Association of diabetic nephropathy with the severity of obstructive sleep apnea-hypopnea syndrome in patients with type 2 diabetes mellitus

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Abstract. This study aimed to analyze the effect of the severity of obstructive sleep apnea-hypopnea syndrome (OSAHS) on diabetic nephropathy (DN) in patients with type 2 diabetes mellitus (T2DM). A total of 322 patients with T2DM participated in this cross-sectional study. OSAHS was diagnosed according to the apnea-hypopnea index (AHI) and it was categorized as follows: normal, mild, moderate, and severe. Relevant clinical data retrieved from medical charts were cross-analyzed between different groups. The relationship between urinary albumin/creatinine ratio (UACR) and OSAHS parameters, which included AHI, lowest oxygen saturation (L-SaO$_2$), and mean oxygen saturation (M-SaO$_2$), was evaluated by partial correlation analysis. DN stages were classified into a non-DN group, a microalbuminuria group, and a macroalbuminuria group. Multiple factor logistic regression analysis was employed to analyze factors influencing DN. The results showed that mild OSAHS, moderate OSAHS, and severe OSAHS patients had a higher Body mass index (BMI), creatinine (CR) level, UACR, and a longer duration of T2DM ($p < 0.05$) than the non-OSAHS group. The prevalence of DN in the non-OSAHS, mild OSAHS, moderate OSAHS, and severe OSAHS groups was 18.4%, 19.2%, 34.6%, and 49.4%, respectively ($p < 0.05$). Multiple factor logistic regression analysis revealed that systolic blood pressure (SBP) ($OR = 1.03$), AHI ($OR = 1.02$), and duration of T2DM ($OR = 1.04$) were correlated with DN ($p < 0.05$). These findings revealed that OSAHS is highly prevalent in T2DM and AHI is independently associated with the presence of DN.

Key words: Type 2 diabetes mellitus, Obstructive sleep apnea-hypopnea syndrome, Diabetic nephropathy, Urinary albumin/creatinine ratio

OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME (OSAHS) is characterized by the collapse of the upper airway, which leads to hypoxemia and sleep fragmentation. The main symptoms of OSAHS include interval snoring, periods of stopped breathing and waking up during sleep, sweating and excessive urine at night, dizziness and headache in the morning, and daytime fatigue and sleepiness. The prevalence of OSAHS was estimated to be 2–4% in 2004 [1], which increased with increasing age and diagnostic levels. Currently, the mean prevalence of OSAHS among male was 22% (9–37%), while it was 17% (4–50%) among female [2]. However, the majority of OSAHS cases have not been diagnosed and treated in a timely and effective manner.

Type 2 diabetes mellitus (T2DM) is a major public health problem due to high rates of morbidity, mortality, disability, and high medical costs. The increased prevalence of T2DM is a serious burden on public health, because the disease is not only a risk factor for both microvascular and macrovascular diseases, but is also associated with all-cause mortality [3]. Diabetic nephropathy (DN), a common type of diabetic microvascular complication, constitutes the main type of chronic kidney disease and the leading cause of renal failure and dialysis worldwide. A number of studies have shown that 10–40% of diabetic patients have DN [4-7], and its prevalence continues to increase year by year. Therefore, early identification of risk factors for DN has a effect on its occurrence and development. Consequently, this may result in a significant reduction in the incidence of macrovascular events and improvement in the survival rate, as well as the quality of life of T2DM patients.

According to the literature, the prevalence of OSAHS in T2DM patients ranges from 23–86.6% [8-11]. In some prospective longitudinal studies, patients with severe sleep apnea or sleep-disordered breathing (SDB) were significantly more likely to have diabetes than those without sleep apnea or SDB [12-14]. Many studies have
shown that T2DM or insulin resistance is associated with OSAHS but is independent of obesity after adjusting for confounders [8, 12, 13, 15-19]. In addition, OSAHS increases the risk of developing diabetes, independent of other risk factors [13, 14]. However, to date, less is known about the correlation between OSAHS and DN [20] and whether the severity of OSAHS increases the risk of DN in patients with T2DM [21-23]. Since both T2DM and OSAHS can cause high morbidity and adversely affect public health, it is of clinical significance to early identify patients with risk factors of DN and explore the correlation between OSAHS and DN.

**Patients and Methods**

**Study population**

Patients with T2DM admitted to the First Affiliated Hospital of Chongqing Medical University from September 2013 to September 2018 were selected as subjects. T2DM was diagnosed according to WHO criteria. The exclusion criteria were as follows: subjects with type 1 diabetes or other types of diabetes mellitus, subjects undergoing treatment for OSAHS, head and neck malignant tumors, acute infection, non-diabetic nephropathy including chronic glomerulonephritis, urinary tract infection, and genitourinary malignancy; patients with mental disorders that may interrupt data collection; and subjects with other comorbid conditions that may affect the diagnosis of OSAHS by polysomnography, including pulmonary disease, neuromuscular disease, and cardiac diseases, and any other unstable medical condition that may block the application of polysomnography, such as pulmonary disease, non-diabetic nephropathy, including chronic glomerulonephritis, urinary tract infection, and genitourinary malignancy; patients with mental disorders that may interrupt data collection; and subjects with other comorbid conditions that may affect the diagnosis of OSAHS by polysomnography, including pulmonary disease, neuromuscular disease, and cardiac diseases, and any other unstable medical condition that may block the application of polysomnography, such as chronic glomerulonephritis, urinary tract infection, and genitourinary malignancy; patients with mental disorders that may interrupt data collection; and subjects with other comorbid conditions that may affect the diagnosis of OSAHS by polysomnography, including pulmonary disease, neuromuscular disease, and cardiac diseases, and any other unstable medical condition.

**Collection of Clinical Data**

The data collected were obtained from medical records. The demographic and medical history included age, gender, the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), and duration of T2DM. BMI was calculated as body weight divided by squared height. Subjects were asked to rest in a quiet environment for 30 minutes before blood pressure (BP) was measured, then the SBP and diastolic blood pressure (DBP) were measured with the subject in a seated position. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg or taking antihypertensive drugs. Fasting was started at 10 PM the previous night, and blood and urine samples were collected the next morning before breakfast to measure total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and creatinine (CR).

The estimated glomerular filtration rate (eGFR), which represents renal function, was calculated according to the CKD-EPI equation published by Americans, based on age, gender, and serum creatinine.

**Assessment of DN**

According to the consensus of the American Diabetes Association and the National Kidney Foundation, the diagnosis of early diabetic nephropathy is based on UACR [24]. DN was classified into two stages, microalbuminuria and macroalbuminuria. Clinically, UACR at 30–300 mg/g is often referred to as microalbuminuria, while UACR greater than 300 mg/g is called macroalbuminuria.

**Sleep apnea test**

All participants completed a night of sleep apnea monitoring by polysomnography (Polysonmography Alice 5, Philips). Polysomnography (PSG) monitoring was performed on all subjects throughout the night (more than 7 hours), during which synchronized eye movements, mouth-nose airflow, chest and abdomen activity, blood oxygen saturation, electroencephalogram, and electrocardiogram were recorded. The monitoring results were automatically analyzed by the Alice software and then interpreted by an expert. To nose and mouth breathing during sleep airflow disappear or weakened obviously, down is greater than or equal to 90%, compared with baseline duration is greater than or equal to 10 s, called sleep apnea. Hypopnea was defined as: (1) during sleep, oronasal airflow decreases by 30% or more from the baseline level, accompanied by a decrease in blood oxygen saturation of 4% or more, for 10 s or longer; Or (2) the oronasal airflow decreased by 50% or more from the baseline level and the oxygen saturation decreased by 3% or more for a duration of 10 s or longer. The apnea-hypopnea index (AHI) was defined as the sum of sleep apnea and hypopnea divided by sleep time (hours). All participants’ AHI, L-SaO2, and M-SaO2 were recorded. The diagnosis of OSAHS was made if the AHI was ≥5 times per hour. The OSAHS classifications are: under 5 times per hour, non-OSAHS; between 5 to 15 times per hour, mild OSAHS; between 15 to 30 times per hour, moderate OSAHS; and more than 30 times per hour, severe OSAHS.

**Statistical analysis**

Statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). The Mean and
standard deviation were used to describe continuous variables with a normal distribution. Categorical data were presented as percentages, and other data were reported as the median (p25–p75). Categorical variables were tested with the χ² test. The Mann-Whitney U test was used to examine the differences between groups with discrete variables or continuous variables without a normal distribution, and then the post hoc test adjusted with a Bonferroni correction was employed for the comparisons between groups. Partial correlation analysis was used to analyze the correlation between UACR and OSAHS parameters. ANOVA was applied to compare the continuous variables with a normal distribution among multiple groups, and comparisons between groups were performed with the LSD-t test. Factors associated with DN were analyzed by logistic regression. All statistical tests were two-sided, and a value of p less than 0.05 was considered statistically significant.

**Results**

The mean age of our samples was around 56.8 ± 12.2, including 233 males (72.4%) and 89 females (27.6%). In these samples, the prevalence of DN was around 37.3% (120/322) and the prevalence of OSAHS was around 88.2% (284/322). The detail characteristics of patients are shown in Table 1. Only 11.8% of patients with T2DM did not have OSAHS, whereas 16.2% had mild OSAHS, 24.2% had moderate OSAHS, and 47.8% had severe OSAHS. Table 2 lists the variables of all participants. There were statistically significant differences in age, BMI, DBP, TG, UACR, CR, DN rate, and duration of T2DM between the four groups (p < 0.05). The duration of T2DM, BMI, and UACR in the severe group was higher than that in the non-OSAHS group, the mild group, and the moderate group, respectively, and the differences were statistically significant. However, there were no significant differences in terms of sex, SBP, eGFR, TC, LDL-C, CR, hypertension, hyperlipidemia, M-SaO², SBP, DBP, ACEI/ARB, ARB, and AHI among the three groups. When compared with the non-OSAHS group, the microalbuminuria group and macroalbuminuria group were statistically significant for BMI, UACR, AHI, SBP, and hypertension. Moreover, the AHI and L-SaO² were significantly different between the non-DN, microalbuminuria, and macroalbuminuria groups, whereby the mean AHI increased with increasing severity of DN and L-SaO² decreased with increasing severity of DN.

Partial correlation analysis was used to analyze the correlation between the UACR and OSAHS parameters. As shown in Table 4, UACR had slightly positive correlation with AHI (r = 0.223, p < 0.001), but negatively correlated with L-SaO² (r = –0.123, p = 0.029) after adjusting for BMI, duration of T2DM, age, SBP, DBP, HbA1c, and FPG. UACR was not correlated with M-SaO².

We compared the prevalence of DN in the non-OSAHS, mild OSAHS, moderate OSAHS, and severe OSAHS patients. As shown in Table 2, the prevalence of DN in the four groups, non-OSAHS, mild OSAHS, moderate OSAHS, and severe OSAHS, was 18.4%, 19.2%, 34.6%, and 49.4%, respectively (p < 0.001). These results indicated that the prevalence of DN increased with increasing severity of OSAHS.

Logistic regression analysis was used to analyze risk factors related to DN (Table 5). The results indicated that DN is significantly correlated with SBP (OR = 1.03, 95%CI 1.01–1.05, p = 0.004), duration of T2DM (OR = 1.04, 95%CI 1.00–1.08, p = 0.047), and AHI (OR = 1.02, 95%CI 1.01–1.03, p = 0.003), after adjusting for SBP, DBP, BMI, AHI, duration of T2DM, L-SaO², hypertension, the use of ACEI/ARB, and M-SaO².

**Discussion**

In the present study, our results indicate that: (1) patients with T2DM complicated with mild, moderate, or severe OSAHS have CR and UACR levels that are sig-
Table 2  Clinical characteristics of the 322 subjects according to the apnea-hypopnea index (AHI)

| Variable                  | non-OSAHS n = 38 | mild-OSAHS n = 52 | moderate-OSAHS n = 78 | severe-OSAHS n = 154 | p value |
|---------------------------|------------------|-------------------|-----------------------|----------------------|---------|
| Age (years)               | 58.9 ± 13.8      | 56.4 ± 12.4       | 60.4 ± 12.0           | 54.5 ± 11.4          | 0.003   |
| Male sex (%)              | 71.1             | 63.4              | 69.2                  | 76.6                 | 0.380   |
| BMI (Kg/m²)               | 24.8 ± 3.3       | 26.1 ± 3.0        | 27.1 ± 3.2            | 29.1 ± 3.7           | <0.001  |
| Hypertension (%)          | 57.9             | 57.7              | 56.4                  | 61.0                 | 0.911   |
| SBP (mmHg)                | 144.9 ± 21.4     | 142.4 ± 17.7      | 140.7 ± 20.5          | 143.6 ± 20.0         | 0.674   |
| DBP (mmHg)                | 83.9 ± 12.6      | 81.6 ± 11.0       | 82.7 ± 12.8           | 86.8 ± 12.9          | 0.025   |
| hyperlipidemia (%)        | 63.2             | 53.8              | 50.0                  | 64.9                 | 0.127   |
| CR (umol/L)               | 74.0 ± 20.5      | 75.6 ± 22.9       | 75.2 ± 17.4           | 83.6 ± 32.6          | 0.033   |
| eGFR (mL/min/1.73 m²)     | 94.9 (85.8, 102.6) | 96.1 (81.6, 105.1) | 91.8 (73.8, 102.1)   | 95.1 (74.4, 105.8)   | 0.679   |
| UACR (mg/g)               | 3.9 (0.6, 17.6)  | 7.3 (2.8, 16.9)   | 11.7 (3.1, 39.0)     | 26.3 (4.9, 83.3)     | <0.001  |
| HbA1c (%)                 | 7.5 ± 1.9        | 7.9 ± 2.0         | 7.8 ± 1.7             | 8.3 ± 2.0            | 0.069   |
| FPG (mmol/L)              | 7.4 ± 2.6        | 8.2 ± 2.7         | 8.2 ± 3.5             | 8.5 ± 3.1            | 0.239   |
| duration of T2DM (years)  | 2.2 ± 3.3        | 4.5 ± 5.8         | 6.3 ± 6.7             | 7.3 ± 6.8            | <0.001  |
| DN (%)                    | 18.4             | 19.2              | 34.6                  | 49.4                 | <0.001  |
| the use of ACEI/ARB (%)    | 44.7             | 38.5              | 38.5                  | 46.1                 | 0.627   |

Values are expressed as the mean ± SD, numbers with percentages in parentheses, or median values with the interquartile range in parentheses. TC, cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HbA1c, Hemoglobin A1c; FPG, fasting plasma glucose; CR, creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, Body mass index; T2DM, type 2 diabetes mellitus; UACR, the ratio of urinary albumin to creatinine; OSAHS, obstructive sleep apnea-hypopnea syndrome; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers. a p < 0.05, compare with Non-OSAHS group; b p < 0.05, compare with Mild-OSAHS group; c p < 0.05, compare with Moderate-OSAHS group.

Table 3  Comparison of baseline characteristics in patients with non-DN, microalbuminuria group, and macroalbuminuria group

| Variable                  | Non-DN group n = 202 | microalbuminuria group n = 89 | macroalbuminuria group n = 31 | p value |
|---------------------------|----------------------|-----------------------------|-----------------------------|---------|
| Age (years)               | 56.9 ± 11.9          | 56.2 ± 13.3                 | 57.4 ± 11.4                 | 0.876   |
| Male sex (%)              | 69.3                 | 78.67                       | 74.2                        | 0.252   |
| BMI (Kg/m²)               | 27.1 ± 3.7           | 28.5 ± 3.3                 | 28.9 ± 4.7                 | 0.002   |
| Hypertension (%)          | 51.0                 | 68.5                        | 83.9                        | <0.001  |
| SBP (mmHg)                | 138.8 ± 18.5         | 146.1 ± 18.3               | 160.5 ± 22.0               | <0.001  |
| DBP (mmHg)                | 83.3 ± 11.1          | 86.9 ± 14.5                | 87.1 ± 15.8                | 0.043   |
| hyperlipidemia (%)        | 57.9                 | 59.6                        | 67.7                        | 0.378   |
| HbA1c (%)                 | 7.9 ± 1.9            | 8.2 ± 2.0                  | 8.2 ± 1.9                  | 0.352   |
| FPG (mmol/L)              | 8.1 ± 3.2            | 8.5 ± 2.8                  | 8.6 ± 3.4                  | 0.388   |
| duration of T2DM (years)  | 5.0 ± 5.8            | 7.9 ± 7.4                 | 7.0 ± 6.8                  | 0.001   |
| AHI (times/hour)          | 28.6 ± 23.9          | 42.6 ± 27.6               | 50.6 ± 25.6                | <0.001  |
| L-SaO₂ (%)                | 76.3 ± 12.3          | 73.8 ± 16.0                | 68.7 ± 16.3                | 0.013   |
| M-SaO₂ (%)                | 93.0 ± 5.0           | 91.4 ± 10.1                | 91.2 ± 4.8                 | 0.108   |
| eGFR (mL/min/1.73 m²)     | 96.3 (84.0, 105.7)   | 90.3 (71.5, 105.2)         | 64.5 (40.0, 92.4)          | <0.001  |
| UACR (mg/g)               | 4.7 (1.8, 11.3)      | 52.7 (37.9, 96.0)          | 882.9 (494.1, 1804.0)      | <0.001  |
| the use of ACEI/ARB (%)    | 36.1                 | 50.6                        | 64.5                        | 0.003   |

L-SaO₂, the lowest oxygen saturation; M-SaO₂, mean oxygen saturation; AHI, apnea-hypopnea index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers. a p < 0.05, compare with Non-DN group; b p < 0.05, compare with microalbuminuria group.
indicated that AHI, the gold standard for diagnosing OSAHS was higher than in patients without OSAHS; (3) AHI is positively correlated with UACR, while L-SaO$_2$ is negatively correlated with UACR; (4) With the increasing severity of OSAHS, patients with T2DM are more prone to affect DN. These results are consistent with previous findings reported by other groups [25, 26]. (2) The prevalence of DN in patients with mild OSAHS, moderate OSAHS, and severe OSAHS was higher than in patients without OSAHS; (3) AHI is positively correlated with UACR, while L-SaO$_2$ is negatively correlated with UACR; (4) With the increasing severity of OSAHS, patients with T2DM are more prone to affect DN.

Our results showed that the prevalence of OSAHS diagnosed with AHI ≥5 times per hour in hospitalized T2DM patients was 88.2%, which is consistent with previous studies [8-12, 27]. The high prevalence of OSAHS in our study might be due to the fact that most of the people included in this study were overweight or obese. The prevalence of OSAHS in T2DM ranged from 23% to 86.6% [8-11], and this high variability may be due to differences in study design, study population, demographic factors, test methods, and diagnostic criteria. According to a previous report by Foster et al. [11], the prevalence of OSAHS in obese patients with T2DM was as high as 88%. Therefore, physicians should be particularly aware of the possibility of OSAHS in obese patients with T2DM, especially in individuals with higher BMI [11].

According to previous studies, DN was less likely to be staged or diagnosed based on the level of UACR. UACR has not been employed to assess the prevalence of DN between non-OSAHS, mild OSAHS, moderate OSAHS, and severe OSAHS patients in previous relevant studies. Therefore, we compared the prevalence of DN among these four groups and found that the prevalence of OSAHS in the mild OSAHS, moderate OSAHS, and severe OSAHS groups was significantly higher than that in the group only affected with T2DM. At the same time, partial correlation analysis showed that AHI was positively correlated with UACR, while L-SaO$_2$ was negatively correlated.

DN is a microvascular complications of diabetes. At present, studies regarding the association between OSAHS and DN are scarce and controversial [26-29]. Furukawa et al. [27] showed that five or more 3% oxygen desaturation index (ODI) events per hour might be an independently associated risk factor for microalbuminuria in Japanese women with T2DM after adjustment for confounders, whereby ODI was examined by a pulse oximeter. One study by Buyukaydin et al. [28] analyzed the CR, urea nitrogen, urinary albumin excretion rate, and other indicators in 52 patients with T2DM complicated by OSAHS, but found no correlation between them and AHI. However, this study did not analyze other parameters for OSAHS, and the sample size was relatively small. In some other studies [21, 29], Sleep-Disorder Breathing (SDB) was defined as a Respiratory Event Index (REI) ≥5 events per hour, which had an independent association with UACR in patients with T2DM. However, in these studies, a portable polygraph, which could neither be used for sleep staging nor distinguish between obstructive sleep apnea and central sleep apnea, was used to assess SDB rather than PSG. Another multicenter, cross-sectional study [26] in 880 patients with T2DM showed that CT90%, the cumulative time of SPO$_2$ below 90%, was simultaneously associated with DN, microalbuminuria, and macroalbuminuria, while the average SPO$_2$ and CT90% were markedly associated with microalbuminuria. Although AHI was not associated with microalbuminuria, it was associated with macroalbuminuria and renal insufficiency. To verify the relationship between OSAHS and DN, we divided the

### Table 4: Correlation between UACR and OSAHS parameters

| Parameter       | r    | p      |
|-----------------|------|--------|
| AHI (1 times/hour) | 0.223 | <0.001 |
| L-SaO$_2$ (1%)   | -0.123 | 0.029  |
| M-SaO$_2$ (1%)   | -0.084 | 0.139  |

Partial correlation analysis was used to analyze the correlation between UACR and OSAHS parameters. Each parameter was analyzed separately after adjustment for age, BMI, duration of T2DM, SBP, DBP, FBG, and HbA1c.

### Table 5: Logistic regression analysis of patients with and without DN for factors associated with DN

| Variable          | $\beta$ | OR (95% CI) | p value |
|-------------------|---------|-------------|---------|
| SBP (1 mmHg)      | 0.029   | 1.03 (1.01–1.05) | 0.004  |
| DBP (1 mmHg)      | -0.007  | 0.99 (0.97–1.02) | 0.536  |
| BMI (Kg/m$^2$)    | 0.045   | 1.05 (0.97–1.13) | 0.262  |
| AHI (1 times/hour)| 0.018   | 1.02 (1.01–1.03) | 0.003  |
| Duration of T2DM (years)| 0.040 | 1.04 (1.00–1.08) | 0.047  |
| L-SaO$_2$ (1%)    | -0.002  | 1.00 (0.98–1.02) | 0.837  |
| M-SaO$_2$ (1%)    | -0.018  | 0.98 (0.94–1.03) | 0.473  |
| hypertension (1%) | -0.034  | 0.97 (0.43–2.20) | 0.959  |
| the use of ACEI/ARB(1%) | -0.136 | 0.87 (0.49–1.57) | 0.648  |

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, Body mass index; T2DM, type 2 diabetes mellitus; L-SaO$_2$, the lowest oxygen saturation; M-SaO$_2$, mean oxygen saturation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers. OR, odds ratio; 95% CI, 95% confidence interval; p value $< 0.05$ was significant.
recruited patients into non-DN, microalbuminuria and macroalbuminuria groups. Our results revealed that the microalbuminuria and macroalbuminuria groups had a higher BMI, duration of T2DM, SBP, prevalence of hypertension, but lower L-SaO\textsubscript{2}, than the non-DN group. Additionally, logistic regression analysis (Table 5) indicated that DN was significantly associated with SBP and duration of T2DM after adjusting for SBP, DBP, BMI, AHI, duration of T2DM, L-SaO\textsubscript{2}, M-SaO\textsubscript{2}, the use of ACEI/ARB, and hypertension. This is consistent with findings from previous studies [30, 31]. Meanwhile, we also found that AHI, which is a surrogate marker of OSAHS, was independently related to DN. The findings regarding the association between OSAHS and DN are consistent with prior observations [27, 29].

To date, the mechanisms underlying the relationship between OSAHS and DN remain largely unknown, but several explanations have been proposed. Firstly, OSAHS induces intermittent hypoxia, which can excite the sympathetic nerves [32], thus causing an increase in angiotensin-II secretion resulting in vasoconstriction, and ultimately leading to ischemic damage. Second, hypoxemia and hypercapnia from OSAHS can activate the renin-angiotensin-aldosterone system [33], which leads to increased glomerular pressure and urinary protein excretion. In our cross-sectional data, the use of ACEI/ARB which affects above mechanisms increased with the progression of DN, however, the significant relation between DN and AHI was independent from the use of ACEI/ARB. Third, intermittent hypoxia can cause oxidative stress and an inflammatory reaction, which can lead to atherosclerosis and endothelial dysfunction, and, consequently, result in glomerular hyperfiltration [34]. On the other hand, elevated hemoglobin and red blood cells due to intermittent hypoxia result in increased blood viscosity, which can aggravate ischemia and hypoxia in local tissues.

However, it is worth noting that our research has some shortcomings. First, we cannot conclude that there is a causal relationship between DN and OSAHS in this cross-sectional study. Therefore, future longitudinal studies are needed to shed light on whether there is a causal relationship and to investigate the effect of continuous positive airway pressure on DN. Second, the fairly small sample size is insufficient to analyze the correlation between diseases, which may affect the robustness of the study. Third, a single measurement of UACR was a limitation of this study due to its fluctuation, which may lead to data drift. Even though previous studies have used a single UACR measurement [21, 27, 29, 35], multiple measurements of UACR values are recommended in clinical settings and for future perspective studies. Finally, the exclusion criteria for this study was to exclude patients receiving OSAHS treatment, but this study included 232 moderate to severe patients who were internationally recommended for continuous positive airway pressure (CPAP) treatment. The sample population tends to include those who are unwilling to receive treatment for OSAHS. Poor adherence may be related to socioeconomic status, education, physical illness, or ventilator. In addition, we found that AHI, SBP, and duration of T2DM were independently associated with DN even after adjustment for other factors, and AHI was positively correlated with UACR. These results suggest that AHI which represents the extent of OSAHS, may be related to the progression of DN. Future prospective studies are needed to determine the effect of OSAHS on DN development in T2DM and to clarify the effect of the therapy of OASHS on DN.

**Conclusions**

Our study has shown that OSAHS is highly prevalent in hospitalized patients with T2DM. AHI is independently associated with the presence of DN after adjusting for SBP, DBP, BMI, AHI, duration of T2DM, L-SaO\textsubscript{2}, hypertension, the use of ACEI/ARB, and M-SaO\textsubscript{2}. OSAHS may be an independent associated risk factor for DN in patients with T2DM.

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**Disclosure**

No conflicts of interest exist.

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