Obesity, Obstructive Sleep Apnoea, and Metabolic Syndrome: The Fatal Association

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Abstract

Obesity is the most common health risk for individuals of all age groups across the globe. Obstructive sleep apnoea (OSA) is now recognized as a major health problem in developed countries. The prevalence of OSA is undoubtedly rising given the epidemic of obesity. Recent data also suggest that OSA is associated with metabolic syndrome. Pathophysiological triggers of intermittent hypoxia and sleep fragmentation in OSA is responsible for cardiometabolic dysfunction. The potential mechanisms of OSA-obesity-metabolic syndrome interaction involve sympathetic activation, oxidative stress, inflammation and neurohumoral changes. In spite of support for an independent role of OSA in the contribution towards metabolic dysfunction, obesity plays a determinant role in initiating both these conditions.

Keywords: obesity, cardiometabolic dysfunction, metabolic syndrome

Introduction

The obesity epidemic and its impact on the prevalence of both metabolic syndrome and OSA are well recognized. OSA is widely prevalent in patients with obesity, diabetes, and hypertension. Clustering of cardiovascular risk factors (metabolic syndrome or Syndrome X) was recognized as early as the 1920s and is currently thought to be linked to obesity and OSA. Given the obesity epidemic at hand, the prevalence of both metabolic syndrome and OSA are rising. In patients with established coronary artery disease, treatment of OSA may confer long term cardiovascular benefits. Our understanding of the relative importance and interactions of these cardiovascular disease mechanisms and risk factors in patients with OSA may have direct implications for the development of targeted preventive and therapeutic strategies.[1] The results of various studies have undisputedly shown that appropriate treatment of OSA with Continuous Positive Airway Pressure (CPAP) therapy significantly reduces blood pressure[2] and other cardiovascular complications like CAD, arrhythmias and stroke. Treatment of OSA also improves the altered metabolic physiology in patients with syndrome X. Further a new syndrome, syndrome-Z was recognized to highlight the dreadful combination of syndrome-X and OSA as a risk factor for coronary artery disease (CAD).

Obesity

Obesity is a complex disease involving an excessive amount of body fat. Obesity is a risk factor for diabetes, hypertension, obstructive sleep apnoea and cardiovascular events [3] and increases mortality, especially in middle-aged adults. In adults, obesity is diagnosed when the body mass index (BMI) is 30 Kg/M^2 or more. Obesity rates are also increasing in children.[4] Since obese children tend to become obese adults, the cardiometabolic disease associated with obesity could begin in childhood.[5]

Individuals with high body mass index (BMI) are

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classified as overweight when BMI is between 25-29.9, class-1 obesity when BMI is between 30-34.9, class-II Obesity when BMI is between 35-40 and class-III obesity when BMI is more than 40.

Obesity is characterized by the expansion of white adipose tissue, as a result of increased size (hypertrophy), and, additionally, by an increased number of adipocytes (hyperplasia). Adipose tissue is a central player in metabolic regulation through the production and release of multiple adipokines.[6] Moreover, adipocytes and inflammatory cells, such as macrophages, show a high degree of interaction in obesity.[7]

The localization of excess white adipose tissue in the body carries relevant metabolic consequences. Increased visceral fat mass is associated with more severe health effects compared to peripheral obesity, which is characterized by the predominant accumulation of subcutaneous fat. The expansion of visceral fat increases the risk of developing insulin resistance (IR), type-II diabetes, atherosclerosis, OSA, steatohepatitis, and cardio- and cerebrovascular disease. Changes in body weight are known to affect OSA severity. Most adult patients with OSA have central obesity and increased visceral fat,[8] the latter being associated with neck adiposity, increased upper airway fat and metabolic abnormalities.[9]

The adverse consequences of obesity may be attributed in part to comorbidities, but results from several observational studies detailed by the Expert Panel on the Identification, Evaluation, and Treatment of Overweight Adults, show that obesity on its own is associated with increased cardiovascular morbidity and mortality and greater all-cause mortality.[10] For a person with a BMI of 25-28.9 kg/m^2, the relative risk for coronary heart disease is 1.72. The risk progressively increases with an increasing BMI; with BMIs greater than 33 kg/m^2, the relative risk is 3.44. Similar trends have been demonstrated in the relationship between obesity and stroke or chronic heart failure. For persons with severe obesity (BMI ≥40), life expectancy is reduced by as much as 20 years in men and by about 5 years in women.

Many clinical and biochemical factors associated with increased cardiovascular risk (i.e., dyslipidaemia, arterial hypertension, hyperglycaemia, hyperuricaemia and microalbuminuria) are often present in visceral (or central) obesity. The term "adiposopathy" has been proposed to indicate the strong link between visceral fat and obesity-associated metabolic abnormalities.[11]

Treatment of obesity starts with comprehensive lifestyle management which includes diet, physical activity and behavior modification. In addition, several surgical options are also available for morbid obesity.

Obstructive Sleep Apnoea

The spectrum of breathing disorder ranges from intermittent, partial obstruction of the airway without sleep disturbance (snoring) to frequent arousals associated with hypoxemia leading to sleep fragmentation and daytime sleepiness. There will be recurrent episodes of cessation of respiration (apneas), decrements in airflow (hypopneas), or respiratory event related arousals (RERAS). This spectrum ranges from snoring, upper airway resistance syndrome (UARS), sleep hypopnea syndrome, to obstructive sleep apnea syndrome (OSAS) of which OSAS is the most severe form having a considerable impact on the individual's health (Figure 1).

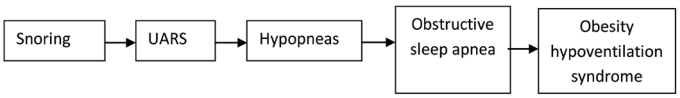

Figure 1: Spectrum of sleep-disordered breathing

Obstructive sleep apnea affects approximately 10% of middle-aged men and 5% of women and is, therefore, a common condition. The prevalence of clinically significant obstructive sleep apnea (OSA) in middle-aged adults is estimated to be 2–5% in males and 2% in females. However, 82% of men and 93% of women suffering from moderate to severe sleep apnea have not been clinically detected or treated. There are many serious consequences for undiagnosed and untreated OSA. The quality of life of these patients is seriously impaired mainly due to their excessive daytime sleepiness. These patients also suffer from psychological impairment such as cognitive dysfunction, decreased vigilance, disturbed concentration and memory, increased mental stress, fatigue, general mood disorders, and male sexual dysfunction.[12] There is an estimated three- to seven-fold greater prevalence of motor vehicle accidents involving drivers with OSA.[13] Most of these accidents are attributed to poor vigilance and falling asleep while driving.

The cardiovascular consequences of untreated OSA are coronary artery disease, congestive heart failure, myocardial infarction, stroke, systemic hypertension, and pulmonary hypertension.[14] The association between hypertension and OSA is well established. It is shown that hypertension associated with untreated OSA is often refractory and that a high prevalence of OSA has been observed in men with therapy-resistant hypertension.[15] Patients with OSA have many

features in common with those with syndrome X, including systemic hypertension which is commonly reported. Obstructive sleep apnea (OSA) has been linked to increased cardiovascular morbidity and mortality [16] and can be considered an independent risk factor for CAD. Pathophysiologic mechanisms that are present in patients with OSA, including sympathetic activation, endothelial dysfunction, oxidative stress, systemic inflammation, hypercoagulability, hyperleptinemia, and insulin resistance, may influence the development and progression of cardiac and vascular pathology. These mechanisms are found to be common for both metabolic syndrome and OSA.

Metabolic Syndrome (Syndrome-X)

Metabolic Syndrome" or "Syndrome X" constitutes one of the most important risk factors for CAD. The diagnosis of metabolic syndrome is made when an individual has three of the following five characteristics: increased waist circumference, high blood pressure, elevated fasting glucose, elevated triglycerides, and decreased high-density lipoprotein (HDL) cholesterol. The criteria proposed by 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) are the most current and widely used. According to the ATP III criteria, the metabolic syndrome is identified by the presence of three or more of these components:

- Central obesity as measured by waist circumference: In men greater than 40 inches and in women greater than 35 inches
- Fasting blood triglycerides greater than or equal to 150 mg/dL
- Blood HDL cholesterol: In men less than 40 mg/dL and in women less than 50 mg/dL
- Blood pressure greater than or equal to 130/85 mmHg
- Fasting blood glucose greater than or equal to 110 mg/dL

Other important features of the metabolic syndrome include microalbuminuria, hypercoagulability, increased inflammation, endothelial dysfunction, poor cardiorespiratory function and sympathetic activation. Cardiovascular metabolic syndrome X is becoming very common in India.

Coughlin and colleagues [17] performed a cross-sectional study of 61 otherwise healthy subjects with OSA and 29 subjects without OSA. To mitigate confounding due to obesity, they also matched 34 of the OSA patients by body-mass index (BMI) to the 29 controls. Their results suggest that the prevalence of the metabolic syndrome is about 40% greater in patients with OSA. Also, proper management of syndrome X reduces the apnea hypopnea index in patients with co-existent OSA thus underlying the importance of simultaneous management of both the conditions.

Syndrome-Z

It has even been suggested that the metabolic syndrome (Syndrome X) may co-exist with OSA (Syndrome Z).[18] Syndrome Z was introduced in medical practice by Ian Wilcox in 1996.[18] Wilcox attached the respiratory partner for CAD risk, OSA, to syndrome X (Table 1). The importance lies in the fact that the medical fraternity is now challenging CAD by risk factor modification, but one of the major culprits, OSA, remains largely unnoticed and undertreated.

Table 1: Components of syndrome Z

1	Hypertension
2	Glucose intolerance
3	Low serum high-density lipoprotein (HDL)-cholesterol
4	Elevated serum triglyceride
5	Abdominal obesity
6	OSA

Interaction

It is conceivable that OSA and obesity may interact and potentiate their detrimental consequences. OSA-associated metabolic abnormalities have been reproduced in animal models exposed to a pattern of intermittent hypoxia similar to that found in humans with sleep-disordered breathing.[19] However, hypoxia of adipocytes could play an important role in the metabolic disturbances associated with obesity.[20] In addition, OSA and obesity share common mechanisms. Nocturnal ischemia in these patients is probably a result of simultaneous oxygen desaturation, increased sympathetic activity, tachycardia and increased systemic vascular resistance, a prothrombotic state, and any underlying subclinical coronary artery disease. Experimental studies support the theory that there might be a cause-and-effect relationship between OSA and atherosclerosis. OSA and metabolic syndrome share the common pathophysiologic mechanism increasing CAD risk.

Human obesity is usually associated with high plasma leptin and attenuated leptin signalling (leptin resis-

tance).[21] Leptin might be involved in the pathogenesis of hypoventilation disorders and its transcription is activated by exposure to continuous severe hypoxia in vitro.[22] In recent years, the role of leptin in immune function and inflammation has been increasingly studied, and some data indicate that leptin could contribute to the pathogenesis of atherosclerotic lesions by promoting inflammation.[23] Adiponectin exerts an insulin-sensitizing action, and its levels are decreased in obesity.[24] Adiponectin has anti-atherogenic and anti-inflammatory properties, and its circulating levels are lower than normal in patients with type-II diabetes, metabolic syndrome (MetS), hypertension and coronary artery disease.[25] The protective role of adiponectin and its modulation by hypoxia suggest that it may be a useful marker of metabolic dysfunction in obesity and OSA.

Although inflammation contributes to the development of IR and MetS,[26] the sequence of events leading to the inflammatory response in the adipose tissue is incompletely defined. An increased adipocyte size may be an important signal, through dysregulation of insulin signaling at the level of insulin receptor substrates (IRS). Phosphorylation of IRS-1, an early event in insulin signaling, is decreased in large adipocytes.[27]

Independent association between OSA and metabolic syndrome were assessed in two case-controlled studies on Caucasian men and reported a 6-9-fold cardiovascular risk in these subjects.[28] In a community-based study among Chinese subjects,[29] a positive correlation was demonstrated between AHI and the number of metabolic components. There are other studies also demonstrating association between sleep-disordered breathing and metabolic factors within the metabolic syndrome, independent of obesity.

OSA and Obesity

Obesity is considered an important risk factor for the development of OSA.[30] It also plays an important role in the pathogenesis of the metabolic syndrome.[31] Positive correlations between the severity of OSA and the degree of obesity in various ethnic populations have been established through epidemiologic studies.[32] Waist-to-hip ratio, waist circumference, and neck circumference are found to be better predictors of OSA severity than BMI.[33] How adiposity and its distribution predispose to the development of OSA is not clearly described. Greater mechanical load imposed by central obesity on the upper and lower respiratory tracts and obesity-related inflammation may predispose to pharyngeal collapse.[30] On the other hand, OSA itself may modulate the secretion of hormones and other biological mediators which in turn lead to obesity.

It is proved through a longitudinal cohort study that a 10% weight loss was associated with a 26% decrease in AHI.[34] It is also proved that weight loss could result in complete resolution of OSA in the mild-to-moderate AHI range.[35] Weight reduction is best achieved by reducing energy intake through dietary modifications and enhancing energy expenditure through physical activity. Bariatric surgery has been used and shown to improve the metabolic profile as well as sleep-disordered breathing in morbidly obese individuals.

OSA and Insulin Resistance

Insulin resistance and glucose intolerance are two essential components of metabolic syndrome. There are pieces of evidence of a positive and independent association between OSA and insulin resistance or glucose intolerance.[36] Subjects with OSA may have multiple factors leading to insulin resistance and glucose intolerance. Central obesity itself leads to insulin resistance through increased lipolysis and fatty acid availability.[37] Insulin resistance was observed not only in obese but also in non-obese patients suffering from OSA.[38]

In the Wisconsin Sleep Cohort study conducted on 1300 subjects, an independent relationship between OSA and diabetes was not established even after a 4-year follow-up, despite a higher prevalence of diabetes in OSA subjects.[39] Intravenous glucose tolerance test did not show impaired insulin sensitivity or impaired insulin secretion in diabetic with OSA.

OSA and Dyslipidemia

Obesity is associated with increased plasma lipids, and adipose tissue distribution.[40] The American Sleep Heart Health Study reported that HDL-cholesterol levels were inversely related to AHI levels, independent of obesity. Similarly, triglycerides levels were positively correlated with AHI in younger men and women, but not in the elderly.[41] Many patients attending the sleep clinic show a higher prevalence of dyslipidemia compared with those without OSA, after adjustment for BMI. A significant association between high AHI and the presence of CAD and dyslipidemia was shown by case-controlled studies. Even though few observational studies reported that treatment with nasal CPAP improved lipid parameters; it was not validated through randomized, controlled studies. It is proved that low-density lipoprotein is more injurious to endothelial cells and underlying smooth muscle cells, and is thus more atherogenic.

Pathogenesis of Cardio-Metabolic Dysfunction in OSA

Intermittent hypoxemia with re-oxygenation and sleep fragmentation may lead to multiple events altering cellular metabolism. Obstructive sleep apnea is considered to be a chronic stress state with activation of neuro-humoral pathways that participate in metabolic regulation. Obese subjects have increased sympathetic activity, and in subjects with OSA, there is the further elevation of sympathetic activity more than what is attributed to obesity.[42] Surges of sympathetic overactivity causes transient increases in systemic blood pressure. Sympatho-adrenal activation persists in the day, as evidenced by sympathetic nerve activity and catecholamine output.[43] This sympathetic activation may modulate many other mechanisms or mediators, including the angiotensin-renin system, insulin and adiponectin, which may all contribute to cardiometabolic dysfunction in OSA.[43] Sympathetic overactivity in OSA is an important factor in the pathogenesis of hypertension.[44] At the same time, its role in glucose and lipid metabolism is less clear. Changes in the duration or quality of sleep may affect neuroendocrine and metabolic function.[45] OSA subjects have been reported to have an altered pattern of cortisol secretion. [46] Obstructive sleep apnea may also modulate hormones that regulate energy metabolism. These patients have lower leptin levels, in proportion to weight gain. [47]

The recurrent intermittent hypoxia with reoxygenation, may result in the generation of oxidative stress, which itself lead to cardiometabolic dysfunction.[48] Obesity and metabolic syndrome have been associated with this enhanced oxidative stress.[48] It is proved in animal models that intermittent hypoxia induces various metabolic alterations, such as insulin resistance and dyslipidemia.[49] These patients have increased levels of various oxidative stress markers, such as nitric oxide, 8-isoprostane, reactive oxygen species, and lipid peroxidation.

It is believed that inflammation plays a pivotal role in the pathogenesis of endothelial dysfunction, insulin resistance and lipid peroxidation. Inflammation is a key component in OSA. Inflammation in OSA, independent of obesity, is evidenced by activation of neutrophils, lymphocytes, monocytes, and platelets; activation of NF-κB and increased circulating levels of pro-inflammatory cytokines.[50] Expression of adipocytokines in the obesity state is associated with inflammation. In obesity, inflammation occurs in adipose tissue and has an impact on glucose, lipid and energy metabolism. It is possible that OSA-induced intermittent hypoxia may interact with adiposity to promote metabolic dysfunction.

Intervention

Nowadays, the focus is on the primary prevention of coronary artery disease (CAD), which means risk factor modification. Early recognition of risk factors and primary prevention have significantly decreased the morbidity and mortality associated with CAD. The risk assessment and preventive therapy is a combined decision taken by the patient and their physician. Modifiable risk factors for coronary artery disease include:

- Type 2 diabetes mellitus
- Hypertension
- Smoking
- Dyslipidemia
- Obesity
- Metabolic syndrome

Lifestyle modification with diet, exercise, and smoking cessation is crucial to reduce cardiovascular risk factors. Further control of hypertension, diabetes, and hyperlipidemia is essential to reduce the risk of CAD. Replacing saturated fats with dietary mono-saturated and polyunsaturated fats are found to be beneficial to reduce cardiovascular risks. Besides, dietary sodium reduction is found to have reduced blood pressure and decreased risk for cardiovascular events.

Physical activity is also equally beneficial for CAD risk reduction. Moderate activities like brisk walking, cycling, active yoga, and swimming or vigorous activities like jogging/running, biking playing tennis, etc. may help in reducing the risks. Weight loss has consistently shown to improve the cardiovascular risk profile. Strong recommendations include high levels of physical activities, a low-calorie diet, and if possible, weight-loss maintenance programs.

Control of hypertension by pharmacological management along with non-pharmacological measures is recommended to reduce cardiovascular morbidity. Weight loss also has a positive impact on lowering blood pressure.

Diabetes mellitus is another important cardiovascular disease risk. Dietary modifications using a heart-healthy diet and physical activities are encouraged. Additionally, weight loss is recommended if the individual is overweight or obese. Metformin can also be considered as first-line therapy for type 2 DM to im-

prove the glycemic index and reduce cardiovascular risk.

Most of the above measures have a positive impact on obesity and OSA. These measures also help to control the two important health risk of metabolic syndrome such as diabetes and hypertension. OSA symptoms are well controlled on weight reduction and many of the pathophysiological changes associated with OSA can be controlled with weight reduction and CPAP therapy.

Conclusion

Obesity is a primary determinant of OSA and metabolic syndrome. OSA can modify the components of metabolic syndrome and vice versa. Early diagnosis and treatment of OSA is the cornerstone in the management of metabolic syndrome and hence CAD. The important measures include weight reduction, regular exercises, control of hypertension and diabetes, along with treatment of OSA. Thus clinicians should keep a high index of suspicion for obesity, OSA and MetS while dealing with patients with cardiovascular morbidity.

References:

1. Harilakshmanan P, Arun P, Sethu Babu, Ravindran C. Syndrome Z- A case report. *Pulmon 2006*;8:3: 91-94
2. DS Hui, KW To, FW Ko, JP Fok, MC Chan, JC Ngai, AH Tung, CW Ho, MW Tong, C-C Szeto, CM Yu. Nasal CPAP reduces systemic blood pressure in patients with OSA and mild sleepiness. *Thorax 2006*; 61:1083-1090
3. Jensen MK, Chiuve SE, Rimm EB, et al. Obesity, behavioral lifestyle factors, and risk of acute coronary events. *Circulation 2008*; 117: 3062–3069. Google Scholar
4. Jackson-Leach R, Lobstein T. Estimated burden of paediatric obesity and co-morbidities in Europe. Part 1. The increase in the prevalence of child obesity in Europe is itself increasing. *Int J Pediatr Obes 2006*; 1: 26–32. CrossRefPubMedGoogle Scholar
5. Cali AM, Caprio S. Obesity in children and adolescents. *J Clin Endocrinol Metab 2008*; 93: Suppl. 1, s31–s36. CrossRefPubMedGoogle Scholar
6. Trayhurn P, Wood S. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr 2004*; 92: 347–355.CrossRefPubMedWeb of ScienceGoogle Scholar
7. Hotamisligil GS. Inflammation and metabolic disorders. *Nature 2006*; 444: 860–867.CrossRefPubMedGoogle Scholar
8. Grunstein RR, Wilcox I, Yang TS, *et al*. Snoring and sleep apnoea in men: association with central obesity and hypertension. *Int J Obes Relat Metab Disord 1993*; 17: 533–540. PubMedGoogle Scholar
9. Katsuki A, Sumida Y, Urakawa H, et al. Increased visceral fat and serum levels of triglyceride are associated with insulin resistance in Japanese metabolically obese, normal weight subjects with normal glucose tolerance. *Diabetes Care 2003*; 26: 2341–2344. Google Scholar
10. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual deaths attributable to obesity in the United States. *JAMA. 1999* Oct 27. 282(16):1530-8. [Medline].
11. Bays HE, Gonzales-Campoy JM, Bray GA, *et al.* Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther 2008*; 6: 343–368.CrossRefPubMedGoogle Scholar
12. Martin SE, Engleman HM, Deary IJ, Douglas NJ. The effect of sleep fragmentation on daytime function. *Am J Respir Crit Care Med 1996*; 153:1328–32.
13. Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep 1997*; 20:608–613.
14. Leung RS, Bradley DT. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med 2001*; 164:2147–2165.
15. Lavie P, Hoffstein V. Sleep apnea syndrome: a possible contributing factor to resistant hypertension. *Sleep 2001;* 24(6):721–725.
16. Apoor S. Gami, Virend K. Somers. Obstructive sleep apnea, metabolic syndrome and cardiovascular outcomes. *European Heart Journal 2004*; 25:709–711.
17. Coughlin S. Mawdsley, L., Mugarza, JA *et al.* Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J 2004*; 25:735–41.
18. Wilcox I, McNamara SG, Collins FL *et al*. "Syndrome Z": the interaction of sleep apnoea, vascular risk factors and heart disease. *Thorax 1998*; 53(Suppl 3):25–28.
19. Bonsignore MR, Eckel J. Metabolic aspects of obstructive sleep apnoea syndrome. *Eur Respir Rev 2009*; 18: 113–124. Google Scholar
20. Yin J, Gao Z, He Q, *et al*. Role of hypoxia in obesity-induced disorders of glucose and lipid metabolism in adipose tissue. *Am J Physiol Endocrinol Metab 2009*; 296: E333–E342. Google Scholar
21. Myers MGJ, Leibel RL, Seeley RJ, *et al*. Obesity and leptin resistance: distinguishing cause from effect. *Trends Endocrinol Met 2010*; 21: 643–651.CrossRefPubMedGoogle Scholar
22. Ambrosini G, Nath AK, Sierra-Honigmann MR, *et al.* Transcriptional activation of the human leptin gene in response to hypoxia. *J Biol Chem 2002*; 277: 34601–34609. Google Scholar
23. Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. *Circulation 2008*; 117: 3238–3249. Google Scholar
24. Nawrocki AR, Rajala MW, Tomas E, *et al.* Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *J Biol Chem 2006*; 281: 2654–2660. Google Scholar

25. Han SH, Sakuma I, Shin EK, *et al*. Antiatherosclerotic and anti-insulin resistance effects of adiponectin: basic and clinical studies. *Prog Cardiovasc Dis 2009*; 52: 126–140. CrossRefPubMedGoogle Scholar
26. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest 2006*; 116: 1793–1801. CrossRefPubMedGoogle Scholar
27. Varlamov O, Somwar R, Cornea A, *et al*. Single-cell analysis of insulin-regulated fatty acid uptake in adipocytes. *Am J Physiol Endocrinol Metab 2010*; 299: E486–E496. Google Scholar
28. Coughlin SR, Mawdsley L, Mugarza JA, *et al*. Obstructive sleep apnea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J 2004*; 25:735–41.
29. Lam JCM, Lam B, Lam CL, *et al.* Obstructive sleep apnea and the metabolic syndrome in community-based Chinese subjects in Hong Kong. *Resp Med 2006*; 100(6):980–87
30. Schwartz AR, Patil SP, Laffan AM, Polotsky VY, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanism and therapeutic approaches. *Proc Am Thorac Soc 2008*; 5(2):185–92.
31. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome: a new worldwide definition. *Lancet 2005*; 366:1059–1062.
32. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc 2008*; 5:136–43.
33. de Sousa AGP, Cercato C, Mancini MC, Halpern A. Obesity and obstructive sleep apnea. *Obes Rev 2008*; 9:340–54.
34. Peppard PE, Young T, Palta M, Dempsey J, Skareyd J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA 2000*; 284:3015–21.
35. Lam B, Sam K, Mok WY, *et al.* Randomised study of three non-surgical treatments in mild to moderate obstructive sleep apnoea. *Thorax 2007*; 62(4):354–59.
36. Börntorp P. Metabolic implications of body fat distribution. *Diabetes Care 1991*; 14:1132–43.
37. Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc 2008*; 5(2):207–17.
38. Ip MS, Lam B, Ng MMT, Lam WK, Tsang KWT, Lam KSL. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med 2002*; 165:670–76.
39. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and Type II diabetes: a population-based study. *Am J Respir Crit Care Med 2005*; 172:1590–95.
40. Anderson AJ, Sobocinski KA, Freedman DS, *et al.* Body fat distribution, plasma lipids and lipoproteins. Arteriosclerosis 1998; 8:88–94.
41. Newman AB, Nieto FJ. Relationship of sleep-disordered breathing to cardiovascular risk factors. The Sleep Heart Health Study. *Am J Epidemiol 2001*; 154:50–59.
42. Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in OSA. *J Clin Invest 1995*; 96:1897–1904.
43. Wolk R, Shamsuzzaman, Somers VK. Obesity, sleep apnea and hypertension. *Hypertension 2003*; 42:1067–74.
44. Pratt-Ubunama MN, Nichizaka MK, Boedefeld RL, *et al.* Plasma aldosterone is related to severity of obstructive sleep apnea subjects with resistant hypertension. *Chest 2007;* 131:453–59.
45. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of Type 2 diabetes. *Diabetes Care 2006*; 29:657–61.
46. Ip MS, Mokhlesi B. Sleep and glucose intolerance/diabetes mellitus. *Sleep Med Clin 2007*; 2:19–29.
47. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med 2004*; 1(3):e62.
48. Trayhurn P, Wang B, Wood IS. Hypoxia in adipose tissue: Bases for the dysregulation of tissue function in obesity? *Br J Nutr 2008*; 100:227–35.
49. Li J, Savransky V, Nanayakkara A, Smith PL, O'Donnell CP, Polotsky VY. Hyperlipidemia and lipid peroxidation are dependent on the severity of chronic intermittent hypoxia. *J Appl Physiol 2007*; 102:557–63.
50. Lam DCL, Xu A, Lam KSL, *et al.* Serum adipocyte-fatty acid binding protein (A-FABP) level is elevated in severe obstructive sleep apnea (OSA) and correlates with insulin resistance. *Eur Respir J 2009*; 33:346–51.

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