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Relationship between the severity of obstructive sleep apnea and impaired glucose metabolism in patients with obstructive sleep apnea

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Summary
Background: The relationship between the severity of obstructive sleep apnea (OSA) and impaired glucose metabolism (IGM) has not yet been fully elucidated in patients with OSA. Accordingly, we sought to clarify this relationship in Japanese patients with OSA.
Methods: The study population consisted of 129 Japanese patients with OSA (apnea-hypopnea index [AHI] $\geq$5). A 75-g oral glucose tolerance test was performed in all patients who had not been diagnosed as diabetes mellitus (DM). IGM was defined as either diabetes mellitus (DM) or impaired glucose tolerance (IGT).
Results: IGM was observed in 78 (60.5%) patients: DM in 39 (30.2%) and IGT in 39 (30.2%). The frequency of IGM was significantly different among patients with AHI $\geq$30, those with 15 $\leq$ AHI $<$ 30, and those with AHI $<$15 (72.1%; 53.7%; 35.0%; respectively, $p = 0.001$). Univariate logistic regression analyses showed male sex, the BMI, the AHI, and the lowest SpO_2 to be significantly associated with IGM. A stepwise multivariate logistic regression analysis showed a male sex and the AHI to be independently associated with IGM.
Conclusion: IGM was observed in 60.5% of Japanese patients with OSA (AHI $\geq$5), and the prevalence of IGM increased according to the severity of OSA. Furthermore, the AHI was independently associated with IGM, thus suggesting that OSA may contribute to the development of IGM.

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway collapse during sleep. Previous studies have shown that OSA is associated with insulin resistance,[1–9] which thus plays an important role in the

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development of impaired glucose metabolism (IGM), although some conflicting results exist with regard to this association.[10,11] There has so far only been one paper[12] investigating the exact prevalence of IGM evaluated by a 75-g oral glucose tolerance test in patients with OSA. In the study, Meslier et al.[12] reported that impaired glucose tolerance (IGT) and diabetes mellitus (DM) were observed in 20.0% of and 30.1% of 494 French men with OSA (apnea-hypopnea index [AHI] $\geq$10), respectively. However, the relationship between the severity of OSA and IGM has not yet been fully elucidated in patients with OSA. In this study, we examined this relationship in Japanese patients with OSA.

Materials and methods

Patients

Between April 2006 and September 2007, there were 137 consecutive Japanese patients who underwent overnight polysomnography for clinically suspected OSA at our hospitals and who did not meet the following exclusion criteria. The exclusion criteria were signs or symptoms of congestive heart failure, left ventricular ejection fraction <55%, previous cerebrovascular diseases, neurological diseases, or chronic respiratory diseases. Of 137 patients, eight patients had the AHI <5. Finally, 129 patients (110 men and 19 women, median age of 63 years) who were diagnosed to have OSA (AHI $\geq$5) were analyzed. No patients with type 1 DM were included in the present study. The patients were divided into the following three groups based on the AHI: patients with AHI $\geq$30 (group A, $n = 68$), those with $15 \leq$ AHI < 30 (group B, $n = 41$), and those with AHI <15 (group C, $n = 20$). Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg. Dyslipidemia was defined as serum low-density lipoprotein cholesterol level $\geq$3.6 mmol/l [140 mg/dl], high-density lipoprotein cholesterol level <1.0 mmol/l [40 mg/dl], or triglyceride level $\geq$1.7 mmol/l [150 mg/dl]. Coronary artery disease was defined as luminal diameter stenosis of $\geq$75% in at least one of the coronary arteries on coronary angiography, previous myocardial infarction, previous coronary revascularization therapy, or vasospastic angina pectoris confirmed by a methyl-ergonovine or acetylcholine provocation test. The study protocol was approved by the ethics committee at our institution, and informed consent was obtained from each patient before the study.

Oral glucose tolerance test

A 75-g oral glucose tolerance test was performed in 102 patients (79.1%) who had not been diagnosed to have DM. The patients were considered to have DM if they had a fasting plasma glucose level $\geq$7 mmol/l [126 mg/dl] and/or a plasma glucose level $\geq$11.1 mmol/l [200 mg/dl] at 2 h after the glucose load. IGT was defined as a plasma glucose level of $\geq$7.7 mmol/l [140 mg/dl] and <11.1 mmol/l [200 mg/dl] at 2 h after the glucose load. IGM was defined as either DM or IGT.

Overnight polysomnography

Overnight polysomnography was performed using a computerized system (E-series, Compumedics, Abbotsford, Australia). This investigation consisted of monitoring of the electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, thoraco-abdominal excursions, oronasal airflow by an airflow pressure transducer, and arterial oxygen saturation (SpO_2) by pulse oximetry. The polysomnography was manually evaluated by an experienced physician. Central apnea was defined as an absence of oronasal airflow during sleep for $\geq$10 s associated with absent respiratory effort. An obstructive apnea was defined as an absence of oronasal airflow for $\geq$10 s in the presence of out-of-phase thoraco-abdominal effort. A hypopnea was defined as a $\geq$50% reduction in oronasal airflow for $\geq$10 s, associated with a $\geq$3% fall in SpO_2. The AHI was calculated as the mean number of apneas and hypopneas per hour of sleep. In addition, the central or obstructive apnea index was calculated as the mean number of central or obstructive apneas, respectively. As obstructive hypopneas can not be easily distinguished from central hypopneas, we did not calculate the central or obstructive hypopnea index.

Statistical analysis

Continuous data are expressed as mean $\pm$ SD or median (first to third quartiles), and categorical data are expressed as number (%). Comparisons of categorical data among the three groups were analyzed by the Fisher's exact or chi-square test. One-factor analysis of variance with Scheffe's post hoc test was used for comparisons of normally distributed continuous data. When continuous data were not normally distributed, the Kruskal-Wallis test with the Scheffe's post hoc test was used. Univariate and multivariate logistic regression analyses were performed to determine the factors associated with IGM. A p value <0.05 was considered to be statistically significant. All analyses were performed using the SPSS 12.0J software package for Windows (SPSS Inc, Tokyo, Japan).

Results

The patient characteristics are shown in Table 1. The BMI was significantly greater in group A (27.3 ± 4.1 kg/m^2) than in groups B (25.1 ± 2.9 kg/m^2, $p < 0.05$) and C (23.7 ± 2.7 kg/m^2, $p < 0.05$). There were no significant differences in age, body height, gender, frequency of hypertension, hyperlipidemia, current smoking, or coronary artery disease, and medications, such as antihypertensive drugs and statins, among the three groups.

The overnight polysomnographic findings are shown in Table 2. The total sleep time was significantly shorter in group A (369 ± 110 min) than in group C (446 ± 108 min, $p < 0.05$). The obstructive apnea index, central apnea index, and total time of $SpO_2 < 90\%$ were significantly greater in group A than in groups B ($p < 0.05$) and C ($p < 0.05$). The lowest SpO_2 was significantly lower in group A than in groups B ($p < 0.05$) and C ($p < 0.05$).

Fig. 1 shows the prevalence of IGM among the three groups. IGM was observed in 78 (60.5%) patients: DM in 39 (30.2%) and IGT in 39 (30.2%). The prevalence of IGM

Table 1 Patient characteristics.

Variables	Group A ($n = 68$)	Group B ($n = 41$)	Group C ($n = 20$)
Age, yrs	63.5 (50.0–72.8)	68.0 (56.0–73.0)	54.5 (37.3–69.0)
Men	62 (91.2)	33 (80.5)	15 (75)
Body height, cm	166 ± 6.8	163 ± 9.8	163 ± 9.7
BMI, kg/m^2	27.3 ± 4.1*	25.1 ± 2.9	23.7 ± 2.7
Hypertension	50 (73.5)	34 (82.9)	12 (60)
Dyslipidemia	49 (72.1)	30 (73.2)	12 (60)
Current smoker	15 (22.1)	10 (24.4)	4 (20)
Coronary artery disease	10 (14.7)	14 (34.1)	3 (15)
Medications			
Diuretics	7 (10.2)	6 (14.6)	3 (15)
Ca antagonists	37 (53.6)	24 (34.8)	8 (11.6)
α blockers	8 (11.8)	4 (9.8)	2 (10)
β blockers	11 (16.2)	15 (36.6)	5 (25)
ACEI/ARB	31 (45.6)	22 (53.7)	6 (30)
Statins	19 (27.9)	15 (36.6)	3 (15)

Data are presented as the means ± SD, medians (first to third quartiles) or No. (%).
BMI = body mass index; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II type 1 receptor blockers.
Group A = patients with AHI ≥30; group B = those with 15 ≤ AHI <30; group C = those with AHI <15.
*$p < 0.05$ vs. groups B and C.

differed significantly among the three groups (group A, 72.1%; group B, 53.7%; group C, 35.0%; $p = 0.001$).

Univariate logistic regression analyses showed a male sex, the BMI, AHI, and the lowest SpO_2 to be significantly associated with IGM (Table 3). Table 4 shows the results of a multivariate logistic regression analysis performed to determine independent factors of IGM. Since the lowest SpO_2 correlated strongly with the AHI ($r = 0.77$, $p < 0.001$), the lowest SpO_2 was not included in this analysis. A multivariate logistic regression analysis showed a male sex and the AHI to be independently associated with IGM (odds ratio 4.48 [95% CI 1.44–13.9] and odds ratio 1.03 [95% CI 1.01–1.05], respectively) (Table 4). When the lowest SpO_2 was used as an independent variable instead of the AHI, a multivariate logistic regression analysis showed a male sex and the lowest SpO_2 were independently associated with IGM (odds ratio 6.45 [95% CI 1.96–21.5] and odds ratio 0.91 [95% CI 0.85–0.96], respectively).

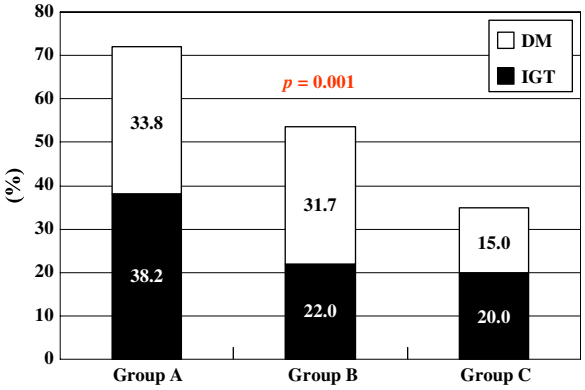

Figure 1 The prevalence of impaired glucose metabolism. Group A = patients with AHI ≥30; group B = those with 15 ≤ AHI < 30; group C = those with AHI <15; IGT = impaired glucose tolerance; DM = diabetes mellitus; $p = 0.001$ among the three groups.

Discussion

In the present study, IGM was observed in 60.5% of Japanese patients with OSA (AHI ≥5). This prevalence is obviously

Table 2 Overnight polysomnographic findings.

Variables	Group A ($n = 68$)	Group B ($n = 41$)	Group C ($n = 20$)
Sleep period time, min	555±80	535±95	546±103
Total sleep time, min	369±110**	401±101	446±108
AHI	53.8 (41.9–65.3)*	22.1 (18.7–25.2)**	8.4 (7.0–11.8)
Obstructive apnea index	18.5 (11.0–37.9)*	3.7 (2.1–7.2)	0.8 (0.03–2.3)
Central apnea index	0.9 (0.0–3.0)*	0.2 (0.0–0.7)	0.0 (0.0–0.2)
Lowest SpO_2, %	77.4±7.8*	84.6±5.2	88.7±4.0
Total time of SpO_2 <90% during sleep, min	19.2 (5.7–46.9)*	1.9 (0.3–7.4)	0.05 (0.0–1.0)

Data are presented as the means ± SD or medians (first to third quartiles).
AHI = apnea-hypopnea index; SpO_2 = arterial oxygen saturation.
*$p < 0.05$ vs. groups B and C, **$p < 0.05$ vs. group C.

Table 3 Univariate logistic regression analysis to determine factors related to IGM.

Variables	Odds (95% CI)	p value
Age, yrs	1.01 (0.99–1.04)	0.39
Male (0 = no, 1 = yes)	5.52 (1.85–16.5)	0.002
BMI, kg/m^2	1.16 (1.04–1.29)	0.009
Hypertension (0 = no, 1 = yes)	1.64 (0.74–3.65)	0.23
Dyslipidemia (0 = no, 1 = yes)	1.84 (0.86–3.97)	0.12
Current smoker (0 = no, 1 = yes)	1.09 (0.47–2.55)	0.84
Coronary artery disease (0 = no, 1 = yes)	0.94 (0.40–2.23)	0.89
AHI	1.03 (1.01–1.05)	0.001
Lowest SpO_2, %	0.92 (0.87–0.97)	0.04
Time of SpO_2 <90%, min	1.01 (0.99–1.02)	0.08
Diuretics (0 = no, 1 = yes)	0.61 (0.22–1.76)	0.36
Ca antagonists (0 = no, 1 = yes)	1.04 (0.51–2.10)	0.92
α blocker (0 = no, 1 = yes)	1.73 (0.51–5.84)	0.38
β blockers (0 = no, 1 = yes)	1.25 (0.52–2.90)	0.60
ACEI/ARB (0 = no, 1 = yes)	1.40 (0.68–2.86)	0.36

Abbreviations are the same as in Tables 1 and 2.
CI = confidence interval.

Table 4 Stepwise multivariate logistic regression analysis to determine the independent factors related to IGM.

Variables	Odds (95% CI)	*p* value
Male (0 = no, 1 = yes)	4.48 (1.44–13.9)	0.01
AHI	1.03 (1.01–1.05)	0.003

Abbreviations are the same as in Tables 1–3.

higher than the expected prevalence of IGM in the general population of Japanese adults: a large-population study reported that the prevalence of IGM evaluated by a 75-g oral tolerance test was 20.4% in 2,534 Japanese aged >40 years.[13] Meslier et al.[12] reported IGM to be observed in 50.1% of 494 French men with OSA (AHI ≥10). In the present study, the prevalence of IGM was 69% in 100 men with an AHI ≥10. This prevalence is significantly higher than the prevalence of IGM ($p < 0.001$) in the study by Meslier et al.[12] This difference might be due to patient selection. In the present study, of 100 men with an AHI ≥10, 62 (62%) had severe OSA (AHI ≥30). On the other hand, in the study of Meslier et al., the prevalence of severe OSA was 52.8% of 494 men with an AHI ≥10. Since the present study indicates that the AHI is an independent factor for IGM, the high prevalence of IGM in the present study is likely to contribute, at least partly, to the high prevalence of severe OSA. Alternatively, there might be a stronger association of OSA with IGM in Japanese patients with OSA than in Caucasian patients with OSA.

Since IGM is a well-established risk factor for future cardiovascular diseases,[13–17] a high prevalence of IGM in patients with OSA and a significant association between the severity of OSA and IGM may therefore, at least partly, explain why patients with OSA are at high risk for cardiovascular events.[18–25]

Although our study naturally cannot clarify the causality between OSA and IGM, there are several lines of evidence that support a causal relationship between the both. First, the activation of the sympathetic nervous system, which is observed in patients with OSA,[26–30] could impair glucose homeostasis by increasing glycogen breakdown and gluconeogenesis. Second, sleep loss and sleep deprivation accompanied by OSA could cause IGM through the activation of the sympathetic nervous system as well as the activation of the hypothalamic-pituitary-adrenal axis.[31–33] Third, recurrent intermittent hypoxia caused by OSA could directly cause IGM.[34–38] Experimental data in humans have shown that exposure to high altitude or hypobaric hypoxia acutely impairs insulin sensitivity.[36,38] OSA-associated hypoxia and hypoxia/reoxygenation increases the production of reactive oxygen species and also activates redox-sensitive transcription factors including nuclear factor kappa B, thus resulting in an increased production/release of tumor necrosis factor-α,[39,40] which thus plays an important role in the development of insulin resistance.[41,42] In the present study, the lowest SpO_2 also was independently associated with IGM. This result supports that hypoxia caused by OSA could contribute to the development of IGM. Fourth, obesity, a major risk factor for IGM as well as OSA, may also contribute to the high prevalence of IGM in patients with OSA, although the multivariate logistic regression analysis did not identify the BMI as an independent factor for IGM in the present study. Since the BMI is lower in Japanese patients with OSA than in Caucasian patients with OSA,[43] the result may not apply to Caucasian patients with OSA.

The present study has a few certain limitations. First, the sample size of the present study was relatively small. Therefore, further studies with a larger population are needed to confirm our results. Second, it cannot be perfectly denied that the high prevalence of IGM in the present study might be due to the selection bias. In addition, in the present study, there were several exclusion criteria, and the frequencies of hypertension and dyslipidemia were fairly higher. Therefore, the prevalence of IGM in the present study may not represent that in the general Japanese population with OSA. Third, the present study included patients who were treated with diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, α blockers, and β blockers, all of which could possibly affect the glucose metabolism. However, a multivariate logistic regression analysis did not identify these drugs as independent factors for IGM.

In conclusion, IGM was observed in 60.5% of Japanese patients with OSA (AHI ≥5), and the prevalence of IGM was found to increase according to the severity of OSA. Furthermore, the AHI was independently associated with IGM, thus suggesting that OSA may contribute to the development of IGM.

Conflict of interest statement

All authors have no conflicts to disclose.

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