# Obstructive Sleep Apnea and Metabolic Syndrome
## Alterations in Glucose Metabolism and Inflammation

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**Metabolic syndrome (MS), the commonly used term for the clustering of obesity, insulin resistance, hypertension, and dyslipidemia, affects millions of people worldwide, and is associated with an increased risk of cardiovascular disease and type 2 diabetes. Recently, it has been suggested that obstructive sleep apnea (OSA), an increasingly prevalent condition, may contribute to the development of MS and diabetes. Despite substantial evidence from both clinical and population studies to suggest an independent link between OSA and metabolic abnormalities, the issue still remains controversial. Obesity, particularly visceral obesity, is an important factor in the assessment of adverse metabolic outcome in OSA. Further prospective and interventional studies, with adequate sample sizes and longer follow-up, rigorous control for adiposity, and, ideally, randomization and control for any therapeutic intervention, are clearly needed to address the direction of causality. There are multiple mechanistic pathways involved in the interaction between OSA, obesity, and metabolic derangements. Chronic intermittent hypoxia and sleep fragmentation with sleep loss in OSA are likely key triggers that initiate or contribute to the sustenance of inflammation as a prominent phenomenon, but their complex interplay remains to be elucidated. In summary, OSA may represent a novel risk factor for MS and diabetes, and thus clinicians should be encouraged to systematically evaluate the presence of metabolic abnormalities in OSA and vice versa.**

**Keywords:** sleep apnea; metabolic syndrome; glucose metabolism; inflammation

Obstructive sleep apnea (OSA) is an increasingly prevalent condition that is characterized by repetitive upper airway obstructions resulting in intermittent hypoxia and sleep fragmentation caused by arousals. Recently, there has been great interest in the interaction between OSA and metabolic dysfunction. In particular, OSA has been independently associated with insulin resistance, suggesting that OSA may be an important factor for the development of type 2 diabetes and the so-called metabolic syndrome (MS), that is, the constellation of obesity, insulin resistance, hypertension, and dyslipidemia. In the following sections, we review the current evidence that links OSA to MS, with a particular emphasis on alterations in glucose metabolism and the risk of type 2 diabetes. We also discuss some potential mechanisms proposed for these links, particularly the role of inflammation.

## METABOLIC SYNDROME

MS refers to a constellation of metabolic disturbances that predicts an increased risk of atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (1). Since its first description in the 1920s with reference to the clustering of hypertension, hyperglycemia, and gout, the definition of MS has undergone several modifications (1, 2). The core components of MS are widely accepted to be composed of obesity, insulin resistance, hypertension, and dyslipidemia, but various expert groups have developed different clinical criteria, means of combination, and threshold values for the definition of the syndrome, and such differences need to be taken into account in the comparison of data relating to MS. Many features have been reported to be associated with MS, including the proinflammatory state, the prothrombotic state, hyperleptinemia, hypoadiponectinemia, hyperuricemia, endothelial dysfunction, microalbuminuria, and others (1).

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) report (3) recommended the use of five variables with set threshold values for each variable, allowing easy clinical identification of MS: hypertension, insulin resistance or glucose intolerance, low serum high-density lipoprotein (HDL) cholesterol, elevated serum triglyceride, and abdominal obesity. Any subject meeting three of these five criteria would be classified as having MS. Due to ethnic differences in attributable health risks, the threshold criteria for waist circumference in the definition of abdominal obesity need to take account of ethnicity (2). Although the pathogenesis of MS and its individual components has not yet been fully delineated, abdominal obesity and insulin resistance have stood out as the key drivers of the syndrome (2, 4). Other factors such as genetic predisposition, physical inactivity, ageing, inflammation and hormonal dysregulation are also implicated in its development (1). On the basis of the NCEP ATP III definition, the NHANES III (Third National Health and Nutritional Examination Survey) estimated that the age-adjusted prevalence of MS in the United States was 23.7%, with the highest prevalence in Mexican Americans (5). The prevalence of MS may vary substantially among different places all over the globe (5), but there is a common trend of increasing prevalence of MS and its health consequences as the obesity epidemic sweeps across populations in both developed and developing countries (1, 5).

## OSA AND MS

The past two decades have seen a growing recognition of the presence of various types of metabolic dysfunction in subjects with OSA, and the association of OSA and MS was highlighted as "syndrome Z" in the late 1990s (6). However, little of the abundant literature regarding MS has characterized subjects in terms of sleep-disordered breathing. There is growing experimental and clinical evidence for an independent contribution of OSA toward the development and/or severity of individual metabolic disorders and the syndromic entity. On the contrary, MS and its components—in particular, obesity and insulin resistance/diabetes mellitus—may have conductive influence on the development of sleep apnea, and it has been proposed that OSA itself may well be a "metabolic disorder" and a component of MS (7).

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Table 1 summarizes the studies that examined the relationship between OSA and MS as a syndromic entity. In a case-controlled study comparing 61 white men with OSA at a sleep clinic, with 43 control subjects without OSA, Coughlin and colleagues reported that OSA, defined by an apnea–hypopnea index (AHI) of greater than 15, was independently associated with an increased prevalence of MS (odds ratio, 9.1) (8). OSA was also independently associated with most of the individual metabolic parameters. Gruber and colleagues similarly found that subjects with OSA were about six times more likely to have MS than were the subjects without OSA, adjusted for body mass index (BMI), smoking, and age, but OSA was not independently associated with the insulin resistance state (9). In a community-based cohort of 255 middle-aged Chinese men and women in Hong Kong, Lam and colleagues demonstrated that subjects with OSA, defined as an AHI of 5 or greater (37% of the study sample) had a fivefold risk of having MS (10). Apart from age and BMI, MS was one of the independent determinants of OSA, and there was an increasing association with MS as the severity of OSA increased. Sasanabe and colleagues evaluated 819 Japanese patients with OSA and 89 control subjects, and also demonstrated a higher prevalence of MS in both men and women with OSA (11). In this cohort, OSA was predictive of MS in men, but not in women, in whom only BMI predicted MS. Information on the effect of treatment of OSA on MS entity is scanty. Coughlin and colleagues studied 34 obese subjects with OSA without overt cardiometabolic disease, 27 of whom were classified as having MS by the NCEP ATPIII criteria, in a randomized, crossover, placebo-controlled study (12) (Table1). It was found that 6 weeks of active treatment with continuous positive airway pressure (CPAP) reduced waking blood pressure, but did not produce any improvement in insulin resistance or serum lipids, nor the proportion of subjects classified as having MS. The latter is probably not unexpected, given the trial duration and sample size, and the need to improve more than one parameter beyond certain threshold values before a subject would be able to change his/her status with regard to MS. There are also very scanty data on the potential effect of treatment of OSA on the major clinical outcomes of MS—namely, atherosclerotic CVD and diabetes mellitus. A study that followed up 89 subjects with OSA treated with CPAP, half of whom also had MS at baseline, reported less CVD events in those with MS than those without MS, during a mean period of 22 months (13). CPAP compliance data did not modify the outcome, but details of pharmacotherapy for metabolic control during the follow-up period were not available. Obviously, prospective studies with longer follow-up and rigorous characterization of subjects would be needed to address this issue.

These aforementioned studies evaluated MS as an entity. A number of other studies have not addressed the syndromic entity as an outcome measure, but did evaluate multiple parameters that comprise MS. In the Sleep Heart Health Study of over 6,000 adults with a mean age of 64 years, sleep-disordered breathing was examined in relation to multiple cardiovascular risk factors, including components of MS (14). On adjustment for age and BMI, there was a significant association of the

**TABLE 1. STUDIES EXAMINING THE ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA AND METABOLIC SYNDROME IN ADULTS**

| Reference | Design | Study Population | Main Results |
|---|---|---|---|
| Coughlin and colleagues (8) | Case controlled (matched for BMI)<br>OSA: AHI $>$ 15<br>Control subjects: AHI $<$ 5<br>MS: NCEP (ATP III) criteria | All men<br>61 OSA<br>43 Control subjects | Independent* associations between:<br>1. OSA and MS (OR, 9.1)<br>2. OSA and systolic and diastolic blood pressure, fasting insulin, triglyceride, HDL cholesterol, total/HDL cholesterol |
| Gruber and colleagues (9) | Case controlled<br>OSA: AHI criteria not given<br>MS: International Diabetes Federation criteria | 38 OSA<br>41 Control subjects | Independent* association between:<br>1. OSA and MS (OR, 5.9)<br>2. No independent association between OSA and insulin resistance (assessed by HOMA) |
| Lam and colleagues (10) | Community based<br>Full PSG<br>OSA: AHI $\geqslant$ 5<br>MS: NCEP (ATP III) criteria† | Chinese<br>30–65 yr old<br><br>255 Subjects (150 men and 105 women) | OSA and MS (OR, 5.3)<br>Independent association between OSA and waist, diastolic blood pressure*, fasting glucose*, MS*<br>Independent determinants of OSA: age, gender, BMI, MS |
| Sasanabe and colleagues (11) | Sleep clinic and community volunteers<br>Full PSG<br>OSA: AHI $\geqslant$ 15<br>Control subjects: AHI $<$ 5<br>MS: criteria for Japanese population | Japanese<br>819 OSA (719 men and 100 women)<br>89 Control subjects | Independent* association between OSA and MS in men, but not in women |
| Parish and colleagues (137) | Retrospective PSG and chart review | 228 Consecutive patients<br>146 OSA<br>82 No OSA | Higher prevalence of MS in patients with OSA (60 vs. 40%) |
| Coughlin and colleagues (12) | Randomized, controlled crossover study<br>CPAP vs sham CPAP<br>MS: NCEP (ATP III) criteria | 34 Men<br>Mean AHI = 40<br>Mean BMI = 36<br>Mean age= 49 yr | No change in proportion of subjects with MS with CPAP treatment<br>Significant decrease in blood pressure |

*Definition of abbreviations*: AHI = apnea–hypopnea index; ATP = Adult Treatment Panel; BMI = body mass index; CPAP = continuous positive airway pressure; HDL = high-density lipoprotein; HOMA = homeostatic model assessment; MS = metabolic syndrome; NCEP = National Cholesterol Education Program; OR = odds ratio; OSA = obstructive sleep apnea; PSG = polysomnogram.

* After adjustment for confounders inclusive of age and BMI.

† Waist criteria for obesity in Asians used.

respiratory disturbance index with increasing waist:hip ratio, hypertension, hypercholesterolemia in men, and with low HDL cholesterol and hypertriglyceridemia in women. As part of the Korean Health and Genome study, prevalence of habitual snoring, as a surrogate marker of sleep-disordered breathing, was found to have a dose-dependent relationship with the number of MS components (15). In a matched-control study of men, OSA was associated with insulin resistance, levels of total cholesterol, HDL cholesterol, and leptin, after adjustment for central obesity, age, and alcohol consumption (16). Most studies explored obese subjects, whereas a case-control study in Japan investigated lean men (mean BMI, $\sim$23 kg/m$^2$) with OSA and subjects without OSA matched for abdominal visceral fat on computerized tomographic quantification (17). OSA was found to be associated with hypertension, dyslipidemia, insulin resistance, and fasting hyperglycemia, as well as a higher visceral-to-subcutaneous fat ratio, suggesting that OSA itself may predispose to the development of various types of metabolic dysfunction, and thus MS, without the presence of excess visceral adiposity. In contrast to the above positive reports, a study on Indian men reported that OSA was not independently associated with any of the components of MS, including hypertension, insulin resistance, and dyslipidemia, and obesity was the major determinant of metabolic aberrations (18).

An extensive review of the relationships between OSA and various individual components of MS is beyond the scope of this article. Cardiovascular aspects of MS, including hypertension, are described elsewhere in this symposium (145). In the following sections, we will focus on alterations in glucose metabolism in OSA and review the role of inflammation in the mechanistic links between OSA and MS.

## OSA AND ALTERATIONS IN GLUCOSE METABOLISM

MS was previously known as the "insulin resistance syndrome," reflecting the important position of insulin resistance in MS (4), although there is recent controversy regarding the relative roles of abdominal obesity and insulin resistance as the driving force for MS (2). Insulin resistance is a precursor state of diabetes mellitus, and MS is also highly predictive of diabetes mellitus. If OSA does contribute causally to the severity of insulin resistance, it may also indirectly fuel other derangements attributable to insulin resistance, such as hypertension, hypertriglyceridemia, and visceral obesity, perpetuating the disturbances in MS and further add to its cardiovascular sequelae. Thus, any independent contribution of OSA toward insulin resistance and/or glucose homeostasis would have a magnifying effect on the clinical outcomes. OSA, insulin resistance, and MS are closely related to indices of obesity and central obesity, including BMI, waist circumference, and neck circumference (19). Obesity is believed to play an important etiological role in the development of upper airway collapse, probably through adverse effects on ventilatory control and anatomical/mechanical loading. However, presence of adiposity has many further implications on the manifestations and sequelae of OSA. Visceral fat is a metabolically active tissue, producing large amounts of proinflammatory or vasoactive substances, which play important roles in the regulation of metabolic and vascular function (20). Central obesity is considered to be a very important determinant of MS (66). OSA may well modulate the expression of adipose tissue–derived mediators, which in turn determine the development of various features in MS as well as cardiovascular diseases (20). Hence, it is necessary to address obesity and visceral obesity as a confounder in the delineation of the relationships of OSA, MS, and glucose metabolism.

A rapidly growing number of studies, involving a diverse range of patient populations, suggest that the presence and/or severity of OSA are linked to alterations in glucose metabolism independently of the degree of obesity. Most of these studies have been based on cross-sectional data that simply suggest an association, but the prospective studies that support a causal link are still very few. In an attempt to establish a direction of causality, investigators have also used interventional approaches and thus explored changes in glucose metabolism after treatment of OSA with CPAP.

The various methods used in the assessment of glucose homeostasis are briefly described in Table 2. A number of studies used one or more glucose measures, including fasting blood glucose and hemoglobin A1c levels, and oral glucose tolerance test (OGTT). In several studies, the degree of insulin resistance was estimated by fasting insulin levels and homeostatic model assessment (HOMA) index. Some studies included hyperinsulinemic euglycemic clamp, the "gold standard" technique for the measurement of insulin sensitivity. In a few studies, the presence of diabetes was based on patient self-report or physician diagnosis. In studies where OSA was diagnosed by polysomnography, the AHI and the degree of intermittent hypoxia (as assessed by the lowest oxygen saturation or percent time below 90% oxygen saturation) were the most commonly used markers of severity of OSA. Several epidemiologic studies used self-reports of habitual snoring and/or observed apneas as surrogate markers for OSA.

### Cross-sectional Studies

Numerous cross-sectional clinical studies consistently found an independent link between the presence and severity of OSA and glucose intolerance, insulin resistance, and diabetes (8, 16, 17, 21–28). A small number of studies, however, did not report positive findings (9, 18, 29). In the largest clinic sample to date, Meslier and colleagues (24) performed overnight polysomnography and OGTT in 595 men who were referred to a sleep clinic for suspected OSA. Diabetes was found in about one third of the patients who were diagnosed with OSA. Furthermore, the increasing severity of OSA was associated with worsening glucose tolerance and insulin resistance, independently of age and BMI. These latter findings were in agreement with those of Makino and colleagues (27), who showed an independent association between the severity of OSA and insulin resistance in 213 patients without diabetes with OSA. Kono and colleagues (17) studied 42 lean men with OSA and 52 control subjects who were matched for age, gender, BMI, and visceral fat, and found that, in the absence of confounding effects of adiposity, OSA was associated with higher levels of fasting glucose and HOMA index, indicating a more insulin-resistant state.

Similar to the findings from the majority of the clinical studies, several large population studies also identified an independent association between the severity of OSA (defined by polysomnography) and the magnitude of glucose intolerance and insulin resistance (10, 30–35). Of particular importance, the cross-sectional analysis of the large multicenter Sleep Heart Health Study involving 2,656 subjects showed that the severity of OSA (as measured by AHI and oxygen desaturations) was independently associated with both fasting and 2-hour glucose levels during an OGTT (33). Recent findings from a large population study of over 1,000 patients, presented in an abstract form at the International Conference of the American Thoracic Society in 2007, suggest that OSA is independently associated with the incidence of type 2 diabetes, and that increasing severity of OSA is linked to higher risk of developing diabetes (36). A large number of population studies with cross-sectional design found an independent relationship between snoring and

**TABLE 2. VARIOUS METHODS USED IN THE ASSESSMENT OF GLUCOSE METABOLISM**

| Method | Description | Reliability and Interpretation |
|---|---|---|
| Fasting glucose and insulin | Plasma glucose and serum insulin levels are measured in a fasting blood sample | Impaired fasting glucose is diagnosed if fasting glucose levels are between 110 and 125 mg/dl<br>Diabetes is diagnosed if fasting glucose levels are ⩾ 126 mg/dl (138) |
| Hemoglobin A1c | Measured in a single blood sample and reflects mean glycemia over the preceding 2–3 mo | Indicator of glucose control in diabetic patients (normal hemoglobin A1c < 6%) and used in clinical practice for diabetes management<br>Lowering hemoglobin A1c has been associated with a reduction of diabetic complications (138) |
| HOMA index | The normalized product of fasting glucose and insulin calculated using the following formula: (fasting serum insulin × fasting plasma glucose)/22.5 | Reliable and validated estimate of insulin resistance (139)<br>Elevated HOMA levels reflect higher degree of insulin resistance |
| OGTT | After ingestion of 75 g of glucose, blood samples are collected for the measurement of glucose and insulin concentrations at time 30, 60, 90, and 120 min to evaluate glucose tolerance | A clinical tool used for the diagnosis of type 2 diabetes (138)<br>Normal glucose tolerance, impaired glucose tolerance, or diabetes is diagnosed if the glucose level at 2 h is <140 mg/dl, 140–200 mg/dl, or ⩾200 mg/dl, respectively |
| Continuous glucose monitoring system | Glucose concentration in the interstitial fluid is measured using a subcutaneous sensor attached to a continuous monitoring device that records sensor signals every 5 min, providing 288 glucose level readings per day | Used in clinical practice for diabetes management to assess 24-h glucose fluctuations (particularly post-prandial and nocturnal levels) |
| Hyperinsulinemic euglycemic clamp | Insulin sensitivity is quantified by intravenous glucose infusion rate (i.e., glucose uptake by all the tissues in the body) under steady-state conditions of eugylcemia | The gold standard technique used for measurement of insulin sensitivity (140) |
| Intravenous glucose tolerance test | Glucose and insulin concentrations are measured during fasting and after intravenous glucose injection at frequent intervals for 4 h | Validated tool that allows simultaneous assessment of glucose tolerance, β-cell responsiveness, and insulin sensitivity using a mathematical model (141) |

*Definition of abbreviations:* HOMA = homeostatic model assessment; OGTT = oral glucose tolerance test.

measures of glucose tolerance (37–46). Importantly, two of these cross-sectional studies only included lean (BMI, <25 kg/m$^2$) subjects and found an independent association between frequent snoring and reduced glucose tolerance (42, 43). Only a few population studies reported negative findings (40, 47, 48).

In summary, the association between OSA and altered glucose metabolism is strongly supported by a large amount of cross-sectional evidence from both clinical and population studies. Because cross-sectional data do not provide definitive evidence, additional studies with prospective and/or interventional designs are needed to address causation.

### Longitudinal Studies

Although there is substantial evidence from cross-sectional studies to support an association between OSA and abnormal glucose metabolism, the longitudinal evidence for the direction of causality comes only from a small number of reports. Two large population studies used habitual snoring as a surrogate marker of OSA and investigated the development of type 2 diabetes over a 10-year follow-up period. Both of these studies used statistical methods to control for age, weight gain, alcohol, smoking, physical activity, and other confounding factors. In the first study involving 2,688 Swedish men aged 30–69 years, habitual snoring was found to be an independent risk factor for incident diabetes (49). The second study comes from the Nurses' Health Study Cohort, including 69,852 female nurses in the United States aged 30–55 years. The authors found that regular snoring was associated with twofold increased risk of developing diabetes.

In the only longitudinal study that used polysomography to assess OSA, Reichmuth and colleagues (50) analyzed the data from 1,387 subjects in the Wisconsin Sleep Cohort. The authors reported that diabetes was more prevalent in OSA independent of other risk factors at baseline, but no independent relationship was found between OSA and incident diabetes at 4-year follow-up. A limitation of this study is that the duration of follow-up was only 4 years. Thus, further longitudinal studies would be necessary to fully examine the role of OSA in the development of diabetes and to provide causal evidence.

### Effects of CPAP Treatment on Glucose Metabolism

Considerable disagreement exists among studies that have examined the effects of CPAP treatment on glucose metabolism (Table 3). The study populations and techniques used to assess glucose metabolism have been variable. The treatment period with CPAP ranged from 1 night to a maximum of 6 months. Most studies did not report objective data on adherence to therapy or include a control group.

Several studies have reported improvements in insulin sensitivity in both patients with diabetes (51–53) and those without (53, 54). Babu and colleagues (55) have shown a significant reduction in post-prandial glucose and hemoglobin A1c levels in patients with diabetes after 3 months of CPAP therapy. Importantly, the authors also found that the decrease in hemoglobin A1c levels was significantly correlated with days of CPAP use in those who were compliant with therapy for more than 4 hours per night. Preliminary evidence presented at conferences suggests a beneficial effect of CPAP treatment on insulin sensitivity (56), fasting (57), and nocturnal (58) glucose levels in patients with and without diabetes.

In contrast to these positive findings, a number of earlier studies with fairly small sample sizes showed no change in fasting or nocturnal glucose and insulin levels (47, 59–62). It is possible that these negative studies may have not been sufficiently powered to detect an effect of CPAP on metabolic measures. Two recent studies, involving randomized designs and relatively larger sample sizes, showed no significant difference in insulin sensitivity or hemoglobin A1c levels after 3 months of therapeutic versus subtherapeutic CPAP use in patients with (63) or without (12) diabetes. Notably, the average nightly therapeutic CPAP use was only 3.6 hours in one study (63) and 3.9 hours in the other (12), which raises the question of whether

**TABLE 3. STUDIES EXAMINING THE EFFECT CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT ON GLUCOSE METABOLISM**

| Reference | Treatment Period | Study Population | Measures of Glucose | Main Results |
|---|---|---|---|---|
| Positive studies | | | | |
| Brooks and colleagues (51) | 4 mo | 10 Severely obese patients with diabetes with OSA | Hyperinsulinemic euglycemic clamp | Improvement in insulin sensitivity |
| Harsh and colleagues (54) | 3 mo | 40 Patients without diabetes with OSA | Hyperinsulinemic euglycemic clamp | Improvement in insulin sensitivity (at 2 d and 3 mo) |
| Harsh and colleagues (52) | 3 mo | 9 Patients with diabetes with OSA | Hyperinsulinemic euglycemic clamp | Improvement in insulin sensitivity (at 3 mo) |
| Babu and colleagues (55) | 3 mo | 25 Patients with diabetes with OSA | 72-h interstitial glucoseHemoglobin A1c | Improvement in 1-h postprandial glucose and decrease in hemoglobin A1c |
| Hassaballa and colleagues (142) | 3–4 mo | 38 Patients with diabetes with OSA | Hemoglobin A1c | Slight decrease in hemoglobin A1c |
| Lindberg and colleagues (53) | 3 wk | 28 Men with OSA28 Matched control men without OSA | Fasting insulin and HOMA | Reductions in fasting insulin levels and insulin resistance |
| Negative studies | | | | |
| Saini and colleagues (59) | 1 Night | 8 Patients with OSA | Profiles of glucose and insulin at night | No change in nocturnal glucose and insulin profiles |
| Cooper and colleagues (60) | 1 Night | 6 Obese men without diabetes with OSA | Profiles of glucose and insulin at night | No change in nocturnal glucose and insulin profiles |
| Stoohs and colleagues (47) | 2 mo | 5 Patients with OSA | Fasting glucose and insulin | Increase in fasting and nocturnal glucose levels |
| | | | Profiles of glucose and insulin at night | No change in fasting or nocturnal insulin levels |
| Saarlainen and colleagues (143) | 3 mo | 7 Patients with OSA | Hyperinsulinemic euglycemic clamp | No improvement in insulin sensitivity |
| Ip and colleagues (61) | 6 mo | 9 Patients with OSA | Fasting glucose and insulin | No change in fasting glucose and insulin levels |
| Sumurra and colleagues (144) | 2 mo | 16 Patients with OSA | Hyperinsulinemic euglycemic clamp OGTT | No change in insulin sensitivity and glucose tolerance |
| Czupryniak and colleagues (62) | 1 night | 9 Patients without diabetes with OSA | Nocturnal interstitial glucose | Increase in nocturnal glucose |
| | | | Fasting insulin and HOMA | No difference in fasting insulin levels and insulin resistance |
| Coughlin and colleagues (12) | 6 wk | 34 Obese patients with OSA | HOMA | No change in insulin sensitivity with therapeutic CPAP compared with placebo CPAP |
| West and colleagues (63) | 3 mo | 42 Patients with OSA | Hemoglobin A1c, HOMA, and euglycemic clamp | No change in hemoglobin A1c or insulin sensitivity with therapeutic CPAP compared with placebo CPAP |

*Definition of abbreviations*: CPAP = continuous positive airway pressure; HOMA = homeostatic model assessment; OGTT = oral glucose tolerance test; OSA = obstructive sleep apnea.

insufficient CPAP use is a potential confounding factor in the above-mentioned negative findings.

Taken together, there is clearly a need for future, large-scale, randomized, well controlled CPAP studies with better compliance to therapy and long-term follow-up to fully investigate the effects of CPAP treatment on glucose control. Such interventional studies would be essential to address the question of whether OSA is causally linked to alterations in glucose metabolism.

### Possible Mechanisms Linking OSA to Altered Glucose Metabolism

Although several plausible explanations have been proposed, the exact mechanisms for abnormalities in glucose metabolism in OSA are not fully understood. It is likely that multiple interrelated factors contribute to the complex interactions between OSA, obesity, and glucose control. OSA is intrinsically associated with chronic intermittent hypoxia and sleep loss (due to sleep fragmentation), which may adversely affect glucose homeostasis (Figure 1). Increased sympathetic activation, dysregulation of the hypothalamus–pituitary axis, generation of reactive oxygen species (ROS), and activation of inflammatory pathways have all been proposed as intermediate mechanisms that could lead to alterations in glucose metabolism in OSA. The potential additive and interactive effects of the two key features of OSA (i.e., intermittent hypoxia and sleep fragmentation) on glucose metabolism remain to be fully elucidated. Here, we briefly discuss the evidence from animal models of intermittent hypoxia and the data from human studies of sleep loss. The role of oxidative stress and inflammation in the metabolic derangements are addressed in detail in subsequent sections of this article.

In leptin-deficient obese mice, Polotsky and colleagues (64) found that the exposure to chronic intermittent hypoxia (30-s hypoxia alternating with 30-s normoxia for 12 h/d) for 12 weeks led to a time-dependent increase in fasting insulin level and worsening of glucose tolerance and, ultimately, deterioration of insulin resistance. More recently, Iiyori and colleagues (65) exposed lean mice to intermittent hypoxia (to 5–6% minimum $F_{I_{O_2}}$ at 60 cycles/h) or intermittent air during 9 hours. The authors found that, in lean mice, the whole-body insulin sensitivity, as assessed by hyperinsulinemic eugylcemic clamp, decreased after exposure to intermittent hypoxia. Notably, this decrease in insulin sensitivity was found to be independent of an activation of the autonomic nervous system, which contradicts the evidence supporting the pathophysiologic link between sympathetic activation, intermittent hypoxia, and insulin resistance (66).

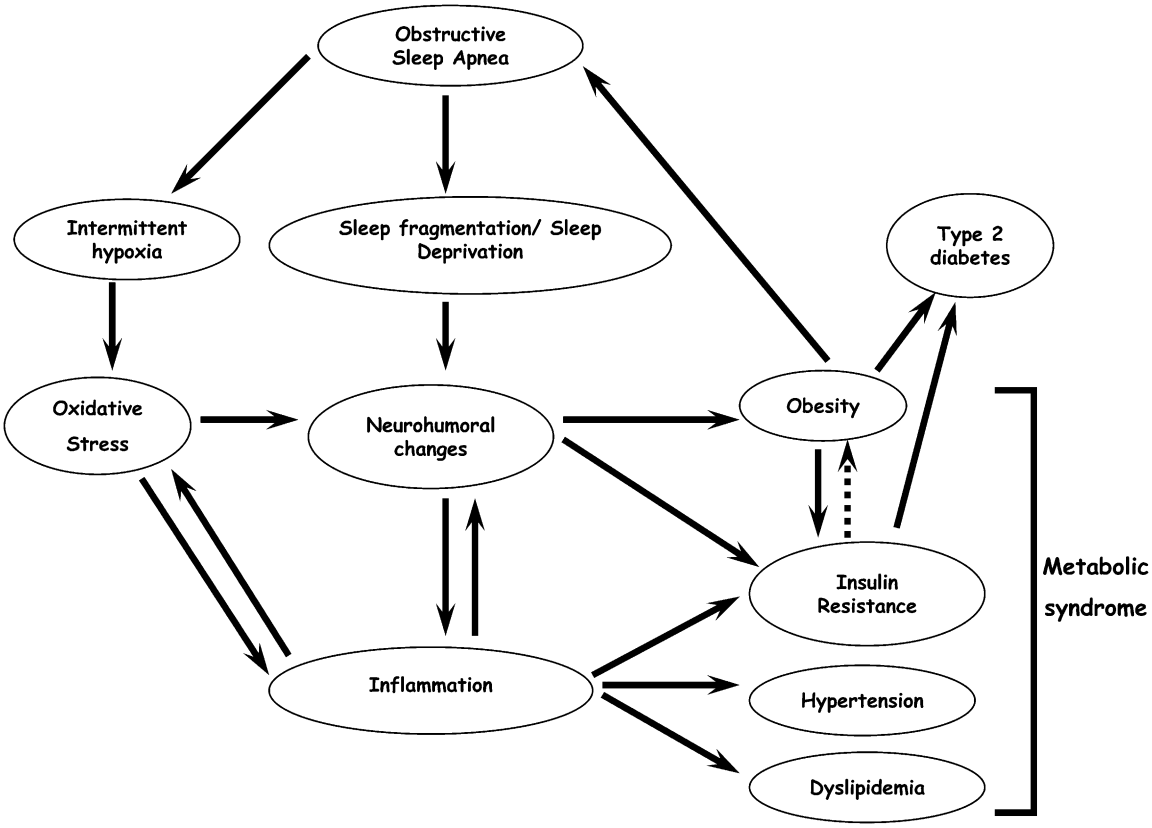


*Figure 1.* Possible mechanistic links between obstructive sleep apnea, metabolic syndrome, and type 2 diabetes.

There is compelling evidence from epidemiologic, clinical, and laboratory studies to indicate that sleep loss may have deleterious effects on glucose metabolism. To date, there are six prospective epidemiologic studies, coming from different countries and subject populations, that suggest a causative role for short sleep duration and/or disturbed sleep in the development of diabetes (67–72). These studies consistently showed an increased risk of developing diabetes in individuals who reported short sleep durations and/or difficulties sleeping at baseline. Only one study, which also involved the smallest sample size, did not report positive findings (73). Some limitations of these epidemiologic studies include the lack of objective assessment of sleep by polysomnography and inadequate control for potential confounders that were not assessed during those fairly long follow-up periods (ranging from 7 to 35 yr). Recently, a large, population-based, cross-sectional, multicenter study reported that sleep duration of 6 hours or less or 8 hours or more was independently associated with increased risk of type 2 diabetes in middle-aged women, but not in men (74). In a clinic-based sample of patients with type 2 diabetes, the sleep duration and quality (as assessed by Pittsburgh Sleep Quality Index) were significant predictors of glucose control as measured by hemoglobin A1c levels (75). These population and clinical observations are well supported by controlled laboratory studies showing that reductions in sleep duration in healthy young adults results in a marked decrease in glucose tolerance and an increased risk of diabetes (76, 77).

## OSA AND MS: ROLE OF INFLAMMATION

Recurrent obstructive events with intermittent hypoxia and sleep fragmentation in OSA are postulated to be primary triggers for a cascade of pathogenetic mechanisms that predispose to the development of various cardiometabolic features seen in MS.

The effects of intermittent hypoxia exposure simulating that seen in human OSA has been investigated in experimental models of animals and cell cultures, and there is supportive evidence for the generation of some of the core features in MS, including hypertension (78), insulin resistance (64, 65), and atherogenic dyslipidemia (79). Repetitive episodes of intermittent hypoxia followed by reoxygenation, as seen in OSA, simulate ischemia–reperfusion, which may result in the generation of ROS. A number of observational studies have demonstrated that OSA is independently associated with increased markers of oxidative stress (80–84). ROS can up-regulate transcription factors that control inflammatory pathways, such as nuclear factor (NF)-κB, with subsequent downstream effects on the development of the cardiometabolic factors in MS. On the other hand, OSA also leads to sleep fragmentation and relative sleep loss. Short sleep duration has been shown to predispose to hypertension (85), and also obesity and adverse glucose homeostasis (76, 86, 87). Mechanistically, sleep deprivation may modulate neurohumoral pathways (88–90), activate systemic inflammation (91), as well as increase susceptibility to oxidative stress (92). These processes are subject to multiple feedback and feed-forward mechanisms, potentially encouraging the perpetuation of the metabolic aberrations (Figure 1).

Abdominal obesity *per se* appears to induce a state of low-grade inflammation, with adipocytes and macrophages in adipose tissues being major sources of proinflammatory mediators (20). The association of MS with inflammation is well acknowledged (1, 20), but the underlying mechanisms are not well understood, and probably, in part, reflects the contribution from expanded adipose tissue mass. There is controversial evidence

that proinflammatory adipocytokines may play a role in the generation of insulin resistance and MS (93). Furthermore, atherosclerosis is now established to be a chronic inflammatory condition (94). Hence, inflammation may serve as an important mechanistic link in the complex interplay of OSA and cardiometabolic dysfunction.

### Proinflammatory Cytokines

The most commonly studied proinflammatory cytokines in OSA are probably tumor necrosis factor (TNF)-α and IL-6. Macrophages infiltrating white adipose tissue are a rich source of TNF-α and IL-6, especially in obesity. Data from human and animal studies suggest that TNF-α and IL-6 may induce insulin resistance, and elevated levels of these cytokines have often been reported in MS (1, 20). They were also postulated to be mediators of sleepiness and fatigue in OSA (7, 23). A number of studies have reported a significant elevation of TNF or IL-6 levels in OSA compared with BMI-matched control subjects (95, 96) or an effect of AHI on cytokine levels independent of adiposity (23, 97), although others did not find any independent association (16). T lymphocytes of subjects with OSA were also shown to express more proinflammatory cytokines (98). Observational studies of CPAP treatment reported a decrease in these proinflammatory activities (96, 98). Furthermore, TNF (−308) gene polymorphism has been demonstrated to be associated with OSA, suggesting that inflammation is involved in the pathogenesis of the condition (99).

### Leukocyte Adhesion, Platelet Activation, and Other Prothrombotic Activity

Activated leukocytes express cell adhesion molecules that mediate interactions with the endothelium, initiating vascular inflammation. MS is associated with increased circulating levels of cell adhesion molecules (20). Subjects with OSA have demonstrated elevated circulating levels of soluble cell adhesion molecules or increased expression on circulating monocytes, both of which decreased with CPAP treatment (100–102). Dyugovskaya and colleagues reported that T cells from patients with OSA were more adhesive and cytotoxic to target cells, and these were reduced after CPAP treatment (98). Platelet activation has also been described in subjects with OSA, and decreased with CPAP treatment in nonrandomized studies (103, 104).

Among the prothrombotic factors, fibrinogen and plasminogen activator inhibitor-1 (PAI-1) have been most prominently clustered with MS. Fibrinogen is hepatically synthesized in response to inflammatory triggers. Elevated fibrinogen levels have been described in subjects with OSA, although a more recent work from Saletu and colleagues did not find any independent association of fibrinogen levels with sleep-disordered breathing variables in an analysis of 147 patients from the sleep laboratory (105, 106). PAI-1 is a fat-derived prothrombotic factor, and von Kanel and colleagues showed that PAI-1 was increased in subjects with OSA, independent of obesity (107). Subsequently, an analysis of pooled data from the two previous studies indicated that MS interacted with AHI in the determination of PAI-1 levels, and that AHI only predicted PAI-1 levels in the absence of MS (107).

### NF-κB Activation

NF-κB is the master switch in the transcription of numerous genes involved in the inflammatory pathway, and is involved in the pathogenesis of MS and atherosclerosis; hence, NF-κB activation may be a key link between OSA and cardiometabolic risks (108, 109). Enhanced oxidant stress can stimulate NF-κB, and inflammation also appears capable of triggering further oxidative stress, thus maintaining the pathogenesis of cardiometabolic aberrations. Circulating neutrophils and monocytes from subjects with OSA showed elevated NF-κB binding activity compared with that of control subjects, and this was reversed by CPAP treatment in a small number of subjects with severe OSA (110, 111). In an *in vitro* model of Hela cell cultures exposed to intermittent hypoxia of 5 minutes alternating with normoxia of 10 minutes, selective activation of NF-κB was demonstrated (112). Mice exposed to intermittent hypoxia, simulating closely that of human cycles of OSA, also demonstrated enhanced activation of NF-κB, especially in vascular tissues, and this was temporally associated with increased expression of inducible nitric oxide (NO) synthase, an NF-κB–dependent gene product (111). In contrast, human studies have consistently shown a decrease in circulating NO derivatives (113, 114) and also impaired NO-dependent endothelial function in subjects with OSA (115).

### C-reactive Protein

C-reactive protein (CRP) as a biomarker of inflammation has been of particular interest to clinicians due to its clinical utility in CVD risk stratification, in addition to other cardiovascular risk factors (116). Elevated CRP levels are associated with MS (117), and levels have been observed to increase in a graded manner with increasing number of components of MS (118). In over 8,000 participants in the NHANES III, the age-adjusted prevalence of elevated CRP levels was 2.8-times higher in those with MS than in those without the syndrome (118). Data on the associations between OSA and CRP have been conflicting (95, 106, 119–123). Several groups have studied CRP levels in obese men with no prevalent medical conditions and identified an independent correlation between severity of OSA and CRP levels, controlled for BMI (95, 106) as well as waist, percentage body fat on bioimpedance and total sleep time (123). On the other hand, several studies have reported negative results (28, 121, 124, 125). In a large cohort of 239 subjects, including some with hypertension, no independent association between OSA and CRP levels was identified after adjustment for BMI and neck size (121). Recently, a study comparing three groups of subjects with different OSA severity matched for age and BMI (mean BMI, ∼31 kg/m$^2$), and a forth group of obese subjects with OSA matched in AHI to the severe OSA group, identified no significant difference in the three BMI-matched groups, whereas the obese group had higher CRP than its AHI-matched counterpart. The findings supported that CRP was determined by obesity rather than by OSA severity (125). Information from interventional studies is limited and similarly conflicting. Two observational studies have shown a decrease in hsCRP (high sensitivity CRP) levels in obese subjects with OSA after treatment with CPAP (95, 120), whereas another found no change in either obese or nonobese subjects with OSA (124). Thus, an independent role of OSA in the determination of CRP levels remains controversial and subject to further research.

### Adipokines as Mediators of Metabolic Dysfunction in OSA

Leptin is a predominantly fat-derived hormone. Apart from its well-known role in energy regulation, leptin has pleiotropic functions, such as respiratory stimulant effect (126) and effects on the vasculature (127). MS has been postulated to be a leptin-resistant syndrome, and baseline leptin levels were found to be an independent predictor of MS in an 8-year follow-up study (128). There have been a number of observational studies with conflicting results on the relationship between circulating leptin levels and OSA. Several studies demonstrated a higher leptin level in subjects with OSA compared with BMI-matched con-

trol subjects, suggesting a relative leptin-resistant state in OSA (16, 61, 129), but others found no significant association between the two after adjusting for obesity (109, 130). Observational studies have reported a decrease in leptin levels without a change in BMI after CPAP treatment (61, 131); this effect was confined to nonobese subjects in a study by Barcelo and colleagues (132). Adiponectin is another adipocyte-derived molecule with antiinflammatory and insulin-sensitizing properties *in vitro*, and hypoadiponectinemia has been suggested to play an important role in the development of diabetes mellitus or MS (93). However, several studies on adiponectin and OSA have been negative, showing no significant independent relationship between the two (16, 18, 27), wheras one study showed a trend of decreasing adiponectin levels according to OSA severity, independent of insulin resistance and BMI (133).

## CONCLUSIONS

Despite the rather prolific data that suggest a contributing role of OSA toward the various components of MS and the entity itself, the exact relationship between OSA and MS remains controversial. The majority of the cross-sectional studies lack adequate sample size or rigorous control for confounding factors—in particular, visceral obesity. Data from prospective or retrospective long-term follow-up of well-characterized populations are limited, and nonexistent on the link between OSA and MS as a syndromic entity. Interventional studies have mostly been observational, involving a small number of subjects, with inadequate power to support negative findings definitively, and were probably of insufficient duration for certain metabolic changes to take place. Most of the studies regarding MS have not characterized subjects in terms of sleep-disordered breathing, and whether OSA adds to clinical outcomes that are above and beyond that attributed to MS or its components has barely been addressed. Thus, the further elucidation of the relationship between the often-overlapping entities of obesity, OSA, MS, and type 2 diabetes remains an arduous challenge. In this regard, there is rapidly growing evidence to suggest an independent association between OSA and alterations in glucose metabolism—namely, glucose intolerance, insulin resistance, and type 2 diabetes. Recent reports indicate a high prevalence of type 2 diabetes in patients with OSA (134–136). Despite the abundance of cross-sectional evidence for the link between OSA and abnormal glucose control, further well-designed longitudinal and interventional studies are clearly needed to address the direction of causality. An improved understanding of the relationship between OSA and alterations in glucose metabolism may have important public health implications. Both OSA and MS, and their outcomes, regardless of whether they are independent, additive, or synergistic, are well established to be modifiable by lifestyle measures and other more specific interventional therapies. Therefore, the imminent need for heightened awareness of their strong association and, thus, early detection of comorbidity cannot be overemphasized.

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