Glucose Intolerance in Japanese Patients with Obstructive Sleep Apnea

Kazuo Otake, Ryuiji Sasanabe, Rika Hasegawa, Katsuhisa Banno, Reiko Hori, Yoshihito Okura, Kunio Yamanouchi and Toshiaki Shiomi

Abstract

Objective Obstructive sleep apnea syndrome (OSAS) often accompanies obesity and diabetes mellitus. This study was performed to investigate the prevalence of glucose intolerance and to determine independent predictors for insulin resistance in patients with OSAS.

Methods A cross-sectional study of 679 OSAS patients with an apnea-hypopnea index (AHI) ≥ 5/h and 73 controls subjects (AHI < 5/h) was done in a tertiary university-based medical center. They were assessed by nocturnal polysomnography and underwent an oral glucose tolerance test.

Results The prevalence of diabetes mellitus in OSAS patients was higher than that of the control group (25.9% vs. 8.2%, p < 0.001) and 424 patients (62.4%) received a new diagnosis of impaired glucose tolerance or diabetes mellitus. The very severe OSAS group (AHI ≥ 45/h) had significantly higher homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA beta-cell function than the other OSAS groups (AHI < 45/h) and the control group. In a logistic regression model adjusting for potential confounders: age, AHI, minimum SpO2, and body mass index (BMI), only BMI was associated with insulin resistance (HOMA-IR > 3) (odds ratio: 1.272, 95% confidence interval 1.206-1.343, p < 0.0001).

Conclusion Glucose intolerance was more common in patients with OSAS. Insulin resistance was associated not with AHI but rather with BMI.

Key words: sleep apnea, insulin resistance, glucose tolerance test, obesity, body mass index, metabolic syndrome

(Inter Med 48: 1863-1868, 2009)
(DOI: 10.2169/internalmedicine.48.2465)

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder which is characterized by repetitive cessation of breathing during sleep and daytime consequences which include subjective daytime sleepiness, impaired cognitive function, and impaired memory (1). The prevalence of OSAS is high (2-4% of the adult population) (2); a recent review estimates that OSAS affects approximately 5% of adults (3). This problem is also common in Asians (4). OSAS has been reported to be associated with high rates of morbidity and mortality due to cardiovascular diseases (5). Previous reports have shown a linked relationship between OSAS and obesity (6). Obesity may play a role in the development of diabetes mellitus, hypertension, and hyperlipidemia (7). Thus, patients with OSAS may be burdened with multiple risk factors related to obesity for cardiovascular diseases.

Metabolic syndrome, a constellation of cardiovascular risk factors that includes obesity, hypertension, insulin resistance, and dyslipidemia, has been reported to be common in patients with OSAS (8). Insulin resistance, a key component of cardiovascular diseases, is an association linked with obesity; however the results of published data on the relationship between OSAS and glucose intolerance are conflicting (9-12). It is still controversial whether or not OSAS independently plays a role in the development of glucose intolerance or diabetes mellitus. In this study we performed a cross-sectional study in Japanese patients with OSAS to...
clarify the prevalence of glucose intolerance in OSAS patients and to determine what measurement is a predictor of insulin resistance in OSAS patients.

Methods

Subject

We selected all patients who were referred to the Aichi Medical University Hospital, Sleep Disorders Centre for an assessment of OSAS. There were 752 eligible patients (663 men and 89 women), who gave informed consent. Then we enrolled all of the patients diagnosed as having OSAS based on overnight polysomnography. The diagnosis of OSAS was based on the conventional criteria (13), including an apnea-hypopnea index (AHI) ≥5/h and pathological daytime sleepiness. The Epworth sleepiness scale was used to quantify subjective daytime sleepiness (14). Patients who had been diagnosed as having diabetes mellitus before assessment of OSAS were excluded. As a result, there were 679 patients with a definite diagnosis of OSAS. These patients were divided into four groups based on the severity of OSAS, i.e., a mild OSAS (AHI: 5 to 14.9/h), moderate OSAS (AHI: 15 to 29.9/h), severe OSAS (AHI: 30 to 44.9/h), and very severe OSAS (AHI: ≥45/h) group.

Seventy-three control subjects with an AHI <5/h were selected. They were referred to the Sleep Disorders Center because of snoring or observed episodes of apnea and underwent polysomnography, but were otherwise healthy.

Polysomnography

Nocturnal polysomnography was performed with multichannel monitoring that includes neurophysiological variables (electroencephalogram, electrooculogram, chin electromyogram, tibialis anterior electromyogram) and cardiorespiratory variables (chest wall motion, abdominal motion, nasal pressure, arterial oxygen saturation, and electrocardiogram). Continuous recordings were obtained with a computerized diagnostic system (P series™: Compumedics, Melbourne, Australia; or Alice 4™: Respironics Inc., Pittsburgh, PA). The sleep record was analyzed manually according to the criteria of Rechtshaffen and Kales using a 30-second epoch (15). The hourly number of episodes of apnea plus hypopnea in sleep combined was defined as the AHI and was calculated as an indicator of the severity of OSAS (13).

Assessment of glucose intolerance

On the morning after the sleep study, all patients and controls underwent blood tests and oral glucose tolerance test (OGTT), with an overnight fast. We obtained informed consent for the tests. After collecting a fasting blood sample, glucose load of 75 g was ingested over 5 minutes. Blood samples were collected 30 minutes, 60 minutes, 90 minutes, 120 minutes, and 180 minutes after the test load. Blood glucose and plasma insulin concentrations were measured in each sample. The blood glucose level was measured by an HK G-6-PDH assay using an H-7700 autoanalyzer (Hitachi, Tokyo, Japan); the plasma insulin concentration was quantified by an FEIA assay using an AIA1800 analysis machine (Toso, Tokyo, Japan). Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA beta-cell function (beta-CF), described in detail elsewhere (16). We defined insulin resistance as HOMA-IR >3. The hemoglobin A1c (HbA1c) was also measured in patients and controls.

Diagnostic criteria of glucose intolerance and diabetes mellitus

The diagnosis for diabetes mellitus and impaired glucose tolerance (IGT) was based on the criteria by the Japan Diabetes Society (17). Diabetes mellitus was diagnosed if fasting blood glucose concentration was equal to or over 126 mg/dL or when postload blood glucose was equal to or over 200 mg/dL, 2 hours after a glucose load; IGT was diagnosed if post glucose concentration ranged between 140 to 199 mg/dL, 2 hours after a glucose load. Based on the results of OGTT, patients and controls were classified into three groups: a normal glucose tolerance (NGT) group, an impaired glucose tolerance (IGT) group, and a type 2 diabetes mellitus (type 2 DM) group.

Statistical analysis

Statistical analysis was performed using StatView software version 5.0 (SAS Institute, Cary, NC). Continuous variables were expressed as the mean ± standard deviation (SD). Comparisons of continuous clinical variables between controls and OSAS groups with different categorization by AHI were done by Turkey-Kramer multiple comparison procedure. In addition, logistic regression analysis was done to determine which independent variable may predict HOMA-IR, an index of insulin resistance. The odds ratio (OR) and 95% confidence interval (CI) were calculated. Significance of differences was accepted at p<0.05 or p<0.01.

Results

Characteristics of OSAS patients and controls

A total of 679 patients with OSAS and 73 control subjects were enrolled in this study. The characteristics of patients and controls are presented in Table 1. The patients with very severe OSAS and controls were significantly younger than other OSAS groups. The mean BMI of the very severe OSAS patients was greater than controls and other OSAS groups.

Prevalence of glucose intolerance and diabetes mellitus

The prevalence of type 2 DM or IGT in each OSAS group and control group is presented in Fig. 1. Among the 679 OSAS patients, 424 patients (62.4%) received a new diagnosis of IGT (36.5%) or type 2 DM (25.9%). In the very
Table 1. Clinical Features and Characteristics Related to Glucose Metabolism of OSAS Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Mild OSAS AHI &lt;5</th>
<th>Moderate OSAS AHI 5-14.9</th>
<th>Severe OSAS AHI 15-29.9</th>
<th>Very severe OSAS AHI &gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>73</td>
<td>155</td>
<td>160</td>
<td>108</td>
<td>256</td>
</tr>
<tr>
<td>Age (years)</td>
<td>*45.2±3.7</td>
<td>51.6±12.9</td>
<td>51.0±13.3</td>
<td>52.5±12.8</td>
<td>*46.1±12.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8±5.4</td>
<td>26.1±4.1</td>
<td>25.6±3.7</td>
<td>26.4±3.3</td>
<td>**30.3±5.7</td>
</tr>
<tr>
<td>AHI (/h)</td>
<td>2.0±1.2</td>
<td>9.5±3.0</td>
<td>21.6±4.1</td>
<td>37.4±4.6</td>
<td>66.9±16.5</td>
</tr>
<tr>
<td>Minimum SpO₂ (%)</td>
<td>89.3±6.4</td>
<td>84.7±6.6</td>
<td>81.1±7.0</td>
<td>77.9±8.2</td>
<td>68.5±9.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.17±0.6</td>
<td>5.35±0.80</td>
<td>5.29±0.54</td>
<td>5.47±0.63</td>
<td>5.62±0.99</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>94.71±10.53</td>
<td>97.73±22.28</td>
<td>97.00±14.32</td>
<td>97.78±14.50</td>
<td>100.55±23.30</td>
</tr>
<tr>
<td>2h PG (mg/dL)</td>
<td>138.58±54.33</td>
<td>159.23±65.02</td>
<td>153.65±53.94</td>
<td>170.51±63.61‡</td>
<td>182.03±65.83‡</td>
</tr>
<tr>
<td>F-IRI (μU/mL)</td>
<td>10.29±6.99</td>
<td>9.81±6.78</td>
<td>10.26±6.63</td>
<td>10.51±7.31</td>
<td>14.89±11.89#</td>
</tr>
<tr>
<td>ΣPG/ΣIRI</td>
<td>76.2±46.20</td>
<td>6.2±41.30</td>
<td>7.1±19.20</td>
<td>9.2±62.38</td>
<td>7.1±57.2IRI</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.45±1.30</td>
<td>2.47±2.15</td>
<td>2.54±1.87</td>
<td>2.57±1.98</td>
<td>3.78±3.788</td>
</tr>
<tr>
<td>HOMA beta-CF</td>
<td>121.80±78.58</td>
<td>113.51±71.99</td>
<td>115.90±69.92</td>
<td>121.30±78.11</td>
<td>169.22±145.77#</td>
</tr>
</tbody>
</table>


Continuous variables are expressed by mean ± standard deviation.

*The mean age in control group and very severe OSAS group was significantly younger than other OSAS subgroups (p<0.05). **The mean BMI in the very severe OSAS group was significantly higher than those of other OSAS subgroups and controls (p<0.05). † very severe OSAS group vs. other OSAS subgroups and controls (p<0.05), ‡very severe OSAS group vs. mild and moderate OSAS groups and controls (p<0.05), § very severe OSAS group vs. mild and moderate OSAS groups and controls (p<0.05).

Changes in glucose level and insulin levels during oral glucose tolerance test

Changes in glucose level and insulin level during OGTT in each OSAS group and control group are presented in Fig. 2. The glucose level in the time from 30 to 120 min in the very severe group was significantly increased, compared to the control group, and compared to the mild and moderate groups in the time from 60 min to 120 min. As for the insulin level, a significant difference between the very severe group and other groups were observed before OGTT.

The insulin level in the time from 60 min to 180 min in the very severe group was significantly increased, compared to the control group, and compared to the mild and moderate groups in the time from 120 min to 180 min.

Parameters of glucose metabolism

Characteristics related to glucose metabolism of OSAS patients and controls are presented in Table 1. Hemoglobin A1c of the severe OSAS group (AHI>45/h) was significantly increased compared to the control group and the moderate OSAS group. Fasting insulin level, HOMA-IR, and HOMA beta-CF of the very severe OSAS group were significantly higher than those of the other OSAS subgroups and controls.

Furthermore, since insulin secretion itself was assumed to be impaired in patients with diabetes mellitus, we excluded patients diagnosed with type 2 DM (n=176). Then we compared the HOMA-IR and HOMA beta-CF of the very severe OSAS group among IGT and NGT groups (n=503). As a result, the severe OSAS group had significantly higher HOMA-IR and beta CF than the other OSAS subgroups and the control group.

Predictors for insulin resistance in OSAS patients

A logistic regression analysis was performed to determine the independent association of insulin resistance (HOMA-IR >3), using a model whose explanation factors were age, BMI, AHI, and minimum SpO₂. Although there were no associations between insulin resistance and age, AHI, or minimum SpO₂, only BMI was associated with insulin resistance (odds ratio: 1.272, 95% confidence interval: 1.206-1.343, p<0.0001) (Table 2).

Discussion

This is the first study that revealed a relationship between severe OSAS, 71.9% of the patients had IGT or type 2 DM. The prevalence of type 2 DM in each OSAS group was higher than controls group: 8.2% for controls vs. 19.4% for mild OSAS group (p<0.01), vs. 20.0% for moderate OSAS group (p<0.05), vs. 24.1% for severe OSAS group (p<0.01), vs. 34.4% for very severe OSAS group (p<0.0001).
OSAS and glucose intolerance using a large sample of Asians. We found that more than 25% of OSAS patients were diagnosed as having type 2 DM. The SOS study from Sweden to investigate the prevalence of diabetes mellitus in 3,034 obese people showed that the prevalence of diabetes mellitus in men with OSAS (18.9%) was slightly higher than that of men without OSAS (17.1%), whereas the incidence of diabetes mellitus in women with OSAS (14.8%) was higher than that of women without OSAS (8.9%) (18).

A cross-sectional study from the Wisconsin Sleep Cohort showed that 14.7% of patients with OSAS (AHI>15/h) had diabetes (12). The prevalence of diabetes in patients with OSAS in the two reports was lower than that of our study, which was likely due to the difference of diagnostic methods for diabetes. In addition, 36.5% of patients with OSAS were found to have IGT. The result supports that this population group is more likely to have cardiovascular disease, since insulin resistance plays a major role in the development and progression of the atherosclerosis.

Insulin resistance was associated with BMI and AHI did not predict glucose intolerance, which was not consistent with the previously published results. Tiihonen et al assessed insulin resistance using an OGTT in 18 patients suspected of having OSAS to study the association of insulin resistance with age, BMI, and 4% oxygen desaturation index, and concluded that the most reliable predictor for insulin resistance was not BMI but the 4% oxygen desaturation index (19). Furthermore, de la Eva et al showed that the fasting insulin level was associated with the severity of OSAS independent of BMI (20). A study by Ip and colleagues showed that BMI was the major determinant of insulin resistance in patients with OSAS, however despite controlling for obesity and other confounding factors of insulin resistance, AHI and/or minimum SpO2 were also associated with fasting insulin level and HOMA-IR (12). The three results suggest that sleep breathing disorder may have an independent adverse effect for insulin resistance. Sample size, methods to evaluate insulin resistance, and diagnostic criteria may have affected the difference between our result and others. In addition, although we used the parameters indicating OSAS, such as AHI and the minimum oxygen saturation for analysis, other factors may have affected the indices for evaluating the severity of OSAS, leading to the result that OSAS did not affect insulin resistance. Recently Sulit et al assessed several oxygen-saturation variables (e.g. 2% for percentage of time spent with an oxygen saturation<90%, 95% for average oxygen saturation, and 90% for minimum oxygen saturation) for measurements of the severity of OSAS and found that the strongest index associated with impaired glucose tolerance was time spent at an oxygen saturation of <90%; individuals with at least 2% of time spent at a saturation level less than 90% (21).

Some hormones (e.g. leptin, adiponectin) and body fat distribution may partly affect insulin resistance in patients with OSAS, since there may be a relationship between central obesity and leptin secretion. Insulin resistance through leptin regulation has been suggested in OSAS patients. Polotsky et al concluded that the increase in insulin resistance in the intermittent response of hypoxemia may depend on impaired regulation of leptin on insulin resistance using mouse models with inherited obesity (22). Punjabi and col-

**Table 2. Predictors for Insulin Resistance in OSAS Patients**

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.011 (0.995 - 1.027)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.272 (1.206 - 1.343)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AHI (/h)</td>
<td>0.999 (0.989 - 1.009)</td>
<td>NS</td>
</tr>
<tr>
<td>Minimum SpO2 (%)</td>
<td>1.002 (0.978 - 1.027)</td>
<td>NS</td>
</tr>
</tbody>
</table>

OSAS: obstructive sleep apnea syndrome, BMI: body mass index, AHI: apnea-hypopnea index, OR: odds ratio, CI: confidence interval.
leagues investigated the relation between sleep breathing disorders and insulin resistance in 150 obese middle age men using PSG and OGT, concluded that the incidences of type 2 DM and IGT are increased in OSAS patients (AHI > 5/h), even after adjustment for BMI and body fat percentage (9). In contrast, Stoolh et al measured insulin sensitivity of 50 obese women, and concluded that increased insulin resistance may be present in patients with OSAS (AHI >10/h), compared to subjects without OSAS, however increased insulin resistance may be associated not with AHI but with BMI (23). Thus, the BMI used herein as the index for obesity may not correctly reflect the amount of visceral obesity in our study. Hormonal effect and body fat distribution needs to be considered in evaluating glucose tolerance in patients with OSAS, which is a future topic.

In the present study, the change of insulin resistance before and after treatment of OSAS was not documented, since long-term outcome data on glucose-insulin metabolism after CPAP treatment was not available. Harsch et al evaluated insulin resistance of 40 OSAS patients before and after continuous positive airway pressure (CPAP) treatment using hyperinsulinemic euglycemic clamp studies, and found that insulin resistance improved after CPAP therapy, especially in non-obese patients (24). In contrast, Smurra et al reported that CPAP treatment does not affect glucose-insulin metabolism in sleep apneic patients (25). Thus, the effect of treatment intervention for OSAS on glucose-insulin metabolism remains unclear. In a future study we will clarify the change of glucose-insulin metabolism before and after CPAP treatment in patients with OSAS.

In conclusion, glucose intolerance was common in patients with OSAS. A high prevalence of diabetes mellitus and insulin resistance was observed in the severe OSAS group. BMI was the only predictor of insulin resistance in patients with OSAS.

References


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