Gender Differences in the Clinical Features of Sleep Apnea Syndrome

Yuki Mieno¹, Masamichi Hayashi¹, Hiroki Sakakibara², Hiroshi Takahashi³, Shiho Fujita⁴, Sumito Isogai¹, Yasuhiro Goto¹, Sakurako Uozu¹, Mitsushi Okazawa⁵ and Kazuyoshi Imaizumi¹

Abstract:
Objectives  Sleep apnea syndrome is more prevalent among men than women and is frequently accompanied by metabolic syndrome (MetS). However, gender differences in the effect of sleep-disordered breathing (SDB) leading to the risk of MetS remain unclear. The aim of our study was to investigate the clinical characteristics of SDB in women and the differential influence of SDB on MetS between genders.
Methods  In a single-center retrospective study, we compared the data of 1,809 consecutive SDB patients by gender to clarify the characteristics of sleep disorders in women. We also compared the prevalence of MetS and its related abnormalities by gender. A logistic regression analysis was used to determine the contributory factors for MetS.
Results  The mean age and proportion of patients over 50 years of age were higher in women than in men. SDB was milder in women than in men according to polysomnography findings. Elevated Hemoglobin A1c levels and hyperlipidemia were less frequent in women than in men. The MetS prevalence was similar in women and men (30.0% vs. 35.2%). A logistic regression analysis showed that the apnea-hypopnea index (AHI) was an independent risk factor for MetS in both genders, but that female gender was independently associated with a decreased prevalence of MetS and its related abnormalities.
Conclusion  Female SDB patients tend to be older with milder apnea and sleepiness than male SDB patients. A higher AHI is a significant risk factor for MetS in both genders, although female gender is an independent inhibitory factor for developing MetS in SDB patients.

Key words: Sleep apnea, Gender, Polysomnography, Metabolic syndrome

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Introduction

Sleep-disordered breathing (SDB) and sleep apnea syndrome are more prevalent among men than women. According to the Wisconsin Sleep Study in the United States, the prevalence of SDB among subjects with an apnea-hypopnea index (AHI) ≥5 was 24.0% in men and 9.0% in women (1). Those with an AHI ≥5 and accompanying symptoms of daytime drowsiness were diagnosed with SDB, the prevalence of which was 4.0% in men and 2.0% in women (1). Based on epidemiological data, the ratio of men to women with SDB was approximately 2:3:1 (2) whereas the ratio of men to women with SDB diagnosed in sleep laboratories was much more striking at approximately 8:10:1 (3).

SDB is a significant risk factor for cardio-cerebrovascular diseases, such as obesity, hypertension, hyperlipidemia, and glucose metabolic disorder. Therefore, the prevalence of metabolic syndrome (MetS) is extremely high in patients with severe SDB (4). These complications are thought to re-
result from insulin resistance in SDB, and SDB itself may be a cause of insulin resistance (5-8). Previous large-scale epidemiological surveys have reported a relationship between SDB and insulin resistance (9, 10). Marin et al. reported that untreated obstructive sleep apnea syndrome in men with an AHI ≥30 (average age, 50 years) increased the cardiovascular risk by 3-fold compared with healthy subjects, and 10% of patients were likely to die of cardiovascular diseases within 10 years (11). However, in women, no significant association between mortality and SDB was identified in a large-scale epidemiological study (12).

In the general Japanese adult population, the prevalence of MetS diagnosed by the Japanese Committee of the Criteria for MetS (JCCMS) is higher in men (12.0%) than in women (1.3%) (13). SDB is frequently accompanied by MetS; however, gender differences in the influence of SDB on MetS remain unclear. In addition, whether or not the influence of apnea on the development of MetS differs by gender is also unclear.

The aim of our study was to clarify the clinical features of female SDB and to investigate the gender differences in the influence of SDB on MetS.

**Methods**

**Patients**

This single-center retrospective study evaluated consecutive patients who visited Fujita Health University Hospital with symptoms suggestive of SDB between 2003 and 2012. We included patients over 20 years of age who underwent polysomnography (PSG) and were diagnosed with SDB with an AHI ≥5. We excluded patients with complications of narcolepsy, rapid eye movement (REM) sleep behavior disorders, non-REM parasomnia, and restless leg syndrome. The study protocol was approved by the Clinical Research Ethical Review Board of Fujita Health University (Fujita IRB #10-183).

**Polysomnography**

Each patient underwent overnight full PSG in a sleep laboratory at Fujita Health University Hospital. PSG included electroencephalography, electrooculography, electromyography of the chin, and electrocardiography, as well as assessments of the nasal and oral flows, thoracic and abdominal respiratory movements, and percutaneous arterial oxygen saturation (SpO2). Nasal flows were recorded with thermal sensors and pressure sensors. Oral flows were recorded with thermal sensors. Thoracic and abdominal respiratory movements were measured by inductive plethysmography. SpO2 was monitored continuously with a pulse oximeter. Respiratory events were diagnosed in accordance with the criteria of the American Academy of Sleep Medicine (14). In brief, apnea was defined as the cessation of airflow for at least 10 seconds, and hypopnea was defined as an abnormal respiratory event with a ≥30% reduction, relative to baseline, in the thoraco-abdominal movement or airflow lasting for at least 10 seconds and accompanied by > 4% oxygen desaturation.

Sleep stages were scored in accordance with the international criteria proposed by Rechtschaffen and Kales (15). All of the above physiological data were recorded on one of the following three polygraphs: an Alice 3 System (Healthdyne, Atlanta, GA, USA), a Somnostar (Carefusion, San Diego, CA, USA), or a Sandman (Embla, Ontario, Canada). Arousals were classified according to the American Academy of Sleep Medicine criteria of 1999 (16).

**Procedures and Measurements**

Before the start of PSG, we measured the height, weight, body mass index (BMI), systolic and diastolic blood pressures, neck circumference, abdominal circumference at the level of the umbilicus, and buttock circumference. The Epworth Sleepiness Scale (ESS) was used for the subjective analysis of daytime sleepiness. The morning after PSG, all patients underwent general blood sampling and a 75-g oral glucose tolerance test (OGTT). Patients who had already been diagnosed with diabetes were excluded from the OGTT. Plasma glucose and serum insulin levels were determined at 0, 30, 60, 90, and 120 minutes. Glucose levels < 110 mg/dL at baseline and <140 mg/dL at 120 minutes in OGTT were defined as normal, and diabetes mellitus was diagnosed if the glucose levels were ≥126 mg/dL at baseline and ≥200 mg/dL at 120 minutes on the OGTT. Patients falling into neither of these categories were considered to have borderline diabetes mellitus (17). Insulin resistance was determined using the homeostasis model assessment for insulin resistance (HOMA-IR): (fasting insulin [μU/mL] × fasting plasma glucose [mg/dL]) / 405 (18).

**The Diagnosis of MetS.**

The presence of MetS was determined according to the JCCMS criteria. In brief, men and women with a waist circumference of ≥85 cm and ≥90 cm, respectively, and who met at least two of the following four criteria were diagnosed with MetS: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or being treated for hypertension; triglyceride (TG) level ≥150 mg/dL or being treated for high TG; high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL; and fasting blood glucose level ≥110 mg/dL, or diagnosed with diabetes mellitus.

**Statistical Analyses**

Because data were not normally distributed according to the Shapiro-Wilk’s test, the results were presented as the medians and interquartile range. The univariate analysis and comparisons between two groups were performed by the Wilcoxon test or Pearson’s chi-squared test. In this study, we compared the clinical data of our SDB patients with the data from other reliable cohort studies with clearly reported sample sizes, average values, and standard deviations (19, 20). A logistic regression analysis was performed.
to determine the differential contribution of multiple factors. All analyses were performed using the JMP software program, (version 9.0.2 for Windows, Japanese version; SAS Institute Inc., Tokyo, Japan).

Results

Patient Characteristics

We enrolled a total of 1,809 consecutive SDB patients (1,531 men and 278 women). The main complaints of patients in our study were heavy snoring, witnessed apnea, and excessive daytime sleepiness. Women complained of a greater variety of symptoms than men, such as interrupted sleep, insomnia, body pain, and nocturia. The median ages of the men and women were 52 and 59 years, respectively, with the age distribution by gender differing significantly (Figure). Men in their 50's were the largest group, followed by men in their 40s. In contrast, nearly 80% of women were ≤50 years of age. The male-to-female ratios of all patients, patients <50 years of age, and patients ≥50 years of age were 5.2, 8.8, and 3.8 respectively. Smoking status also differed by gender, with 32% of men and 8.1% of women being current smokers (Table 1).

Table 1 summarizes the anthropometrical parameters of SDB patients in our study. The median index and distribution of BMI classification were similar between the genders. The neck and abdominal circumferences were larger in men than in women.

Different Characteristics of Sleep Disorders and PSG Findings Between Genders.

Next, we compared the characteristics of sleep disorders in SDB patients by gender. The ESS scores and detailed PSG findings are shown in Table 2. Women had lower ESS scores than men. PSG findings showed that the apnea index (AI) and AHI were lower, the duration of time with SpO2 < 90% shorter, and the desaturation slighter in women than in men. In contrast, women had a shorter total sleep time (TST) and lower sleep efficacy and arousal index than men. Nocturnal awakening was more common in women than in men. With regard to sleep stages, the third and fourth stages comprised a greater proportion of sleep time in women than in men. The distribution of patients by SDB severity also differed between genders. More than 60% of men were categorized as having severe SDB, whereas mild, moderate, and severe SDB were evenly distributed among women.

Gender Differences in the Prevalence of MetS and Related Abnormalities in SDB Patients (Table 3)

We analyzed the prevalence of MetS and its related factors in our patients. The MetS prevalence did not differ significantly between men (35.2%) and women (30.0%) with SDB. While no gender differences were found in the blood pressure, the abdominal circumference was higher in men (78.1%) than in women (42.2%). An assessment of the parameters of lipid metabolism showed that a higher percentage of men had TG concentrations ≥150 mg/dL and HDL-C <40 mg/dL. Although abnormal Hemoglobin A1c (HbA1c) levels (≥5.8%) were significantly more frequent in women than in men, there were no gender differences in the prevalence of abnormalities in other factors related to glucose metabolism, including the fasting blood glucose levels, fasting insulin levels, HOMA-IR, and diabetic pattern on the 75-g OGTT. There were also no gender differences in the preva-

Table 1. Patients Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Male (n=1,531)</th>
<th>Female (n=278)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>years</td>
<td>52.0(41.0-61.0)</td>
<td>59.0(51.0-67.0)</td>
</tr>
<tr>
<td>Smoking status(never : ex : current)</td>
<td>%</td>
<td>22.4: 45.6: 32.0</td>
<td>76.9: 15.0: 8.1</td>
</tr>
<tr>
<td>BMI*</td>
<td>≥25Kg/m²</td>
<td>60.2%</td>
<td>59.4%</td>
</tr>
<tr>
<td>BMI* classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(underweight : normal : overweight : obese)</td>
<td>%</td>
<td>1.7: 38.1: 39.9: 20.4</td>
<td>2.2: 38.4: 33.0: 26.5</td>
</tr>
<tr>
<td>Neck circumference</td>
<td>cm</td>
<td>39.0(37.5-41.5)</td>
<td>35.0(33.0-37.5)</td>
</tr>
<tr>
<td>Abdominal circumference</td>
<td>cm</td>
<td>91.3(85.5-98.0)</td>
<td>88.0(80.0-96.5)</td>
</tr>
<tr>
<td>Buttock circumference</td>
<td>cm</td>
<td>97.0(92.0-102.0)</td>
<td>96.0(90.0-103.0)</td>
</tr>
</tbody>
</table>

BMI: Body mass index

Data are expressed as median with IQR (interquartile range) except for BMI and smoking status classification.
lence of an abnormal BMI.

**Impact of Female Gender on the Prevalence of MetS and Impaired Glucose Tolerance in SDB Patients**

A multivariate logistic regression analysis showed that the AHI (adjusted odds ratio [aOR] 1.014; 95% confidence interval [CI] 1.008-1.023, p<0.0001), age (aOR 1.031; 95% CI 1.019-1.044, p<0.0001), BMI (aOR 1.276; 95% CI 1.276-1.388, p<0.0001), and smoking status (aOR 1.885; 95% CI 1.288-2.771, p=0.001) were independent risk factors for MetS (Table 4). The AHI was also an independent risk factor for indicators of impaired glucose tolerance, including HOMA-IR score (aOR 1.008; 95% CI 1.001-1.014, p<0.05) and the diabetic pattern on the 75-g OGTT (aOR 1.012; 95% CI 1.006-1.019, p<0.001) (data not shown).

Female gender was also significantly associated with a reduced prevalence of MetS (aOR 0.580; 95% CI 0.365-0.912, p=0.018) (Table 4). We therefore investigated whether or not the gender of SDB patients influenced the prevalence of abnormalities in factors related to MetS and impaired glucose tolerance, independent of the AHI, age, BMI, and smoking status. As shown in Table 5, female gender was independently associated with a decreased prevalence of abnormal serum TG levels, HDL-C levels, and abdominal circumference. Gender differences did not contribute to an abnormal HOMA-IR or impaired glucose tolerance.
Table 4. A Multiple Regression Analysis on the Prevalence of the Metabolic Syndrome in SDB Patients.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI*</td>
<td>1.014</td>
<td>1.076-1.023</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.031</td>
<td>1.019-1.044</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI**</td>
<td>1.329</td>
<td>1.276-1.388</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never Smoker (vs. current)</td>
<td>1.885</td>
<td>1.288-2.771</td>
<td>0.001</td>
</tr>
<tr>
<td>Ex smoker (vs. current)</td>
<td>1.617</td>
<td>1.156-2.264</td>
<td>0.005</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.58</td>
<td>0.365-0.912</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*AHI: apnea hypopnea index  **BMI: Body mass index

Table 5. Impact of Female Gender on the Prevalence of the Metabolic Syndrome and Impaired Glucose Tolerance in SDB Patients.

<table>
<thead>
<tr>
<th>Metabolic syndrome prevalence</th>
<th>Adjusted odds ratio*</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal circumference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male ≥85cm</td>
<td>1</td>
<td>0.581</td>
<td>0.365-0.921</td>
</tr>
<tr>
<td>Female ≥90cm</td>
<td>1</td>
<td>0.026</td>
<td>0.014-0.048</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td>1</td>
<td>0.955</td>
</tr>
<tr>
<td>≥130mmHg and/or ≥85mmHg</td>
<td>1</td>
<td>0.943</td>
<td>0.647-1.437</td>
</tr>
<tr>
<td>Fasting blood glucose level</td>
<td>≥110mg/dL</td>
<td>1</td>
<td>0.478</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>≥150mg/dL</td>
<td>1</td>
<td>0.032</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;40mg/dL</td>
<td>1</td>
<td>0.708-1.743</td>
</tr>
<tr>
<td>HOMA-IR **</td>
<td>≥2.5</td>
<td>1</td>
<td>0.689</td>
</tr>
<tr>
<td>75-g oral glucose tolerance test</td>
<td>Diabetic***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as OR with 95% CI.

*Odds ratios were adjusted for age, Body mass index, and apnea hypopnea index (AHI), and smoking status (never, ex, current).

**HOMA-IR : homeostasis model assessment for insulin resistance

***75-g oral glucose tolerance test diabetic: fasting blood glucose level ≥126mg/dL or 2 hour OGTT glucose level ≥200mg/dL.

Finally, we evaluated the influence of SDB (AHI) on the prevalence of MetS and impaired glucose tolerance in men and women separately (Table 6). A multivariate logistic regression analysis with adjustments for the age, BMI, and smoking status showed that the AHI was independently associated with an increased prevalence of MetS (OR 1.022 95% CI 1.007-1.039 p=0.0048) and abnormalities in serum TG levels, HDL-C levels, and HOMA-IR in women. In men, the AHI was independently associated with an increased prevalence of MetS and abdominal circumference, fasting blood glucose, serum TG levels, and the diabetic pattern on the 75-g OGTT.

### Discussion

The prevalence of SDB is higher in men than in women and is higher in postmenopausal women than in premenopausal women (21). Our study showed that the number of female SDB patients increased from 50 years of age, with female patients ≥50 years of age being rare. Although we were unable to obtain information on the menopausal status of women in this study, the mean age of natural menopause in Japanese women is 49.33 years (22). Therefore, our results suggest that the incidence of sleep disorders in women increases drastically after menopause. Furthermore, female hormones may inhibit the onset of SDB (23). Previous studies have similarly shown that progesterone increases the hypercapnic and hypoxic ventilatory responses and activates the upper airway muscles (23), leading to the suppression of SDB onset. In addition, the rates of obesity are higher in men <50 years of age and women ≥50 years of age (20), a finding that may correlate with the increased number of female SDB patients after menopause. However, our study also showed significant gender differences among SDB patients ≥50 years of age.

AHI and sleepiness have been shown to be milder in women than in men, even among older subjects, suggesting that factors other than female hormones, such as anatomical differences in the jaw, face, and upper airway structures between genders, may be related to the relative mildness of SDB in women (24). Our study found that the neck and abdominal circumferences were lower in women than in men, although no marked difference in the buttock circumference was noted. While women tend to develop subcutaneous fat
showed that the AHI was an independent risk factor for MetS in men, whereas the BMI was the only independent risk factor for MetS in women (30). Furthermore, the pattern of fat tissue distribution may be associated with the gender-based differences in the severity of SDB.

Previous studies have found that SDB and MetS frequently accompany each other (4), with this combination further increasing the risk of cardiovascular disease based on sclerosis of the arterial walls and vasculitis (26). SDB-induced hypoxemia and its rapid recovery cause oxidative stress, inducing the activation of reactive oxygen species-sensitive transcription factors (nuclear factor-kappa B and activator protein 1) (27), followed by the production of inflammatory cytokines (tumor necrosis factor-α and interleukin-6) (28), which are presumably linked to the onset of insulin resistance (5-8) and MetS (4).

Elevated HbA1c (≥5.8%) was observed in 24.8% of male SDB patients and 32.3% of female SDB patients, with both being significantly higher than in the general population in 16.4% of men and 10.9% of women, p<0.001 each) (11). Our study also revealed that an increased AHI was significantly related to increased insulin resistance (abnormal HOMA-IR) and lower glucose tolerance (abnormal 75-g OGTT results) in accordance with previous reports (29). Although the MetS prevalence in the general Japanese population is higher in men than in women (12.0% vs. 1.3%) (13), the MetS prevalence among SDB patients in our study did not differ markedly between genders.

A previous study also showed that risk factors for MetS (diagnosed according to the criteria of the JCCMS) differed between Japanese men and women (30). Furthermore, the age, BMI, and AHI were independently associated with MetS in men, whereas the BMI was the only independent risk factor for MetS in women. In contrast, our analysis showed that the AHI was an independent risk factor for MetS in both genders. We found that female gender was inversely associated with MetS prevalence, i.e. apneic women may be resistant to MetS. Nevertheless, our findings indicated that the AHI was still an independent risk factor for MetS in women. The differences in these results between studies may be due to the sample size in our study being larger than in other studies (30).

Several limitations associated with the present study warrant mention. First, as all of our study subjects were Japanese, caution should be exercised when applying these results to other ethnic populations. The gender differences observed in our study may differ for other ethnicities with different physical characteristics. Second, we were unable to obtain information about the menopausal status of the women in this study. Therefore, we were unable to compare the SDB characteristics in women before and after menopause. Third, we enrolled patients who visited the outpatient clinic with symptoms or were referred from other doctors for suspicion of SDB. Asymptomatic patients and patients with atypical symptoms were not included in our study. Fourth, our study was a retrospective analysis in a single university hospital, suggesting the need for a large, prospective, multi-center study to confirm our findings.

In conclusion, female SDB patients tended to be older with milder apnea and sleepiness than male SDB patients. This study clearly demonstrates that a higher AHI is a significant risk factor for MetS in both genders. However, female gender was inversely associated with MetS prevalence independently of other factors, such as apneic severity, suggesting that apnea may make women more resistant to MetS than men. Further prospective observational studies in the entire Japanese population are warranted to confirm these findings.

The authors state that they have no Conflict of Interest (COI).

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AUTHOR CONTRIBUTIONS: K.I. assumes responsibility for the content of the manuscript. Y.M., M.H., H.S., and M.O. con-
tributed to the study design.

Y.M., H.S., H.T., S.I., Y.G., and K.I. contributed to the data analysis. Y.M., S.F., and S.U. contributed to the data collection. Y.M., M.H., H.S., and K.I. contributed to the writing of the manuscript.

References


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