ORIGINAL RESEARCH PAPER

Pulmonary Medicine

COMORBIDITIES ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA : AN OVERVIEW

KEY WORDS:

Deepanjali Sharma* Jr. Resident, Department of Respiratory Medicine, IMS, BHU, Varanasi (UP), India *Correspondence Author

J. K. Mishra Prof. & Head of Department of Respiratory Medicine, IMS, BHU, Varanasi (UP), India

Deepak Shah Assistant Professor of Department of Respiratory Medicine, IMS, BHU, Varanasi (UP), India

Introduction:
Obstructive sleep apnea (OSA) is a potentially disabling chronic condition characterized by disruptive snoring, partial or complete recurrent upper airway obstruction during sleep, resulting in periods of apnea, oxyhemoglobin desaturation, and frequent night awakenings with excessive daytime sleepiness as a consequence, reducing performance at work and in social activities.

Obstructive Sleep Apnea (OSA) and Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) are two subsets of Sleep-related breathing disorders and together termed as Obstructive Sleep Apnea Syndrome (OSAS).

OSAS is a far more common problem in today's world than generally believed with the rise of lifestyle diseases in epidemic proportions. In the Indian population where life style related morbidity rates are increasing also has a very large population with undiagnosed OSA and OSAHS. [1] According to Indian studies obstructive sleep apnea (OSA) varies from 4.4% to 13.7% and OSAHS from 2.4% to 2.8% in general population, where as the global prevalence of OSA varies from 0.3 % to 5.1% only. Studies from India have also shown male predominance over females with the prevalence of OSA 4.4 % to 19.7% and 2.5% to 7.4%. [2,3].
The prevalence of OSA among obese patients has been reported to exceed by 30 per cent and 60-90 per cent of adults with OSA are overweight and the relative risk of sleep apnea from obesity with a BMI >30 kg/m^2 may be as great as 10 per cent. [4]

The most common symptoms of OSA include loud snoring, breathing pauses and choking episodes during sleep, sleep fragmentation, excessive daytime sleepiness, headache at awakenings and progressive deterioration of attention and memory [5]

The term 'Apnea' is defined as a reduction in the airflow signal by 80% or greater with persistent respiratory effort lasting 10 seconds or longer and 'Hypopnea' as a reduction in the airflow signal by 30% or greater with persistent respiratory effort lasting at least 10 seconds associated with a desaturation of 4% or greater. [6] As hypopnoeas lead to the same clinical consequences as apneas, the apnoea-hypopnoea index (AHI) or respiratory disturbance index (RDI) is widely used for the diagnosis and the assessment of the severity of OSA. The AHI refers to the mean number of apnoeas or hypopneas per hour of sleep [7].

OSA is defined as apnea-hypopnea index (AHI) > 5 that is more than five episodes per hour of cessation of breathing for at least 10 seconds on an overnight polysomnographic study [6] and the severity of sleep apnoea can be graded as mild sleep apnoea when AHI: 5 to 15 events per hour, moderate sleep apnea when AHI: 15 to 30 events per hour and severe sleep apnea, AHI greater than 30 events per hour [8]

Sleep is a major buffer for hormonal release, glucose regulation and cardiovascular functions [4].

Short sleep duration and poor quality of sleep, increasingly common in our modern society, have many effects on our endocrine and metabolic functions. During respiratory events there is a fall in oxygen saturation, causing activation of the baroreflex, triggering a response of the sympathetic nervous system, dysregulation of the hypothalamus-pituitary axis, adrenergic discharge leading to tachycardia and hypertension peaks, long-term dysfunction of the baroreflex, systemic inflammation, and metabolic dysregulation with insulin resistance. This process repeats itself many times during sleep in apneic patients [9].

Comorbid conditions associated with OSA include hypertension, atrial fibrillation, congestive heart failure, stroke, metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, erectile dysfunction in men, hypercoagulable states and platelet dysfunction giving rise to pulmonary embolism, deep vein thromboses etc. These comorbidities are associated with increased mortality compared with the general population of the same age group [10].

These adverse consequences result in significant burden on public health care by generating a high financial and social impact. However, awareness regarding diagnostic options, management and consequences of untreated comorbities with OSA remains inadequate

OSA and Metabolic Syndrome:
Metabolic syndrome is characterized by five variables - hypertension, insulin resistance or glucose intolerance, low serum high-density lipoprotein cholesterol, elevated serum triglyceride and abdominal obesity. Subjects meeting three of these five criteria are classified as having metabolic syndrome .OSA is independently associated with metabolic syndrome. Dysregulation of the hypothalamus-pituitary axis due to chronic intermittent hypoxia and sleep deprivation with sleep loss may play a role in triggering inflammation leading to metabolic syndrome. Obesity, particularly central adiposity, is a potent risk factor for sleep apnea. [11] Subjects with OSA have a proinflammatory state, a prothrombotic state, hyperleptinemia, hypoadiponectinemia, hyperuricemia, endothelial dysfunction and microalbuminuria, all of which promote development of metabolic syndrome. [12]

OSA and Cardiovascular Dysfunction:
The mechanisms by which OSA increases the risk of cardiovascular diseases include intermittent hypoxia, sleep fragmentation, sleep deprivation, which causes sympathetic activation, increase of reactive oxygen species, activation of inflammatory pathways, and prothrombotic factors.[10,13]

OSA is a systemic disease that causes an increase in inflammatory cytokines, like C-reactive protein (CRP), tumor necrosis factor A (TNF-A) and interleukin-6 (IL-6)[14-16]. Increased sympathetic activity, oxidative stress, systemic inflammation, endothelial dysfunction, metabolic dysregulation and intrathoracic pressure changes during OSA are contributory factors for cardiovascular consequences in OSA [17]. Many risk factors of OSA (age, male gender and obesity) are also risk factors for cardiovascular disease.

Association with conditions like diabetes mellitus and hypertension are known to increase the risk for cardiovascular disease. The prevalence of cardiac arrhythmias and coronary heart disease (CHD) are higher in patients with severe OSA (RDI >30) [18] Bradyarrhythmias are also reported in OSA and can occur with a structurally normal heart. Effective CPAP therapy has been shown to attenuate bradyarrhythmias and reduces risk of sudden death. [19, 20, 21]

There is a close link between OSA and heart failure by their close association with aging and obesity. The Framingham study has shown that increasing BMI is directly correlated with incident heart failure and may be mediated in part by OSA [22]. Incident atrial fibrillation, an important risk factor for heart failure, is also associated with the degree of oxyhemoglobin desaturation in OSA [22-24]. Repetitive upper airway closure in OSA can have deleterious effects on cardiac function. With the addition of CPAP for 1 month, it has been shown that treatment of coexisting OSA by CPAP reduces systolic BP and improves left ventricular systolic function in medically treated patients with heart failure [25]. In patients with congestive heart failure and OSA receiving 3 months of CPAP, it has been shown that there is significant improvements in left ventricular ejection fraction and reductions in urinary catecholamines.

OSA and Systemic Hypertension:

OSA increases the relative risk of hypertension; independent of other confounding factors [26].A link also has been established between sleep-disordered breathing to chronically elevated BP [27]. Disordered breathing during sleep has been found to be associated with acute peripheral vasoconstriction and rise in BP during sleep[28].Several studies showed that reduction in nocturnal O_2 saturation increased the likelihood of developing hypertension[29] .There is probably a risk factor for hypertension and consequent cardiovascular morbidity in the general population[27].CPAP has been shown to acutely attenuate sympathetic drive and nocturnal BP in OSA[30].Studies from uncontrolled and highly selected populations have suggested improvement in BP control with CPAP [31].

OSA & stroke

It has been observed that modest-to-severe levels of sleep apnea are associated with an approximately threefold increased risk of ischemic stroke in men [32]. The risk of mortality from stroke increases proportionately with OSA severity [33]. It is also feasible that stroke may itself predispose to sleep-disordered breathing. Apneic events of OSA have been found to be associated with reduced cerebral blood flow and this predisposes to thrombosis [34]. The higher rates of atrial fibrillation observed in subjects with OSA have reported an increase in the risk of embolic events in such patients. It has been observed that sleep apnea occurs frequently after stroke and CPAP treatment has been found to improve neurological recovery after stroke [35, 36]. It is further reported that CPAP treatment reduces excess risk of mortality in patients with moderate-to-severe OSA and acute ischemic stroke [37].

Neurocognitive & PsychiatricAbnormalities:

Low oxygen saturation levels during apneic events, severe sleep fragmentation, and excessive daytime sleepiness lead to increased risk of development of mental disoreders like anxiety, depression, psychosis etc in subjects with OSA.

Neurocognitive consequences include decrease in alertness, memory deficit, reduced vigilance, impaired executive function, psychomotor speed deficits, increased risk for automobile and occupational accidents and decreased quality of life [38]. This impairment in cognitive functions in OSA patients has been found due to consequent reductions in gray matter volume of left hippocampus and right frontal gyrus. Significant improvement in gray matter of these areas has been seen following treatment with CPAP for 3 months [39, 40].

Psychomotor speed deficit has also been observed in moderate-to-severe OSA [41]. Studies have demonstrated a decline in learning abilities [42]. Executive functions that are found to be impaired in OSAS are mental flexibility, planning, analysis, synthesis and organizational skills [43, 44] and semantic language deficits [45,46]. CPAP treatment is found to be effective in improving some cognitive functions (memory and psychomotor speed) [47]. Although higher executive functions and verbal fluency may not improve following treatment with CPAP [48]

OSA and Other Complications

It has been reported that there is a high prevalence of erectile dysfunction in OSA patients. The mean nocturnal oxygen saturation was independently associated with erectile dysfunction suggesting that intermittent nocturnal hypoxia observed in OSA contributes to the development of erectile dysfunction [49].Treatment with nasal CPAP has been found to resolve erectile dysfunction resulting in improvement in quality of life [50]. It was observed that abdominal aortic aneurysm is highly prevalent in OSA and there was further expansion of abdominal aortic aneurysm in patients with severe OSA [51]. Several studies have also shown that sleep-disordered breathing was associated with deep vein thrombosis and pulmonary embolism in patients with OSA, and this association was independent of established risk factors for thrombosis [52]. The prevalence of GastroEsophaegeal Reflux Disease (GERD) in OSA patients is significantly higher than the general population. Recent studies have shown that treatment with a continuous positive airway pressure (CPAP) device significantly reduces the symptoms of GERD and the exposure of acid pH in the esophagus as well as improves the number of awakenings and apnea indexes [53].

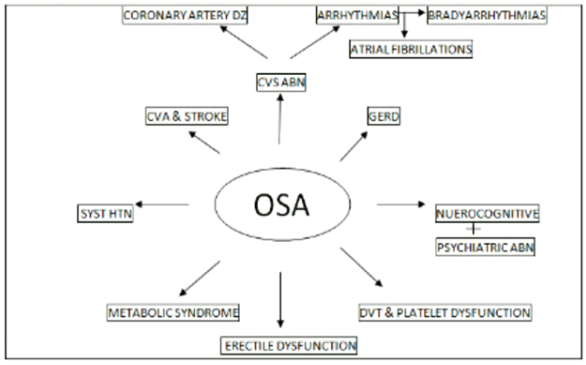

FIG1-1: Above figure demonstrates the various comorbidities associated with Obstructive Sleep Apnea

Conclusion:

Obstructive sleep apnea (OSA)-induced biological changes include intermittent hypoxia, intermittent hypercapnia, intrathoracic pressure changes, sympathetic activation and sleep fragmentation. These biological changes lead to oxidative stress, systemic inflammation, metabolic dysregulation, and hypercoagulation and neurohumoral changes.

There is a close relationship of OSA, obesity and metabolic syndrome leading to increased cardiovascular morbidity and mortality.

OSA has been reported to increase the risk for systemic hypertension, pulmonary vascular disease, ischemic heart disease, cerebral vascular disease, congestive heart failure and arrhythmias. However, a causal relationship is difficult to establish as many risk factors of OSA are also known risk factors of cardiovascular diseases.

OSA, if untreated, is associated with increased cardiovascular mortality in both men and women. There is significant reduction in mortality in both when OSA is treated with continuous positive airway pressure.

Patients with risk factors for sleep apnea should be properly investigated, since the failure to identify the sleep disorder may contribute to therapeutic failure in the treatment of comorbidities. Recent years have noticed an increased awareness of OSA with an explosion of research publications in this field but the diagnosis of OSA is based on expensive polysomographic studies are lacking in many institutes in India. A cost-effective diagnostic test is required to diagnose this condition in a large number of patients. There is

also a need to identify other modalities of treatment. Close interaction of basic, clinical and public health scientists are essential to unravel many of the unknown features of OSA to provide quality care to patients.

Randomized interventional studies with adequate follow-up and longitudinal studies, in future, shall answer many of the controversial issues in OSA.

REFERENCES:

1. Prasad CN. Obstructive Sleep Apnea Hypopnea Syndrome – Indian scenario. Perspectives in medical research 2013; 1: 22-25
2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002; 165:1217-39.
3. Sharma SK, Ahluwalia G. Epidemiology of adult obstructive sleep apnea syndrome in India. Indian J Med Res 2010; 131: 171-5.
4. Jamie C.M. Lam & Mary S.M. Ip. Sleep & the metabolic syndrome.Indian J Med Res 2010; 131(2): 206-16.
5. Patil SP, Schneider H, Schwartz AR, et al. Adult obstructive sleep apnea. Pathophysiology and diagnosis. Chest 2007;132:325-37
6. Parish JM; Adam T; Facchiano L. Relationship of Metabolic Syndrome and Obstructive Sleep Apnea. J Clin Sleep Med 2007;3(5):467-72.
7. American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine task force. Sleep 1999; 22: 667-89
8. Alfred P. Fishman, MD, Jack A. Elias, MD, Jay A. Fishman, MD,Text book of Fishman's Pulmonary Diseases and Disorders. Fourth Edition, New York: McGraw-Hill; 2008. p.1679-735.
9. Jennum P, Sjřl A. Epidemiology of snoring and obstructive sleep apnoea in a Danish population, age 30-60. J Sleep Res 1992;1(4): 240–244
10. Galletti F, Barbato A, Versiero M, Iacone R, Russo O, Barba G, et al. Circulating leptin levels predict the development of metabolic syndrome in middle-aged men: An 8-year follow-up study.JHypertens 2007;25:1671.
11. Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. Am. J. Physiol. Heart Circ. Physiol. 279(1), H234–H237 (2000).
12. Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. Proc. Am. Thorac. Soc. 5(2), 207–217 (2008).
13. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, Oda N, et al. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:625-30.
14. Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. Lancet Respir Med 2013;1(4):329–338
15. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab 1997;82(5):1313–1316
16. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998;83(3):847–850
17. Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. Eur. Respir. J. 8(7), 1161–1178 (1995).
18. Mehra R, Benjamin EJ, Shahar E et al. Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. Am. J. Respir. Crit. Care Med. 173(8), 910–916 (2006).
19. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am. J. Cardiol. 52(5), 490–494 (1983).
20. Marin JM, Carrizo SJ, Vicente E, Agusti AG. 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(9464), 1046–1053 (2005).
21. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. Ann. Intern. Med. 156(2), 115–122 (2012).
22. Kenchaiah S, Evans JC, Levy D et al. Obesity and the risk of heart failure. N. Engl. J. Med. 347(5), 305–313 (2002).
23. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am. J. Respir. Crit. Care Med. 160(4), 1101–1106 (1999).
24. Gami AS, Hodge DO, Herges RM et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J. Am. Coll. Cardiol. 49(5), 565–571 (2007).
25. Kaneko Y, Floras JS, Usui K et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N. Engl. J. Med. 348(13), 1233–1241 (2003).
26. Nieto FJ, Young TB, Lind BK et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 283(14), 1829–1836 (2000).
27. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N. Engl. J. Med. 342(19), 1378–1384 (2000).
28. Golbin JM, Somers VK, Caples SM. Obstructive sleep apnea, cardiovascular disease, and pulmonary hypertension. Proc. Am. Thorac. Soc. 5(2), 200–206 (2008).
29. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ320(7233), 479–482 (2000).
30. Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure: a placebo trial. Hypertension 35(1 Pt 1), 144–147 (2000).
31. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 359(9302), 204–210 (2002).
32. Redline S, Yenokyan G, Gottlieb DJ et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am. J. Respir. Crit. Care Med. 182(2), 269–277 (2010).
33. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N. Engl. J. Med. 353(19), 2034–2041 (2005).
34. Netzer N, Werner P, Jochums I, Lehmann M, Strohl KP. Blood flow of the middle cerebral artery with sleep-disordered breathing: correlation with obstructive hypopneas. Stroke 29(1), 87 93 (1998).
35. Minnerup J, Ritter MA, Wersching H et al. Continuous positive airway pressure ventilation for acute ischemic stroke: a randomized feasibility study. Stroke 43(4), 1137–1139 (2012).
36. Bravata DM, Concato J, Fried T et al. Continuous positive airway pressure: evaluation of a novel therapy for patients with acute ischemic stroke. Sleep 34(9), 1271–1277 (2011).
37. Martínez-García MA, Soler-Cataluńa JJ, Ejarque-Martínez L et al. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. Am. J. Respir. Crit. Care Med. 180(1), 36–41 (2009).
38. Beebe DW, Groesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep 26(3), 298–307 (2003).
39. Canessa N, Castronovo V, Cappa SF et al. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am. J. Respir. Crit. Care Med. 183(10), 1419–1426 (2011).
40. Thomas B, Rice1 TB, Strollo PJ, Morrell MJ. Update in sleep medicine. Am. J. Respir. Crit. Care Med. 18, 1271–1274 (2012).
41. Felver-Gant JC, Bruce AS, Zimmerman M, Sweet LH, Millman RP, Aloia MS. Working memory in obstructive sleep apnea: construct validity and treatment effects. J. Clin. Sleep Med. 3(6), 589–594 (2007).
42. Décary A, Rouleau I, Montplaisir J. Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. Sleep 23(3), 369–381 (2000).
43. Lau EY, Eskes GA, Morrison DL, Rajda M, Spurr KF. Executive function in patients with obstructive sleep apnea treated with continuous positive airway pressure. J. Int. Neuropsychol. Soc. 16(6), 1077–1088 (2010).
44. Saunamäki T, Jehkonen M, Huupponen E, Polo O, Himanen SL. Visual dysfunction and computational sleep depth changes in obstructive sleep apnea syndrome. Clin. EEG Neurosci. 40(3), 162–167 (2009).
45. Andreou G, Agapitou P. Reduced language abilities in adolescents who snore. Arch. Clin. Neuropsychol. 22(2), 225–229 (2007).
46. Lim W, Bardwell WA, Loredo JS et al. Neuropsychological effects of 2-week continuous positive airway pressure treatment and supplemental oxygen in patients with obstructive sleep apnea: a randomized placebo-controlled study. J. Clin. Sleep Med. 3(4), 380–386 (2007).
47. Sánchez AI, Martínez P, Miró E, Bardwell WA, Buela-Casal G. CPAP and behavioral therapies in patients with obstructive sleep apnea: effects on daytime sleepiness, mood, and cognitive function. Sleep Med. Rev. 13(3), 223–233 (2009).
48. Ferini-Strambi L, Baietto C, Di Gioia MR et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res. Bull. 61(1), 87–92 (2003).
49. Budweiser S, Enderlein S, Jörres RA et al. Sleep apnea is an independent correlate of erectile and sexual dysfunction. J. Sex. Med. 6(11), 3147–3157 (2009).
50. Gonçalves MA, Guilleminault C, Ramos E, Palha A, Paiva T. Erectile dysfunction, obstructive sleep apnea syndrome and nasal CPAP treatment. Sleep Med. 6(4), 333–339 (2005).
51. Mason RH, Ruegg G, Perkins J et al. Obstructive sleep apnea in patients with abdominal aortic aneurysms: highly prevalent and associated with aneurysm expansion. Am. J. Respir. Crit. Care Med. 183(5), 668–674 (2011).
52. Arzt M, Luigart R, Schum C et al. for the working group 'Circulation and Sleep' of the German Society of Sleep Research and Sleep Medicine (DGSM). Sleep-disordered breathing in deep vein thrombosis and acute pulmonary embolism. Eur. Respir. J. 40(4) 919–924 (2012).
53. Shepherd KL, James AL, Musk AW, Hunter ML, Hillman DR, Eastwood PR. Gastro-oesophageal reflux symptoms are related to the presence and severity of obstructive sleep apnoea. J Sleep Res 2011;20(1 Pt 2):241–249