IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 5 Ser.8 (May. 2021), PP 01-07
www.iosrjournals.org

Association between Obstructive Sleep Apnea and Vascular Diseases; Literature Review

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Abstract
The relationship between sleep diordered breathing (SDB) and stroke not only opens a multidisciplinary area of research for patient care for Cardio-Cerebro-Vascular disorders but also understanding the association between brain-heart-lung in both normal and disease functions. Obstructive sleep apnea (OSA) is an independent risk factor among Hypertension (HTN), Atrial Fibrillation (AF), Type 2 Diabetes Mellitus (T2DM), Stress, smoking, use of alcohol and obesity in aggravating known vascular diseases as reported by many studies. We attempted to review the available published data to outline that how cardio-pulmonary pathophysiological processes are affected by OSA leading to the high prevalence of both cardiovascular and cerebrovascular comorbidities and mortality rates. We learned that OSA by influencing the cardiovascular disease (CVD) risks, directly or indirectly increases the risk of stroke and impaired cognitive outcomes, and bi-directionally stroke can aggravate the sleep disordered breathing. As the OSA is associated with pathogenesis of cerebrovascular disease, therefore early screening and diagnosis of OSA can be helpful in preventing the serious consequences of cerebrovascular conditions. Clinical management with CPAP therapy and behavior therapy plays an important role in significant therapeutic outcomes of OSA measured by reduction in apnea-hypopnea index (AHI). Future directions are towards working on biological markers i.e. Matrix metalloproteinase-9 (MMP-9) and identifying the various other phenotypes. MMP-9 may be a target for development of selective inhibitors as adjuvant treatment of OSA to reduce cardiovascular and cerebrovascular comorbidities and thus mortality.
Databases: *Google scholar, PubMed*
Keywords: *obstructive sleep apnea, stroke, cardiovascular disease, comorbidities*

Date of Submission: 07-05-2021 Date of Acceptance: 22-05-2021

I. Introduction

The relationship between Sleep disordered breathing (SDB) and stroke opens not only a multidisciplinary area of research for patient care for Cardio-Cerebro-Vascular disorders but also understanding the relation between brain-heart-lung in both normal and disease functions. In adults OSA aggravate the comorbid cardiovascular and cerebrovascular disorders and the patients with CVD showed high prevalence of OSA as reported by various studies (1-3). Sleep disordered Breathing (SDB) may be obstructive sleep apnea (OSA) or central sleep apnea (CSA) or mixed apnea i.e. loss of respiratory efforts and obstruction which causes cessation of airflow due to absence of respiratory efforts and blockage in upper airways.

Apnea; is a condition when inspiration gets stopped for 10seconds or more during a respiratory cycle.

Hypopnea; is about 30% or more reduction in inflow of air and thus dropping oxygenation and arousal from sleep.

Apnea – Hypopnea Index (AHI); is observation of apnea-hypopnea per hour.

Respiratory cycle; regulatory brainstem center generates signals that travel through peripheral nerves to activate the respiratory muscles and negative intrathoracic pressure is developed for airway patency. It is reported that in susceptible patients the obstruction in airways can be due to relaxation of genioglossus muscle that makes fall of tongue within the pharynx posteriorly (4). Yet clear understanding of airway obstruction is required to establish individualized treatment guidelines

Signs and Symptom of SA; during sleep the signs and symptoms may include snoring, witnessed apnea, gasping, insomnia or disturbed and non-refreshing sleep. While in day time signs and symptoms may be morning headache, sleepiness, loss of concentration, memory disorders, mood swings and sexual dysfunction.

Diagnosis of Sleep Apnea; Polysomnography and repetition of polysomnography according to clinical picture of the patients is the diagnostic criteria of SDB (5). Although the diagnostic efficiency of portable home sleep apnea testing (HSAT) devices is lower than full night or repetitive polysomnography, but these are economical

and useful alternatives to measure heart rate, oximetry, chest and abdominal plethysmography, arterial tonometry and nasal pressure.

Clinical Prediction Tools; Different questionnaires like Berlin Questionnaire, STOP-BANG Questionnaire, Epworth Sleepiness Scale and STOP Questionnaire are used to evaluate the OSA in out-door patients in follow up visits and monitoring. These are helpful in quick assessment of the treatment effectiveness and useful adjunctive in screening and diagnosis of OSA with polysomnography. These questionnaires include inquiry of information regarding different signs and symptoms of OSA and allied cardiovascular disorders e.g. snoring, daytime sleepiness, hypertension, apnea or choking, obesity, age, neck size and gender (6).

II. Association Between Osa And Vascular Diseases

Underlying Mechanism

OSA adversely affects almost all body organs thus over-all health and quality of life. The Oxidative stress, inflammation, sympathetic activation, endothelial dysfunction, neuro-hormonal changes, thrombophilia, and hemodynamic changes are the underlying mechanisms linked with respiratory dysfunction during sleep and result in worsening of health conditions and poor quality of life **(7).**

There is a link between cardiovascular diseases and sleep disorders particularly obstructive sleep apnea (OSA) because sleeping disorders like apnea or hypopnea adversely affect the cardiovascular physiology due hypoxemia, sympathetic activity, acute and pulmonary systemic hypertension and decreased stroke volume.(8). Moreover myocardial ischemia is associated with respiratory events and apnea can trigger transient ischemic attacks (TIA). It is known that different cardiovascular events occur after awakening.

OSA by influencing the CVD risks, directly or indirectly increases the risk of stroke, and bi-directionally stroke can aggravate the sleep disordered breathing as reported by (9). Data suggested that OSA is associated with pathogenesis of cerebrovascular disease and therefore early screening and diagnosis of OSA can be helpful in preventing the serious consequences of cerebrovascular conditions.(10-13)

Discussion

The prevalence of cardiovascular diseases is high all over the world, therefore, along with development of treatment strategies the focus on minimizing the risk factors are equally important to prevent the detrimental cardiovascular events that end up in morbidities and mortality. (6). Tietjens et al., also suggested various treatment options for clinical management of OSA patients with CVD. In contrast (14, 15) showed that findings of RCTs couldn't favor the idea that treating OSA can significantly improve the cardiovascular events. This may be attributed to the fact that diagnosis and treatment of OSA may have different effects on various cardiovascular events. Still further studies required. Most of the cardiovascular diseases may be linked with sleep disorders in middle age and elderly population (16).

Vascular diseases associated with OSA

Following vascular diseases are associated with OSA in one way or other:-

Hypertension; Data demonstrated the direct association of resistant hypertension with severity of OSA, therefore, diagnosis and treatment of OSA is very important to prevent cardiovascular morbidity and mortality (17).

Pulmonary Hypertension (PH); OSA and PH are also strongly associated because apneic – hypopnic episodes during sleep play critical role in pathophysiology of pulmonary hypertension. Longer hypoxia can irreversibly increase the pulmonary vascular resistance and thus the OSA is linked with high mortality in patients with severe PH (18).

Heart Failure; Some studies reported high prevalence of CSA compared to OSA in patients with HF (19, 20), however, both forms coexist in significant number of patients where one form acts as dominant phenotype. Polysomnography is the preferred diagnostic option in these patients. OSA is associated with HF, and OSA is more prevailing in patients with HF than general population. A study showed that ventricular function and cardiac injury can be predicted by the severity of OSA. There was observed statistically significant association between grades of diastolic dysfuntion variables and severity grades of OSA. This study concluded severe grades of OSA are strongly associated with higher grades of diastolic dysfuntion and circulating levels of cardiac biomarkers. Furthermore, vicious cycles of frequent apnea or hypoxemia are associated with recurrent myocardial injury that increase the risk of HF espacially diastolic dysfuntion in patients with OSA (21).

Atrial Fibrillation; Like OSA, AF is also common and the prevalence of OSA in patients of AF is considerably high as reported by data. It has been observed that both these conditions are independently associated, may be due to changes in activity of autonomic nervous system during sleep and sleep apnea-hypopnea episodes. A cohort of black and white adults was selected to determine the association of OSA risk and AF in Reasons for Geographic And Racial Differences in Stoke (REGARDS) Trial. It was found that high risk of OSA was associated with prevaling AF among blacks (22).

Arrythmias; There is also association between arrhythmias and OSA. OSAS is prevailing in western countries. Marti-Almor et al. reviewed published data to assess that whether, OSAS is one of the triggering factor of arrhythmia and increases the CVD and mortality. There is lack of evidence by interventional RCTs to establish that treatment of OSAS can reduce the cardiac arrhythmias, which are triggered by repetitive hypoxemia, hypercapnia, acidosis, intrathoracic pressure fluctuations, re-oxygenation and arousals during apnea and hypopnea. There are recommendations for early diagnosis and treatment to prevent morbidities and reduce mortality (23)**.**

Coronary Artery Disease (CAD) and Cerebrovascular Disease; Altered sympathetic activity, oxidative stress, resistant hypertension, endothelial dysfunction and metabolic dysregulation are pathophysiologic processes attributed to coronary artery disease (CAD) and cerebrovascular disease. OSA with Cerborvascular disease (CVD) is highly prevailing (61.9%). This is thought that proper diagnosis and treatmet may prevent and reduce the risk of cerebrovascular issues in patients with OSA (24).

Stroke; OSA by influencing the CVD risks, directly or indirectly increases the risk of stroke, and bi-directionally stroke can aggravate the sleep disordered breathing as reported by (9). Data suggested that OSA is associated with pathogenesis of cerebrovascular disease and therefore early screening and diagnosis of OSA can be helpful in preventing the serious consequences of cerebrovascular conditions.(10-13) Lipford et al. observed that there is strong a association between OSA and Cardio-embolic (CE) Stroke and also evaluated the causes of ischemic stroke in OSA and how to prevent risk of recurrence of stroke in OSA patients (25).

In a review article McDermott and Brown reported that there is reasonable physiological link between sleep apnea (pre, post and wakeup stroke) and stroke. This article presented recent work for last 18months. Among all kinds poststroke apnea is the most prevailing and attributed to worse outcomes and recurrences of stroke about two times. Physiological tests are required for diagnosis of sleep apnea and the role of CPAP treatment is yet, to be established (26).

Wake up Stroke (WUS); Schutz et al. evaluated the association between OSA and WUS i.e. stroke after awakening from sleep. This large, population based stroke cohort study showed that onset of stroke during sleep is not linked with preexisting OSA. Of 30% participants, showed WUS and the prevalence of WUS was same in participants with and without OSA and WUS was not associated with OSA in men or women (Schütz et al., 2021). In a meta-analysis, Xiao et al. presented that their results showed patients with WUS were more prone to have severe SDB thereby presenting respiratory effects. This was recommended that potential surfferers of stroke should be managed clinically and be given treatment for serever sleep apnea syndrome (SAS) (27).

As both OSA and Stroke have same risk factors (like obesity, HTN, alcohol use and T2DM), there is complex bidirectional relationship between them, although not clearly understood, because interventional studies in this context are rare (9); but following are important clinical considerations:-

1. SDB should be considered in prevention of primary and secondary stroke.
2. Detrimental effects of stroke may be avoided by treatment of SDB.

Ischemic Stroke; OSA contributes as not only a predisposing but also as a trigger of ischemic stroke events. Already existing symptoms of OSA may cause WUS. OSA should be treated to prevent stroke (28).

Vascular Dementia; Culebras and Anwar reported that, of 17% and 9%, 50-70yrs men and women respectively, are affected by SA syndrome that increases the risk of HTN, stroke, MI, AF and associated with Vascular dementia. This is recommended that proper treatment may reduce the effects of risk factors of stroke and progression of subcortical ischemic vascular disorder (29).

Perioperative Risk; If the perioperative management of comorbid OSA not succeeded, then it increases the postoperative risks of respiratory complications. Preoperative and Perioperative management of comorbid OSA is necessary as it not only increases the risks of respiratory complications but also the cardiac complications including AF, after the surgery (30).

Metabolic Syndrome; Data from different controlled studies showed an independent association of OSA with metabolic dysfunction that is linked with CVD consequences. These studies reported effectiveness of CPAP therapy in the management of OSA that improved sensitivity of insulin (31-33).

III. Recommendations

Tietjens et al., recommended that as the OSA is highly prevalent in patients with CVD the sleep apnea should be screened in these patients and managed clinically by using questionnaires and diagnosis by polysomnography in high risk CVD patients followed by suitable treatment of OSA (6).

Treatment of OSA

The patients with cardiovascular disease and also have AHI 5 or above (mild OSA i.e. 5-15 AHI) with sleep apnea or patients with AHI 15 or above (moderate i.e. 15-30 AHI) with or without CVD require medical treatment for OSA. Severe OSA is indicted by AHI above 30. Beneficial effects of OSA treatment on comorbidities are still uncertain, but recent reports emphasize to focus on careful assessment (symptoms and

particular organ damage) of comorbid conditions while selecting treatment for OSA in particular ype of population with OSA e.g. female, elderly due to different pathophysiologic and clinical presentation (34, 35)
The review of Tietans et al highlights following treatment options;

1. **Positive airway pressure (PAP);** first line therapy of OSA is PAP that is reported to improve the AHI, day time sleepiness and quality of life. PAP therapy can be continuous PAP (CPAP) or bi-level PAP (BiPAP). CPAP is preferred modality in OSA while BiPAP is useful in OSA patients with hypoventilation syndrome and in patients who cannot tolerate CPAP and in some cases of CSA.

The pneumatic splinting of upper airways that reduces obstruction and apnea is the underlying mechanism of PAP therapy. Manual titration of PAP to relieve airway obstruction and to maintain tolerance of patient is also employed.

In a meta-analysis Baessler et al demonstrated that CPAP therapy is effective in treating OSA by reducing the biomarkers like interleukin-6, C-reactive protein and tumor necrosis factor – α (TNF) (36). Further, CPAP treatment reduces the chatecholamines which are increased due to OSA. This was observed that withdrawal of CPAP reversed the high levels of chatecholamines (37) in OSA patients.

CPAP treatment can prevent the recurrence of stroke and improves recovery form stroke at 6-12month follow-up. Good CPAP adherence involves careful selection of the patients, manual CPAP titration and close follow ups. (38). Further, Brill et al. in a meta-analysis reported in a review that Most of the RCTs concluded that CPAP treatment is beneficial in neurological recovery, once the treatment is tolerated by the patient with SDB (39).

A study analyzed the effects of CPAP treatment in patients with OSA. Patients were approached with questionnaire about Cardiovascular events and CPAP treatment. The OSA patients without CPAP treatment significantly suffered from more cardiovascular events as compared to CPAP treated OSA patients (2.66 hazard ratio, partially adjusted for age, AHI and smoking). Therefore, treatment with CPAP in patients with OSA can reduce the cardiovascular events (14, 40)

2. **Behavior therapy or Life Style Modifications;** it has been reported that behavioral therapy comprises of weight control or loss through medicines or surgery and reducing use of alcohol and sedatives (Benzodiazepines, opiates, CNS depressants). This has been reported in different studies that life style changes significantly reduce the risks of cardiovascular events and reduction in AHI in OSA patients.

Chirinos et al. suggested that progressive inflammatory processes are directly linked with grade of obesity and this is the inflammatory state due to chronic intermittent hypoxia in OSA patients that causes vascular damages (41).

Prevention (controlling obesity) and treatment (CPAP therapy) of OSA may prevent and reduce damaging effects of stroke and recurrence of cardiovascular events and improve other comorbid conditions in high risk patients, espacially in Asian population and in developing countries compared to USA (42)

The AHI and body mass index (BMI) can be correlated, because the increase in levels of biomarkers as a result of hypoxia is linked with macrophages of adipose tissues and this relationship synergizes the effects of OSA. Therefore, weight control as adjuvant of CPAP therapy is more effective in treating OSA (41)..

3. **Positional Therapy;** can be used as adjunctive of OSA treatment. The supine position during sleep makes more reduction in airway, therefore positioning device is used to maintain non supine position during sleep as reported in different studies that positioning is significant in normalizing AHI.

4. **Mechanical Devices;** these devices increase the cross sectional area at velopharynx and oropharynx in upper airway and thus decrease apneic episodes during sleep and AHI. e.g. mandibular advancement device an tongue retaining device. These devices are preferred when patients cannot tolerate PAP therapy.

5. **Surgical Intervention;** obstruction in upper airway (nasal, upper and lower pharyngeal or global) can be removed by surgery. Surgical procedure can be primary therapy in anatomic obstruction and considered as secondary line in patients who cannot tolerate PAP therapy and mechanical devices.

IV. Future Directions

Although OSA and CVD are linked together but even randomized trials could not demonstrate treatment strategies to improve these comorbid conditions. Therefore, need is still there for further studies in this area. The current data indicates the impact of diagnosis and therapy of OSA that differs for particular allied disease processes. Thus, the need is for more advanced and specific clinical guidelines for solving this prevailing problem.

- **Biological Marker of OSA and cerebro-cardio vascular problems**

Like other factors OSA is also strongly associated with events linked with cardiovascular and cerebrovascular problems. The identification and development of biomarkers may allow for clinically significant treatment strategies to reduce cardiovascular consequences of OSAS. Matrix metalloproteinase-9 (MMP-9) being biological marker and inflammatory mediator is a potential messenger between OSA and comorbidities caused by OSA. Levels of MMP-9 and its endogenous inhibitors were found higher in OSA, HTN, MI and Post MI HF.

Therefore, MMP-9 may be a target for development of selective inhibitors as adjuvant treatment of OSA to reduce cardiovascular and cerebrovascular comorbidities and thus mortality (43)

- **Phenotype determination**

The OSA Phenotypes were divided on the basis of clinical symptoms, biomarkers and experimental data driven approach. But still various clinical phenotypes are unrevealed e.g. OSA in pre- and post- menopausal women, race and ethnic differences. Also the phenotyping body position and sleep architecture may affect vascular disease differently and provide interventional strategies in positional therapy. OSA subtypes may respond differentially to treatment. The evaluation of OSA phenotypes at risk for stroke and CVD may provide framework for future clinical trials with the aim to reduce morbidity and mortality. Novel genetics and biomarkers are important for further advances in determining the complex underlying association in different populations (44).

ABBREVIATIONS

AHI; Apnea-Hypopnea Index
COPD; Chronic Obstructive Pulmonary Disease
CPAP; Continuous Positive Airway Pressure
CVD; Cardio Vascular Disease
HF; Heart Failure
HTN; Hypertension
MI; Myocardial Infaraction
MMP-9; Matrix metalloproteinase-9
OSA; Obstructive Sleep Apnea
OSAS; Obstructive Sleep Apnea Syndrome
PAP; Positive Airway Pressure
SA; Sleep Apnea
SAS; Sleep Apnea Syndrome
SDB; Sleep Disordered Breathing
T2DM; Type 2 Diabetes Mellitus
WUS; Wake up Stroke
RCTs; Randomized Control Trials
TIA; Transient Ischemic Attack
ORs; Odd Ratios

Aknowledgements

I would like to to express my sincere gratitude to my supervisor doctor Cheng Chu (Neurology Department, Affiliated Hospital of Yangzhou University) for her guidance, support and encouragement in my time of writing this paper.

CONFLICT OF INTEREST

There are no conflicts of interest.

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Salman Mohamud Nur, et. al. "Association between Obstructive Sleep Apnea and Vascular Diseases; Literature Review."*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(05), 2021, pp. 01-07.