Obstructive Sleep Apne (OSA) and Metabolic Disorders

Dr. Nileena NKM, Dr. Pon Thelac, Dr. Lakshmi Ranganathan, Dr. Nagarajan Ramakrishnan

Nithra Institute of Sleep Sciences, Chennai

Introduction

Obstructive sleep apnea (OSA) is characterized by snoring, periods of partial or complete cessation of airflow, and multiple arousals that are often associated with non-refreshing sleep and excessive daytime sleepiness (EDS). The overall prevalence of adult OSA ranges from 9% to 38% and has been reported to be higher among men and the elderly[1]. Metabolic syndrome includes a group of abnormalities characterized by raised glucose levels, elevated blood pressure, high triglycerides and low levels of High-Density Lipoprotein cholesterol, and increased waist circumference. This syndrome, referred to as Syndrome X, frequently co-exists with sleep apnea and is collectively referred to as Syndrome Z[2]. OSA has independently been observed to be prevalent in adults with hypertension (HTN) and diabetes mellitus (DM)[3]. The associations were significantly strong that measures had been taken to modify treatment guidelines[4]. Despite literature supporting the detrimental effects of OSA on DM and HTN in an individual, underdiagnosis of OSA prevails even in tertiary care centers[3].

Obstructive Sleep Apnea and Diabetes Mellitus

Mechanisms

Various studies have investigated the potential mechanisms which influence the relationship between OSA and DM and have established bidirectionality. However, most of them focussed on the effect of OSA on DM rather than exploring the converse.

The two main characteristics of OSA that are responsible for the derangement of glucose metabolism are intermittent hypoxia (IH) and sleep fragmentation. They bring about their influence via various mechanisms such as activation of the sympathetic nervous system and hypothalamic-pituitary axis and changes in the inflammatory pathways[5]. There is a tilt in sympathetic-parasympathetic balance, causing an increase in insulin resistance through the following mechanisms

- Increased proinflammatory cytokines affecting pancreatic β-cells [5]
- Reduced conversion of proinsulin to insulin[6]
- Down regulation of adiponectin and an increase in resistin[6]

Increased levels of systemic inflammation and oxidative stress present in DM and diabetic neuropathy may impair neurochemical control of upper airway or respiratory muscles and predispose to OSA[7].

OSA and the Spectrum of T2DM

OSA can have a bearing on the whole timeline of the disease of T2DM, i.e., from its onset to the development of complications. Multiple studies[5,8] of both cross-sectional and longitudinal designs have established that OSA was associated with impaired glucose tolerance independent of underlying obesity and previous euglycemic status. A meta-analysis estimated that the risk for new-onset diabetes was increased by 63% in moderate to severe OSA[9]. Uncontrolled OSA not only affects glycemic control but also increases the risk for the development of both microvascular and macrovascular complications seen in diabetic populations[6,10].

Address for communication: Door # 29, Plot # 1997 J Block, 13th Main Road Annanagar, Chennai 600 040, India
Ph # +91 44 4350 2252 Email: ram@nithra.com

Effects of OSA Treatment on Glucose Metabolism

The impact of treatment of OSA on the glycemic profile has been evaluated in various studies. Prospective studies have shown that Continuous Positive Airway Pressure (CPAP) use significantly improved glycemic control[5], improved Oral Glucose Tolerance, and reduced 24-hour blood pressure compared to placebo[6]. Three months of regular CPAP treatment was required to elicit these influences[6].

Obstructive Sleep Apnea and Hypertension

The link between OSA and HTN has been established in various studies, and OSA is recognized as one of the causeof secondary hypertension. Studies also explored the possible underlying pathophysiology to explain the same.

Mechanisms

The pathophysiology of hypertension in OSA is complex and is dependent on various factors such as sympathetic tone, peripheral vasoconstriction, increased renin-angiotensin-aldosterone activity, and altered baroreceptor reflexes, as shown in figure 1 (Masoor Ahmad, 2017)[11]. The idea of reciprocal causality has been supported by experimental data in animals where acute BP (blood pressure) surges have been shown to increase upper airway obstruction. Accordingly, results have been demonstrated in humans where phenylephrine mediated rise in BP resulted in lower daytime genioglossus electromyographic activity. Potential mechanisms that can contribute to upper airway collapsibility include the inhibitory effect of baroreceptor activation on upper airway dilator muscle or a change in brain perfusion by an upsurge in mean arterial pressure[11].

Effect of OSA on Management of HTN

There is overwhelming evidence to support the detrimental effect of OSA on the management of HTN. The Wisconsin Sleep Cohort Study found a dose-response relationship with increasing OSA severity and incidence of HTN [12]. In addition, a cross-sectional study in Canada demonstrated that an

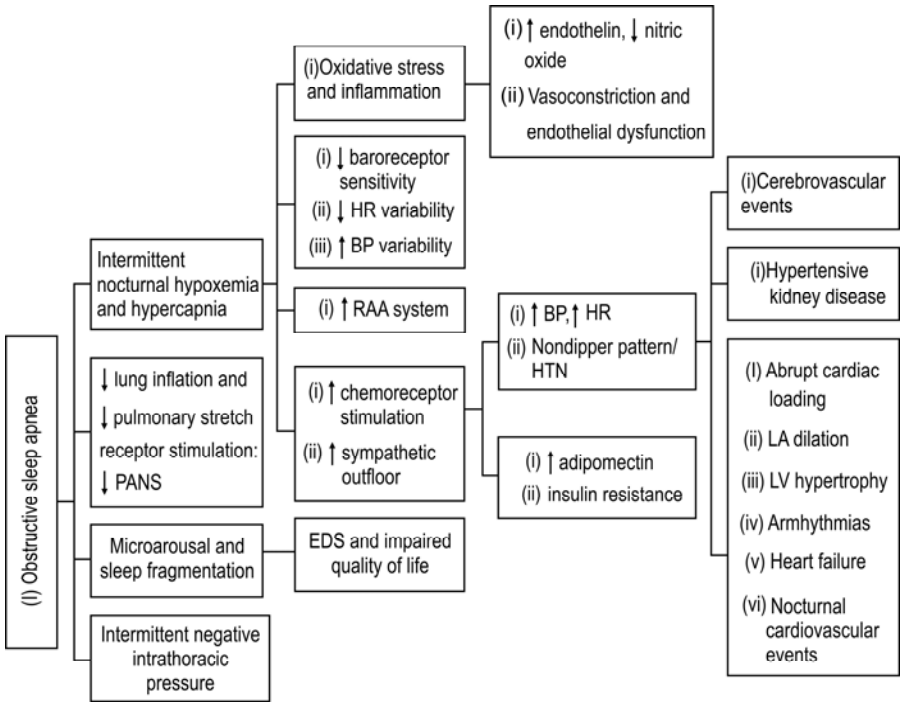

Figure 1 - Mechanisms linking OSA and HTN (Masoor Ahmad, 2017)11

increase in the AHI by one event/h was associated with a 1% risk of having hypertension. Though not many studies have been done to confirm, increased nocturnal blood pressure due to OSA has been postulated to cause increased cardiovascular complications[13]

Specific antihypertensive pharmacotherapy in OSA

B-blockers and aldosterone antagonists may be the best treatment options for hypertension in OSA patients. Aldosterone levels are generally normal in OSA except in patients with treatment-resistant hypertension or severe OSA. Various studies have investigated the association between resistant hypertension and OSA, and it was confirmed when Pratt-Ubunama et al. demonstrated that OSA was present in 85% of subjects with resistant HTN[14]. The aldosterone antagonist spironolactone has been very effective in decreasing the severity of OSA, especially in the case of resistant hypertension. Conversely, there has been some incriminating evidence advising against the use of ACE inhibitors in hypertensive OSA patients. Enalapril induced a dry cough and increased upper airway inflammation (measured by exhaled nitric oxide, a marker of airway inflammation), subsequently causing OSA exacerbation, all of which resolved following cessation of enalapril[11].

Effects of OSA Treatment on Hypertension

In a randomized study, three months of CPAP use was shown to cause a significant decrease in daytime, night-time, systolic, and diastolic BP in previously categorized prehypertensive patients with severe OSA[15]. A meta-analysis including 32 studies with regards to the effect of CPAP on hypertension revealed modest but significant reductions in diurnal and nocturnal SBP and DBP[16]. Numerous meta-analyses have demonstrated only a mild decrease in BP of about 1.3 to 3 mm Hg with CPAP. The extent of the fall in BP depended on numerous factors like CPAP, duration of treatment, use of CPAP during REM sleep, presence of daytime somnolence, baseline BP and severity of OSA. Patients with OSA of severe category, high BMI, untreated hypertension, nocturnal hypertension/non-dipper pattern, and resistant hypertension were found to benefit the most with CPAP therapy.

Chicken or EGG Situation

Despite the establishment of bidirectionality, temporality remains an enigma. This could be attributed to the presence of various shared risk factors like obesity, increasing age, male gender, raised triglycerides, waist circumference, and smoking[8,11]. Notably, greater BMI was associated with more morbidities in western countries. However, amongst Asians, visceral obesity and waist circumference correlated significantly with the development of OSA and insulin resistance.[8]

OSA and Dyslipidemia

Mechanisms

Repetitive episodes of apneas and hypopneas lead to a state of IH, which further alters a myriad of key biochemical processes like increasing gene expression of the hypoxia-inducible factor (HIF) with subsequent propagation of inflammation and an oxidative state. The catecholamine may modulate the activity of hormone-sensitive lipase (HSL) in the adipose tissue, leading to the breakdown of triglycerides (TG) into free fatty acids (FFA) and glycerol, which then will be resynthesized in the liver and form Very low-density lipoproteins (VLDL). Also, increased sympathetic nervous activity seen in OSA may decrease low-density lipoproteins (LDL) and TG clearance. Insulin resistance associated with OSA leads to decreased activity of LPL and subsequent formation of LDL subclass. Furthermore, Diet-induced dyslipidemia together with IH may lead to an upregulation

in lipid synthesis, as was shown in mouse models. [17]

GUT Microbiota causing metabolic Disease- A Possibility

Evidence suggests OSA can alter the gut microbiome (GM) and may promote OSA-associated co-morbidities, including diabetes, hypertension, and cognitive problems. Researchers from the University of Missouri School of Medicine and MU Health Care have discovered how OSA-related sleep disturbances affect the gut microbiome in mice and how transplanting those gut bacteria into other mice can cause changes to sleep patterns in the recipient mice. GM can influence health and sleep quality through the brain-gut microbiome axis (BGMA). Ongoing research is involved in the relationship between the brain and the gut to determine how changes in the gut microbiome can affect sleep structure and, in turn, how OSA can contribute to co-morbidities[17]

Clinical Implications of the Association between OSA and Dyslipidemia

An increased amount of nocturnal FFA was shown to be associated with accelerated cardiac disease progression in patients with OSA and concomitant heart failure. Most of the studies that have explored the effect of management of OSA on lipid profile have shown mixed results. Most of these studies have been of observational designs and were of a smaller sample size. These differences in research methodology and the studied population explains these conflicting results in clinical research on OSA and dyslipidemia[18].

Obstructive Sleep Apnea and Obesity

The relationship between OSA and obesity is probably the first link established between OSA and a metabolic disorder. Obesity is attributed to be one of the major risk factors for the development of OSA. OSA prevalence can amount to up to 45% among obese patients. A similar finding can be observed even among the pediatric and adolescent age group. As mentioned before, obesity seems to be one of the most frequently occurring shared risk factors among various metabolic disorders.

Mechanisms

Obesity through anatomic alterations predisposes to upper airway obstruction during sleep. Site of fat deposition, especially around the upper airway, trunk, and chest, can impart more influence than adipose tissue elsewhere. Obesity may contribute to upper airway collapsibility and reduced lung volumes (especially central obesity). Obesity may impair neuromuscular control as well[19,20].

The literature describes bidirectionality in this relationship between OSA and obesity. Sleep fragmentation in OSA may contribute to leptin insensitivity and increase ghrelin secretion, which stimulates appetite and thereby cause weight gain[19].

Clinical Implications of the Association between OSA and Obesity

Weight loss remains a major treatment modality for treating OSA. Controlled studies have inferred that a 10 to 15% reduction in body weight can result in approximately a 50% reduction in sleep apnea severity[21,22]. Behavioral therapies like a very low-calorie diet and supervised lifestyle interventions have shown mixed results. Economic feasibility, dropout rates may contribute to the same. Pharmacological interventions in the form of sibutramine have been tried with significant success, though inferior to that of CPAP. Though sibutramine did not bring significant reductions in AHI levels, it was associated with improved nocturnal oxygen levels. Surgical procedures including laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG), and laparoscopic biliopancreatic diversion have been studied and

showed significant improvement in OSA and sleep quality in addition to expected weight reduction. Review studies exploring the feasibility of surgical options in OSA with obesity inferred a resolution up to 80%.

While considering the bidirectionality, it seems reasonable to expect that management of OSA will cause weight loss through improved physical activity and reduced daytime somnolence. However, the results of a meta-analysis[23] that elucidated the impact of CPAP on weight loss were rather counter-intuitive. Various hypotheses have been formulated to explain the same.

- CPAP increases slow-wave sleep, which is associated with anabolism
- Patients with OSA tend to eat calorie-dense foods
- Effect of CPAP on leptin mechanism, though controversial, may promote weight gain

So, we can conclude that management of OSA and obesity should invariably include weight loss management

Recognition and Management of OSA in Clinical Practice

OSA is a commonly underdiagnosed entity even in tertiary care centers[3]. Asking relevant clinical history can help in narrowing down the high-risk patients. The presence of nocturnal symptoms such as snoring, choking, dryness of throat, nocturia, and/or diurnal symptoms like intense sleep inertia, morning headaches, excessive daytime sleepiness, fatigue, mood swings, or cognitive disturbances as elicited by the patient or their family member can help in suspecting comorbid OSA. STOPBANG questionnaire, Berlin questionnaire, and/or Epworth Sleepiness Score[24] are some validated tools that the physicians can use to screen patients presumed to have OSA and decide on the need for referring to sleep specialists for focused evaluation and further management

The evaluation includes Polysomnogram, simply referred to as a sleep study, which could be of different levels based on the number of parameters measured. Although, attended PSG in sleep lab (Level 1) is considered to be the gold standard, Level III or Home Sleep Testing (HST) involving fewer parameters can produce comparable results and might be the only feasible option in a resource-limited setting, especially in the present pandemic scenario. The diagnosis and severity stratification of OSA depends on the AHI, which is the average number of abnormal breathing events per hour of sleep, which is derived from the PSG. An individualized approach is necessary depending on the severity, clinical presentation, comorbidities, and maxillofacial profile. Behavioral approaches (like improving sleep hygiene, dietary habits, and exercise), surgical options (maxillofacial surgery or bariatric surgery), and oral appliances are considered along with the PAP (Positive Airway Pressure) therapy, which is the first line of treatment. The decision with regards to treatment modality is a shared one, and it is important to educate the patient with regards to the compliance and long-term consequences if left untreated. Also, the primary physician should be aware of the increased perioperative risk in case the patient requires surgery as all metabolic disorders along with OSA can influence the perioperative prognosis[25]. The need for regular PAP use, at least two weeks before a planned surgical procedure, apart from improvement of metabolic profile and the necessity to continue the therapy post-operatively, has to be emphasized as well.

Conclusion

OSA is common and, when unrecognized, can have a detrimental impact on the overall prognosis and management of metabolic disorders. It is imperative that physicians educate themselves with regards to OSA so that they can screen patients

effectively and refer them appropriately. They can also play a major role in monitoring their compliance to PAP therapy and/ or other behavioral modifications. It is crucial that every diabetes clinic has a protocol aiding in diagnosing and treating comorbid OSA so that holistic care and better quality of life are provided.

References

1. Senaratna C V, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC (2017) Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev 34:70–81
2. Castaneda A, Jauregui-Maldonado E, Ratnani I, Varon J, Surani S (2018) Correlation between metabolic syndrome and sleep apnea. World J Diabetes 9:66–71
3. Tentu A, Singh S, Singh S, Singh N, Dash C, Singh V, Laxmivandana R, Warrier R (2020) Association of metabolic syndrome in obstructive sleep apnea patients: An experience from zonal tertiary care hospital in Eastern India. Indian J Respir Care 9:71
4. (2018) Correction to: 2017 {ACC}/{AHA}/{AAPA}/{ABC}/{ACPM}/{AGS }/{APhA}/{ASH}/{ASPC}/{NMA }/{PCNA} Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart . Hypertension. https://doi.org/10.1161/hyp.0000000000000076
5. Pamidi S, Tasali E (2012) Obstructive Sleep Apnea and Type 2 Diabetes: Is There a Link? Front Neurol. https://doi.org/10.3389/fneur.2012.00126
6. Doumit J, Prasad B (2016) Sleep Apnea in Type 2 Diabetes. Diabetes Spectr 29:14–19
7. Bottini P, Redolfi S, Dottorini ML, Tantucci C (2008) Autonomic Neuropathy Increases the Risk of Obstructive Sleep Apnea in Obese Diabetics. Respiration 75:265–271
8. Tahrani AA (2017) Obstructive sleep apnoea in diabetes: Does it matter? Diabetes Vasc Dis Res 14:454–462
9. WANG XIA, BI Y, ZHANG Q, PAN F (2012) Obstructive sleep apnoea and the risk of type 2 diabetes: A meta-analysis of prospective cohort studies. Respirology 18:140– 146
10. Viswanathan V, Ramalingam IP, Ramakrishnan N (2017) High Prevalence of Obstructive Sleep Apnea among People with Type 2 Diabetes Mellitus in a Tertiary Care Center. J Assoc Physicians India 65:38–42
11. Ahmad M, Makati D, Akbar S (2017) Review of and Updates on Hypertension in Obstructive Sleep Apnea. Int J Hypertens 2017:1–13
12. Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective Study of the Association between Sleep-Disordered Breathing and Hypertension. N Engl J Med 342:1378–1384
13. Phillips C, O'Driscoll (2013) Hypertension and obstructive sleep apnea. Nat Sci Sleep 43
14. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA (2007) Plasma Aldosterone Is Related to Severity of Obstructive Sleep Apnea in Subjects With Resistant Hypertension. Chest 131:453–459
15. Drager LF, Pedrosa RP, Diniz PM, Diegues-Silva L, Marcondes B, Couto RB, Giorgi DMA, Krieger EM, Lorenzi-Filho G (2011) The Effects of Continuous Positive Airway Pressure on Prehypertension and Masked Hypertension in Men With Severe Obstructive Sleep Apnea. Hypertension 57:549–555
16. Montesi SB, Edwards BA, Malhotra A, Bakker JP (2012) The Effect of Continuous Positive Airway Pressure Treatment on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Sleep Med 08:587–596
17. Mirrakhimov AE, Ali AM (2013) Pathobiology of Obstructive Sleep Apnea-Related Dyslipidemia: Focus on the Liver. {ISRN} Cardiol 2013:1–5
18. Barros D, Garc\'\ia-R\'\io F (2018) Obstructive sleep apnea and dyslipidemia: from animal models to clinical evidence. Sleep. https://doi.org/10.1093/sleep/zsy236
19. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK (2010) Interactions Between Obesity and Obstructive Sleep Apnea. Chest 137:711–719
20. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL (2008) Obesity and Obstructive Sleep Apnea: Pathogenic Mechanisms

and Therapeutic Approaches. Proc Am Thorac Soc 5:185–192

21. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, Smith PL (1991) Effect of Weight Loss on Upper Airway Collapsibility in Obstructive Sleep Apnea. Am Rev Respir Dis 144:494–498
22. SMITH PL (1985) Weight Loss in Mildly to Moderately Obese Patients with Obstructive Sleep Apnea. Ann Intern Med 103:850
23. Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Bensenor IM, Lotufo PA (2014) Effects of {CPAP} on body weight in patients with obstructive sleep apnoea: a metaanalysis of randomised trials. Thorax 70:258–264
24. Amra B, Rahmati B, Soltaninejad F, Feizi A (2018) Screening Questionnaires for Obstructive Sleep Apnea: An Updated Systematic Review. Oman Med J 33:184–192
25. Candiotti K, Sharma S, Shankar R (2009) Obesity, obstructive sleep apnoea, and diabetes mellitus: anaesthetic implications. Br J Anaesth 103:i23--i30