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SCIENTIFIC INVESTIGATIONS

Independent Contributions of Obstructive Sleep Apnea and the Metabolic Syndrome to the Risk of Chronic Kidney Disease

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Study Objectives: This retrospective study was conducted to evaluate the associations and interactions among obstructive sleep apnea (OSA), chronic kidney disease (CKD), and metabolic syndrome (MS).

Methods: This study included 1,732 subjects (1,482 male and 250 female) in whom OSA was diagnosed by polysomnography. The severity of OSA was defined as mild, moderate, or severe with an apnea-hypopnea index (AHI) score of 5 to < 15, 15 to < 30, and ≥ 30 events/h, respectively. CKD was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 or albuminuria.

Results: The prevalence of MS was 29.2% (n = 505). One hundred twenty-nine subjects (7.4%) had CKD. In subjects with MS, CKD prevalence increased progressively with OSA severity: 7.4%, 12.5%, and 15.8% in those with mild, moderate, or severe OSA, respectively (P = .025). Each 10-point increment in AHI score was independently associated with a 1.15-fold higher prevalence of CKD [95% confidence interval (CI), 1.036–1.280; P = .009] after adjustment for all individual components of MS. On the contrary, in those without MS, AHI was not associated with increased odds for CKD [odds ratio, 1.054; 95% CI, 0.930–1.195].

Conclusions: The independent association between OSA severity and CKD prevalence was observed only in subjects with MS. Further studies are needed to ascertain if OSA contributes to the development of CKD in subjects with MS.

Keywords: chronic kidney disease, metabolic syndrome, obstructive sleep apnea, risk factors

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INTRODUCTION

Chronic kidney disease (CKD) is associated with increased morbidity and mortality as well as decreased quality of life.[1–3] An estimated 8% to 16% of the general population has CKD; the prevalence of CKD is increasing steadily, and this increase has become a worldwide public health problem.[4–6] Therefore, identifying and managing modifiable risk factors related to CKD is important. Age, sex, diabetes, hypertension, glomerulonephritis, and cigarette smoking are well-known risk factors for CKD.[7,8] In addition, metabolic syndrome (MS), a combination of metabolic abnormalities including central obesity, impaired glucose metabolism, high blood pressure, and dyslipidemia, has been suggested as a potential risk factor of CKD.[9] These multifactorial conditions may affect the development of CKD independently or by interacting with each other.[9,10]

Obstructive sleep apnea (OSA) is a common sleep disorder that is characterized by recurrent episodes of upper airway collapse, resulting in intermittent hypoxemia and recurrent arousals from sleep.[11] An insufficient oxygen supply to the brain tissue due to hypoxemic events in OSA is thought to induce daytime hypersomnolence, fatigue, poor quality of life, and increased overall morbidity and mortality that may overlap with characteristics of CKD.[12] In addition to episodes of apnea, volume overload, secondary hyperaldosteronism, increased sympathetic activity, vasoconstriction, and increased inflammatory markers may be mediators linking OSA and CKD.[13]

Indeed, several epidemiological studies have suggested a possible link between OSA and CKD.[14–17] Molnar et al. have reported incident OSA is associated with incident CKD after adjusting for age, sex, race, and baseline renal function in a large cohort of United States Veterans.[16] In a cohort study by Lee et al., OSA was related to an increased risk for CKD as well, although the diagnoses of OSA and CKD relied on administrative claims data.[17] Moreover, it has been reported that OSA is accompanied by end-stage renal disease (ESRD) in

BRIEF SUMMARY

Current Knowledge/Study Rationale: The association between obstructive sleep apnea (OSA) and chronic kidney disease (CKD) has been suggested but this link may be mediated by metabolic syndrome (MS). This study evaluated the associations between OSA severity and CKD with a focus on the possible interaction of MS in this association.

Study Impact: OSA was independently associated with an increased prevalence of CKD only in subjects with MS. These findings suggest that OSA might be an additional burden that exacerbates the risk of CKD in subjects with MS.

more than half of patients (50% to 70%).[18,19] It was reported that fluid overload contributed to the pathogenesis of OSA in ESRD, and that fluid removal by ultrafiltration attenuated sleep apnea without altering uremic status.[20] However, the causal relationship between OSA and CKD is still unclear. A high rate of comorbidity between OSA and CKD may be a simple reflection of shared common risk factors.

OSA is closely associated with insulin resistance. Hypoxia and sleep fragmentation in OSA are known to induce glucose dysregulation and insulin resistance.[21] In addition, it has been reported that OSA was independently associated with the overall prevalence of MS.[22] Yet, it is not certain whether that presence of MS could be an additive effect on OSA severity or CKD prevalence or not. Therefore, we investigated the associations between OSA and CKD with a focus on a possible MS interaction in a large retrospective cross-sectional study.

METHODS

Study Population

We identified subjects who participated in a comprehensive health checkup service after OSA was diagnosed by polysomnography (PSG) at Samsung Medical Center in Seoul. The health service program includes a medical questionnaire, anthropometry investigation, and laboratory tests. Between January 2000 and December 2014, OSA was diagnosed by PSG in a total of 7,302 subjects. Of these, we included 1,732 subjects who received a medical checkup. The median and interquartile range (IQR) for lapse between laboratory tests and the PSG was 8.2 months (IQR, 2.4–42.6 months). This retrospective study protocol was reviewed and approved by the Institutional Review Board at Samsung Medical Center. The requirement of informed consent was waived because we used nonidentifiable data that were collected routinely during the health screening process.

Data Collection and Definitions

For each subject, the following information was collected: sex, age, body weight, height, smoking status, and medical history (diabetes mellitus, hypertension, and hyperlipidemia). Waist circumference was measured at the level of the umbilicus. Fasting venous blood was obtained from each subject and used for measurement of the levels of total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, glucose, and serum creatinine (sCr). A random urine sample was obtained for measurement of the albumin-to-creatinine ratio (ACR) or urinalysis. The urine dipstick tests used in our center react only to albumin and not to total proteinuria. In addition, fasting morning urine samples were collected to examine proteinuria in our subjects. Thus, we expected a positive dipstick test would reflect glomerular albuminuria. Estimated glomerular filtration rate (eGFR) was calculated according to the equation of the Chronic Kidney Disease Epidemiology Collaboration as follows:

$$\text{eGFR (mL/min/1.73 m}^2) = 141 \times \min(\text{sCr}/\kappa, 1)^{\alpha} \times \max(\text{sCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} (\times 1.018 \text{ if female}) (\times 1.159 \text{ if black})$$

where κ is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, min is the minimum of sCr/κ or 1, and max is the maximum of sCr/κ or 1.[23] MS was defined according to the criteria of the Adult Treatment Panel Guideline III[24] and central obesity criteria for Koreans[25] as three or more of the following risk factors: (1) high triglyceride level (≥ 150 mg/dL) or drug treatment for elevated triglyceride level, (2) low HDL-cholesterol level (< 40 mg/dL in men or < 50 mg/dL in women), (3) elevated fasting glucose level (≥ 100 mg/dL) or drug treatment for elevated glucose level, (4) high blood pressure (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg) or drug treatment for hypertension, and (5) abdominal obesity (waist circumference ≥ 90 cm in men or ≥ 85 cm in women). Abdominal obesity was also assumed for a body mass index (BMI) ≥ 30 kg/m^2.[26] CKD was defined as an eGFR ≤ 60 mL/min/1.73 m^2 or albuminuria (ACR ≥ 30 mg/g or urine dipstick values of 1+ to 4+).

Overnight Polysomnography

PSG were performed during 1 night of observation with standard electrodes and sensors using the Embla N7000 system (Medcare Flaga, Reykjavik, Iceland). Electroencephalography electrodes were applied at C3-A2, C4-A1, F3-A2, F4-A1, O3-A2, and O2-A1, and 4 electrooculography electrodes were applied on both sides, superior and inferior to the eyes, to record horizontal and vertical eye movements. Chin and both anterior tibialis electromyography and electrocardiography sensors were applied. Two plethysmography belts were used to monitor thoracic and abdominal movements. Nasal and oral airflow was measured with a nasal pressure transducer and thermistor. Oxygen saturation was measured by pulse oximetry on the index finger. Synchronized video monitoring was used to monitor abnormal sleep breathing or movements. We collected the following data from PSG: sleep parameters (time in bed, total sleep time, sleep latency, wake after sleep onset [WASO], sleep efficiency, arousal index); sleep stage (N1, N2, N3, R) %; and apnea-hypopnea index (AHI). Between 2000 and 2007, hypopneas were scored using reduction in amplitude of oronasal thermistor signal associated with either a 3% decrease in oxyhemoglobin saturation or an event-related arousal.[27] Since 2007, we followed new scoring criteria for hypopnea with this standard definition: a 30% reduction in airflow in association with a 4% fall in oxyhemoglobin saturation.[28] Apnea was defined as the complete cession of airflow for at least 10 seconds, and hypopnea was defined as a moderate reduction in airflow (> 30%) for at least 10 seconds with oxygen desaturation ≥ 4% or arousal.[28] Obstructive apnea is determined if it meets apnea criteria and is associated with continued or increased inspiratory effort throughout the entire period of absent airflow. Central apnea is scored if it meets apnea criteria and is associated with absent inspiratory effort throughout the entire period of absent airflow. AHI is expressed here as the number of apnea and hypopnea events per hour of sleep. The severity of OSA was defined as mild, moderate, or severe for AHI scores 5 to < 15, 15 to < 30, and ≥ 30 events/h, respectively.

Statistical Analyses

Continuous variables are expressed as the median and interquartile range, and were compared using the Mann-Whitney

Table 1—Baseline characteristics of study subjects according to MS status.

	Without MS (n = 1,227)	With MS (n = 505)	*P*
Age, years	54 (48–60)	54 (47–60)	.459
Sex, male, n (%)	1,019 (83.0)	463 (91.7)	< .001
Hypertension, n (%)	350 (28.5)	358 (70.9)	< .001
Diabetes mellitus, n (%)	108 (8.8)	177 (35.0)	< .001
Total cholesterol, mg/dL	192 (171–218)	194 (167–216)	.486
LDL cholesterol, mg/dL	123.0 (105.0–144.0)	119.0 (98.0–142.0)	.013
Triglyceride, mg/dL	108.0 (80.0–143.0)	183.0 (134.0–243.5)	< .001
HDL cholesterol, mg/dL	52.0 (45.0–61.0)	41.0 (36.0–51.0)	< .001
Fasting glucose, mg/dL	92.0 (87.0–99.0)	104.0 (95.0–116.0)	< .001
Creatinine, mg/dL	0.99 (0.88–1.08)	0.97 (0.88–1.10)	.358
eGFR, mL/min/1.73 m^2	85.2 (76.2–94.9)	86.6 (76.0–96.7)	.383
Urine ACR, mg/g	5.17 (2.69–9.15)	9.05 (4.14–22.14)	< .001
CKD, n (%)	64 (5.2)	65 (12.9)	< .001
eGFR < 60 mL/min/1.73 m^2, n (%)	34 (2.8)	22 (4.4)	.064
Albuminuria, n (%)	36 (2.9)	47 (9.3)	< .001
SBP, mmHg	118 (109–127)	127 (115–138)	< .001
DBP, mmHg	75 (69–82)	80 (73–89)	< .001
Waist circumference, cm	86.0 (82.0–90.0)	94.0 (90.8–99.0)	< .001
BMI, kg/m^2	24.4 (22.9–26.0)	26.7 (25.0–29.1)	< .001

Data are medians (interquartile range) or n (%) as indicated. ACR = albumin to creatinine ratio, BMI = body mass index, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MS = metabolic syndrome, SBP = systolic blood pressure.

U test. Categorical variables are expressed as percentages and were compared using the chi-square test. The Kruskal-Wallis test was used to compare differences in the median AHI according to the number of MS components. Separate univariate logistic regression analyses for the prevalence of CKD were conducted according to the presence or absence of MS because the association between OSA and CKD was dependent on the presence of MS. Multivariable logistic regression analysis was used to assess the independent contributions of individual components of MS, AHI, arousal index, and WASO to the prevalence of CKD in subjects with MS. We examined for interaction term to evaluate whether MS is an effect modifier of the association between AHI and CKD. All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, Illinois, United States). *P* values < .05 were considered to be significant.

RESULTS

Comparing Demographics and Sleep Parameters Between Subjects With MS and Those Without MS

The overall study sample comprised 1,732 subjects (1,482 male and 250 female). The prevalence of MS was 29.2% (n = 505). Of the total subjects, 569 were defined as having MS based on BMI because waist circumference was unavailable. The baseline characteristics grouped according to MS status are summarized in **Table 1**. The AHI was significantly higher in subjects with MS than in those without the syndrome (**Table 2**). Severe OSA was more prevalent in subjects with MS than in those without the syndrome ($P < .001$). The frequencies of mild, moderate, and severe OSA were 38%, 30%, and 32%, respectively, in subjects without MS and 24%, 29%, and 48%, respectively in those with the syndrome. Median AHI increased progressively with the number of MS components ($P < .001$ for trends) (**Figure 1**). Sleep quality also deteriorated in subjects with MS compared to those without the syndrome. Compared to subjects without MS, those with the syndrome had lower nadir oxygen desaturation (84% versus 82%, $P < .001$) and more fragmented sleep (27.4 events/h versus 32.2 events/h for arousal index $P < .001$; 21.7% versus 25.1% for N1 sleep proportion, $P < .001$).

Different Association Between OSA and CKD in Accordance with MS

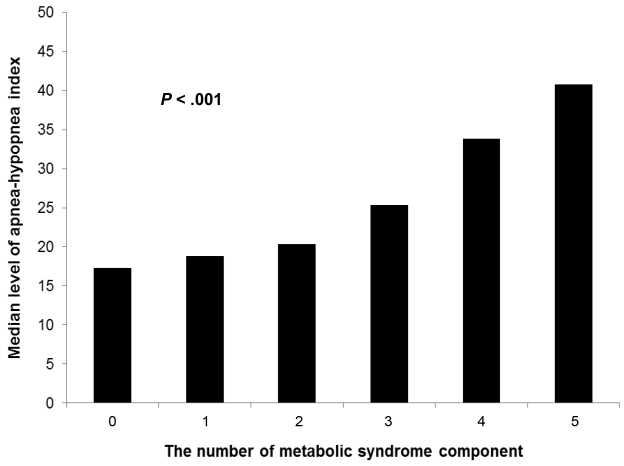
One hundred twenty-nine subjects (7.4%) had CKD. The prevalence of CKD differed according to OSA severity: 5.3%, 7.2%, and 9.7% in subjects with mild, moderate, and severe OSA, respectively ($P = .015$ for trend). Interestingly, the association between CKD prevalence and OSA severity differed according to MS status (**Figure 2**). In subjects without MS, CKD prevalence was not related to OSA severity: 4.8%, 5.1%, and 5.9% had mild, moderate, and severe OSA, respectively ($P = .469$ for trend). Consistently, the AHI was not associated with an increased odds ratio (OR) for CKD in subjects without MS [OR, 1.054; 95% confidence interval (CI), 0.930–1.195] (**Table 3**). By contrast, CKD prevalence increased progressively with OSA severity in subjects with MS: 7.4%, 12.5%, and 15.8% had mild, moderate, and severe OSA, respectively ($P = .025$ for trend). In addition, each 10-point increment in the

Table 2—Polysomnography-based sleep parameters according to MS status.

	Without MS (n = 1,227)	With MS (n = 505)	*P*
Total sleep time, min	321.0 (253.5–379.5)	323.0 (259.5–374.3)	.950
Sleep onset latency, min	6.5 (3.5–13.0)	6.5 (3.0–12.5)	.314
REM latency, min	89.0 (66.0–131.3)	85.8 (63.5–126.1)	.126
WASO, %	14.1 (8.5–23.8)	14.5 (8.7–21.4)	.541
Sleep efficiency, %	83.5 (72.9–89.8)	84.0 (75.6–89.9)	.342
Sleep stage, %			
N1	21.7 (15.0–31.1)	25.1 (16.6–34.9)	< .001
N2	55.7 (47.7–62.7)	53.4 (45.5–61.0)	.001
N3	1.0 (0.0–5.4)	0.8 (0.0–3.6)	.067
R	17.6 (12.1–22.3)	17.7 (12.5–22.3)	.967
Nadir SaO_2, %	84.0 (80.0–88.0)	82.0 (75.0–86.0)	< .001
AHI, events/h	18.9 (10.8–35.3)	28.1 (15.9–50.9)	< .001
Central apnea, events/h, mean ± SD	1.7 ± 6.3	1.6 ± 5.0	.759
Apnea index, events/h, mean ± SD	11.6 ± 17.4	18.4 ± 22.2	< .001
OSA, n (%)			< .001
Mild	463 (37.7)	121 (24.0)	
Moderate	372 (30.3)	144 (28.5)	
Severe	392 (31.9)	240 (47.5)	
Arousal index, events/h	27.4 (19.6–39.1)	32.2 (22.7–46.3)	< .001
Respiratory arousal index, events/h	12.4 (6.9–24.8)	19.5 (9.8–35.9)	< .001
PLMS index, events/h	21.6 (10.1–41.0)	24.1 (11.5–44.8)	.487
Movement arousal index, events/h	1.1 (0.4–3.6)	1.2 (0.4–2.9)	.778

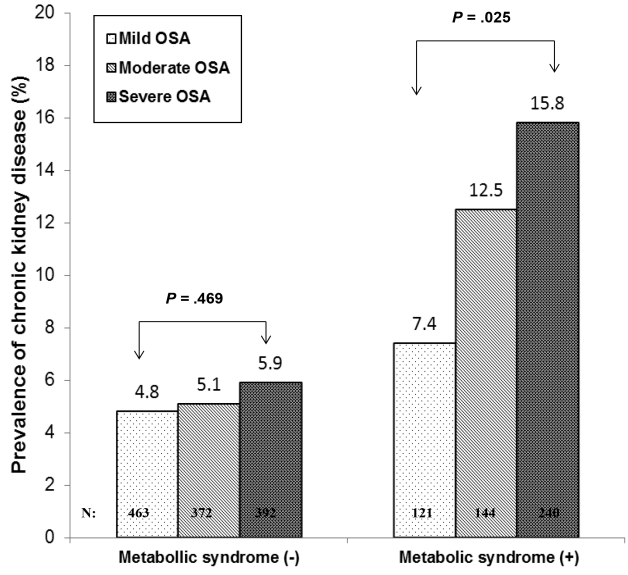
Data are medians (interquartile range), mean ± SD or n (%) as indicated. AHI = apnea-hypopnea index, MS = metabolic syndrome, OSA = obstructive sleep apnea, PLMS = periodic leg movement during sleep, REM = rapid eye movement, SaO_2 = oxygen saturation, SD = standard deviation, WASO = wake after sleep onset.

Figure 1—The median AHI increased progressively with the number of MS components.



P < .001 for trends.

Figure 2—The prevalence of CKD according to OSA in subjects with and without MS.



In subjects without MS, OSA severity was not related to CKD prevalence (*P* = .469 for trend). By contrast, CKD prevalence increased progressively with OSA severity in subjects with MS (*P* = .025 for trend). CKD = chronic kidney disease, OSA = obstructive sleep apnea, MS = metabolic syndrome.

AHI score was associated with a 1.16-fold higher prevalence of CKD (95% CI, 1.054–1.275) in subjects with MS. However, when we analyzed the total cohort as one group and adjusted for the presence of MS, significant interaction between MS and AHI was not observed (*P* = .156 for interaction). Arousal index and WASO were also associated with a higher prevalence of CKD (OR, 1.02; 95% CI, 1.007–1.033 and OR, 1.045; 95% CI, 1.020–1.071, respectively) but only in subjects with MS.

In a sensitivity analysis the association between AHI and CKD remained unchanged when we only included the 1,407 patients in

Table 3—Odds ratios for chronic kidney disease according to MS status: univariate analyses.

	Without MS	With MS
AHI, increments of 10 events/h	1.054 (0.930–1.195)	1.160 (1.054–1.275)*
LDL cholesterol, mg/dL	1.002 (0.994–1.010)	1.001 (0.993–1.009)
Triglyceride, mg/dL	1.002 (0.999–1.005)	1.001 (1.000–1.003)
HDL cholesterol, mg/dL	0.966 (0.944–0.989)*	0.985 (0.961–1.010)
Fasting glucose, mg/dL	1.009 (0.997–1.022)	1.007 (0.997–1.017)
Systolic blood pressure, mmHg	1.017 (1.001–1.033)*	1.015 (1.000–1.031)
Waist circumference, cm #	1.029 (0.985–1.075)	1.046 (1.012–1.081)*
BMI, kg/m^2	1.030 (0.939–1.129)	1.076 (1.005–1.151)*
No. of MS components	1.651 (1.160–2.349)*	1.569 (1.077–2.285)*
Arousal index, events/h	1.011 (0.997–1.025)	1.020 (1.007–1.033)*
WASO, %	1.013 (0.991–1.034)	1.045 (1.020–1.071)*

Values are presented as odds ratios (95% confidence interval). * = $P < .05$. # = there were missing data on waist circumference in 569 participants. AHI = apnea-hypopnea index, BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MS = metabolic syndrome, WASO = wake after sleep onset.

Table 4—The independent association between AHI and CKD in individuals with MS (n = 505).

	OR (95% CI)	*P*
Model 1		
Age, year	1.044 (1.014–1.074)	.003
Female	0.882 (0.322–2.417)	.807
AHI, increments of 10 events/h	1.178 (1.064–1.304)	.002
No. of MS components	1.527 (1.039–2.245)	.031
Model 2		
Age, years	1.064 (1.031–1.098)	< .001
AHI, increments of 10 events/h	1.152 (1.036–1.280)	.009
BMI, kg/m^2	1.092 (1.010–1.182)	.027
Triglyceride, mg/dL	1.002 (0.999–1.004)	.136
HDL cholesterol, mg/dL	0.982 (0.954–1.011)	.223
Fasting glucose, mg/dL	1.006 (0.995–1.017)	.270
Systolic blood pressure, mmHg	1.013 (0.997–1.029)	.120

Since we were missing data on waist circumference in 569 participants, we instead used BMI in the regression models. Model 1 included age, sex, AHI and number of metabolic syndrome components. Model 2 included age, sex, AHI, triglyceride, HDL cholesterol, glucose, systolic blood pressure, and BMI. AHI = apnea-hypopnea index, BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, HDL = high-density lipoprotein, OR = odds ratio.

Table 5—The independent association between arousal index and CKD in individuals with MS (n = 505).

	OR (95% CI)	*P*
Model 1		
Age, years	1.041 (1.012–1.070)	.006
Female	0.862 (0.314–2.365)	.773
Arousal index, events/h	1.020 (1.007–1.034)	.003
No. of MS components	1.543 (1.048–2.271)	.028
Model 2		
Age, year	1.057 (1.026–1.089)	< .001
Arousal index, events/h	1.018 (1.004–1.032)	.009
BMI, kg/m^2	1.106 (1.025–1.194)	.010
Triglyceride, mg/dL	1.002 (1.000–1.004)	.128
HDL cholesterol, mg/dL	0.983 (0.955–1.012)	.247
Fasting glucose, mg/dL	1.006 (0.996–1.017)	.246
Systolic blood pressure, mmHg	1.013 (0.997–1.029)	.133

Because we were missing data on waist circumference in 569 participants, we instead used BMI in the regression models. Model 1 included age, sex, arousal index and number of MS components. Model 2 included age, sex, arousal index, triglyceride, HDL cholesterol, glucose, systolic blood pressure, and BMI. BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, HDL = high-density lipoprotein, MS = metabolic syndrome, OR = odds ratio.

whom the time interval between laboratory tests and PSG was less than 5 years (median, 4.8 months; IQR 1.8–17.5 months).

Independent Associations of MS Components and Sleep Parameters With CKD in Subjects With MS

Multivariate analysis revealed that AHI was independently associated with CKD in subjects with MS (**Table 4**). The AHI was associated with an increased prevalence of CKD independently of the number of MS components (OR, 1.178; 95% CI, 1.064–1.304 for each 10-point increment). The OR for AHI did not change after adjustment for all individual components of MS (OR, 1.152; 95% CI, 1.036–1.280 for each 10-point increment). Separate multivariate analyses showed that arousal index (OR, 1.018; 95% CI, 1.004–1.032) and WASO (OR, 1.041; 95% CI, 1.014–1.070) were associated with increased prevalence of CKD independent of individual MS components in subjects with MS (**Table 5** and **Table 6**).

When we adjusted the model for hemoglobin A1c and diabetes status instead of glucose level, the findings on the association between CKD prevalence and AHI remained unchanged (OR, 1.151; 95% CI, 1.036–1.279). In addition, the findings on the association between CKD prevalence and AHI remained unchanged (OR, 1.224; 95% CI, 1.062–1.410) for nondiabetic subjects with MS (n = 328)

Data on smoking status were verified in only 913 subjects. Smoking was more prevalent in subjects with MS compared to those without MS (29.6% versus 22.2%, respectively; $P = .018$). In a subgroup analysis of the subjects with data on smoking status, after further adjustment for smoking status, AHI was also independently associated with higher prevalence of CKD

Table 6—The independent association between WASO and CKD in individuals with MS (n = 505).

	OR (95% CI)	*P*
Model 1		
Age, years	1.012 (0.982–1.043)	.436
Female	0.661 (0.214–2.040)	.472
WASO, %	1.043 (1.016–1.071)	.001
No. of MS components	1.476 (0.987–2.208)	.058
Model 2		
Age, year	1.032 (0.999–1.066)	.061
WASO, %	1.041 (1.014–1.070)	.003
BMI, kg/m^2	1.123 (1.037–1.217)	.004
Triglyceride, mg/dL	1.001 (0.999–1.003)	.414
HDL cholesterol, mg/dL	0.986 (0.957–1.016)	.348
Fasting glucose, mg/dL	1.006 (0.995–1.018)	.260
Systolic blood pressure, mmHg	1.013 (0.997–1.030)	.121

Because we were missing data on waist circumference in 569 participants, we instead used BMI in the multivariate analyses. Model 1 included age, sex, WASO, and number of MS components. Model 2 included age, sex, WASO, triglyceride, HDL cholesterol, glucose, systolic blood pressure, and BMI. BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, HDL = high-density lipoprotein, MS = metabolic syndrome, OR = odds ratio, WASO = wake after sleep onset.

in subjects with MS (OR, 1.242; 95% CI, 1.052–1.465) but not in those without MS (OR, 1.016; 95% CI, 0.861–1.199). In our study, 24 subjects were categorized as those with CKD based on the positive urine dipstick criterion. When we analyzed the data excluding them, the main findings of this study were similar (data not shown).

DISCUSSION

This large cross-sectional study demonstrated that the association between the prevalence of CKD and OSA severity was affected by MS status. In subjects with MS, CKD prevalence increased with the severity of OSA. Furthermore, the AHI was associated with an increased prevalence of CKD independently of MS components. However, in subjects without MS, CKD prevalence was not associated with the severity of OSA. These findings suggest that OSA alone does not increase the risk of CKD, whereas in subjects with MS, OSA might be an additional burden that exacerbates the risk of CKD.

The potential effect of OSA on the development and progression of CKD has been reported recently. A cross-sectional study of obese adults reported that greater OSA severity was associated with a higher serum creatinine concentration.[15] Chou et al. also showed that the severity of OSA correlated positively with renal functional impairment in patients without diabetes or hypertension.[29] A longitudinal study by Ahmed et al. found that nocturnal hypoxia was significantly associated with the risk of accelerated loss of kidney function.[30] Sakaguchi et al. showed similar findings in nonobese patients with CKD.[31] However, the study by Canales et al. did not find a significant association between renal function and sleep-disordered breathing.[32] In the study by Iseki et al., the AHI was not a significant determinant of CKD in patients with sleep apnea.[14] Thus, the association between OSA and CKD remained controversial. Recently, two large cohort studies suggested that OSA was an independent risk factor for CKD when OSA or CKD was determined by diagnosis codes in the studies.[16,17] However, metabolic abnormalities were not considered in one study and comorbid medical conditions were decided by diagnosis codes in the other study. Therefore, unadjusted metabolic abnormalities might have been involved in the association between OSA and CKD.

In the current study, we found a significant relationship between CKD and OSA only in subjects with MS, which indicates that the association between OSA and CKD is dependent on the presence of MS. Our findings may be one explanation for the inconsistent results in previous studies. The AHI was a significant contributor to the prevalence of CKD only in subjects with MS and their relationship was independent of dyslipidemia, hypertension, impaired glucose metabolism, and BMI in those with MS.

We found that subjects with MS had more fragmented sleep and more severe OSA compared to subjects without MS. Arousal index and respiratory-related arousals were much higher in subjects with MS compared to subjects without MS. Higher prevalence of severe OSA and higher AHI in subjects with MS indicated that patients with MS have more serious and prevalent OSA and related poor sleep quality than patients without MS. Moreover, the significant association between increased CKD prevalence and arousal index (OR, 1.018) or WASO (OR, 1.041) in subjects with MS may support the plausible link between CKD and OSA mediated through MS.

The reason that the association between CKD and OSA differed according to the presence or absence of MS is uncertain. OSA may be related to CKD by virtue of overlapping conditions such as obesity, hypertension, and diabetes, although it is difficult to determine the exact degree of each condition's influence.[33–35]

OSA may contribute to CKD through several possible mechanisms. Chronic intermittent hypoxia caused by OSA may activate the renin-angiotensin system and the sympathetic nervous system that may result in kidney damage by facilitating hypertension, fibrosis, and glomerular hyperfiltration.[36] It is also possible that OSA-induced intermittent hypoxia generates reactive oxygen species and induces systemic inflammation, which may lead to endothelial dysfunction and contribute to proteinuria and decreased eGFR.[36–38]

In this study, significant interaction between MS and AHI was not observed. We cannot clearly identify the reason for the negative results of the interaction analysis, but it may be due to two facts. One possible reason is that the non-MS group was larger than the MS group, and the other is that the 95% CI for hazard ratios of AHI for CKD overlapped in both groups.

It has been reported that OSA is associated with diabetic nephropathy. A previous longitudinal study showed that OSA was independently associated with diabetic nephropathy and a greater decline in eGFR in adults with type 2 diabetes.[39] The current study demonstrated that OSA severity was associated with higher prevalence of CKD in subjects with MS. When we conducted analyses after exclusion of the subjects with diabetes, the association between CKD prevalence and AHI

remained unchanged. Therefore, the association between OSA and CKD can be evident in subjects with metabolic abnormalities such as diabetes and MS.

This study has several limitations. First, the subjects were a cohort that received a general health checkup in a single center and may not be representative of the general population. In addition, there was the potential for selection bias in this study because these subjects were referred to a sleep study for evaluating snoring; this might result in the much higher proportion of men in this sample. This might also limit the generalizability of the study findings. However, this study included a relatively large and homogenous group of subjects. Furthermore, all of them received a diagnosis of OSA by PSG. To our knowledge, this is the first study to assess the relationship between OSA, CKD, and MS in a large number of adults. Second, we could not confirm a causal relationship between OSA and CKD because of the cross-sectional study design. However, the results of this study suggest that the risk of CKD might be increased when combined with OSA and MS. Third, there might be a misclassification error in the diagnosis of CKD because diagnosis was based on single measurements of eGFR and urinary ACR. Misclassification error tends to weaken the association between a mediator and an outcome. Previous literature describing the Multiple Risk Factor Intervention Study data has demonstrated that single measurements of dipstick proteinuria and eGFR can be predictors of ESRD.[40] Fourth, we did not systematically search for and exclude participants with urinary tract infections or hematuria. However, we suspect that the prevalence of these two conditions would be low in participants undergoing a comprehensive health checkup. Fifth, waist circumference is considered a better marker of central adiposity. However, because we were missing data on waist circumference in 569 participants, we instead used BMI in the regression model. Last, we did not have a control group without OSA. However, we were able to demonstrate a clear association between various categories of OSA severity in subjects with MS.

In conclusion, this study suggests that OSA alone does not increase the risk for CKD but OSA may be an additional burden that exacerbates the risk for CKD in subjects with MS. It raises the possibility that the effect of OSA on cardiovascular diseases depends on MS status. Additional studies are needed to evaluate if OSA contributes to the development of CKD in subjects with MS.

ABBREVIATIONS

ACR, albumin-to-creatinine ratio
AHI, apnea-hypopnea index
BMI, body mass index
CI, confidence interval
CKD, chronic kidney disease
eGFR estimated glomerular filtration rate
ESRD, end-stage renal disease
HDL, high-density lipoprotein
IQR, interquartile range
MS, metabolic syndrome
OR, odds ratio
OSA, obstructive sleep apnea
PSG, polysomnography
sCr, serum creatinine
WASO, wake after sleep onset

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