Obstructive sleep apnoea: a stand-alone risk factor for chronic kidney disease

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Abstract

Background. Previous studies have found an association between obstructive sleep apnea (OSA) and chronic kidney disease (CKD). However, subjects with confounding factors such as diabetes and hypertension were not excluded. The purpose of the present study was to determine whether patients with OSA without meeting criteria for diabetes or hypertension would also show increased likelihood of CKD.

Methods. We prospectively enrolled adult patients with a chief complaint of habitual snoring. Overnight polysomnography, fasting blood triglyceride, cholesterol, glucose, insulin, creatinine, albumin and hemoglobin A1c, and first voiding urine albumin and creatinine were examined. Estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), homeostatic model assessment-insulin resistance and percentage of CKD were calculated.

Results. The final analyses involved 40 patients who were middle-aged [44.8 (8.6) years] predominantly male (83%), obese [body mass index, 28.2 (5.1) kg/m2] and more severe OSA, with an apnea–hypopnea index (AHI) of 51.6 (39.2)/h. The mean eGFR and UACR were 85.4 (18.3) mL/min/1.73m2 and 13.4 (23.4) mg/g, respectively. The prevalence of CKD in severe OSA subjects is 18%. With stepwise multivariate linear regression analysis, AHI and desaturation index were the only independent predictor of UACR (β = 0.26, P = 0.01, R² = 0.17) and eGFR (β = 0.32, P < 0.01, R² = 0.32), respectively.

Conclusions. High prevalence of CKD is present in severe OSA patients without hypertension or diabetes. Significantly positive correlations were found between severity of OSA and renal function impairment.

Keywords: albuminuria; glomerular filtration rate; kidney; obstructive sleep apnea

Introduction

Chronic kidney disease (CKD) affects 10–13% of the general population and is associated with substantial morbidity, including poor health outcome, particularly cardiovascular
diseases and end-stage kidney disease [1,2]. This common disease has become a major public health problem. The latest health care cost for CKD patients is currently estimated at 57.5 billion US dollars (near 28% of total Medicare spending) and this is rapidly growing [3]. CKD is defined and staged according to estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² or eGFR >60 mL/min/1.73m² with kidney damage, such as microalbuminuria [urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g], renal histological abnormalities and other abnormalities in blood or urine test [4]. Hypertension and diabetes are the two major causes of CKD but 25.6% of patients have unexplained CKD [5].

Obstructive sleep apnea (OSA) affects ~2–4% of middle-aged adults in developed countries [6,7]. OSA events can induce significant intermittent hypoxemia, hemodynamic instability and increased sympathetic activity [8]. Patients with OSA were evidenced to have oxidative stress, an inflammatory state, increased mean blood pressure and endothelial injury [8]. Similar physiological stressors may contribute to albuminuria and renal injury in diabetic nephropathy [9]. Thus, we hypothesized that individuals with OSA and without known diabetes or hypertension would have an increased likelihood of markers of CKD.

Previous studies have found an association between OSA and CKD, but it is difficult to ascertain how much of the relationship may be ascribed to hypertension or diabetes in these patients and whether individuals without diabetes and hypertension also have an increased risk of CKD. For example, an increased risk of sleep apnea in early CKD patients was found in a retrospective study which included diabetics and hypertensives [10]. In another study, the prevalence of CKD was found to be higher across all individuals diagnosed with OSA in a sleep clinic but here again, the group included individuals with confounding conditions [11]. Similarly, Fleischmann et al. [12] found that apneic events predicted the severity of CKD but did not analyze in a group excluding diabetes and hypertension. Similar findings have been observed for UACR, where associations have been found between the apnea hypopnea index (AHI) and the UACR but not with both diabetics and hypertensives excluded [13,14].

Thus, the purpose of the present study was to determine whether patients presenting to the sleep clinic without meeting criteria for diabetes or hypertension would also show increased likelihood of CKD. Such a finding would substantiate OSA as an independent risk factor for CKD.

Materials and methods

Clinical patients

The Research and Ethics Committee of the Chang Gung Memorial Hospital in Taiwan approved the study protocol in advance (CGMHIRB no. 970231C), and each patient provided informed consent before participating. This study was funded by Change Gung Memorial Hospital (CMRP no. G660241). We prospectively included patients presenting to the Sleep Clinic for overnight polysomnography (PSG) between November 2007 and October 2009 who were >20 years old and had a chief complaint of habitual snoring. We excluded patients diagnosed with hypertension, diabetes mellitus (DM), abnormal renal function, liver cirrhosis, chronic obstructive pulmonary disease, hematological disease, autoimmune disease, cancer or who had suffered a recent infection.

We further excluded patients with a fasting sugar level >126 mg/dL or hemoglobin A1c (HbA1c) >6.4% (as having DM) and patients with a serum creatinine level >1.4 mg/dL, as having renal function impairment. We excluded patient who were hypertensive, defined as a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg for two consecutive measurements taken immediately after overnight PSG.

Sleep study

Conventional overnight PSG (Embla N7000; Medcare, Reykjavik, Iceland) was performed in a sleep laboratory between the hours of 22:00 and 06:00–07:00 to document sleep parameters and architecture. Measures were made under quiet dark conditions and included two electroencephalogram channels (C3/A2 and C4/A1), a bilateral electro-oculogram, chin and left and right anterior tibial electromyograms, an electrocardiogram, airflow (using nasal and buccal thermistors), chest and abdominal wall movements (using inductive respiratory plethysmography bands), snoring (using a neck microphone) and arterial oxygen saturation (SpO2; using pulse oximetry). Video recordings were used to assess the behavior of patients. All measurements were collected with a computerized sleep system (Somnologica Studio 3.0; Medcare). On the basis of the recommendations of the American Academy of Sleep Medicine (2005) [15], apnea was defined as a cessation of airflow for at least 10 s. Hypopnea was defined as an abnormal respiratory event with at least 30% reduction in airflow compared to the baseline value and lasting at least 10 s and with equal or more than a 4% oxygen desaturation or an arousal. Baseline was defined as the mean amplitude of the three largest breaths in the 2 min preceding the onset of the event. A desaturation episode was defined as a drop of ≥4% in SpO2 induced by an apneic or hypopneic event. The AHI was defined as the combined number of apneic and hypopneic events per hour of total sleep time, and the desaturation index (DI), as the number of desaturation episodes per hour of total sleep time. The variables of gender, age and body mass index (BMI) were recorded simultaneously with PSG. BMI was defined as weight (kilogram) divided by height (square meters).

Biochemical tests

Blood and urine samples were obtained immediately in the morning after the PSG and blood pressure measurements. Fasting glucose and cholesterol levels were determined using an enzymatic method (Synchorn LX20PRO; Beckman Coulter Inc., Fullerton, CA). Triglycerides, blood and urine creatinine and blood albumin levels were determined using a colorimeter (Hitachi 7600-210; Hitachi Ltd., Tokyo, Japan). The methods used to determine HbA1c, insulin and urine albumin levels were high-performance liquid chroma-
Table 1. Demographic characteristics of snorers in our study (total n = 40)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.8 (8.6)</td>
<td>29.3–66.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 (5.1)</td>
<td>20–41.4</td>
</tr>
<tr>
<td>AHI (per h)</td>
<td>51.6 (39.2)</td>
<td>3.1–145.1</td>
</tr>
<tr>
<td>DI (per h)</td>
<td>37.0 (33.3)</td>
<td>0–127.1</td>
</tr>
<tr>
<td>UACR (mg/g)</td>
<td>13.4 (23.4)</td>
<td>1.8–129.8</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>85.8 (18.3)</td>
<td>60.0–141.0</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 (0.2)</td>
<td>0.4–1.3</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>4.4 (0.2)</td>
<td>3.8–4.8</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 (0.3)</td>
<td>4.8–6.3</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.2 (1.8)</td>
<td>0.3–7.7</td>
</tr>
</tbody>
</table>

* eGFR is calculated using the Modification of Diet in Renal Disease formula.

Table 2. Correlation coefficients and stepwise linear regression analyses of the relationships between the UACR and eGFR and demographic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.15</td>
<td>0.36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.25</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.1</td>
<td>0.53</td>
</tr>
<tr>
<td>AHI (per h)</td>
<td>0.39</td>
<td>0.01</td>
</tr>
<tr>
<td>DI (per h)</td>
<td>0.34</td>
<td>0.03</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>-0.09</td>
<td>0.6</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>-0.19</td>
<td>0.24</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>0.29</td>
<td>0.09</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.09</td>
<td>0.59</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.1</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Table 3. Stepwise multivariate linear regression models for UACR and eGFR

<table>
<thead>
<tr>
<th>Variables in the regression model</th>
<th>R²</th>
<th>β</th>
<th>95% CI of β</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>For UACR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI</td>
<td>0.17</td>
<td>0.26</td>
<td>0.063–0.455</td>
<td>0.01</td>
</tr>
<tr>
<td>For eGFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DI</td>
<td>0.32</td>
<td>0.32</td>
<td>0.157–0.472</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Valid sample size n = 37.

Statistical analysis

Categorical data included gender and hyperlipidemia, and numerical data included age, BMI, AHI, DI, UACR, eGFR, blood creatinine, albumin, HbA1c and HOMA-IR. Associations among the variables were investigated with Pearson’s correlation. We analyzed the effects of gender, age, BMI, AHI, DI, hyperlipidemia, HOMA-IR, blood creatinine, albumin and eGFR on UACR and the effects of BMI, AHI, DI, hyperlipidemia, HOMA-IR and albumin on eGFR. These analyses were performed by multivariate stepwise linear regression to exclude confounding factors. Retrospective post hoc power was calculated for all significant variables. All tests were two tailed, and a P-value <0.05 was considered to be statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences 15.0 for Windows (SPSS Inc., Chicago, IL).

Results

Upon diagnosis of OSA or simple snoring from PSG, a total of 64 consecutive outpatients were enrolled in the present study. As expected, high percentages of individuals with OSA had hypertension and/or DM (34%). In addition, one patient was excluded on account of a fever on the day of study. Another patient who was definitely classified as having renal function impairment by eGFR (57.7 mL/min/1.73m²) was also excluded. The other patient who had a high calculated eGFR (229 mL/min/1.73m²) by MDRD formula was adjusted to eGFR = 141 mL/min/1.73m² according to the CKD-EPI creatinine equation [19]. Thus, 40 subjects were included in our analyses. Table 1 shows the demographic characteristics of the included subject. There were 3 subjects (7.5%) with an AHI <5/h (simple snorer), 6 subjects (15%) had mild OSA (AHI 5–15/h) and 3 subjects (7.5%) had an AHI 15–30/h considered moderate OSA and 28 (70%) had what is considered severe OSA (AHI >30/h). Of all 40 patients, 9 (23%) had a BMI <24 kg/m² and 22 (55%) were obese (BMI > 27 kg/m²). AHI was significantly correlated with gender (r = 0.38, P = 0.02), BMI (r = 0.39, P = 0.01) and the DI (r = 0.92, P < 0.01).

Of 37 OSA patients, without diabetes or hypertension or preexisting with kidney function abnormality, 5 (14%) of them met the criteria of CKD disease (4 are Stage 1 and 1 is Stage 2), especially in severe OSA patients (18%). However, no one (0%) met the criteria of CKD in the three simple snorers and in individuals with mild OSA. In addition, no proteinuria was found in any of our OSA patients. By Pearson’s correlation analyses, we found the UACR and eGFR of each patient to be significantly correlated with AHI: AHI versus UACR (r = 0.39, P < 0.05) and AHI versus eGFR (r = 0.46, P < 0.01). Similarly the DI correlated with both the UACR and the eGFR: DI versus UACR, r = 0.34, P < 0.05 and DI versus eGFR, r = 0.51, P < 0.01. Data are summarized in Table 2.
We next performed multivariate linear regression models for associations involving UACR and eGFR. Stepwise linear regression analyses showed that AHI was the only independent predictor of UACR ($\beta = 0.26$, $P = 0.01$, $R^2 = 0.17$, 95% confidence interval (CI) of $\beta = 0.063–0.455$) and DI was the only independent predictor of eGFR ($\beta = 0.32$, $P < 0.01$, $R^2 = 0.32$, 95% CI of $\beta = 0.157–0.472$). Data are summarized in Table 3. Retrospectively, the power of AHI for UACR and DI for eGFR were 0.72 and 0.93, respectively.

We next compared the AHI versus UACR relationship with relationships between DI versus UACR, occult diabetic (using HOMA-IR) versus UACR, BMI versus UACR and triglyceride versus UACR. Results for each of these are presented in Figure 1. In summary, the only significant relationship was between AHI or DI and UACR. The UACR was >30 mg/g (microalbuminuria) in five patients, all of whom also had an AHI >30/h. The mean (± standard error) of UACR in simple snorers, mild, moderate and severe OSA groups were 3.6 (0.4), 5.2 (1), 10.5 (3.5) and 16.5 (5) mg/g, respectively. A wider range of UACR was found in more severe OSA groups.

In a similar fashion, we next explored the relationship between DI and eGFR, comparing these data with linear relationships between eGFR and AHI, UACR, BMI, HOMA-IR and triglyceride. As summarized in Figure 2, the significant relationships in these individuals were eGFR to AHI, DI, BMI and HOMA-IR: AHI versus eGFR ($r^2 = 0.21$, $P < 0.01$), DI versus eGFR ($r^2 = 0.26$, $P < 0.01$), BMI versus eGFR ($r^2 = 0.17$, $P < 0.01$) and HOMA-IR versus eGFR ($r^2 = 0.14$, $P = 0.02$). No significant association was found between eGFR and UACR in our subjects (Figure 2B). In addition, most of our CKD patients had an increased eGFR.

**Discussion**

In the present study, we found that a high percentage (18%) of severe OSA patients who were non-hypertensive,
nondiabetic and had no preexisting kidney abnormality have CKD. In addition, UACR is independently correlated with the severity of OSA. A significant association between eGFR and frequency of desaturation was identified in our study. A correlation between UACR and the severity of OSA or duration of oxygenation desaturation during sleep has previously been reported [13,14,20]. However, these previous studies did not exclude patients with DM or hypertension or the effect of eGFR—conditions in which UACR is known to be influenced. BMI and hyperlipidemia are reported to contribute to increases in eGFR and UACR [21]. We used a stepwise regression model and found only AHI to be independently correlated with UACR and eGFR. Daytime activity is known to influence urine albumin excretion rates, and UACR is \( \sim 25\% \) lower during sleep than during waking periods [21]. We reduced the potential for variation in UACR by using first voiding urine. By excluding all the confounding factors, our study strongly supports the concept that there is a specific association between renal injury and OSA. In addition to traditional factors [4], we demonstrate that OSA may be a risk factor for initiation and progression of CKD (Figure 3).

In Figure 2, linear relationships between eGFR and variables. Significantly positive correlations are showed between AHI and eGFR (A), desaturation index and eGFR (C), BMI and eGFR (D) and HOMA-IR and eGFR (E). However, no strong correlation is found between UACR and eGFR (B) and triglyceride and eGFR (F). eGFR is calculated using the Modification of Diet in Renal Disease formula.

In Figure 3, risk factors for initiation and progression of CKDs. In addition to traditional factors, OSA may be a new risk factor for initiation and progression of CKD.
Obstructive sleep apnea 2249

results to other ethnicities. In the south-east Asian, one should carefully extrapolate our
management of UACR [30]. Since all subjects in our study were
in high-density lipoprotein levels, smoking, salt intake,
some confounding factors that contribute to microalbuminuria
exclude other confounding factors in our study. In addition,
relative small sample size may be criticized to statistically
end point in gauging clinical efficacy of therapy for OSA.

OSA and higher eGFR, we should consider eGFR as an
management. At the same time, in managing individuals with
find a significant positive relationship between glomerular
ence the course of progression of CKD, independently of
suggests that OSA could induce hyperfiltration and influ-
regression [9]. In the present study, 14% of non-hyperten-
itive, non-diabetic OSA patients had an UACR >30 mg/g,
which could place them at increased risk of progression to
proteinuria, although this will require further study. There is
growing evidence in a variety of populations that even low
grade albuminuria is associated with an increased risk of
progressing atherosclerosis, developing new-onset diabetes,
coronary heart disease and death [22–24]. The mean UACR
of the general population is reported to be in the range of
5.91–6.5 mg/g [23]. However, relatively healthy individuals
with a UACR not significantly greater than the upper limit
of this range (>6.7 mg/g) have been found to be at an
increased risk of mortality [25]. Wang et al. [26] reported an
~2-fold risk of developing hypertension in men with a
UACR >6.66 mg/g and in women with a UACR >15.24
mg/g. We also found 30% of our OSA patients to have a
UACR between 6.7 and 30 mg/g, suggesting that they could be
at an increased risk of experiencing cardiovascular events
or developing hypertension.

The association between eGFR and severity of OSA re-
ains controversial. Both positive and negative correlations
have been reported, when diabetics and hypertensives are
included [12,27–29]. More studies demonstrated hyperfil-
tration condition in OSA patients [27,28]. However, glomer-
ular hyperfiltration is a well-established phenomenon
in diabetic patients of early diabetic nephropathy [9]. We
find a significant positive relationship between glomerular
filtration rate and the frequency of desaturation—DI. This
suggests that OSA could induce hyperfiltration and influ-
ence the course of progression of CKD, independently of
diabetes.

Several studies have demonstrated that glomerular hyper-
filtration in OSA patients may be reversed after continuous
positive airway pressure therapy [27–29]. These findings
highlight the importance of assessing eGFR in OSA man-
agement. At the same time, in managing individuals with
OSA and higher eGFR, we should consider eGFR as an
end point in gauging clinical efficacy of therapy for OSA.

Our study is subject to some limitations. Although the
power of AHI and DI for UACR and eGFR were >0.70, the
relative small sample size may be criticized to statistically
exclude other confounding factors in our study. In addition,
some confounding factors that contribute to microalbuminu-
uria were not considered in our study, such as decreasing in
high-density lipoprotein levels, smoking, salt intake,
volume status and DD genotype of angiotension [21,30].
Beside, race is also a factor that can affect the measure-
ment of UACR [30]. Since all subjects in our study were
south-east Asian, one should carefully extrapolate our
results to other ethnicities.

Our study shows the presence of renal injury in nonhyper-
tensive non-diabetic OSA patients, thereby suggesting that
the renal function of OSA patients should be evaluated.
Longitudinal studies are required to clarify how increases in
UACR relate to cardiovascular consequences and how
eGFR changes with disease progression in OSA patients.
The extent to which renal injury can be reversed by treating
OSA also needs further study.

Acknowledgements. Transparency declaration. All authors declare that they have no conflict of interest.


References

Background. Cardiovascular disease (CVD) is the leading cause of death among chronic kidney disease (CKD) patients. Vascular calcification is highly prevalent in this population and is an independent predictor of cardiovascular mortality. Vascular calcification in uraemic patients is known to be an active and regulated process subject to the action of many promoting and inhibitory factors. The role of vitamin D in this process remains controversial. We evaluated the relationship between serum levels of 25-hydroxyvitamin D and vascular calcification evaluated by plain X-ray images, in predialysis patients with CKD stages 4 and 5.

Methods. We performed a cross-sectional study with 210 CKD patients stages 4 and 5 managed at our predialysis unit. Patients were 63.5 ± 13 years of age, 60.5% males, 64.8% diabetics and 47.1% with a history of CVD. Plain X-ray images of pelvis, hands and lateral lumbar spine from all subjects were studied for calculation of semiquantitative vascular calcification scores as described by Adragao and Kauppila.

Results. We found a high prevalence of vascular calcification in our population. Adragao scores revealed only 47 patients (22.4%) without vascular calcification and 120 (57.1%) with scores higher than 3. Kauppila scores revealed only 29 patients (13.8%) without aortic calcifications and 114 patients (54.3%) with scores higher than 7. Higher vascular calcification scores were related to older age, diabetics, history of CVD and lower levels of 25(OH)D. Only 18.5% of patients had adequate levels of 25(OH)D (>30 ng/mL), 53.7% of them had insufficient levels (15–30 ng/mL) and 27.8% had deficient levels.

Vascular calcification and 25-hydroxyvitamin D levels in non-dialysis patients with chronic kidney disease stages 4 and 5

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