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Cardiometabolic Effects of Obstructive Sleep Apnea and Treatment Effects of Oral Appliance: An Updated Review for Dentists

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Obstructive sleep apnea (OSA) is a relatively common, but greatly underdiagnosed sleep-related breathing disorder, characterized by recurrent collapse of the upper airway during sleep. OSA has been associated with a variety of cardiometabolic disease, such as hypertension, coronary artery disease, cardiac arrhythmia, cerebrovascular disease and metabolic dysfunction. Neurocognitive impairment, including excessive daytime sleepiness, increased risk of motor vehicle accidents, is also related to OSA. Sleep fragmentation and related arousals during sleep lead to intermittent hypoxia, sympathetic activation, oxidative stress, systemic inflammation and metabolic dysregulation which provide biological plausibility to this pathologic mechanism. Extensive studies demonstrated that OSA is a modifiable risk factor for the above mentioned diseases and oral appliances (OAs), although continuous positive air pressure (CPAP) is a first-line therapy of OSA, are not inferior to CPAP at least in mild OSA, and may be an alternative to CPAP in CPAP-intolerant subjects with OSA. The goal of this article is to provide a current knowledge of pathologic link between OSA and cardiovascular disease, focusing on intermittent hypoxia, sympathetic activation, oxidative stress and metabolic dysregulation. Then, previous epidemiologic studies will be reviewed to understand the causal relationship between OSA and cardiovascular disease. Finally, the effects of OAs will be updated via recent meta-analyses compared to CPAP.

Key Words: Cardiovascular; Mandibular advancement device; Obstructive sleep apnea; Oral appliance

INTRODUCTION

The third edition of the International Classification of Sleep Disorders-3 identified seven major categories consisting of insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, cardiac rhythm sleep-wake disorders, sleep-related movement disorders, parasomnias, and other sleep disorders (Table 1).[1] Among them, obstructive sleep apnea (OSA) is one of the major phenotypes of sleep-related breathing disorders (Table 2). In terms of mechanical view, OSA is a disease associated with manifestation of ever-increasing resistance to airflow in upper airway cause by intermittent collapse of the upper airway during sleep.

As consequences of repetitive obstruction of airflow, the diagnosis of OSA requires either signs/symptoms (associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnea) or associated medical (hypertension [HTN], coronary artery disease [CAD], arterial fibrillation, congestive heart failure, stroke, diabetes) or psychiatric disorder (cognitive dysfunction, or mood disorder) coupled with five or more predominantly obstructive respiratory events per hour of sleep during polysomnography (PSG).[2] Alternatively, a frequency of obstructive respiratory events ≥15/h satisfies the criteria.

OSA is a common health problem that affects 3% to 7%

Table 1. Seven major sleep disorders categorized by ICSD-3

Diagnostic section
Insomnia
Sleep-related breathing disorders
Central disorders of hypersomnolence
Circadian rhythm sleep-wake disorders
Parasomnias
Sleep-related movement disorders
Other sleep disorders

ICSD, International Classification of Sleep Disorders.

Table 2. Sleep-related breathing disorders

Disorder
Obstructive sleep apnea disorders
Central sleep apnea syndromes
Sleep-related hypoventilation disorders
Sleep-related hypoxemia disorder

of the adult population aged 30 to 70 years in western countries.[3] In Korea, Kim's epidemiologic study[4] that used PSG found that the prevalence of sleep-disordered breathing (SDB, apnea-hypopnea index, AHI ≥5) was 27% and 16% in men and women aged 40 to 69 years.[4] When OSA was defined by an AHI ≥5 and excessive daytime sleepiness, its prevalence was 4.5% in men and 3.2% in women.[4] However, OSA still remains greatly underdiagnosed.[5] This prevalence is likely to increase because of increasing obesity and the aging population.[6] Undiagnosed and untreated OSA may lead to a variety of cardiometabolic disorders. Long-term observation study confirmed a clear association between OSA and cardiovascular disease.[7]

The dentist should have a sound understanding of systemic effect of untreated OSA in order to effectively diagnose and treat OSA.

In this review, intermediate mechanisms underlying the systemic effects of OSA on cardiovascular disease (CVD) will be described and epidemiological evidence supports such a relation also be discussed. Finally, the treatment effects of oral appliance (OA) on CVD will be updated.

UNDERLYING MECHANISM OF OSA FOR CARDIOVASCULAR DISEASE

1. Intermittent Hypoxia

Unique characteristic pattern of OSA is a repetitive episodic hypoxia followed by reoxygenation. Animal studies of Fletcher's group[8,9] have shown that intermittent hypoxia associated with recurrent upper-airway obstruction leads to a significant increase in blood pressure (BP) that that is dependent on peripheral carotid chemoreceptors. This was independent of hypercapnia. Exposure to intermittent hypoxia for 2 weeks also elevated daytime BP and sympathetic activity of healthy subjects.[10] The renin-angiotensin system might be a possible explanation for secondary surge in BP on exposure to intermittent hypoxia. Fletcher's animal[11] experiment demonstrated that sustained alteration in the renin-angiotensin system following acute alteration in BP with intermittent hypoxia and suggested that upregulation of the tissue angiotensin II system appears to be necessary for the chronic BP changes that occur from episodic hypoxia.[11] All of these evidence support the importance of intermittent hypoxia, as the critical abnormality in OSA, leading to the immediate-term and long-term cardiovascular consequences of OSA including systemic HTN, left ventricular hypertrophy, and endothelial dysfunction.[6]

2. Sympathetic Activation

During hypoxia, activation of carotid chemoreceptors results in hyperventilation to enhance oxygen delivery to blood, which is followed by sympathetically mediated vasoconstriction to redistribute oxygenated blood flow to vital organs and simultaneously, parasympathetically activated bradycardia to reduce myocardial oxygen demand.[12-14] Unfortunately, this oxygen-conserving reflex becomes dysfunctional and pathological with the imbalance between sympathetic and parasympathetic activity when the increase in sympathetic activity is sustained in OSA. Somers et al.[13] has demonstrated that patients with OSA have high sympathetic activity even when awake, with further increases in BP and sympathetic activity during sleep. Kumar and Prabhakar[15] have suggested the concept of the carotid body plasticity as a result of intermittent hypoxia. It is thought that the sympathetic hyperactivity persists through the daytime owing to the memory effect of plasticity in the sympathetic activation[6] and this sensitization appears to be associated with reactive oxygen species (ROS) and hypoxia-inducible factor-1.[16] Ultimately, sustained sympathoexcitation

can be seen as a critical mediator between OSA and HTN and has a catastrophizing effect on cardiovascular system. Particularly, in patients with HTN, impaired baroreceptor-chemoreceptor reflex may predispose to excessive autonomic responses to chemoreflex and drug-resistant HTN.[12]

3. Oxidative Stress

Repetitive intermittent hypoxia followed by reoxygenation, as mentioned above, promotes the carotid chemoreceptors via an ROS-dependent pathway[17] and may cause adenosine triphosphate depletion, xanthine oxidase activation, activation of polymorphoneuclear neutrophils and increases the generation of oxygen-derived free radicals.[18] This pathological phenomenon is analogous to a cardiac ischemia-reperfusion injury.[19] An imbalance between pro- and antioxidant system with overproduction of ROS leads to oxidative stress which imparts an tremendous burden the cardiovascular disease. Excessive accumulation of ROS in various organs and systems promotes vascular diseases through direct and irreversible oxidative damage to macromolecules, as well as disruption of redox-dependent vascular wall signaling processes.[20] Vascular damage via increased oxidative stress is involved in the pathogenesis of endothelial dysfunction with likely contribution to cognitive impairment as well as vascular lesion, atherosclerosis, HTN, myocardial injury and stroke.[6] Recurrent intermittent hypoxia contributes vascular dysfunction via systemic inflammation as well as oxidative stress. OSA patients present increased circulating leukocyte,[21] C-reactive protein (CRP),[22] serum amyloid A[23] and cytokines,[24] such as tumor necrosis factor-α and interleukin-6.

4. Metabolic Dysregulation

Many studies have shown that OSA is associated with the development of metabolic syndrome, independent of obesity.[25-30] Coughlin et al.[31] reported that metabolic syndrome was 9.1 times more likely to be present in subjects with OSA. Metabolic syndrome, as a major risk factor for cardiovascular morbidity and mortality,[32] is defined by the presence of at least three of the following signs: abdominal obesity, hypertriglyceridemia, low plasma high-density lipoprotein, hyperglycemia, and elevated BP.[27] Among them, insulin resistance is a primary manifestation of metabolic syndrome and typical feature of OSA.[31,33] Human experiments have demonstrated that acute exposure to hypoxia worsened insulin sensitivity and glucose tolerance.[34,35] It is thought that sympathetic hyperactivity caused by hypoxia in OSA stimulates glycogenolysis, gluconeogenesis and lipolysis and as a result, promotes hyperinsulinemia and insulin resistance.[28,33] Sleep restriction or sleep loss could also affect the process, such as dysfunctional glucose metabolism and upregulation of appetite which can increase the risk of developing type II diabetes by 2 to 3 times.[36-38] Adipose-derived hormones or cytokines should be considered in the understanding of the mechanisms underlying this relation. Previous studies reported the dysfunctional role of leptin and ghrelin, an adipocyte-derived hormone that controls appetite, and increased leptin resistance in OSA.[28,29,39] Adiponectin is an adipocyte-derived cytokine with regulatory function in glucose and lipid metabolism and this anti-inflammatory cytokine is decreased in OSA as well as obesity and metabolic syndrome.[28,40,41] Inflammatory responses with elevated pro-inflammatory cytokines and CRP are also implicated.[28] Fig. 1 illustrates the impact of sleep disturbance and restriction of OSA on metabolic regulation.

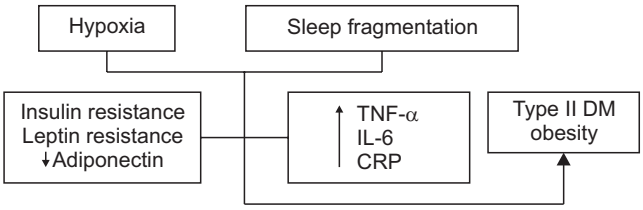

Fig. 1. Impact of sleep disturbance and restriction of obstructive sleep apnea on endocrine-metabolic regulation. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; CRP, C-reactive protein; DM, diabetes mellitus.

EPIDEMIOLOGIC STUDIES ON THE ASSOCIATION BETWEEN OSA AND CARDIOVASCULAR DISEASE

1. Systemic HTN and OSA

Systemic HTN is the most common CVD leading to a significant portion of CVD-related mortality in developed societies and is the best-established cardiovascular consequences of OSA.[6]

A landmark study which studied the association between OSA and HTN was the Wisconsin Sleep Cohort Study with 709 healthy subjects. In this study, 184 of these participants were followed for 8 years with the assessment of baseline PSG. The odds ratio for the presence of HTN was 1.42 (1.13< confidence interval [CI] <1.78) for 0.1< AHI <4.9; 2.03 (1.29< CI <3.17) for 5< AHI <14.9; 2.89 (1.46< CI <5.64) for 15<AHI. This study demonstrated a dose-response relationship as well as a critical causative relationship between OSA and HTN.[42] Interestingly, this relationship was independent of well-known risk factor of HTN. The 2018 meta-analysis on the association of OSA and HTN also confirmed this strong relationship and dose-response relationship.[43] Particularly, OSA was an increased risk factor for resistant HTN (odds ratio [OR], 2.84; 1.70< CI <3.98). In the Wisconsin Sleep Cohort Study, 60% to 80% of resistant HTN which is defined as BP that still remains higher than a reference level despite more than 3 types of antihypertensive showed OSA with the characteristics of non-dipping of BP during sleep. This abnormal pattern of BP pattern during sleep suggests that patients with OSA present dysfunctional autonomic regulation of BP with chronic resetting of the baroreceptors to higher set point of BP.[44,45]

2. CAD and OSA

Although not as extensively studied as HTN, CAD also shares likely causative relationship with OSA.

A prospective cohort study of 1,651 men including OSA patients or simple snorers or healthy men with a follow-up period for a mean of 10 years revealed that untreated severe OSA significantly increased the risk of fatal cardiovascular events, such as death from myocardial infarction or stroke (OR, 2.87; 95% CI, 1.17-7.51). For non-fatal cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography) showed adjusted odds ratio of 3.17 (95% CI, 1.12-7.51) compared with healthy subjects.[7] According to the Dong's meta-analysis[46] of prospective studies on the relation between OSA and cardiovascular risk, individuals with moderate-severe OSA had an almost 2.5-fold risk of cardiovascular events and 1.37 for coronary heart disease. In addition, the severity of OSA is significantly correlated with the severity of CAD in the Jia's prospective study. The Cox regression model presented that the severity of OSA was an independent risk factor of long-term major adverse cardiovascular events (hazard ratio [HR], 1.61; 95% CI, 1.06-3.86).[47]

The important underlying pathophysiology linking the association of OSA and CAD is vascular endothelial dysfunction. Impaired endothelium-dependent vascular relaxation facilitates the atherosclerotic changes and is a prognostic marker of CVD.[48,49]

3. CA and OSA

The association of OSA and cardiac arrhythmia (CA) has been focused in recent years because CA is one of the important cause of cardiovascular morbidity, such as stroke. Previous epidemiologic studies have revealed an increased prevalence of atrial arrhythmia, the most common CA, in patients with OSA.[6]

A large, cross-sectional study of the Sleep Heart Health Study reported that the prevalence of CA was more common in subjects with SDB compared with those without SDB: 4.8% versus 0.9% (p=0.003) for atrial fibrillation (AF); 5.3% versus 1.2% (p=0.004) for nonsustained ventricular tachycardia; 25.0% versus 14.5% (p=0.002) for complex ventricular ectopy.[50] Particularly, subjects with severe SDB presented 2 to 4 times higher adjusted odds of complex arrhythmias than controls.

A meta-analysis of 6 observational studies concluded that OSA increases recurrence risk after cardiac surgery of AF by 25% (risk ratio [RR], 1.25; 95% CI, 0.91-1.27) and OSA diagnosed by PSG is a modifiable risk factor as well as a strong predictor of AF recurrence (RR, 1.40; 95% CI, 1.16-1.27).[51]

As detailed earlier, multifactorial process, such as intermittent hypoxia, hypercapnia, an increased sympathetic activity, increased vascular volume and inflammation in sleep disordered breathing including central sleep apnea as well as OSA leads to myocardial structural and functional changes prompt to CAs.[52]

4. Cerebrovascular Disease and OSA

OSA has been found to be an independent risk factor for stroke in previous epidemiologic studies.[53-56] A cross-sectional results of the Sleep Heart Health Study reported that

sleep disordered breathing was associated with self-reported stroke (The relative odd, 1.58; 95% CI, 1.02-2.46).[56] In a systemic review including 37 studies with 3,242 patients, the prevalence of OSA (apnea hypopnea index [AHI] >10) ranged from 34.5% to 92.3%, the random-effects pooled prevalence was 61.9%.[57] Among them, AHI greater than 30, 20 and 5 was 30.1%, 39.5% and 70.4%, respectively. Central type was only 8.3%. In the study on the prevalence of SDB amongst stroke survivors at 3 years compared to normal elderly patients, prevalence of SDB (AHI ≥5) was 81%.[58] Particularly, hemorrhagic stroke and stroke severity at 1 month were important predictors for the occurrence of AHI ≥15.60.[59] Although two long-term studies showed inconsistent results on the association between the severity of OSA and poor functional outcome of stroke,[58,59] meta-analysis of 17 prospective cohort studies revealed that the pooled relative risks for patients with moderate-severe OSA with the reference group were 2.02 (95% CI, 1.40-2.90).[46]

Many epidemiologic studies clearly show that OSA independently increases the risk of stroke. However, the mechanism of this relation is still unclear. In the experiment of Urbano et al.,[10] patients with OSA have decreased cerebral artery blood flow velocity at baseline and delayed cerebrovascular compensatory response to changes in BP but not to CO_2. The results of this study suggests impaired cerebral autoregulation in OSA which may increase the risk of cerebral ischemia during OSA.[60] On the other hand, cerebrovascular reactivity (CVR) is associated with an increased risk of stroke did not differ between OSA and non-OSA subjects for isoxic tension despite the increased CVR in hypoxia.[61]

TREATMENT EFFECTS OF OA FOR OSA

In this section, treatment effects of OAs for OSA will be discussed in terms of respiratory effect as a direct outcome (e.g., AHI) and systemic effect as an indirect health outcome (e.g., BP), O2 desaturation) through reviewing updated systemic review and meta-analyses. Particularly, respiratory and systemic effects of OA will be compared with the CPAP, which is currently the gold standard of OSA treatment.

A systemic review and meta-analysis was conducted with a total of 7 studies (4 observational studies, 2 randomized clinical trials [RCT]) which were published until December 15, 2011 to evaluate the effect of OAs on BP.[62] The pooled estimate of mean changes for AHI reduction was −12.07% (95% CI, −9.7 to −14.3; p<0.001). The mean reduction in systolic and diastolic pressure was −2.7 mmHg (95% CI, −0.5 to −4.6; p=0.040) and −2.7 mmHg (95% CI, −0.9 to −4.6; p=0.004), respectively. The mean arterial pressure also showed significant change of −2.4 mmHg (95% CI, −4.01 to −0.80; p=0.003). The OAs revealed a favorable respiratory and systemic effect on the previous meta-analysis. The AHI reduction and magnitude of change in BP showed significantly moderate correlation (r=0.31, p=0.002). Although the number of 2.7 mmHg in reduction of BP seems small at a glance, this small reduction of BP has enormous clinical implication. A decrease in 2 mmHg diastolic BP would result in a decrease in the prevalence of HTN by 17%, in the risk of coronary heart disease by 6%, and in the risk of stroke and transient ischemic attacks by 15%.[63] Furthermore, a reduction of 5 mmHg in diastolic BP across a population of 420,000 individuals was associated with ≥34% less stroke and 21% less coronary heart disease.[64] In 2015, a meta-analysis was conducted to compare the treatment effect of CPAP versus mandibular advancement devices (MADs) versus inactive control on BP.[65] Unlike a meta-analysis in 2013,[62] this study in 2015 included only RCTs. Among retrieved 55 RCTs, there was a total of 4 RCTs comparing the effect of CPAP versus MADs. Comparing with an inactive control, CPAP and MADs presented a reduction in systolic BP of 2.5 mmHg (95% CI, 0.8 to 2.3 mmHg; p<0.001) and 2.1 mmHg (95% CI, 0.8 to 3.4 mmHg; p=0.002), respectively. In diastolic BP, CPAP and MADs comparing with an inactive control also showed superior effect of 2.0 mmHg (95% CI, 1.3 to 2.7 mmHg; p<0.001) and 1.9 mmHg (95% Cl, 0.5 to 3.2 mmHg; p=0.008), respectively. There was no significant difference between CPAP and MADs in the systemic effect of BP reduction. This recent meta-analysis including only RCT studies demonstrated that both of CPAP and OAs are associated with reductions in BP and effect of OAs in BP is not inferior to CPAP. In a meta-analysis on the various cardiovascular effects (e.g., BP, heart rate, heart rate variability, circulating cardiovascular biomarkers, endothelial function and arterial stiffness) of OAs in OSA, pooled data of the 11 RCTs showed that OAs and CPAP was equally effective in reducing BP like the previous systemic

reviews.[66] However, OAs did not show generally significant effect in reduction of heart rate. Unlike the significant effect of CPAP from extensive literature on cardiovascular outcomes including improved inflammatory markers,[67] decrease in arterial stiffness[68] and reduction of risk of cardiovascular mortality,[69] the treatment effects of OAs on heart rate variability, circulating cardiovascular biomarkers, endothelial function and arterial stiffness were inconclusive due to small numbers of included subjects and heterogeneity of studies. Only one observation study observed the effect of CPAP versus OAs on cardiovascular mortality in 570 subjects with severe OSA (AHI ≥30/h) and 269 subjects as a control group (AHI <5/h) for a median of 79 months (Interquartile range, 76-88 months).[70] Although residual AHI for OAs-treated patients was significantly higher than CPAP-treated patients, there was no difference in cardiovascular death rate between two treatments (HR, 1.08; 95% CI, 0.55-1.74; p=0.71).

On the other hand, the systemic review on RCTs of MADs and CPAP for OSA, published in 2016, particularly compared the treatment effect (AHI reduction, subjective sleepiness) of MADs with CPAP according to the severity of OSA.[71] 73 Both of MADs and CPAP significantly reduced AHI by −9.3/h for MADs (p<0.001) and −25.4/h for CPAP (p<0.001). For subgroup analysis, differences in AHI between MADs and CPAP was significant for both moderate and severe OSA (p<0.001). There was no direct comparison between CPAP versus MADs in mild OSA, but in comparison with a control of conservative management, the estimated reduction in AHI was −2.4 events/h for CPAP and −7.79 events/h for MADs. The results of direct and indirect comparisons suggest that CPAP is the most clinically effect treatment at reducing AHI in moderate to severe OSA, but MADs may be not inferior or superior to CPAP in mild cases. Particularly, for CPAP-intolerant patients, MADs, as an alternative treatment option, are better than no treatment for moderate and severe cases. In subjective sleepiness assessed by Epworth Sleepiness Scale, both CPAP and MAD reduced sleepiness to a similar extent.[71]

In one randomized crossover study, effects of CPAP versus MADs on health outcomes consisting two dimension (cardiovascular and neurobehavioral outcomes) were compared after 1 month of treatment.[72] Quality of life as well as sleepiness overall improved on both treatments by similar amounts and this result was consistent with the outcomes of a recent meta-analysis on health-related quality of life related to effects of CPAP and MADs.[73] As described earlier, CPAP was more efficacious than MAD in reducing the majority of respiratory index including AHI and MADs was not inferior to CPAP in reducing BP. However, the compliance of CPAP (5.2±2.0 h/night) was significantly lower than MADs (6.5±1.3 h/night) (p<0.0001) and treatment preference of MADs (51.0%) was superior to that of CPAP (23.1%).[73] This relative superiority of MADs in compliance suggests important clinical implication that greater efficacy of CPAP might be offset by inferior compliance compared to MAD, leading to similar effectiveness.

On the other hand, driving performance, as another important aspect of health outcomes of OSA, should be considered. Untreated OSA is a significant contributor to motor vehicle crashes[74] and it is well known that CPAP significantly reduces motor vehicle collisions.[75] In one RCT study, OAs like CPAP showed substantial improvement in driving performance after treatment during 2-3 months.[76] Lastly, can treatment of OSA, as an independent risk factor for type 2 diabetes, improve glucose metabolism? Although current data available is still limited and less clear, it is consistently suggested that CPAP could affect glucose metabolism via decreasing insulin resistance, increasing insulin sensitivity and possibly increasing glycemic control.[77,78] The studies on the effect of OAs on glucose metabolism in OSA and diabetes are more limited than CPAP. Further studies on the metabolic effects of OAs are warranted.

CONCLUSION

OSA is not a simple problem of repetitive mechanical obstruction of upper airway but a complex systemic disease that can adversely affect the cardiovascular, endocrine-metabolic and neurocognitive system and in vice versa. Intermittent hypoxia, sympathetic activation, oxidative stress, systemic inflammation and metabolic dysregulation provide biological plausibility to this pathologic mechanism. Although CPAP, a gold standard treatment of OSA, presents the most efficacious outcomes in respiratory index and most of pathologic systemic conditions, OAs are still

of importance with CPAP in the treatment of OSA in that compliance and adherence is better than CPAP.

OSA is an intriguing field expanding the horizon of dentistry and treatment area and the review on the understanding of vicious cycles between OSA and systemic condition and treatment effects of OAs will contribute to the insights for dentists.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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