Obstructive Sleep Apnea is Associated with Diabetes in Sleepy Subjects

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ABSTRACT

Background: Although obstructive sleep apnea (OSA) has been linked to insulin resistance and glucose intolerance, it is unclear whether there is an independent association between OSA and diabetes mellitus (DM) and whether all patients with OSA are at risk. The objective of this study was to determine the association between OSA and DM in a large cohort of patients referred for sleep diagnostic testing.

Methods: Cross-sectional analysis of participants in a clinic-based study conducted between July 2005 and August 2007. Diabetes was defined by self-report and concurrent use of diabetic medications (oral hypoglycemics and/or insulin). Sensitivity analysis was performed using a validated administrative definition of diabetes. Obstructive sleep apnea was defined by the respiratory disturbance index (RDI) using polysomnography or ambulatory monitoring. Severe OSA was defined as an RDI >30 hr⁻¹. Subjective sleepiness was defined as an Epworth Sleepiness Scale score ≥10.

Results: Complete data was available in 2149 patients. The prevalence of DM increased with increasing OSA severity (p<0.001). Severe OSA was associated with DM following adjustment for patient demographics, weight, and neck circumference (Odds Ratio 2.18; 95% CI: 1.22, 3.89; p<0.01). Following a stratified analysis, this relationship was observed exclusively in sleepy patients: Odds Ratio 2.59 (95% CI: 1.35, 4.97) vs. non-sleepy patients: 1.16 (95% CI: 0.31, 4.37).

Conclusions: Severe OSA is independently associated with DM in patients who report excessive sleepiness. Future studies investigating the impact of OSA treatment on DM may wish to focus on this patient population.

INTRODUCTION

Severe OSA has been reported to be independently associated with cardiovascular disease and death.[1-4] More recently, OSA has been associated with increased insulin resistance [5-7] but it is unclear whether there is an independent relationship with diabetes mellitus (DM).

Previous studies evaluating the association between OSA and DM have been limited by the lack of an objective measure of OSA,[8,9] and the absence of a robust definition of DM.[10,11] In contrast, the Sleep Heart Health Study evaluated 2,656 patients in a clinic based cross-sectional sample,[12] and reported an independent association between OSA and glucose intolerance. The Wisconsin Sleep Cohort study also demonstrated an independent association between OSA and DM.[13] However, the absence of an increased incidence of DM in the longitudinal follow-up of this cohort raises some doubts about the strength of association between these two conditions. Moreover, a recent randomized control trial by West et al. failed to find any improvement in glycemic control or insulin resistance in 42 patients, following continuous positive airway pressure (CPAP) therapy.[14]

The inability to identify ‘at risk’ patients may explain the heterogeneity of results. The association of OSA severity and cardiovascular risk has been established in several studies.[1-4] More recently, the notion that non-sleepy OSA patients may represent a different risk stratum than sleepy patients has been raised.[15] Identification of subgroups of OSA patients that are at increased risk of developing DM would be helpful in assessing therapeutic strategies. Thus, the primary objective of this study was to determine the association between OSA severity and DM...
given the potential that only some OSA patients are at increased risk for DM. The secondary objective was to investigate whether OSA patients who report sleepiness have a greater risk of DM than those who do not.

METHODS

Study population

This project was part of a larger study investigating health care utilization among patients with OSA. Between July 2005 and August 2007, we included all patients over 18 years who were referred for sleep diagnostic testing at either the Foothills Medical Centre or private respiratory care companies within the Calgary Health Region (population ~1.3 million). Over the recruitment period, nearly all sleep diagnostic testing was conducted in these facilities. We excluded patients who had a previous diagnosis of OSA or had prior sleep diagnostic testing (PSG or ambulatory monitoring).

Within the Calgary Health Region, virtually all patients undergo ambulatory monitoring as their initial sleep diagnostic test. Consequently, the majority of patients undergoing polysomnography at the Foothill Medical Centre Sleep Centre have already undergone ambulatory monitoring and were not included within the polysomnography group.

Baseline clinical and demographic information was collected for all participants prior to sleep diagnostic testing. This included age, gender, body mass index (BMI), neck circumference, smoking status (self-reported) and home address. Each participant also completed the Epworth Sleepiness Scale (ESS), a self-administered questionnaire that provides a measure of daytime sleepiness.[16] Co-morbidity was determined through the use of a questionnaire administered by trained personnel in which patients were asked to report the presence of specific co-morbidities including hypertension, asthma, depression, cardiac arrhythmia, myocardial infarction, chronic obstructive pulmonary disease (COPD), diabetes, heart failure, and stroke. Patients also listed their current medications. This study was approved by the Ethics Review Board of the University of Calgary.

Study Variables

Obstructive Sleep Apnea

OSA was diagnosed by ambulatory monitoring at home with the Remmers Sleep Recorder or by attended polysomnography (PSG) in the sleep laboratory at Foothills Medical Centre. OSA severity was defined by the respiratory disturbance index (RDI) as follows: no OSA (RDI <5 hr⁻¹), mild OSA (RDI = 5-14.9 hr⁻¹), moderate OSA (RDI = 15-29.9 hr⁻¹), and severe OSA (RDI ≥30 hr⁻¹). Moderate OSA was defined based on Medicare funding criteria (RDI >15 hr⁻¹). The definition for severe OSA was based on cohort studies, which linked severe OSA (RDI ≥30 hr⁻¹) with hypertension, myocardial infarction, stroke or death.[1-4]

Polysomnography

PSG data were recorded by a computerized system (Sandman Elite Version 8.0, Nellcor Puritan Bennett (Melville) Ltd, Kanata, Ontario, Canada). This included a standardized montage: three electroencephalograms (C4/A1, C3/A2, O1/A2), bilateral electro-oculograms (EOG), submental electromyogram (EMG), bilateral leg EMGs, and electrocardiography (ECG). Airflow was measured using a nasal pressure transducer (Braebon Medical Corp, Ontario, Canada). Respiratory effort was assessed by inductance plethysmography (Respitrace Ambulatory
Monitoring, Ardsley, New York, USA), and oxygen saturation was recorded by oximetry (953 Finger Flex Sensor; Healthdyne Technologies).

The RDI was defined as the number of apneas and hypopneas per hour of sleep. Apnea was defined as a cessation of airflow for at least 10 seconds. Hypopnea was defined as an abnormal respiratory event lasting 10 seconds or more, with at least a 30% reduction in thoracoabdominal movement or airflow compared to baseline, and associated with at least a 4% oxygen desaturation.

**Ambulatory monitoring**
The Remmers Sleep Recorder (SagaTech Electronics Ltd, Calgary, Canada) is an ambulatory monitor that measures snoring, oxygen saturation, respiratory airflow (by monitoring nasal pressure), and body position. The RDI is derived from automated analysis of the oximetry signal using a 4% desaturation threshold. This algorithm uses both shape and magnitude of oxygen desaturation to score respiratory events.[17] Ambulatory studies are manually reviewed by the interpreting physician with the flow signal being used for quality assurance purposes. Ambulatory studies are repeated if there are discrepancies between the automatically scored respiratory events and the airflow channel. This monitor has excellent agreement with the polysomnographically determined AHI.[17] It has also been validated as a clinical management tool.[18,19]

**Diabetes Mellitus**
We defined diabetes mellitus (DM) by self-report and concurrent use of diabetic medications (oral hypoglycemic and/or insulin). Sensitivity analysis was performed with a validated administrative algorithm.[20] Using the patient’s unique Provincial Health Number (PHN), the cohort was linked to two Alberta Health and Wellness administrative databases, the hospitalization discharge database, and the physician claims database. For each patient, all hospitalization and physician claims information was obtained for a two-year period prior to sleep diagnostic testing. The administrative algorithm defines diabetes by either 1 hospitalization with a diagnosis of DM or 2 physician claims for DM within a two-year period. It has a sensitivity of 86% and a specificity of 97%.

**Co-morbidity**
Validated algorithms were used within the questionnaire to define each co-morbid condition (in addition to DM).[21-25] These algorithms were further supplemented by the ICD-10 coding scheme developed by Quan et al.[26] For co-morbidities that did not have validated algorithms (specifically COPD, depression and cardiac arrhythmia), ICD-9-CM and ICD-10 diagnostic codes were identified within the ICD-9-CM and ICD-10 manuals.[27,28] Within the administrative datasets, the condition was considered present if the algorithm defining the condition was satisfied. Co-morbidities that did not have a validated algorithm were considered present if at least one diagnostic code for the condition, within either the physician claims data or hospitalization data, was recorded within the two-year period prior to sleep diagnostic testing.

**Statistical Analysis**
Patient characteristics were described using mean and standard deviation for normally distributed variables. In cases of highly skewed or clearly non-normal distributions, the median and the inter-quartile range (IQR) were reported. Means and proportions were compared using analysis of variance and chi-squared tests respectively. The Kruskal-Wallis test was used to compare skewed variables. Baseline characteristics were stratified by OSA severity.
To determine the relationship between OSA severity and prevalent DM, multivariate logistic regression with backward selection techniques was used. Significant predictors of DM were identified by univariate analysis. Saturated multivariate models were constructed using these significant predictors. In addition, relevant interaction terms were developed. These included OSA severity x sleepiness. We developed further reduced models based on the presence or absence of effect modification and confounding by the specified predictors. The fit of each model was also assessed by the likelihood ratio test.

We calculated crude odds ratios (OR) for prevalent DM by comparing the odds of DM in each of the three severity levels of OSA (mild: RDI 5-14.9; moderate: RDI 15-29.9; severe: RDI ≥30) to the odds of DM in those without OSA (RDI <5). A logistic regression model was employed to obtain odds ratios after adjustment for age, gender, BMI, neck circumference and smoking status. BMI was modeled as a continuous and categorical variable (normal weight (<25 kg/m²), overweight (25-29.9 kg/m²) and obese (≥30 kg/m²)). There were no differences in the odds ratios when BMI was modeled in either format and consequently BMI was treated as a categorical variable for ease of interpretation. Age was also modeled as a continuous and categorical variable. When modeled as a categorical variable, subjects were categorized as ≥65 yrs or <65 yrs of age. Continuous age and BMI were assessed for non-linearity by the likelihood ratio test of its squared and cubic terms. The linearity assumption was not violated in either variable.

A sensitivity analysis was performed in which similar models were developed using the validated administrative algorithm to define prevalent DM as the outcome variable. A stratified analysis was performed in which crude and adjusted OR’s for prevalent DM were generated by level of daytime sleepiness. A participant was considered sleepy if ESS ≥10. Finally, a sensitivity analysis for the type of diagnostic test (ambulatory monitoring or polysomnography) was conducted.

For all statistical tests, p<0.05 was considered statistically significant. All analyses were performed using STATA 10.0 (Statacorp, College Station, Texas).

RESULTS

From July 2005 to August 2007, 2295 patients were referred for sleep diagnostic testing, of whom 78 (3.4%) patients refused to participate and 42 (1.8%) patients lived outside Alberta and were therefore excluded. Of the remaining 2175 patients, 26 (1.2%) were excluded because they were absent from the Alberta Health and Wellness registry, which resulted in a final study population of 2149. Figure 1 summarizes the recruitment process and diagnostic testing. Characteristics of the study population are summarized in Table 1A. There were 1346 males and 803 females with a median BMI of 31.3 kg/m² (IQR: 27.3-36.6) and mean age of 50.1 yrs (±12.9). Based on RDI criteria, 432 (20.1%) patients did not have OSA, 738 (34.3%) had mild OSA, 443 (20.6%) had moderate OSA and 536 (24.9%) had severe OSA.

The overall prevalence of DM was 8.1% and it increased as OSA severity increased (p<0.001) (Table 1A). A number of other variables also increased in association with OSA severity, including age, BMI, neck circumference and ESS (p<0.001). Furthermore, co-morbidities such as hypertension, myocardial infarction, heart failure, and stroke increased in association with OSA severity (Table 1B).
Table 1A. Patient Demographics (n=2149)

<table>
<thead>
<tr>
<th></th>
<th>No OSA (RDI &lt;5)</th>
<th>Mild OSA (RDI 5-14.9)</th>
<th>Moderate OSA (RDI 15-29.9)</th>
<th>Severe OSA (RDI ≥30)</th>
<th>All</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (% all)</td>
<td>432</td>
<td>738</td>
<td>443</td>
<td>536</td>
<td>2149</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>197</td>
<td>463</td>
<td>281</td>
<td>405</td>
<td>1346</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age yrs, mean (SD)</td>
<td>44.0</td>
<td>50.0</td>
<td>52.8</td>
<td>53.0</td>
<td>50.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>27.8</td>
<td>30.6</td>
<td>32.0</td>
<td>34.5</td>
<td>31.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>kg/m² median (IQR)</td>
<td>(24.9-32.2)</td>
<td>(27.2-35.4)</td>
<td>(28.1-36.8)</td>
<td>(30.4-39.8)</td>
<td>(27.3-36.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>89</td>
<td>116</td>
<td>60</td>
<td>89</td>
<td>354</td>
<td>0.11</td>
</tr>
<tr>
<td>n (%)</td>
<td>(20.6)</td>
<td>(15.8)</td>
<td>(16.5)</td>
<td>(16.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck circumference</td>
<td>14.9</td>
<td>15.8</td>
<td>16.3</td>
<td>17.1</td>
<td>16.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>inches mean (SD)</td>
<td>(1.5)</td>
<td>(1.7)</td>
<td>(1.8)</td>
<td>(1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>10.9</td>
<td>10.7</td>
<td>11.4</td>
<td>12.3</td>
<td>11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>(5.1)</td>
<td>(5.3)</td>
<td>(5.4)</td>
<td>(5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>19</td>
<td>40</td>
<td>33</td>
<td>82</td>
<td>174</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(self-report + meds) n (%)</td>
<td>(4.4)</td>
<td>(5.4)</td>
<td>(7.4)</td>
<td>(15.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>29</td>
<td>61</td>
<td>42</td>
<td>111</td>
<td>243</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(admin algorithm) n (%)</td>
<td>(6.7)</td>
<td>(8.3)</td>
<td>(9.5)</td>
<td>(20.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ESS = Epworth Sleepiness Score; IQR = Inter-quartile Range; SD = Standard Deviation
* Chi-squared test, analysis of variance
## Table 1B. Patient Co-Morbidities Stratified by OSA Severity (n=2149)

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>No OSA (n=432)</th>
<th>Mild OSA (n=738)</th>
<th>Moderate OSA (n=443)</th>
<th>Severe OSA (n=536)</th>
<th>All (n=2149)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n (%)</td>
<td>83 (19.2)</td>
<td>205 (27.8)</td>
<td>183 (41.3)</td>
<td>243 (45.3)</td>
<td>714 (33.2)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td>n (%)</td>
<td>128 (29.6)</td>
<td>202 (27.4)</td>
<td>123 (27.8)</td>
<td>120 (22.4)</td>
<td>573 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>n (%)</td>
<td>53 (12.3)</td>
<td>78 (10.6)</td>
<td>63 (14.2)</td>
<td>53 (9.9)</td>
<td>247 (11.5)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>n (%)</td>
<td>15 (3.5)</td>
<td>24 (3.3)</td>
<td>15 (3.4)</td>
<td>23 (4.3)</td>
<td>77 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n (%)</td>
<td>4 (0.9)</td>
<td>15 (2.0)</td>
<td>8 (1.8)</td>
<td>26 (4.9)</td>
<td>53 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>n (%)</td>
<td>2 (0.5)</td>
<td>9 (1.2)</td>
<td>5 (1.1)</td>
<td>13 (2.4)</td>
<td>29 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>n (%)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>3 (0.7)</td>
<td>5 (0.9)</td>
<td>9 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-squared test (3 degrees of freedom)
DM was associated with severe OSA (Table 2). The unadjusted OR (95% CI) for DM with severe OSA was 3.93 (2.34, 6.58, p<0.001). This relationship was not significant in patients with mild OSA (OR: 1.25 (95% CI: 0.71, 2.18, p=0.44)) or moderate OSA (OR: 1.75 (95% CI: 0.98, 3.13, 0.06)). Nevertheless, there was a dose-response relationship between the severity of OSA and the prevalence of DM (p value for trend <0.001).

Following adjustment for age, BMI, gender, neck circumference and smoking status, the OR for the presence of DM was 2.18 (95% CI: 1.22, 3.89, p=0.008) in patients with severe OSA, but the OR for DM was not statistically significant in patients with mild or moderate OSA. Furthermore, modifying the definition of DM did not alter the relationship. Using a validated administrative algorithm, the OR for the presence of DM in patients with severe OSA was 1.82 (95% CI: 1.07, 3.10, p=0.027). However, using the administrative algorithm, the relationship between severe OSA and DM was attenuated and non-significant when age was modeled as a continuous variable (OR for Severe OSA: 1.57 (95% CI: 0.87, 2.83, p=0.14)).

**Table 2. Odds of Prevalent Diabetes Mellitus by OSA Severity**

**Definition: Diabetes (self-report + medications)**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Model</th>
<th>Adjusted for age and gender</th>
<th>Multivariate adjusted model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Mild OSA</td>
<td>1.25 (0.71, 2.18)</td>
<td>0.44</td>
<td>1.21 (0.69, 2.13)</td>
</tr>
<tr>
<td>Moderate OSA</td>
<td>1.75 (0.98, 3.13)</td>
<td>0.059</td>
<td>1.65 (0.91, 2.97)</td>
</tr>
<tr>
<td>Severe OSA</td>
<td>3.93 (2.34, 6.58)</td>
<td>&lt;0.001</td>
<td>3.79 (2.23, 6.45)</td>
</tr>
</tbody>
</table>

- Reference group is patients with no OSA
* multivariate model adjusted for age, gender, body mass index, neck circumference, and smoking status.

**Definition: Diabetes administrative algorithm (2 physician claims or 1 hospitalization within a 2 year period)**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Model</th>
<th>Adjusted for age and gender</th>
<th>Multivariate adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Mild OSA</td>
<td>1.25 (0.79, 1.98)</td>
<td>0.34</td>
<td>1.14 (0.72, 1.82)</td>
</tr>
<tr>
<td>Moderate OSA</td>
<td>1.46 (0.89, 2.38)</td>
<td>0.14</td>
<td>1.26 (0.76, 2.09)</td>
</tr>
<tr>
<td>Severe OSA</td>
<td>3.63 (2.36, 5.58)</td>
<td>&lt;0.001</td>
<td>3.18 (2.04, 4.95)</td>
</tr>
</tbody>
</table>

- Reference group is patients with no OSA
* multivariate model adjusted for age, gender, body mass index, neck circumference, and smoking status.
A stratified analysis was performed to assess the influence of sleepiness on the OR of prevalent DM (Table 3). Severe OSA was associated with DM exclusively in sleepy patients (ESS ≥10). This was observed in both the unadjusted models (Sleepy Severe OSA: OR 4.11 (95% CI: 2.30, 7.33) vs. Non-sleepy Severe OSA: OR 2.79 (95% CI: 0.87, 9.00)) and fully adjusted models (Sleepy Severe OSA: OR 2.59 (95% CI: 1.35, 4.97) vs. Non-sleepy Severe OSA: OR 1.16 (95% CI: 0.31, 4.37)).

Table 3. Odds of Prevalent Diabetes Mellitus by OSA Severity (Stratified by Level of Daytime Sleepiness)

<table>
<thead>
<tr>
<th>Unadjusted model</th>
<th>Sleepy (ESS ≥10)</th>
<th>Non Sleepy (ESS &lt;10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Mild OSA</td>
<td>1.24 (0.65, 2.38)</td>
<td>0.51</td>
</tr>
<tr>
<td>Moderate OSA</td>
<td>1.70 (0.87, 3.32)</td>
<td>0.12</td>
</tr>
<tr>
<td>Severe OSA</td>
<td>4.11 (2.30, 7.33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate-adjusted model</th>
<th>Sleepy (ESS ≥10)</th>
<th>Non Sleepy (ESS &lt;10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Mild OSA</td>
<td>0.98 (0.50, 1.94)</td>
<td>0.96</td>
</tr>
<tr>
<td>Moderate OSA</td>
<td>1.13 (0.54, 2.32)</td>
<td>0.75</td>
</tr>
<tr>
<td>Severe OSA</td>
<td>2.59 (1.35, 4.97)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

- Reference group is patients with no OSA
* multivariate model adjusted for age, gender, body mass index, neck circumference, and smoking status.

Sensitivity Analysis

Sensitivity analysis was performed using a full model including co-morbidities, medication class, and oxygen saturation profile. The association between OSA and DM remained unchanged using a full model including co-morbidities and medications. Furthermore, the association was still observed whether the patients had undergone ambulatory monitoring or polysomnography. After the exclusion of patients undergoing polysomnography, the association between OSA and DM remained (OR 1.92 (95% CI: 1.03, 3.59, p=0.040)).
Hypoxemia was not independently associated with DM, when analyzed as a continuous variable (% time spent below SaO2 = 90%, p=0.36), or a categorical variable (12% spent below SaO2 = 90%, p=0.60). Furthermore, the inclusion of measures of hypoxemia within the logistic models, did not alter the significant association between severe OSA and DM in sleepy subjects (OR 2.47 (95% CI: 1.23, 4.98, p=0.011).

**DISCUSSION**

Diabetes mellitus is associated with severe OSA (RDI $>$ 30 hr$^{-1}$). This association remains statistically significant even after adjustment for age, BMI, gender, neck circumference and smoking status. However, this relationship appears to be limited to patients who report excessive daytime sleepiness.

Our findings compliment what has already been observed in other large cohort studies. The Sleep Heart Health Study confirmed the diagnosis of OSA objectively with unattended home PSG and found an independent association between OSA and glucose intolerance in a sub-set of 2,656 patients.[12] However, it remains unclear if patients with glucose intolerance are at the same risk of micro/macrovascular disease, as those with DM. The Wisconsin Sleep Cohort Study ($n=1,387$) reported an independent association between OSA, diagnosed by attended polysomnography, and a robust definition of DM (physician diagnosis or glucose control). These findings differed from ours in that the association between OSA and DM existed at all levels of OSA severity, without an apparent “dose-response” relationship. Our findings are more consistent with previous studies wherein the risk of cardiovascular disease and death was restricted to those with severe OSA.[1,4,29,30] A novel finding in our study was that the association between OSA and DM occurred only in patients who reported excessive daytime sleepiness. The notion that OSA patients who are sleepy have a different risk profile to those who are not sleepy has been raised in the context of long term cardiovascular disease and the response to CPAP therapy.[15,31,32] Similarly, our study suggests that reported history of sleepiness may help to identify OSA patients who have an increased risk of DM.

Although previous literature has demonstrated an association between intermittent hypoxia/OSA and both insulin levels and insulin resistance; [5,33,34] in this population, hypoxemia was not independently associated with DM, nor did the inclusion of measures of hypoxemia alter the association between severe OSA and DM in sleepy patients. It is entirely possible that sleepiness is acting as a marker of the sleep disrupting effects of OSA, independent of hypoxemia. It has been shown that isolated sleep fragmentation or sleep deprivation may also result in cardiovascular and metabolic effects.[35-38] A study by Morrell et al. showed that sleep fragmentation was associated with elevated systemic blood pressure in people with an AHI $<$ 1 event/hr.[35] Furthermore, sleep fragmentation has been shown to augment sympathetic nervous activity, resulting in higher metabolic rates during sleep and elevated catecholamine secretion.[7,37-39]

The association between sleepiness and DM is also biologically plausible. Specifically, the presence of abnormally high sympathetic output has been proposed as a potential mechanism for the association between OSA and insulin resistance/glucose intolerance.[7,37,38,40] Earlier work by Spiegel et al. demonstrated that sleep debt significantly affected carbohydrate metabolism and endocrine function.[40] In a sample of healthy males, 6 nights of restricted sleep resulted in significant increases in sympathetic nervous activity, glucose intolerance, and elevated evening cortisol levels. It has been hypothesized that elevated evening cortisol levels may reflect impairment in the negative feedback control of the hypothalmo-pituitary-adrenal
axis, resulting in insulin resistance.[41] Finally, Vgontzas et al. has shown that elevated plasma levels of inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 in patients with sleep disorders, including OSA, are also associated with excessive daytime sleepiness.[38]

Our study has several limitations. Firstly, it is possible that we underestimated the prevalence of DM since our definition required both a report of physician-diagnosed diabetes and the use of specific medication (oral hypoglycemic and/or insulin). Consequently, patients whose DM was treated with lifestyle modification, or who were prescribed medication but did not use it, would not have been identified as having DM. Notwithstanding this limitation, sensitivity analysis using the validated administrative algorithm did not alter our results.

Secondly, it is possible that we did not adequately account for the confounding effect of adiposity through the measurement of BMI and neck circumference alone. It has been established that BMI does not discriminate between muscle and adipose tissue or provide an assessment of body fat distribution. Thus, residual confounding may result in an overestimate of the true association between OSA and DM.

Thirdly, subjects were recruited from patients referred for sleep diagnostic testing, which raises the possibility of referral bias. However, all patients seen at private respiratory companies as well as at the sleep centre had sleep diagnostic testing prior to consultation with a sleep physician. Our patient population was not selected by sleep physicians, but rather reflects those in the community who are suspected of having OSA by their primary care physician.

Finally, the use of ambulatory monitoring rather than attended PSG to determine RDI may be regarded as a limitation. However, the ambulatory monitor we used has been validated against PSG both in terms of bias as well as in the clinical management of OSA.[17-19] While the monitor has not been validated in patients with co-morbidities, sensitivity analysis accounting for co-morbidities or measures of hypoxemia did not change the results.

In summary, OSA is associated with DM in this referred population, but only in those with severe disease (RDI ≥30 hr⁻¹) who report excessive sleepiness. Further investigation is required to prove a causal relationship and to identify the physiologic mechanisms that are responsible. The inclusion of both sleepy and non-sleepy patients in previous studies may explain their heterogenous results and conclusions. Future interventional studies designed to evaluate the impact of OSA treatment on DM should consider selecting patients with severe OSA who report excessive daytime sleepiness.

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**Competing Interests:** All authors have no competing interests.

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Figure 1. Patient Flow Diagram

Total number of participants referred for sleep assessment (n = 2295)

Number refused consent (n = 78)

Number of consented participants referred for sleep assessment (n = 2217)

Out-of-province residents (n = 42)

Number of Alberta residents sent to AHW for data linkage (n = 2175)

Number of patients not identified in AHW registry file (n = 26)

Participants with complete sleep test data and linked to AHW registry file (n = 2149)

Location of sleep diagnostic testing

- Participants referred to Alberta Lung Association Sleep Center (n = 1761)
- Participants referred to homecare facility within community (n = 388)

Type of sleep diagnostic testing

- Ambulatory Monitoring (n = 1782)
- Overnight Polysomnography (n = 367)
  - 197 Split-night tests
  - 170 Diagnostic tests
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