Obstructive Sleep Apnea
An Unexpected Cause of Insulin Resistance and Diabetes

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INTRODUCTION
Obstructive sleep apnea (OSA), which results from upper airway occlusion during sleep, affects at least 4% of men and 2% of women.\textsuperscript{1} In addition to excessive daytime somnolence with impairment in cognitive and other functional domains, a substantial body of evidence from large-scale epidemiologic, cross-sectional, and prospective studies demonstrates that OSA is an independent risk factor for cardiovascular and cerebrovascular morbidity and mortality. The Sleep Heart Health Study (SHHS), which included more than 6000 subjects, and the Wisconsin Sleep Cohort study, which followed more than 1500 subjects, established associations of OSA with all-cause mortality, as well as with cardiovascular mortality, that were independent of confounding factors such as age, sex, and obesity. Independent associations of OSA with hypertension, congestive heart failure, coronary artery disease, cerebrovascular disease,
and cardiac arrhythmias have also been reported.\textsuperscript{2-4} However, the specific mechanisms whereby OSA leads to these adverse cardiovascular and cerebrovascular outcomes have not been definitively delineated. Candidate mechanisms include apnea-induced sympathetic nervous system activation, endothelial dysfunction, systemic inflammation, oxidative stress, increased coagulability, and metabolic dysfunction leading to insulin resistance, diabetes, and the metabolic syndrome (MS). This article focuses on the association of OSA, and its component physiologic perturbations, with abnormalities in insulin and glucose metabolism as a potential mechanism linking OSA with type 2 diabetes and cardiometabolic disorders.

OBSERVATIONAL STUDIES LINKING OSA WITH ABNORMALITIES OF INSULIN AND GLUCOSE METABOLISM AND TYPE 2 DIABETES

Collective evidence from cross-sectional studies over the last two decades has linked OSA with glucose intolerance, insulin resistance, and type 2 diabetes. However, because risk factors for OSA and metabolic dysfunction overlap, it has been difficult to definitively identify an independent impact of OSA.

As a symptom suggestive but not diagnostic of OSA, self-reported snoring has been used as a limited surrogate marker for OSA in population-based studies. In a 10-year prospective study of 2668 Swedish males between the ages of 30 and 69, subjects were surveyed regarding the presence of habitual snoring and a self-reported diagnosis of diabetes.\textsuperscript{5} The aim of the study was to determine if a relationship exists between diabetes and habitual snoring relative to obesity. The self-reported incidence of diabetes over 10 years was higher in habitual snorers (5.4%) compared with those without habitual snoring (2.4%) (\textit{P}<.001). Considering obesity, 13.5\% of obese snorers developed diabetes compared with 8.6\% of obese nonsnorers, although this did not reach significance (\textit{P} = .17). However, after adjustment for potential confounders including age, weight, smoking, alcohol dependence, and physical inactivity, the odds ratio (OR) for development of self-reported diabetes was higher in obese snorers, 7.0 (95\% CI 2.9, 16.9), than in obese nonsnorers, 5.1 (95\% CI 2.7, 9.5). The investigators concluded that habitual snoring increases the risk for developing diabetes in obese males; however, without objective measures of OSA and diabetes. These results are intriguing but not definitive.

The SHHS is a prospective cohort study comprised of subjects initially recruited from nine ongoing epidemiologic investigations of cardiovascular disease. Subjects were recruited without regard to signs or symptoms of OSA. Full ambulatory polysomnographic testing to assess for the presence and severity of OSA was performed in each of the 6441 participants at entry to the SHHS. Fasting insulin and glucose levels, as well as oral glucose tolerance tests (OGTTs), were performed in 2656 of the SHHS subjects within a year of enrollment. Impaired glucose tolerance was defined as a fasting plasma glucose level of 110 to 125 mg/dl and a 2-hour OGTT glucose level greater than or equal to 140 mg/dl but less than 200 mg/dl. Diabetes was diagnosed based on a fasting plasma glucose greater than or equal to 126 mg/dl or 2-hour OGTT greater than or equal to 200 mg/dl. The presence and severity of OSA was measured by the apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep: normal <5/h, mild 5–14/h, moderate >15–29/h, severe >30/h). Subjects with an AHI in the moderate or severe ranges had an increased prevalence of impaired fasting and 2-hour OGTT glucose levels compared with subjects with a normal AHI (17.5\% and 8.8\% of the cohort, respectively, in subjects with AHIs >15/h compared with 8.7\% and 4.0\% in subjects with AHIs <5/h). After adjusting for potential confounders, including age, gender, smoking status, body mass index
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(BMI), waist circumference, and self-reported sleep duration, subjects with mild or moderate-to-severe OSA had ORs of 1.27 (95% CI 0.98, 1.64) and 1.46 (95% CI 1.09, 1.97), respectively, for glucose intolerance compared with subjects with AHIs less than five events per hour of sleep. Severity of nocturnal hypoxemia, measured by the average oxyhemoglobin saturation during sleep and percentage of sleep time with oxyhemoglobin saturation below 90%, was independently associated with glucose intolerance, even after adjustment for confounding covariates. As a marker of insulin resistance, the homeostasis model assessment (HOMA-IR) index was calculated. Higher AHI, in the moderate-to-severe range, as well as greater severity of nocturnal hypoxemia, were associated with increased HOMA-IR values, providing evidence for an association of OSA severity with insulin resistance.

Another landmark study is the Wisconsin Sleep Cohort, a population-based longitudinal study established in 1988 that followed middle-aged subjects for 20 years, all of whom had polysomnographic testing at entry. Cross-sectional and prospective data from this cohort were analyzed to determine the prevalence and incidence of type 2 diabetes and if there is evidence for an independent association between diabetes and OSA. Diabetes was defined by a physician diagnosis of diabetes or a fasting glucose of greater than or equal to 126 mg/dl. Polysomnographic testing, followed by a fasting plasma glucose determination, was performed in 1387 participants at entry into the Wisconsin Sleep Cohort. Similar to observations from the SHHS, severity of OSA, as defined by the AHI, was correlated with the prevalence of diabetes: 2.8% of subjects with an AHI of less than five per hour had a diagnosis of diabetes compared with 14.7% of subjects with an AHI of greater than or equal to 15 per hour. The OR for having a diabetes diagnosis was 2.30 (95% CI 1.28, 4.11; \( P < .005 \)) in subjects with an AHI of greater than or equal to 15 per hour compared with subjects with an AHI of less than five per hour, after adjustment for age, sex, and body habitus. However, a-4 year longitudinal analysis of 978 participants without diabetes at entry did not demonstrate a statistically significant association of diabetes incidence with severity of OSA at baseline after adjustment for age, gender, and waist circumference.

In the Australian community of Busselton, Marshall and colleagues studied a sample of 399 participants (294 male subjects) who had OSA assessed by overnight home sleep respiratory monitoring followed by determination of fasting blood glucose. Moderate-to-severe OSA was a univariate risk factor for prevalent diabetes (OR = 4.37, 95% confidence limit [CL] = 1.12, 17.12) and, longitudinally, an independent risk factor for a 4-year incident diabetes (OR = 13.45, 95% CL = 1.59, 114.11) after adjustment for age, gender, BMI, waist circumference, high-density lipoprotein (HDL) cholesterol, and mean arterial pressure. Mild OSA, as in the Wisconsin Sleep cohort, was not associated with an increased risk of incident diabetes compared with subjects without OSA.

Evidence for an association between OSA and the development of diabetes was also demonstrated in another community-based study with a longer follow-up of an average of 11.3 years. Initially, 141 men without diabetes underwent overnight respiratory monitoring at baseline and then followed for 11 years with plasma glucose and serum insulin sampling. Twenty-three subjects developed diabetes at the end of the follow-up period. Nocturnal hypoxemia, as defined by an oxygen desaturation index (ODI, number of oxygen desaturation events per hour) greater than five per hour was associated with an OR of 4.4 (95% CI 1.1–18.1) for development of diabetes, after adjusting for age, BMI, and hypertension at baseline. The HOMA-IR index was used as a measure of insulin resistance. An abnormal HOMA-IR was significantly associated with metrics describing OSA severity, including an AHI greater than five per hour, ODI greater than five per hour, and low minimum nocturnal arterial oxygen
saturation. Nine of the subjects diagnosed with OSA were treated with continuous positive airway pressure (CPAP) therapy for a mean of 9.3 years by the end of the follow-up period. The incidence of diabetes was lower in subjects with OSA who were treated with CPAP therapy compared with those who were untreated. These findings add to the evidence linking OSA with incident insulin resistance and diabetes. Although the numbers are small and observational, results of this study also suggest a potential role for CPAP therapy in mitigating the adverse effects of OSA on glycemic control.

PREVALENCE OF OSA IN SUBJECTS WITH TYPE 2 DIABETES

Several, but not all, of the population-based studies previously described demonstrated an independent association of OSA with both prevalent and incident insulin resistance, and type 2 diabetes. Conversely, other studies have assessed the prevalence of OSA in patients with type 2 diabetes and have found remarkably high prevalence rates of OSA. In the SHHS, 58% of subjects with type 2 diabetes had an abnormal AHI.\textsuperscript{10–12} The prevalence of OSA in obese subjects with type 2 diabetes was also assessed with ambulatory nocturnal respiratory monitoring in the Sleep AHEAD study, a four-site ancillary study of the Look AHEAD Trial (Action for Health in Diabetes). Look AHEAD is a 16-center trial investigating the long-term health impact of lifestyle intervention designed to achieve and maintain weight loss in more than 5000 obese adults with type 2 diabetes. Sleep testing was performed in 306 participants in the Sleep AHEAD study. Remarkably, 86.6% of obese subjects with type 2 diabetes in this study had an abnormal AHI indicating sleep apnea. The mean AHI in this cohort was 20.5 plus or minus 16.8 per hour, which indicates moderate OSA.\textsuperscript{10}

INSULIN AND GLUCOSE HOMEOSTASIS ASSESSMENT IN PATIENTS WITH OSA

Observational data linking OSA with impairment of insulin sensitivity, independent of obesity, have been evident for more than a decade. Using an OGTT with calculation of composite and hepatic insulin sensitivity indices, Tassone and colleagues\textsuperscript{13} demonstrated reduced insulin sensitivity in obese OSA patients compared with BMI-matched obese controls without OSA. Insulin sensitivity indices were impaired in both of these groups compared with normal BMI subjects without OSA. These findings imply that, although obesity impairs insulin sensitivity, further impairment is induced by an independent effect of OSA. In another investigation, Ip and colleagues\textsuperscript{14} used the HOMA to evaluate the association of OSA with insulin resistance. Although obesity was a major determinant of insulin resistance, metrics describing the severity of OSA, including the AHI and minimum oxygen saturation during sleep were independent determinants of insulin resistance. The association between OSA and insulin resistance was evident in both obese and nonobese OSA subjects. A subsequent study using the frequently sampled intravenous glucose tolerance test with minimal model analysis, which assessed various parameters describing insulin sensitivity, glucose effectiveness (ie, the ability of glucose to influence its own production and use, independent of insulin), and pancreatic β-cell function, was performed in non-diabetic subjects with OSA. Dual energy x-ray absorptiometry (DEXA) scans were used to assess body fat composition. OSA was associated with reduced insulin sensitivity independent of percent body fat, age, and sex. Measures of pancreatic β-cell function were also reduced in moderate-to-severe OSA. This study provides further evidence that OSA impairs insulin sensitivity, glucose effectiveness, and pancreatic β-cell function independent of the effects of obesity.\textsuperscript{15}
IMPACT OF OSA ON GLYCEMIC CONTROL IN TYPE 2 DIABETES

The impact of OSA on insulin and glucose metabolism should be evident in patients with type 2 diabetes and OSA. Aronsohn and colleagues studied 60 type 2 diabetic subjects consecutively recruited from outpatient primary care and endocrinology clinics. Overnight polysomnography (PSG) was performed to assess for OSA and a hemoglobin A1c (HbA1c) level was obtained in all subjects. Again, a remarkably high prevalence of OSA was demonstrated in this diabetic cohort with 77% of subjects having an abnormal AHI greater than or equal to five per hour. Increasing severity of OSA was significantly correlated with worsening glycemic control, assessed by higher HbA1c. This finding was independent of age, sex, race, BMI, number of diabetes medications, and years of diabetes. Compared with patients without OSA, the adjusted mean HbA1c was increased by 1.49% in mild OSA, 1.93% in moderate OSA, and 3.69% in severe OSA compared with subjects without OSA.

INDEPENDENT ASSOCIATION OF OSA WITH THE METABOLIC SYNDROME

Another important link between OSA and the development of diabetes and cardiovascular disease is syndrome Z, a term developed to describe the association of OSA with the metabolic syndrome, which is a combination of obesity, insulin resistance, hypertension, and dyslipidemia. The OR for metabolic syndrome in OSA has been documented to range from fivefold to as high as ninefold, compared with subjects without OSA, independent of age and BMI. In a Chinese community-based study of 255 subjects, severity of OSA correlated with an increasing prevalence of the metabolic syndrome. A Japanese case-control study analyzed lean men with an average BMI of 23 kg/m² with and without OSA and demonstrated an association of OSA with three components of the metabolic syndrome: insulin resistance, hypertension, and dyslipidemia. This study suggested that, although OSA and the metabolic syndrome are closely linked to obesity, OSA may be an independent risk factor for the metabolic syndrome.

PATHOPHYSIOLOGY OF OSA AND POTENTIAL LINKS TO INSULIN RESISTANCE AND TYPE 2 DIABETES

OSA results from upper airway occlusion during sleep, usually in the velopharyngeal and retroglossal regions. Both anatomic factors, including enlarged soft tissues of the upper airway and narrowed craniofacial skeletal structure, as well as insufficient neural drive to the upper airway dilator muscles during sleep, contribute to OSA. Upper airway occlusion can be partial, resulting in hypopneas, or complete, resulting in apneas. These disordered breathing events may cause several pathophysiologic perturbations. First, some degree of arousal from sleep occurs at the termination of obstructive apneic events, which is necessary to reactivate inspiratory drive to the upper airway dilator muscles that reopens the closed upper airway. These arousals, which are often observed on the cortical electroencephalogram (EEG), result in fragmentation of sleep and contribute to daytime somnolence, which is a characteristic clinical feature of OSA. In addition, activation of the autonomic nervous system occurs in association with obstructive apneas and hypopneas, with parasympathetic activity predominating during apneas and sympathetic tone increasing at the termination of apneic events. In addition, elevated levels of circulating and urinary catecholamines have been observed in OSA. Interestingly, elevated sympathetic tone is not only evident during sleep; it also has been demonstrated to persist during the day, when breathing is normal in OSA patients.
Another significant pathophysiologic feature of OSA is intermittent hypoxia (IH) and reoxygenation that accompanies apneic events (Fig. 2). IH has physiologic consequences that differ from those of chronic hypoxia. Repetitive decreases and increases in oxygen saturation contribute to formation of reactive oxygen and nitrogen species that increase oxidative stress and can activate redox-sensitive cellular signaling pathways.²³⁻²⁷

**CHRONIC IH AND INSULIN RESISTANCE**

Although some investigators contend that obesity is the main risk factor responsible for the association of OSA with diabetes, a large body of evidence is accumulating that links the pathophysiologic perturbations of OSA, independent of the effects of

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**Fig. 1.** An epoch (30-second segment) of a polysomnographic recording demonstrating an obstructive apnea. Note that the termination of the apnea is associated with an arousal from sleep, indicated by an increase in EEG frequency and submental EMG tone. Note the decrease in heart rate during the apnea with an increase after apnea termination. ABD, abdomen; EEG, electroencephalogram; EMG, submental electromyogram; EOG, electrooculogram; INSP. FLOW, inspiratory flow; LEG, anterior tibialis electromyogram; SaO₂, saturation level of oxygen.

**Fig. 2.** Five-minute segment of a polysomnographic recording showing recurrent apneas and intermittent episodes of oxygen desaturation followed by reoxygenation (intermittent hypoxemia and reoxygenation) characteristic of severe OSA. SaO₂, saturation level of oxygen.
Obesity, with alterations of insulin and glucose metabolism. Animal and human data indicate that long-term exposure to IH, such as that occurring in association with OSA, can alter glucose homeostasis and insulin resistance. Exposure of lean mice to IH during their sleep period was accomplished by placing animals in chambers in which the fraction of inspired oxygen (FiO\textsubscript{2}) was decreased from 21% to between 5% and 6% with a return to 21% once each minute during their sleep period, thereby mimicking the IH associated with severe OSA. Exposure protocols ranged from several hours to several months. Insulin sensitivity was assessed during exposure to IH using the hyperinsulinemic-euglycemic clamp technique in chronically instrumented but unhandled mice. IH-induced insulin resistance was evidenced by a 21% reduction in the exogenous glucose necessary to maintain euglycemia during the hyperinsulinemic-euglycemic clamp. In additional, fasting hyperglycemia was observed because of IH. Thus, these data provide strong evidence for a causal relationship between exposure to IH and insulin resistance that is independent of obesity. Similar findings to those observed in lean mice were also seen in mice with diet-induced obesity and in genetically obese mice.\textsuperscript{28,29}

Potential mechanisms that could explain these findings include an impact of IH on hepatic glucose output as well as on glucose uptake in skeletal muscle. In these studies, IH did not affect hepatic glucose output; however, IH significantly impaired glucose uptake by skeletal muscle. The impact of IH was most pronounced in oxidative muscle fibers, whereas glycolytic muscle fibers were unaffected. Thus, glucose disposition in oxidative muscle tissue is apparently impaired by IH in a manner that is independent of obesity.\textsuperscript{28,30}

CHRONIC INTERMITTENT HYPOXIA, OXIDATIVE STRESS, AND SYSTEMIC INFLAMMATION

Oxidative stress and systemic inflammation induced by IH is another potential mechanism that may lead to insulin resistance and pancreatic β-cell dysfunction in OSA. IH has shown to increase generation of free radicals, including reactive oxygen species (ROS) and reactive nitrogen species. Mitochondrial dysfunction induced by hypoxia is an important source of these free radicals. Other sources of ROS resulting from IH include NADPH oxidase and xanthine oxidase. Overproduction of free radicals can damage macromolecules. Elevated markers of lipid peroxidation, a contributing factor to atherosclerosis, which has been reported in OSA patients, provides evidence that this effect may be clinically significant.\textsuperscript{26}

In addition, activation of redox-sensitive nuclear transcription factors, such as nuclear factor kappa beta (NF-κβ) and hypoxia-inducible factor 1-α (HIF-1α), has also been observed because of IH in animal models and in humans with OSA.\textsuperscript{25,31,32} In fact, in in vitro studies IH selectively induces NF-κβ expression, whereas continuous hypoxia does not. Furthermore, HIF-1α is better expressed following exposure to IH than with continuous hypoxic stimulation.\textsuperscript{33} These transcription factors regulate expression of genes that encode proinflammatory cytokines, proteins important in adaptation to hypoxia, as well as proteins that regulate lipogenesis and lipolysis, among many other genes. Several animal models have demonstrated that long-term exposure to IH increases circulating proinflammatory cytokines, activates leukocytes, and causes endothelial dysfunction with accelerated atherosclerosis.\textsuperscript{25–27} In subjects with OSA, the degree of NF-κβ expression in circulating neutrophils was highly correlated with indices of apnea severity. Furthermore, NF-κβ activity was reduced to baseline levels following 1 month of therapeutic CPAP.\textsuperscript{25} Elevated circulating levels of tumor necrosis factor α (TNF-α), interleukin
(IL)-6, IL-8, IL-1β, adhesion molecules, and C-reactive protein (CRP) have all been observed in OSA, with decreases after CPAP therapy. Evidence from human and animal studies suggests that TNF-α and IL-6 may contribute to insulin resistance. Furthermore, elevated levels of some of these cytokines, including CRP, IL-6, and IL-1β independently predict an increased risk for type 2 diabetes. Thus, systemic inflammation, induced by IH, which is characteristic of OSA, may represent another mechanism through which OSA may contribute to abnormal insulin and glucose metabolism and development of type 2 diabetes.

**IMPACT OF IH ON PANCREATIC β-CELL FUNCTION**

The development of insulin resistance is only one factor that can lead to development of clinical diabetes. Impaired pancreatic β-cell function may reduce compensatory increases in insulin secretion that are necessary to maintain normal blood glucose levels in the setting of insulin resistance. Diabetes can develop when β-cells are unable to compensate for insulin resistance. Recent data indicate that IH may also impair pancreatic β-cell function. Adult male lean mice were exposed to IH for 8 hours during their sleep period for 30 days. Exposed mice demonstrated elevated plasma fasting insulin without a change in glucose, indicating insulin resistance. However, no evidence for pancreatic β-cell proliferation or hypertrophy was observed. In fact, insulin content was decreased in pancreatic islets taken from animals exposed to IH. Furthermore, IH-exposed animals demonstrated severely impaired glucose-stimulated insulin secretion. Impairment of insulin synthesis and processing was subsequently demonstrated in these pancreatic β-cells. Additional experiments demonstrated that mitochondrial-derived ROS may play an important role in IH-induced pancreatic β-cell dysfunction.

**SYMPATHETIC NEURAL ACTIVATION**

Another potential mechanism that might link IH with peripheral insulin resistance is an increase in sympathetic neural activity that occurs in response to IH in animal models and to OSA in humans. Catecholamines increase insulin resistance and decrease insulin-mediated glucose uptake in the periphery. Furthermore, activation of the hypothalamic pituitary adrenal axis is known to impair insulin sensitivity and increase mobilization of glucose. The impact of activation of the sympathetic nervous system resulting from IH on insulin resistance was assessed in animal studies that used the ganglionic blocker hexamethonium to prevent autonomic activation. Blockade of autonomic activity had no impact on development of insulin resistance in response to IH. Therefore, at least in animal models of IH, mechanisms other than sympathetic neural activation are responsible for development of insulin resistance. Nevertheless, in the clinical setting, overactivation of the sympathetic nervous system and the hypothalamic pituitary adrenal axis (due to sleep apnea and its associated sleep fragmentation) may contribute to insulin resistance in OSA.

**ADIPOSE TISSUE HYPOXIA AND SYSTEMIC INFLAMMATION**

There has been a remarkable evolution in contemporary understanding of the role of white adipose tissue (WAT) in normal physiologic function and in response to endogenous stressors. The traditional view of WAT as a reservoir of stored energy in the form of triacylglycerols has been replaced by a more expansive concept of WAT as an endocrine organ involved in different metabolic activities as well as the site of a major group of secretory cells, the adipocytes. Such a conceptual change in the functional
status of WAT was motivated by the discovery of the hormone leptin that was coded for by the ob gene in the obese (ob/ob) mouse. Interestingly, leptin affects central neural structure via the melanocortin system of the hypothalamus (arcuate nucleus) and is associated with cessation of feeding and with energy expenditure, whereas, in the periphery, it increases hepatic lipid oxidation and lipolysis in skeletal muscle and adipocytes. Equally important, adipocytes are also known to secrete other hormones and cytokines (adipokines) that have important functions in health and disease, including (1) adiponectin and resistin for glucose metabolism, (2) cholesteryl ester transfer protein for lipid metabolism, (3) angiotensinogen and angiotensin II necessary for blood pressure homeostasis, and (4) plasminogen activator inhibitor-1 (PAI-1) for coagulation. However, much recent work has focused on the inflammatory adipokines, which include cytokines, chemokines, and acute phase proteins (haptoglobin and PAI-1), and their roles in the development of obesity-related insulin resistance. A large number of cytokines and chemokines are secreted by adipocytes; these include TNF-α, IL-1β, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1), macrophage migration inhibitory factor (MIF), and transforming growth factor β (TGF-β). Proinflammatory secretory products of adipocytes are associated with obesity-induced proinflammatory states as they are elevated in the circulation of obese subjects with insulin resistance, whereas the antiinflammatory adipokine, adiponectin, is diminished in the circulation of obese subjects with insulin resistance.

Our understanding of the link between disease and obesity was advanced considerably by the recognition that visceral obesity represented a state of chronic mild inflammation due to secreted adipokines. Additionally, because adipose tissue increases in size, macrophages are attracted and retained within adipose tissue by the actions of the chemokines MCP-1 and MIF, respectively. Consequently, a massive infiltration of type M1-macrophages occurs and these secrete the proinflammatory adipokines IL-6 and TNF-α. Hence, the effect of M1-macrophage arrival in adipose tissues is to increase the degree of inflammation in already inflamed tissues. Such inflammatory processes play a significant role in the cause of insulin resistance via inhibition of adipocyte storage of lipids, secretions of adipokines, enhanced lipolysis, and reduced reesterification of free fatty acids (FFAs) resulting in elevation of FFAs in the circulation.

Although several hypotheses have been raised to explain the cause of inflammation in adipose tissue, there is mounting evidence that hypoxia occurs within enlarged regions of visceral adipose tissue. As adipose hypertrophy ensues, a reduction in adipose tissue blood flow occurs. Further complicating perfusion of adipose tissue is the increase in dimensions of adipocytes (some exceeding 150 μm in diameter); hence, limited or no perfusion occurs due to the diffusion limitation of oxygen (~100 μm). As previously discussed, hypoxic stress is associated with activation of inflammatory signaling pathways, including the transcription factors hypoxia-inducible factor 1α (HIF-1α) and NF-κβ. OSA prevalence in the obese population has generated the hypothesis that OSA may exacerbate adipose tissue hypoxia, thus contributing to adipose tissue inflammation and providing an additional pathway leading to insulin resistance with the clinical sequelae of cardiometabolic disorders.

HUMAN STUDIES LINKING IH AND SLEEP FRAGMENTATION WITH INSULIN RESISTANCE AND PANCREATIC β-CELL DYSFUNCTION

The data linking insulin resistance and pancreatic β-cell dysfunction with IH have been observed in animal studies. However, recent experiments in healthy human volunteers have corroborated these findings. Louis and Punjabi exposed 13 healthy subjects to
5 hours of IH by altering the inspired $\text{FiO}_2$ from room air to 5% oxygen approximately 25 times per hour during wakefulness, simulating the degree of IH observed in moderate OSA. A frequently sampled intravenous glucose tolerance test was performed with assessment of insulin-dependent and insulin independent measures of glucose disposal. Five hours of exposure to IH led to decreased insulin sensitivity that was not accompanied by a commensurate increase in insulin secretion. In addition, decreased glucose effectiveness, which indicates the ability of glucose to enhance its disposal independent of insulin, was observed. An increase in sympathetic nervous system activity, without a change in serum cortisol levels, also occurred.

Another physiologic perturbation of OSA is recurrent arousals from sleep that cause sleep fragmentation. Disturbed sleep may also lead to alterations in insulin and glucose metabolism. The impact of sleep fragmentation on glucose and insulin metabolism was similarly tested in healthy human volunteers with the frequently sampled intravenous glucose tolerance test. Sleep was fragmented by inducing microarousals on the cortical EEG with mechanical and auditory stimuli presented 30 times per hour during sleep, simulating the arousal frequency and sleep disruption observed in moderate-to-severe OSA. Results were compared with a night of undisturbed sleep. Insulin sensitivity and glucose effectiveness were reduced by 20% and 25%, respectively, after sleep fragmentation. In addition, an increase in sympathetic nervous system activity was observed with elevated morning serum cortisol levels. Thus, sleep fragmentation, such as that occurring in OSA, can also adversely affect glucose homeostasis independent of IH.

**CPAP THERAPY IN OSA AND CHANGES IN INSULIN SENSITIVITY**

Some observational studies have indicated that CPAP therapy for OSA not only relieves symptoms related to sleep apnea, it also improves insulin sensitivity. However, the reported impact of CPAP on insulin sensitivity is variable among studies, with some investigators demonstrating significant improvement either in all subjects or in a subset of subjects, whereas others note no change. This disparity may be related to differences in methods of assessment of insulin sensitivity, variation in study population characteristics, and variable adherence to CPAP therapy. For example, in subjects with moderate-to-severe OSA using CPAP therapy, an observational study demonstrated significant improvement in insulin sensitivity after 2 days and after 3 months using the hyperinsulinemic-euglycemic clamp technique. However, the improvement in insulin sensitivity was most pronounced in subjects with a BMI less than 30 kg/m$^2$. A recent meta-analysis of 12 prospective observational studies of nondiabetic adults newly diagnosed with moderate-to-severe OSA demonstrated that 3 to 24 weeks of CPAP treatment resulted in a significant decrease in insulin resistance as assessed by the homeostasis model for insulin resistance (HOMA-IR).

Several randomized, controlled trials have shown significant improvements in insulin sensitivity in OSA patients treated with CPAP, compared with sham-CPAP, as assessed by the Gutt index, quantitative insulin sensitivity check index (QUICKI), short insulin tolerance test, and the hyperinsulinemic-euglycemic clamp technique, as well as other metrics of insulin-glucose metabolism. One study showed a trend toward improvement in insulin sensitivity after CPAP therapy using the hyperinsulinemic-euglycemic clamp (glucose clamp–derived index of insulin sensitivity [SI Clamp]), although the degree of improvement did not reach statistical significance. Mean nightly hours of CPAP use in that study were only 3.6, which might explain the failure to obtain a statistically significant result. In support of this contention, another randomized, placebo-controlled study demonstrated incremental improvement in the
insulin sensitivity index with each additional hour of nightly CPAP use. This finding highlights the importance of optimal nightly adherence to CPAP therapy to achieve beneficial outcomes. In that study, however, significant improvements in insulin sensitivity were only observed in subjects with severe OSA (AHI ≥ 30 per hour). In another study, nightly CPAP therapy for OSA resulted in a significant increase in glucose disappearance rate (K_{gtt}) in as little as 1 week. Other placebo-controlled studies demonstrated a trend toward, but not statistically significant, improvement in insulin sensitivity with CPAP therapy for OSA as assessed by the HOMA-IR technique.

Some of the variability in results of these outcome studies may reflect not only differences in patient characteristics and CPAP adherence rates; they may also reflect differing methodologies used to assess insulin sensitivity. For example, the QUICKI has a substantially better linear correlation with SIClamp than HOMA-IR and performs better in patients with insulin resistance. Likewise, HOMA-IR is a good surrogate for the effect of insulin on hepatic glucose production, but may not accurately represent other sites of insulin response and may be less accurate in the setting of severely impaired pancreatic β-cell function. Furthermore, OSA, and its treatment with CPAP, may alter various aspects of insulin and glucose metabolism, including skeletal muscle insulin sensitivity and pancreatic β-cell function that may not be adequately assessed by these metrics.

**CPAP THERAPY IN OSA AND CHANGES IN GLYCOSYLATED HEMOGLOBIN**

The percentage of HbA1c, a marker of long-term glucose control in diabetic individuals, has been positively correlated with severity of OSA in patients with type 2 diabetes. HbA1c increased by an average of 1.49%, 1.93%, and 3.69%, respectively, in patients with mild, moderate, and severe OSA, after adjusting for age, gender, BMI, race, number of antidiabetic medications, exercise, duration of diabetes, and total sleep time compared with patients without OSA. Several studies have shown improvement in HbA1c after 3 months of CPAP therapy. Predictably, the degree of improvement in HbA1c was related to the number of hours of nightly CPAP usage. In one study, subjects who used CPAP for more than 4 hours per night (mean 6.6 hours per night) achieved the greatest improvement in HbA1c. In contrast, in another investigation in which the mean duration of nightly CPAP use was only 3.6 hours per night (SD = 2.8), improvement in HbA1c was not observed. These findings indicate that CPAP therapy may improve glucose control in type 2 diabetes, but adequate nightly adherence to CPAP is essential to achieve this beneficial outcome.

**IMPACT OF CPAP THERAPY FOR OSA ON THE METABOLIC SYNDROME**

Previous studies have shown that OSA may independently contribute to development of MS. Components of MS include systemic arterial hypertension, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, abdominal obesity, and insulin resistance. This constellation of conditions significantly increases risk for cardiovascular and cerebrovascular disease and diabetes.

The effect of CPAP therapy for OSA on MS has been explored by several investigators. In a randomized, placebo-controlled study, 20% of subjects with MS and OSA who were treated with CPAP for 3 months showed reversal of MS components and no longer met criteria for this condition after treatment of OSA. In contrast, another randomized, controlled study, with a shorter duration of CPAP therapy (6 weeks), did not demonstrate a change in the portion of subjects meeting criteria
for MS despite significant reductions in blood pressure.\textsuperscript{58} Of all of the components of MS, CPAP therapy seems to have the greatest impact on systemic arterial pressure. The latter study, as well as several other randomized, placebo-controlled studies, demonstrated significant reduction in arterial blood pressure with CPAP therapy for OSA.\textsuperscript{55,58,60} Further evidence for the impact of CPAP therapy on hypertension in OSA comes from a study that showed that when CPAP was withdrawn from previously treated OSA subjects, systemic arterial pressure significantly increased.\textsuperscript{66}

Another component of MS, hyperlipidemia, may also be affected by OSA and may improve with CPAP therapy. Animal models have shown that IH increases serum triglyceride and low-density lipoprotein (LDL)-cholesterol levels, possibly by increasing activity of sterol regulatory element–binding protein-1 and sterol-coenzyme A desaturase-1, which enhances conversion of saturated to monounsaturated fatty acids, increases serum triglycerides, and promotes lipoprotein secretion.\textsuperscript{68} In accord with these findings, lipid profiles in OSA patients have been shown to improve with CPAP therapy and include changes in serum triglycerides, LDL, non-HDL, total cholesterol, and HDL to total cholesterol ratio.\textsuperscript{55,60}

Abdominal or visceral obesity is another feature of MS that has been associated with increased cardiovascular risk that may also be improved with CPAP therapy for OSA. In a randomized, controlled study, in which nearly half of the study participants had both OSA and type 2 diabetes, significant reduction in BMI, in addition to decreases in visceral and subcutaneous fat, was observed after 3 months of CPAP.\textsuperscript{60} However, other randomized, controlled studies of nondiabetic OSA subjects failed to demonstrate an impact of CPAP therapy on visceral, subcutaneous, or hepatic fat distribution.\textsuperscript{53,54,67}

Although some data remain conflicting, evidence is mounting that CPAP therapy for moderate-to-severe OSA may improve components of MS, which may ultimately reduce cardiovascular and cerebrovascular risks.

**SCREENING FOR OSA IN PATIENTS WITH TYPE 2 DIABETES**

Both type 2 diabetes and OSA are independently associated with increased cardiovascular and cerebrovascular risk.\textsuperscript{69} Furthermore, the incidence of OSA in obese type 2 diabetic individuals has shown to be quite high.\textsuperscript{10} Thus, identification and treatment of OSA in patients with type 2 diabetes may be of paramount importance for successful cardiometabolic risk reduction.

Classic symptoms of OSA include heavy snoring, witnessed pauses of breathing during sleep and daytime somnolence.\textsuperscript{69} Anatomic factors such as obesity (BMI>30 kg/m\textsuperscript{2}), large neck circumference (>16 inches for women, >17 inches for men), a crowded oropharynx with a low lying soft palate, large base of tongue, and tonsillar hypertrophy, as well as craniofacial abnormalities such as retrognathia, increase the risk of OSA.\textsuperscript{70} However, many patients with OSA may not volunteer OSA-related symptoms at routine office visits, necessitating active questioning or screening. Although questions regarding OSA symptoms should ideally be part of routine history and physical examinations, this may not always be practical. Thus, several self-administered screening tools have been developed that can facilitate identification of patients who may require referral for further assessment of OSA.

The Epworth Sleepiness Scale (ESS) measures subjectively reported tendency to doze off during a variety of situations. However, the ESS is only 39.0% sensitive for detection of moderate-to-severe OSA. The STOP-Bang questionnaire is an eight-item questionnaire that assesses risk factors for OSA. A STOP-Bang score greater than or equal to three has 87% sensitivity, but low specificity (43.3%), for identifying
moderate-to-severe OSA. Increasing the cutoff score for the STOP-Bang to a range of five to eight increases specificity but reduces sensitivity.\textsuperscript{71} The ten-question Berlin questionnaire is composed of three categories. A high risk of OSA is identified by positive answers in two or more categories, which yields 78.6\% sensitivity, with 50.5\% specificity, for detection of moderate-to-severe OSA.\textsuperscript{72,73} The Sleep Apnea Clinical Score is a 36-item questionnaire that has been validated for calculation of likelihood ratios for the presence of OSA.\textsuperscript{74} A score of greater than or equal to 15 yields a likelihood ratio of 4.45 of moderate-to-severe sleep apnea.\textsuperscript{75} The sensitivities and specificities of these tools are listed in Table 1. The STOP-Bang questionnaire and the Berlin questionnaire can each be completed in less than 5 minutes, allowing them to be used as effective OSA screening tools in a busy clinical setting. Although the sensitivity of the ESS for OSA is relatively low, it can also provide useful data regarding the degree of daytime somnolence and its improvement with treatment.

**DIAGNOSIS AND TREATMENT OF OSA**

Once a patient is referred for further sleep evaluation, the diagnosis of OSA, and its severity, should be assessed by recording physiologic parameters during sleep. The gold standard is attended PSG performed in a sleep laboratory that comprehensively assesses sleep and breathing with recordings of the EEG, electromyogram, electrooculogram, ECG, nasal/oral airflow, thoracic and abdominal respiratory effort, oxygen saturation, and an audio recording of snoring throughout the night.\textsuperscript{76} An alternative, more limited respiratory assessment, performed during home sleep testing (HST), has recently gained popularity and it may be useful in cases in which the pretest probability of moderate or severe OSA is high.\textsuperscript{77} The main advantages of HST are reduced costs compared with PSG and a more familiar environment for the patient.\textsuperscript{78} However, HST has many limitations that can reduce its usefulness because it usually only monitors airflow, respiratory effort, and oxygen saturation with no objective measure of sleep duration or sleep quality. This may lead to underestimation of the severity and impact of sleep-disordered breathing, particularly in patients with milder degrees of OSA. In addition, because sleep is not objectively recorded during most HSTs, false-negative results may occur in patients with coexisting insomnia. HSTs are also inadequate for assessment of other sleep disorders or for assessment of sleep-disordered breathing in patients with significant comorbid cardiopulmonary disease. Therefore, patients suspected of having OSA with negative HST results should usually be referred for confirmatory in-laboratory PSG.\textsuperscript{76}

Various treatment modalities are available for OSA. Successful therapeutic outcome depends on tailoring treatment recommendations to patient-specific needs and

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<th>Table 1 Predictive parameters for the Epworth Sleepiness Scale, STOP-BANG questionnaire, and Berlin questionnaire for moderate-to-severe OSA</th>
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<td>Epworth Sleepiness Scale</td>
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<td>Sensitivity (%)</td>
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<td>Specificity (%)</td>
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expectations, with strong consideration given to comorbidities such as cardiac, pulmonary, and cerebrovascular disease, as well as to coexisting sleep disorders such as insomnia. CPAP therapy is the mainstay of treatment of OSA, with randomized, placebo-controlled trials clearly demonstrating improvement in quality of life metrics, daytime somnolence, and neurobehavioral performance, not only in subjects with moderate-to-severe OSA, but also in subjects with milder sleep apnea.\textsuperscript{79,80} Several alternatives to CPAP therapy that also have demonstrated efficacy include mandibular advancement oral appliance therapy, surgical approaches to the upper airway, and bariatric surgery in appropriately selected patients. Because OSA is a chronic condition, long-term disease management to assure compliance with effective therapy is essential to achieve optimal functional outcomes as well as cardiovascular risk reduction.\textsuperscript{81}

**SUMMARY**

Epidemiologic studies demonstrated a high prevalence of insulin resistance and type 2 diabetes in patients with OSA. Furthermore, an extremely high prevalence of OSA has been documented in obese patients with type 2 diabetes. The pathophysiology of OSA, which includes sleep fragmentation, activation of the sympathetic nervous system, and IH resulting from recurrent apneas, may contribute to abnormal glucose and insulin metabolism. Both animal and human studies demonstrated that IH, with its associated systemic inflammation and oxidative stress, contributes to hepatic and peripheral insulin resistance as well as to pancreatic $\beta$-cell dysfunction, independent of obesity. Recognition of OSA in patients with type 2 diabetes is important because effective treatment with CPAP may improve insulin sensitivity, HbA1C, systemic hypertension, and other components of MS that contribute to long-term cardiovascular and cerebrovascular risk.

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