Sleep Disordered Breathing and Metabolic Syndrome

F. Javier Nieto, MD, MPH, PhD; Paul E. Peppard, PhD; Terry B. Young, PhD

ABSTRACT

Background: Sleep disordered breathing (SDB) has been associated with cardiovascular disease, hypertension, and insulin resistance. This article examines the association between SDB and the prevalence of metabolic syndrome (MS) in a community-based sample.

Methods: A subset of participants in the Wisconsin Sleep Cohort Study (N=546) participated in an ancillary study to measure vascular and metabolic function. SDB was characterized using the apnea-hypopnea index (AHI) obtained in the polysomnography study closest to the collection of the metabolic measures. MS was defined using the National Cholesterol Education Program definition, and the homeostasis model assessment method (HOMA) was used to characterize insulin resistance.

Results: SDB was significantly correlated with insulin resistance (Spearman r correlation between AHI and HOMA=0.30, P<0.0001). Compared with those without SDB (AHI <5), the age-sex-adjusted odds ratios of MS associated with mild (AHI 5-14.9) and moderate/severe SDB (AHI ≥15 or CPAP) were 4.0 (95% CI 2.6, 6.3) and 5.3 (95% CI 3.2, 8.8), respectively. Additional adjustment for markers of sympathetic or neuroendocrine activation (urinary norepinephrine, cortisol, heart rate variability) did not materially alter these estimates. These associations were weaker but remained statistically significant after adjusting for body mass index.

Conclusion: SDB might be considered an integral component of MS.

INTRODUCTION

Recent estimates suggest that more than 20% of US adults have metabolic syndrome (MS). Similarly, sleep disordered breathing (SDB), a condition characterized by repeated episodes of apnea and hypopnea during sleep, is estimated to affect 5%-10% of middle-aged adults and 20%-30% of the elderly. Clinical and population-based studies have shown that patients with SDB have many features in common with those with MS, including hypertension, diabetes and insulin resistance, abdominal obesity, and dyslipidemia. Postulated mechanisms explaining these associations include the autonomic and hypothalamic-pituitary-adrenal axis (HPA) activation that result from the intermittent hypoxemia and sleep fragmentation associated with SDB.

This article explores the association between SDB and MS and possible mechanisms in a sample of participants in the Wisconsin Sleep Cohort Study (WSCS).
BMI was 31.1 kg/m² (standard deviation, 6.9 kg/m²).

Mean AHI was 7.6. A total of 150 participants (27%) had mild SDB and 103 (19%) had moderate or severe SDB. AHI was significantly correlated with HOMA ($r_s=0.30$, $P<0.0001$) and with urinary norepinephrine levels ($r_s=0.22$, $P<0.0001$), but not with urinary cortisol or heart rate variability.

The overall prevalence of MS in the sample was 32% (n=174), and it was higher in females than in males (38% vs 27%, $P=0.004$). The age- and gender-adjusted odds ratios of MS increased with the level of SDB in a dose-response fashion (Table 1). Participants with moderate or severe SDB were more than 5 times as likely as those with no evidence of SDB to have MS. Adding markers of autonomic or neuroendocrine function to the model (norepinephrine, cortisol, heart rate variability) did not substantially alter these estimates. On the other hand, when BMI was added to the model, the odds ratios reflecting the association between SDB and metabolic syndrome were weaker but remained statistically significant.

**DISCUSSION**

In the present cross-sectional analysis, we found that SDB is strongly associated with the prevalence of metabolic syndrome. Our results are consistent with previous reports on the association of SDB with diabetes and insulin resistance.\(^8\text{–}^{11}\) They are also consistent with a recent experimental study in 118 nondiabetic subjects, which showed that SDB is associated with a delayed decline in glucose levels following a glucose injection and with decreased insulin sensitivity.\(^23\)

The association in our study appears to be independent of markers of sympathetic and HPA axis activation, which have been postulated as potential mechanisms,\(^18\) but was weakened after additional adjustment for BMI. The latter, however, might be the result of overadjustment and co-linearity stemming from the strong cor-

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**Table 1. Odds Ratio of Metabolic Syndrome According to Sleep Disordered Breathing Severity, Wisconsin Sleep Cohort, n=546**

<table>
<thead>
<tr>
<th></th>
<th>Mild SDB (AHI 5-14.9)</th>
<th>Moderate/severe SDB (AHI ≥15 or CPAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Limits</td>
</tr>
<tr>
<td>Adjusted for age, sex</td>
<td>4.0</td>
<td>2.6, 6.3</td>
</tr>
<tr>
<td>plus urinary norepinephrine</td>
<td>3.9</td>
<td>2.5, 6.2</td>
</tr>
<tr>
<td>plus urinary cortisol</td>
<td>3.9</td>
<td>2.4, 6.2</td>
</tr>
<tr>
<td>plus heart rate variability</td>
<td>4.1</td>
<td>2.5, 6.5</td>
</tr>
<tr>
<td>plus body mass index</td>
<td>2.5</td>
<td>1.5, 4.2</td>
</tr>
</tbody>
</table>

Abbreviations: SDB, sleep disordered breathing; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure.

A subset of 546 participants from the WSCS was selected to participate in an ancillary study to measure additional cardiovascular and metabolic parameters between October 2004 and December 2007. The PSG study closest in time to the ancillary study was used to characterize the participants’ sleep. The mean lag time between the sleep study and the ancillary study was 2.2 years (range 0.6-9.6 years).

Body mass index (BMI) was calculated as weight (kg) divided by height (meters) squared. Serum glucose, insulin, triglycerides and high-density lipoprotein (HDL) cholesterol, and urinary cortisol and epinephrine were measured in the University of Wisconsin Hospital clinical laboratory using standard methods. Metabolic syndrome was defined using the National Cholesterol Education Program criteria,\(^21\) which requires at least 3 of the following factors: high fasting glucose, high blood pressure, elevated triglycerides, low HDL, and abdominal obesity (defined by waist circumference.) The homeostasis model assessment method (HOMA),\(^22\) based on fasting insulin and glucose values, was used to characterize insulin resistance. Heart rate variability was measured by the standard deviation of the normal-to-normal resting rate intervals in a 5-minute electrocardiogram recording.

Chi-square and t-tests were used to compare proportions and means, respectively. Spearman correlation coefficient ($r_s$) was used to evaluate the ordinal correlation between continuous variables. Logistic regression was used to assess the relationship between predictors and the MS. All statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

**RESULTS**

Among participants in the study (N=546), 306 (56%) were male; mean age at the time of the ancillary study was 59.9 years (range 43-77 years); 56 (10%) were current smokers, and 283 (52%) were hypertensive. Mean BMI was 31.1 kg/m² (standard deviation, 6.9 kg/m²).

Mean AHI was 7.6. A total of 150 participants (27%) had mild SDB and 103 (19%) had moderate or severe SDB. AHI was significantly correlated with HOMA ($r_s=0.30$, $P<0.0001$) and with urinary norepinephrine levels ($r_s=0.22$, $P<0.0001$), but not with urinary cortisol or heart rate variability.

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relation between BMI and waist circumference, 1 of the components of the metabolic syndrome definition.

CONCLUSION

These results add to the evidence suggesting that metabolic disturbances might be 1 of the pathways for the cardiovascular effects of SDB. Along with evidence that the relation between sleep disorders and obesity might be bi-directional,24-25 they also support the notion that SDB might be 1 of the components of the MS, constituting a cluster that has been termed “syndrome Z.”13

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