



Mini Review

The Pathophysiological Relationship and Treatment Progress of Obstructive Sleep Apnea Syndrome, Obesity, and Metabolic Syndrome



Jixiang Li^{1#}, Liang Zeng^{2#} and Tong Feng^{3*} 

¹Cardiology Department, Danling County People's Hospital, Danling County, Meishan, Sichuan, China; ²Mingjian Town Health Center, Mabian Yi Autonomous County, Leshan, Sichuan, China; ³The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, China

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Abstract

Patients with obstructive sleep apnea (OSA) and metabolic syndrome (MetS) have a higher prevalence and mortality rate of cardiovascular diseases, posing a significant burden on both individuals and society. Although the precise pathophysiological relationship between OSA and MetS remains unclear, their bidirectional interaction may create a harmful cycle of mutual reinforcement. This review explored the current treatment progress for OSA and MetS, including continuous positive airway pressure therapy, weight management, and metabolic surgeries. Studies indicate that while continuous positive airway pressure therapy effectively alleviates OSA symptoms, its impact on metabolic markers is limited, emphasizing the importance of long-term weight control. Metabolic surgeries, such as gastric bypass and sleeve gastrectomy, significantly reduce weight and directly improve metabolic abnormalities associated with MetS, such as insulin resistance and dyslipidemia, thereby lowering the risk of cardiovascular diseases. In contrast, mandibular advancement devices primarily improve symptoms of OSA and indirectly enhance metabolic function by improving sleep quality and reducing intermittent hypoxemia. Although mandibular advancement devices have a limited direct impact on metabolic parameters, they may offer potential benefits in lowering blood pressure and managing MetS. Understanding and breaking the cycle between OSA and MetS can significantly reduce the associated cardiovascular risks.

Introduction

Cardiovascular diseases are associated with high prevalence and mortality rates. Individuals with both obstructive sleep apnea (OSA) and metabolic syndrome (MetS) face a significantly increased risk of developing cardiovascular disease compared to the general population.^{1,2} This elevated risk imposes a substantial burden on individuals, their families, and society. Although the precise relationship between OSA and MetS remains unclear, thoroughly investigating this connection is crucial. Identifying risk factors and understanding the interplay between these conditions can help prevent disease

progression, improve patient outcomes, enhance the quality of life, and ultimately yield positive socioeconomic impacts.

Concepts and epidemiology of OSA syndrome and MetS

Respiratory pauses and hypoventilation are recognized as common characteristics of OSA. Despite persistent efforts to breathe, the upper airway undergoes partial or complete collapse during sleep, leading to decreased blood oxygen levels, increased sleep disruptions, and excessive daytime sleepiness. Epidemiological studies indicate that OSA affects 14% of the global population, with a higher prevalence among individuals aged 30–69.³ Typical symptoms of OSA include daytime drowsiness, fatigue, difficulty concentrating, memory issues, and headaches, all of which can significantly diminish a patient's quality of life. OSA is characterized by recurring airway collapse during sleep, resulting in decreased blood oxygen levels, chronic intermittent hypoxia, and disrupted sleep patterns. Common indicators of OSA include snoring, episodes of breathing cessation during sleep, and daytime sleepiness.

MetS is a complex metabolic disorder characterized by a combination of risk factors that increase the likelihood of cardiovascular and cerebrovascular diseases. MetS was first defined by the

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***Correspondence to:** Tong Feng, The Second School of Clinical Medicine, Southern Medical University, No. 1023 Shatai South Road, Baiyun District, Guangzhou, Guangdong 510515, China. ORCID: <https://orcid.org/0009-0004-6324-8502>. Tel: +86-18583681025, E-mail: 543051181@qq.com

#Contributed equally to this work.

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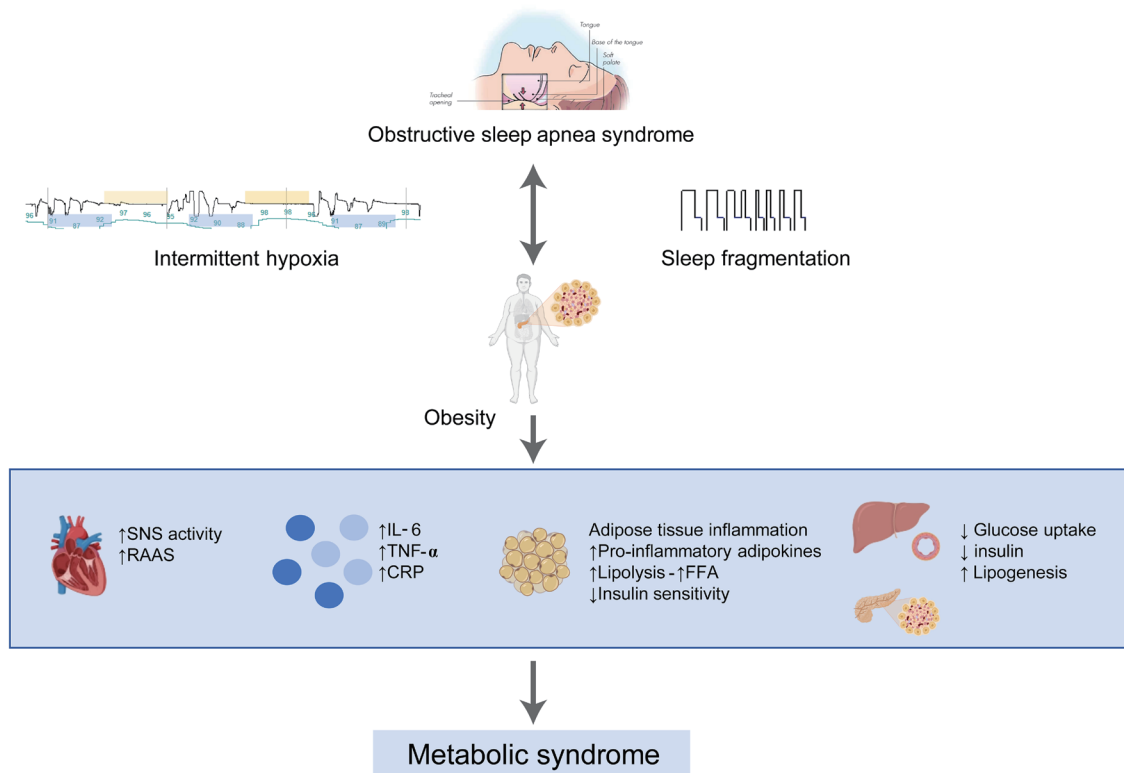


Fig. 1. Putative mechanisms connecting obstructive sleep apnea (OSA), obesity, and metabolic syndrome (MetS). Double-headed arrow (between “Obstructive sleep apnea syndrome” and “Obesity”): This indicates a bidirectional relationship between Obstructive sleep apnea syndrome and obesity. Intermittent hypoxia may lead to obesity, and obesity may exacerbate the effects of intermittent hypoxia. Downward arrow (from “Obesity” to the blue box): This shows that obesity acts as a critical intermediary process leading to the subsequent mechanisms involved in metabolic syndrome. Downward arrow (from the blue box to “Metabolic Syndrome”): This indicates that the various physiological mechanisms and pathological changes within the blue box collectively contribute to the development of metabolic syndrome. CRP, C-reactive protein; FFA, free fatty acids; IL-6, interleukin 6; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TNF- α , tumor necrosis factor-alpha.

World Health Organization in 1998, with subsequent descriptions provided by the International Diabetes Federation and the National Cholesterol Education Program Adult Treatment Panel III (hereinafter referred to as NCEP-ATP III). Notably, high blood sugar levels, central obesity, high blood pressure, and abnormal lipid levels are commonly included in the diagnostic criteria for MetS. According to the NCEP-ATP III, the prevalence of MetS in the United States is estimated to be 24%, based on the National Health and Nutrition Examination Survey.⁴

The relationship between OSA and MetS

Individuals diagnosed with OSA face a significantly elevated risk of developing MetS compared to the general population. The relationship between OSA and MetS is bidirectional, potentially perpetuating a harmful cycle. A comprehensive clinical study in China revealed MetS prevalence rates of 18.6%, 30.4%, 43.8%, and 57.1% in patients with no, mild, moderate, and severe OSA, respectively.⁵ Conversely, around 60.5% of individuals diagnosed with MetS also experience moderate to severe OSA.⁶ A prospective cohort study found that approximately 17.2% of OSA patients developed MetS within six years, highlighting an independent connection between the two conditions.⁷

The significant comorbidity between OSA and MetS can be attributed to common risk factors such as obesity, aging, and

unhealthy lifestyle choices. A four-year follow-up study of the Wisconsin Sleep Cohort Research has shown that for every 10% increase in body weight, the apnea-hypopnea index (AHI) increased by 32%, with an incidence of moderate to severe OSA increasing sixfold. Conversely, for every 10% decrease in weight, AHI decreases by 26%.⁸ Central obesity, a key feature of MetS, is closely linked to fat accumulation around the neck, which exacerbates upper airway obstruction during sleep compared to fat deposition in other body regions. It is estimated that 50% to 60% of obese individuals with MetS also have OSA.⁹

Numerous studies have underscored the high prevalence of OSA in MetS patients and vice versa, with both conditions significantly elevating the risk of cardiovascular diseases. This overlap in prevalence between OSA and MetS, along with their shared association with cardiovascular risks, emphasizes the importance of recognizing and addressing the complex interplay between sleep disorders and metabolic dysregulation (Fig. 1).

The correlation between OSA and obesity

Accumulation of visceral fat, particularly in obese individuals, presents a significant risk factor for OSA, as indicated by previous research. Analysis of intra-abdominal fat areas in obese individuals with and without OSA reveals that those with OSA tend to have markedly larger visceral fat areas and higher ratios of visceral fat

to total fat compared to their non-OSA counterparts.¹⁰

Various studies have proposed a potential link between OSA and body mass index (BMI) through the hormone leptin. Leptin binds to the OB receptor on the surface of the hypothalamus, initiating the JAK-STAT signaling pathway, which leads to increased expression of anorexigenic peptides and decreased appetite.¹¹ OSA could contribute to obesity by elevating BMI, lowering leptin levels, raising ghrelin levels, and intensifying cravings. The disrupted sleep patterns and frequent awakenings associated with OSA may interfere with hormone regulation, potentially resulting in heightened hunger and a preference for calorie-dense foods. Furthermore, daytime fatigue and reduced energy levels might stifle motivation for physical activity, further fueling weight gain.

The connection between OSA and hypertension

Data from the extensive Wisconsin Sleep Cohort study suggest a significant association between OSA severity and blood pressure (BP) over time. In a four-year follow-up, individuals with mild and moderate-to-severe OSA had odds ratios of 2.89 (95% confidence interval, 1.46–5.64) and 1.42 (95% confidence interval, 1.13–1.78), respectively, for developing hypertension compared to those without sleep-disordered breathing, regardless of factors such as BMI, waist circumference, neck circumference, age, gender, baseline hypertension status, and other confounding variables.¹²

Intermittent hypoxemia (IH), a prominent feature of OSA, can trigger spikes in BP and excessive activity of the sympathetic nervous system through carotid chemoreceptors in OSA patients.¹³ Normally, during sleep in healthy individuals, sympathetic activity decreases, and parasympathetic dominance prevails, contributing to the physiological nocturnal “dipping” of BP and heart rate.¹⁴ The loss or reduction of this dipping pattern is common in OSA and has been linked to a heightened risk of cardiovascular diseases. Periodic episodes of intermittent hypoxia and hypercapnia resulting from apneic-hypopneic episodes can induce changes in autonomic nervous function that counteract the natural nocturnal dipping of BP.¹⁵ Notably, OSA patients may also have consistently elevated BP while awake, possibly due to increased sympathetic drive.

The connection between OSA and diabetes

The correlation between OSA and hyperglycemia has been widely documented, particularly in individuals with type 2 diabetes mellitus (T2DM). Sleep disorders, including OSA, are more prevalent in people with T2DM, negatively impacting overall well-being, mood, and quality of life. Additionally, individuals with sleep disorders like OSA are at an increased risk of developing metabolic disorders such as T2DM.

The mechanisms through which OSA may contribute to the development of diabetes are complex and varied. Animal studies have demonstrated that simulating the intermittent episodes of deoxygenation/reoxygenation seen in OSA, known as IH, can disrupt glucose regulation.¹⁶ Research involving participants exposed to IH has shown impaired insulin sensitivity and glucose tolerance.¹⁷ In addition to IH, sleep fragmentation due to frequent awakenings in OSA also negatively impacts insulin sensitivity, although empirical evidence on this effect is limited. The exact pathways through which IH and sleep fragmentation affect glucose metabolism are not fully understood, but potential factors include increased sympathetic activity, oxidative stress, and inflammation.¹⁸ Sympathetic nervous system activation, in addition to raising blood pressure, can reduce tissue sensitivity to insulin. Elevated levels of inflam-

matory cytokines in OSA patients have been linked to insulin resistance and local or systemic inflammation.¹⁹

The connection between OSA and dyslipidemia

Regarding the relationship between OSA and dyslipidemia, studies have shown a significant association between OSA severity and levels of high-density lipoprotein (HDL). Higher AHI values have been linked to lower HDL levels.²⁰ Research on OSA patients has consistently reported decreased HDL levels, along with elevated levels of total cholesterol, triglycerides (TG), and low-density lipoprotein (LDL).²¹ CIH in OSA can lead to increased TG levels by promoting the production of TG-related proteins and enzymes in the liver. Additionally, the heightened sympathetic activity in OSA patients may impact the synthesis of lipoprotein lipase, resulting in reduced serum HDL levels. Previous studies have suggested that blocking alpha-1 receptors could raise HDL levels and lower TG levels, indicating a possible link between sympathetic overactivity in OSA and altered lipid profiles.²²

The influence of various treatments on MetS and its components

Causal inference requires interventional studies to demonstrate the effect of treating OSA on preventing and reversing MetS, typically defined as having fewer than three MetS criteria at the end of follow-up. Currently, most studies have focused only on the impact of interventions on individual components of MetS, and there is no evidence to suggest that treating OSA can prevent the onset of MetS.

Patients with OSA have shown a significant, though small, weight gain after receiving continuous positive airway pressure (CPAP) therapy,²³ an effect that is particularly noticeable in patients with type 2 diabetes.²⁴ This observation contradicts the previously described relationship between obesity and OSA. However, the weight gain following CPAP therapy may be due to changes in different body components. Recent meta-analyses have shown no association between CPAP use and the volume of subcutaneous or visceral fat tissue.²⁵ CPAP may increase lean body mass, suggesting that the weight gain induced by CPAP may reflect positive changes in body composition.²⁶

A meta-analysis of randomized controlled trials on CPAP found improvements in insulin resistance among OSA patients but no significant changes in fasting glucose or HbA1c levels.^{27,28} During long-term follow-up, CPAP failed to sustain improvements in glycemic control or reduce insulin resistance. The largest and longest study to date, a sub-study of the multi-center randomized controlled trial, involved 2,687 subjects with a median follow-up of 4.3 years and aimed to determine the impact of long-term CPAP treatment on glycemic control and diabetes risk in patients with cardiovascular disease and OSA.²⁹ Participants were randomly assigned to the CPAP treatment group or the usual care group, and the incidence of diabetes was recorded. The results showed no significant differences in blood glucose, HbA1c, or the use of antidiabetic medications between the CPAP treatment group and the usual care group in patients with pre-existing diabetes. Similarly, no significant differences were found between the two groups in patients with prediabetes or newly diagnosed diabetes. Notably, women with OSA and diabetes who received CPAP therapy had better glycemic control, whereas women assigned to the usual care group experienced worsening glycemic control during follow-up. This suggests a gender difference in the link between OSA and metabolic dysregulation, warranting further research. The lack of

Table 1. Treatment methods for OSA with MetS

Treatment method	Description	Impact
Continuous positive airway pressure	Primary treatment for moderate to severe OSA; addresses upper airway collapse, hypoxia, and symptoms like snoring	Decreases the occurrence of MetS, but has no significant impact on lipid levels, inflammatory markers, insulin resistance, or MetS
Weight management and lifestyle modifications	Involves dietary adjustments, physical activity, improved sleep habits, smoking cessation, and regular monitoring	Crucial for reversing metabolic disorders; improves sleep quality and AHI
Metabolic surgeries	Includes laparoscopic sleeve gastrectomy, laparoscopic Roux-en-Y gastric bypass, and biliopancreatic diversion	Enhances OSA symptoms, weight management, and metabolic health
Mandibular advancement devices (MADs)	Suitable for mild to moderate OSA; advances the lower jaw to keep the airway open	Reduces blood pressure, but limited impact on fasting blood sugar and lipid profiles; effects on MetS prevalence need further study

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; MADs, mandibular advancement devices; MetS, metabolic syndrome; OSA, obstructive sleep apnea.

differences may be due to insufficient CPAP usage, as one week of 8-h nightly CPAP has been shown to improve glycemic control.³⁰

CPAP can reduce blood pressure by lowering sympathetic activation and vascular injury caused by intermittent hypoxia. Although CPAP treatment can lower blood pressure, the improvement is modest, with a 24-h average blood pressure reduction of 2 mmHg.³¹ However, CPAP can significantly improve conditions in patients with resistant hypertension, playing an important clinical role in managing hypertension in these patients.

A meta-analysis of randomized controlled trials with control groups showed that CPAP treatment significantly reduced total cholesterol, particularly in younger and more obese patients, but had no significant effect on LDL-C, HDL-C, or triglyceride levels.³² A 2020 study assessing the impact of long-term CPAP treatment on dyslipidemia found significant reductions in total cholesterol and LDL-C levels after both short-term and long-term CPAP therapy, but no changes in triglyceride or HDL-C levels.³³ Similarly, the European Sleep Apnea Database (ESADA) cohort investigated the effect of long-term CPAP treatment on lipid levels, and unadjusted analyses showed improvements in all lipid levels after CPAP treatment.³⁴ However, after adjusting for age, gender, lipid-lowering medications, weight changes, CPAP adherence, and duration, only total cholesterol levels showed a significant reduction, with the duration of CPAP treatment being the only independent predictor of cholesterol reduction. Dyslipidemia in OSA patients with MetS is a long-term process influenced by multiple factors, of which OSA is only one. HDL-C is primarily influenced by genetic factors and is not easily modified by various interventions.

In patients with MetS and severe OSA, eight weeks of CPAP treatment was associated with improvements in cardiovascular risk markers, specifically reductions in blood pressure and total cholesterol levels. However, these benefits were observed only in patients with high CPAP adherence (≥ 4 h of nightly use) and continued medication use.³⁵ In 2009, a small prospective study with 20 subjects evaluated the effect of one year of CPAP treatment on the prevalence of MetS in patients diagnosed with both OSA and MetS. After one year of CPAP follow-up, the prevalence of MetS decreased by 45%.³⁶ In 2013, Hoyos and colleagues utilized retrospective data from a randomized trial to assess the effect of 12 weeks of CPAP treatment on the reversal of MetS.³⁷ This study included 65 patients with moderate to severe OSA who were on antihypertensive and lipid-lowering medications. Of the 18 patients with MetS before treatment, three reversed MetS after three months of CPAP intervention. One patient in the placebo CPAP group experienced such reversal ($P > 0.05$). This suggests

that 12 weeks of CPAP treatment had no significant impact on the development or reversal of MetS. However, the adherence to CPAP treatment in the CPAP group was 3.6 h per night, making it difficult to determine whether poor adherence may have diminished potential metabolic benefits. In 2022, Sara conducted a randomized controlled trial specifically addressing whether treating OSA with CPAP promotes MetS reversal.³⁸ One hundred patients completed the study (50 in each group). The average adherence to CPAP was 5.5 ± 1.5 h per night. Compared to placebo, CPAP treatment resulted in a higher reversal rate of MetS (18% vs. 4%; $P = 0.04$), but most patients retained this diagnosis, suggesting that the effect of OSA on MetS may be limited.

Despite the metabolic benefits of CPAP therapy for OSA patients, it may not be the most effective treatment. In contrast, lifestyle interventions have a more significant impact on MetS in OSA patients. Lifestyle intervention is the cornerstone treatment for MetS, and the Mediterranean diet has been shown to reduce the risk of MetS and improve each of its components.³⁹ A study comparing changes in metabolic indices over 24 weeks between weight loss combined with CPAP therapy and CPAP therapy alone found that levels of C-reactive protein, insulin resistance, and triglycerides decreased only in the weight loss group, while they remained unchanged in the CPAP-only group.⁴⁰ This indicates that combining CPAP with lifestyle interventions is crucial for improving disease outcomes in OSA patients. There is an interaction between the components of MetS, where weight loss can lead to changes in other components, such as lipid profiles and fasting glucose. Therefore, lifestyle intervention is an essential and effective treatment for OSA.

Improving the AHI and sleep quality alone may not reverse metabolic disorders; sustained weight loss is crucial. Treatment strategies for individuals presenting with OSA and MetS symptoms may include weight management and lifestyle modifications involving dietary adjustments, physical activity, improved sleep habits, smoking cessation, and regular medical monitoring.⁴¹ In certain cases, metabolic surgeries like laparoscopic sleeve gastrectomy, laparoscopic Roux-en-Y gastric bypass, and biliopancreatic diversion with duodenal switch might be considered. Following such interventions, patients typically observe marked improvements in OSA symptoms, weight management, and metabolic health.⁴²

For individuals with mild to moderate OSA, mandibular advancement devices (MADs) can be a suitable option. Some studies suggest that MADs could reduce blood pressure in patients, although they may not have a significant impact on fasting blood sugar and lipid profiles.^{43,44} The effects of MADs on the prevalence of MetS among OSA patients warrant further investigation (Table 1).

Future directions

Future research should explore the molecular mechanisms underlying the relationship between OSA and MetS, with a focus on the role of chronic intermittent hypoxia in metabolic dysfunction. Longitudinal studies assessing the long-term impact of integrated treatment strategies, including CPAP therapy, lifestyle interventions, and metabolic surgeries, on both OSA and MetS are highly needed. Additionally, further investigation into personalized therapeutic approaches based on genetic and gender-specific factors could improve clinical outcomes and inform tailored management strategies.

Conclusions

Chronic episodes of intermittent hypoxia, hypercapnia, and disrupted sleep patterns associated with OSA may contribute to the development or worsening of MetS. Conversely, the components of MetS can also influence OSA, creating a cycle of mutual reinforcement. OSA tends to cluster with MetS components, which are known risk factors for cardiovascular disease, thereby increasing the likelihood of cardiovascular events. The intricate interplay between OSA and MetS warrants further exploration. Proper elucidation of the link between these conditions, along with strategies to break the cycle between them, could significantly reduce the cardiovascular risk associated with OSA and MetS.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

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