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SCIENTIFIC INVESTIGATIONS

Obstructive sleep apnea during rapid eye movement sleep in patients with diabetic kidney disease

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Study Objectives: Although recent studies suggest that obstructive sleep apnea during rapid eye movement (REM) is associated with different cardiometabolic and neurocognitive risks compared with non-REM (NREM) sleep, there is no information on whether obstructive sleep apnea during REM and/or NREM sleep is independently associated with diabetic kidney disease (DKD).

Methods: In this cross-sectional study, 303 patients with type 2 diabetes who were followed up at our diabetes outpatient clinic underwent all-night polysomnography. Logistic regression analysis was performed to determine the separate effects of obstructive sleep apnea during REM and/or NREM sleep (REM and/or NREM-apnea-hypopnea index [AHI]) and several other polysomnography parameters on DKD after adjustment for several known risk factors for DKD.

Results: The median (interquartile range) AHI, REM-AHI, and NREM-AHI of the patients (age 57.8 ± 11.8 years, male sex 86.8%, hypertension 64.3%, and DKD 35.2%) were 29.8 (18.0–45.4), 35.4 (21.1–53.3), and 29.1 (16.3–45.4) events/h, respectively. REM-AHI quartiles, but not NREM-AHI quartiles, correlated independently and significantly with DKD (P = .03 for linear trend, odds ratio (OR), and 95% confidence interval for Q2: 3.14 (1.10–8.98), Q3: 3.83 (1.26–11.60), Q4: 4.97 (1.60–15.46), compared with Q1). In addition, categorical AHI (P = .01, OR, and 95% confidence interval for ≥ 15 to < 30: 1.54 (0.64–3.71), ≥ 30: 3.08 (1.36–6.94) compared with < 15), quartiles of AHI (P = .01), quartiles of lowest arterial oxyhemoglobin saturation (P < .01), quartiles of percentage of time spent with arterial oxyhemoglobin saturation < 90 (P < .01), and quartiles of mean arterial oxyhemoglobin saturation were independently associated with DKD.

Conclusions: Obstructive sleep apnea, especially during REM sleep, is a potential risk factor for DKD.

Keywords: sleep disorders; sleep apnea syndrome; diabetic kidney disease; rapid eye movement sleep; diabetic angiopathy; type 2 diabetes

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Recent studies have shown that obstructive sleep apnea is associated not only with hyperglycemia but with actual diabetes-related endpoints, including diabetic kidney disease (DKD). On the other hand, although obstructive sleep apnea during rapid eye movement (REM) and non-REM sleep leads to different cardiometabolic and neurocognitive complications, whether REM-related obstructive sleep apnea is associated with DKD is not clear because all previous studies used home sleep apnea testing, which does not distinguish between REM- and non-REM–apnea-hypopnea index.

Study Impact: In this study, we showed that overall apnea-hypopnea index and REM–apnea-hypopnea index, but not non-REM–apnea-hypopnea index, were independently correlated with DKD after adjusting several known risk factors for DKD. Obstructive sleep apnea, especially during REM sleep, is a potential risk factor for DKD.

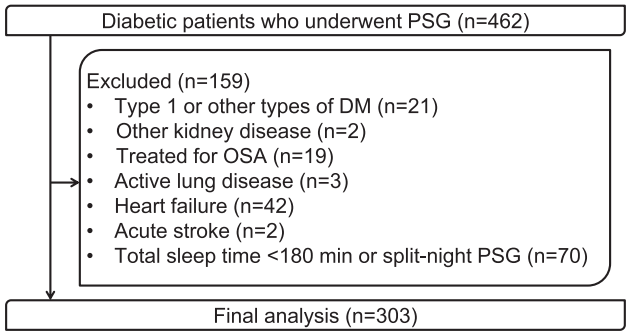
INTRODUCTION

Sleep-disordered breathing, including obstructive sleep apnea (OSA), is characterized by repetitive upper airway collapse during sleep and causes nocturnal hypoxemia. This hypoxemia causes increased sympathetic activity, oxidative stress, thalamic-pituitary-adrenal axis activity, inflammation, and changes in adipokine, resulting in increased insulin sensitivity and hyperglycemia.[1] Clinical studies have shown that OSA is associated with hyperglycemia, which can be improved by continuous positive airway pressure therapy, suggesting a causal relationship between OSA and hyperglycemia,[2,3] although some studies have failed to show this relationship.[4,5]

Recent studies also have shown that OSA is associated not only with hyperglycemia but with actual diabetes-related endpoints (eg, diabetic microcomplications), including diabetic kidney disease (DKD).[6–10] For example, it was reported that the estimated glomerular filtration rate (eGFR) decreased faster in type 2 diabetes mellitus (T2D) patients with OSA after an average of 2.5 years of follow-up compared with similar patients without OSA.[11] Similarly, our previous study showed that the severity of OSA is independently associated with the presence of albuminuria, which is an early marker of DKD.[10]

On the other hand, growing evidence suggests that OSA during rapid eye movement (REM) and non-REM (NREM) sleep leads to different cardiometabolic and neurocognitive complications.[12,13]

Figure 1—Flowchart of the patient recruitment process.



DM = diabetes mellitus, OSA = obstructive sleep apnea, PSG = polysomnography.

This difference stems from the fact that OSA is more frequent and of longer duration in REM sleep and is associated with more severe hypoxemia than in NREM sleep,[14] probably owing to greater pharyngeal muscle relaxation, reduction in the hypoxic and hypercapnic ventilatory response throughout REM sleep, and higher arousal threshold.[15,16] For example, the apnea-hypopnea index (AHI) during REM sleep (REM-AHI) is associated with future onset of hypertension, whereas NREM-AHI is not.[17] In addition, REM-AHI is associated with nondipping of nocturnal blood pressure,[18] metabolic syndrome,[19] and a composite cardiovascular endpoint.[20]

Whether REM-related OSA is associated with DKD is not clear so far, however, because all previous studies used home sleep apnea testing (HSAT), which does not distinguish between REM- and NREM-AHI. The present in-hospital full polysomnography study was conducted to determine the association between REM-related OSA and DKD.

METHODS

Patients

We screened 462 patients with diabetes who were followed up at our diabetes outpatient clinic and had undergone overnight polysomnography at our sleep center during May 2004 to June 2013. The following patients were excluded from the study: (1) age < 20 years; (2) had type 1 or other types of diabetes; (3) had other types of kidney diseases or were on hemodialysis; (4) had active pulmonary disease; (5) had a history of heart failure; (6) had a history of acute stroke (within 3 months before polysomnography); (7) had been treated for OSA at the time of polysomnography; or (8) had polysomnographically confirmed total sleep time < 180 minutes, including patients with split-night polysomnography (ie, both diagnostic polysomnography and continuous positive airway pressure titration polysomnography performed on the same night). **Figure 1** shows a flowchart of the patient-recruitment process. One hundred and fifty-nine patients who met the above-mentioned exclusion criteria were excluded from a total of 462 patients with diabetes. Thus, the data of 303 patients were analyzed in the total AHI analysis. In addition, patients with REM sleep < 30 minutes (n = 121) were excluded from REM and/or NREM-AHI analysis,[21] and the data of 182 patients were analyzed in the REM and/or NREM analysis. The study was approved by the Toranomon Hospital Human Ethics Review Board (no. 1263) with a waiver of the requirement to obtain informed consent from the patients based on the fact that polysomnography was part of the overall clinical management of the patients.

Definitions and data collection

The diagnosis of T2D was based on the Japan Diabetes Society Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus.[22] Patients who took hypoglycemic agents and who had no history of type 1 or other types of diabetes were also regarded as having T2D. The glycated hemoglobin (HbA1c) value was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated by the following equation: HbA1c (%) = 1.02 × HbA1c (Japan Diabetes Society) (%) + 0.25 (%).[23]

DKD was defined as the presence of microalbuminuria (³3.4 mg/mmol creatinine) or low eGFR (< 60 ml/min/1.73m^2). eGFR was determined using following equation established by the Japanese Society of Nephrology: eGFR (ml/min/1.73 m^2) = 194 × [serum creatinine]$^{-1.094 \times \text{age} - 0.287}$ (× 0.739 for females).[24]

Patients with systolic blood pressure³ 140 mm Hg, diastolic blood pressure³ 90 mm Hg,[25] or taking any antihypertensive medications were regarded as hypertensive. Non–high-density lipoprotein cholesterol was calculated by total cholesterol–high-density lipoprotein cholesterol.

Based on self-administered questionnaires and medical records, we gathered information on known risk factors for DKD, including duration of diabetes and smoking status. All medications used by the participants at the time of polysomnography were listed. At the time of polysomnography, fasting venous blood was drawn, and morning urine sample was obtained for laboratory testing.

Polysomnography

All patients underwent fully attended in-hospital polysomnography at our hospital. The details of the polysomnography and the scoring system are described elsewhere.[26–28] Briefly, polysomnography was performed using a digital polygraph (SomnoStar α Sleep System; SensorMedics Corp., Yorba Linda, California) manned by a sleep technician. Generally accepted definitions and scoring methods were used (*apnea* was defined as a reduction of airflow by > 90% for at least 10 seconds; *hypopnea* was defined as a reduction of airflow by > 30% for at least 10 seconds with 3% oxygen desaturation [using a baseline of 120 seconds] or an arousal). In each case, the respiratory events were manually scored, and the AHI was calculated per hour of sleep. According to the clinically used criteria, AHI values were divided into three categories: AHI < 15, ≥ 15 to < 30, and ≥ 30 events/h. In REM and/or NREM-AHI analysis, quartiles of REM and/or NREM-AHI were used based on the previous reports.[17,29]

Statistical analysis

All data are presented as mean ± standard deviation or median (interquartile range) according to the quartiles of REM-AHI. In all tests, a P value < .05 was considered statistically significant. All statistical analyses were performed using the SPSS Statistics Software version 22.0 (SPSS Japan Inc., Tokyo, Japan) except for

Table 1—Characteristics of participating patients.

	Overall (n = 303)	REM Sleep ≥ 30 Min (n = 182)	REM-AHI				*P* Value
			Q1	Q2	Q3	Q4	
Age, y	58.5 ± 11.9	57.8 ± 11.8	58.3 ± 2.3	60.5 ± 10.4	57.3 ± 12.5	55.3 ± 12.0	.20
Male sex, n (%)	260 (85.8)	158 (86.8)	38 (86.4)	42 (89.4)	40 (88.9)	38 (82.6)	.59
Duration of T2D, y	5 (0–13)	5 (1–12)	6 (1–11)	8 (0–14)	5 (0–10)	4 (1–11)	.83
Smoking, n (%)	71 (23.4)	44 (24.2)	11 (25.0)	14 (29.8)	12 (26.7)	7 (15.2)	.24
DKD, n (%)	124 (40.9)	64 (35.2)	9 (20.5)	18 (38.3)	19 (42.2)	18 (39.1)	.01
HT, n (%)	208 (68.6)	117 (64.3)	21 (47.7)	31 (66.0)	29 (64.4)	36 (78.3)	.00
BMI, kg/m^2	27 (24–29)	26 (24–29)	24 (23–27)	25 (24–29)	27 (25–29)	28 (25–32)	< .01
HbA1c (NGSP), %	7.3 (6.8–8.4)	7.4 (6.8–8.5)	7.4 (6.7–8.9)	7.1 (6.7–7.7)	7.9 (7.2–9.0)	7.4 (7.0–8.5)	.01
HbA1c (IFCC), mmol/mol	56 (50–68)	57 (50–69)	57 (49–73)	53 (49–60)	62 (55–75)	57 (52–69)	.01
non-HDLC, mg/dl	145 (124–166)	141.3 ± 32.1	140.6 ± 33.8	140.0 ± 27.6	146.2 ± 33.9	138.7 ± 33.4	.69
Insulin use, n (%)	18 (5.9)	13 (7.1)	1 (2.3)	3 (6.4)	7 (15.6)	2 (4.3)	.39
ACEI/ARB use, n (%)	87 (28.7)	48 (26.4)	10 (22.7)	15 (31.9)	12 (26.7)	11 (23.9)	.94
Statin use, n (%)	71 (23.4)	45 (24.7)	9 (20.5)	14 (29.8)	9 (20.0)	13 (28.3)	.88
Sleep pills use, n (%)	30 (9.9)	19 (10.4)	3 (6.8)	5 (10.6)	4 (8.9)	7 (15.2)	.25
AHI, events/h	34.6 (20.4–55.1)	29.8 (18.0–45.4)	15.6 (8.0–29.8)	29.7 (19.0–39.9)	33.9 (21.8–48.8)	42.3 (27.5–64.6)	< .01
REM-AHI, events/h	39.7 (21.1–55.2)	35.4 (21.1–53.3)	12.8 (7.2–17.7)	28.6 (23.7–31.3)	44.1 (41.2–48.2)	62.1 (56.1–69.8)	< .01
NREM-AHI, events/h	34.5 (18.0–56.8)	29.1 (16.3–45.4)	17.7 (7.2–32.7)	30.2 (18.1–42.5)	32.6 (18.0–49.6)	38.5 (23.5–64.7)	< .01
Lowest SaO_2, %	78 (71–84)	80 (72–85)	84 (81–89)	82 (72–86)	76 (67–81)	76 (70–81)	< .01
T90SPT, %	10.4 (2.4–35.4)	6.6 (1.6–22.3)	1.4 (0.3–6.4)	4.2 (1.3–17.2)	9.9 (4.6–30.8)	11.3 (6.1–8.0)	< .01
Mean SaO_2, %	94 (91–95)	94 (92–95)	95 (94–96)	94 (92–95)	93 (91.0–94.8)	93 (91–94)	< .01
Total sleep time, min	352 (305–394)	379 (337–409)	385 (345–424)	376 (336–415)	363 (333–399)	377 (338–407)	.52
REM sleep time, min	37 (21–54)	49.5 (40–61)	54 (43–71)	50 (43–64)	47 (37–64)	45 (39–53)	.04
ESS	8 (3–11)	8 (3–12)	7(3–10)	6 (2–10)	9 (5–13)	8 (3–13)	.18

Values are mean ± standard deviation, median (interquartile range) or percentage (%). ACEI = angiotensin converting enzyme inhibitor, AHI = apnea-hypopnea index, ARB = angiotensin receptor blockers, BMI = body mass index, DKD = diabetic kidney disease, ESS = Epworth Sleepiness Scale, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HT = hypertension, IFCC = International Federation of Clinical Chemistry and Laboratory Medicine, NGSP = National Glycohemoglobin Standardization Program, NREM = non-REM, REM = rapid eye movement, SaO_2 = arterial oxyhemoglobin saturation, T2D = type 2 diabetes, T90SPT = percentage of time spent with SaO_2 < 90%.

the Cochran-Armitage trend test using the R Software (version 3.6.1).[30]

Differences among the four groups of quartiles of REM-AHI were tested by one-way analysis of variance for normally distributed continuous variables, by Kruskal-Wallis test for continuous variables with skewed distribution pattern, and by the Cochran-Armitage trend test for categorical variables.

The association of OSA with DKD was assessed using the forced logistic regression analysis. In AHI and other parameters analysis, the model was adjusted for age, sex, body mass index, T2D duration, smoking, hypertension, HbA1c, non–high-density lipoprotein cholesterol, use of insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blockers, statins, and sleeping pills. In REM and/or NREM-AHI analysis, the model was adjusted for the covariates, with $P < .2$ in the univariable analysis because only 64 patients in the REM and/or NREM-AHI analysis had DKD. In the multivariable models, quartiles of REM-AHI and NREM-AHI were mutually adjusted for each other. In these analyses, all continuous variables with skewed distribution were treated as natural logarithm-transformed continuous variables. When the data contained zero values, natural log transformation using the formula natural logarithm-transformed X = log (X + .01) was applied.[31]

For AHI analysis, categorical AHI (< 15, ≥ 15 to < 30, ≥ 30) was included in the model as the independent variables because few patients had AHI < 5. In addition, quartiles of AHI were included in the model. In REM and/or NREM-AHI analysis, quartiles of REM and/or NREM-AHI were included in the model after adjustment for the aforementioned factors. Similarly, multivariable logistic regression analyses, including quartiles of lowest arterial oxyhemoglobin saturation (SaO_2), percentage of time spent with SaO_2 < 90% (T90SPT), or mean SaO_2 were developed.

RESULTS

Patient characteristics

Table 1 lists the characteristics of all participating patients according to the quartiles of REM-AHI. The prevalence

Table 2—Results of univariable analysis for diabetic kidney disease.

	Overall (n = 303)			REM Sleep ≥ 30 Min (n = 182)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y	1.06	1.03–1.08	< .01	1.06	1.03–1.09	.00
Male sex, male vs female	1.73	0.86–3.49	.12	2.65	1.02–6.91	.046
Duration of T2D, y	1.07	0.99–1.16	.08	1.07	0.96–1.19	.22
Smoking, yes vs no	0.85	0.48–1.47	.55	0.92	0.44–1.91	.82
HT, yes vs no	1.78	1.05–3.01	.03	1.63	0.83–3.22	.16
BMI, kg/m^2	0.80	0.19–3.44	.76	0.59	0.08–4.34	.60
HbA1c (NGSP), %	0.99	0.22–4.39	.98	0.94	0.14–6.19	.95
HbA1c (IFCC), mmol/mol	0.99	0.22–4.39	.98	0.94	0.14–6.19	.95
non-HDLC, mg/dl	0.62	0.24–1.60	.33	0.99	0.99–1.00	.26
Insulin use, yes vs no	1.24	0.48–3.24	.66	1.37	0.44–4.29	.58
ACEI/ARB use, yes vs no	1.77	1.06–2.97	.03	1.57	0.79–3.12	.197
Statin use, yes vs no	1.26	0.73–2.19	.41	1.09	0.53–2.22	.82
Sleep pills use, yes vs no	1.73	0.79–3.81	.17	1.11	0.40–3.07	.85
AHI, events/h	1.69	1.22–2.35	< .01	1.45	0.93–2.26	.10
REM-AHI, events/h	1.04	0.83–1.30	.72	1.44	0.94–2.22	.10
NREM-AHI, events/h	1.63	1.19–2.22	< .01	1.35	0.90–2.03	.15
Lowest SaO_2, %	0.23	0.05–1.03	0.05	0.40	0.05–3.03	.37
T90SPT, %	1.25	1.11–1.41	< .01	1.18	1.02–1.37	.03
Mean SaO_2, %	0.02	0.00–1.51	.07	0.01	0.00–10.07	.17
Total sleep time, min	0.68	0.23–2.01	.49	1.00	0.99–1.01	.86
REM sleep time, min	0.93	0.80–1.07	.29	3.06	1.09–8.66	.04
ESS	0.95	0.87–1.04	.29	0.97	0.86–1.09	.62

ACEI = angiotensin converting enzyme inhibitor, AHI = apnea-hypopnea index, ARB = angiotensin receptor blocker, BMI = body mass index, CI = confidence interval, DKD = diabetic kidney disease, ESS = Epworth Sleepiness Scale, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HT = hypertension, IFCC = International Federation of Clinical Chemistry and Laboratory Medicine, NGSP = National Glycohemoglobin Standardization Program, NREM = non-rapid eye movement, OR = odds ratio, REM = rapid eye movement, SaO_2 = arterial oxyhemoglobin saturation, T2D = type 2 diabetes, T90SPT = percentage of time spent with SaO_2 < 90%.

of severe OSA (AHI ≥ 30) and severe REM-related OSA (REM-AHI ≥ 30) were 57.4% and 59.9%, respectively. The four REM-AHI groups differed significantly with respect to the proportion of patients with DKD, patients with hypertension, BMI, HbA1c, AHI, REM and/or NREM-AHI, lowest SaO_2, T90SPT, and REM sleep time.

Table 2 shows the results of univariable analyses using DKD as the dependent variable.

Table S1 in the supplemental material shows the prevalence of DKD in relations to quartiles of PSG variables

REM and/or NREM-AHI analysis

Figure 2 and Table 3 show the results of multivariable logistic regression analysis for DKD using both quartiles of REM-AHI and quartiles of NREM-AHI. In this analysis, the quartiles of REM-AHI (P = .04 for trend) were independently associated with DKD, whereas quartiles of NREM-AHI were not (P = .19 for trend). The OR and 95% confidence interval for each quartile of REM-AHI compared with Q1 (Reference) were the following: Q2, 3.23 (1.09–9.52), Q3, 4.03 (1.33–12.23), Q4, 4.99 (1.50–16.64).

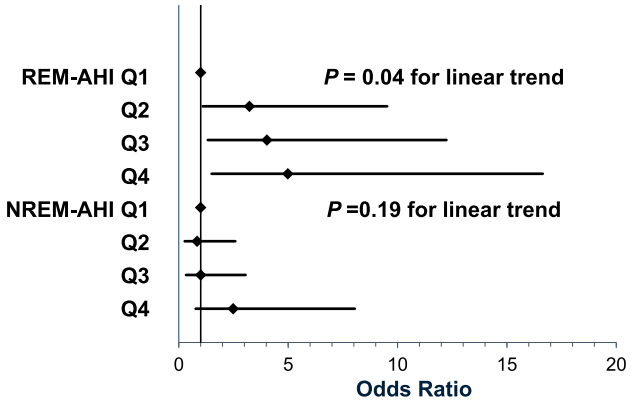
AHI and other parameters analysis

Figure 3 and Table 4 show the results of multivariable logistic regression analysis for DKD using categorical AHI, quartiles of AHI, lowest SaO_2, quartiles of T90SPT, or quartiles of mean SaO_2. In this analysis, categorical AHI (P = .01 for trend) and age (odds ratio:1.07; 95% CI: 1.04–1.10, P < .01) were independently associated with DKD. The odds ratio and 95% confidence interval for each AHI categories compared with AHI < 15 (reference) were as follows: ≥ 15 to < 30: 1.541 (0.640–3.710), ≥30: 3.078 (1.364–6.943). Similar results were obtained when quartiles of AHI, lowest SaO_2, quartiles of T90SPT, or quartiles of mean SaO_2 were included in the model (Table 4).

DISCUSSION

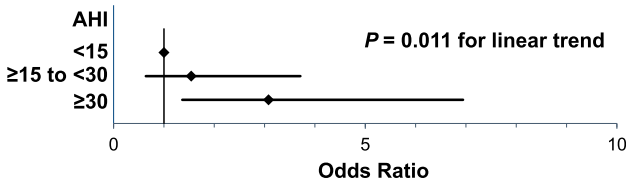
We showed for the first time that AHI during REM sleep, but not that during NREM sleep, is independently associated with DKD. In addition, we also demonstrated the association between AHI, lowest SaO_2, T90SPT, or mean SaO_2 with DKD using not HSAT but polysomnography.

Figure 2—Results of logistic regression analysis for diabetic kidney disease using quartiles of REM and/or NREM-AHI.



The model was adjusted by age, sex, body mass index (BMI), type 2 diabetes (T2D) duration, smoking, hypertension, hemoglobin A1c (HbA1c), non-high-density lipoprotein cholesterol, insulin use, angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blockers use, statin use and sleep pill use. AHI = apnea-hypopnea index, NREM = non-rapid eye movement, REM = rapid eye movement.

Figure 3—Results of logistic regression analysis for diabetic kidney disease using categorical AHI.



The model was adjusted by age, sex, body mass index (BMI), type 2 diabetes (T2D) duration, smoking, hypertension, hemoglobin A1c (HbA1c), non-high-density lipoprotein (HDL) cholesterol, insulin use, angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blockers use, statin use and sleep pill use. AHI = apnea-hypopnea index.

Analysis of the REM and/or NREM-AHI showed the independent association of REM-AHI with DKD, suggesting that REM-related OSA is a risk factor for diabetic microcomplications. Previous studies showed that REM-related OSA is associated with glucose metabolism, which is one of the main risk factors for DKD. For example, REM-AHI was reported to be strongly associated with insulin resistance,[13] interstitial glucose concentration measured by continuous glucose monitoring system,[32] and HbA1c,[29] compared with NREM-related OSA. In addition, REM-AHI was found to be associated with hypertension, which is another risk factor for DKD.[17,33] Thus, the present study confirmed that REM-related OSA is associated not only with risk factors for diabetic microcomplications (ie, hyperglycemia or hypertension) but with actual diabetes-related endpoint (ie, DKD). The association between REM-AHI and diabetic microcomplications reported here adds support to our previous findings of the independent association between REM-AHI and diabetic retinopathy.[34]

In the present study, REM-AHI was associated with DKD even after adjustment for HbA1c or the presence of hypertension, suggesting another pathway that links REM-related OSA to DKD. One plausible mechanism is that hypoxemia induced by REM-related OSA directly exacerbates DKD. Previous studies have suggested that OSA-induced intermittent hypoxemia can potentially cause increased oxidative stress,[35] sympathetic nervous system overactivity,[36] activation of the renin-angiotensin-system[37] and advanced glycation end products,[38] all of which are known risk factors for DKD. In addition, REM sleep is associated with greater sympathetic activity compared with NREM sleep,[39] and OSA is worse during REM sleep, which includes more frequent events, longer-duration events, and greater oxygen desaturation associated with respiratory events.[12] We propose that REM-related OSA strongly stimulates oxidative stress, sympathetic nervous system overactivity, and activation of the renin-angiotensin-system compared with NREM-related OSA, resulting in exacerbation of DKD.

Our all-night polysomnographic study also showed independent associations between AHI, lowest SaO_2, T90SPT, or mean SaO_2 with DKD. These results are similar to those reported in previous HSAT studies.[9–10,40–42] For example, our previous study using HSAT showed the independent association of microalbuminuria with categorical respiratory event index (< 15, 15 to < 30, ≥ 30).[10] In another cohort study, eGFR fell faster in patients with OSA than in OSA-free individuals.[11] Furthermore, 3% oxygen desaturation index,[40] lowest SaO_2[41] and T90SPT[42] were independently association with DKD in previous HSAT studies. Since only a few studies assessed the association between OSA and DKD and almost all studies used HSAT,[9] the present study using polysomnography confirmed the robust association between OSA and DKD.

This study has several strengths and limitations. The strength points include the following: first, this study did not use HSAT, but rather all-night polysomnography, for the assessment of severity of OSA; and second, the results were adjusted for several known risk factors for DKD. The American Academy of Sleep Medicine Clinical Practice Guideline recommended that if a single HSAT is negative, polysomnography should be performed for the diagnosis of OSA.[43] Furthermore, a recent study showed that HSAT seems to underestimate OSA severity[44] which may result in weaker association between OSA and DKD. The limitations of this study are as follows. First, the cross-sectional nature of the study cannot confirm causality between OSA and DKD. A longitudinal study or interventional study is needed to confirm causality. Second, our study population included relatively few female patients. Because REM-related OSA occurs more commonly in women than in men,[45,46] further studies that include more females are needed to generalize our findings to all T2D patients. Third, our study used single morning urine sample for the assessment of microalbuminuria. Although previous studies used a single urine measurement,[11,40] obtaining a couple of urine samples for such assessment will be needed in future studies. Fourth, this study defined patients with AHI < 15 as reference because this study had few patients with AHI < 5; however, the third edition of the *International Classification of Sleep Disorders* defines OSA

Table 3—Results of univariable and multivariable logistic regression analysis for diabetic kidney disease using both quartiles of REM-AHI and quartiles of NREM-AHI (n = 182).

	Median Value	Unadjusted				Adjusted			
		B	OR	95% CI	*P* Value	B	OR	95% CI	*P* Value
REM-AHI					.05				.04
Q1	12.8		1 (ref)				1 (ref)		
Q2	28.6	1.04	2.83	1.09–7.37	.03	1.17	3.23	1.09–9.52	
Q3	44.1	1.18	3.26	1.25–8.50	.02	1.39	4.03	1.33–12.23	
Q4	62.1	1.22	3.40	1.29–8.99	.01	1.61	4.99	1.50–16.64	
NREM-AHI					.67				.19
Q1	9.2		1 (ref)				1 (ref)		
Q2	21.7	0.08	1.08	0.43–2.71	.87	−0.18	0.84	0.27–2.58	
Q3	36.0	0.21	1.23	0.50–3.04	.65	0.00	1.00	0.33–3.05	
Q4	63.3	0.52	1.68	0.70–4.05	.25	0.91	2.49	0.77–8.05	

The model was adjusted for age, sex, hypertension, and use of angiotensin converting enzyme inhibitor/angiotensin receptor blockers. In the multivariable models, quartiles of REM-AHI and NREM-AHI were mutually adjusted for each other. AHI = apnea-hypopnea index, B = coefficient, CI = confidence interval, DKD = diabetic kidney disease, NREM = non-REM, OR = odds ratio, ref = reference, REM = rapid eye movement.

Table 4—Results of logistic regression analysis for diabetic kidney disease using categorical AHI (< 15, ≥ 15 to < 30, ≥ 30), quartiles of AHI, quartiles of lowest SaO_2 or quartiles of T90SPT (n = 303).

	Median Value	Unadjusted				Adjusted			
		B	OR	95% CI	*P* Value	B	OR	95% CI	*P* Value
Categorical AHI					< .01				.01
< 15	9.0		1 (ref)				1 (ref)		
≥ 15 to < 30	22.6	0.53	1.70	0.77–3.78	.19	0.43	1.54	0.64–3.71	.33
≥ 30	51.9	1.63	2.89	1.42–5.90	< .01	1.12	3.08	1.36–6.94	< .01
Quartiles of AHI					.02				.01
Q1	12.8		1 (ref)				1 (ref)		
Q2	27.4	0.13	1.13	0.57–2.27	.72	0.05	1.05	0.48–2.30	
Q3	43.1	0.60	1.82	0.91–3.63	.09	0.53	1.69	0.78–3.67	.18
Q4	70.7	0.94	2.56	1.29–5.08	< .01	1.40	4.06	1.70–9.73	< .01
Lowest SaO_2					< .01				< .01
Q1	87.0		1 (ref)				1 (ref)		
Q2	81.0	0.49	1.62	0.82–3.22	.17	0.61	1.84	0.86–3.97	.12
Q3	74.0	1.19	3.27	1.60–6.69	< .01	1.48	4.39	1.94–9.96	< .01
Q4	64.0	0.82	2.27	1.14–4.51	.02	1.47	4.35	1.83–10.34	< .01
T90SPT					< .01				< .01
Q1	0.8		1 (ref)				1 (ref)		
Q2	5.6	0.88	2.41	1.18–4.92	.02	0.61	1.85	0.83–4.09	.13
Q3	18.4	0.90	2.46	1.19–5.07	.02	0.98	2.66	1.18–6.03	.02
Q4	60.1	1.39	4.02	1.96–8.24	< .01	1.91	6.73	2.77–16.35	< .01
Mean SpO_2					.07				.02
Q1	95.0		1 (ref)				1 (ref)		
Q2	94.0	0.05	1.05	0.46–2.39	.91	−0.22	0.80	0.31–2.09	.65
Q3	92.0	0.73	2.08	1.02–4.27	.045	0.60	1.82	0.75–4.41	.18
Q4	88.0	0.83	2.29	1.03–5.08	.04	1.40	4.06	1.40–11.78	.01

The model was adjusted for age, sex, BMI, T2D duration, smoking, hypertension, HbA1c, non-HDL cholesterol, and use of insulin, ACE inhibitor/angiotensin receptor blockers, statin and sleeping pills. ACE = angiotensin converting enzyme, AHI = apnea-hypopnea index, B = coefficient, BMI = body mass index, CI = confidence interval, Hb1AC = hemoglobin 1Ac, OR = odds ratio, ref = reference, SaO_2 = arterial oxyhemoglobin saturation, T90SPT = percentage of time spent with SaO_2 < 90.

as a PSG-determined obstructive respiratory disturbance index (RDI) ≥ 5 events/h associated with the typical symptoms of OSA (eg, unrefreshing sleep, daytime sleepiness, fatigue or insomnia, awakening with a gasping or choking sensation, loud snoring, or witnessed apneas), or an obstructive RDI ≥ 15 events/h (even in the absence of symptoms).[43] Fifth, although we showed independent associations between DKD and lowest SaO_2 or T90SPT, we do not have REM and/or NREM-lowest SaO_2 or REM and/or NREM-T90SPT data. Further studies including such parameters will be needed in the future studies. Sixth, we excluded patients with REM sleep of less than 30 minutes according to the previous report.[21] This is because REM-AHI should be considered imprecise if the amount of REM sleep is less than 30 minutes. This criterion, however, has the potential to exclude patients with severe REM-related OSA who are at the greatest risk for DKD because severe REM-related OSA causes frequent arousals during REM sleep, resulting in shorter REM sleep time.

In conclusion, our study demonstrated that REM-AHI, but not NREM-AHI, is independently linearly associated with DKD. OSA, especially during REM sleep, is a potential risk factor for DKD and should be screened in patients with T2D. Further studies that assess the effect of adherent continuous positive airway pressure treatment on preventing the progression of DKD will be needed.

ABBREVIATIONS

AHI, apnea-hypopnea index
CI, confidence interval
DKD, diabetic kidney disease
eGFR, estimated glomerular filtration rate
HbA1c, glycated hemoglobin
HSAT, home sleep apnea testing
NREM, non-rapid eye movement
OSA, obstructive sleep apnea
RDI, respiratory event index
REM, rapid eye movement
SaO_2, arterial oxyhemoglobin saturation
T2D, type 2 diabetes mellitus
T90SPT, percentage of time spent with SaO2 <90%

REFERENCES

1. Tahrani AA. Obstructive sleep apnoea in diabetes: does it matter? *Diab Vasc Dis Res.* 2017;14(5):454–462.
2. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. *Chest*. 2017;152(5):1070–1086.
3. Mokhlesi B, Grimaldi D, Beccuti G, Van Cauter E. Effect of one week of CPAP treatment of obstructive sleep apnoea on 24-hour profiles of glucose, insulin and counter-regulatory hormones in type 2 diabetes. *Diabetes Obes Metab.* 2017; 19(3):452–456.
4. Loffler KA, Heeley E, Freed R, et al.; SAVE Substudy Investigators. Continuous positive airway pressure treatment, glycemia, and diabetes risk in obstructive sleep apnea and comorbid cardiovascular disease. *Diabetes Care*. 2020;43(8):1859–1867.
5. Shaw JE, Punjabi NM, Naughton MT, et al. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. *Am J Respir Crit Care Med.* 2016;194(4):486–492.
6. Altaf QA, Dodson P, Ali A, et al. Obstructive sleep apnea and retinopathy in patients with type 2 diabetes. A longitudinal study. *Am J Respir Crit Care Med.* 2017;196(7):892–900.
7. Nishimura A, Kasai T, Tamura H, et al. Relationship between sleep disordered breathing and diabetic retinopathy: analysis of 136 patients with diabetes. *Diabetes Res Clin Pract.* 2015;109(2):306–311.
8. Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes. *Am J Respir Crit Care Med.* 2012;186(5):434–441.
9. Leong WB, Jadhakhan F, Taheri S, Thomas GN, Adab P. The association between obstructive sleep apnea on diabetic kidney disease: a systematic review and meta-analysis. *Sleep*. 2016;39(2):301–308.
10. Nishimura A, Kasai T, Kikuno S, et al. Effect of sleep-disordered breathing on albuminuria in 273 patients with type 2 diabetes. *J Clin Sleep Med.* 2018;14(3): 401–407.
11. Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. *Diabetes Care*. 2013;36(11):3718–3725.
12. Varga AW, Mokhlesi B. REM obstructive sleep apnea: risk for adverse health outcomes and novel treatments. *Sleep Breath.* 2019;23(2):413–423.
13. Chami HA, Gottlieb DJ, Redline S, Punjabi NM. Association between glucose metabolism and sleep-disordered breathing during REM sleep. *Am J Respir Crit Care Med.* 2015;192(9):1118–1126.
14. Findley LJ, Wilhoit SC, Suratt PM. Apnea duration and hypoxemia during REM sleep in patients with obstructive sleep apnea. *Chest*. 1985;87(4): 432–436.
15. Shea SA, Edwards JK, White DP. Effect of wake-sleep transitions and rapid eye movement sleep on pharyngeal muscle response to negative pressure in humans. *J Physiol.* 1999;520(Part 3):897–908.
16. Douglas NJ, White DP, Weil JV, et al. Hypoxic ventilatory response decreases during sleep in normal men. *Am Rev Respir Dis.* 1982;125(3):286–289.
17. Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep apnea during REM sleep and hypertension. results of the Wisconsin Sleep Cohort. *Am. J. Respir. Crit. Care Med.* 2014;190(10):1158–1167.
18. Mokhlesi B, Hagen EW, Finn LA, Hla KM, Carter JR, Peppard PE. Obstructive sleep apnoea during REM sleep and incident non-dipping of nocturnal blood pressure: a longitudinal analysis of the Wisconsin Sleep Cohort. *Thorax*. 2015; 70(11):1062–1069.
19. Acosta-Castro P, Hirotsu C, Marti-Soler H, et al. REM-associated sleep apnoea: prevalence and clinical significance in the HypnoLaus cohort. *Eur Respir J.* 2018; 52(2):1702484.
20. Aurora RN, Crainiceanu C, Gottlieb DJ, Kim JS, Punjabi NM. Obstructive sleep apnea during REM sleep and cardiovascular disease. *Am J Respir Crit Care Med.* 2018;197(5):653–660.
21. Mokhlesi B, Punjabi NM. "REM-related" obstructive sleep apnea: an epiphenomenon or a clinically important entity? *Sleep*. 2012;35(1):5–7.
22. Seino Y, Nanjo K, Tajima N, et al.; Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. *J Diabetes Investig.* 2010;1(5):212–228.
23. Kashiwagi A, Kasuga M, Araki E, et al.; Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Investig.* 2012;3(1):39–40.
24. Matsuo S, Imai E, Horio M, et al.; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis.* 2009;53(6):982–992.
25. Shimamoto K, Ando K, Fujita T, et al.; Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res.* 2014;37(4):253–390.
26. Ueno K, Kasai T, Brewer G, et al. Evaluation of the apnea-hypopnea index determined by the S8 auto-CPAP, a continuous positive airway pressure device, in patients with obstructive sleep apnea-hypopnea syndrome. *J Clin Sleep Med.* 2010;6(2):146–151.

27. Ikeda Y, Kasai T, Kawana F, et al. Comparison between the apnea-hypopnea indices determined by the REMstar Auto M series and those determined by standard in-laboratory polysomnography in patients with obstructive sleep apnea. *Intern Med.* 2012;51(20):2877–2885.
28. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2012;8(5):597–619.
29. Grimaldi D, Beccuti G, Touma C, Van Cauter E, Mokhlesi B. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. *Diabetes Care*. 2014;37(2): 355–363.
30. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018. Available from: http://www.R-project.org/. Accessed Feb 19, 2019.
31. Haas DC, Foster GL, Nieto FJ, et al. Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. *Circulation*. 2005;111(5): 614–621.
32. Bialasiewicz P, Czupryniak L, Pawlowski M, Nowak D. Sleep disordered breathing in REM sleep reverses the downward trend in glucose concentration. *Sleep Med.* 2011;12(1):76–82.
33. Appleton SL, Vakulin A, Martin SA, et al. Hypertension is associated with undiagnosed OSA during rapid eye movement sleep. *Chest.* 2016;150(3): 495–505.
34. Nishimura A, Kasai T, Kikuno S, et al. Apnea hypopnea index during rapid eye movement sleep with diabetic retinopathy in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2019;104(6):2075–2082.
35. Lavie L. Oxidative stress--a unifying paradigm in obstructive sleep apnea and comorbidities. *Prog Cardiovasc Dis.* 2009;51(4):303–312.
36. Turek NF, Ricardo AC, Lash JP. Sleep disturbances as nontraditional risk factors for development and progression of CKD: review of the evidence. *Am J Kidney Dis.* 2012;60(5):823–833.
37. Hanly PJ, Ahmed SB. Sleep apnea and the kidney: is sleep apnea a risk factor for chronic kidney disease? *Chest.* 2014;146(4):1114–1122.
38. Tan KC, Chow WS, Lam JC, et al. Advanced glycation endproducts in nondiabetic patients with obstructive sleep apnea. *Sleep*. 2006;29(3):329–333.
39. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest.* 1995;96(4):1897–1904.
40. Furukawa S, Saito I, Yamamoto S, et al. Nocturnal intermittent hypoxia as an associated risk factor for microalbuminuria in Japanese patients with type 2 diabetes mellitus. *Eur J Endocrinol.* 2013;169(2):239–246.
41. Kosseifi S, Bailey B, Price R, Roy TM, Byrd RP Jr, Peiris AN. The association between obstructive sleep apnea syndrome and microvascular complications in well-controlled diabetic patients. *Mil Med.* 2010;175(11):913–916.
42. Leong WB, Nolen M, Thomas GN, Adab P, Banerjee D, Taheri S. The impact of hypoxemia on nephropathy in extremely obese patients with type 2 diabetes mellitus. *J Clin Sleep Med.* 2014;10(7):773–778.
43. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med.* 2017;13(3):479–504.
44. Bianchi MT, Goparaju B. Potential underestimation of sleep apnea severity by at-home kits: rescoring in-laboratory polysomnography without sleep staging. *J Clin Sleep Med.* 2017;13(4):551–555.
45. O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med.* 2000;161(5):1465–1472.
46. Resta O, Carpanano GE, Lacedonia D, et al. Gender difference in sleep profile of severely obese patients with obstructive sleep apnea (OSA). *Respir Med.* 2005; 99(1):91–96.

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