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Obstructive Sleep Apnea and Type 2 Diabetes*

Interacting Epidemics

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Type 2 diabetes is a major public health concern with high morbidity, mortality, and health-care costs. Recent reports have indicated that the majority of patients with type 2 diabetes also have obstructive sleep apnea (OSA). There is compelling evidence that OSA is a significant risk factor for cardiovascular disease and mortality. Rapidly accumulating data from both epidemiologic and clinical studies suggest that OSA is also independently associated with alterations in glucose metabolism and places patients at an increased risk of the development of type 2 diabetes. Experimental studies in humans and animals have demonstrated that intermittent hypoxia and reduced sleep duration due to sleep fragmentation, as occur in OSA, exert adverse effects on glucose metabolism. Based on the current evidence, clinicians need to address the risk of OSA in patients with type 2 diabetes and, conversely, evaluate the presence of type 2 diabetes in patients with OSA. Clearly, there is a need for further research, using well-designed studies and long-term follow-up, to fully demonstrate a causal role for OSA in the development and severity of type 2 diabetes. In particular, future studies must carefully consider the confounding effects of central obesity in examining the link between OSA and alterations in glucose metabolism. The interactions among the rising epidemics of obesity, OSA, and type 2 diabetes are likely to be complex and involve multiple pathways. A better understanding of the relationship between OSA and type 2 diabetes may have important public health implications. (CHEST 2008; 133:496–506)

Key words: diabetes; glucose intolerance; insulin resistance; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; DI = disposition index; Hb = hemoglobin; HOMA = homeostatic model assessment; IVGTT = IV glucose tolerance test; OGTT = oral glucose tolerance test; OSA = obstructive sleep apnea

Type 2 diabetes is a major chronic disease with high morbidity, mortality, and economic burden.^{1,2} There is an alarming rise in the prevalence of type 2 diabetes that may be largely attributed to the epidemic of obesity.³ Excess weight is also an important factor for

obstructive sleep apnea (OSA),⁴ an increasingly common sleep disorder that is characterized by repetitive upper airway obstructions leading to intermittent hypoxia and sleep fragmentation. Data from the 2005 “Sleep in America” poll of the National Sleep Foundation⁵ indicate that as many as one in four adults and 57% of obese individuals are at high risk for OSA, which is consistent with the fact that OSA remains frequently undiagnosed.⁶ Young et al⁷ have estimated that the prevalence of OSA (apnea-hypopnea index [AHI], ≥ 5) in adults 30 to 69 years of age is approximately 17%, and the proportion of mild-to-moderate OSA attributable to excess weight is 41 to 58%.

There is rapidly growing evidence from population, clinic-based, and laboratory studies to suggest that these two expanding epidemics, namely, type 2 diabetes and OSA, may be associated independently of the

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Table 1—Population-Based Studies Linking OSA Defined by Polysomnography to Altered Glucose Metabolism and Type 2 Diabetes*

Study/Year	Study Sample	Measures of Glucose Metabolism	Main Findings
Stoohs et al ⁴⁸ /1996	50 (34 women) healthy subjects, United States	<i>In vivo</i> insulin action by insulin suppression test	Elevated insulin resistance in OSA (AHI ≥ 10) is entirely dependent on BMI
Elmasry et al ⁷³ /2001	116 hypertensive men, Sweden	Fasting glucose, fasting insulin, and HbA1c	Higher prevalence of severe OSA (AHI ≥ 20) in diabetic patients than normoglycemic subjects (36% vs 14.5%, respectively). The severity of OSA is associated with indices of glucose metabolism in normoglycemic subjects independently of central adiposity and antihypertensive use
Punjabi et al ⁷⁴ /2002	155 men, United States	OGTT and HOMA	Increasing severity of AHI and oxygen desaturations were associated with worsening glucose tolerance and insulin resistance after adjustment for BMI and percentage of body fat
Ip et al ⁷⁵ /2002	270 (197 men) Chinese individuals	Fasting insulin and HOMA	AHI and minimum oxygen saturation are independent determinants of insulin resistance
Punjabi et al ⁷⁶ /2004	Sleep Heart Health Study, United States, 2,656 (1,214 men) participants	Fasting and 2-h glucose during OGTT, and HOMA	AHI and average oxygen saturation are independently associated with both fasting and 2-h glucose levels; independent link between degree of insulin resistance and severity of OSA
Reichmuth et al ¹¹ /2005†	Wisconsin Sleep Cohort, United States, 1,387 (779 men) participants, 4-yr follow-up in 987 subjects	Diabetes diagnosed by physician and/or fasting glucose concentration of ≥ 126 mg/dL	More prevalent diabetes with OSA (AHI ≥ 15): OR, 2.3 (95% CI, 1.28–4.11) after adjustment for age, gender, and body habitus; no independent relationship between incident diabetes and OSA at 4-yr follow-up
Lam et al ⁷⁷ /2006	255 (150 men) Chinese individuals	Fasting glucose	Association between OSA and fasting glucose after adjustment for age, gender, BMI, smoking, and alcohol use; adjusted OR for fasting glucose concentration of ≥ 110 mg/dL, 2.74 (95% CI, 1.16–6.49) for AHI ≥ 5 vs < 5
Okada et al ⁷⁸ /2006	207 Japanese men	HbA1c and fasting glucose	Higher levels of HbA1c and fasting glucose in sleep apnea patients (AHI ≥ 15) compared to nonapneic subjects with similar BMI
Sulit et al ⁷⁹ /2006	Cleveland Family Study, United States, 394 (177 men) subjects	OGTT	Threshold dose response for measures of hypoxic stress (≥ 2% time spent < 90% oxygen saturation) and glucose intolerance; adjusted OR, 2.33 (95% CI, 1.38–3.94)

*OR = odds ratio; CI = confidence interval. Bold type indicates negative studies.

†Includes prospective data analysis.

degree of adiposity. In a report by West et al,⁸ the overall prevalence of OSA in diabetic men was estimated at 23% compared with 6% in a community-based sample. A preliminary analysis of cross-sectional data from a multicenter study⁹ revealed an exceptionally high prevalence of undiagnosed OSA in obese patients with type 2 diabetes with > 75% of patients having moderate-to-severe OSA diagnosed by polysomnography. These remarkable associations raise the possibility that OSA may be a novel risk factor for type 2 diabetes and/or, conversely, that chronic hyperglycemia may promote OSA. Whether the treatment of OSA may delay the development or reduce the severity of type 2 diabetes is another important question.

In this article, we will review the current evidence from population, clinic-based, and interventional studies that links OSA to alterations in glucose metabolism and type 2 diabetes, and will briefly discuss the poten-

tial mechanisms that may play a role in this link. It is noteworthy that OSA has also been linked to the metabolic syndrome, a clinical entity that is closely related to type 2 diabetes risk and is most commonly defined as a cluster of cardiometabolic abnormalities including hypertension, dyslipidemia, obesity, and insulin resistance. A comprehensive review of the putative relationship between OSA and the metabolic syndrome is beyond the scope of this article.

EVIDENCE FROM POPULATION-BASED STUDIES

A growing number of epidemiologic studies, originating from various geographic regions and involving diverse study populations, have suggested the existence of an independent link between markers of severity of OSA and an increased risk of type 2 diabetes. The association between OSA and altered

glucose metabolism is well supported by a large set of cross-sectional studies, but there are still very few longitudinal studies, which may indicate a direction of causality. In some studies, the assessment of the presence and the severity of OSA was based on polysomnography (Table 1^{11,48,73–79}), and in others snoring was used as a surrogate marker of OSA (Table 2^{13,14,16–18,80–85}). Polysomnographic studies have used the AHI and the degree of oxygen desaturation (lowest oxygen saturation or percent time spent below 90% oxygen saturation) as measures of

the severity of OSA. Metabolic assessments have been more variable and have included levels of fasting blood glucose, insulin, and hemoglobin (Hb) A1c (a measure of glucose control over a 3-month period), and the estimation of insulin resistance by homeostatic model assessment (HOMA; defined as the normalized product of fasting glucose by fasting insulin). In some studies,¹⁰ glucose tolerance was assessed by the oral glucose tolerance test (OGTT), a clinical tool that is used for the diagnosis of type 2 diabetes. During the OGTT, after the ingestion of

Table 2—Population-Based Studies Linking Snoring to Altered Glucose Metabolism and Type 2 Diabetes*

Study/Year	Study Sample	Measures of Glucose Metabolism	Main Findings
Norton and Dunn ⁸⁰ /1985	2,629 (1,411 men) participants, Canada	Self-reported diabetes	Association between snoring and its frequency, and the presence of diabetes
Jennum et al ⁸¹ /1993	804 men and women who were 70 yr old, Denmark	OGTT	Snoring was associated with abnormal glucose tolerance after adjustment for gender, BMI, physical activity, and alcohol and tobacco use
Grunstein et al ⁸² /1995	Swedish Obese Subjects Cohort, 3,034 (1,324 men) participants; age range, 37–57 yr	Fasting glucose and insulin	Loud snoring and witnessed apneas were associated with higher fasting insulin levels after adjustment for body fat distribution
Enright et al ¹⁶ /1996	Cardiovascular Health Study, 5,201 (43% men) participants aged \geq 65 yr	Self-reported diabetes, hypoglycemic medication use, fasting glucose, or OGTT	Snoring and observed apneas were independently associated with diabetes in elderly women but not in elderly men
Elmasry et al ¹⁴ /2000†	2,668 Swedish men; age range, 30–69 yr	Self-reported diabetes	Habitual snoring is an independent risk factor for incident diabetes at 10-yr follow-up; obese men who reported snoring at baseline were seven times more likely to have diabetes develop
Al-Delaimy et al ¹³ /2002†	US Nurses Health Study, 69,852 female nurses; age range, 30–55 yr	Diabetes based on composite criteria using clinical and laboratory findings	Regular snoring is independently associated with twofold increased risk of developing diabetes at 10-yr follow-up
Renko et al ⁸³ /2005	593 (245 men) participants, of whom 553 had no prior diagnosis of diabetes, Finland	OGTT	Habitual snoring was independently associated with diabetes and decreased insulin sensitivity; habitual snorers, compared to nonsnorers, had twice the risk of having diabetes
Shin et al ¹⁷ /2005	2,719 nondiabetic, nonobese Korean men	OGTT	Habitual snoring was independently associated with elevated postload 2-h glucose and insulin levels
Joo et al ¹⁸ /2006	6,981 (3,362 men) nonobese participants; age range, 40–69 yr; Korea	HbA1c	Frequent snoring is independently associated with elevated HbA1c levels ($>$ 5.8%)
Thomas et al ⁸⁴ /2006	8,325 (2,550 men); age range, 50–85 yr; China	Diabetes defined by fasting glucose concentration of \geq 7 mmol/L or hypoglycemic medication use	Snoring was an independent predictor of diabetes after controlling for potential confounders including central adiposity
Lindberg et al ⁸⁵ /2007	6,799 Swedish women; age range, 20–99 yr	Self-reported diabetes	“Snoring and excessive daytime sleepiness” is an independent risk factor for diabetes
Onat et al ¹⁵ /2007	119 (61 men) Turkish patients	HOMA	Habitual snoring and witnessed apneas were associated with metabolic syndrome but not with insulin resistance (estimated by HOMA)

*Bold type indicates negative studies.

†Includes prospective data analysis.

75 g of glucose, blood samples are collected for the measurement of glucose and insulin concentrations at 30, 60, 90, and 120 min. Normal glucose tolerance, impaired glucose tolerance, or diabetes is diagnosed if the glucose level at 2 h is < 140 mg/dL, between 140 and 200 mg/dL, or ≥ 200 mg/dL, respectively. A few studies have used physician diagnosis¹¹ or self-report^{14,16,80,85} of type 2 diabetes.

Table 1 summarizes the findings from the nine studies^{11,48,73-79} that have assessed OSA by polysomnography. In cross-sectional analyses, all but the earliest study (which also involved the smallest sample size) found an association between the increased severity of OSA and alterations in glucose metabolism consistent with an increased risk of diabetes. The only prospective study¹¹ that used polysomnography to assess OSA did not find an independent relationship between the severity of OSA at baseline and the incidence of diabetes, but the duration of follow-up was only 4 years. New preliminary findings from a large population study¹² involving > 1,000 patients suggest that OSA is independently associated with the incidence of type 2 diabetes, and that the increasing severity of OSA is associated with an increasing risk of developing type 2 diabetes. Table 2 summarizes the findings from 12 studies^{13-18,80-85} that have explored the relationship between snoring and the parameters of glucose tolerance. Ten of these studies^{15-18,80-85} were cross-sectional in design, and two large studies^{13,14} reported a longitudinal analysis. Only 2 of the 12 studies^{15,16} reported negative findings. One study¹⁵ that did not find an association between snoring and altered glucose metabolism involved a very small number of subjects ($n = 119$), while several studies^{13,14,16-18,80,82,84,85} reporting positive findings involved thousands of patients. In a large cross-sectional study, Enright et al¹⁶ found an independent association between snoring and observed apneas in elderly women but not in elderly men. The two prospective studies were consistent in revealing an increased risk of developing diabetes in men¹⁴ and women¹³ with habitual snoring at a 10-year follow-up. The increase in the risk of diabetes developing was sevenfold for men, but only twofold for women. Of note, two large cross-sectional studies from Korea^{17,18} involved only subjects who were neither overweight nor obese (body mass index [BMI], < 25 kg/m^2) and thus did not have this major risk factor for diabetes. Nevertheless, frequent snoring was associated with reduced glucose tolerance, as assessed by abnormal OGTT results¹⁷ and higher levels of HbA1c.¹⁸

There is thus strong evidence to indicate that OSA and the risk of type 2 diabetes are associated, but the evidence supporting a role for OSA in the development of type 2 diabetes is still fairly limited. The reverse direction of causality (*ie*, that diabetes may be a cause of breathing abnormalities during sleep) is also possible

as autonomic neuropathy could indeed disturb the control of respiration.^{19,20} Using cross-sectional data from the Sleep Heart Health Study, Resnick et al²¹ reported that after adjustment for BMI and other potential confounders, there was no difference between diabetic and nondiabetic participants in the frequency and severity of obstructive respiratory events. A limitation of the study is that the presence of diabetes was based on self-report or on the use of oral hypoglycemic medications or insulin. Since diabetes remains undiagnosed for many years, it is possible that a substantial number of individuals were misclassified as "nondiabetic." Nevertheless, the authors also found that diabetes was associated with periodic breathing, an abnormality of the central control of ventilation.

In summary, there is increasing epidemiologic evidence suggesting that habitual snoring and OSA have adverse effects on glucose tolerance, insulin resistance, and the risk of diabetes mellitus, that are independent of the degree of obesity. Definitive evidence supporting the direction of causality is still needed.

EVIDENCE FROM CLINIC-BASED STUDIES

Clinic-based studies examining the association between OSA and glucose metabolism have consistently used laboratory polysomnography to define the presence and the severity of OSA (Table 3^{22-31,86-88}). In the largest clinic-based sample to date, Meslier et al²² studied 595 men who were referred to a sleep laboratory for suspected OSA. The cross-sectional data from polysomnography and 2-h OGTTs revealed that type 2 diabetes was present in 30.1% of OSA patients and 13.9% of nonapneic snorers. Fasting and postload blood glucose levels increased and insulin sensitivity decreased with rising severity of OSA, independent of age and BMI. Similarly, Makino et al²³ analyzed cross-sectional data from 213 Japanese patients with OSA and found that insulin resistance, estimated by HOMA, was independently associated with the severity of OSA. In a recent case-control study, Peltier et al²⁴ found that 79.2% of patients with OSA ($n = 24$) had impaired glucose tolerance and 25.0% had previously undiagnosed type 2 diabetes. Another recent case-control study in lean Japanese men,²⁵ in which visceral adiposity (quantified by abdominal CT scan) was controlled for, showed that OSA was independently associated with elevated fasting glucose levels. A few studies, however, have reported negative findings. In 1994, Davies and coworkers²⁶ reported no significant hyperinsulinemia in a small number of patients with sleep apnea and snorers compared with control subjects individually matched for age, BMI, and smoking, and drinking habits. Similarly, two case-control studies^{27,28}

Table 3—Clinic-Based Studies Examining the Relationship Between OSA and Glucose Metabolism*

Study/Year	Study Sample	Main Findings
Tiiohonen et al ⁸⁶ /1993	18 morbidly obese OSA patients with variable degrees of glucose intolerance and diabetes; age range, 21–78 yr	Insulin resistance (derived from areas under the glucose and insulin curves during OGTT) is related to the severity of OSA
Davies et al ²⁶ /1994	15 OSA patients and 18 snorers compared with age-, sex-, and BMI-matched control subjects	No significant difference in fasting insulin in OSA or snorers compared to matched control subjects
Strohl et al ⁸⁷ /1994	Cross-sectional study of 261 (mean age, 47 yr) lean and obese men	Independent link between OSA and fasting insulin but not fasting glucose levels
Vgontzas et al ³¹ /2000	14 OSA patients and 11 obese control subjects	Higher fasting glucose and insulin levels in OSA compared to obese control subjects
Meslier et al ²² /2003	Cross-sectional 595 men; age range, 21–78 yr	High prevalence of type 2 diabetes and impaired glucose tolerance in OSA; association between severity of OSA and markers of glucose tolerance independent of age and BMI
Tassone et al ³⁰ /2003	30 (21 men) obese OSA patients and 27 (12 men) weight-matched control subjects	Obese patients with OSA are more insulin resistant than patients with simple obesity, independent of the degree and distribution of obesity
Coughlin et al ⁸⁸ /2004	61 men with OSA and 43 obese control subjects	Independent link between OSA and fasting insulin level but not fasting glucose level
McArdle et al ²⁹ /2007	21 men with OSA and 21 age- and weight-matched control subjects	Higher insulin resistance (estimated by HOMA) in OSA compared to age- and weight-matched control subjects
Gruber et al ²⁷ /2006	38 patients with OSA and 41 control subjects without OSA	No significant independent link between OSA and insulin resistance (estimated by HOMA)
Sharma et al ²⁸ /2007	40 patients with OSA, 40 matched nonapneic obese control subjects, and 40 normal weight control subjects	No significant difference in insulin resistance (estimated by HOMA) in OSA patients as compared to obese control subjects
Peltier et al ²⁴ /2007	24 patients with OSA compared to 9 patients without OSA	High prevalence of type 2 diabetes and impaired glucose tolerance in OSA patients compared to patients without OSA after controlling for age, gender, and BMI
Makino et al ²³ /2006	Cross-sectional study of 213 (183 men) nondiabetic patients with OSA	Association between the severity of OSA and insulin resistance (estimated by HOMA), independent of obesity
Kono et al ²⁵ /2007	42 men with OSA and 52 men without OSA matched for age, BMI, and visceral fat	OSA is independently associated with higher fasting glucose levels

*Bold type indicates negative studies.

published in 2006 and involving a larger number of patients did not find an independent link between OSA and insulin resistance.

Despite differences in sample size, study design, measurement techniques, cut points, and control for possible confounders, the majority of clinic-based studies (10 of 13 studies^{22–25,29–31,86–88}) were consistent in finding an independent association between OSA and abnormal glucose metabolism. Most studies used BMI to account for obesity, which may not be an adequate measure of body fat distribution. Indeed, central obesity and visceral fat accumulation play a key role in several metabolic alterations including insulin resistance. To that effect, several studies have also used measurements of body fat distribution by waist/hip ratio^{28–30} and visceral fat^{23,25,31} to account for the possible confounding effects of central adiposity.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT ON GLUCOSE METABOLISM

Numerous studies have examined the effects of continuous positive airway pressure (CPAP) treat-

ment on glucose metabolism both in diabetic and nondiabetic populations. There is accumulating evidence suggesting that metabolic abnormalities can be partially corrected by CPAP treatment, which supports the concept of a causal link between OSA and altered glucose control. In one study, Harsch et al³² performed a hyperinsulinemic euglycemic clamp evaluation in 40 nondiabetic patients with moderate-to-severe OSA. The hyperinsulinemic euglycemic clamp is considered to be the “gold standard” technique for the measurement of insulin sensitivity, which is quantified by the glucose infusion rate (*ie*, glucose uptake by all of the tissues in the body) under steady-state conditions of euglycemia.³³ The authors found that CPAP therapy significantly improved insulin sensitivity after only 2 days of treatment and that the improvement persisted at the 3-month follow-up with no significant changes in body weight. Interestingly, the improvement was minimal in patients with a BMI of > 30 kg/m², suggesting that in frankly obese individuals OSA may play a minor role in determining insulin sensitivity. In another study,³⁴ the same group reported that insulin sensitivity in nine obese patients with type 2

diabetes was improved after 3 months of CPAP treatment, but not after 2 days of CPAP treatment. This finding suggests that the time course of improvement may be longer in obese patients who are diabetic.³⁴ Earlier studies using euglycemic clamps yielded conflicting results. Brooks et al³⁵ showed an improvement in insulin sensitivity after 4 months of CPAP therapy in 10 severely obese diabetic patients, whereas two other investigations^{36,37} could not confirm this finding in nondiabetic patients.

Babu et al³⁸ measured HbA1c levels and performed 72 h of continuous monitoring of interstitial glucose levels in 25 diabetic patients before and after 3 months of CPAP therapy. Interstitial glucose levels were measured using a subcutaneous glucose sensor attached to a continuous monitoring device that recorded sensor signals every 5 min, providing 288 glucose level readings per day.³⁸ The authors found that 1-h postprandial interstitial glucose levels were significantly reduced after about 3 months of CPAP use. There was also a significant decrease in HbA1c levels in the 17 patients with a baseline HbA1c level of > 7%. Furthermore, the reduction in HbA1c levels significantly correlated with the number of days of CPAP use in subjects who showed adherence to therapy for > 4 h per night. A retrospective analysis³⁹ of 38 diabetic patients confirmed a slight, but clinically significant, decrease in HbA1c levels after 3 to 4 months of CPAP therapy. More recently, in a population-based sample, Lindberg et al⁴⁰ showed reductions in fasting insulin levels and insulin resistance (estimated by HOMA) after 3 weeks of CPAP treatment in 28 men with OSA compared with matched nonapneic (AHI, < 10) control subjects followed over the same time period without CPAP therapy. Three independent preliminary studies presented in abstract form have suggested a positive response to CPAP therapy with improvements in insulin sensitivity,⁴¹ fasting,⁴² and nocturnal⁴³ glucose levels in both diabetic and nondiabetic patients with OSA. Several previous studies^{44–45} did not show a beneficial effect of CPAP treatment on glucose metabolism. In particular, a recent study⁴⁹ using a randomized controlled crossover design showed no change in insulin resistance, estimated by HOMA, despite significant improvements in daytime BP and baroreceptor sensitivity in 34 nondiabetic patients after 6 weeks of CPAP therapy. The latter finding raises the possibility that the relative time courses of the response to CPAP treatment may differ between cardiovascular and metabolic variables. A preliminary analysis from another randomized control trial⁵⁰ also failed to show an improvement in HbA1c levels and insulin resistance in type 2 diabetic patients with OSA after 3 months of therapeutic CPAP use.

The conflicting results from studies that examined the response to CPAP treatment could be partly attrib-

uted to differences in sample sizes and populations, variable durations of therapy, lack of objective adherence data, and the possibility of changes in body composition during the study period. The duration of CPAP use ranged from a single night to a maximum of 6 months, and the use of CPAP for ≥ 4 h per night was considered as “adherent” in the studies that reported adherence data. Whether “longer duration of therapy and better adherence” with CPAP treatment is necessary to correct the metabolic abnormalities is not known. In this context, it is noteworthy that there is evidence for a reduction in visceral fat supporting the idea that there may be long-term favorable metabolic effects for CPAP therapy.⁵¹

POTENTIAL MECHANISMS LINKING OSA TO ALTERATIONS IN GLUCOSE METABOLISM

The pathophysiologic mechanisms leading to alterations in glucose metabolism in OSA patients are likely to be multiple. High sympathetic nervous system activity, intermittent hypoxia, sleep fragmentation and sleep loss, dysregulation of the hypothalamic-pituitary axis, endothelial dysfunction, and alterations in cytokine and adipokine release have all been proposed as potential mechanisms for abnormal glucose metabolism in OSA patients. In the following sections, we will briefly discuss the current evidence for the two main characteristics of OSA, namely, intermittent hypoxia and sleep fragmentation/sleep loss, which may exert adverse effects on glucose control.

Intermittent Hypoxia

OSA typically results in long-term exposure to intermittent hypoxia via repetitive oscillations in oxygen saturations with subsequent chemoreceptor-mediated sympathetic activation.⁵² Experimental animal models of intermittent hypoxia have been developed to evaluate the potential mechanisms for alterations in glucose metabolism in OSA patients. Polotsky et al⁵³ reported that leptin-deficient obese mice, exposed to intermittent hypoxia (*ie*, 30 s of hypoxia alternating with 30 s of normoxia for 12 h per day) for 12 weeks, developed a time-dependent increase in fasting serum insulin levels and worsening glucose tolerance, consistent with an increase in insulin resistance. Very recently, Iiyori et al⁵⁴ performed hyperinsulinemic euglycemic clamps to examine the role of hypoxia on glucose metabolism in lean mice exposed to either intermittent hypoxia (to 5 to 6% of the nadir fraction of inspired oxygen at 60 cycles per hour for 9 h) or intermittent air. The authors found that intermittent hypoxia, in the absence of the confounding effects of obesity, decreased whole-body insulin sensitivity and muscle

Table 4—Prospective Epidemiologic Studies That Examined the Association Between Poor or Short Sleep and Type 2 Diabetes Risk*

Study/Year	Follow-up Period	Sample	Results
Ayas et al ⁶² /2003	10 yr	US Nurses Health Study; 70,026 female nurses aged 30–55 yr; study started in 1976	15–30% increased risk of incident diabetes associated with sleep duration ≤ 6 h relative to 7–8 h; after adjusting for BMI, the association was no longer significant, but sleep duration ≤ 5 h remains associated with 37% higher risk of symptomatic diabetes
Kawakami et al ⁸⁹ /2004	8 yr	2,649 Japanese men; study started in 1984	Men who reported a high frequency of difficulty initiating or maintaining sleep at baseline were two to three times more likely to have diabetes develop
Nilsson et al ⁹⁰ /2004	7–22 yr	6,599 Swedish men aged 35–51 yr; study started in 1974–1984	50% increase in risk of incident diabetes among men who reported difficulty falling asleep or using sleeping pills
Mallon et al ⁶³ /2005	12 yr	1,187 Swedish men and women; study started in 1983	Nearly fivefold increase in risk of incident diabetes among men who reported difficulty maintaining sleep or having sleep duration ≤ 5 h; no significant associations found between sleep and diabetes risk among women
Bjorkelund et al ⁹¹ /2005	32 yr	600 Swedish women; study started in 1968–1969	No association between the incidence of diabetes and the self-reported sleep problems, sleep medication use, or sleep duration at baseline
Meisinger et al ⁹² /2005	Average: 7.5 yr	8,269 German men and women aged 25–74 yr at baseline	Significant increased risk of incident type 2 diabetes for those who reported difficulty maintaining sleep at baseline in both genders
Yaggi et al ⁹³ /2006	15–17 yr	Massachusetts Male Aging Study, 1,709 men aged 40–70 yr; study started in 1987–1989	Sleep duration ≤ 6 h/night compared to 7 h was associated with twice the risk of having diabetes develop

*Bold type indicates negative studies.

glucose utilization with no change in hepatic glucose output. Interestingly, the reduction in insulin sensitivity was not prevented by pharmacologic blockage of autonomic nervous activity, suggesting that intermittent hypoxia can cause insulin resistance independently of an activation of the autonomic nervous system. This latter finding does not support the pathophysiologic evidence linking intermittent hypoxia, increased sympathetic activity, and decreased insulin sensitivity. In fact, sympathetic activation can affect glucose homeostasis by increasing muscle glucogen breakdown, hepatic glucose output, and the release of free fatty acids via the stimulation of lipolysis.

Studies⁵⁵ in humans at high altitude have indicated that sustained hypoxia adversely affects glucose tolerance and insulin sensitivity. In a laboratory study, Oltmanns et al⁵⁶ performed hyperinsulinemic euglycemic clamps in 14 healthy men both during normoxia and after 30 min of acute hypoxia at an oxygen saturation of 75%. Acute sustained hypoxia resulted in glucose intolerance that was associated with increases in heart rate and plasma epinephrine levels. To date, alterations in glucose metabolism have not been studied using human models of intermittent hypoxia that seek to more closely mimic OSA. One study⁵⁷ indicated that, in healthy humans, a 20-min exposure to intermittent voluntary hypoxic apnea resulted in a sustained elevation of muscle sympathetic nerve activity and that hypoxia was the primary mediator of this response.

The cyclic phenomenon of hypoxia-reoxygenation, as

occurs in OSA patients, also represents a form of oxidative stress leading to the increased generation of reactive oxygen species^{58,59} during reoxygenation, similar to that seen in ischemia-reperfusion. This oxidative stress induces the activation of adaptive pathways, including reduced nitric oxide bioavailability, enhanced lipid peroxidation, and the up-regulation of transcriptional factors such as nuclear factor- κ B and hypoxia-inducible factor 1. Increased oxidative stress has been shown^{60,61} to be an important mechanism for insulin resistance and the onset of diabetes. The contribution of specific pathways involved in hypoxic stress to alterations in glucose metabolism in OSA patients remains to be investigated. In summary, animal models demonstrate an adverse effect of intermittent hypoxia on glucose metabolism, but evidence from human data is still very limited.

Sleep Fragmentation and Sleep Loss

OSA generally involves a reduction in total sleep time and is invariably associated with sleep fragmentation. These two consequences of OSA could both have a deleterious impact on glucose tolerance and result in an increase in diabetes risk. There is substantial evidence from both epidemiologic and laboratory studies to indicate that short sleep times and/or sleep fragmentation in the absence of breathing disturbances may adversely affect glucose metabolism. Table 4^{62,63,89–93} summarizes the current prospective epidemiologic evidence, suggesting a causative

role for short sleep times and/or sleep fragmentation in the development of type 2 diabetes. Six of the seven studies^{62,63,89,90,92,93} to date have reported positive findings. The only negative study finding involved by far the smallest number of subjects. The studies with positive results have originated from different geographic locations and subject populations. The results have been consistent in indicating an increased risk of developing diabetes in subjects who at baseline were nondiabetic and reported short sleep durations or difficulties initiating or maintaining sleep. The possible presence of OSA was not assessed or controlled for in most of these studies. The Nurses Health Study⁶² showed an association between short sleep and increased risk of diabetes in subjects who reported never snoring. In another study, Mallon et al⁶³ reported that both short sleep duration and frequent snoring were associated with a higher incidence of diabetes.

A few laboratory studies in healthy young subjects have found that, under well-controlled conditions, restricting sleep duration has an adverse impact on glucose tolerance. The earliest study⁶⁴ examined the effects of 6 nights of 4 h spent in bed (*ie*, the “sleep debt” condition) compared to 7 nights of 12 h spent in bed (*ie*, the “fully rested” condition). At the end of each condition, the subjects underwent an IV glucose tolerance test (IVGTT) and a 24-h period of frequent blood sampling. The IVGTT is a commonly used and validated tool that allows the simultaneous assessment of glucose tolerance, β -cell responsiveness, and insulin sensitivity using a mathematical model.⁶⁵ The rate of glucose clearance postinjection was 40% slower in the sleep debt condition compared to the fully rested condition. The initial release of insulin following glucose injection, referred to as the “acute insulin response to glucose,” was 30% lower when the subjects were in the state of sleep debt than when they were fully rested. A trend for reduced insulin sensitivity, suggesting that higher amounts of insulin were needed to metabolize the injected glucose bolus, was also evident but failed to reach statistical significance. The product of acute insulin response to glucose \times insulin sensitivity, the so-called disposition index (DI), is a validated marker of diabetes risk; DI values of $\geq 2,000$ are typical of subjects with normal glucose tolerance, while DI values of $< 1,000$ have been reported in populations of subjects who are at high risk for type 2 diabetes. In the sleep-debt condition, the DI was 40% lower than that after sleep recovery, and 3 of the 11 subjects had DI values of $< 1,000$. The profiles of glucose and insulin levels following breakfast ingestion were in agreement with the results of the IVGTT, with higher glucose levels despite similar levels of insulin after short sleep, compared to long sleep. Taken together, the findings indicated that glucose metabo-

lism in these young lean adults who submitted to < 1 week of sleep restriction was similar to the typical glucose metabolism of older adults with impaired glucose tolerance (*ie*, a prediabetic state). The findings of this first sleep-debt study were confirmed in a second study⁶⁶ that examined the impact of sleep restriction (4 h in bed for 2 nights) compared to sleep extension (10 h in bed for 2 nights) using a randomized crossover design. After the second night of each condition, the caloric intake was replaced by constant IV glucose infusion, and blood samples were collected every 20 min. After sleep restriction, morning glucose levels were higher and insulin levels were lower than after sleep extension. These laboratory findings are consistent with the epidemiologic evidence and suggest that reduced total sleep time has adverse effects on glucose metabolism.

A cross-sectional study⁶⁷ explored the possibility for an association between short sleep duration and the severity of preexisting diabetes. Self-reported sleep duration and quality and HbA1c levels, which is a key marker of glucose control, were examined in African Americans with type 2 diabetes. Sleep quality was assessed using the Pittsburgh Sleep Quality Index. The perceived sleep debt was calculated as the difference between the preferred and actual weekday sleep duration. After controlling for age, gender, BMI, and insulin use, the authors found that, in patients without diabetic complications, the levels of HbA1c were associated with perceived sleep debt but not sleep quality. In contrast, in patients with at least one diabetic complication, HbA1c level was associated with sleep quality but not with perceived sleep debt. The magnitude of the effects of sleep duration or quality was comparable to that of widely used oral antidiabetic drugs. The Pittsburgh Sleep Quality Index does not assess the presence of OSA but includes questions about breathing and snoring, which were used to estimate the risk of OSA. Patients who indicated that their sleep was disturbed three or more times per week because of difficulty breathing or coughing/snoring, and patients who responded that their bed partners had noticed loud snoring or breathing pauses one or more times per week were classified as being at high risk for OSA. The high-risk group also included patients who indicated during the initial interview that they had OSA. Twenty-three of 122 patients (19%) were classified as being at high risk for OSA, and they had a higher mean HbA1c level than those at low OSA risk (9.7% vs 7.9%, $p < 0.01$) despite no differences in diabetic complications or insulin treatment. The associations between HbA1c level and sleep duration and quality were similar after excluding patients who were at high OSA risk.

OSA involves sleep fragmentation by microarous-

als and lower amounts of deep slow-wave sleep, and this might have intrinsic adverse effects on glucose tolerance, independently of reductions in sleep duration. In a recent study,⁹⁴ the impact of deep slow-wave sleep on glucose metabolism (as assessed by IVGTT) was examined in young healthy adults who were studied under the following two conditions in randomized order: (1) after 2 consecutive nights of undisturbed “baseline” sleep; and (2) after 3 consecutive nights of “experimental suppression of slow-wave sleep” by acoustic stimuli. All-night selective suppression of slow-wave sleep, without a change in total sleep time, resulted in marked decreases in insulin sensitivity without adequate compensatory increases in insulin release, leading to reduced glucose tolerance and increased diabetes risk. The reduction in insulin sensitivity was associated with elevated daytime sympathetic activity (as assessed by heart rate variability). Notably, the magnitude of the decrease in insulin sensitivity was strongly correlated with the magnitude of the reduction in slow-wave sleep, but not with the measures of sleep fragmentation. The findings from this experimental study⁹⁴ suggest that reduced sleep quality with low levels of slow-wave sleep, as it occurs in the majority of OSA patients, may contribute to their increased risk of diabetes. Another study⁶⁹ that also used acoustic stimulation to suppress slow-wave sleep showed an elevation of plasma catecholamine levels that was correlated with the degree of sleep fragmentation. One study⁶⁸ has examined the role of sleep fragmentation by acoustic stimuli on metabolic rate (derived from O₂ uptake and CO₂ output) throughout the night in healthy young men and showed increased metabolic rate compared to a normal sleep condition. Thus, it is possible that shallow and/or fragmented sleep in patients with OSA is associated with an elevation of sympathetic nervous activity, and thus of catecholamine release and metabolic rate, independently of the effects of breathing disturbances, which in turn could lead to alterations in glucose metabolism. In this context, it is noteworthy that recurrent partial sleep restriction without sleep fragmentation also increases sympathetic nervous activity.

FUTURE DIRECTIONS

There is compelling evidence that OSA represents a significant risk factor for cardiovascular disease and mortality.^{70–72} Rapidly accumulating data from several population and clinic-based studies summarized in this article also indicate that there is an independent association between OSA and altered glucose metabolism, suggesting that OSA might be a novel risk factor for the

development of type 2 diabetes. Nevertheless, it should be recognized that obesity, in particular visceral adiposity, remains a major confounder in the relationships among insulin resistance, reduced glucose tolerance, and OSA. Further large-scale studies in carefully selected patient populations with OSA, adequately controlled for potential confounders, are needed. For example, studies in lean individuals with OSA or in obese OSA patients who are stratified according to their metabolic status and fat distribution might provide important new insights on this topic. Randomized controlled studies of CPAP treatment vs sham CPAP, including large sample sizes, objective documentation of adherence to therapy, and long-term follow-up will help to better characterize the subgroups of patients who show a clinically significant metabolic improvement.

Based on the current evidence, it is noteworthy to urge clinicians to systematically evaluate the risk of OSA in type 2 diabetic patients and, conversely, to assess glucose tolerance in patients with known OSA. Finally, there is undoubtedly a need for additional basic and clinical research to fully elucidate the complex interactions among obesity, type 2 diabetes, and OSA. A better understanding of the underlying mechanisms and clinical implications of the link between OSA and type 2 diabetes may have important public health consequences, and could lead to novel therapeutic strategies in these ever-growing patient populations.

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Obstructive Sleep Apnea and Type 2 Diabetes*

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