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REVIEW ARTICLE

Sleep Disturbance and the Risk of Cardiovascular Diseases

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Abstract

In many observational studies, cardiovascular diseases as well as metabolic dysfunction have been identified as major manifestations of sleep disorders. Several mechanisms have been proposed to explain this association. In addition to the discoveries of interconnected mechanisms, a novel therapeutic approach needs to be explored. This review attempts to develop a better understanding of future research by examining the inter-relationship between sleep disorders and cardiovascular risk factors.

Keywords: Sleep disturbance, Sleep apnea, Insomnia, Cardiovascular diseases, Arrhythmias

Introduction

In order to maintain overall health and well-being, adequate restful sleep is crucial. However, it has become increasingly difficult to obtain 'restful sleep' due to the prevalence of sleep disorders across the globe. Sleep disorders are a cluster of conditions that affect the ability to sleep well on a regular basis and consequently cause significant impairments in physiological, social and occupational functions. Several examples of sleep disorders include insomnia, sleep-related breathing disorders, hyper-somnolence, and parasomnias.[1] The inability to perform a variety of neurocognitive tasks (learning and memory, logical reasoning, and mathematical calculations) is a very real and documented consequence of sleep disorders. Several studies in recent years suggest that there are prominent factors that contribute to sleep deprivation and/or poor-quality sleep leading to the risk of developing metabolic and cardiovascular disorders/ diseases (CVDs). The understanding of sleep as a multidimensional concept is important for better prevention and treatment of CVDs.[2-4] The physiological process of sleep is intimately linked with CVDs and other health outcomes through intermediate pathways. The activity of the autonomic nervous system is crucial for maintaining cardiovascular health and varies with sleep stage. While sympathetic activity peaks during rapid eye movement (REM) sleep, parasympathetic activity peaks during N3 of sleep (slow-wave sleep). An autonomic rhythm requires regular transitions between sleep stages without excessive arousals or fragmentation.[3] Sleep disturbances lead to changes in circadian rhythms, blood pressure, heart rate, insulin sensitivity, fluid, and electrolyte balance. Several risk factors for cardiovascular disease are affected by abnormal circadian variability. Sleep disordered breathing is common in people with, or at risk of, CVDs and those with obesity , hypertension, coronary disease, heart failure, or atrial fibrillation.[5] In case of obstructive sleep apnea, intermittent hypoxemia and fluctuations in intra-thoracic pressure lead to an increased risk of CVDs cardiovascular disease by triggering endothelial dysfunction, oxidative stress, and systemic inflammation.[6] Sleep disorders indirectly affect cardiovascular health by affecting behavioral and psychological factors such as diet, physical activity, stress, and depression[7]. From the animal studies to

large human epidemiological studies, obstructive sleep apnea (which has a prevalence rate of 4-14% among various populations) is associated with an increased prevalence and incidence of systemic hypertension.[2,8] The dose-dependent association was also observed between sleep apnoea severity and risk of developing hypertension, obesity, and insulin resistance. People with abnormal sleep durations and obstructive sleep apnea (OSA) are more likely to develop coronary artery disease and stroke. In further observational studies, treating OSA was associated with lower rates of CVDs and mortality.[9] Recent data linking sleep with CVDs and other chronic disease conditions provides a strong foundation to integrate sleep health issues with cardiovascular abnormalities and risk factors in critical research areas. Accordingly, the current review attempts to find out the correlation between CVD risk and suboptimal sleep.

3.1 Impact of sleep duration on CVDs and other co-morbidities

3.1.1. Ischemic heart diseases

Despite using different methodologies, several studies involving large populations concluded that short sleep duration (5-6 h a night) is more likely to increase the risk of ischemic heart disease (IHD) and stroke than a normal rest period (6-8 h a night). Among short sleepers, the average increase in IHD and stroke risk was 48 and 15%, respectively. [10] In a meta-analysis of total 67 research studies, Jiawei et al.,[11] found a U-shape relationship between sleep duration and incidences of coronary artery diseases and stroke. Compared with 7 h per day, an hour decrease was associated with 6%, 6%, 7%, and 5% increased risk of all-cause mortality (6%), total CVD (6%), coronary artery disease or CHD (7%), and stroke (5%), respectively. Comparatively, an hour increase in sleep duration was associated with 13, 12, 5, and 18% increase in the afore mentioned risks, respectively.

3.1.2. Arrhythmias

A REM sleep-related sympathetic surge is associated with nocturnal arrhythmias. In response to sympathetic overactivity, the heart rate and blood pressure increase, resulting in endothelial dysfunction through platelet aggregation and plaque formation (atherosclerosis). Disrupted plaques may release proarrhythmic factors. If metabolic demands are elevated during sleep, then neural overactivity may result in arrhythmias. There is a decrease in 'Hypocretin' (hypothalamic neuropeptides) synthesis causing an increased production of monocytes and accelerating plaque formation[12]. According to a meta-analysis, Negar et. al.[13] concluded that both longer and shorter sleep durations were associated with increased risk of arrhythmias, with shorter sleep durations being the highest risk.[13] Experiments have shown that sleep deprivation can reduce the left atrial early diastolic strain rate in healthy adults. According to heart rate variability studies, atrial arrhythmias (10-25%) result from excessive vagal activity triggered by increased adrenergic activity. Hypertension without nocturnal fall in blood pressure often is associated with arrhythmias.[14]

3.1.3. Hypertension

Nighttime sleep results in a reduction in blood pressure (10%) compared to daytime wakefulness (also referred to as the nocturnal dip in blood pressure). It is possible to consider the non-dipping pattern of circadian variation as a sign of hypertension as it raises the overall blood pressure throughout the day. Certain sectional studies have consistently and significantly linked sleep duration (less than 5 h per night) to hypertension risk. In the sleep heart health study (n = 6132), the prevalence of hypertension was 59, 62, and 67% in mild, moderate, and severe sleep apnea, respectively.[15] In a study conducted in elderly men, short sleep was found to be an independent predictor of hypertension. wherein, a significant reduction in the slow wave sleep phase (a restorative phase of sleep) was observed.[16] Hypertension is related with activation of the sympathetic nervous system, stimulation of the renin-angiotensin-aldosterone system and impairment of endothelial function. The high prevalence of obstructive sleep apnea in the general population, hypertensive patients and especially obese individuals and patients resistant to antihypertensive therapy, highlights the need for effective screening, diagnosis and treatment of obstructive sleep apnea to decrease cardiovascular risk.[17] Moreover, the subgroup studies indicate that

prevalent hypertension is associated with short sleep durations among women (over 65 years of age) and East Asians.[18] Despite its association with CVDs, longer sleep duration does not appear to have a significant impact on blood pressure.[16]

3.1.4. Weight gain

In cross-sectional studies, sleep duration and weight gain have been examined. A meta-analysis of 17 studies found that a reduction in 1 h of sleep per day is associated with an increase in body mass index (BMI) of 0.35 kg/m^2. Although longitudinal studies are fewer in number, the results suggest that short duration of sleep can predict body weight gain independent of baseline weight and covariates. A longitudinal study by Chaput et.al.[19] also noted weight gain with longer sleep duration.

3.1.5. Type 2 diabetes mellitus

Abnormal sleep durations are associated with metabolic disruptions that lead to glucose intolerance and hyperglycemia. Shorter sleep durations cause acute changes in metabolism. However, prolonged sleep restriction alters the circadian rhythm, resulting in a lower metabolic rate and ultimately hyperglycemia.[20] The direct relationship between restricted sleep and altered molecular pathways is well established in clinical and experimental studies. In the first study of its kind, researchers observed a 30% reduction in the *in-vivo* phosphorylation process in adipocytes (resulting from reduced insulin response) after four nights of sleep deprivation.[21] Studies conducted in populations around the world indicated that individuals who sleep less than 6 h/ night have 28% increased risk of developing type 2 diabetes as compared to those who sleep 6 to 8 h/ night.[22]

3.2. Impact of poor sleep quality on CVDs and other co-morbidities

Obstructive sleep apnea that affects 15% of the population is the most common sleep disorder while others are irregular sleep patterns, somnolence when sleep occurs outside the sleep – wake cycle.[3]

3.2.1. Ischemic heart diseases

As evident by the good prognosis of CVDs (after treating obstructive sleep disorders), the prevalence of obstructive sleep apnea is higher in those with coronary artery diseases (CADs), arrhythmias, and CVDs. Some key triggering factors for CVDs in patients with sleep breathing disorders are intermittent hypoxia (IH), sleep fragmentation and intra-thoracic pressure swings. The impact of IH on CVD development is mediated through systemic inflammation, sympathetic stimulation, and metabolic dysfunction.[23] In a large Spanish cohort study, the long-term cardiovascular outcomes of patients with varying degrees of sleep disordered breathing were compared. Sleep disordered breathing (SDB) is a term used to describe patterns of nocturnal breathing disturbances that cause ventilatory abnormalities such as hypoxemia and hypercapnia. It includes obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoventilation, and Cheyne-Strokes breathing (CSB)[24] In a cohort of 1651 individuals, untreated OSA patients were significantly linked with fatal and non-fatal cardiovascular diseases.[25]

A clinic-based longitudinal study conducted by Peker et al.,[26] for a period of 7 years showed an increase in CAD in middle aged OSD patients. Compared to normal sleep, OSA was found to be associated with almost a five-fold increase in the risk of developing CADs. OSA is often associated with severe nocturnal angina that can be reversed by continuous positive airway pressure (CPAP).

3.2.2. Arrhythmias

As there are several other confounding factors associated with OSA which cannot be controlled, it is difficult to define the prevalence and incidence of arrhythmias after the onset of OSA. Despite this, few studies have rigorously examined this association. Up to 50% of OSA patients suffer from nocturnal arrhythmias. In an early study, Guilleminault et al.[27] found that 48% of OSA cases had nocturnal arrhythmias and conduction abnormalities. The association of OSA with cardiac arrhythmias has been reported in numerous clinical studies since then.[28] The authors found that nocturnal hypoxia was a strong independent predictor of atrial fibrillation (AF) in individuals younger than 65 years of age who did not initially have AF. An observational study reported that the risk of recurrence of AF after

successful treatment is 82% higher in those who have not been treated for OSA.[29]

3.2.2. Hypertension

Many observational studies have found a correlation between sleep disorders, main OSA, and the increased risk of hypertension. An observational study of 4 years duration found that mild OSA subjects were twice as likely to develop hypertension as normotensive subjects. The overall 24 h ambulatory blood pressure profile is also affected by sleep breathing disorders. These include higher daytime and nighttime blood pressure, no dipping pattern, and a higher morning surge. A recent meta-analysis study of 1562 OSA patients revealed that 59.1% of them had nocturnal non-dipping blood pressure, which is a risk factor for developing hypertension later in life.[30] There is a bidirectional relationship between the abnormal blood pressure profile of ambulatory blood pressure monitoring and OSA. Genta-Pereira et al.[31] and colleagues have demonstrated that individuals with reverse dipping patterns (systolic blood pressure ratio >1.0) were four times more likely to suffer from OSA.

3.2.3. Weight gain

Emerging evidence indicates that OSA and obesity are linked in two ways. According to a recent study on OSA alone, prevalence rates rise to 20% and 7% for mild and moderate to severe OSA for individuals with a body mass index (BMI) of 25–28 kg/m^2, respectively. Overweight contributes directly to the development of OSA as OSA produces obesity. In obese people, leptin levels are higher, which have negative effects on respiratory drive. Weight gain alters upper airway anatomy and function, reduces resting load volumes, and reduces the amount of oxygen that reaches the lungs.[32] Although findings from CPAP studies are inconsistent, treating OSA for obesity has been found beneficial and gaining attention of clinicians.[33]

3.2.4. Type 2 diabetes

Type 2 diabetes is a common risk factor and co-morbid condition associated with CVDs. OSA patients are more likely to suffer from type 2 diabetes, which has a prevalence of 15-30%. In order to quantify the impact of OSA on the development of diabetes, polysomnography and respiratory polygraphy studies have been conducted. Between mild and severe OSA, the HbA1c ranges between 0.5 and 3.7%.[34] Studies have assessed the therapeutic utility of treating OSA in the management of diabetes mellitus. Of seven such studies, two showed a 0.4% decrease in HbA1c after CPAP treatment was implemented for six months in OSA patients. Mokhlesi et al. reported in another study that CPAP induced significant decreases in blood glucose levels after a week.[35]

3.3 Putative biological linking mechanisms

The reviewed literature indicates different mechanisms explaining why CVDs and associated risk factors are more prevalent in people with abnormal sleep patterns.

a. Endothelial dysfunction: The endothelial lining of the blood vessel is exposed to any kind of physical or chemical alteration. Endothelial cells secrete nitric oxide (NO) into the surrounding vascular smooth muscle cells in order to maintain vascular homeostasis. As a result of endothelial dysfunction, there is reduced vasodilation, increased vasoconstriction, and increased prothrombotic properties. The Trondelag health study (HUNT studies 2 & 3) explored the connection between insomnia and endothelial dysfunction. It has been found that insomnia is a significant risk factor for myocardial ischemia. There were certain symptoms of insomnia found to be gender-related, such as the inverse association between endothelial dysfunction and women, and the opposite for men. In contrast, partial sleep deprivation has consistently been associated with decreased vasodilation. Covassin et al,[36] observed a decrease in flow-mediated dilation (FMD) during sleep deprivation in a controlled study. Similarly, reduced FMD was observed in shift workers as compared to their normal day baseline. Flow-mediated dilatation (FMD) is a commonly used noninvasive measure of endothelial function. Decreased FMD is a significant symptom of insomnia.[37] The development of endothelial dysfunction has been ascribed to a variety of mechanisms including inflammation, growth factors and adhesion molecules.[38] Furthermore, it has been reported that microvascular endothelial function is affected by obstructive sleep apnea syndrome

(OSAS) predominantly through increased oxidative stress, and treatment of OSAS may improve endothelial function mainly by reducing oxidative stress.[39]

b. Autonomic imbalance: Sleep apnoea patients have elevated levels of catecholamines in plasma and urine, suggesting hyperactivity of the sympathetic nervous system. Furthermore, pharmacological, and surgical blockade of the sympathetic nervous system can eliminate the increase in blood pressure. In addition to repeated apneic and hypopneic cycles, hypercapnia is believed to increase sympathetic activity mediated by chemoreceptor reflexes. By up-regulating the renin-angiotensin system and down-regulating nitric oxide synthases, sympathetic overdrive is most frequently observed as a result of elevated blood pressure. The presence of cardiovascular dysfunction in sleep disorder patients is thought to be a result of hypertension in advanced stages.[40]

c. Inflammation: Recent observational studies have shown elevated levels of inflammatory markers, including c-reactive proteins, adhesion molecules, and IL-8, along with the severity of the apnea-hypopnea index. Further, some studies have found decreased levels of TNF-a and IL-6 following CPAP treatment. Numerous mechanisms have been proposed for linking systemic inflammation to cardiovascular abnormalities. By causing an increase in inflammatory cytokines, inflammation causes endothelial dysfunction, which leads to hypertension and CVDs.[41]

d. Hypercoagulability: Sleep deprivation and fragmentation may contribute to elevated levels of Von Willebrand factor, which may be indicative of a prothrombotic state. Patients with OSA present higher levels of pro-coagulant factors such as fibrinogen, activated clotting factors and platelet activities. Through plaque formation and endothelial dysfunction, hypercoagulability plays an important role in the development of cardiovascular diseases.[42]

e. Other hormonal influences: sleep disorders have been shown to increase obesity, which has been linked to CVDs. It has been suggested that the presence of obesity, a CVD risk factor, in sleep disorder patients is due to an increased level of leptin and ghrelin, and a decrease in adiponectin. In addition to their effects on appetite control, calorie intake, and inflammatory reactions, these hormones also affect body weight. In terms of the patho-physiology of the association of sleep with diabetes, some researchers have found that intermittent hypoxia coupled with sleep restrictions can lead to a dysregulation of insulin sensitivity and glucose metabolism. Overactivity of sympathetic neurons and parasympathetic withdrawal are the most likely causes of glucose intolerance. The state of inflammation may also contribute to insulin resistance. For example, monocyte chemoattractant protein-1 levels are elevated in OSA, which may be involved in the pathogenesis of insulin resistance.[43]

3.4. Future perspectives: Use in therapeutics

The findings of the observational studies cited above suggest that cardiovascular disorders risk factors closely correlate with sleep disorders. Optimum sleep could be the target of future interventional studies to treat CVDs. Positive airway pressure technique has some hemodynamic effects and may lower cardiac preload and afterload, so it may be used with pharmacological therapies to treat CVDs. Although the existing data is too limited to be applied in clinics, some exciting findings have shown the scope of future interventional studies.

Conclusion

By treating sleep disorders, it is possible to reduce the risk of cardiovascular diseases (CVD), hypertension, diabetes, and obesity which may occur as a result of sleep disorders. It is, however, necessary to explore more amounts of clinic-based data in order to be able to apply knowledge in a way that offers optimal benefits to patients.

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