

Obstructive Sleep Apnea Therapy and Metabolic Outcomes

Harnet K. Walia, MD^{a,b,*}, Reena Mehra, MD, MS^{b,c,d}

KEYWORDS

- Obstructive sleep apnea • Metabolic syndrome • Obesity • Hypertension
- Continuous positive airway pressure

KEY POINTS

- There are both epidemiologic and experimental data implicating obstructive sleep apnea (OSA) as a key pathophysiologic factor in the evolution of metabolic dysfunction and as a culprit in increasing cardiovascular risk.
- The metabolic syndrome consists of a constellation of clinical risk factors encompassing truncal obesity, atherogenic dyslipidemia, elevated blood pressure, low glucose tolerance, and hyperinsulinemia, which in aggregate set the stage for the development of diabetes mellitus and cardiovascular disease.
- Conceptual frameworks are emerging with respect to the mechanistic underpinnings of OSA including intermittent hypoxia, sleep fragmentation, systemic inflammation and oxidative stress that contribute to the various facets of metabolic dysfunction.
- Reversal of the adverse accompanying pathophysiologic effects of OSA can have an impact on metabolic outcomes.
- The data suggests that treatment of OSA may ameliorate some of the metabolic parameters of metabolic syndrome.

INTRODUCTION

Aligned with the obesity epidemic, metabolic dysfunction has evolved into a highly prevalent condition with pervasive, far-reaching public health implications. The metabolic syndrome, a term characterized by a clustering of independent cardiovascular risk factors, has a current estimated prevalence of 30% in the United States population,

with projections for a continued increase in frequency slated to reach levels in the epidemic realm.¹ The metabolic syndrome consists of a constellation of clinical risk factors encompassing truncal obesity, atherogenic dyslipidemia (high levels of triglyceride and low levels of high-density lipoprotein [HDL] cholesterol), elevated blood pressure (BP), low glucose tolerance, and hyperinsulinemia in the context of a prothrombotic

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^a Center for Sleep Disorders, Neurologic Institute, Cleveland Clinic, 11203 Stokes Boulevard, 2nd Floor, Cleveland, Ohio 44104, USA; ^b Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA; ^c Sleep Disorders Research, Center of Sleep Medicine, Neurologic Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA; ^d Molecular Cardiology Department, Lerner Research Institute, Heart and Vascular Institute, Respiratory Institute, 9500 Euclid Avenue, Cleveland, Ohio, 44195, USA

* Corresponding author.

E-mail address: WALIAH@ccf.org

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state and upregulation of systemic inflammation, which in aggregate set the stage for the development of diabetes mellitus and cardiovascular disease.^{1,2} These risk factors result in serious adverse health effects by interacting synergistically to increase cardiovascular morbidity and mortality by 2- to 3-fold.^{1,2} Diagnostic evaluation and targeted intervention coupled with identification of critical contributors of metabolic syndrome are paramount in the paradigm of cardiovascular risk reduction. Reduction of cardiovascular risk is of the utmost importance from the standpoint of public health imperatives as well as in targeting reduction of the high economic costs associated with cardiovascular disease, namely, estimated direct and indirect costs of \$500 billion in 2010 with \$150 billion resulting from loss of productivity related to disability and death.³

A wealth of both epidemiologic and experimental data have implicated obstructive sleep apnea (OSA) as a key pathophysiologic factor in the evolution of metabolic dysfunction and as a culprit in increasing cardiovascular risk. A singular challenge in investigating the interrelationships of obesity, metabolic syndrome, and OSA has been to effectively take into consideration and dissect the influence of OSA on metabolic syndrome independent of the effect of obesity. OSA is a highly prevalent disorder affecting approximately 15% of adults, characterized by reduction in upper airway muscle tone during sleep resulting in repetitive complete (resulting apnea) or partial (resulting in hypopnea) upper airway closure in the presence of continued thoracoabdominal effort and, often, paradox. OSA results in accompanying physiologic perturbations including intermittent hypoxia, ventilatory overshoot hyperoxia, intrathoracic pressure alterations, autonomic instability, and sleep fragmentation. These effects then lead to further adverse effects including increased systemic inflammation and elevated oxidative stress. The apnea-hypopnea index (AHI) is considered as the disease-defining metric for OSA, and is defined by the number of apneas and hypopneas per hour of sleep. Other measures used to ascertain the severity of OSA include the oxygen desaturation index and percentage of sleep time spent in hypoxia. Conceptual frameworks are emerging with respect to the mechanistic underpinnings of OSA that contribute to the various facets of metabolic dysfunction, which are elaborated in this article. Furthermore, the effect of the reversal of the adverse accompanying pathophysiologic effects of OSA on metabolic outcomes is reviewed herein. These areas of investigation are of paramount importance in achieving the goal of effective treatment of metabolic parameters to

mitigate cardiovascular risk, particularly in light of data demonstrating synergism of OSA and metabolic syndrome in increasing cardiovascular risk.⁴

EPIDEMIOLOGY AND INTERRELATIONSHIPS OF OBSTRUCTIVE SLEEP APNEA, METABOLIC SYNDROME, AND OBESITY

Identified relationships of OSA and metabolic syndrome are not unanticipated given the overlap of established associated factors including obesity, diabetes mellitus, and cardiovascular disease. The co-occurrence of metabolic risk factors for both type 2 diabetes and cardiovascular disease (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension) suggested the existence of a "metabolic syndrome," also known as insulin resistance syndrome. According to criteria proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, the metabolic syndrome is defined by the presence of 3 or more of the following: (1) abdominal obesity with waist circumference greater than 40 inches (102 cm) in men and 35 inches (88 cm) in women, (2) serum triglycerides of 150 mg/dL, (3) HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women, (4) BP greater than 130/85 mm Hg or drug treatment for hypertension, and (5) fasting glucose level greater than 110 mg/dL.⁵ The prevalence of metabolic syndrome as defined by NCEP criteria as per National Health and Nutrition Examination Survey (NHANES) data has undergone a substantive increase from 22% in NHANES 1988 to 1994 to 34.5% in NHANES 1999 to 2002.⁶ Along these lines, as expected, an age-dependent increase in the prevalence of metabolic syndrome was also observed. Corroborating data from a large epidemiologic cohort, the Framingham Heart Study involving 3500 participants without diabetes or cardiovascular disease at baseline, demonstrated an increase in prevalence of metabolic syndrome of 26.8% in men and 16.6% in women at baseline, and an almost doubling of prevalence of the metabolic syndrome in both men and women after an 8-year follow-up period.⁷ A likely contributing factor to the noted dramatic increase in prevalence of metabolic syndrome is the concordant obesity epidemic, which has been observed across a range of ethnicities.⁸

OSA is also a highly prevalent disorder with prevalence estimates of 9% to 24%,⁹ with a distinct risk-factor profile characterized by increased risk in men; positive linear relationships with increasing age; and augmented risk related to obesity, owing to mechanical effects on the upper airway predisposing to collapsibility, as well as

neurohumoral effects of adipokines and craniofacial structural alterations resulting in compromise of upper airway caliber and function.¹⁰ Adverse effects of OSA, including intermittent hypoxia and autonomic nervous system fluctuations, contribute to the increased risk of intermediate cardiovascular factors comprising metabolic syndrome, as well as a wealth of data supporting relationships between OSA and increased cardiovascular morbidity and mortality.^{11,12} Although obesity can be posited as the culprit connecting OSA and metabolic syndrome, mounting data indicate that this is not entirely the case. Metabolic syndrome has been noted to be significantly associated with moderate to severe OSA in a comparison with obese controls, suggesting that obesity-independent OSA pathophysiologic pathways are contributing to the evolution of metabolic syndrome.¹³ Amassing evidence also demonstrates a relative synergism of the presence of OSA and metabolic syndrome, such that the burden of cardiovascular disease is far greater with both of these factors compared with either alone.¹⁴ It has been posited that OSA, given its coaggregation and synergism with metabolic syndrome, may represent a salient component of metabolic syndrome constituting a cluster that has been termed Syndrome Z.¹⁵ The co-occurrence of OSA and metabolic syndrome, Syndrome Z,¹⁵ recently has been identified to be associated with a significantly greater atherogenic burden and higher prevalence of calcified carotid artery atheromas when compared with OSA alone in the absence of metabolic syndrome,¹⁶ and is also correlated with intracoronary stenosis detected by multislice computed tomography.¹⁷ Syndrome Z also appears to be related to alterations in cardiac morphology, specifically left ventricular hypertrophy and diastolic dysfunction.¹⁸ Epidemiologic data from the Wisconsin Sleep Cohort support strong associations between OSA and metabolic syndrome. Age-adjusted and sex-adjusted associations resulted in a 4-fold increased odds of metabolic syndrome in those with moderate to severe OSA, which persisted after adjustment for markers of sympathetic or neuroendocrine activation (urinary norepinephrine, cortisol, heart-rate variability); after further adjustment for obesity this was mitigated to a 2.5-fold increased odds of metabolic syndrome, although it remained significant.¹⁹ Furthermore, in a hospital-based urban northern Indian population, those with OSA were 4 times more likely to have metabolic syndrome than those without OSA, supporting the notion of consistent relationships across different ethnic groups.²⁰ The strong magnitude of association between OSA and

metabolic syndrome was further substantiated by data from a British study showing a 9-fold increased likelihood of metabolic syndrome in men with OSA even after consideration of obesity.¹³ Taken together, accumulating evidence points to a steadily increasing prevalence of metabolic syndrome and a high prevalence of OSA, with risk-factor profiles derived from a “common soil,” and relationships that are strong in magnitude seemingly demonstrating a consistent pattern of independence from obesity.¹³

PHYSIOLOGIC AND BIOLOGICAL MECHANISMS OF ALTERED METABOLIC REGULATION IN OBSTRUCTIVE SLEEP APNEA

The mechanisms linking OSA and alterations in metabolic regulation are likely to be multifactorial. OSA via repetitive upper airway collapse results in bouts of intermittent hypoxia, hyperoxia, hypercapnia, sympathetic nervous system activation, and sleep disruption/fragmentation, which may be detrimental to glucose and lipid metabolism via intermediate mechanisms that include upregulation of pathways of systemic inflammation and oxidative stress and abnormalities of the hypothalamic-pituitary axis. This section focuses primarily on the impact of OSA-related intermittent hypoxia, sleep fragmentation, and increased systemic inflammation on metabolic function, as gaining a firm understanding of these concepts not only is crucial in setting the stage for the examination of interventional trial data targeting reversal of OSA pathophysiology on metabolic outcomes, but also is instrumental in the interpretation of these data.

Impact of Hypoxemia on Metabolic Function

Experiments in animal models have shown that intermittent hypoxia can decrease insulin sensitivity and induce glucose intolerance.^{21,22} Some of these effects may occur via the sympathetic nervous system and altered autonomic function, the latter of which is impaired in OSA and also in prediabetic persons with impaired glucose metabolism.²³ Catecholamines also inhibit insulin secretion by activating α 2-adrenoreceptors in β cells.²⁴ Exposure to intermittent hypoxia in young healthy adults has been shown to impair insulin sensitivity with a lack of compensatory hyperinsulinemia, suggesting a concordant suppression of β -cell function.²⁵

Independently of autonomic nervous system activation, in animal models intermittent hypoxia contributes to decreased glucose utilization in oxidative muscle fibers.²⁶ Furthermore, intermittent hypoxia contributes to increased β -cell proliferation and cell death, the latter secondary to

oxidative stress.²⁷ Increased oxidative stress, increased lipid peroxidation, and upregulation of nuclear factor κ B (NF- κ B) and hypoxia-inducible factor 1 are likely the main mechanisms of insulin resistance induced by hypoxia.²⁸

Similar relationships have been confirmed in human studies examining the effects of intermittent hypoxia on metabolic regulation. Specifically, a study randomizing participants to 5 hours of intermittent hypoxia versus normoxia during wakefulness supported the notion that hypoxic stress in OSA may increase the predisposition for metabolic dysfunction by impairing insulin sensitivity, glucose effectiveness, and insulin secretion.²⁵ Moreover, in a large, prospective Japanese study involving about 4000 middle-aged individuals, nocturnal intermittent hypoxia (3% oxygen saturation dips $\geq 15/h$ on pulse oximetry at baseline) was established as a risk factor for development of type 2 diabetes mellitus after a 3-year median follow-up period (1.7-fold risk of incidental diabetes mellitus compared with those without significant hypoxia) after adjustment for multiple confounders.²⁹ In the Cleveland Family study, measures of hypoxic stress (time spent with $<90\%$ O₂ saturation) were the strongest polysomnographic index associated with glucose intolerance.³⁰

Relationship of Sleep Fragmentation with Metabolic Regulation

Although sleep fragmentation may occur in various sleep disorders, it is a cardinal feature of OSA and results in alterations in glucose metabolism independent of sleep duration. Both human and animal experimental data support the notion of sleep fragmentation representing an allostatic load on the endocrine and autonomic systems, potentially resulting in development of metabolic dysregulation.³¹ For instance, it is recognized that the initiation of slow-wave sleep coincides with hormonal changes that affect glucose homeostasis.³² As such, all-night selective suppression of slow-wave sleep for 3 consecutive nights has been shown to result in an approximately 25% reduction in insulin sensitivity without adequate compensatory increase in insulin secretion, thereby leading to reduced glucose tolerance and increased risk of developing diabetes.³² Moreover, 2 days of enforced sleep fragmentation resulting in poor sleep quality and reduced slow-wave sleep yielded similar results.³² Nonselective fragmentation of sleep induced by auditory and mechanical stimuli across all stages for 2 nights is also associated with a decrease in insulin sensitivity and non-insulin-dependent glucose disposal, the latter referring to glucose mobilization independent of an insulin

response.³³ Of note, fasting intravenous glucose tolerance testing was used in this study, a technique considered to be the gold standard in the assessment of glucose regulation.³³ Sleep fragmentation also led to an increase in morning cortisol levels and a shift in sympathovagal balance toward an increase in sympathetic nervous system modulation and reduction in parasympathetic activity, hence shedding light on potential mechanistic underpinnings.³³ Moreover, chronic sleep loss related to sleep-disordered breathing is likely to worsen the metabolic disturbances and may predispose to insulin resistance.³⁴ Experimental animal studies using intravenous glucose tolerance testing before and after an 8-day period of sleep restriction and disturbance, in the absence of sleep curtailment, resulted in hyperglycemia and decreased insulin levels, further corroborating the results from human studies.³⁵ More recent experimental data further support this premise, and extend the length of sleep fragmentation to 14 days using a sleep interruption model intended to minimize stressful stimulation to the animal. Findings in the latter work demonstrated not only an impact on peripheral glucose metabolism but also on appetite, with evidence of hyperphagia in the absence of weight gain suggesting alterations in the metabolic rate as a potential culprit.³⁶

Systemic Inflammation and Oxidative Stress in Obstructive Sleep Apnea as Instigators of Altered Metabolic Function

Inflammation has been proposed as a putative mechanism of cardiovascular risk in patients with OSA, and it may also impair insulin action in peripheral tissues. Intermittent hypoxia and sleep fragmentation in OSA are postulated to be triggers of the cascade of inflammation in the adipose tissue and vascular compartment, and thus an array of inflammatory products may be released.³⁷ Multiple inflammatory markers and mediators, including NF- κ B, C-reactive protein, tumor necrosis factor α , and interleukin-6, are elevated in patients with OSA,³⁸ and these markers have been noted to be culprits in inducing insulin resistance.³⁹ The authors' group has shown relationships between markers of systemic inflammation (including soluble interleukin-6 receptor) and increasing severity of OSA, independent of confounding by obesity and apparent diurnal patterns such that morning levels were more closely tied to OSA severity, potentially signifying a reflection of overnight OSA-related physiologic stress.⁴⁰ The presence of these markers of inflammation in metabolic syndrome⁴¹ support that OSA may play a role in development of metabolic syndrome. Furthermore, the

adipokines, including leptin, ghrelin, and adiponectin, are altered in patients with OSA and can promote metabolic syndrome.³⁸ Because of the close association between inflammation and insulin resistance, it has been suggested that visceral obesity is a potential pathogenic factor in promoting inflammation and leading to insulin resistance and sleep apnea.⁴² Elevated oxidative stress is emerging as a central player in the pathogenesis of metabolic syndrome, and may represent a unifying factor in progression of disease. In particular, oxidative stress has been identified as a major mechanism underlying the microvascular and macrovascular complications in metabolic syndrome.⁴³ OSA has been recognized as providing the ideal milieu for oxidative stress to occur, given the repetitive intermittent bouts of hypoxemia and subsequent episodes of reoxygenation, which may lead to generation of free radicals and a state of enhanced oxidative stress. This resultant state of augmented oxidative stress may thus lead to the metabolic insults seen in the representative components of metabolic syndrome.

EFFECT OF OBSTRUCTIVE SLEEP APNEA TREATMENT WITH CONTINUOUS POSITIVE AIRWAY PRESSURE ON LIPID BIOLOGY AND VISCERAL ADIPOSITY

It has been hypothesized that continuous positive airway pressure (CPAP) via amelioration of breathing disturbances during sleep can improve the lipid profile, such as total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, triglycerides, and apolipoproteins A, B, and C. However, despite mechanistic studies consistently demonstrating relationships between OSA and lipid biosynthesis and regulation, the effect of CPAP on lipids has revealed conflicting results. Several studies have shown that CPAP treatment is beneficial for improving the lipid profile of OSA patients. A meta-analysis of 2 randomized, placebo-controlled trials in OSA patients compared the effect of therapeutic and subtherapeutic CPAP treatment on cholesterol and triglycerides. There was a significant reduction in total cholesterol levels among patients receiving therapeutic CPAP for a short treatment duration of 1 month compared with those receiving subtherapeutic CPAP, and no significant changes were observed in serum triglycerides in either group.⁴⁴ A large study of OSA patients showed a small but statistically significant increase in HDL cholesterol after 6 months of CPAP therapy. Significant improvements in serum levels of HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides in OSA patients with baseline

abnormal lipid/lipoprotein serum levels were also noted.⁴⁵ Data from a smaller randomized trial showed an improvement in postprandial triglycerides and total cholesterol levels in patients with moderate to severe OSA with CPAP therapy.⁴⁶ A significant improvement in the ratio of HDL to total cholesterol and levels of total cholesterol, triglycerides, and LDL and non-HDL cholesterol with autoadjusting positive airway pressure (PAP) was noted in a randomized controlled trial, with a significant increase in HDL cholesterol noted only in more adherent patients.⁴⁷ It remains unclear, however, whether the improvement in lipid profiles may be secondary to concomitant reduction in body mass index, or secondary to direct reversal of OSA adverse physiologic effects with PAP. On the other hand, data from several studies have suggested that CPAP treatment does not improve serum lipid levels. In a randomized, controlled, crossover trial, obese Caucasians with symptoms of OSA underwent intervention with 6 weeks of therapeutic versus sham CPAP without an appreciable change in lipids. In the therapeutic CPAP group, there was no significant change in cholesterol triglycerides, HDL cholesterol, and LDL cholesterol after CPAP treatment.⁴⁸ Similarly, in a double-blind, randomized controlled trial of therapeutic and sham CPAP for 3 months in men with type 2 diabetes and OSA, no significant reduction in total cholesterol, HDL cholesterol, or triglycerides was observed before and after treatment.⁴⁹

Visceral adipose mass is considered to be a more accurate measure of dysfunctional adipose tissue than body mass index when considering facets of metabolic syndrome. Quantitative radiologic measures of visceral adiposity using standard computed tomography (CT) scans have been reported as the gold-standard method for assessing visceral adiposity, given its ability to precisely and reliably measure abdominal fat compartments.⁵⁰ In a randomized crossover trial involving those with moderate to severe OSA, a significant reduction in visceral fat in addition to subcutaneous fat was noted,⁴⁷ which is contrary to the findings of another randomized trial that failed to demonstrate reduction in visceral abdominal fat over a 12-week period and did not show improvement at 6 months during an uncontrolled portion of the study.⁵¹ Two other recent trials performed over an 8-week period did not show reduction in visceral abdominal fat with CPAP treatment of OSA.^{52,53}

Overall, the effect of CPAP on visceral abdominal fat has been inconsistent, with some studies showing improvement in the amount of visceral fat. This finding may be attributable to the relatively

limited duration of OSA treatment implemented in these trials.^{54,55}

OBSTRUCTIVE SLEEP APNEA TREATMENT AND HYPERTENSION

OSA has been linked with hypertension (HTN), an increased prevalence of a nondipping BP pattern, and increased risk of resistant HTN. Apnea-related arousals and/or hypoxemia can result in sympathetic nervous system activation, leading to elevated nocturnal or daytime BP. The guidelines on HTN detection and treatment recommend evaluation of OSA as a cause of difficult-to-treat HTN.⁵⁶ Numerous studies, ranging from uncontrolled studies through clinical observational to randomized double-blind trials, have investigated the effect of CPAP on HTN (**Table 1**). However, the effect of CPAP treatment on BP was highly variable, and some individuals do not show any antihypertensive benefit other than having manifested a very high BP response. This variability in response can be explained by multiple reasons: most studies were of small sample size; most studies were performed in a single center; the methods used for measuring BP such as the 24-hour ambulatory BP monitoring or office BP measurement varied widely between the studies; and studies included patients with and without hypertension, as well as different types of hypertension and treatment interventions. Furthermore, the method used to diagnose OSA varied; the studies had different designs, such as crossover or parallel; studies used different interventions such as sham CPAP, subtherapeutic CPAP, drug therapy, or conservative treatment in control participants; and the duration of intervention varied between different studies. Even the meta-analyses of randomized trials are limited by the trials they included, and many of the trials did not involve the patients most likely to benefit, which may explain the variability of the results. Use of CPAP has generally shown a consistent, albeit modest, antihypertensive benefit. Patients who are most likely to benefit include those with more severe OSA, and higher baseline pretreatment BP levels, and patients more compliant with CPAP use.

Two large, randomized controlled trials evaluating the role of CPAP in HTN were recently published.^{57,58} The first was randomized, multicenter, double-blind, placebo-controlled trial of 340 patients, primarily men (81%), which showed a statistically significant decline in 24-hour arterial BP, systolic BP (SBP), and diastolic BP (DBP) by 1.5, 2.1, and 1.3 mm Hg, respectively. Mean nocturnal BP decreased by 2.0 mm Hg after 3 months of treatment in patients with newly diagnosed HTN.⁵⁷ This observed reduction was smaller than

anticipated and did not achieve the 3-mm Hg drop in mean 24-hour ambulatory BP that the trial was powered to detect. In the second study, the Spanish Sleep and Breathing Group trial of more than 350 asymptomatic individuals with severe OSA in which one arm was treated with CPAP, at 1-year follow-up the group treated with CPAP had a significant reduction in SBP and DBP of 1.9 mm Hg and 2.2 mm Hg, respectively. The most significant reduction in BP was seen in patients who used CPAP for more than 5.6 hours per night.⁵⁸

Several meta-analyses suggest that the beneficial effects of CPAP on BP are detectable in the first few weeks of treatment, this being counterintuitive to what one may expect, as the vascular remodeling and other structural cardiovascular changes are not expected to be evident in short-term trials of CPAP treatment, and longer treatment may be needed to obtain greater reductions in BP. However, results from randomized trials have found significant reductions in BP within a few weeks of CPAP treatment.⁵⁹⁻⁶¹

A 2007 meta-analysis of 10 randomized controlled trials did not show any difference in SBP or DBP between the PAP and the control group using ambulatory BP monitoring and office BP measurements combined.⁶² In another meta-analysis including 16 trials conducted between 1996 and 2006 and a total of 818 patients, a small but statistically significant mean net change in SBP of 2.5 mm Hg and DBP of 1.8 mm Hg was observed. Net reductions in BP were not statistically different between daytime and nighttime. This meta-analysis included predominantly obese middle-aged men and comprised studies that were not blinded.⁶³

In one of the prospective observational studies with a longer follow-up of 55 patients, a significant decrease was shown only for DBP (−2.2 mm Hg) but not SBP or 24-hour mean arterial BP. Subgroup analyses, however, showed that 24-hour mean BP did decrease significantly in patients with uncontrolled HTN at entry (−4.4 mm Hg, $P = .01$) as well as in those with high CPAP compliance (−5.3 mm Hg, $P = .01$).⁶⁴

A significant decrease in BP was reported by Pepperell and colleagues⁶¹ in 118 patients, with the largest effect on BP observed with CPAP in severe OSA (oxygen desaturation index >33/h, decrease in BP of 5.1 mm Hg). Moreover, use of therapeutic CPAP for more than 5 hours per night showed a greater trend toward decreased BP. Becker and colleagues⁶⁵ showed the largest reduction in BP of about 10 mm Hg SBP, mean arterial BP, and DBP in a 9-week double-blind trial in patients with moderate to severe sleep apnea.

This drop in BP was seen in patients with therapeutic CPAP treatment with an approximately 95% reduction in AHI. Despite the reduction in AHI by 50%, in the subtherapeutic control group there was no significant reduction in BP. Coughlin and colleagues⁴⁸ showed a reduction in mean SBP and DBP of 6.7 mm Hg and 4.9 mm Hg, respectively, with CPAP in obese individuals, and there were no changes in metabolic parameters.

In another randomized study that used ambulatory BP measurements in patients with OSA, a 12-week CPAP regimen resulted in a reduction in 24-hour mean BP and DBP by 3.8 and 3.5 mm Hg, respectively. In this study, the majority of subjects were not sleepy based on the Epworth Sleepiness Scale (ESS) score.⁶⁶ Whereas some of the trials have shown improvement in BP with CPAP in hypersomnolent patients,⁵⁹ Robinson and colleagues⁶⁷ showed no significant improvement in BP with CPAP in nonhypersomnolent patients, suggesting a role of hypersomnolence in the pathogenesis of HTN caused by OSA. There have been other randomized trials reinforcing the improvement of various BP measurements with CPAP.⁶⁸

The effect on BP by CPAP withdrawal has also been measured, which showed an increase in morning SBP and DBP and morning heart rate, along with increases in other clinical features and inflammatory markers of OSA.⁶⁹ In 2011, Drager and colleagues⁷⁰ showed the impact of CPAP on a novel group of patients with pre-HTN and or masked HTN. Thirty-six male patients randomized to no treatment and CPAP for 3 months showed a significant reduction of pre-HTN (from 94% to 55%) and masked HTN (from 39% to 5%). This finding is important from clinical standpoint, as most patients with pre-HTN develop HTN later. This study is the first to evaluate the effect of BP in pre-HTN patients. Overall, CPAP has been shown to have a modest effect in reducing BP, which also is important from the clinical viewpoint because it can have a significant effect in reducing comorbidity.

Most results available on the effect on BP of an oral appliance are based on observational data. Most studies showed a significant improvement in BP in mild to moderate sleep apnea with use of an oral appliance.^{71,72} A Chinese study of 46 patients compared a group wearing an oral appliance monitored by ambulatory BP with a nontolerated oral appliance treatment group.⁷³ There was a significant improvement in SBP, DBP, 24-hour and diurnal SBP, and mean arterial pressure in the oral appliance group in comparison with the other group after 12 weeks of treatment. Another observational study involving 161 patients showed improvement in SBP, DBP, and mean arterial

BP.⁷⁴ A small study involving only 11 subjects with an oral appliance showed improvement in ambulatory BP monitoring after titration.⁷⁵ A randomized, controlled, crossover trial of 61 patients showed significant reduction in mean 24-hour DBP and awake BP; however, no reduction was seen in SBP.⁷⁶ Andren and colleagues⁷⁷ conducted a long-term follow-up study of patients with mild OSA, and showed that a reduction in SBP and DBP was maintained after 3 years of use of a mandibular advancement oral appliance. A meta-analysis indicated the pooled estimate of mean changes and the corresponding 95% confidence interval (CI) for SBP, DBP, and mean arterial BP, respectively, from each trial were: -2.7 mm Hg (95% CI: -0.8 to -4.6); -2.7 mm Hg (95% CI: -0.9 to -4.6); and -2.40 mm Hg (95% CI: -4.01 to -0.80).

The clinical significance of SBP and DBP reductions of 2 to 4 mm Hg can be put into perspective by data showing a 15% and 42% reduction in the risk of coronary artery disease and stroke, respectively, with a reduction in BP of 5 mm Hg.⁷⁸ With respect to the effect of OSA treatment on BP reduction, there is a clinically significant cardiovascular benefit to OSA treatment in potentially reducing adverse cardiovascular outcomes, for which hypertension represents a firm risk factor. Areas of future work should focus on better understanding the relationships of OSA and nondipping BP profiles, in particular to examine the potential benefits of chronotherapy for antihypertensive medication in OSA patients. Use of supplemental oxygen as a treatment of OSA-related intermittent hypoxia may also serve to blunt sympathetic nervous system surges and reduce BP; therefore interventional trials examining this effect are desired. Along these lines, results of a multicenter, randomized controlled trial involving patients from cardiology clinics with moderate to severe OSA randomized to CPAP, supplemental oxygen, or a healthy lifestyle are forthcoming. Moreover, OSA as a culprit of resistant hypertension and nondipping BP patterns needs to be addressed from the standpoint of ascertaining improvement in BP profiles in this high-risk group.

EFFECT OF POSITIVE AIRWAY PRESSURE AND NON-POSITIVE AIRWAY PRESSURE MODALITIES OF OBSTRUCTIVE SLEEP APNEA THERAPY ON COMPONENTS OF METABOLIC SYNDROME

Uncontrolled Trials

Several uncontrolled trials have focused on the effect of CPAP therapy on OSA and its impact on metabolic syndrome. These studies have been

Table 1
Studies investigating the effect of CPAP on blood pressure

Authors, ^{Ref.} Year	Type	N	Male (%)	Age (y)	Intervention	Duration	OSA	BP	Effect of Treatment on BP Parameters
Duran-Cantolla et al, ⁵⁷ 2010	Randomized controlled double-blind trial	340	81	53.2, 51.7	CPAP and sham CPAP (<1 cm H ₂ O)	3 mo	AHI >15	History of HTN or on antihypertensive medications	↓ in ABP by 1.5 mm Hg ↓ SBP 2.1 mm Hg, ↓DBP 1.3 mm Hg
Becker et al, ⁶⁵ 2003	Randomized controlled trial	32	60	54.4, 52.3	CPAP and subtherapeutic PAP	9 wk	AHI ≥5, ESS 10	None	↓ 9.9 mm Hg, MBP and SBP and DBP ↓ by 10 mm Hg
Pepperell et al, ⁶¹ 2002	Randomized controlled parallel-group trial	118	100	51	Therapeutic and subtherapeutic CPAP (1 cm H ₂ O)	1 mo	ESS >9, ODI (4%) >10	None	↓ MAP by 2.5 mm Hg Effect more pronounced in severe OSA
Robinson et al, ⁶⁷ 2006	Randomized controlled crossover trial	35	31	54	Auto PAP and subtherapeutic CPAP	1 mo	ODI (4%) >10	Excluded BP <140/90 or not on antihypertensive	No significant difference in mean 24-h BP in nonhypersomnolent patients
Hui et al, ⁶⁶ 2006	Randomized controlled parallel-group trial	28	22/6, 21/7	50.3, 51.2	Therapeutic (10.7 cm H ₂ O) CPAP and subtherapeutic CPAP (4 cm H ₂ O)	12 wk	AHI >5 with symptoms of OSA	None	↓ in 24-h mean BP by 3.8 mm Hg and DBP by 3.5 mm Hg
Coughlin et al, ⁴⁸ 2007	Randomized controlled crossover trial	34	100	49.0 ± 8.3	CPAP and sham CPAP	6 wk	AHI >15	Excluded BP >180/110	↓ in SBP and DBP by 6.7 and 4.9 mm Hg, no change in metabolic parameters

Kohler et al, ⁶⁹ 2011	Randomized controlled trial	41	19/1, 21/0	63.6, 61.8	CPAP or withdrawal CPAP (subtherapeutic CPAP)	2 wk	ODI (4%) ≥ 10	Excluded inadequately controlled HTN	CPAP withdrawal was associated with increase in morning office SBP (8.5 mm Hg), morning DBP (6.9 mm Hg)
Drager et al, ⁷⁰ 2011	Randomized controlled trial	36	100	43 CPAP 44 control	No treatment or CPAP treatment (based on PSG)	3 mo	AHI >30	Pre-HTN (SBP 120–139, DBP 80–89), masked HTN (AABP 135>85)	CPAP (from 126 \pm 5 to 121 \pm 7 mm Hg; $P = .001$) and a trend DBP (from 75 \pm 7 to 73 \pm 8 mm Hg; $P = .08$). Significant reduction in frequency of pre-HTN (from 94% to 55%; $P = .02$) and masked HTN (from 39% to 5%; $P = .04$) only in the CPAP group
Barbe et al, ⁵⁸ 2010	Randomized controlled trial	359	100	56 \pm 10	CPAP or conservative treatment	1 y	AHI >19, ESS <11	SBP >140 or DBP >90	Reduction of in SBP and DBP of 1.9 mm Hg and 2.2 mm Hg, respectively. Most significant reduction in BP seen in patients who used CPAP for more than 5.6 h per night
Faccenda et al, ⁵⁹ 2001	Randomized controlled crossover trial	68	81	50	CPAP or oral placebo	4 wk	AHI >15	24 h BP	1.5 mm Hg reduction in DBP

Abbreviations: ABP, ambulatory blood pressure (mm Hg); AHI, apnea-hypopnea index; BP, blood pressure (mm Hg); CPAP, continuous positive airway pressure; DBP, diastolic blood pressure (mm Hg); HTN, hypertension; MAP, mean arterial blood pressure (mm Hg); ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polysomnography; SBP, systolic blood pressure (mm Hg).

limited by their small sample size, uncontrolled nature, and varying consideration of primary and secondary outcomes. One of the first studies reporting the effect of OSA treatment with CPAP on metabolic syndrome assessed this effect on insulin resistance as ascertained by the insulin sensitivity index gleaned from the gold-standard hyperinsulinemic euglycemic clamp studies, which were performed in 40 patients over a 3-month period.⁷⁹ The degree of apnea was moderate to severe (AHI >20) and the investigators observed a significant increase in insulin sensitivity after 2 days of CPAP treatment, which persisted at 3 months and appeared to be most pronounced in the nonobese individuals (ie, those with a body mass index <30 kg/m²). These effects were noted in the absence of significant changes in body mass index. The investigators surmised that the early improvement in insulin sensitivity may be secondary to reversal of sympathetic nervous system surges related to OSA, and that the preferential benefit noted in the nonobese may reflect primarily an obesity-driven source of insulin resistance in obese individuals with a lesser extent of OSA influence in this setting. Limitations of this study included the involvement of only men, with results generalizable as such, and also that only a small proportion of individuals had impaired glucose tolerance.⁷⁹

Another clinic-based study of primarily men who were morbidly obese (mean body mass index of 43 ± 8.7 kg/m²) showed an improvement in postprandial glucose values as well as a reduction in hemoglobin A_{1c} (HbA_{1c}) levels in those with a baseline HbA_{1c} level of greater than 7%. Furthermore, there was a relationship of improved glucose handling relative to PAP usage such that in those individuals using CPAP for greater than 4 hours per day, the reduction in HbA_{1c} level correlated with the days of CPAP usage; this finding was not observed in those less adherent with therapy.⁸⁰ Similarly, findings from another study with a small sample size demonstrated a correlation of hypoxemia in patients with OSA and HbA_{1c} levels in a group ranging from normal to prediabetic and diabetic. Individuals with optimal adherence after 3 to 5 months of CPAP therapy showed a significant reduction in HbA_{1c} levels.⁸¹

Two months of CPAP therapy in a small study showed improvement in cardiovascular risk profiles of patients with severe OSA and concurrent metabolic syndrome, resulting in reductions in BP, total cholesterol levels, insulin resistance measured by Homeostatic Model Assessment—Insulin Resistance (HOMA-IR), tumor necrosis factor α , and oxidative stress markers. Similar to other data, these beneficial effects of therapy were

observed in those who used CPAP for more than 4 hours per day.⁸² A few studies have assessed metabolic parameters of individuals undergoing treatment for OSA over a more prolonged period of time. Specifically, another study involving a small sample size but following patients with OSA and on CPAP for a 1-year period, demonstrated a 45% reduction in prevalence of metabolic syndrome and an improvement in HDL cholesterol as well as waist circumference and body mass index; however, no improvement was noted in fasting blood glucose, triglyceride, or BP levels.⁸³ A 6-month study of male patients with moderate to severe OSA treated with autoadjusting CPAP showed that treatment resulted in a reduction in prevalence of metabolic syndrome from 63.5% to 47.3%, primarily attributable to reductions in BP and triglycerides.⁸⁴

In summary, results from uncontrolled interventional studies appear to be somewhat consistent in demonstrating improvements in metabolic parameters, albeit showing discrepancies regarding which specific components of metabolic syndrome show improvement. Data suggest that early improvements are noted (as soon as 2 days after therapy) and that effects may be more pronounced in the nonobese. The degree of improvement in metabolic function also appears to be related to the level of CPAP adherence. The results seem to be generalizable to primarily men. Of note, some of the studies showed improvement in body mass index during follow-up, precluding one's ability to effectively ascertain whether improvements in metabolic function were related to direct treatment of OSA or indirect improvement in anthropometrics. Overall these studies were limited by smaller sample sizes, mostly shorter duration of the therapy, limited generalizability, and few gold-standard techniques used to assess insulin resistance.

Randomized Controlled Interventional Trials

There have been 6 randomized controlled trials that have evaluated the role of CPAP in reversing metabolic abnormalities in patients with OSA (**Table 2**). These trials have examined populations with different ethnic backgrounds and differing background characteristics of subjects, and have used varying study designs and eligibility criteria as well as different durations of therapy.

The largest and, likely, most appropriately powered trial to examine the effects of PAP on metabolic function was a randomized, crossover, double-blinded, controlled trial based in India involving 86 participants, with the goal of assessing the reversal of metabolic syndrome with

Table 2
Controlled trials evaluating the role of CPAP in reversing metabolic abnormalities in patients with OSA

Authors, ^{Ref.} Year	Age (y)	Gender	Body Mass Index (kg/m ²)	Number	Power Calculations	Study Design	OSA Definition	Predefined Outcome	Duration	Type of Treatment	Findings
Weinstock et al, ⁸⁵ 2012	54 Range: 18–75	42% males with baseline impaired glucose tolerance, USA	39	50, n = 1 lost to follow- up	80% power to detect difference in glucose tolerance status (anticipating 20%–35% CPAP and 10%–15% of sham improved to normal)	Randomized, crossover, double-blind trial with 1 mo washout and 2 wk run-in period, the latter to assess adherence	AHI >15	Primary: Normalization of mean 2 h oral glucose tolerance testing Secondary: Improvement in ISI (0, 120)	8 wk of CPAP or sham CPAP followed by alternative therapy after 1 mo washout	CPAP vs sham CPAP, CPAP adherence 4.8 h/d	13.3% improvement in ISI and 28.7% reduction in 2 h insulin level in CPAP group in severe OSA (AHI >30) Impaired glucose tolerance normalized after CPAP with moderate OSA and obesity Each hour of active CPAP associated with improvement in insulin sensitivity (0, 120) A subset of participants underwent CPAP treatment for 12 wk without improvement in insulin sensitivity

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Table 2
(continued)

Authors, ^{Ref.} Year	Age (y)	Gender	Body Mass Index (kg/m ²)	Number	Power Calculations	Study Design	OSA Definition	Predefined Outcome	Duration	Type of Treatment	Findings
Hoyos et al, ⁵¹ 2012	49 ± 12	100% males, Australia	31.3 ± 5.2	65, 13 with-drawals post random-ization		Randomized parallel-design controlled trial	AHI ≥ 20	Primary: Change in visceral abdominal fat Secondary: Change in insulin sensitivity index and liver fat, body composition and metabolic markers	12 wk	CPAP vs sham CPAP followed by 12 wk of CPAP for both groups, mean CPAP adherence 3.6 h	No significant improvement in metabolic outcomes including visceral abdominal fat At 24 wk, improvement of insulin sensitivity was noted
Sharma et al, ⁴⁷ 2011	45 Range: 30–65	84% males in CPAP first 95% males in sham CPAP first ESS 14.8 ± 3.7 in CPAP group vs 14.1 ± 3.5 in sham group India	33.8	86	80% power to detect a 15% reduction in metabolic syndrome	Randomized, crossover double-blind trial with 1 mo washout period	AHI ≥ 15	Primary: 15% reduction in metabolic syndrome	12 wk	Auto PAP vs sham CPAP, CPAP adherence 4.8 ± 1.4 h	11% of the CPAP group vs 1% of the sham group had reversal of the metabolic syndrome (<i>P</i> = .003). Decrease in systolic and diastolic BP, total cholesterol, non-HDL, triglycerides, and glycated hemoglobin. Decrease in BMI, visceral and subcutaneous fat

Lam et al, ⁸⁶ 2010	46.3 ± 10.2	100% males, China	27.5 ± 3.7	61, n = 1 lost to follow-up	90% power to detect difference in insulin tolerance test (Kitt) 1.7 ± 1.5 mmol/min	Randomized parallel-design controlled trial	AHI ≥15	Primary: Change in short insulin tolerance test	1 wk followed by 11 wk of open study	Auto CPAP for 1 wk and fixed PAP for 11 wk vs sham CPAP	Early improvement in insulin sensitivity (P = .022) which was not sustained at 12 wk, improvement in insulin sensitivity in subgroup with BMI >25 kg/m ²
Coughlin et al, ⁴⁸ 2007	49 ± 8.3	All males, Caucasian, no diabetes mellitus, ESS ≥10, UK	36.1 ± 7.6	34, 1 withdrawal	90% power to detect 20% reduction of metabolic syndrome	Randomized, controlled, blinded crossover trial	AHI >15	Primary: Metabolic syndrome, HOMA, Change in waking BP or glucose, baroreceptor sensitivity	6 wk	CPAP vs sham CPAP, mean CPAP adherence 3.9 h (range 0–7.4)	No change in HOMA-IR, or lipids, mean systolic and diastolic BP decreased by 6.7 and 4.9 mm Hg, respectively
West et al, ⁴⁹ 2007	Range: 18–75	All males with diabetes mellitus and sleepiness (ESS ≥9), UK	CPAP: 36.6 ± 4.9 Sham: 36.8 ± 4.6	42, n = 2 lost to follow-up	90% power to detect 0.8 difference in HbA1c	Randomized parallel-design double-blind trial	>10 oxygen saturation dips of >4%/h	Primary: HbA1c; also examined were HOMA and euglycemic hyperinsulinemic clamp	12 wk	Auto CPAP vs placebo CPAP, mean usage of CPAP 3.6 ± 2.8 h	No change in glycemic index and insulin resistance (HbA1c, euglycemic clamp, HOMA, adiponectin)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; HbA1c, hemoglobin A_{1c}; HDL, high-density lipoprotein cholesterol; HOMA (-IR), Homeostasis Model Assessment (Insulin Resistance); ISI, Insulin Sensitivity Index; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea.

3 months of autoadjusting PAP followed by 3 months of sham PAP (or vice versa) separated by a 1-month washout period to minimize carry-over effects.⁴⁷ The study involved predominantly obese, middle-aged men with moderate to severe OSA (overall mean AHI of 48) and excessive daytime sleepiness, but without diabetes mellitus. The sample had a high degree of sleepiness, with an ESS score of 14.8 ± 3.7 in the PAP-first group versus 14.1 ± 3.4 in the sham-first group. The PAP adherence noted in this trial was higher than that of other studies, namely 4.8 ± 1.4 hours of daily usage. Autoadjusting PAP treatment compared with sham PAP was associated with a significant reduction in glycated hemoglobin, triglycerides, and total cholesterol, as well as a significant increase in HDL cholesterol to total cholesterol ratio. The reversal of metabolic syndrome (primary outcome) was observed in 13% of participants using autoadjusting PAP therapy, compared with 1% with sham PAP. Concomitant significant reductions in body mass index, visceral fat, and subcutaneous fat were seen in treatment with autoadjusting PAP in comparison with the control period. In subgroup analyses, significant improvement in carotid intima-media thickness was noted among the more adherent patients, suggesting a potential role for PAP therapy in reversing endothelial damage caused by OSA and metabolic syndrome.⁴⁷

Another recent study using a crossover design involved 50 obese, middle-aged individuals with moderate to severe OSA (AHI 44 ± 27 in the CPAP-first group and 32 ± 20 in the sham CPAP group) and impaired glucose tolerance who were randomized to 8 weeks of CPAP followed by sham CPAP (or vice versa) after a 1-month washout period.⁸⁵ Education on healthy lifestyle behavior was provided to all participants. Adherence to CPAP was similar to that of the India-based study, at average 4.8 hours of daily usage. Overall, there was no improvement in the primary outcome, insulin sensitivity, in those on CPAP versus sham CPAP; however, in subgroup analyses those with severe OSA had 13% improvement noted in the Insulin Sensitivity Index (0, 120) and a 28% reduction in the 2-hour insulin level after CPAP in comparison with those on sham CPAP. Moreover, each additional hour of active CPAP usage was associated with a significant improvement in the Insulin Sensitivity Index, and this improvement was more pronounced in sleeper participants. This study demonstrated a dose-response effect for both the severity of disease and adherence to treatment.⁸⁵ Contrary to the study based in India, there was no reduction in CT-based ascertainment of visceral abdominal

fat with CPAP versus sham CPAP, suggesting that the reduction in adiposity as a result of CPAP may have been driving the improvement in metabolic parameters in the study by Sharma and colleagues,⁴⁷ and could potentially account for the differences in the study results. Alternatively, the reduction in visceral fat may have been a result of differential behavioral or lifestyle habits rather than a direct effect of CPAP; however, there was no evidence of this, based on the social and lifestyle habits collected.

The goal of a parallel-group randomized controlled trial involving 61 middle-aged, overweight, Chinese men with moderate to severe OSA was to examine the effect of 1 week of auto-titrating CPAP versus sham CPAP on short insulin tolerance test (SITT) results and then to perform an extended investigation of effects of 12 weeks of CPAP.⁸⁶ Insulin sensitivity, measured by the SITT, was shown to be significantly improved after 1 week of CPAP, and the effect was sustained at 12 weeks in only a subgroup of overweight/obese individuals (body mass index $>25 \text{ kg/m}^2$). The results are consistent with the observation of early improvement of insulin sensitivity in response to CPAP noted in uncontrolled trial data; however, the lack of sustained effects may be due to lack of a control comparison arm. Interestingly, the sustained metabolic improvement in those who were overweight/obese counters the existing uncontrolled data.⁸⁶

Two randomized controlled trials based in the United Kingdom examined the effect of moderate to severe OSA treatment on components of metabolic syndrome in men.^{48,49} The first involved middle-aged, obese men without diabetes mellitus participating in a randomized crossover study, with results consistent with lack of reversal of metabolic syndrome with 6 weeks of CPAP versus sham CPAP (mean CPAP adherence 3.9 hours). Although reductions in SBP and DBP were noted, there was no change in the HOMA-IR (measure of insulin sensitivity) nor was there improvement in the lipid profile. Of note, lack of use of a washout period to minimize the potential carryover effect of CPAP is a methodologic flaw of this study, and an important aspect to bear in mind when interpreting results.⁴⁸ The other randomized, parallel-design United Kingdom-based study involving middle-aged, obese men with diabetes mellitus failed to show evidence of reduction in HbA1c with 12 weeks of autoadjusting CPAP versus sham CPAP. Although the euglycemic hyperinsulinemic clamp technique was used in this study, the small sample size and lower CPAP adherence, which were also issues with the other United Kingdom study, may have precluded

ascertainment of significant findings.⁴⁹ Subgroup analyses were performed in both of these studies with respect to good versus poor CPAP adherence, with consistency in findings of lack of improvement in metabolic parameters.^{48,49}

Contrary to other studies, the parallel-design randomized controlled trial involving middle-aged, obese Australian men with moderate to severe OSA considered visceral abdominal fat as a primary outcome after 12 weeks of CPAP versus sham CPAP.⁵¹ No differences were observed in insulin sensitivity, visceral abdominal fat, and liver fat at 12 weeks. At 24 weeks, after an additional 12 weeks of treatment for the entire group (those randomized to CPAP and sham CPAP), insulin sensitivity, but not visceral abdominal fat or liver fat, were improved over baseline. These findings suggest that a longer duration of OSA treatment may be required to observe substantive improvements in metabolic function.⁵¹

Two recent meta-analyses have explored the relationship of CPAP with its effect on metabolic outcomes. The first meta-analysis examined 3 parallel-group trials, 2 crossover, randomized controlled trials, and 1 randomized trial of 296 subjects. This meta-analysis did not show any influence of CPAP on plasma insulin or HOMA-IR, adiponectin levels, or HbA1c values.⁸⁷ The second meta-analysis evaluated the impact of CPAP on glycated hemoglobin. This meta-analysis included 9 observational studies and randomized trials of 151 subjects, and treatment durations ranging from 41 days to 6 months. The analysis concluded that CPAP usage in the short term did not show a reduction in HbA1c.⁸⁸

Effect of Non-Positive Airway Pressure Modalities of Obstructive Sleep Apnea Therapy on Components of Metabolic Syndrome

There are limited data on the direct effect of bariatric surgery as treatment of OSA on metabolic parameters. Based on a recent systematic review involving 69 studies and 13,900 patients, one can surmise that irrespective of the type bariatric surgery (ie, Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, or biliopancreatic diversion), improvement in OSA severity ensued after the bariatric intervention.⁸⁹ Data have also been amassed from numerous studies highlighting remission of type 2 diabetes after the bariatric procedures.⁹⁰ Furthermore, in a recent single-center, randomized controlled trial comparing intensive medical therapy with surgical treatment involving gastric bypass or sleeve gastrectomy as a means to improve glycemic control in obese patients with

uncontrolled type 2 diabetes (and a high prevalence of metabolic syndrome), 12 months of medical therapy plus bariatric surgery achieved glycemic control in significantly more patients than did medical therapy alone.⁹¹ Similar to evaluating PAP trials in OSA on metabolic function, it is unclear whether an improvement in metabolic regulation in treated OSA is a function of direct effects of reversing OSA pathophysiology versus reduction in body fat, or as a direct or indirect result of OSA treatment. A recently published randomized trial helps to shed light on the answer to this question.⁹² The trial involved obese patients with moderate to severe OSA randomized to conventional weight loss versus laparoscopic adjustable gastric banding, and examined the AHI as well as changes in anthropometrics and metabolic variables. Despite major differences in weight loss, there was no statistically significant reduction in AHI between the 2 groups, nor was there significant improvement in metabolic syndrome, lipid profile, or glycemic control. These findings imply that despite weight reduction, if OSA is not adequately ameliorated by intervention (in this case bariatric surgery), achieving improvement in metabolic parameters does not occur. These data suggest that addressing OSA pathophysiology in the face of weight loss is likely a key factor in improving metabolic function.⁹² Regarding investigation of the effects of other non-PAP therapies for OSA on metabolic function such as oral appliances and upper airway surgery, there are virtually no data that investigate the effects on glucose homeostasis or lipid profiles, underscoring the need for future research in these areas.

SUMMARY

In summary, these uncontrolled and controlled studies across a vast array of different ethnicities and racial backgrounds show that the effects of OSA treatment on metabolic outcomes have been discrepant, despite adequate biological plausibility to support the notion of anticipated benefits of therapeutic interventions for OSA on metabolic regulation. The external validity of existing studies applies primarily to middle-aged, obese men. Although the data from the PAP randomized controlled trials have been inconsistent, 3 of the 6 trials conducted to date that demonstrated improvements in metabolic function, either overall or in subgroup analyses, involved larger sample sizes and were likely more appropriately powered to detect changes in metabolic outcomes.^{47,85,86} Moreover, 2 of the 3 trials that showed significant metabolic improvements used crossover designs, which are inherently more

efficient and allow for enhanced power given a similar number of participants enrolled in a parallel-design trial.^{47,85} The randomized trial studies involved predominantly obese, sleepy, middle-aged participants, and all except 1 involved primarily male participants, thereby limiting the associated generalizability, and highlighting the need to focus future investigations on the metabolic function of nonobese individuals or women. Although 2 of the uncontrolled studies involved a follow-up period of 6 to 12 months, the randomized controlled trials involved follow-up periods of 6 to 12 weeks, time frames that may be too short to appreciate metabolic improvements. Differences in the usage of static versus autoadjusting CPAP also characterize these studies and may also lead to differences in results. For example, if a certain subset of participants was more likely to have positional or rapid eye movement sleep-related OSA, perhaps more benefit may have been gleaned with autoadjusting than with static CPAP. Varying approaches were used in assessing insulin resistance in the randomized clinical trials, with only 1 study using the gold-standard euglycemic hyperinsulinemic clamp technique to characterize insulin resistance. Of interest, the results of the latter study were not consistent with beneficial effects of CPAP on metabolic parameters; however, the study was limited by a smaller sample size and potentially suboptimal adherence.⁴⁹ There appears to be some evidence to suggest that CPAP results in improvement in metabolic syndrome and some of its components. It is worthwhile noting that data from the largest study to date did show reversal of metabolic syndrome with OSA treatment using autotitrating PAP. It is unclear whether this is a reflection of enhanced ability to detect differences because of better power, superior CPAP adherence, the use of autoadjusting PAP, consideration of a group with pronounced daytime sleepiness and severe OSA, and/or improvements in visceral adiposity, thereby translating into metabolic improvements.⁴⁷ Another factor to consider is differential ethnicity-oriented OSA treatment effects on metabolic regulation, based on genetic susceptibility in this specific group of Indian participants.⁴⁷

However, it is still not unambiguous that CPAP treatment of OSA decreases insulin resistance and/or improves glucose intolerance. Larger-scale randomized controlled trials with assessments of insulin sensitivity and glucose tolerance are needed to estimate the effects of CPAP in OSA patients on metabolic outcomes, perhaps with a focus on those with more severe OSA burden. Although data from bariatric intervention

in OSA reflect lack of improvement in metabolic parameters despite weight loss in the setting of nonsignificant reversal of OSA, thereby suggesting weight-independent effects of OSA treatment on metabolic regulation, adequately powered studies should be focused on addressing and better understanding the impact of weight changes on metabolic function in OSA treatment. The interplay of excessive daytime sleepiness should also be investigated, as it seems that sleepier individuals with OSA may potentially derive more metabolic benefit from OSA treatment. Questions regarding optimal duration and the amount of CPAP still remain unanswered, and will need to be addressed in future studies. Future interventional studies should also focus on populations that have not been examined closely thus far, including women, nonobese individuals, and those with severe OSA, as the latter group may in particular derive treatment benefit from a metabolic standpoint based on preliminary subgroup analyses of existing trial data. Such interventional studies are essential to delineate the causes of OSA and alterations in glucose metabolism, and the treatment effects of CPAP intervention in this patient population.

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