectional nature of the study does not prove cause-effect relationships between OSA and metabolic and inflammatory markers.

5. Conclusion

Patients with MetS frequently have OSA. Increased prevalence and severity of hypertriglyceridemia and hyperglycemia, as well as other indicators of metabolic and inflammatory dysregulation (cholesterol/HDL ratio, uric acid, and C-reactive protein) are all independently linked to OSA. Regardless of daytime sleepiness, our data clearly suggest that patients with MetS ought to be examined for OSA. We believe that having OSA can worsen MetS and raise cardiovascular morbidity and death even more.

References

[1] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, et al.; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005; 112: 2735–2752. Erratum in: Circulation;112, e297.

[2] Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, et al. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population-based cohort study. BMJ 2006; 332: 878–882.

[3] Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007; 49: 403– 414.

[4] Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. Stroke 2006;37: 1060–1064.

[5] Ryan CM, Bradley TD. Pathogenesis of obstructive sleep apnea. J Appl Physiol 2005; 99: 2440- 2450.

[6] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002; 165: 1217–1239.

[7] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000; 342: 1378–1384.

[8] Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, et al. Sleep-Disorder breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002;165: 677–682.

[9] Li J, Thorne LN, Punjabi NM, Sun CK, Schwartz AR, et al. Intermittent hypoxia induces hyperlipidemia in lean mice. Circ Res 2005; 97: 698–706.

[10] Savransky V, Jun J, Li J, Nanayakkara A, Fonti S, Moser AB, et al. Dyslipidemia and atherosclerosis induced by chronic intermittent hypoxia are attenuated by deficiency of stearoyl coenzyme A desaturase. Circ Res 2008;103: 1173–1180.

[11] Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J 2004;25: 735–741.

[12] Gruber A, Horwood F, Sithole J, Ali NJ, Idris I. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovasc Diabetol 2006; 5: 22.

[13] Kono M, Tatsumi K, Saibara T, Nakamura A, Tanabe N, et al. Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome. Chest 2007;131:1387–1392.

[14] Sasanabe R, Banno K, Otake K, Hasegawa R, Usui K, et al. Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. Hypertens Res 2006; 29:315– 322.

[15] Parish JM, Adam T, Facchiano L. Relationship of metabolic syndrome and obstructive sleep apnea. J Clin Sleep Med 2007; 13: 355–362.

[16] Nock NL, Li L, Larkin EK, Patel SR, Redline S. Empirical evidence for "syndrome Z": a hierarchical 5-factor model of the metabolic syndrome incorporating sleep disturbance measures. Sleep 2009;32: 615–622.

[17] Venkateswaran S, Shankar P. The prevalence of syndrome Z (the interaction of obstructive sleep apnoea with the metabolic syndrome) in a teaching hospital in Singapore. Postgrad Med 2007; J 83: 329–331.

[18] Drager LF, Queiroz EL, Lopes HF, Genta PR, Krieger EM, et al. Obstructive sleep apnea is highly prevalent and correlates with impaired glycemic control in consecutive patients with the metabolic syndrome. J Cardiometab Syndr 2009; 4: 89–95.

[19] Chin K, Oga T, Takahashi K, Takegami M, Nakayama-Ashida Y, et al. Associations between obstructive sleep apnea, metabolic syndrome, and sleep duration, as measured with an actigraph, in an urban male working population in Japan. Sleep 2010; 33: 89–95.

[20] Lam JC, Lam B, Lam CL, Fong D, Wang JK, et al. (2006) Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong. Respir Med 2006;100: 980–987.

[21] Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002; 2462–4.

[22] Chien MY, Lee P, Tsai YF, Yang PC, Wu YT. C-reactive protein and heart rate recovery in middle-aged men with severe obstructive sleep apnea. Sleep Breath 2012; 16: 629–37.

[23] Tauman R, Ivanenko A, O'Brien LM, Gozal D. Plasma C-reactive protein levels among children with sleep-disordered breathing. Pediatrics 2004; 113: e564–9.

[24] Larkin EK, Rosen CL, Kirchner HL, Storfer-Isser A, Emancipator JL, Johnson NL, et al. Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration. Circulation 2005; 111: 1978–84.

[25] Hotamisligil GS, Spiegelman BM. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. Diabetes 1994; 43: 1271–8.

[26] Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 2001; 280: E745–51

[27] Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, 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.

[28] Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002; 165: 677–82.

[29] Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 2004; 160: 521–30.

[30] Kritikou I, Basta M, Vgontzas AN, Pejovic S, Liao D, Tsaoussoglou M, et al. Sleep apnoea, sleepiness, inflammation and insulin resistance in middle-aged males and females. Eur Respir J 2014; 43: 145–55.

[31] Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165: 670–6.

[32] Polak J, Shimoda LA, Drager LF, Undem C, McHugh H, Polotsky VY, et al. Intermittent hypoxia impairs glucose homeostasis in C57BL6/J mice: partial improvement with cessation of the exposure. Sleep 2013; 36: 1483–90; 1490A-1490B.

[33] Chopra S, Rathore A, Younas H, Pham LV, Gu C, Beselman A, et al. Obstructive sleep apnea dynamically increases nocturnal plasma free fatty acids, glucose, and cortisol during sleep. J Clin Endocrinol Metab 2017; in press.

[34] Polotsky VY, Patil SP, Savransky V, Laffan A, Fonti S, Frame LA, et al. Obstructive sleep apnea, insulin resistance, and steatohepatitis in severe obesity. Am J Respir Crit Care Med 2009; 179: 228–34.

[35] Aronsohn RS, Whitmore H, Van Cauter E, Tasali E. Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. Am J Respir Crit Care Med 2010; 181: 507–13.

[36] Hirotsu C, Tufik S, Guindalini C, Mazzotti DR, Bittencourt LR, Andersen ML (2013) Association Between Uric Acid Levels and Obstructive Sleep Apnea Syndrome in a Large Epidemiological Sample. PLoS ONE 8(6): e66891.

[37] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Jama. 2001;285(19):2486–2497.

[38] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539–553.

[39] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al.; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42: 1206–1252.

[40] Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, et al. Early Signs of Atherosclerosis in Obstructive Sleep Apnea. Am J Respir Crit Care Med 2005;172: 613–618.

[41] Drager LF, Queiroz EL, Lopes HF, Genta PR, Krieger EM, et al. (2009) Obstructive sleep Apnea is highly prevalent and correlates with impaired glycemic control in consecutive patients with the metabolic syndrome. J Cardiometab Syndr 2009;4: 89–95.

[42] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14: 540–545.

[43] Isomaa B, Almgren P, Tuomi T, Forse´n B, Lahti K, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24: 683–689.

[44] Arnlo¨v J, Ingelsson E, Sundstro¨m J, Lind L. Impact of body mass index and the metabolic -syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 2010; 121:230–236.

[45] Nock NL, Li L, Larkin EK, Patel SR, Redline S (2009) Empirical evidence for ‘‘syndrome Z’’: A hierarchical 5-factor model of the metabolic syndrome incorporating sleep Disturbance measures. Sleep 32: 615–622.

[46] Foster GD, Sanders MH, Millman R, Zammit G, Borradaile KE, et al. Obstructive sleep Apnea among obese patients with type 2 diabetes. Diabetes Care 2009;32: 1017–1019.

[47] Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, et al. Sleep apnea and Day time sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000; 85: 1151–1158.

[48] Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 370: 1829–1839. Erratum in: Lancet.2008;372:292.

[49] Bos MJ, Koudstaal PJ, Hofman A, Witteman JCM, Breteker MMB (2006) Uric acid is a risk factor for myocardial infarction and stroke. Stroke2006; 37: 1503–1507.

[50] Lui MM, Lam JC, Mak HK, Xu A, Ooi C, et al. C-reactive protein is associated with Obstructive sleep apnea independent of visceral obesity. Chest 135: 950–956. Erratum in: Chest 2009;135:1406.

[51] Li J, Thorne LN, Punjabi NM, Sun CK, Schwartz AR, et al. Intermittent hypoxia induces hyperlipidemia in lean mice. Circ Res 2005; 97: 698–706

[52] Ryan S, Taylor CT, McNicholas WT (2005) Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 112: 2660–2667.

[53] Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008; 31: 1071–1078.