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Characteristics of sleep-disordered breathing in Japanese patients with type 2 diabetes mellitus

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Abstract

Sleep-disordered breathing (SDB), especially sleep apnea-hypopnea syndrome, is often observed in patients with type 2 diabetes mellitus; but there are only a few studies on SDB in Japanese diabetic subjects. We investigated the prevalence of SDB in diabetic patients; associations between severity of sleep apnea (SA) and clinical factors, visceral fat, and adiponectin; and associations between type of SA and clinical factors. In the present study, 40 Japanese diabetic patients underwent overnight cardiorespiratory monitoring, and night and morning measurements of serum adiponectin concentrations. Sleep apnea was detected in Japanese diabetic patients at a high prevalence (77.5%). The following variables were associated with SDB: age, body mass index, estimated visceral fat area, and nocturnal reduction in serum adiponectin concentrations. The prevalence of central sleep apnea (CSA, ≥5/h) was 32.3% among diabetic SDB patients. Diabetic SDB patients with CSA had higher hemoglobin, increased intima-media thickness, and higher plasma brain natriuretic peptide levels than those without CSA (<5/h). In conclusion, our study demonstrated a high prevalence of SDB in Japanese diabetic patients, which correlated with visceral fat area and adiponectin. A high frequency of CSA was noted in diabetic SDB patients, together with high hemoglobin, high brain natriuretic peptide, and increased intima-media thickness. The present results of prevalence of SDB may be relevant to the higher incidence of cardiovascular disease in diabetic patients, which need to be clarified in future studies.
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1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is the most common form of sleep-disordered breathing (SDB) and is known to be potentially associated with atherosclerosis and cardiovascular disease (CVD) [1-3]. The presence and severity of sleep apnea-hypopnea syndrome (SAS) are defined by the apnea-hypopnea index (AHI), in conjunction with symptoms such as excessive daytime sleepiness [4]. Previous studies demonstrated the possible association between visceral obesity and SAS [5,6], and recent studies reported that obese subjects with SAS also have low serum adiponectin concentrations [7-9].

More recent research demonstrated the likelihood of a relationship between SDB and type 2 diabetes mellitus (T2DM) [10]. In February 2007, the International Diabetes Federation Taskforce on Epidemiology and Prevention stated that the pathophysiologic stress imposed by hypoxemia and sleep fragmentation might be involved in the pathogenesis of insulin resistance and pancreatic β-cell dysfunction through various biological mechanisms, such as direct effects of hypoxemia, sympathetic nervous system activation, systemic inflammation, hypothalamic-pituitary-adrenal dysfunction, dysregulation of adipocytokines, sleep architecture, and other factors [10-14]. Both SAS/SDB and T2DM are strongly associated with CVD [5]. On the other hand, several studies have demonstrated high prevalence of SDB in diabetic subjects [15-20]. The reported prevalence of sleep apnea in American adults with T2DM is 72.4% (AHI levels of ≥5 events per hour) [20]. However, the frequency

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and characteristics of SDB in Japanese patients with T2DM have not been well clarified. We investigated the incidence of SDB in Japanese patients with T2DM to assess the prevalence of SDB and elucidate the clinical variables associated with SDB.

2. Subjects and methods

2.1. Subjects

We enrolled 40 Japanese subjects with T2DM who had been hospitalized at the Department of Endocrinology and Metabolic diseases of Osaka University Hospital because of poor glycemic control and/or the staging of complications during the period from February 2006 to March 2007 (31 men and 9 women; age, 58.7 ± 2.1 years [mean ± SEM]; range, 29-78 years). *Type 2 diabetes mellitus* was defined according to the World Health Organization criteria and/or treatment of diabetes mellitus. The present study was approved by the ethics committee of Osaka University, and a written informed consent was obtained from each participant.

2.2. Cardiorespiratory monitoring

Each participant underwent overnight cardiorespiratory monitoring (Somté; Compumedics, Melbourne, Australia). The recorded signals were analyzed for the number of apneas and hypopneas during sleep. The oxygen desaturation index (ODI), lowest oxygen saturation, baseline oxygen saturation, and time at desaturation less than 90% in minutes of total bedtime for the entire night were measured. *Apnea* was defined if the amplitude of the airflow or respiratory band data decreased to less than 30% of baseline amplitude for at least 10 seconds. *Hypopnea* was defined if airflow or respiratory effort decreased to less than 70% of baseline for at least 10 seconds associated with greater than 4% desaturation but did not meet the criteria for an apnea. *Apnea-hypopnea index* was defined as the total number of apneas/hypopneas per hour of sleep time [4]. Sleep apnea (SA) was categorized into obstructive (OSA), central (CSA), and mixed SA [21-23]. Obstructive sleep apnea represented absence of airflow for at least 10 seconds but presence of thoracoabdominal movement (the amplitude of thoracic or abdominal band data remained at least 15% of baseline amplitude). Central sleep apnea represented lack of airflow for at least 10 seconds without thoracoabdominal movement [4] (the amplitude of thoracic or abdominal band data decreased <15% of baseline amplitude). Mixed apnea represented lack of airflow for at least 10 seconds with an initial central component followed by obstructive component [24]. There is no consensus on the classification of hypopnea into CSA or OSA component; and thus, hypopneas were classified into obstructive apnea. In the present study, we defined subjects who had obstructive sleep apnea-hypopnea index (OSAHI) of at least 5 and central sleep apnea index (CSAI) less than 5 as obstructive dominant, OSAHI less than 5 and CSAI at least 5 as central dominant, and OSAHI at least 5 and CSAI at least 5 as mixed type. All recordings were scored manually by an experienced polysomnographic technologist [25], and the duration of sleep was estimated using the self-reported sleep time and the recording data.

2.3. Anthropometry and laboratory measurements

Height, weight, and waist circumference were measured in standing position. Waist circumference at the umbilical level was measured with a nonstretchable tape in late expiration while standing (in centimeters). Visceral fat area (VFA) was estimated by bioelectrical impedance analysis (BIA) [26]. *Hypertension* was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or treatment of hypertension. Subjects with a previous diagnosis of dyslipidemia and hypertension who were on medications for any of these conditions were included in this study. *Dyslipidemia* was defined as a low-density lipoprotein cholesterol concentration greater than 140 mg/dL, triglyceride concentration greater than 150 mg/dL, high-density lipoprotein cholesterol concentration less than 40 mg/dL, and/or treatment of dyslipidemia. *Metabolic syndrome* was defined based on the published criteria of the metabolic syndrome for the Japanese population [27]. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR (microunits per milliliter × milligrams per deciliter) = (fasting immunoreactive insulin × fasting glucose)/405. Diabetic retinopathy was assessed by an ophthalmologist. Subjects with overt diabetic nephropathy represented those with urinary albumin greater than 300 mg/d. Diabetic neuropathy represented the presence of 2 of the following 3 clinical findings: subjective symptoms (pain, numbness, itchiness, coldness, warmness, and weakness), absence of deep tendon reflex, and loss of vibration. Subjects on medications known to increase serum adiponectin levels, such as pioglitazone [28], and subjects with renal dysfunction (creatinine >1.5 mg/dL) were excluded from this study because renal dysfunction is reported to alter serum adiponectin level [29].

Venous blood samples were collected for measurements of hemoglobin, hematocrit, creatinine, hemoglobin A_{1c} (HbA_{1c}), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and brain natriuretic peptide (BNP) after awakening while the subject was in the supine position. For the purpose of the present study, serum samples that were obtained from each patient and stored at −20°C were thawed and assayed for adiponectin levels using sandwich enzyme-linked immunosorbent assay (Otsuka, Tokushima, Japan) [7,30]. In 15 (48.4%) of the 31 subjects with both SDB and T2DM, serum adiponectin concentrations were measured before sleep (at 8:00 PM) and after awakening (at 7:00 AM).

Two-dimensional and Doppler echocardiography (SSA-660A; Toshiba, Tokyo, Japan) was performed from standard parasternal views in the resting state, in left lateral position.

This provided left ventricular ejection fraction (LVEF). Maximum carotid intima-media thickness (IMT) and mean IMT of the common carotid artery were also measured in supine position (SSA-660A, Toshiba). Maximum IMT was measured on both the right and left sides in the observation-possible areas of the common carotid artery, bulbus, and internal carotid artery, except the external carotid artery. The mean IMT represented the average of the values of the right and left common carotid arteries, but not the bulbus, determined at 3 points of measurements. The ankle-brachial index (ABI) and the carotid-femoral pulse wave velocity (PWV) were analyzed with a noninvasive autonomic device (model BP-203RPE; Nihon Colin, Tokyo, Japan). To evaluate diabetic autonomic neuropathy, electrocardiogram data were recorded after at least 15 minutes of supine resting during wakefulness; and 100 consecutive R-R intervals were analyzed. The average value (M) of an R-R interval and the standard deviation were determined from this analysis, and coefficient of variation (CVR-R) was computed using the following formula: CVR-R (percentage) = standard deviation/M × 100. However, atrial fibrillation rhythm was not measured.

2.4. Statistical analysis

Data are presented as mean±SEM and compared by 1-way or 2-way analysis of variance with Fisher protected least significant difference test for multiple-group analysis, unpaired Student t test, or Mann-Whitney U test for data with only 2 groups. The frequencies of each group were compared by the χ^2 test. Relationships between 2 continuous variables were analyzed using scatter plots and Pearson correlation coefficients. In all cases, 2-tailed P values were used; and P values < .05 were considered statistically significant. All analyses were performed with the StatView software version 5.0 (HULINKS, Tokyo, Japan).

3. Results

3.1. Characteristics of T2DM subjects enrolled in the present study

Table 1 summarizes the characteristics of the subjects enrolled in this study. Of the 40 patients with T2DM studied, 9 were found to have no SA. The prevalence of SA in subjects with T2DM was 77.5% (Fig. 1). The values of AHI, 4% ODI, and the percentage of time spent with arterial O_2 saturation recorded by a pulse oximeter (SpO_2) at less than 90% were significantly higher and the lowest SpO_2 were significantly lower in T2DM patients with SDB than those with DM but without SDB. The T2DM patients with SDB were older and had higher body mass index (BMI), larger waist circumference for men, larger cardiothoracic ratio (CTR), higher HOMA-IR, and lower baseline SpO_2 than SAS patients without T2DM. There was a significant correlation between AHI and VFA measured by BIA in all subjects (n = 21), in men (n = 13), and in women (n = 8) (r = 0.80, P < .001; r = 0.79, P < .001; and r = 0.85, P < .01, respectively; Fig. 2). There was no significant difference in the use of each antidiabetic therapy between diabetic patients with and without SDB.

Table 1
Characteristics of T2DM subjects without or with SDB

	DM without SDB (n = 9)	DM with SDB (n = 31)	P value
Age, y	49.8 ± 4.2	61.2 ± 2.2	<.05
Sex (male/female)	6/3	21/10	NS
BMI, kg/m^2	23.9 ± 1.6	29.6 ± 1.4	<.05
Waist, cm (male)	83.8 ± 4.4	100.2 ± 3.7	<.05
Waist, cm (female)	93.7 ± 9.4	101.9 ± 5.7	NS
Current smoking	4	8	NS
CTR, %	44.0 ± 1.8 (n = 8)	51.3 ± 1.0 (n = 28)	<.01
Hb, g/dL	14.5 ± 0.6	14.0 ± 0.4	NS
Ht, %	42.1 ± 1.8	41.6 ± 1.7	NS
Creatinine, mg/dL	0.76 ± 0.08	1.26 ± 0.25	NS
Duration of DM, y	11 ± 3	15 ± 2	NS
HbA_{1c}, %	8.4 ± 0.7	8.1 ± 0.3	NS
HOMA-IR, U	1.5 ± 0.4 (n = 4)	3.6 ± 0.5 (n = 15)	<.05
DM neuropathy	3 (33%)	18 (62%)	NS
DM retinopathy	1 (11%)	9 (33%)	NS
DM nephropathy	2 (22%)	14 (43%)	NS
Mets	4	22	NS
Hypertension	4	19	NS
Dyslipidemia	4	12	NS
History			
Coronary artery diseases	1	5	NS
Cerebrovascular diseases	0	2	NS
LVEF, %	68.2 ± 3.0 (n = 7)	65.5 ± 1.5 (n = 27)	NS
Mean IMT, mm	0.95 ± 0.12 (n = 6)	0.98 ± 0.05 (n = 25)	NS
Max IMT, mm	1.48 ± 0.12 (n = 6)	1.82 ± 0.17 (n = 23)	NS
ABI	1.16 ± 0.03 (n = 8)	1.14 ± 0.02 (n = 30)	NS
PWV, cm/s	1337 ± 78 (n = 8)	1690 ± 77 (n = 30)	<.05
CVR-R, %	3.7 ± 0.6 (n = 7)	2.6 ± 0.4 (n = 24)	NS
AHI, events/h	2.4 ± 0.49	30.3 ± 3.9	<.01
Baseline SpO_2, %	97.2 ± 0.3	95.0 ± 0.4	<.05
Lowest SpO_2, %	90.3 ± 1.5	78.6 ± 2.1	<.05
4% ODI, events/h	1.6 ± 0.7	21.4 ± 4.9	<.01
% <90% time	0.05 ± 0.04	9.97 ± 3.21	<.01
Current medication (SU/BG/αGI/insulin)	1/1/2/8	4/3/2/20	NS

Mean ± SEM. Numbers of available data are shown in each parenthesis. Ht indicates hematocrit; Mets, metabolic syndrome; 90% <time, time at desaturation less than 90 % in minutes of total bedtime; SU, sulfonylurea; BG, biguanide; αGi; α-glucosidase inhibitor; NS, not significant.

3.2. Nocturnal changes in adiponectin concentrations in diabetic patients with SDB and without SDB

Next, we focused on the nocturnal changes in serum adiponectin concentrations in diabetic patients, as reported previously [7], by measuring night and early morning levels in 24 such patients. Individual data are shown in Fig. 3A. The percentage change in serum adiponectin level (Δadiponectin = [serum adiponectin concentrations after awakening − before sleep]/before sleep [percentage]) in diabetic SDB

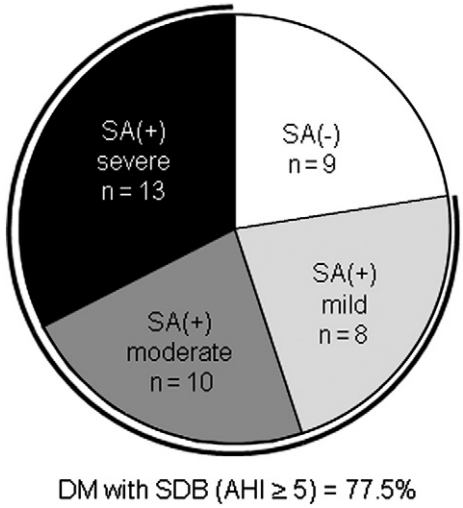

Fig. 1. Prevalence of SA in patients with T2DM. The diagnosis of SA was based on AHI of at least 5 and classified as mild AHI (≥5 to <15), moderate AHI (≥15 to <30), or severe AHI (≥30) according to the guidelines of the American Academy of Sleep Medicine Task Force [4].

patients (n = 9) was −3.4% ± 1.8%, whereas in diabetic non-SDB patients (n = 15), it was 4.7% ± 2.6% ($P < .05$); the difference between the 2 groups was significant (Fig. 3B). In diabetic SDB patients, the aforementioned reduction in serum adiponectin concentration was noted even in patients with mild SA (Fig. 3C).

3.3. Distribution of SA types and characteristics of diabetic patients with SDB

Next, we investigated the frequency of various types of SA in diabetic SDB patients. The incidence of CSA (ie, central dominant [n = 7] and mixed [n = 3]) was 32.3% in diabetic patients. The clinical characteristics of diabetic CSA less than 5 and CSA at least 5 patients are shown in Table 2. The CSA at least 5 group had higher hemoglobin, hematocrit, and mean IMT compared with the CSA less than 5 group. No difference was found in other variables between the 2 groups. There was no significant difference in Δadiponectin between CSA at least 5 group (n = 9) and CSA less than 5 group (n = 4) (Table 2), although the CSA at least 5 group tended to show a decrease in the morning level, although it was not statistically significant. Plasma BNP concentrations were significantly higher in the CSA at least 5 group than in the CSA less than 5 group (Table 2, $P < .05$).

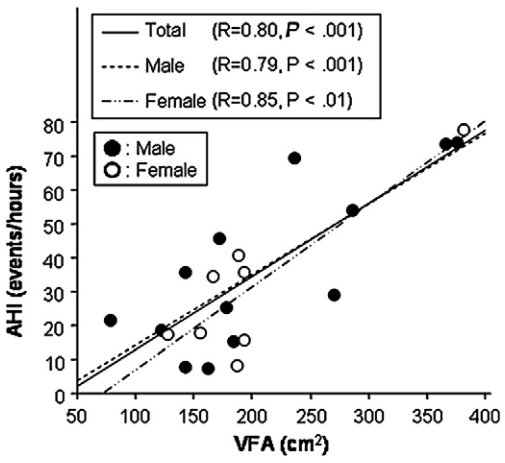

Fig. 2. Relationship between VFA and AHI in 21 patients. Visceral fat area was estimated by BIA [26].

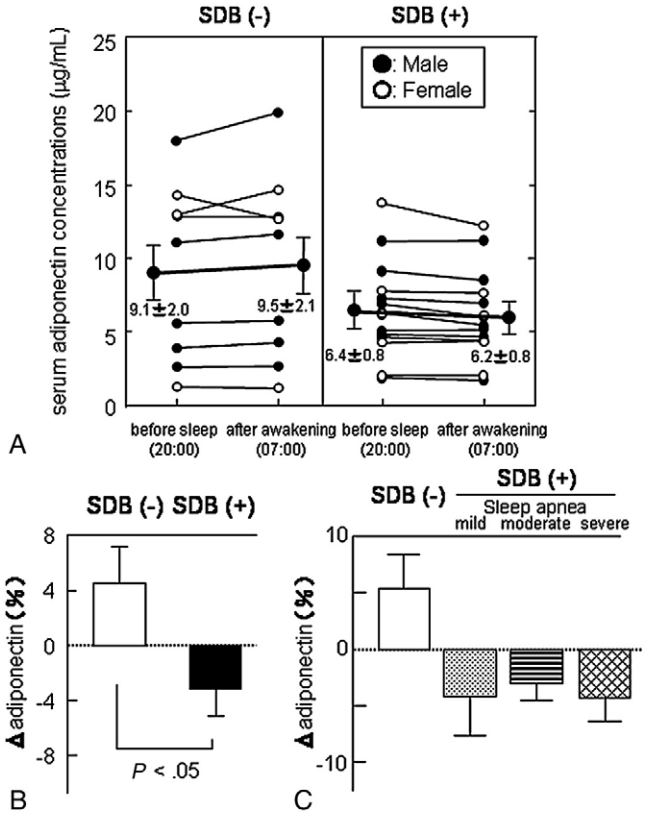

Fig. 3. Serum adiponectin concentrations before sleep and after awakening in T2DM patients without SDB (n = 9) and with SDB (n = 15). A, Serum adiponectin concentrations quantified by enzyme-linked immunosorbent assay. B, ΔAdiponectin in diabetic patients without SDB and with SDB, and in 3 classes of SA severity (C). Data are mean ± SEM.

4. Discussion

The major findings of the present study were as follows: (1) there was a high prevalence of SDB in Japanese T2DM patients (77.5%), consistent with previous studies [20]; (2) diabetic SDB patients were significantly older and more obese than non-SDB diabetic patients; (3) visceral fat accumulation correlated with the severity of SA in diabetic patients; (4) there were nocturnal falls in serum adiponectin concentrations in diabetic SDB patients, similar to our previous report in patients with severe OSAHS [7]; and

Table 2
Characteristic of diabetic SDB subjects without or with CSA

	CSA (<5) (n =21)	CSA (≥5) (n =10)	Univariate *P* value
Age, y	60.0 ± 2.9	63.8 ± 3.1	NS
Sex (male/female)	12/9	9/1	NS
BMI, kg/m^2	28.9 ± 1.6	31.0 ± 2.6	NS
Waist, cm (male)	94.0 ± 4.0	105.9 ± 6.4	NS
Waist, cm (female)	100.3 ± 2.3	77 (n = 1)	–
Current smoking	3	5	NS
CTR, %	51.5 ± 1.2 (n = 21)	49.4 ± 1.7 (n = 8)	NS
Hb, g/dL	13.1 ± 0.4	15.8 ± 0.4	<.01
Ht, %	39.3 ± 1.3	47.0 ± 1.3	<.01
Creatinine, mg/dL	1.35 ± 0.36	1.02 ± 0.11	NS
Duration of DM, y	16 ± 3	15 ± 3	NS
HbA_{1c}, %	8.1 ± 0.5	8.2 ± 0.5	NS
HOMA-IR, U	2.8 ± 0.5 (n = 10)	4.8 ± 1.3 (n = 5)	NS
DM neuropathy	13 (62%)	8 (80%)	NS
DM retinopathy	7 (33%)	3 (30%)	NS
DM nephropathy	9 (43%)	7 (70%)	NS
Mets	14	7	NS
Hypertension	12	7	NS
Dyslipidemia	10	2	NS
History			
CAD	3	2	NS
Cerebrovascular disease	1	1	NS
LVEF, %	65 ± 2 (n = 18)	65 ± 3 (n = 9)	NS
Mean IMT, mm	0.92 ± 0.05 (n = 17)	1.11 ± 0.06 (n = 8)	<.05
Max IMT, mm	1.62 ± 0.21 (n = 15)	2.19 ± 0.23 (n = 8)	NS
ABI	1.15 ± 0.02	1.13 ± 0.03	NS
PWV, cm/s	1654 ± 107	1787 ± 109	NS
CVR-R, %	2.7 ± 0.4 (n = 17)	2.3 ± 0.3 (n = 7)	NS
AHI, events/h	25.3 ± 4.6	40.8 ± 6.3	NS
Baseline SpO_2, %	95 ± 1	95 ± 1	NS
Lowest SpO_2, %	79 ± 3	78 ± 3	NS
4% ODI, events/h	19 ± 6	24 ± 7	NS
% <90% time	10.3 ± 3.9	8.3 ± 5.3	NS
ΔAdiponectin	8.8 ± 1.9 (n = 9)	5.0 ± 1.1 (n = 4)	NS
BNP	22.2 ± 8.1 (n = 5)	77.7 ± 0.7 (n = 7)	<.05

Mean ± SEM. Numbers of available data are shown in each parenthesis. CAD indicates coronary artery disease.

(5) the CSA phenotype was associated with higher hemoglobin, thickened arterial wall, and elevated BNP in diabetic subjects.

Katsumata et al [15] reported high incidence of SAS in male diabetic Japanese subjects. To our knowledge, the present study is the first to assess the prevalence of SDB in male and female Japanese patients with T2DM. As reported previously in American subjects [20], such patients were also older and more obese, although the BMI of Japanese diabetic SDB patients was lower than that of the American subjects. Previous studies demonstrated the possible association between visceral fat accumulation and severity of SA [5,6]. The present study also suggested a link between visceral fat accumulation and severity of SA in Japanese diabetic patients (Fig. 2). Taken together, visceral fat accumulation, SDB, and T2DM may form a pathologic complex associated with high risk for CVD [31-33]. Measurement of not only BMI but also VFA, using bioelectrical impedance or computed tomography, may be clinically useful in the assessment of diabetic SDB subjects.

Both SDB and T2DM patients exhibit dysregulated production of adipocytokines, such as monocyte chemoattractant protein−1, leptin, and other proteins [18,34-37]. The biological functions of adiponectin, which was identified as an adipocytokine in the human adipose complementary DNA library [38], include improvement of glucose metabolism [39] and prevention of atherosclerosis [40]. Serum adiponectin concentrations are low in visceral obesity [29], insulin resistance [41], T2DM [42], and OSAHS [7]. Furthermore, our recent report showed a nocturnal fall in circulating adiponectin concentrations in severe OSAHS subjects and that such reduction was probably due to nocturnal hypoxic stress [7]. The present study also found a significant reduction in circulating adiponectin concentrations during sleep in diabetic SDB patients (Fig. 3B). Although our previous study in nondiabetic patients found nocturnal reduction in serum adiponectin concentrations only in severe OSAHS [7], the present study demonstrated such reduction to occur also in diabetic patients with mild SA (Fig. 3C). Patients with both DM and SDB who sustain chronic hypoxemia and elevated oxidative stress may be more susceptible to hypoxic stress during sleep, although a larger study is required to confirm these results. Nocturnal reduction in plasma adiponectin concentrations may be important when designing strategies to prevent CVD in diabetic patients with SDB.

The incidence of CSA in the present study was 32.3% in diabetic patients with SDB (n = 31). It has been suggested that an exaggerated ventilatory response to changes in $PaCO_2$ is crucial for the development of CSA [43-45]. To address the underlying cause of the high incidence of CSA in DM, we should analyze arterial blood gases, including systemic arterial $PaCO_2$ and PaO_2. The present study demonstrated that CSA correlates with elevated hemoglobin concentration [45], high BNP [46,47], and increased carotid vessel thickness [48,49]. These data emphasize the need to check for CSA in T2DM patients with atherosclerosis or impaired cardiac function.

We described here the prevalence and characteristics of SDB in Japanese patients with T2DM. The results showed a high prevalence of SDB in T2DM patients, and it is therefore necessary to diagnose and treat SDB from the standpoint of prevention of CVD in diabetic patients. Large-scale interventional trials, such as weight reduction, intensive antidiabetes therapy, treatment using nasal continuous positive airway pressure, or combinations of these therapies, should be provided to assess the effects of appropriate treatment on the outcome of diabetic patients with SDB.

4.1. Study limitations

There are several limitations to this study. First, we enrolled in the present study 40 hospitalized Japanese patients during the period between February 2006 and March

2007, who represent consecutive patients. In the present study, there might be a selection bias admittedly for severely affected patients because they were the ones who required hospital admission. Although inadequate data were collected from those patients who opted not to participate in the study, there appeared to be no selection bias regarding study participation. Second, we could not find a sufficient number of control subjects matched for age and/or weight to diabetic patients with SDB in the present study. Third, stepwise multiple regression analysis was conducted to identify parameters that significantly contribute to SDB. Multivariable analysis could not be conducted because of the sample size. Further large-scale prospective study is required for confirmation. Finally, we performed screening of SA using type 3 cardiopulmonary monitoring in the current study. This device without the electroencephalogram cannot record the sleep stage and is therefore not accurate in patients with certain comorbidities. Accurate evaluation of SA warrants the measurement of esophageal pressure to distinguish CSA event from OSA event, although all recordings in the present study were subsequently scored manually by an experienced registered polysomnographer using a simplified cardiorespiratory monitoring device [25].

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