Association of Nocturnal Hypoxemia with Progression of CKD

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Summary

Background and objectives Nocturnal hypoxemia is highly prevalent among patients with CKD. Nocturnal hypoxemia contributes to systemic inflammation, oxidative stress, endothelial cell dysfunction, and activation of the renin-angiotensin system, which are common pathologic mechanisms of CKD progression. This study investigated whether nocturnal hypoxemia is independently associated with CKD progression.

Design, setting, participants, & measurements This two-center retrospective cohort study included 161 patients with stages 3–4 CKD enrolled from January of 2009 to July of 2011 with a body mass index less than 25.0 kg/m². The 4% oxygen desaturation index, the number of events per hour in which oxygen saturation decreases by >4% during sleep, was measured, and the declining rate of the estimated GFR was followed over 1 year. The severity of nocturnal hypoxemia was categorized as none (oxygen desaturation index<5.0), mild (5.0≤oxygen desaturation index<15.0), or moderate to severe (15.0≤oxygen desaturation index).

Results The mean estimated GFR of the total cohort at baseline was 31 ml/min per 1.73 m². Eighty patients (49.7%) were diagnosed with nocturnal hypoxemia; 64 patients were diagnosed with mild nocturnal hypoxemia, and 16 patients were diagnosed with moderate-to-severe nocturnal hypoxemia. The estimated GFR declined three- to fourfold faster in patients with moderate-to-severe nocturnal hypoxemia than patients with no or mild nocturnal hypoxia (the mean values [95% confidence intervals] were −2.14 [−1.06 to −3.21], −3.02 [−1.31 to −4.74], and −8.59 [−2.00 to −15.2] ml/min per 1.73 m² per year in the no, mild, and moderate-to-severe nocturnal hypoxia groups, respectively; P=0.003). Nocturnal hypoxemia remained a significant predictor of decline in estimated GFR after adjustment for various baseline clinical factors.

Conclusions In nonobese patients with CKD, nocturnal hypoxemia is an independent risk factor of a rapid decline in kidney function.

Introduction

Sleep disordered breathing (SDB) is a common clinical condition among patients with CKD; its prevalence has been reported to be as high as 65% (1–4) compared with approximately 20% in the general population (5,6). The hallmark of SDB is its recurrent episodes of hypoxia–reoxygenation sequence coupled with the majority of apnea events throughout the night. This intermittent nocturnal hypoxemia (NH) causes oxidative stress by increasing the generation of reactive oxygen species through activation of hypoxia-inducible factor-1 and NADPH oxidase-2 (7–11). In addition, NH can directly activate the sympathetic nervous system (12) and the renin-angiotensin system (13) and promote inflammation (14,15) and endothelial cell dysfunction (16), contributing to the development of atherosclerosis. In fact, one of the most deleterious aspects of NH is its independent risk for cardiovascular mortality in patients with end stage kidney disease (ESKD) (17–20) as well as the general population (21–24).

In addition to its harmful effects on the cardiovascular system, NH may contribute to the progression of CKD based on the accumulating evidence that hypoxia plays a significant role in tubulointerstitial injury in the kidney as part of the final common pathway to ESKD (25). We and others have performed cross-sectional studies showing a significant negative association between the prevalence and/or severity of SDB and kidney function in the CKD population (1–4,26). To date, there is only a single cohort study of the longitudinal relationship between SDB and kidney function, which showed that NH was a significant predictor of accelerated loss of kidney function (27). However, the majority of the participants in that study had maintained baseline kidney function (mean estimated GFR [eGFR]=70.8 ml/min per 1.73 m²) and severe obesity, which hampered the generalization of the finding to the general CKD population.

Both CKD and SDB are now becoming major public health problems that affect mortality and quality of life in a large proportion of the adult population.
worldwide (28–30). In this circumstance, it is especially of
importance to elucidate their interrelationship. In the cur-
current cohort study, we aimed to study the clinical impact of
NH on kidney function among patients with stages 3 and 4
CKD. In particular, we enrolled patients whose body mass
index (BMI) was less than 25.0 kg/m², the normal range
for body weight as defined by the World Health Organi-
zation (31,32), to assess the association between NH and
kidney function independently from obesity.

Materials and Methods
Participants
A retrospective two-center cohort study was conducted
in the nephrology units of two tertiary care hospitals in
Japan: Osaka General Medical Center and Ohmihachiman
Community Medical Center. Both of these centers have
conducted CKD educational programs covering approxi-
ately 1 week of hospitalization. This program, targeted at
stable CKD patients regardless of the presence or absence
of sleep complaints, was intended to educate patients about
their kidney disease and provide individualized nutritional
therapy. No specific comorbidities influenced or hindered
participation in this program. As a routine screening exam-
ination for NH, 4% oxygen desaturation index (ODI) was
measured in essentially all participants in this program,
regardless of their clinical characteristics. The participants
in this study were recruited at Osaka General Medical
Center from May of 2009 to June of 2011 and Ohmihachiman
Community Medical Center from January of 2009 to July of
2011. In light of the study object, we included only patients
with stages 3–4 CKD (15≤eGFR≤60 ml/min per 1.73 m²)
whose BMI was less than 25.0 kg/m². The eGFR was cal-
culated from the equation for estimating GFR for Japanese
individuals (33).

There were four exclusion criteria: patients were (1) fol-
lowed up for less than 6 months, (2) diagnosed with
chronic obstructive pulmonary disease, (3) receiving oxy-
gen supplementation or continuous positive airway pres-
ure (CPAP) therapy with good adherence (defined as use
for an average of 4 hours a night on at least 70% of nights),
and (4) hospitalized for acute complications, such as AKI,
acute heart failure, stroke, or infection, but did not partic-
ipate in the CKD educational program.

The study protocol was approved by the Faculty of
Medicine Ethics Committees of both Osaka General
Medical Center and Ohmihachiman Community Medical
Center.

Outcome
All participants were followed by a nephrologist for at
least 1 year after the measurement of 4% ODI, and serum
creatinine (Scr) levels were measured after 3, 6, and 12
months. The outcome was the slope of the eGFR versus
time plot (eGFR slope; milliliters per minute per 1.73 m² per
year). Regression lines for eGFR over time were created
from the four eGFR data points (measured at baseline and
after 3, 6, and 12 months) (least-squares method) to
obtain a regression coefficient for each subject.

The eGFR data for one of three follow-up points were
missing for nine participants; in these cases, the regression
coefficients were calculated from the eGFR at baseline and
the available two follow-up points.

Pulse Oximetry
The arterial oxygen saturation (SpO2) during sleep of
each subject was monitored transcutaneously using a pulse
oximeter (PULSOX; Teijin Pharma, Ltd., Japan) in an un-
attended manner. The sampling frequency of this monitor
was 1 Hz. Desaturation was defined as a >4% drop in the
SpO2 level from the baseline level; the 4% ODI was the
number of desaturation events per hour of recording time,
which was calculated using computer software. The partic-
ipants were divided into three groups according to com-
monly used conventional cutoff values of 4% ODI: the no
(ODI<5), mild (5≤ODI<15), and moderate-to-severe
(15≤ODI) NH groups (34). In addition, we also calculated
the duration of SpO2<90%.

To examine the relationship between 4% ODI and apnea–
hypopnea index (AHI) in this cohort, AHI was simul-
taneously measured using a type 3 portable monitor
(Morpheus; Teijin Pharma Ltd., Japan) in the participants
of one of two nephrology centers (Osaka General Medical
Center; n=41). The definitions of apnea and hypopnea
were according to The AASM Manual for the Scoring of
Sleep and Associated Events: Rules, Terminology and Tech-
ical Specifications (35). There was a strong correlation between 4%
ODI and AHI as determined by Spearman’s rank correla-
tion coefficient (P<0.001, r=0.86). The sensitivity and spec-
ficity of the ODI≥5 for the AHI≥5 were 77.2% and 89.5%,
respectively, and the sensitivity and specificity of the ODI≥15
for the AHI≥15 were 80.0% and 100%, respectivly.

Baseline Characteristics
The participant demographics and laboratory data, in-
cluding age, sex, BMI, CKD etiology, medications used
(angiotensin-converting enzyme inhibitors, angiotensin II
receptor blockers, aldosterone receptor antagonists, and
statins), Scr, serum albumin, and 24-hour urine protein
(UP), were obtained from their medical records.

At Osaka General Medical Center, BP was measured
using a fully automatic device with the patient in a sitting
position after awaking in the morning. At Ohmihachiman
Community Medical Center, the patients underwent am-
bulatory BP monitoring, and the BP average over 24 hours
was used for the analysis. Mean BP was defined as the
diastolic pressure plus one third of the pulse pressure.

Statistical Analyses
Data were presented as the number (percent) for cate-
gorical variables and the mean ± SD for continuous vari-
ables with normal distribution or median (interquartile
range) for data with skewed distribution. A normal quantile-
quantile plot was used to assess the normality of each vari-
able. The baseline characteristics and eGFR slope were
compared across the three NH groups using the chi-
squared test, ANOVA with the Tukey–Kramer posthoc
test, and the Kruskal–Wallis test as appropriate. The corre-
lation between 4% ODI as a continuous variable and the
eGFR slope was assessed using Pearson’s product–moment
correlation coefficient. To investigate an independent
association between the NH groups and the eGFR slope, a mixed effect multiple linear regression model was constructed, in which all baseline characteristics (age, sex, eGFR, BMI, mean BP, UP, serum albumin, type 2 diabetic nephropathy, and medications [angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, aldosterone receptor antagonists, and statins]) were included as fixed effects and center as a random effect. In addition, we performed the same analyses to estimate the correlation between the duration of SpO2<90% (as a continuous variable) and eGFR slope.

Data were missing for BP (n=1), serum albumin (n=3), and UP (n=2); because of the small number of missing data, all results were based on the available data without using any imputation method. All reported P values were two-sided, and values of P<0.05 were considered to indicate statistical significance. Statistical analyses were performed using StataIC 12 Statistical Software (StataCorp LP, College Station, TX).

Results

During the enrollment period, a total of 190 patients with stages 3–4 CKD whose BMI was less than 25.0 kg/m² underwent the screening examination for NH; of these patients, 29 patients were excluded from the study (2 patients were diagnosed with chronic obstructive pulmonary disease, 16 patients were hospitalized for AKI and systemic infection, and 11 patients were followed up for less than 6 months). No participants received oxygen supplementation or CPAP therapy with good adherence. The remaining 161 participants were eligible for additional analysis. The baseline characteristics according to three NH groups are summarized in Table 1. The mean BMI was slightly but significantly higher in the mild and moderate-to-severe NH groups than the non-NH group. The etiologies of CKD were hypertensive nephrosclerosis (n=59), type 2 diabetic nephropathy (n=39), chronic GN (n=35), polycystic kidney disease (n=3), hydronephrosis (n=2), other (n=3), and unknown (n=20). No patients with chronic GN were on active immunosuppressive therapy, including oral steroids. The prevalence of type 2 diabetic nephropathy was approximately two times as high in the moderate-to-severe NH group as the other two groups, although this difference was not statistically significant.

Figure 1 shows the eGFR slope for each NH group. The eGFR declined three- to fourfold faster in the moderate-to-severe NH group than the non- and mild NH groups (mean levels ± SD were −2.14±4.86, −3.02±6.86, and −8.59±12.37 ml/min per 1.73 m² per year in the non-, mild, and moderate-to-severe NH groups, respectively; P=0.003, ANOVA). This significant association was maintained after excluding those patients with missing follow-up data on SCr (P=0.02, ANOVA). A subcohort analysis including only patients with type 2 diabetic nephropathy found a similar result (data not shown). A significant negative correlation was observed between eGFR slope and 4% ODI treated as a continuous variable (Pearson’s r=−0.17, P=0.02). Moreover, NH remained a significant predictor of a rapid decline in kidney function in the mixed effect linear regression model adjusting for center and all kinds of baseline characteristics (P=0.03) (Table 2). Additional analyses of the relationship between duration of SpO2<90% and eGFR slope were performed in 120 participants whose data on duration of SpO2<90% were available. A significant negative correlation was found in the Pearson’s product–moment correlation coefficient.

### Table 1. Baseline characteristics of 161 patients with CKD stratified by the severity of nocturnal hypoxemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=161)</th>
<th>Severity of Nocturnal Hypoxia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (n=81)</td>
<td>Mild (n=64)</td>
<td>Moderate to Severe (n=16)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>68.8±11.4</td>
<td>66.8±12.9</td>
<td>71.0±9.8</td>
</tr>
<tr>
<td>Man, n (%)</td>
<td>122 (75.8)</td>
<td>57 (70.4)</td>
<td>52 (81.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.8 (20.1, 23.1)</td>
<td>21.1 (19.6, 22.6)</td>
<td>22.1 (20.8, 23.7)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, n (%)</td>
<td>39 (24.2)</td>
<td>15 (18.5)</td>
<td>17 (26.6)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>129.5±17.9</td>
<td>127.0±17.6</td>
<td>131.8±17.9</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>77.0±17.2</td>
<td>76.8±18.8</td>
<td>78.4±16.4</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.85±0.59</td>
<td>1.87±0.65</td>
<td>1.88±0.53</td>
</tr>
<tr>
<td>Estimated GFR, ml/min per 1.73 m²</td>
<td>31±11</td>
<td>31±11</td>
<td>30±10</td>
</tr>
<tr>
<td>Urine protein, g/d</td>
<td>0.22 (0.06, 0.79)</td>
<td>0.22 (0.06, 0.79)</td>
<td>0.24 (0.07, 0.88)</td>
</tr>
<tr>
<td>Serum albumin, g/d</td>
<td>3.68±0.62</td>
<td>3.62±0.74</td>
<td>3.82±0.38</td>
</tr>
<tr>
<td>ACEI/ARB use, n (%)</td>
<td>115 (71.4)</td>
<td>51 (63.0)</td>
<td>51 (79.7)</td>
</tr>
<tr>
<td>Aldosterone receptor antagonists, n (%)</td>
<td>7 (4.4)</td>
<td>4 (4.9)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>44 (27.5)</td>
<td>20 (24.7)</td>
<td>19 (30.2)</td>
</tr>
</tbody>
</table>

Values are the mean ± SD, median (interquartile range), or number (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 2 receptor blocker.

*p<0.05 versus the non-NH group (posthoc Tukey–Kramer test).
Table 2. Mixed effects multivariate linear regression model for declining rate of estimated GFR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized Partial Regression Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>-0.02</td>
<td>0.80</td>
</tr>
<tr>
<td>Sex, man</td>
<td>0.06</td>
<td>0.42</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.02</td>
<td>0.77</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>-0.09</td>
<td>0.23</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>0.06</td>
<td>0.40</td>
</tr>
<tr>
<td>Nocturnal hypoxemia</td>
<td>-0.16</td>
<td>0.03</td>
</tr>
<tr>
<td>Estimated GFR, ml/min per 1.73 m²</td>
<td>-0.19</td>
<td>0.008</td>
</tr>
<tr>
<td>Urine protein, g/d</td>
<td>-0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>0.05</td>
<td>0.46</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td>0.05</td>
<td>0.51</td>
</tr>
<tr>
<td>Aldosterone receptor antagonist use</td>
<td>0.03</td>
<td>0.66</td>
</tr>
<tr>
<td>Statin use</td>
<td>-0.08</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Model adjusted for center, age, sex, estimated GFR, body mass index, mean BP, urine protein, serum albumin level, type 2 diabetic nephropathy, and medications used (ACEIs/ARBs, aldosterone receptor antagonists, and statins). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 2 receptor blocker.

Discussion

The major finding of this cohort study was that NH was significantly associated with a faster decline in eGFR among patients with CKD whose BMI was less than 25.0 kg/m². Although high prevalence of NH and its risk for cardiovascular mortality has been shown among ESKD patients (17–20), little is known about NH in the nondialysis CKD population. To the best of our knowledge, this study is the first longitudinal study of nonobese patients with CKD to show a significant influence of NH on the progression of kidney failure. The several previous cross-sectional studies showing a significant association between SDB and kidney function in patients with CKD (1–4,26) support our findings. As mentioned above, the single previous longitudinal study (27) showing a faster declining rate of eGFR in patients with NH than in patients without NH is difficult to extrapolate to the CKD population because of their maintained baseline kidney function. In addition, the participants in that study were severely obese (mean BMI=35.7 kg/m² in patients with NH versus mean BMI=30.6 kg/m² in patients without NH). Because obesity is both a risk factor for the progression of kidney failure (36–38) and a major cause of NH (39), it could confound the relationship between NH and deterioration of kidney function. To address this concern, we included only patients with CKD whose BMI was less than 25.0 kg/m²; although BMI still differed significantly between the NH groups in our cohort, this small difference seems insufficient to explain the remarkably steeper eGFR slope observed in the moderate-to-severe NH group. In addition, we showed in our multivariate analysis that the significant relationship between NH and CKD progression was independent of BMI.

Several mechanisms by which NH could accelerate CKD progression can be hypothesized. NH causes hypertension through activation of the renin-angiotensin system and the sympathetic nervous system (12,13). Therefore, NH could contribute to CKD progression by increasing BP. In our study, however, BP level did not differ significantly among the NH groups. The reason for this finding is unclear, but it may be partly because CKD itself is a strong cause of hypertension, thus masking the influence of NH on BP in this population. In addition, our patients were participating in the CKD educational programs and therefore, received intensive pharmaceutical treatment for hypertension and instruction in dietary sodium restriction. Indeed, the BP level in all NH groups was close to the optimal level for the prevention of CKD progression (40). Taken together, in the current study, hypertension did not likely mediate the association between NH and CKD progression.

Rather, our finding of an independent relationship between the eGFR slope and NH suggests the presence of a direct NH-related kidney injury pathway. NH is known to induce systemic inflammation, oxidative stress, endothelial cell dysfunction, and activation of the renin-angiotensin system (7–11,13–16), all of which are also intimately involved in CKD progression (25,41). NH can,
Therefore, be assumed to impede kidney function through these pathologic factors, possibly through ischemic tubulo-interstitial and vascular damage. Additional studies should investigate the precise mechanisms underlying the promotion of CKD progression by NH.

Our results have an important clinical implication. Kidney failure and nephrotic proteinuria have been reported to cause obstructive sleep apnea, mainly because of airway edema resulting from fluid overload and low osmolality (42–44). In turn, this study has shown the possible adverse effects of NH on kidney function in patients with CKD. Therefore, CKD and NH seem to aggravate each other. This reciprocal relationship and their common background of metabolic syndrome are anticipated to form a vicious cycle, resulting in a remarkable clustering of cardiovascular risk within an individual CKD patient. Additional clinical studies are warranted to verify whether NH is truly a risk factor for cardiovascular disease in the CKD population and whether CPAP treatment could modify this risk.

Several limitations to the interpretation of the results of this study should be noted. First, this study cannot prove a causal relationship between NH and CKD progression because of its observational nature. Although our multivariate analysis was controlled for several major clinical factors related to both CKD progression and NH, the possibility of residual confounding by unmeasured factors, such as the presence or absence of cardiovascular complications, cannot be excluded. Second, because of the retrospective data collection from two independent nephrology centers, the examination procedures and laboratory measurements methods, especially BP monitoring, were not unified and standardized across the centers. We, therefore, used a mixed effect model including center as a random effect to incorporate center-to-center variation and within-center clustering into the multivariate analysis. We also confirmed that BP level did not differ significantly among the three NH groups when analyzed separately within each center (data not shown), which was also true of the total cohort. Third, given the short follow-up duration of 1 year, the slope of eGFR assessed in this study might have in

in non-Asian populations (47). Therefore, the generalizability of our findings to the younger, obese, and non-Asian population is uncertain, although the study by Ahmed et al. (27), which targeted younger and much more obese participants than those patients in our study, showed that NH was a significant predictor of the rapid decline of kidney function.

In conclusion, NH, a frequent comorbidity of CKD, was an independent risk factor of a rapid decline in kidney function in nonobese patients with CKD. The precise mechanisms underlying kidney injury by NH should be further investigated. The close relationship between NH and CKD and their association with metabolic syndrome are anticipated to pose a currently unrecognized but serious cardiovascular risk in the CKD population. Additional studies are needed to determine whether CPAP therapy improves renal prognosis and reduces cardiovascular risk in this population.

Disclosures
None.

References


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