High Prevalence of Obstructive Sleep Apnea and Its Association with Renal Function among Nondialysis Chronic Kidney Disease Patients in Japan: A Cross-Sectional Study

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Summary

Background and objectives Obstructive sleep apnea (OSA) affects one of five adults in the general population. Although a high prevalence of OSA has been reported among dialysis patients, the association between nondialysis chronic kidney disease (CKD) and OSA has not been fully investigated. This cross-sectional study aimed to investigate the prevalence of OSA among nondialysis CKD patients in Japan and the association between renal function and OSA.

Design, setting, participants, & measurements Consecutive nondialysis CKD patients hospitalized mainly for CKD educational program, regardless of their sleep complaints, were enrolled. The diagnosis of OSA and its severity were measured using a type 3 portable monitor.

Results Overall (n = 100, 68.0% male, median age 66.5 years, body mass index [BMI] 23.1 kg/m², estimated GFR [eGFR] 28.5 ml/min per 1.73 m²), 65% were diagnosed as OSA: mild OSA (apnea-hypopnea index [AHI] 5.0 to 14.9) in 32%, moderate OSA (AHI 15.0 to 29.9) in 25%, and severe OSA (AHI ≥ 30.0) in 8%. Multivariate logistic regression analysis revealed that a 10-ml/min per 1.73 m² decrease in eGFR was associated with a 42% increased odds of OSA after adjustment for age, BMI, and diabetes mellitus. Moreover, in a generalized linear model, eGFR was inversely correlated with AHI after adjustment for covariates.

Conclusions This study demonstrated a high prevalence of OSA among nondialysis CKD patients in Japan and that the increased risk of OSA was significantly associated with decreased GFR among these patients. Further investigations are warranted to determine OSA’s direct influence on cardiovascular disease.


Introduction

Obstructive sleep apnea (OSA) affects approximately one in five adults in the general population, wherein most remain undiagnosed (1). Recently, OSA has been widely recognized as an important risk factor for hypertension (2), cardiovascular disease (CVD), stroke, and death (3). Its underlying pathogenesis, particularly intermittent hypoxia, triggers sympathetic nerve activity (4), systemic inflammation (5), and oxidative stress (6), causing endothelial cell dysfunction and arteriosclerosis (7).

On the other hand, chronic kidney disease (CKD) is now becoming a major public health problem because it is not only a risk for end-stage renal disease but is also closely related to CVD (8,9). Among end-stage renal disease patients, the high prevalence of OSA and its influence on cardiovascular events have been reported (10,11). However, the association between nondialysis CKD and OSA has not been fully investigated, although sleep complaints are highly prevalent in this population (12). We conducted this cross-sectional study to estimate the prevalence of OSA among nondialysis CKD patients in Japan, wherein we also investigated the association between OSA and renal function.

Materials and Methods

Subjects In this cross-sectional study, we examined 100 consecutive nondialysis CKD patients who were hospitalized in our unit mainly for a CKD educational program from May 2009 to April 2010. This program was intended to educate patients about their renal disease and to provide individualized nutritional therapy and treatment options for end-stage renal disease; its duration was approximately 1 week. This program was targeted at stable CKD patients, regardless of their sleep complaints or complications associ-
ated with OSA (e.g., obesity, diabetes mellitus, and CVD), and excluded the following: (1) patients who had already undergone renal replacement therapy, (2) those who presented with acute renal failure, and (3) those with severe acute complications such as acute coronary syndrome, acute heart failure, stroke, and systemic infection. According to the National Kidney Foundation definition, CKD was defined as estimated GFR (eGFR) of <60 ml/min per 1.73 m² and/or evidence of kidney damage (e.g., proteinuria) lasting for at least 3 months. The eGFR was calculated by applying a modified equation for estimating the GFR for Japanese individuals as follows: $eGFR = 194 \times \frac{\text{sCr}}{\text{age}^{-0.287}} \times 0.739$ (if female), where sCr was the serum creatinine level in milligrams per deciliter (13). Proteinuria was defined as a urine dipstick test result of ≥1+. The Faculty of Medicine Ethics Committee at Osaka General Medical Center approved this study protocol. Informed consent was obtained from all of the patients before the commencement of the study.

Definition of Hypertension, Diabetes Mellitus, and Pre-Existing CVD

Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg, measured by automatic devices in a sitting position, and/or use of antihypertensive medication. Diabetes mellitus was ascertained by a fasting glucose concentration ≥126 mg/dl, nonfasting glucose concentration ≥200 mg/dl, a hemoglobin A1c value ≥6.5%, and/or use of antidiabetic agents including insulin. Pre-existing CVD included myocardial infarction, angina, congestive heart failure, and stroke, which were noted from medical records.

OSA Examination

The diagnosis of OSA and its severity were measured using a type 3 portable monitor (Morpheus, Teijin Pharma Ltd., Japan). The accuracy of this type of portable monitor in diagnosing OSA and measuring its severity with high reproducibility comparative with full polysomnography was recently validated (14–16). This monitor was used to record thoracoabdominal respiratory movements, oxygen saturation, nasal airflow, and heart rate. During sleep, respiratory movements were recorded by strain gauges, nasal airflow was recorded by a pressure sensor, and oxygen saturation was recorded by a pulse oximeter. The recorded signals were stored in a Compact Flash memory card and analyzed later by sleep medicine technicians blinded to the patients’ medical information.

We scored the apnea and hypopnea according to the definitions of the American Academy of Sleep Medicine (17): Apnea was defined as cessation of breathing for at least 10 seconds and hypopnea was defined as a >50% reduction in the amplitude of nasal pressure associated with a ≥3% reduction in oxygen saturation for at least 10 seconds. The apnea-hypopnea index (AHI) was the total number of apnea and hypopnea occurrences per hour of the total sleep time length. Obstructive apnea events were distinguished from central events by the continued presence or absence of respiratory efforts during the apnea events. OSA was diagnosed when AHI was >5.0, in which obstructive apnea events comprised >50% of total apnea events (17). Sleep complaints of the subjects were not examined in this study.

Outcomes and Covariates

The primary outcomes were the prevalence of OSA and its severity (AHI). Patient characteristics that might be associated with the outcomes, including age, gender, body mass index (BMI), diabetes mellitus, and pre-existing CVD were considered as explanatory variables.

Statistical Analyses

Continuous variables are presented as median values or interquartile ranges, and categorical variables are presented as frequency (number) and proportions. Logistic regression analysis was used to evaluate the associations between the likelihood of OSA and covariates. Because the logit of the likelihood of OSA and BMI was not in a linear relationship, BMI was treated as a categorical variable (21 ≥ and 21 < kg/m²). Covariates of $P < 0.2$ in univariate analysis were further examined by multivariate analysis.

To assess the correlation between AHI and continuous variables, Spearman rank correlation coefficient was used because the distribution of AHI was non-Gaussian. Inter-group comparisons of AHI among categorical variables were performed by Mann–Whitney U test. Multivariate associations between AHI and the covariates of $P < 0.2$ in univariate analysis were further examined by a generalized linear model in which the link function was chosen to be the natural logarithm and the distribution to be a gamma distribution for the best-fitting model according to the Akaike information criterion.

All results were based on the available data analyses without any imputation procedure. $P < 5\%$ was considered statistically significant. All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, version 2.7.1, R Development Core Team) and JMP 8 (SAS Institute).

Results

The clinical characteristics of the subjects are summarized in Table 1. A total of 100 consecutive patients were enrolled for the examination. The ratio of men to women was approximately 2:1. The median BMI was 23.1 kg/m², and the proportion of obesity (BMI ≥ 30 kg/m²) was only 4%. The subjects in this study had a wide range of renal status.

| Table 1. Clinical characteristics of 100 patients with nondialysis CKD |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Age (years)                 | 66.5 (58.0 to 74.8) | Gender            | male              | female            |
|                             |                   | BMI (kg/m²)       | 25.1 (20.8 to 24.8) | 32.2              |
| Creatinine (mg/dl)          | 2.11 (1.35 to 5.70) | eGFR (ml/min/1.73 m²) | 28.5 (8.0 to 40.0) |
| Diabetes mellitus           | 31 (31.0)         | Hypertension      | 80 (80.0%)        |
| Pre-existing CVD            | 27 (27.0%)        |

Data are presented as number (%) or median (interquartile range).
function, with eGFR values ranging from 4 to 89 ml/min per 1.73 m². The distribution of the subjects in each CKD stage is shown as follows: stage 1 and 2, 9%; stage 3, 32%; stage 4, 24%; and stage 5, 35%.

The prevalence of subjects with AHI ≥ 5.0 was 65%, and all of them were classified as OSA. The median AHI was 8.0, with the proportion of mild OSA (AHI 5.0 to 14.9) being 32%, moderate OSA (AHI 15.0 to 29.9) 25%, and severe OSA (AHI ≥ 30.0) 8%. The median number of central sleep apnea events was 0.2 per hour (interquartile range 0.0 to 0.8).

The associations between the likelihood of OSA and the covariates obtained are presented in Table 2. In univariate analysis, a decrease in eGFR as well as higher BMI (BMI ≥ 21 kg/m²) and older age were significantly associated with an increased likelihood of OSA. In multivariate analysis, a 10-ml/min per 1.73 m² decrease in eGFR was associated with a 42% increased odds of the likelihood of OSA after adjustment for age, BMI, and diabetes mellitus.

The univariate correlations between AHI and continuous variables are shown in Table 3, and the intergroup comparisons of AHI among categorical variables are shown in Table 4. A decrease in eGFR was significantly correlated with an increase in AHI (ρ = 0.225, P = 0.02; Figure 1). An increase in age (ρ = 0.253, P = 0.01) and BMI (ρ = 0.460, P < 0.001) were also significantly associated with an increase in AHI. Diabetic patients had a significantly higher AHI than did nondiabetic patients (P = 0.02; Table 4). Table 5 shows the associations between AHI and covariates in multivariate analysis using the generalized linear model in which eGFR and BMI were independently and significantly associated with AHI.

Table 2. The associations between the likelihood of OSA and covariates in univariate and multivariate logistic regression analyses

| Covariates | Univariate | | | Multivariatea |
|------------|------------|---|---|---|---|
| Age (per increase in 10 years) | 1.70 (1.22 to 2.49) | 0.003 | 1.46 (0.94 to 2.36) | 0.1 |
| Gender | | | | |
| female | 1.00 (reference) | 0.2 | 1.00 (reference) | 0.2 |
| male | 1.79 (0.71 to 4.44) | 0.2 | 1.42 (1.08 to 1.97) | 0.02 |
| BMI (kg/m²) | ≤21 | 1.00 (reference) | 0.0001 | 1.00 (reference) | 0.0002 |
| >21 | 7.00 (2.61 to 18.8) | | 10.2 (3.27–37.0) | |
| eGFR (per decrease in 10 ml/min per 1.73 m²) | 1.39 (1.14 to 1.75) | 0.001 | 1.42 (1.08 to 1.97) | 0.02 |
| Diabetes mellitus | no | 1.00 (reference) | 0.07 | 1.57 (0.53–4.93) | 0.4 |
| yes | 2.48 (0.94–6.55) | | | |
| Pre-existing CVD | no | 1.00 (reference) | | | |
| yes | 1.48 (0.57, 3.83) | | | |

OR, odds ratio; CI, confidence interval.
aModels adjusted for age, BMI, eGFR, and diabetes mellitus.

Table 3. Univariate correlations between AHI and continuous variables using Spearman rank correlation coefficient

<table>
<thead>
<tr>
<th>Variables</th>
<th>ρ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.253</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.460</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>0.225</td>
<td>0.02</td>
</tr>
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</table>

Table 4. Univariate comparisons of AHI among categorical variables by Mann–Whitney U test

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median AHI (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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<tr>
<td>male</td>
<td>8.45 (4.48 to 18.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>female</td>
<td>6.05 (2.23 to 16.0)</td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>13.4 (5.60 to 23.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>no</td>
<td>6.50 (3.15 to 15.6)</td>
<td></td>
</tr>
<tr>
<td>Pre-existing CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>12.8 (4.60 to 22.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>no</td>
<td>7.10 (3.05 to 15.6)</td>
<td></td>
</tr>
</tbody>
</table>

IQR, interquartile range.

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**Discussion**

In this cross-sectional study, we found a high prevalence (65%) of OSA among nondialysis CKD patients in Japan; furthermore, approximately one third of the patients had moderate or severe OSA. Our study also demonstrated that decreased GFR was a significant predictor of OSA among these patients.

To the best of our knowledge, this is the first study to demonstrate a high prevalence of OSA among nondialysis CKD patients in Japan. Although end-stage renal disease patients have been reported to have a high prevalence of OSA (10,18), OSA among nondialysis CKD patients has not been fully investigated despite the high prevalence of sleep complaints in this population (12). Iseki et al. reported that the prevalence of nondialysis CKD among sleep-disordered breathing patients was significantly higher than those in general screening populations (30.5% versus 9.1%) (19). However, the prevalence of OSA among nondialysis patients in Japan; furthermore, approximately one third of the patients had moderate or severe OSA. Our study also demonstrated that decreased GFR was a significant predictor of OSA among these patients.

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correlated with serum urea concentrations but not with creatinine clearance (23). However, their study was limited by its small sample size, with a relatively narrow range of renal function and lack of adjustment for potent covariates including age, BMI, and diabetes mellitus. Later, Canales et al. enrolled 2696 community-dwelling men aged over 65 years (mean [SD] = 73.0 [5.5] years). They did not detect a significant association between renal function and sleep-disordered breathing (24). However, most of their subjects were generally healthy elderly men with mean serum creatinine levels of 0.99 mg/dl, and only 14.8% had eGFR < 60 ml/min per 1.73 m². Furthermore, in >80% of their subjects, the increase in serum creatinine levels was <0.2 mg/dl in the 3.4 years before study enrollment, suggesting that these subjects did not represent the general CKD population. They mentioned that there might be a threshold at which the association between renal function and OSA could be detected. We enrolled subjects with a wide range of renal function and could accordingly identify the association between OSA and nondialysis CKD.

There are several reasons why the increased risk of OSA is significantly associated with decreased GFR among these patients. First, the upper airway dimensions in patients with renal failure are prone to narrowing. Beauchamp et al. reported that the pharyngeal cross-sectional area measured by pharyngometry in end-stage renal disease patients was 12% less than that in the normal renal function control group matched for BMI (25). They insisted that this difference was clinically significant because in another study as little as a 6% reduction in the pharyngeal crosssectional area led to a 73% increase in AHI (26). Such pharyngeal narrowing was considered to occur because of upper airway edema due to systemic fluid overload and upper airway dilator muscle dysfunction due to neuropathy or myopathy associated with chronic uremia (27). Second, ventilation control is known to be instable in CKD patients. Because chemoreflex responsiveness has been reported to be augmented in patients with end-stage renal disease, possibly because of the accumulation of uremic molecules or metabolic acidosis, this destabilized respiratory control—as explained by a high “loop gain” theory—can contribute to the pathogenesis of OSA (28). Although these two mechanisms have been established in hemodialysis patients, it is plausible that they are also applicable to the nondialysis CKD population.

There may be another explanation for the increased risk of OSA being significantly associated with decreased GFR among these patients. It could be assumed that OSA has an adverse effect on renal function. The most direct mechanism may be chronic elevations in BP through heightened symp-
thetic nerve tone (4), which also activates the renin-angiotensin-aldosterone system, causing glomerular hyperfiltration (28). At the same time, OSA promotes systemic oxidative stress, microinflammation, and endothelial dysfunction (5–7), which are now believed to be the major pathogenic mechanisms of chronic renal ischemia and the progression of CKD. Furthermore, because there is increasing evidence that CKD and OSA have a strong relationship with CVD (2,3,8,9), the vicious cycle between CKD and OSA and the accompanying metabolic syndrome are probably involved in the development of CVD. There needs to be a further prospective study to determine whether OSA truly represents a risk factor for end-stage renal disease and CVD in the CKD population and to analyze the effect of treatment by continuous positive airway pressure.

In this study, age and gender were not associated with the likelihood of OSA. These results are inconsistent with previous studies involving general populations. In general populations, older age (1) and male gender (29) have been significantly associated with the increased prevalence of OSA. Although we assume that the sample size was not adequate for detecting the statistical significance of this finding, it may imply that renal failure was a more potent contributing factor to OSA than were age and gender.

The potential limitations of this study are as follows. First, the cross-sectional nature of this study hindered the assessment of the causal relationship between the decline in renal function and the prevalence and severity of OSA, which should be ascertained by longitudinal studies. Second, there is an issue of selection bias in the study enrollment given that the subjects were referred to nephrologists and designated to attend a CKD educational program. However, this bias is not likely to be substantial because we enrolled consecutive patients with the indication of the program not on the basis of sleep complaints or conditions associated with OSA. In fact, the characteristics of our study subjects were very similar to those found by Imai et al. in their analysis of a large representative cohort of 2977 Japanese CKD patients (30). The median BMI was 23.1 kg/m² in our study and 23.5 kg/m² in that of Imai et al.; the percentage of obese patients was 4% and 5%, of diabetes mellitus was 31.0% and 36.7%, of hypertension was 80.0% and 81.5%, and of pre-existing CVD was 27.0% and 25.6%, respectively. Third, in Japan, where obesity is less prevalent and craniofacial bone structure differences might be a more important factor in OSA as compared with Caucasian populations (31), the external validity of our results to other ethnic groups remains to be elucidated.

In conclusion, this study demonstrated a high prevalence of OSA among nondialysis CKD patients in Japan. Our study also demonstrated that the increased risk of OSA was significantly associated with decreased GFR, suggesting that renal function and OSA were closely related and might aggravate each other. Further prospective investigations are warranted to determine how these directly influence each other. The effect of OSA and its treatment by continuous positive airway pressure on the morbidity and mortality of CVD in this population must also be elucidated.

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Disclosures
None.

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