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REVIEW

Obstructive Sleep Apnea, Inflammation, and the Metabolic Syndrome

Andrew D. Calvin, M.D., M.P.H.,[1] Felipe N. Albuquerque, M.D.,[2]
Francisco Lopez-Jimenez, M.D., M.Sc.,[2] and Virend K. Somers, M.D., Ph.D.[2]

Abstract

The combination of metabolic syndrome and obstructive sleep apnea (OSA) has been termed "syndrome Z." The prevalence of both OSA and metabolic syndrome is increasing worldwide, in part linked to the epidemic of obesity. Beyond their epidemiologic relationship, growing evidence suggests that OSA may be causally related to metabolic syndrome. We are only beginning to understand the potential mechanisms underlying the OSA–metabolic syndrome interaction. Although there is no clear consensus, there is growing evidence that alterations in the hypothalamic–pituitary axis, generation of reactive oxygen species (ROS) due to repetitive hypoxia, inflammation, and generation of adipokines may be implicated in the changes associated with both OSA and metabolic syndrome. Whether some or all of these metabolic alterations mechanistically link OSA to metabolic syndrome remains to be proven, but it is an area of intense scientific interest.

Introduction

Metabolic syndrome describes a combination of metabolic disturbances that together increase the risk of type 2 diabetes mellitus and atherosclerotic cardiovascular disease.[1] The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) report[2] defines metabolic syndrome as three or more of the following five variables: hypertension, insulin resistance, low high-density lipoprotein cholesterol (HDL-C), elevated serum triglyceride, and abdominal obesity. Using the NCEP ATP III definition, the Third National Health and Nutritional Examination Survey estimated that the prevalence of metabolic syndrome in the United States was approximately 24%.[3] The combination of obstructive sleep apnea (OSA) and metabolic syndrome has been referred to as "syndrome Z." [4] Although metabolic syndrome and OSA may simply be coincident syndromes, there is growing, albeit inconclusive, evidence that the pathophysiology of OSA and metabolic syndrome overlap considerably. This review will focus on the potential mechanistic links between sleep apnea and the metabolic syndrome, with a particular focus on inflammation.

Definition of OSA

The primary cause of OSA is inspiratory collapse of the pharyngeal airway. This portion of the airway has little rigid support and is largely dependent on neuromuscular control to maintain patency. Patients with OSA have an anatomically small pharyngeal airway, which in adults is primarily due to obesity and is improved by weight loss[5] and in children is most commonly due to enlarged tonsils and adenoids.[6] While awake, this leads to greater airway resistance that activates mechanoreceptors to trigger reflex pharyngeal dilator muscle activity, thus maintaining airway patency.[6,7] During sleep, dilator muscle activity is diminished, leading to pharyngeal narrowing and intermittent collapse of the upper airway.[8] This can lead to a combination of hypopneas, or reduction in airflow associated with a fall in oxygen saturation, or apneas, or complete cessation of airflow. The number of apneas and hypopneas per hour of sleep is termed the apnea–hypopnea index (AHI) and has been used as a marker of OSA severity. The diagnosis of OSA can be made when the AHI is >5 in a patient with excessive daytime sleepiness.[9] Apneas and hypopneas lead to hypoxia and hypercapnia, which stimulate ventilatory drive and ultimately

[1]Mayo School of Graduate Medical Education and [2]Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota.

arousal from sleep and restoration of airway patency. The intermittent hypoxia can be severe, with arterial oxygen saturation dropping to <60% in some patients and associated with a disruption of normal autonomic and hemodynamic responses to sleep,[10] including increased sympathetic activity to peripheral blood vessels leading to vasoconstriction and acute increases in blood pressure.[11,12]

OSA is associated with negative outcomes. Data from the Wisconsin Sleep Cohort Study showed a linear relationship between 24-hour blood pressure and AHI, independent of potential confounders.[13] Numerous studies have examined the effect of continuous positive airway pressure (CPAP) therapy on blood pressure, and three meta-analyses concluded that CPAP had significant but very modest effects on blood pressure.[14–16] In a prospective study of all patients referred to a heart failure clinic for systolic heart failure (ejection fraction <45%), Wang et al. showed that 26% of patients who had systolic heart failure also had OSA. In a study of subjects with OSA, Romero-Corral et al. showed that moderate and severe OSA were associated with impaired left and right systolic ventricular function.[17] OSA may conceivably be even more common among heart failure subjects with preserved ejection fraction, and in one study was present in >50% of heart failure subjects with preserved ejection fraction.[18] Furthermore, CPAP therapy has been shown to improve diastolic function.[19] There are no long-term OSA-related trials of CPAP for the prevention or treatment of heart failure. OSA has also been implicated in a potentially important risk factor for stroke,[20,21] sudden cardiac death,[22] and both atrial and ventricular arrhythmias.[5]

Epidemiology of OSA and Metabolic Syndrome

Sleep disordered breathing, which includes both OSA and central sleep apnea (CSA), is estimated to affect over 15 million adults in the United States, with 4% of men and 2% of women meeting the minimum diagnostic criteria for sleep apnea syndrome defined as an AHI of ≥5 together with hypersomnolence. However, the majority of subjects with an AHI ≥5 are asymptomatic.[23]

Multiple studies have shown an epidemiologic relationship between OSA and metabolic syndrome,[24,25] with an increasing association of metabolic syndrome with OSA severity.[26] Coughlin et al. examined the role of 6 weeks of CPAP therapy, showing that CPAP improved hypertension but not insulin resistance nor lipid profile.[27] No long-term studies have yet been performed examining the potential role of CPAP therapy in the prevention of metabolic syndrome.

Sleep disordered breathing is associated with increased risk for several of the criteria for metabolic syndrome. The Korean Health and Genome Study found that habitual snoring, a surrogate marker of OSA, was related to the number of metabolic syndrome components in a dose-dependent manner.[28] The Sleep Heart Health Study found a significant association between the respiratory disturbance index and waist-to-hip ratio, hypertension, and hypercholesterolemia in men, and low HDL-C and hypertriglyceridemia in women.[29] A matched-control study among men found that after adjustment for central obesity, age, and alcohol consumption, OSA was associated with insulin resistance, total cholesterol, HDL-C, and leptin.[30] In a study of lean individuals, a Japanese study found that OSA was associated with hypertension, dyslipidemia, insulin resistance, and fasting hyperglycemia and the ratio of visceral-to-subcutaneous fat, suggesting that OSA by itself may promote metabolic dysfunction and fat maldistribution.[31] However, a study in Indian men and women found no relationship between OSA and hypertension, insulin resistance, dyslipidemia, or obesity.[32]

OSA, Insulin Resistance, and Diabetes

OSA has been linked to diabetes mellitus. A high prevalence of OSA has been reported in patients with diabetes mellitus type 2, with up to a 70% prevalence of moderate or severe OSA among obese diabetics who admitted to heavy snoring or excessive daytime sleepiness.[33] The Nurses' Health Study Cohort showed that regular snoring was associated with an approximately doubled risk of type 2 diabetes over 10 years.[34] A Swedish study showed that obese subjects who did not snore were five-fold more likely to develop type 2 diabetes over a 10-year follow-up period, and that obese snorers were seven-fold more likely to develop type 2 diabetes over the same time period compared to nonobese nonsnorers.[35]

OSA also appears to be associated with insulin resistance independent of obesity. Patients with OSA have higher fasting blood glucose levels and higher plasma insulin levels, independent of obesity.[36–40] One study reported that the number of hypoxic episodes correlated with insulin resistance,[41] with another showing a modest correlation between AHI and fasting insulin, but not fasting blood glucose levels.[42]

The data on the effect of CPAP therapy for the treatment of diabetes and insulin resistance are mixed. Some investigators report a reduction in insulin resistance in obese patients with OSA and type 2 diabetes treated with CPAP,[39,43] whereas others found that while CPAP improved hypertension and daytime sleepiness, insulin resistance did not change.[44] A systematic review and meta-analysis of 24 prior studies concluded that while there seems to be a link between OSA and impaired glucose homeostasis, the treatment of OSA with CPAP yielded inconsistent results, and overall CPAP is not associated with an improvement glucose tolerance, perhaps because of poor compliance with CPAP or irreversible changes associated with OSA.[45]

OSA and the Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis plays an important role in regulating alertness and sleep and likely plays a key role in energy balance, visceral fat distribution, and the pathogenesis of human obesity.[46] The events inherent in OSA, including hypoxemia, brief arousals, and sleep fragmentation, alter normal function of the HPA axis.[47] Sleep deprivation is itself associated with pulsatile cortisol release[48] and, in a small number of healthy young men, increased thyrotropin concentration, evening cortisol concentration, and the activity of the sympathetic nervous system as measured by heart rate variability and reduced glucose tolerance.[49]

In a robust study using serial 24-hour cortisol measurements, nonapneic, obese men had low cortisol secretion, and cortisol secretion was increased by sleep apnea and showed a trend toward return to normal with CPAP therapy.[50] More

recently, Carneiro et al. showed no differences in morning or evening cortisol levels between obese patients with and without OSA, although 24-hour heart rate was greater in those with OSA. However, after 3 months of CPAP therapy, those with OSA showed a reduction in heart rate and greater cortisol suppression after dexamethasone, and the greater dexamethasone suppression correlated with pre-CPAP AHI.[51] The authors concluded that obese men with OSA showed higher activity of the sympathetic nervous system, as evidenced by their higher 24-hour heart rate, but a blunted response to cortisol suppression with dexamethasone, suggesting that those with OSA suffer from abnormally high activation of both the sympathetic nervous system and HPA.

OSA and Inflammation

OSA appears to have an inflammatory component, although the exact mechanisms linking OSA to the inflammatory cascade are unclear. Furthermore, obesity itself appears to be a proinflammatory condition, although the effect of weight loss is unclear. Vibratory trauma associated with snoring is associated with tissue injury in the upper airway,[52–54] which has been shown experimentally to cause elevated interleukin-8 levels.[55]

Repetitive hypoxia and reoxygenation seen in OSA likely lead to oxidative stress[56–58] and the generation of reactive oxygen species (ROS), which may play an important role in activating an inflammatory response among patients with OSA.[59] Conversely, oxidative stress seems to be a consequence of both metabolic syndrome and visceral obesity.[60] Microarray measures of gene transcription in patients with OSA show activation of several pathways that potentially modulate and adapt to increased levels of ROS.[61] Some studies have shown that OSA is associated with increased levels of a variety of oxidants, including oxidized low-density lipoproteins (LDL), which are thought to play a key role in promoting atherosclerosis.[62] Furthermore, ROS may not just be a toxic byproduct of metabolism but may also be a tightly regulated metabolite with important signaling properties and may trigger inflammatory pathways[63] that activate multiple proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-8 via the transcription factors nuclear factor-κB (NF-κB), and activator protein 1.[64]

The proinflammatory transcription factor NF-κB is considered to be the master switch involved in the transcription of multiple genes involved in inflammation, metabolic syndrome, and atherosclerosis.[65,66] Repetitive hypoxia and reoxygenation selectively activate the proinflammatory transcription factor NF-κB,[67] and patients with OSA have been reported to have increased levels of NF-κB in neutrophils and monocytes[68] that correlate with OSA severity and are reduced with treatment by CPAP.[69]

In vitro, cell cultures exposed to intermittent hypoxia show selective activation of NF-κB,[67] and mice exposed to intermittent hypoxia mimicking that seen in human OSA also show increased activation of NF-κB that is temporally associated with increased expression of the NF-κB-dependent gene product nitric oxide synthase (NOS).[70] In contrast, several studies have shown a decrease in circulating nitric oxide (NO) derivatives[71,72] and impaired NO-dependent endothelial function in patients with OSA.[73]

C-reactive protein (CRP) is felt to be a biomarker of inflammation that is produced in response to IL-6,[74] and appears to be an important marker in both cardiovascular disease[75] and the metabolic syndrome,[76] being 2.8 times higher among people with metabolic syndrome than in those without metabolic syndrome.[77] The recent JUPITER Study suggested that pharmacologic reduction of CRP lowered cardiovascular risk.[78] The association between OSA and CRP has been inconsistent, perhaps because CRP is also elevated in obese patients independent of OSA.[79–83] Studies comparing otherwise healthy obese men with and without OSA have found that OSA is associated with increased CRP levels after controlling for body mass index (BMI) in both adults[79,80,84] and children.[85] On the other hand, a recent study comparing groups with different OSA severity matched for age and BMI and a fourth group of obese subjects with OSA matched in AHI to the severe OSA group found no increase in CRP in the three BMI-matched groups, whereas the obese group had higher CRP than the AHI-matched group, suggesting that the elevation in CRP was due to obesity and not OSA.[86]

Studies on the effects of treatment are equally conflicting. A number of studies have shown that successful CPAP therapy can reduce levels of CRP among patients with OSA,[82,87,88] whereas another found no change in CRP among a group of nonobese males with OSA after CPAP treatment,[89] suggesting that the attenuation of CRP is most pronounced among obese subjects with OSA.

TNF-α and IL-6 are two of the most commonly studied proinflammatory cytokines. Macrophages in white adipose tissue are a rich source of TNF-α and IL-6. Human and animal studies suggest that both TNF-α and IL-6 may induce insulin resistance, and elevated levels of these proinflammatory cytokines are been reported in patients with the metabolic syndrome.[1,90] IL-6 has been implicated in arterial plaque formation, plaque rupture, and thrombosis, all of which are felt to play a key role in ischemic cardiomyopathy and myocardial infarction.[91,92] Furthermore, both TNF-α and IL-6 are increased in patients with OSA compared to BMI-matched controls,[40,79,93–95] and AHI is related to these cytokines independent of obesity.[40,96] Multiple studies have reported a decrease in TNF-α[95,97] and IL-6 levels after CPAP treatment. Interestingly, the TNF-α polymorphism, TNF-α (−308A), which is associated with increased TNF-α production, is associated with OSA, suggesting the hypothesis that increased inflammation may in fact be causative of OSA. And finally, OSA is associated with increased monocyte adhesion[98] and γδT lymphocyte activation, which are reduced with CPAP treatment.[99]

OSA and Adipokines

The adipokines are a group of fat-derived cytokines of growing interest. An important adipokine is leptin, which is a hormone derived from adipocytes that regulates appetite and energy expenditure. Leptin is correlated with BMI, insulin levels, and TNF-α levels[100] and may have a respiratory stimulant effect[101] and direct effects on the vasculature.[102]

Metabolic syndrome is considered a leptin-resistant syndrome. Furthermore, leptin levels have been shown to predict the development of metabolic syndrome over an 8-year follow-up period.[103] Patients with sleep apnea have elevated serum leptin levels, even when compared to BMI-matched controls.[30,36,104] Two studies showed a reduction in leptin levels without a change in BMI after CPAP treatment in obese subjects,[36,105] whereas another study replicated the results in

nonobese subjects,[106] and a third study showed that CPAP therapy reduced leptin levels in BMI-matched subjects.[107] However, in one study, the elevated leptin levels were most related to visceral fat and TNF-α and IL-6 elevations, and the AHI did not make an additional contribution, suggesting that OSA may act indirectly through cytokines, adiposity, and insulin resistance to increase leptin levels.[40] Further research is needed to clarify the potential role of leptin in metabolic syndrome and OSA.

Ghrelin, a peptide mainly produced in the stomach,[108] has recently been identified as one of the most important hormones regulating appetite. Ghrelin is reduced in obese patients and rises after weight loss, thereby stimulating appetite.[109] Ghrelin levels have been found to be significantly higher in patients with OSA and reduced after 2 days of CPAP treatment.[107]

Adiponectin is another adipocyte-derived molecule with anti-inflammatory and insulin-sensitizing properties, and low adiponectin levels have been postulated to play an important role in the development of metabolic syndrome and diabetes mellitus.[110] One study showed a trend of decreasing adiponectin with increasing OSA severity independent of insulin resistance and BMI,[111] and another showed that those with OSA had higher adiponectin levels.[112] Other studies have failed to show such a relationship.[31,32,113]

OSA, Sleep Deprivation, Metabolic Syndrome, and Inflammation

A little-studied component of OSA is sleep deprivation. In a key study, Spiegel et al. showed that acute sleep deprivation in healthy young men was associated with reduced serum levels of leptin, increased levels of ghrelin, and increased appetite. Acute sleep deprivation is associated with higher glucose levels, and there is indirect evidence that sleep deprivation alters glucose homeostasis, resulting in high glucose levels, insulin resistance, and risk of diabetes.[114] It is known that CPAP treatment seems to reduce sleep deprivation among patients with OSA,[115] but it is not known if this reduction in sleep deprivation is what drives the normalization of metabolic parameters after successful CPAP treatment.

Sleep deprivation in and of itself seem to be proinflammatory. Meier-Ewert et al. showed that both an 88-hour period of sleep deprivation and a 10-day period of sleep restriction to 4 hours per night was associated with elevated levels of CRP,[116] and a 12-day period of sleep restriction was associated with significantly increased levels of IL-6 and a trend toward higher CRP levels.[117]

Summary

Both OSA and metabolic syndrome are worldwide epidemics that have gained increasing scientific attention. Emerging but mixed data suggest that metabolic syndrome may not be just a comorbidity of OSA, but may also be mechanistically linked through a number of possible pathways. OSA is associated with alterations in the HPA axis that may promote metabolic syndrome. The hypoxia associated with OSA seems to trigger an oxidative stress that may promote development of metabolic syndrome. Multiple inflammatory markers and mediators, including NF-κB, CRP, TNF-α, and IL-6, are elevated in patients with OSA and may play a role in the development of metabolic syndrome. The adipokines, including leptin, ghrelin, and adiponectin, seem to be dysregulated in patients with OSA in ways that promote a positive energy balance, obesity, and metabolic syndrome. Sleep deprivation from OSA may also be implicated due to its effects on both metabolic regulation and systemic inflammation. Identification of mechanistic interactions between OSA and metabolic syndrome may suggest opportunities by which the pathophysiology of OSA can be interrupted to prevent manifestations of the metabolic syndrome.

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Address correspondence to:
Virend K. Somers, M.D., Ph.D.
Professor of Medicine
Division of Cardiovascular Disease
Mayo Clinic College of Medicine
200 First Street SW
Rochester, MN 55905

E-mail: somers.virend@mayo.edu