Original Article

High Prevalence of Chronic Kidney Disease among Patients with Sleep Related Breathing Disorder (SRBD)

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Sleep apnea syndrome, a sleep-related breathing disorder (SRBD) of which obstructive sleep apnea syndrome (OSAS) is representative, is often associated with obesity, and therefore patients with SRBD might have a high prevalence of chronic kidney disease (CKD). However, the relationship between obesity and the prevalence of CKD has not yet been investigated in a large cohort of patients with SRBD. The Okinawa Nakamura Clinic Sleep Apnea Syndrome (ONSLEEP) registry contains records for all patients evaluated by full-scale polysomnography (PSG) from September 1990 to the end of 2003 (*n*=5,651). We studied the total of 4,056 (71.8%) of these patients who had an apnea hypopnea index (AHI) of more than 5 events per hour. The glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease equation in the 1,624 patients for whom serum creatinine data was obtained at the time of the PSG. We defined CKD as a GFR of less than 60 mL/min/1.73 m^2. The mean age was 49.9±13.5 (mean±SD) years; the mean body mass index (BMI) was 28.4±5.0 (mean±SD) kg/m^2. We compared the findings with those from participants in the 1993 general screening registry in Okinawa (*n*=94,267). From among the total 94,267 screening participants, we selected 7,454 subjects who were age- and sex-matched to the experimental group with SRBD; the ratio of cases to controls was thus approximately 1:4. CKD was detected in 496 (30.5%) patients, with SRBD a higher incidence than that in the screened population (9.1%); the adjusted odds ratio (95% confidence interval) was 4.542 (3.922–5.260, *p*<0.0001). In contrast to the screened population, the prevalence of CKD decreased as BMI increased (it was 35.7% in SRBD patients with a BMI<25.0 kg/m^2, 31.4% in those with a BMI 25.0 to 29.9 kg/m^2, and 25.2% in those with a BMI ≥30.0 kg/m^2); in the controls the values were 8.1%, 10.5%, and 10.6%, respectively. Taken together, these results suggest that surveillance of CKD is warranted among SRBD patients, particularly those who are not obese. (*Hypertens Res* 2008; 31: 249–255)

***Key Words*: sleep apnea, obesity, chronic kidney disease, screening, proteinuria**

Introduction

Obstructive sleep apnea syndrome (OSAS) affects 4% of middle-aged men and 2% of middle-aged women and is often associated with obesity (*1–3*). The disorder is widely accepted to be associated with a high rate of morbidity and mortality, mostly due to cardiovascular disease and traffic accidents (*4–7*). Chronic kidney disease (CKD) has recently been established as a risk factor for cardiovascular disease (*8–10*). In addition, obesity and cardiovascular disease are associated with CKD (*11*). Several reports have revealed a positive relationship between body mass index (BMI) and the prevalence and incidence of CKD (*12*, *13*).

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Table 1. Comparison of the Backgrounds of Patients with Sleep-Related Breathing Disorder (SRBD) with Serum Creatinine Data (Studied) and Those without (Not-Studied)

Variables	Studied	Not-studied	*p* value
Number	1,624	2,432	
Age at PSG, years	49.9±13.5	52.1±13.1	<0.001
Men, *n* (%)	1,318 (81.2)	1,941 (79.8)	n.s.
Height, cm	162.8±8.6	162.1±8.6	<0.05
Weight, kg	75.4±15.6	72.8±14.5	<0.001
BMI, kg/m^2	28.4±5.0	27.6±4.5	<0.001
AHI, events/h	45.3±33.3	36.0±31.9	<0.001
Pulmonary function			
Tested, *n* (%)	1,430 (88.1)	1,497 (61.6)	<0.001
Abnormal, *n* (%)	238 (16.6)	311 (20.8)	n.s.

Data are mean±SD. PSG, polysomnography; BMI, body mass index; AHI, apnea hypopnea index. Normal pulmonary function is defined as forced expiratory volume (FEV) 1.0≥70% and % vital capacity ≥80%. n.s., not significant.

Table 2. Comparison of the Backgrounds of Patients with Sleep-Related Breathing Disorder (SRBD) and the Screened Population in Okinawa

Variables	SRBD patients	Screened population	*p* value
Number	1,624	7,454	
Age, years	49.9±13.5	50.2±13.6	n.s.
Men, %	81.2	79.9	n.s.
Height, cm	162.8±8.6	159.8±8.5	<0.001
Weight, kg	75.4±15.6	62.4±10.8	<0.001
BMI, kg/m^2	28.4±5.0	24.3±3.3	<0.001
Serum creatinine, mg/dL	1.22±0.45	1.05±0.27	<0.001
eGFR, mL/min/1.73 m^2	67.7±14.7	78.3±14.6	<0.001
CKD,%	30.5	9.1	<0.001

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease. eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation. CKD was defined as eGFR<60 mL/min/1.73 m^2. n.s., not significant.

The effects of obesity differ among ethnic groups (*14*). Asians are more vulnerable to diseases associated with obesity, such as diabetes mellitus and metabolic syndrome (*15*, *16*). Few epidemiologic studies have reported a relationship between sleep related breathing disorder (SRBD) and CKD, at least in Japanese or other Asian populations. There have been several reports on the paradoxical effect of BMI on survival in other chronic conditions, such as in outpatients with established heart failure (*17*) or rheumatoid arthritis (*18*), and in those on chronic hemodialysis (*19*).

Since 1990, we have followed patients with SRBD diagnosed by full-scale polysomnography (PSG) at the Nakamura Clinic in Okinawa. One of the authors (H.N.) is a founder of the clinic and was involved with the treatment. We investigated the prevalence and determinants of CKD among those diagnosed with SRBD (apnea-hypopnea index, AHI≥5 events/h) in a large, non-selected population of SRBD patients in a single institution. We believe our SRBD registry is one of the largest in Japan. In addition, for purpose of comparison, we randomly selected a sample of the general population from among the participants of a screening program in the same area (*12*, *20*). The findings of the present study indicate a high prevalence of CKD among SRBD patients.

Methods

Sleep Apnea Patients

We enrolled all subjects (n=5,651) that were examined by PSG from September 1990 to December 31, 2003 in the Nakamura Clinic, Okinawa, Japan. All subjects were evaluated using the Sandman computerized PSG system with a standard clinical montage. Two board-certified PSG technologists performed the tests. Sleep-stage scoring was performed at 30-s intervals by trained technicians according to standard criteria. The database was named the Okinawa Nakamura Clinic Sleep Apnea Syndrome (ONSLEEP) registry and contained the clinical and laboratory information of these patients.

The diagnosis of SRBD was based on a full standard PSG

Table 3. Background of Patients with Sleep-Related Breathing Disorder (SRBD) and the Screened Population by Baseline BMI

	BMI, kg/m^2		
	<25.0	25.0 to 29.9	≥30.0
SRBD patients (n=1,624)			
n (% of total)	389 (24.0)	739 (45.5)	496 (30.5)
Men, %	75.6	85.4	79.2
Age, years	52.3±15.4	50.9±12.9	46.5±12.2
BMI, kg/m^2	23.0±1.6	27.3±1.4	34.2±4.1
AHI, events/h	28.3±21.8	41.4±26.7	64.4±39.7
Serum creatinine, mg/dL	1.22±0.32	1.24±0.56	1.19±0.35
eGFR, mL/min/1.73 m^2	65.9±13.8	67.2±14.5	69.9±15.3
CKD, %	35.7	31.4	25.2
Screened population (n=7,454)			
n (% of total)	4,447 (59.7)	2,631 (35.3)	376 (5.0)
Men, %	79.4	81.0	77.7
Age, years	50.0±14.3	50.6±12.4	49.3±12.0
BMI, kg/m^2	22.2±1.9	26.8±1.3	31.9±1.8
Serum creatinine, mg/dL	1.04±0.27	1.07±0.27	1.06±0.21
eGFR, mL/min/1.73 m^2	79.2±14.7	76.8±14.1	77.2±15.6
CKD, %	8.1	10.5	10.6

BMI, body mass index; AHI, apnea hypopnea index; eGFR, estimated glomerular filtration rate. eGFR was calculated using the abbreviated MDRD equation. CKD was defined as eGFR<60 mL/min/1.73 m^2. General screening was performed during April 1993 to March 1998 by the Okinawa General Health Maintenance Association. Data are mean±SD.

(EEG-4415 and EEG-4421: Nihon Kohden, Tokyo, Japan; Alice 3 versions 1.3, 1.8, and 2.2: Healthdyne Technology, Marietta, USA; Alice 4 version 1.8,2.2: Respironics, Murrysville, USA; Alice 5 version 2.2: Respironics; Sandman version 4.3: Mallinckrodt, Hazelwood, USA; and Rembrandt, version 5.2.1: Medicare Automation, Amsterdam, the Netherlands) consisting of an electroencephalogram (EEG), electrooculogram (EOG), submental and tibial electromyogram (EMG), oronasal airflow, thoraco-abdominal movement, and percutaneous arterial oxygen saturation (Sp_{O_2}). Each record was scored visually (manually) by experienced scorers (including two certified technologists) and included a count of all apnea events. Airflow was recorded with a thermister or pressure sensor, respiratory efforts were recorded with strain gauges, and Sp_{O_2} was monitored continuously using a pulse oximeter (OLV-1100: Nihon Kohden; NPB-290: Nellcor Puritan Bennett, Pleasanton, USA). An apnea event was defined as the complete cessation of airflow for more than 10 s and was classified either as obstructive or central, based on the presence or absence of respiratory efforts. Hypopnea was defined as a reduction of at least 50% in oronasal flow for more than 10 s accompanied by a decrease of more than 3% in saturated oxygen (Sp_{O_2}). In every patient, the AHI, lowest Sp_{O_2}, and the percentage of time spent with an Sp_{O_2} <90% were recorded. Conventional spirometry was performed with an automated spirometer (Fudac-50; pulmonary function autoanalyzer; Fukuda Co., Tokyo, Japan; CHESTGRAPH JrHI-101: Chest, Tokyo, Japan). For this registry, we excluded those with a total sleep time of less than 2 h and total time in bed of less than 4 h. Respiratory function was evaluated after the PSG examination in 2,875 patients (72.1%). Normal pulmonary function was defined as % vital capacity (VC) ≥80% and forced expiratory volume (FEV) 1.0 ≥70%; patients with lower values were considered to have pulmonary impairment. A total of 4,056 (89.3%) patients with an AHI of ≥5 events/h at the first PSG, aged between 20 to 89 years, were studied. Fifty-six of these patients were diagnosed with central-type sleep apnea.

Control Subjects

The control subjects in the present study were participants of a previously reported population-based screening program in the same region (*12*, *20*). The program was conducted by the Okinawa General Health Maintenance Association, and involved thorough physical examinations. Subjects that were screened in 1993 and for whom data on serum creatinine (SCr) and BMI were available were used as controls (n=94,267). Among them, we randomly selected subjects matched for sex and age with the SRBD patients group at a case: control ratio of 1:≥4. Hypertension was defined as systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg. Diabetes was suspected in patients with a high fasting blood glucose (FPG) ≥126 mg/dL. A total of 7,454 subjects were eventually selected for analysis in the present study. Unfortunately, there was no information on the diagnosis of SRBD for these subjects.

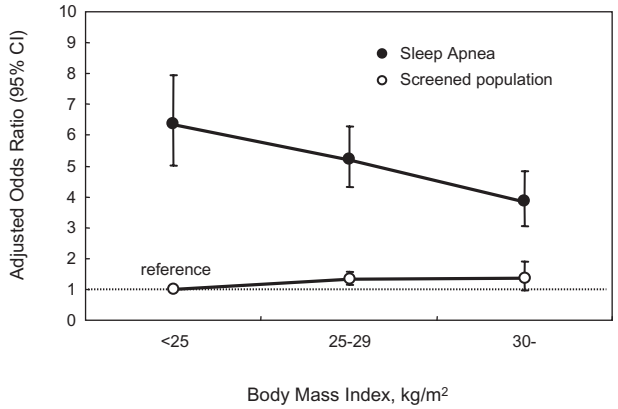

Fig. 1. *Adjusted odds ratio (95% confidence interval) of CKD in each group classified by body mass index (BMI). Reference is the screened population with BMI < 25 kg/m^2.*

Estimation of Glomerular Filtration Rate

For the present study, we estimated the glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) equation. CKD was defined as an eGFR of less than 60 mL/min/1.73 m^2 (*21*). Measurements of SCr were made using an enzymatic assay at the Nakamura Clinic and the modified Jaffe reaction with an auto-analyzer at the OGHMA laboratory for the screened subjects. The relationship between the two methods was:

$$\text{SCr (Jaffe)} = 0.194 + 1.079 \times \text{SCr (enzyme)}.$$

Statistical Analysis

A p value of less than 0.05 was considered to be significant. Data analysis was performed using SAS 8.2 (SAS Institute, Cary, USA). We assessed differences between groups using the χ^2 test and t-test. Multivariate logistic analysis was performed to determine the prevalence of CKD. Results are expressed as adjusted odds ratios with 95% confidence intervals.

Results

The SRBD patient backgrounds are summarized in Table 1. SCr data was available for 1,624 patients (40.0%). The ratio of men to women was 4:1. BMI and AHI were higher among those with studied for SCr. Backgrounds between the SRBD patients and the screened population were different, other than age and sex (Table 2). BMI was significantly higher in SRBD patients than in the screened population. The mean eGFR was 67.7±14.7 (mean±SD) mL/min/1.73 m^2 and that of the screened population was 78.3±14.6 mL/min/1.73 m^2. The median eGFR levels decreased from 75.3 mL/min/1.73 m^2 at age 20 to 29 years to 54.5 mL/min/1.73 m^2 at age 70 years and over in SRBD patients. The prevalence of CKD was higher in the SRBD patients (30.5%) than in the screened population (9.1%). Among the screened subjects, the prevalence of CKD was 5.5% in those that had neither hypertension nor high blood glucose (≥126 mg/dL) and 13.8% in those with both hypertension and high blood glucose.

Clinical characteristics were categorized into three groups: normal BMI of less than 25.0 kg/m^2, overweight (25.0 to 29.9 kg/m^2), and obese (≥30.0 kg/m^2) (Table 3). The prevalence of CKD increased as BMI increased in the screened population, whereas that of the SRBD patients decreased. Figure 1 shows the adjusted odds ratio (95% confidence interval) of CKD based on the three classifications of BMI when a BMI of less than 25.0 kg/m^2 was used as the reference. The prevalence of CKD in SRBD patients was higher than that in the screened population, regardless of the baseline BMI levels.

Table 4 summarizes the results of the multivariate logistic analysis on the prevalence of CKD in SRBD patients and screened subjects. Other than age and sex, there were no significant determinants of CKD in SRBD patients. BMI was a significant determinant of CKD in the screened population. Among the screened subjects, the effect of hypertension (HT) and high fasting plasma glucose (FPG) on the prevalence of CKD was examined (Fig. 2). The age- and sex-adjusted odds ratio (95% confidence interval) was 1.153 (0.738–1.801) for HT (–)/FPG (+), 1.806 (1.368–2.384) for HT (+)/FPG (–), and 2.204 (1.061–4.580) for HT (+)/FPG (+) when the reference was taken as HT (–)/FPG (–).

Discussion

SRBD is common in patients with end-stage renal disease (ESRD) (*22*, *23*). However, few epidemiologic studies have examined the prevalence of CKD (stage 3 and stage 4) in SRBD patients. The findings of the present study suggest that CKD screening might be indicated among the SRBD patient population. Early identification and treatment of CKD might slow the progression to ESRD. Explanations for the high prevalence of CKD in SRBD patients remain speculative, and anemia is cited as one factor (*24*). Hypoxia is a common underlying mechanism for CKD progression (*25*, *26*). SRBD patients are under hypoxic conditions, at least during sleep. In the present study, however, AHI was not a significant determinant of CKD when adjusted for other confounding variables (Table 4). This might have been due to the effects of treatments for SRBD, such as continuous positive airway pressure (CPAP), which is often used for severe cases. CPAP treatment appears to improve the survival rate in CKD patients, although this has not been proved by a randomized controlled study (*2*). Because CPAP treatment decreases hypoxia, it might have a positive effect on kidney function.

Obesity is a major correlate of SRBD in Japanese with a BMI of at least 25 kg/m^2. The mean BMI in our cohort of SRBD patients was 28.4 kg/m^2, which is significantly higher than that in the general screened population in our region (*12*, *20*). Obesity and metabolic syndrome are often associated

Table 4. Odds Ratios (95% Confidence Interval) on the Prevalence of CKD in Patients with Sleep-Related Breathing Disorder (SRBD) and the Screened Population

	Not adjusted	Adjusted
SRBD patients		
Age, years	1.065 (1.055–1.075)[#]	1.062 (1.052–1.072)[#]
Sex, *vs*. women	0.462 (0.357–0.596)[#]	0.648 (0.488–0.819)[#]
BMI, kg/m^2	0.960 (0.939–0.982)[#]	0.999 (0.972–1.027)
AHI, events/h	0.993 (0.990–0.996)[#]	0.998 (0.993–1.002)
Screened population		
Age, years	1.097 (1.088–1.106)[#]	1.097 (1.089–1.106)[#]
Sex, *vs*. women	0.515 (0.430–0.615)[#]	0.361 (0.306–0.427)[#]
BMI, kg/m^2	1.058 (1.031–1.085)[#]	1.032 (1.008–1.057)[#]

CKD, chronic kidney disease; BMI, body mass index; AHI, apnea hypopnea index. Adjusted denotes multivariate logistic analysis performed with all variable included in the table. Screened population is the age and sex–matched participants of the 1993 general screening by Okinawa General Health Maintenance Association. [#]$p<0.001$.

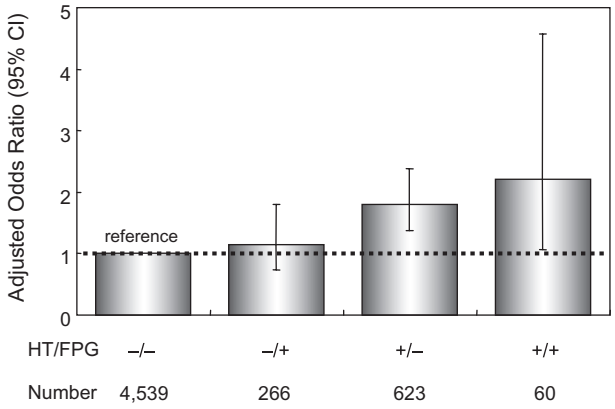

Fig. 2. *Age and sex adjusted odds ratio (95% confidence interval) of CKD in the combination of the presence or absence of hypertension and diabetes mellitus. Hypertension was defined as systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg. High fasting blood glucose (FPG) denotes FPG ≥126 mg/dL. Among the screened subjects, 1,966 (26.4%) screenees did not have data for blood pressure or fasting blood glucose.*

with the prevalence (*27*, *28*) and incidence (*29*) of CKD. Several reports indicate that obesity is related to the development of proteinuria (*30*) and ESRD (*12*, *13*). The present study supports the concept of obesity-related glomerulopathy (*31*). The mean BMI in incident dialysis patients is increasing and is higher than that of the general population in the United States (*32*).

The relationship between BMI and the prevalence of CKD was different between SRBD patients and the screened population (Fig. 1). The reasons for the inverse relationship between BMI and the CKD prevalence remain to be studied. A paradoxical effect of BMI on survival has been reported in patients with chronic diseases such as rheumatoid arthritis (*18*) and in those undergoing chronic dialysis (*19*).

SRBD is often associated with pulmonary impairment. In the present study, pulmonary function was abnormal in 19% of patients that received pulmonary function tests and had some type of lung disorder, such as chronic obstructive pulmonary disease and restrictive impairment in severely obese patients. The impact of pulmonary function on CKD has not been well studied. Pulmonary edema is quite common in advanced CKD and ESRD. Most of our patients had stage 3 and 4 CKD, however, and thus it would have been unusual to see uremic lung or volume overload due to renal failure in these patients. Several reports have demonstrated an improvement or cure of SRBD after renal transplantation (*33*).

Several limitations of this study bear mention. Although this was a retrospective cohort study, the number of subjects was quite large and the study period long. We recruited SRBD patients consecutively from a single center for studying sleep apnea, and not from a random population sample of SRBD patients. Our cohort had a broad range of clinical, demographic, and socioeconomic characteristics of SRBD, which reflect actual daily clinical practice. Our study did not define the factors related to the high prevalence of CKD. Effects of other confounding variables, such as hypertension, diabetes mellitus, metabolic syndrome and other cardiovascular risk factors that are often associated with SRBD must be considered. Based on the data from the control group, the risk of CKD increased twice when combined with hypertension and diabetes mellitus (Fig. 2). The higher the AHI, *i.e*., the more severe the SRBD, the higher the prevalence of such variables, or at least some aspects of these variables (*34–36*). Unfortunately, information concerning comorbid conditions, including SRBD, was not complete in the SRBD patients. In addition, the possible presence of a selection bias cannot be ruled out in this study. Reasons for the measurement of SCr were not clear in this study. SCr was more often measured in severe cases of SRBD (Table 1). We calculated eGFR using a single measurement of SCr. Follow-up of kidney function is

needed to examine the effect of treatments such as CPAP and weight reduction.

Finally, there is not yet a precise equation for estimating GFR in the Japanese (*37*). A SCr calibration might be needed for an international comparison of the prevalence of CKD. Because the method for measuring SCr is regularly monitored in our region, there would be a very small difference, if any, between the Nakamura clinic and OGHMA.

Conclusion

We observed a high prevalence of CKD among patients with SRBD in a single sleep center. There was an inverse relationship between BMI and the prevalence of CKD, and this relationship was not seen in the screened population. Further analyses are required to examine the effects of obesity and other confounding variables related to the prevalence of CKD in patients not on dialysis (*38*). The present study suggests that surveillance of CKD is necessary as a part of an evaluation of SRBD patients, particularly those that are not obese. The incidence and prevalence of SRBD are not known in Japan but might increase as the prevalence of obesity increases.

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