Sleep-disordered Breathing and Insulin Resistance in Middle-aged and Overweight Men

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Sleep-disordered breathing is a prevalent condition associated with impairment of daytime function and may predispose individuals to metabolic abnormalities independent of obesity. The primary objective of this study was to determine the metabolic consequences and community prevalence of sleep-disordered breathing in mildly obese, but otherwise healthy, individuals. One hundred and fifty healthy men, without diabetes or cardiopulmonary disease, were recruited from the community. Measurements included polysomnography, a multiple sleep latency test, an oral glucose tolerance test, determination of body fat by hydrodensitometry, and fasting insulin and lipids. The prevalence of sleep-disordered breathing, depending on the apnea–hypopnea index (AHI) cutoff, ranged from 40 to 60%. After adjusting for body mass index (BMI) and percent body fat, an AHI ≥ 5 events/h was associated with an increased risk of having impaired or diabetic glucose tolerance (odds ratio, 2.15; 95% CI, 1.05–4.38). The impairment in glucose tolerance was related to the severity of oxygen desaturation (ΔSa_{O_2}) associated with sleep-disordered breathing. For a 4% decrease in oxygen saturation, the associated odds ratio for worsening glucose tolerance was 1.99 (95% CI, 1.11 to 3.56) after adjusting for percent body fat, BMI, and AHI. Multivariable linear regression analyses revealed that increasing AHI was associated with worsening insulin resistance independent of obesity. Thus, sleep-disordered breathing is a prevalent condition in mildly obese men and is independently associated with glucose intolerance and insulin resistance.

Keywords: diabetes; glucose tolerance; insulin resistance; prevalence; sleep apnea; sleep-disordered breathing

It is estimated that more than half of the adult population in the United States is overweight or obese. The dramatic increase in the prevalence of obesity over the last two decades has occurred in adult men and women across all ages and in various racial and ethnic groups (1, 2). It is well known that excess weight in adults is associated with increased incidence of hypertension, cardiovascular disease, stroke, and Type 2 diabetes mellitus (3, 4). Several biochemical alterations including low high-density lipoprotein cholesterol, high serum triglycerides, glucose intolerance, and hyperinsulinemia are also common in overweight individuals and are independently associated with increased risk of cardiovascular disease.

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There has also been an increased recognition that specific types of respiratory problems associated with obesity, such as sleep-disordered breathing, impose a significant public health burden (5–7). Sleep-disordered breathing is now recognized as a chronic condition characterized by reduction or complete cessation of airflow during sleep. These episodes of respiratory disturbance may be associated with decreases in oxyhemoglobin saturation and arousal from sleep. The general perception has been that sleep-disordered breathing is associated with moderate to severe levels of obesity because earlier studies were based on clinic-based samples of patients with body mass indices that exceeded 40 kg/m^2 (8–12). However, the prevalence of sleep-disordered breathing in individuals with mild obesity is unknown.

Although the natural history of sleep-disordered breathing remains to be characterized, accumulating evidence suggests that it may be an independent risk factor for hypertension and cardiovascular disease (5–7). A number of studies have also shown that sleep-disordered breathing may be causally associated with metabolic derangements such as glucose intolerance and insulin resistance (13–19). The possibility of a causal link is based on the observation from several studies that sleep loss and hypoxemia are independently associated with glucose intolerance and insulin resistance. Whereas initial reports (13–17) on sleep-disordered breathing and metabolic function were inconclusive, a more recent clinic-based study (18) found that patients with sleep-disordered breathing have significantly higher fasting glucose and insulin levels compared with a group of weight-matched control subjects. The major implication of these findings is that glucose intolerance and insulin resistance associated with sleep-disordered breathing may be intermediate in the putative causal pathway to increased cardiovascular morbidity and mortality (20, 21).

To determine the effects of weight loss and exercise on metabolic function, we have previously conducted a community-based study (22, 23) of minimally obese, but otherwise healthy, individuals. As part of the program dedicated to examining specific cardiovascular risk factors in obesity, we investigated the prevalence of and metabolic profile associated with sleep-disordered breathing in this population. We hypothesized that sleep-disordered breathing would be highly prevalent in mildly obese, but otherwise healthy, individuals. In addition, we hypothesized that even mild degrees of sleep-disordered breathing would be associated with glucose intolerance and insulin resistance. The unique aspects of the current study are that, in contrast to previous work, we were able to examine the impact of sleep-disordered breathing on glucose tolerance and insulin resistance in a sample of overweight subjects recruited from the general population.

METHODS

The components of the parent study have been previously described (22, 23). Briefly, volunteer subjects were recruited from the Baltimore–Washington community. Five hundred and eighty-six individuals re-

sponded to advertisements and were interviewed. Individuals were eligible if they were 45 yr or older and 120–160% of their ideal body weight. The screening process including the advertisements did not include any questions related to sleep or sleep-related problems. Three hundred and forty-nine individuals were eligible after the initial screening and completed a medical history questionnaire. Of these, 121 individuals were ineligible on the basis of their medical history. Exclusionary criteria included the following: cardiopulmonary or vascular disease, hypertension (≥ 160/95 mm Hg or on medication), diabetes mellitus, and hyperlipidemia. The remaining 228 individuals received a medical examination, measurement of blood chemistries, and an exercise treadmill test. Individuals were excluded if they showed fasting hyperglycemia or exercise-induced ischemia. Herein, we report the findings for 150 subjects who met the eligibility criteria and consented to the study protocol. Polysomnography and the daytime multiple sleep latency test (MSLT) were performed on each subject (*see* online data supplement for details). Apnea was defined as complete cessation of airflow for at least 10 s. Hypopnea was defined as a reduction in airflow that was at least 10 s in duration and was associated with an electroencephalographic arousal or a 4% drop in the oxygen saturation (Sa_{O_2}).

Body mass index (BMI), waist-to-hip ratio, body density, percent body fat, and fat-free mass were used as indices of body composition. Body density was measured by hydrodensitometry (24). Percent body fat was then calculated using the Siri equation (25) after correcting for residual lung volume. Fat-free mass was calculated as body weight minus the adipose mass. After an overnight fast, an oral glucose tolerance test (OGTT) was performed with measurement of insulin and glucose levels at baseline and every 30 min for 2 h after the ingestion of the glucose load (40 g/m^2 body surface area). Individuals were considered diabetic if they had a glucose level ≥ 200 mg/dl after the glucose load (26). Impaired glucose tolerance was defined as a 2-h glucose level ≥ 140 and < 200 mg/dl. Three indices of insulin sensitivity were examined: the ratio of fasting glucose (G_0) to fasting insulin (I_0) (27), the homeostasis model assessment (HOMA = $G_0I_0/22.5$) (28), and the composite insulin sensitivity index (29). The composite insulin sensitivity index is calculated as

$$\frac{10,000}{[(G_0I_0)(G_{avg}I_{avg})]^{1/2}}$$

G_{avg} and I_{avg} represent the average glucose and insulin concentrations during the OGTT. Glucose levels were measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Serum insulin levels were measured by radioimmunoassay (30). Total cholesterol, triglyceride, and high-density lipoprotein cholesterol levels were measured enzymatically as previously described (22, 23). Low-density lipoprotein cholesterol was calculated using the equation developed by Friedewald and coworkers (31).

Statistical Analysis

The prevalence of sleep-disordered breathing was determined by using three apnea–hypopnea index (AHI) cut points (≥ 5, ≥ 10, and ≥ 15 events/h). The prevalence of sleep-disordered breathing associated with objective hypersomnolence (MSLT < 10 min) was also determined at the above-described cutpoints. To examine the relationships between sleep-disordered breathing and indices of metabolic function, analyses were conducted in which subjects were categorized on the basis of commonly used clinical cutpoints in AHI: < 5.0, 5.0–19.9, 20–39.9, and ≥ 40 events/h. Analysis of variance was used to determine whether metabolic variables varied across the AHI categories. Alternative cutpoints (i.e., quartiles) in the AHI were also used to examine the associations between sleep-disordered breathing and metabolic function. Because the results did not vary on the basis of the classification used, we report our results by using the aforementioned clinical cutpoints.

Because the results of the OGTT were expressed as a normal, impaired, or diabetic response, ordinal logistic regression (32) was employed to examine the independent predictors of the OGTT (*see* online data supplement for detailed description). Multivariable models included variables that could influence the results of the OGTT, such as BMI and percent body fat. Indices of insulin sensitivity were modeled by multivariable linear regression methods. The relationships between insulin sensitivity and parameters of sleep-disordered breathing severity are described by the regression coefficients from the multivariable linear models. Data analyses were performed with STATA 5.0 statistical software (StataCorp, College Station, TX).

RESULTS

The mean age of the subjects was 58.7 yr (SD, 8.3 yr) and the average BMI was 30.5 kg/m^2 (SD, 2.9 kg/m^2). Sixty-nine subjects (46.0%) were overweight (BMI, 25 to 29.9 kg/m^2) and the remaining 81 subjects (54.0%) were obese (BMI ≥ 30 kg/m^2). Measures of body composition revealed that the study sample had evidence of central adiposity with an average waist circumference of 105.1 cm (SD, 7.8 cm) and an average waist-to-hip ratio of 0.98 (SD, 0.06). The average percent body fat in the sample was 30.3% (SD, 4.7%). Of the 150 subjects, a total of 135 subjects completed the oral glucose tolerance test (OGTT). Average fasting baseline glucose and insulin levels were 102.3 mg/dl (SD, 18.0 mg/dl) and 15.1 μU/ml (SD, 7.7 μl/ml), respectively. The 2-h glucose and insulin levels during the OGTT were 153.5 mg/dl (SD, 54.3 mg/dl) and 120.6 μU/ml (SD, 91.5 μU/ml), respectively. The results of the OGTT revealed that 63 subjects (46.7%) had a normal response, 54 subjects (40.0%) had an impaired response, and 18 subjects (13.3%) had a diabetic response. The average triglyceride and total cholesterol levels were 151.2 mg/dl (SD, 73.2 mg/dl) and 193.0 mg/dl (SD, 33.8 mg/dl). Twenty-seven subjects (18.0%) had elevated triglyceride levels (> 250 mg/dl) and 71 subjects (47.3%) had elevated cholesterol (≥ 200 mg/dl) (33). Polysomnography revealed an average AHI of 17.4 events/h (SD, 19.7 events/h). The average group sleep latency during the MSLT was 11.5 min (SD, 6.1 min).

Using an AHI cutpoint of ≥ 5, ≥ 10, and ≥ 15 events/h as the "disease"-defining cutpoint for sleep-disordered breathing, the overall prevalence was 62.0, 44.7, and 41.3%, respectively. The prevalence of sleep-disordered breathing with hypersomnolence, defined as an MSLT < 10 min (34, 35), at the above-described AHI cutpoints was 27.3, 24.0, and 22.7%, respectively. No significant association was noted between AHI and age. AHI was correlated with BMI ($r = 0.28$, $p < 0.001$) but not with waist circumference ($r = 0.16$, $p = 0.06$), percent body fat ($r = 0.15$, $p = 0.08$), or waist-to-hip ratio ($r = 0.11$, $p = 0.20$).

Table 1 shows the polysomnographic data by AHI category. No significant differences in total sleep time or time to sleep onset at night were noted with increasing AHI. There was, however, a significant change in sleep architecture with an increase in the time to rapid eye movement (REM) sleep and in the amount of Stage 1 sleep and a corresponding decrease in the amount of Stage 2, slow wave, and REM sleep. In addition, subjects with an AHI ≥ 5 events/h demonstrated greater decreases in respiratory event-related decreases in oxygen saturation than did subjects with an AHI < 5 events/h. Moreover, an increased tendency to objective daytime sleepiness during the MSLT was also observed in subjects with increasing AHI.

To examine the relationship between sleep-disordered breathing severity and indices of metabolic function, we examined the distribution of each variable across the four AHI categories. As shown in Table 2, no significant differences were noted in age or waist-to-hip ratio with AHI. However, there was a small but significant increase in BMI and percent body fat with AHI. Whereas baseline glucose levels from the oral glucose tolerance test were not different in the four AHI groups, the 2-h levels showed a significant relationship with increasing AHI (Figure 1). Indices of insulin sensitivity (G_0/I_0, HOMA, and composite index) were also related to the severity of sleep-disordered breathing. Subjects were observed to be increasingly insulin resistant with increasing AHI (Table 2). Ex-

TABLE 1. POLYSOMNOGRAPHIC DATA BY APNEA–HYPOPNEA INDEX CATEGORY

Variable	AHI: < 5 (*n* = 57)	AHI: 5–19.9 (*n* = 39)	AHI: 20–39.9 (*n* = 37)	AHI: ≥ 40 (*n* = 17)
Total sleep time, min	332.5 ± 70.6	317.0 ± 71.9	322.5 ± 62.7	332.3 ± 67.4
Time to sleep onset, min	9.5 ± 9.7	18.0 ± 18.4	17.3 ± 22.3	15.9 ± 16.5
Time to REM onset,* min	102.1 ± 56.3	115.3 ± 75.8	117.7 ± 54.8	147.7 ± 58.7
Sleep architecture				
Sleep efficiency, %	82.1 ± 15.4	77.1 ± 16.7	79.1 ± 13.2	79.0 ± 13.9
Stage 1 sleep,* %	15.3 ± 8.5	21.2 ± 11.5	24.8 ± 12.9	38.7 ± 18.5
Stage 2 sleep,* %	54.1 ± 9.6	49.4 ± 12.4	46.4 ± 10.9	39.3 ± 18.6
Slow wave sleep,* %	9.4 ± 7.3	9.2 ± 12.1	8.9 ± 7.5	3.0 ± 5.2
REM sleep,* %	16.1 ± 6.9	14.2 ± 5.8	12.1 ± 5.7	9.9 ± 5.6
Baseline O_2 saturation, %	94.8 ± 1.9	95.2 ± 2.1	95.2 ± 1.6	95.6 ± 1.6
ΔSa_{O_2},* %	2.5 ± 1.8	3.7 ± 1.6	4.6 ± 2.6	7.1 ± 2.9
MSLT* (median sleep onset), min	11.7 ± 6.0	13.3 ± 6.1	11.1 ± 6.0	7.5 ± 5.3

Definition of abbreviations: MSLT = Multiple Sleep Latency Test; REM = rapid eye movement; Sa_{O_2} = oxygen saturation.
* $p < 0.05$ for trend across AHI categories.

cept for high-density lipoprotein cholesterol levels, serum triglycerides and low-density lipoprotein cholesterol levels were not associated with the severity of sleep-disordered breathing.

Multivariable ordinal logistic and linear regression models were then developed to examine the independent associations between AHI, glucose tolerance, and insulin sensitivity. To adjust for the confounding influence of obesity, we included BMI and percent body fat in these models. Because other anthropometric variables related to obesity, such as the waist-to-hip ratio, were found to not significantly improve model prediction, we present the most parsimonious model that included BMI and percent body fat to account for the effect of obesity. As shown in Table 3, an AHI ≥ 5 events/h was associated with increased risk of worsening glucose tolerance (odds ratio [OR], 2.15; 95% confidence interval [95% CI], 1.05 to 4.38) after adjusting for BMI and percent body fat (Model 1). To determine whether the degree of hypoxemia associated with sleep-disordered breathing was related to glucose intolerance, the average drop in oxygen saturation associated with respiratory events (ΔSa_{O_2}) was included as a continuous variable in the multivariable ordinal logistic regression model (Model 2). For every 4% decrease in Sa_{O_2}, the associated odds ratio for worsening glucose tolerance was 1.99 (95% CI, 1.11 to 3.56) after adjusting for percent body fat, BMI, and AHI.

Insulin resistance was also associated with AHI independent of adiposity. Using multivariable linear regression models that included AHI and percent body fat to predict G_0/I_0, we observed that for a five-point increase in AHI, there was a decrease in G_0/I_0 ratio of 0.25 (95% CI, −0.02 to − 0.48), indicating an insulin-resistant state that is independent of adiposity. Similarly, the previously observed unadjusted associations between AHI and the other two indices of insulin resistance (HOMA and the composite index) remained significant after adjusting for percent body fat. For a five-point change in AHI, the HOMA index increased by 2.11 (95% CI, 0.46 to 3.75) and the composite index decreased by 0.10 (95% CI, −0.02 to −0.18). As with glucose intolerance, insulin resistance also was related to the severity of hypoxemia associated with apneas and hypopneas. Although we did not find a statistically significant association between ΔSa_{O_2} and insuln sensitivity, we did observe an independent relationship between the minimum oxygen saturation at night and two indices of insulin sensitivity (G_0/I_0 and the composite index) after adjusting for percent body fat. For a two-point increase in the minimum oxygen saturation during sleep, there was an increase in the G_0/I_0 ratio of 0.32 (95% CI, 0.03 to 0.61), suggesting a less insulin-resistant state with less hypoxemia during sleep. Similarly, for a two-point increase in minimum oxygen saturation during sleep, the composite index increased by 0.12 (95% CI, 0.02 to 0.22).

DISCUSSION

There are two major findings of our study in a community sample of healthy, but mildly obese, men. First, sleep-disordered breathing was relatively common with prevalence in the range of 40 to 60% for abnormal breathing events during sleep.

TABLE 2. CLINICAL AND METABOLIC DATA BY APNEA–HYPOPNEA INDEX CATEGORY

Variable	AHI: < 5 (*n* = 57)	AHI: 5–19.9 (*n* = 39)	AHI: 20–39.9 (*n* = 37)	AHI: ≥ 40 (*n* = 17)
Age, yr	58.0 ± 8.6	59.3 ± 8.2	59.3 ± 8.2	58.8 ± 8.0
BMI,* kg/m^2	29.9 ± 2.8	30.2 ± 2.7	30.5 ± 3.3	32.7 ± 1.8
WHR	0.96 ± 0.05	1.00 ± 0.07	0.98 ± 0.05	1.00 ± 0.04
Body fat,* %	28.8 ± 4.5	30.9 ± 4.6	31.5 ± 4.2	31.1 ± 5.4
Oral glucose tolerance				
Fasting glucose, mg/dl	99.1 ± 13.2	104.0 ± 21.9	102.0 ± 15.0	111.0 ± 25.3
2-h glucose,* mg/dl	143.1 ± 44.5	148.2 ± 54.0	164.2 ± 55.9	181.3 ± 72.5
Fasting insulin,* μU/ml	13.7 ± 7.5	14.7 ± 7.8	16.4 ± 7.8	18.6 ± 6.8
2-h insulin,* μU/ml	103.9 ± 85.6	109.2 ± 82.9	137.2 ± 80.0	174.2 ± 135.0
Index of insulin resistance				
G_0/I_0*	9.7 ± 5.8	9.0 ± 6.2	7.5 ± 3.2	6.9 ± 3.5
HOMA*	61.9 ± 38.7	71.3 ± 50.5	76.5 ± 44.4	91.7 ± 43.5
Composite*	3.2 ± 2.2	2.9 ± 1.9	2.2 ± 1.0	1.9 ± 1.3
HDL-C,* mg/dl	38.5 ± 7.6	36.6 ± 8.8	34.2 ± 7.7	34.3 ± 9.2

Definition of abbreviations: BMI = body mass index; HOMA = homeostasis model assessment; WHR = waist-to-hip ratio.
* $p < 0.05$ for trend across AHI categories.

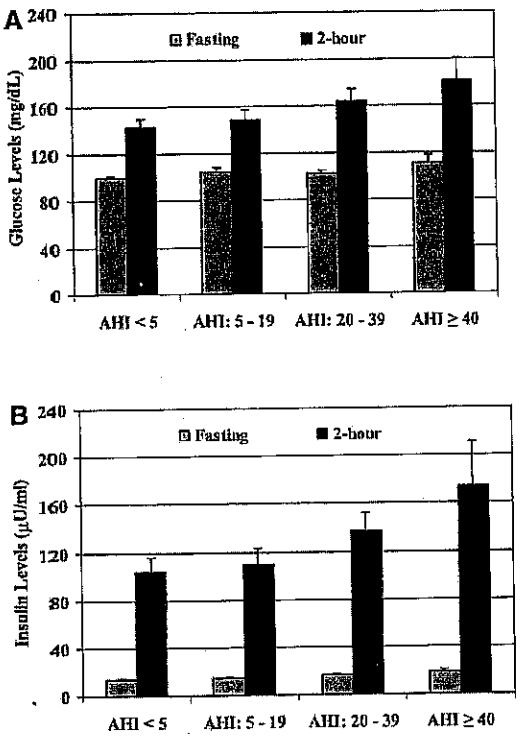

Figure 1. Fasting and 2-h insulin and glucose levels by apnea–hypopnea index (AHI) category (values represent means ± SE). Significant trends ($p < 0.05$) were noted across AHI categories in the fasting insulin level and 2-h glucose and insulin levels.

However, using a more stringent definition, approximately 20 to 30% of the individuals in our sample had sleep-disordered breathing associated with objective daytime sleepiness, defined as a median sleep latency of less than 10 min. Second, sleep-disordered breathing was associated with impaired glucose tolerance and insulin resistance independent of obesity. Because the selection process excluded individuals with prevalent diabetes and cardiovascular disease, we identified a relatively healthy group of individuals at risk for sleep-disordered breathing. The absence of any baseline metabolic abnormalities confirms the fact that our cohort was indeed relatively healthy. In this select group of individuals, we found that moderate to severe sleep-disordered breathing, as assessed by the AHI, was associated with glucose intolerance and insulin resistance. The impairment in metabolic function was independent of adiposity and associated with the degree of nocturnal hypoxemia. The implication of these findings is that the metabolic dysfunction associated with sleep-disordered breathing may increase the risk of cardiovascular morbidity and mortality.

TABLE 3. ORDINAL LOGISTIC REGRESSION MODELS FOR THE RESULTS OF THE ORAL GLUCOSE TOLERANCE TEST

	Adjusted Odds Ratio (95% Confidence Interval)	
Predictor Variable	Model 1*	Model 2†
AHI ≥ 5, events/h	2.15 (1.05–4.38)	1.37 (0.61–3.09)
BMI, kg/m^2	1.20 (1.04–1.38)	1.15 (1.00–1.33)
Percent body fat, %	1.00 (0.92–1.09)	1.02 (0.94–1.12)
ΔSa_{O_2},‡ %	—	1.99 (1.11–3.56)

* Model 1 includes AHI, body mass index (BMI), and percent body fat.
† Model 2 includes AHI, body mass index (BMI), percent body fat, and oxyhemoglobin desaturation (ΔSa_{O_2}).
‡ Odds ratio for a 4% change in ΔSa_{O_2}.

Our finding that sleep-disordered breathing is highly prevalent in minimally obese individuals is consistent with several previous reports. Early epidemiological studies estimated the prevalence of sleep-disordered breathing to be in the range of 1 to 25% (36). These estimates, however, were limited by the sampling methods used to identify the study population, the variability in disease definitions, and in some cases by the abbreviated recording techniques used to monitor sleep. Work from the Wisconsin Sleep Cohort Study indicates that approximately 24% of adult men in the general population have isolated sleep-related disordered breathing events (AHI ≥ 5 events/h) (37). Only 4% of the men in that study were noted to have self-reported daytime sleepiness associated with sleep-disordered breathing. We suspect that the significantly higher prevalence of sleep-disordered breathing with and without daytime sleepiness in our study is due to the selection of a more obese and older population than that included in the Wisconsin Sleep Cohort. Moreover, differences in the methods for characterizing daytime sleepiness between the two studies may also account for some of the differences in the prevalence estimates. Because obesity is a well-known risk factor for sleep-disordered breathing, the finding of a higher prevalence in our study was not surprising. In fact, Young and coworkers (37) have noted that a 1-standard deviation increase in BMI is associated with a 4-fold increase in risk for sleep-disordered breathing. Previous studies that have examined the prevalence of sleep-disordered breathing in severely obese individuals (mean BMI > 40 kg/m^2) noted high prevalence rates of at least 40% (8, 9, 11, 12, 18). However, these studies are limited in their generalizability because of the use of clinic-based samples with severe obesity. In contrast to previous work, the current study selected a healthy group of overweight and mildly obese individuals (mean BMI, 30.5) screened for a wide range of prevalent medical conditions. The high prevalence in our cohort supports the previously reported notion (38) that sleep-disordered breathing continues to be an underappreciated condition.

The high prevalence of sleep-disordered breathing in our cohort provided a unique opportunity to examine the metabolic characteristics associated with sleep-disordered breathing. We found that sleep-disordered breathing was associated with glucose intolerance and insulin resistance independent of obesity and percent body fat. In previous studies of sleep-disordered breathing and metabolic consequences, the relative contribution of obesity has been unclear. Using a comparable study design that screened a smaller sample of normal subjects (15 men, 34 women), Stoohs and coworkers (15) found that insulin resistance was associated with sleep-disordered breathing although the relationship was entirely dependent on BMI. In contrast, a number of clinic-based studies have suggested that sleep-disordered breathing may be independently associated with insulin resistance. In a controlled study by Vgontzas and coworkers (18), patients (n = 14) with sleep-disordered breathing were shown to have elevated fasting glucose and insulin levels compared with weight-matched control subjects. Although we did not find a relationship between fasting glucose levels and the severity of sleep-disordered breathing, there was a significant association between the AHI and 2-h glucose and insulin levels. The differences in baseline glucose values between the two studies can be best explained by differences in the study design and the sample populations. The unique observation in the current study is the striking effect of intermittent hypoxemia associated with apneas or hypopneas on glucose intolerance and insulin resistance. Our data also demonstrate a dose–response relationship between the severity of sleep-disordered breathing and degree of metabolic dysfunction. Thus, these data suggest that early metabolic dysfunction occurs with sleep-disordered breathing before overt clinical manifestations of underlying disease.

Although causality cannot be established between sleep-disordered breathing and insulin resistance in our cross-sectional study, there are several strong lines of evidence that support such a relationship. First, it is well recognized that untreated sleep-disordered breathing is associated with an increase in sympathetic neural traffic that is manifested by elevated levels of muscle sympathetic nerve activity and plasma and urinary catecholamines (39–43). Second, sleep disruption and chronic sleep debt that accompanies sleep-disordered breathing may be independently associated with altered metabolic function. Evidence for this relationship comes from studies of experimental sleep deprivation in normal volunteers illustrating that sleep loss is associated with alterations in glucocorticoid regulation and abnormal glucose tolerance (44, 45). Third, there is evidence that hypoxia alone may directly impair glucose metabolism. Studies of normal subjects and of individuals with chronic respiratory disease demonstrate that hypoxia is associated with impaired glucose tolerance (46, 47). Collectively, the effects of elevated sympathetic nervous system activity, the alterations in glucocorticoid regulation induced by sleep loss, and recurrent intermittent hypoxemia associated with sleep-disordered breathing may facilitate the development of glucose intolerance and insulin resistance.

Several factors have been implicated in the relationship between insulin resistance and cardiovascular disease. Population-based studies reveal that individuals with insulin resistance manifest a characteristic dyslipidemia (i.e., elevated triglycerides, low high-density lipoprotein cholesterol, and compositional changes in low-density lipoprotein particles) that is related to the insulin-resistant state rather than to obesity (48). Accumulating data also indicate that insulin resistance is associated with endothelial dysfunction and impairment of endothelium-dependent vasodilation (49, 50). Moreover, insulin resistance and the compensatory hyperinsulinemia can increase plasma levels of plasminogen activator inhibitor 1, an alteration that decreases fibrinolytic activity (51–54). Taken together, these consequences of insulin resistance can accelerate the formation of atherosclerotic lesions and lead to the development of thrombosis within the vasculature and thereby increase the risk of premature cardiovascular disease.

There are several limitations in the current study. First, the criteria used to select a healthy cohort of overweight men may have influenced our ability to detect associations between sleep-disordered breathing and previously known risk factors. Although we confirmed the well established association of sleep-disordered breathing with elevated percent body fat and obesity, we did not find any relationship between body fat distribution (i.e., waist-to-hip ratio) and the AHI. We suspect that the lack of a significant association is likely due to the selection of men with a narrow distribution of anthropometric measurements. In addition, because the selection criteria excluded individuals with underlying medical comorbidity, we were also unable to detect an association between sleep-disordered breathing and age. A number of previous reports have noted that the risk of sleep-disordered breathing, based on identifying abnormal breathing events during sleep, appears to increase progressively with age (55–57). Second, although the exclusion of women decreased the potential of confounding, it limits the generalizability of our results. We speculate that the clinical consequences related to sleep-disordered breathing may be similar in women provided that disease severity is similar. Third, insulin sensitivity was approximated by using the oral glucose tolerance test instead of the euglycemic insulin clamp, a technique that is considered to be the definitive method to assess insulin sensitivity (58). However, the burden of using the euglycemic insulin clamp technique made it difficult to incorporate this method at the population level. Nevertheless, insulin sensitivity indices derived from the oral glucose tolerance test are strongly related to measures of insulin action as measured with the euglyemic insulin clamp (29). Finally, although we examined the association between the degree of nocturnal hypoxemia and glucose tolerance/insulin resistance, we did not have the data to assess the effects of other physiologic abnormalities that are associated with sleep-disordered breathing such as arousal frequency and increases in respiratory effort.

Despite these limitations, our study has several strengths. First, this is the only study conducted on a sample of overweight and obese volunteer subjects recruited from the general population without regard to sleep-related issues. In general, other investigators have employed sampling strategies based on identifying sleep-related complaints such as snoring (37, 59). Second, the identification of an overweight but otherwise healthy sample without comorbidity limited the number of confounders present in other studies. Third, assessments that included full polysomnography, the Multiple Sleep Latency Test, anthropometry, measurement of body fat, and glucose tolerance allowed for a detailed exploration of the metabolic consequences associated with sleep-disordered breathing.

In summary, sleep-disordered breathing is prevalent in healthy, overweight and mildly obese men and is associated with increased risk for glucose intolerance and insulin resistance. Moreover, we found that the impairment in glucose homeostasis is related to the intermittent hypoxemia that is associated with sleep-disordered breathing. Impaired glucose tolerance and worsening insulin resistance can lead to further weight gain, exacerbating the severity of disordered breathing during sleep. Given that untreated sleep-disordered breathing can directly and indirectly impact cardiovascular disease risk, early identification of sleep-disordered breathing should be considered in mildly obese individuals, particularly in those who complain of sleep-related symptoms. Because as little as 10 to 15% weight loss can reduce or eliminate sleep-disordered breathing (60), low levels of weight reduction may curtail the cardiovascular risk associated with sleep-disordered breathing even in minimally overweight individuals.

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