Original Article

Metabolic Syndrome in Japanese Patients with Obstructive Sleep Apnea Syndrome

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We investigated the prevalence of metabolic syndrome in patients with obstructive sleep apnea syndrome (OSAS) referred to a tertiary university–based medical center. A cross-sectional study of patients with a definite diagnosis of OSAS was performed using new diagnostic criteria for metabolic syndrome that were designed for the Japanese population. Clinical features and comorbidities related to metabolic syndrome were compared between 819 patients with OSAS (719 men and 100 women) and 89 control subjects without OSAS. Metabolic syndrome was significantly more common in the patients with OSAS than in the controls (49.5% *vs.* 22.0% for men, $p<0.01$; 32.0% *vs.* 6.7% for women, $p<0.01$). Men with OSAS (apnea-hypopnea index [AHI]≥5/h) had a higher risk of metabolic syndrome compared with controls (odds ratio [OR]: 3.47; 95% confidence interval [CI]: 1.84–6.53). There was a significantly increased risk of metabolic syndrome in men with moderate OSAS (AHI: 15–29.9/h) (OR: 2.83; 95% CI: 1.42–5.66) and men with severe OSAS (AHI≥30/h) (OR: 5.09; 95% CI: 2.67–9.71). Women with OSAS (AHI≥5/h) also had an increased risk of metabolic syndrome (OR: 6.59; 95% CI: 1.47–29.38), and the risk was significantly higher in women with severe OSAS (AHI≥30/h) (OR 14.00; 95% CI: 2.93–66.82). Risk factors for metabolic syndrome differed by gender: in men, age, body mass index (BMI), and OSAS (AHI≥15/h) were significantly associated with metabolic syndrome, whereas, in women, BMI was the only risk factor for metabolic syndrome. The increase of metabolic syndrome in Japanese OSAS patients suggests that this patient population is burdened with multiple risk factors for cardiovascular disease. (*Hypertens Res* 2006; 29: 315–322)

***Key Words*: obstructive sleep apnea, metabolic syndrome, hypertension, obesity, insulin resistance**

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder that is characterized by repeated episodes of cessation of breathing during sleep and daytime sleepiness. A recent study has suggested that OSAS affects approximately 5% of the adult population (*1*). The recent trend for an increase of obesity may also be contributing to a higher prevalence of OSAS (*2*). Patients with OSAS are reported to have various cardiovascular morbidities that negatively influence their prognosis (*3*, *4*). Because the majority of patients with OSAS are obese, conditions related to obesity, such as hypertension, insulin resistance, and dyslipidemia, may play a role in the development of cardiovascular disease in this patient population (*5*).

Metabolic syndrome is a constellation of cardiovascular risk factors that includes obesity, hypertension, insulin resistance, and dyslipidemia (*6*–*8*). Patients with metabolic syndrome have a higher risk of developing cardiac disease than persons without the syndrome (*9*). A recent report has suggested the existence of a significant relationship between OSAS and metabolic syndrome (*10*). However, there have been few investigations of the relationship between OSAS

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This work was supported in part by a Research Grant from the Suzuken Memorial Foundation of Japan (2004–2005).

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Received October 20, 2005; Accepted in revised form January 27, 2006.

Table 1. Clinical Features and Comorbidities of Men with OSAS

	AHI stratum				
	Controls AHI<5/h	Mild OSAS AHI: 5–14.9/h	Moderate OSAS AHI: 15–29.9/h	Severe OSAS AHI≥30/h	OSAS AHI≥5/h
No. of subjects	59	144	153	422	719
AHI (/h)	2.3±0.2	9.3±0.3**	21.9±0.3**	58.5±1.0**	40.9±1.0**
Mean SpO_2 (%)	97.5±0.1	96.4±0.1**	95.7±0.2**	92.3±0.2**	93.8±0.1**
Minimum SpO_2 (%)	91.8±0.4	86.1±0.5**	82.4±0.5**	72.1±0.5**	77.1±0.4**
Age (years old)	41.7±1.9	46.6±1.1*	51.5±1.1**	48.1±0.6**	48.5±0.5**
Epworth sleepiness scale	9.4±0.7	9.7±0.4	9.3±0.4	10.7±0.3	10.2±0.2
BMI (kg/m^2)	23.3±0.4	25.4±0.3**	25.5±0.3**	29.2±0.3**	27.7±0.2*
Neck circumference (cm)	37.9±0.3	39.1±0.2**	39.3±0.2**	41.9±0.6**	40.8±0.1**
Waist (cm)	84.5±1.0	89.5±0.9**	91.0±0.7**	99.6±0.6**	95.7±0.5**
Hip (cm)	95.4±0.7	98.1±0.7**	97.7±0.5	103.5±0.5**	101.2±0.3**
Waist-hip ratio	0.89±0.01	0.91±0.01*	0.99±0.01**	0.96±0.00**	0.96±0.00**
Systolic blood pressure (mmHg)	120.6±1.9	124.7±1.4	130.5±1.5**	134.8±0.8**	131.9±0.7**
Diastolic blood pressure (mmHg)	75.2±1.5	80.0±1.0**	83.1±1.1**	85.7±0.6**	84.0±0.5**
Fasting plasma glucose (mg/dl)	95.2±2.1	94.8±1.7	97.8±1.4	100.9±1.0*	99.0±0.7
Fasting insulin (μU/ml)	9.7±0.8	10.0±0.7	9.0±0.5	13.8±0.5**	12.1±0.3**
HOMA-IR	2.4±0.2	2.5±0.2	2.2±0.1	3.4±0.1**	3.0±0.1*
β-Cell function	66.9±11.4	93.8±7.4	90.3±7.2	124.6±7.0**	111.2±4.6**
T-cho (mg/dl)	190.4±4.3	198.0±2.7	201.3±2.5*	203.9±1.6**	202.2±1.2*
TG (mg/dl)	150.8±5.0	181.6±11.4	169.6±7.1	198.4±5.8**	188.9±4.4*
HDL-C (mg/dl)	49.3±1.7	50.0±1.2	48.5±1.0	46.6±0.6	47.7±0.5
LDL-C (mg/dl)	114.1±3.8	117.7±2.3	122.9±2.1*	124.6±1.4**	122.9±1.0*
Waist circumference ≥85 cm (%)	55.9	68.8	78.4**	91.2**	84.0**
Dyslipidemia (%)	45.7	56.9	61.4*	71.1**	66.2**
Hypertension (%)	40.7	50.0	64.7**	74.6**	67.6**
Fasting plasma glucose ≥110 mg/dl (%)	11.9	11.8	23.5*	27.7**	23.6*
Metabolic syndrome (%)	22.0	27.1	44.4**	59.0**	49.5**
Ischemic heart diseases (%)	1.7	0.0	3.9	2.8	2.5
Cerebrovascular diseases (%)	1.7	0.7	0.0	3.1	2.1

OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index; BMI, body mass index; HOMA-IR, homeostasis model assessment for estimating insulin resistance; T-cho, serum total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Ischemic heart diseases: angina pectoris, myocardial infarction; cerebrovascular diseases: cerebral infarction, brain ischemia, intracranial embolism and thrombosis, intracranial hemorrhages. Data are presented as the mean±SEM. Dyslipidemia was defined as TG ≥150 mg/dl or HDL-C <40 mg/dl. Hypertension was defined as a systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg. *$p<0.05$, **$p<0.01$ *vs*. controls.

and metabolic syndrome among Asians. We hypothesized that OSAS may be associated with an increase of the risk factors comprising the metabolic syndrome in Japanese as is the case for Caucasians. Accordingly, we investigated clinical features related to metabolic syndrome in a large Japanese population with OSAS.

Methods

Patients

We enrolled all of the patients diagnosed as having OSAS based on overnight polysomnography at the Sleep Disorders Center, Aichi Medical University Hospital. The diagnosis of OSAS was based on the recognized criteria (*11*), including an apnea-hypopnea index (AHI) ≥5/h and pathological daytime sleepiness. The Epworth sleepiness scale was used to quantify subjective daytime sleepiness (*12*). We excluded patients who had congestive heart failure, intrinsic pulmonary disease, and intrinsic renal or liver disease. As a result, there were 819 patients with a definite diagnosis of OSAS.

These patients were divided into three groups based on the severity of OSAS (*11*), *i.e.*, a mild OSAS (AHI: 5–14.9/h), moderate OSAS (AHI: 15–29.9/h), and severe OSAS (AHI: ≥30/h) group.

Table 2. Clinical Features and Comorbidities of Women with OSAS

	AHI stratum				
	Controls AHI < 5/h	Mild OSAS AHI: 5–14.9/h	Moderate OSAS AHI: 15–29.9/h	Severe OSAS AHI ≥ 30/h	OSAS AHI ≥ 5/h
No. of subjects	30	35	25	40	100
AHI (/h)	1.8±0.3	9.6±0.5**	21.2±0.8**	64.2±3.9**	34.4±2.9**
Mean SpO_2 (%)	97.4±0.2	96.7±0.2**	96.3±0.2**	93.0±0.5**	95.1±0.3**
Minimum SpO_2 (%)	90.4±1.0	86.9±0.6**	80.4±1.6**	71.6±1.7**	79.2±1.1**
Age (years old)	44.4±2.7	50.1±2.1	59.6±2.1**	54.2±2.3**	54.1±1.3**
Epworth sleepiness scale	10.8±1.1	9.2±1.0	7.3±1.0*	10.0±0.9	9.1±0.6
BMI (kg/m^2)	23.9±1.1	25.9±1.0	24.4±0.9	31.5±1.4**	27.8±0.7*
Neck circumference (cm)	32.9±0.4	34.5±0.5*	34.0±0.6	37.7±0.7**	35.7±0.4**
Waist (cm)	80.2±2.6	89.9±2.3**	85.9±2.4	101.1±2.6**	93.4±1.6**
Hip (cm)	93.5±1.6	98.5±1.7*	94.4±1.7	105.4±2.6**	100.2±1.3**
Waist-hip ratio	0.85±0.02	0.91±0.02*	0.91±0.02*	0.96±0.02**	0.93±0.01**
Systolic blood pressure (mmHg)	111.1±3.1	117.5±3.6	127.9±4.1**	133.6±2.8**	126.5±2.1**
Diastolic blood pressure (mmHg)	69.8±1.7	75.5±1.7*	80.2±1.9**	82.2±2.5**	79.3±1.3**
Fasting plasma glucose (mg/dl)	90.7±1.8	95.4±2.2	104.3±6.0*	103.4±4.8*	100.9±2.6*
Fasting insulin (μU/ml)	7.8±0.6	9.6±1.0	9.5±1.0	14.7±1.3**	11.6±0.7**
HOMA-IR	1.7±0.2	2.3±0.3	2.6±0.4*	4.0±0.4**	3.0±0.2**
β-Cell function	103.6±8.7	112.8±12.0	93.5±11.8	146.5±10.6**	120.8±6.9
T-cho (mg/dl)	188.4±6.3	214.6±6.4**	203.7±7.0	202.6±4.8	207.1±3.4*
TG (mg/dl)	83.5±6.3	171.7±17.0**	129.7±10.1**	168.7±18.4**	160.0±9.9**
HDL-C (mg/dl)	60.8±2.1	56. 5±2.7	59.0±2.7	51.4±2.1**	55.1±1.5*
LDL-C (mg/dl)	112.5±5.6	127.5±5.2	120.1±6.3	121.7±3.8	123.3±2.8
Waist circumference ≥90 cm (%)	26.7	51.4*	28.0	75.0**	55.0**
Dyslipidemia (%)	26.7	60.0**	48.0	65.0**	59.0**
Hypertension (%)	26.7	34.3	48.0	80.0**	56.0**
Fasting plasma glucose ≥110 mg/dl (%)	13.3	17.1	16.0	25.0	20.0
Metabolic syndrome (%)	6.7	20.0	20.0	50.0**	32.0**
Ischemic heart diseases (%)	0.0	2.8	4.0	2.5	3.0
Cerebrovascular diseases (%)	0.0	0.0	0.0	5.0	2.0

OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index; BMI, body mass index; HOMA-IR, homeostasis model assessment for estimating insulin resistance; T-cho, serum total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Ischemic heart diseases: angina pectoris, myocardial infarction; cerebrovascular diseases: cerebral infarction, brain ischemia, intracranial embolism and thrombosis, intracranial hemorrhages. Data are presented as the mean±SEM. Dyslipidemia was defined as TG ≥150 mg/dl or HDL-C<40 mg/dl. Hypertension was defined as a systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg. *$p<0.05$, **$p<0.01$ *vs*. controls.

Control Group

Eighty-nine control subjects with an AHI < 5/h were enrolled. 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, including 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, USA). The sleep record was analyzed manually according to the criteria of Rechtshaffen and Kales using a 30-s epoch (*13*). The hourly number of episodes of apnea plus hypopnea combined was defined as the AHI and was calculated as an indicator of the severity of OSAS (*11*).

Measurements

We measured the height and weight of all patients at the time of referral to the Sleep Disorders Center. Then the body mass

Table 3. Medications Used by Men with OSAS and Controls on Presentation

Medications (*n* (%))	Controls AHI<5/h	Mild OSAS AHI: 5–14.9/h	Moderate OSAS AHI: 15–29.9/h	Severe OSAS AHI≥30/h	OSAS AHI≥5/h
α_1-Blockers	2 (3.4)	5 (3.5)	5 (3.3)	15 (3.6)	25 (3.5)
β-Blockers	4 (6.8)	7 (4.9)	6 (3.9)	19 (4.5)	32 (4.5)
Calcium channel blockers	7 (11.9)	22 (15.3)	29 (19.0)	54 (12.8)	105 (14.6)
ACE-I, ARB	8 (13.6)	13 (9.0)	19 (12.4)	34 (8.1)	66 (9.2)
Cholesterol reducers: statin	3 (5.1)	11 (7.6)	15 (9.8)	20 (4.7)	46 (6.4)
Triglyceride reducers	3 (5.1)	3 (2.1)	5 (3.3)	10 (2.4)	18 (2.5)
Diuretics	2 (3.4)	2 (1.4)	2 (1.3)	8 (1.9)	12 (1.7)
Hypoglycemic agents	5 (8.5)	2 (1.4)*	7 (4.6)	23 (5.5)	32 (4.5)
Insulin	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.5)	3 (0.4)

OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers. *$p<0.05$ *vs*. controls.

index (BMI) was calculated to quantify the severity of obesity. The neck circumference was measured at the level of the laryngeal prominence while the subject was standing. Waist girth, which was measured at the level of the navel, and standing hip girth were also measured with the subject standing.

Blood Pressure

Blood pressure was measured twice between the hours of 10 and 12 AM with the subject in the supine position after a 5-min rest. An automated oscillometric digital blood pressure monitor (ES-H51; Terumo Corporation, Tokyo, Japan) was used.

Laboratory Tests

All subjects underwent blood tests after an overnight fast on the morning after polysomnography. The fasting blood glucose level was measured by an HK G-6-PDH assay using an H-7700 autoanalyzer (Hitachi, Tokyo, Japan) and the plasma insulin concentration was quantified by an FEIA assay using an AIA1800 analysis machine (Toso, Tokyo, Japan). Insulin resistance was estimated by the homeostasis model assessment method (HOMA-IR) and β-cell function was assessed as described elsewhere (*14*, *15*). Serum cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured by enzyme assays using the H-7700 autoanalyzer (Hitachi).

Diagnosis of Metabolic Syndrome

The definition and diagnosis of metabolic syndrome were based on the published criteria for the Japanese population (*16*). A diagnosis of metabolic syndrome was made if the patient had a waist circumference ≥85 cm for men or ≥90 cm for women and two or more of the following risk factors: 1) triglycerides ≥150 mg/dl or HDL cholesterol <40 mg/dl; 2) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; 3) fasting plasma glucose ≥110 mg/dl. Patients who had previously been diagnosed as having dyslipidemia, hypertension, or diabetes mellitus and were on medications for any of these conditions were also included in the relevant category.

Statistical Analysis

The prevalence of each component of the metabolic syndrome and various other clinical features was compared between the patients and the controls using the Kruskal-Wallis test, Welch's test or the χ^2 test. Continuous variables were expressed as the mean±SEM. The prevalence odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the association of metabolic syndrome with OSAS. A logistic regression was also performed to determine the independent associations of metabolic syndrome with OSAS, adjusting for age and BMI. Significance of differences was accepted at $p<0.05$ or $p<0.01$. All statistical analyses were done with StatView software Version 5.0 (SAS Institute, Cary, USA).

Results

Clinical Profile

A total of 819 patients with OSAS (719 men and 100 women) and 89 control subjects (59 men and 30 women) were enrolled in this study. The characteristics of these groups are presented in Tables 1 and 2. The OSAS patients were significantly older than the controls of both genders at the time of referral 48.5±0.5 years *vs*. 41.7±1.9 years for men ($p<0.01$) and 54.1±1.3 years *vs*. 44.4±2.7 years for women ($p<0.01$). The mean BMI of the OSAS patients was greater than that of the controls 27.7±0.2 kg/m^2 *vs*. 23.3±0.4 kg/m^2 for men ($p<0.01$) and 27.8±0.7 kg/m^2 *vs*. 23.9±1.1 kg/m^2 for women ($p<0.05$). Waist circumference was also larger in the OSAS group than in the controls 95.7±0.5 cm *vs*. 84.5±1.0 cm for men ($p<0.01$) and 93.4±1.6 cm *vs*. 80.2±2.6 cm for women

Table 4. Medications Used by Women with OSAS and Controls on Presentation

Medications (*n* (%))	Controls AHI<5/h	Mild OSAS AHI: 5–14.9/h	Moderate OSAS AHI: 15–29.9/h	Severe OSAS AHI≥30/h	OSAS AHI≥5/h
α_1-Blockers	1 (3.3)	0 (0.0)	0 (0.0)	2 (5.0)	2 (2.0)
β-Blockers	0 (0.0)	2 (5.7)	0 (0.0)	3 (7.5)	5 (5.0)
Calcium channel blockers	3 (10.0)	3 (8.6)	4 (16.0)	12 (30.0)	19 (19.0)
ACE-I, ARB	4 (13.3)	5 (14.3)	2 (8.0)	9 (22.5)	16 (16.0)
Cholesterol reducers: statin	1 (3.3)	5 (14.3)	2 (8.0)	5 (12.5)	12 (12.0)
Triglyceride reducers	1 (3.3)	1 (2.9)	0 (0.0)	1 (2.5)	2 (2.0)
Diuretics	0 (0.0)	2 (5.7)	0 (0.0)	1 (2.5)	3 (3.0)
Hypoglycemic agents	0 (0.0)	1 (2.9)	0 (0.0)	1 (2.5)	2 (2.0)
Insulin	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.0)

OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

($p<0.01$). However, there was no significant difference of subjective daytime sleepiness, which was quantified using the Epworth sleepiness scale, for subjects of either gender. There were no differences between the proportion of cases and controls who had been diagnosed with having ischemic heart diseases or cerebrovascular diseases in either gender.

Medications used by patients with OSAS and controls on referral are presented in Tables 3 and 4. At the time of presentation at the Sleep Disorders Center, there were no differences in drug use between women with OSAS and controls. In contrast, men with mild OSAS were less likely to be treated with hypoglycemic agents than controls.

Features of OSAS

Among the men with OSAS, there were 144 mild cases, 153 moderate cases, and 422 severe cases, while the women with OSAS comprised 35 mild cases, 25 moderate cases, and 40 severe cases. Patients with OSAS had more severe hypoxia than the controls during sleep, based on the mean SpO_2 in sleep 93.8±0.1% *vs*. 97.5±0.1% for men ($p<0.01$) and 95.1±0.3% *vs*. 97.4±0.2% for women ($p<0.01$). The minimum SpO_2 was lower in the OSAS group than in the control group 77.1±0.4% *vs*. 91.8±0.4% for men ($p<0.01$) and 79.2±1.1% *vs*. 90.4±1.0% for women ($p<0.01$). The OSAS patients also had more severe hypoxia than the controls during sleep in the subgroups classified by AHI values (Tables 1 and 2).

Components of the Metabolic Syndrome

In the men with OSAS, a waist circumference ≥85 cm was more common than in the male controls (84.0% *vs*. 55.9%, $p<0.01$) (Table 1). In the women with OSAS, a waist circumference ≥90 cm was more common than in the female controls (55.0% *vs*. 26.7%, $p<0.01$) (Table 2). Hypertension was more common in both the male and female patients with OSAS than the respective control groups 67.6% *vs*. 40.7% for men ($p<0.01$) and 56.0% *vs*. 26.7% for women ($p<0.01$). The prevalence of dyslipidemia was higher in OSAS patients than in the controls 66.2% *vs*. 45.7% for men ($p<0.01$) and 59.0% *vs*. 26.7% for women ($p<0.01$). Men with OSAS were more likely to have a fasting glucose level ≥110 mg/dl than the male controls (23.6% *vs*. 11.9%, $p<0.01$), but the frequency of a fasting glucose level ≥110 mg/dl did not differ between the women with OSAS and the female controls. Insulin resistance, as determined by HOMA-IR, was significantly increased in the OSAS patients compared with the controls.

Prevalence of Metabolic Syndrome

The prevalence of metabolic syndrome was higher in the patients with OSAS than in the controls 49.5% *vs*. 22.0% for men ($p<0.01$) and 32.0% *vs*. 6.7% for women ($p<0.01$) (Tables 1 and 2). In the severe OSAS group, 59.0% of the men had metabolic syndrome, as did 50.0% of the women.

The Association of Metabolic Syndrome with Obstructive Sleep Apnea Syndrome

The men with OSAS were more likely to have metabolic syndrome compared with the male controls (OR 3.47; 95% CI: 1.84–6.53) (Table 5). There was a significantly higher risk of metabolic syndrome in men with moderate OSAS (OR 2.83; 95% CI: 1.42–5.66), as well as men with severe OSAS (OR 5.09; 95% CI: 2.67–9.71). Women with OSAS also had a higher risk of metabolic syndrome (OR 6.59; 95% CI: 1.47–29.38), but only those with severe OSAS had a significantly increased risk (OR 14.00; 95% CI: 2.93–66.82).

Risk factors for metabolic syndrome differed between men and women. In men, age, BMI, and OSAS (AHI≥15/h) were independently associated with metabolic syndrome (Table 6). In contrast, BMI was the only risk factor for metabolic syndrome in women.

Table 5. Odds Ratios for Diagnosis of Metabolic Syndrome in OSAS Patients Stratified by Gender and AHI

AHI (/h)	Men		Women	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
<5	1.00	—	1.00	—
≥5	3.47 (1.84–6.53)	<0.05	6.59 (1.47–29.38)	<0.05
5–14.9	1.31 (0.64–2.69)	NS	3.50 (0.67–18.35)	NS
15–29.9	2.83 (1.42–5.66)	<0.05	3.50 (0.62–19.89)	NS
≥30	5.09 (2.67–9.71)	<0.05	14.00 (2.93–66.82)	<0.05

OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index; OR, odds ratio; CI, confidence interval.

Table 6. Risk Factors for Metabolic Syndrome

	Men		Women	
	OR* (95% CI)	*p* value	OR* (95% CI)	*p* value
Age (years)	1.04 (1.02–1.05)	<0.0001	1.03 (0.99–1.07)	NS
BMI (kg/m^2)	1.19 (1.14–1.24)	<0.0001	1.18 (1.09–1.28)	<0.0001
OSAS (AHI≥15/h)	2.08 (1.41–3.06)	<0.001	2.24 (0.84–5.99)	NS

*Adjusted odds ratio was obtained from logistic regression. AHI, apnea-hypopnea index; BMI, body mass index; OSAS, obstructive sleep apnea syndrome; OR, odds ratio; CI, confidence interval.

Discussion

To our knowledge, this is the first study that has investigated the prevalence of metabolic syndrome in Japanese patients with OSAS using the new criteria for diagnosis of metabolic syndrome in the Japanese population (*16*). We found that patients with OSAS were more likely to suffer from metabolic syndrome than controls who presented to the sleep disorders center but were not found to have OSAS. OSAS has been reported to cause various metabolic abnormalities (*17*), and a previous study has also supported the notion of a high prevalence of metabolic abnormalities in patients with OSAS (*18*). A study performed in the United Kingdom (*10*) estimated that 87% of patients with OSAS had metabolic syndrome, which was a higher percentage than in our series (49.5% for men and 32.0% for women). The mean BMI of patients with OSAS was 35.8±0.9 kg/m^2 in the study performed by Coughlin *et al*. (*10*), which was larger than the mean value in our series. A difference of the mean BMI between Japanese and Caucasians with OSAS may thus have contributed to the reported difference in the prevalence of metabolic syndrome.

We also found that hypertension was more common in our patients with OSAS than in the controls. Millman *et al*. reported that the prevalence of hypertension was 45% in patients with OSAS (*19*). OSAS patients may show an increased prevalence of hypertension at least partly because age and BMI are independent predictors for a higher risk of hypertension. Hypertension has been reported to be the most common component of the metabolic syndrome and the greatest contributor to carotid arteriosclerosis in the Japanese population (*20*). Several groups also reported that hypertension negatively affects cardiac functions and atherosclerosis, thereby contributing to the development of cardiovascular events (*21–25*). Thus, our data may suggest that blood pressure should be controlled to reduce the risk of metabolic syndrome in patients with OSAS.

Recurrent episodes of apnea and hypopnea during sleep cause hypoxemia, arousal, and an increase of sympathetic activity, which has been hypothesized to subsequently increase the daytime blood pressure in OSAS patients (*3*). The Wisconsin Sleep Cohort Study showed a linear increase of both systolic and diastolic blood pressure with increasing AHI (*26*). The Sleep Heart Health Study also demonstrated that the mean systolic and diastolic blood pressure, as well as the prevalence of hypertension, increased significantly with an increase of AHI (*27*). Thus, two large-scale studies that assessed the association of hypertension with AHI found a positive relationship between OSAS and hypertension. In the present study, the prevalence of hypertension increased along with the severity of OSAS in both male and female patients. Tanigawa *et al*. found a significant association of nocturnal oxygen desaturation with high blood pressure among Japanese subjects (*28*), so recurrent episodes of apnea and hypoxia during sleep may contribute to an increase in the prevalence of hypertension among patients with OSAS.

Our patients with OSAS were also more likely to have insulin resistance and dyslipidemia than the controls without OSAS. OSAS has been reported to show an association with the development of type 2 diabetes mellitus, which is thought to be due to increased insulin resistance, and this association was independent of obesity (*17*). However, insulin resistance is strongly associated with obesity, which is common in

OSAS patients. Stoohs *et al*. reported that the association between OSAS and insulin resistance was related to the effect of obesity rather than to any influence of OSAS itself (*29*). In contrast, Ip *et al*. demonstrated that insulin resistance (assessed by HOMA-IR) was significantly predicted by three factors, *i.e.*, BMI, AHI, and minimum SpO_2 (*30*). Another study has shown that an AHI≥5/h is associated with an increased risk of impaired glucose tolerance (OR 2.15; 95% CI: 1.05–4.38) after adjusting for BMI and the percent body fat (*31*). These two studies support the contention that OSAS is positively associated with insulin resistance, with the relationship being independent of obesity. In the present study, an independent relationship between OSAS and insulin resistance was not documented, but both OSAS and obesity may have contributed to the higher prevalence of insulin resistance in our OSAS patients than in the controls. The reason why dyslipidemia is increased in OSAS patients remains unclear, but Li *et al*. recently reported that exposure to intermittent hypoxia for 5 days caused an increase of the serum cholesterol level in mice (*32*). Hypoxia due to OSAS may have an adverse influence on lipid metabolism, but the actual mechanism leading to an increased prevalence of dyslipidemia in patients with OSAS will need to be clarified in the future.

For whatever reason, metabolic syndrome appears to be more common in patients with OSAS than in persons without OSAS. We found that risk factors for metabolic syndrome were age, BMI, and OSAS in men; while BMI was the only risk factor for metabolic syndrome in women. The following limitations and methodological issues of the study should be mentioned. The patients with OSAS showed some differences from our control group, since the OSAS patients were more obese and were older. Recently, Lam *et al*. reported that OSAS was independently associated with age, BMI, and metabolic syndrome (*33*). Thus, the prevalence of metabolic syndrome in the OSAS patients may have been overestimated because age and BMI also influence the development of hypertension, insulin resistance, and dyslipidemia. In addition, the number of women in our study was small, which may have influenced the statistical power of our determination of an independent association between metabolic syndrome and OSAS. Another large-scale study using age- and BMI-matched controls is needed to clarify the relationship between OSAS and metabolic syndrome among Asians.

In conclusion, metabolic syndrome was very common in patients with OSAS who were referred to a tertiary university–based medical center in Japan. Accordingly, it seems reasonable for clinicians to include assessment of metabolic syndrome in the evaluation of patients with OSAS, since these patients may also require treatment for obesity, hypertension, diabetes, and dyslipidemia.

Acknowledgements

We are indebted to Professor Takayuki Ito, Ms. Masako Katada, Ms. Maki Okada, Ms. Aki Arita, Ms. Chihiro Kato, and Mr. Asao Ito for their important contributions to the present study.

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