Journal of
INTERNATIONAL
MEDICAL RESEARCH

Changes of aldosterone levels in patients with type 2 diabetes complicated by moderate to severe obstructive sleep apnea–hypopnea syndrome before and after treatment with continuous positive airway pressure

Jie Zhang [ORCID]**, Lin Tian and Lixin Guo**

Abstract

Objective: Both obstructive sleep apnea–hypopnea syndrome (OSAHS) and type 2 diabetes mellitus (T2DM) are closely related to the renin-angiotensin-aldosterone system. We investigated whether hyperaldosteronemia is found in patients with OSAHS complicated by T2DM and whether continuous positive airway pressure (CPAP) treatment can significantly reduce the aldosterone level.

Methods: Patients with T2DM were classified into an OSAHS group [apnea–hypopnea index (AHI) of ≥ 15] and a control group (without OSAHS; AHI of <5). The OSAHS group was exposed to CPAP for 7 days (7 h/day).

Results: The plasma aldosterone, plasma renin, and urinary aldosterone levels were higher in the OSAHS than control group. The plasma aldosterone and renin levels were significantly lower after than before treatment in the OSAHS group, but they were still higher than the baseline levels in the control group. The post-treatment urinary aldosterone level was significantly higher in the OSAHS than control group. No correlation was found between the AHI and plasma renin, plasma aldosterone, and 24-hour urinary aldosterone levels. The blood glucose level in the OSAHS group did not significantly change after treatment.

Department of Endocrinology, Beijing Hospital, National Center of Gerontology, Beijing, China

Corresponding author:
Lixin Guo, Department of Endocrinology, Beijing Hospital, National Center of Gerontology, No. 1 Dahua Road, Dongdan, Beijing 100730, China.
Email: glx1218@163.com

Conclusions: The plasma and urine aldosterone levels are increased in patients with concurrent T2DM and OSAHS and are significantly reduced by CPAP.
Trial registration: ChiCTR-ION-16009837

Introduction

Studies have shown that type 2 diabetes mellitus (T2DM) is closely related to obstructive sleep apnea–hypopnea syndrome (OSAHS) and the renin-angiotensin-aldosterone system (RAAS). Insulin resistance in patients with T2DM is significantly associated with OSAHS.[1,2] Approximately 40% of patients with OSAHS are diagnosed with concomitant diabetes, and the prevalence of OSAHS in patients with diabetes is 23%. OSAHS increases insulin resistance mainly via intermittent hypoxemia and sleep fragmentation and is mediated by activation of the sympathetic nervous system, altered hypothalamic-pituitary-adrenal axis activity, formation of oxygen free radicals, production of inflammatory cytokines (interleukin-6 and tumor necrosis factor-α), and increased levels of adipocyte-derived factors (leptin, adiponectin, and resistin).[1–3]

T2DM also induces OSAHS or aggravates OSAHS symptoms, and insulin resistance reduces ventilation.[4] Diabetic autonomic neuropathy affects the mechanical and functional aspects of the upper respiratory tract during sleep and subsequently inhibits opening of the upper respiratory tract and reduces the diameter of ventilation, resulting in OSAHS.

T2DM is also closely related to the RAAS in that T2DM activates the RAAS via insulin resistance. RAAS inhibitors significantly increase the sensitivity of insulin.[5] Clinical studies have confirmed the presence of insulin resistance, evaluated through homeostatic model assessment and impaired insulin-stimulated glucose utilization (measured by a euglycemic hyperinsulinemic clamp), in patients with primary aldosteronism but not in individuals with essential hypertension.[6] Furthermore, long-term antihypertensive drug studies have shown that RAAS blockers (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) significantly improve insulin sensitivity and reduce the incidence of T2DM.[7] Several representative studies have also demonstrated that high aldosterone levels are significantly associated with the incidence of T2DM.[8–10] However, no clear conclusion has been reached regarding the relationship between the RAAS and T2DM complicated by OSAHS.

The aim of this study was to confirm that hyperaldosteronemia occurs in patients with OSAHS complicated by T2DM and that continuous positive airway pressure (CPAP) treatment can significantly reduce the level of aldosterone. To verify this, we compared the plasma aldosterone activity, aldosterone–renin ratio, and 24-hour urinary aldosterone levels in patients with T2DM with or without OSAHS before and after CPAP treatment.

Materials and methods

Patients

Patients with T2DM who had undergone polysomnography at the Department of Endocrinology in Beijing Hospital from June 2013 to March 2014 were studied. The study was approved by the ethics committee of Beijing Hospital and was registered in the Chinese Clinical Trial Registry (Registration No: ChiCTR-ION-16009837). All participants provided written informed consent before their participation. The study was conducted from June 2013 to March 2014.

Inclusion criteria

The criteria for inclusion in the study were an age of 20 to 80 years; body mass index (BMI) of $<35 \text{ kg/m}^2$; absence of CPAP or surgical history of uvulopalatopharyngoplasty; diagnosis of T2DM as defined by the World Health Organization criteria; and absence of nasal polyps, tonsils, or uvula hypertrophy during an otolaryngology examination. All patients involved in the study received insulin or oral antidiabetic drugs, and the original regimen was maintained for glycemic control before and after the study. Patients with hypertension had their blood pressure well controlled; their original antihypertensive regimens of diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers were changed to 240-mg verapamil sustained-release tablets once daily at least 2 weeks before the trial.

The patients were divided into two groups according to the polysomnography results:

1. The OSAHS group [patients with T2DM and moderate to severe OSAHS according to a polysomnography device (ResMed, San Diego, CA, USA) with an apnea–hypopnea index (AHI) of ≥ 15]; patients with mild OSAHS were not enrolled
2. The control group (patients with T2DM but without OSAHS, with an AHI of <5)

Exclusion criteria

Patients with the following conditions were not eligible for the study: severe heart disease (acute myocardial infarction, chronic heart failure, valvular heart disease, and cardiomyopathy within 6 months), kidney disease (acute or chronic renal insufficiency, nephrotic syndrome, and nephritis), lung disease (pulmonary bullae, pneumothorax, mediastinal emphysema, chronic obstructive pulmonary disease, pulmonary fibrosis, and tumors), mental illness, craniocerebral trauma, cerebral vascular disease, diabetic ketoacidosis, a diabetic hyperglycemic hyperosmolar state, acute otitis media, partially treated acute infectious disease, thyroid dysfunction, and pituitary and adrenal dysfunction.

Baseline procedures

All patients involved in the study received insulin or oral antidiabetic drugs to maintain glycemic control before and after the study. Euphagia was observed during the study in patients not receiving a sodium-restricted diet. The purpose of the study and the procedures involved were fully explained to all patients. After obtaining informed consent, we collected basic patient information including age, sex, blood pressure, waist-to-hip ratio, BMI, and medication history.

CPAP ventilation treatment

We used a ResMed VPAP™ IV ST-positive airway pressure device (bilevel PAP). In the OSAHS group, the inspiratory pressure was 16 cmH$_2$O and breath pressure

was 6 cmH$_2$O at 1 day before the first day of CPAP treatment, and the pressure index was adjusted once according to the AHI. Subsequently, 7 hours of CPAP treatment (from 10:00 PM the first day to 5:00 AM the next day) was administered continuously to patients in the OSAHS group for 7 days (days 1–7).

Laboratory examinations

Thyroid function parameters, blood biochemistry parameters, glycosylated hemoglobin, fasting insulin, fasting C-peptide, baseline plasma renin activity, and plasma aldosterone were measured on the morning of day 1. Additionally, the 24-hour urinary aldosterone and microalbumin levels were measured. On day 8, the blood biochemistry parameters, plasma renin activity, plasma aldosterone, and 24-hour urinary aldosterone were again measured at 6:00 am. The blood samples were immediately inspected at the Endocrinology Laboratory of the Beijing North Institute of Biological Technology, centrifuged for 5 minutes at 4°C and 2500 rpm, stored at −20°C, and tested in a single batch within 2 weeks. Urine samples after collection were preserved at −20°C and tested within 1 month using an XH6080 radioimmunoassay kit, lot 140220 (Xi'an Nuclear Instrument Factory, Xi'an, China).

Statistical analysis

The sample size calculation suggested that at least 33 patients were needed to guarantee a statistical power of 0.8. Two-sample *t*-tests and a chi squared test were used to compare the patients' general status by eliminating other factors. The mean and standard deviation of the data in the OSAHS group before and after CPAP treatment were calculated and compared using a paired *t*-test to determine treatment efficacy. One-way analysis of variance was

used to evaluate the significance of differences between the two groups. Additionally, a Pearson correlation analysis of the aldosterone level and AHI in all patients was performed, and correlation coefficients and r^2 values were calculated. A *P*-value of <0.05 was considered statistically significant, with a confidence interval of 95%. SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

Results

Baseline characteristics

Forty patients met the inclusion criteria, including 20 patients with OSAHS and 20 controls (Figure 1). The patients comprised 36 men and 4 women with a mean age of 52.97 ± 6.38 years. With the exception of the AHI, no significant differences were found between the two groups (Table 1). All patients' tolerance of CPAP treatment was good, and the mean daily ventilator wearing time was 5.57 ± 1.19 hours.

The blood glucose level and urinary microalbumin excretion rate were lower after than before CPAP treatment in the experimental group, but the differences were not statistically significant (Table 2).

Comparison of baseline aldosterone level between patients with moderate to severe OSAHS and patients in the control group

The levels of plasma aldosterone (lying position, $P = 0.00$; standing position, $P = 0.00$), plasma renin (lying position, $P = 0.00$; standing position, $P = 0.02$), and urinary aldosterone ($P = 0.00$) were significantly higher in the OSAHS than control group. However, there was no significant difference in the plasma angiotensin II levels between the two groups (Table 3).
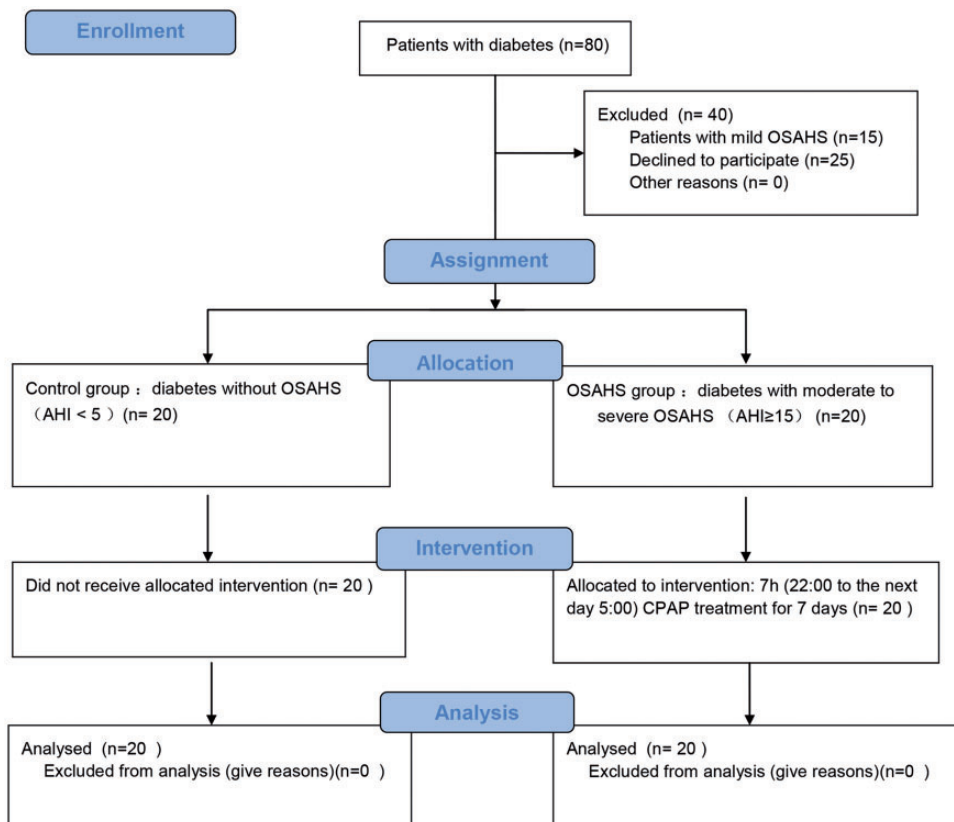
Figure 1. Patient flow in the study. OSAHS, obstructive sleep apnea–hypopnea syndrome; AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure.

Table 1. Demographic characteristics of patients in the OSAHS and control groups.

	OSAHS group (n = 20)	Control group (n = 20)	P value
Age (years)	51.18 ± 7.42	54.79 ± 5.12	0.08
Sex (male:female)	18:2	18:2	–
Oral agents/insulin + oral agents	35%/65%	40%/60%	<0.001*
BMI (kg/m²)	30.43 ± 6.94	25.86 ± 3.91	0.16
Waistline (cm)	99.84 ± 10.31	99.38 ± 9.74	0.70
Glycosylated hemoglobin (%)	9.20 ± 1.37	9.35 ± 1.42	0.76
Fasting blood glucose (mmol/L)	7.99 ± 1.16	6.76 ± 2.02	0.124
Postprandial blood glucose (mmol/L)	10.74 ± 1.84	10.06 ± 2.22	0.336
Triglyceride (mmol/L)	2.41 ± 1.58	1.73 ± 1.23	0.394
Cholesterol (mmol/L)	4.69 ± 0.60	4.99 ± 2.19	0.754
Systolic blood pressure (mmHg)	139.8 ± 15.1	142.8 ± 23.9	0.31
Diastolic blood pressure (mmHg)	74.9 ± 10.1	76.1 ± 9.9	0.20
AHI (times/h)	40.06 ± 21.05	2.79 ± 1.18	0.00*

Data are presented as mean ± standard deviation unless otherwise stated. *P < 0.05.
OASHS, obstructive sleep apnea–hypopnea syndrome; AHI, apnea–hypopnea index; BMI, body mass index.

Table 2. Comparison of blood glucose levels and UAER in the experimental group before and after treatment.

	Pretreatment	Post-treatment	*P* value
Fasting blood glucose (mmol/L)	7.99 ± 1.16	7.65 ± 1.69	0.461
Postprandial blood glucose (mmol/L)	10.74 ± 1.84	9.66 ± 1.26	0.055
UAER (mmol/L)	42.97 ± 77.25	21.83 ± 43.66	0.189

Data are presented as mean ± standard deviation.
UAER, urinary microalbumin excretion rate.

Table 3. Levels of plasma aldosterone, renin, angiotensin II, and urinary aldosterone in the OSAHS and control groups.

	OSAHS group	Control group	*P* value
Plasma aldosterone (lying) (ng/mL)	188.45 ± 67.74	94.35 ± 27.17	0.00*
Plasma aldosterone (standing) (ng/mL)	230.10 ± 82.33	128.80 ± 26.97	0.00*
Plasma renin (lying) (ng/mL·h)	1.33 ± 1.22	0.09 ± 0.05	0.00*
Plasma renin (standing) (ng/mL·h)	2.86 ± 2.81	1.31 ± 0.24	0.02*
Plasma angiotensin II (lying) (pg/mL)	74.8 ± 32.1	80.1 ± 30.7	0.354
Plasma angiotensin II (standing) (pg/mL)	102.6 ± 45.3	170 ± 104.3	0.068
Urinary aldosterone (µg)	2.59 ± 1.74	0.39 ± 0.30	0.00*

Data are presented as mean ± standard deviation. *$P < 0.05$.
OSAHS, obstructive sleep apnea–hypopnea syndrome.

Effect of CPAP treatment on aldosterone excretion

After 7 days of CPAP treatment, the levels of aldosterone (lying position, $P = 0.00$; standing position, $P = 0.01$) and renin (lying position, $P = 0.03$; standing position, $P = 0.02$) in the OSAHS group significantly declined but were still significantly higher than those in the control group (aldosterone in lying and standing positions, $P = 0.01$ and $P = 0.00$, respectively; renin in lying and standing positions, $P = 0.01$ and $P = 0.07$, respectively) (Figures 2 and 3). The levels of angiotensin II and 24-hour urinary aldosterone between the two groups were not significantly different.

In the OSAHS group, the urinary aldosterone level was lower after than before treatment, but the difference was not statistically significant (Table 4). No statistically significant correlation was seen in the AHI, plasma aldosterone level (lying position), or urinary aldosterone level before treatment in the experimental group. Figures 4 and 5 show the AHI and the distribution of the plasma aldosterone and renin levels.

Discussion

This study confirmed the relationship between a higher aldosterone status and the severity of OSAHS. The plasma aldosterone and renin levels (in both the lying and standing positions) and the urinary aldosterone level were higher in the OSAHS than control group. These results demonstrate a strong relationship between OSAHS and the RAAS.[11] The mechanism

Lying and standing plasma aldosterone
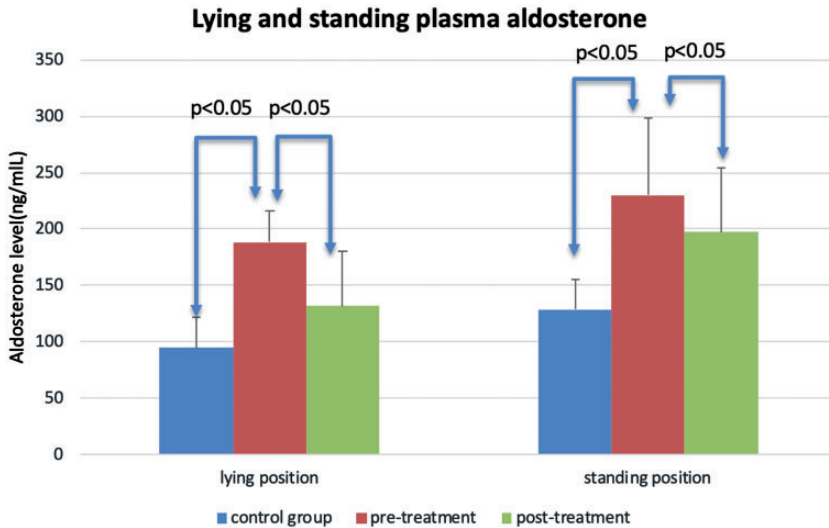
Figure 2. Comparison of blood aldosterone levels (lying and standing positions) before and after continuous positive airway pressure treatment. The levels of plasma aldosterone in the lying and standing positions were significantly decreased after treatment ($P = 0.00$ and $P = 0.01$, respectively), but were still significantly higher than those in the control group ($P = 0.01$ and $P = 0.00$, respectively).

Lying and standing plasma renin
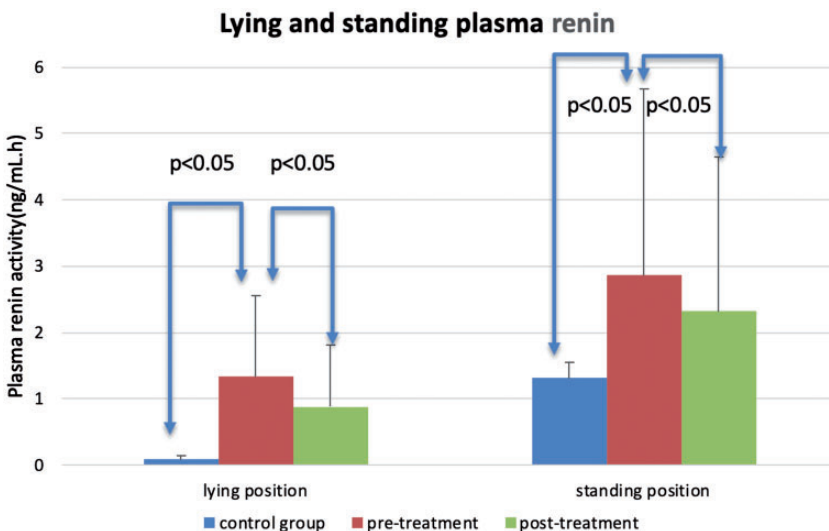
Figure 3. Comparison of plasma renin levels (lying and standing positions) before and after continuous positive airway pressure treatment. Plasma renin levels in the lying and standing positions were significantly decreased after treatment ($P = 0.03$ and $P = 0.02$, respectively), but were still significantly higher than those in the control group ($P = 0.01$ and $P = 0.07$, respectively). The renin levels in the standing position were also higher in the experimental than control group, but the difference was not statistically significant.

Table 4. Changes in levels of plasma aldosterone, angiotensin II, renin, and urinary aldosterone before and after CPAP treatment within the OSAHS group.

	Pretreatment	Post-treatment	P-value
Plasma aldosterone (lying) (ng/mL)	188.45 ± 67.74	131.60 ± 49.15	0.00*
Plasma aldosterone (standing) (ng/mL)	230.10 ± 82.33	197.00 ± 56.86	0.01*
Plasma angiotensin II (lying) (pg/mL)	74.8 ± 32.1	67.2 ± 35.7	0.32
Plasma angiotensin II (standing) (pg/mL)	102.6 ± 45.3	89.8 ± 63.6	0.36
Plasma renin (lying) (ng/mL·h)	1.33 ± 1.22	0.88 ± 0.94	0.03*
Plasma renin (standing) (ng/mL·h)	2.86 ± 2.81	2.32 ± 2.33	0.02*
Urinary aldosterone (μg)	2.59 ± 1.74	2.02 ± 1.02	0.15

Data are presented as mean ± standard deviation. *$P < 0.05$.
CPAP, continuous positive airway pressure; OSAHS, obstructive sleep apnea–hypopnea syndrome.
Normal diet (not sodium-restricted): Plasma renin (ng/mL·h): lying position, 0.05–0.79; standing position, 0.05–0.79. Plasma aldosterone (ng/mL): lying position, 59–174, standing position, 65–296; 24-hour urinary aldosterone (μg): 1.0–8.0.
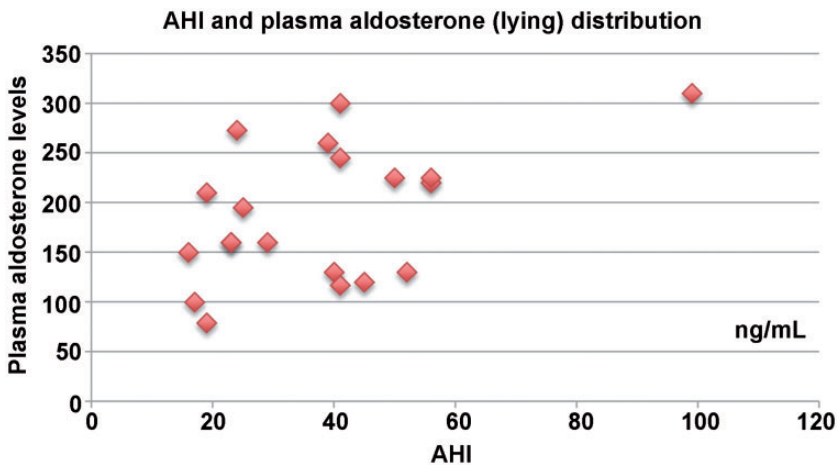
Figure 4. Scatter plot of the AHI and lying plasma aldosterone levels. No significant correlation was found between the AHI and lying plasma aldosterone levels ($r = 0.40$). AHI, apnea–hypopnea index.

is mainly associated with a significant increase in sympathetic nerve activity during the sleep and waking states in patients with OSAHS; stimulation of the hypothalamic-pituitary-adrenal axis also triggers the release of cortisol and other hormones. Hyperinsulinemia and hyperleptinemia activate the RAAS, which leads to elevated aldosterone levels. In this regard, our data are in agreement with those of Moller et al.[12] These authors measured the 24-hour blood pressure and plasma levels of vasoactive hormones in 24 patients with OSAHS and 18 controls and found a higher blood pressure, angiotensin II level, and aldosterone level in patients with OSAHS. The angiotensin II level and blood pressure also showed a positive correlation with each other. However, the BMI was higher in the experimental group with established hypertension. In contrast, there was no significant difference in the average blood pressure or BMI between the experimental and control groups in our study, which underlines the reliability of the experimental
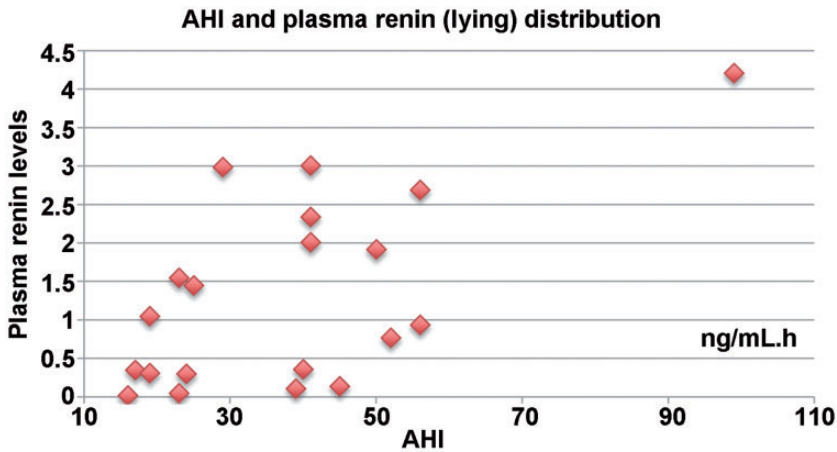
Figure 5. Scatter plot of the AHI and lying plasma renin levels. There was no significant correlation between AHI and lying plasma renin levels (r = 0.40). AHI, apnea–hypopnea index.

results we obtained. Maillard et al.[13] found that the plasma aldosterone level was lower in seven patients with OSAHS without hypertension than in five patients in the control group (527 ± 339 vs. 1346 ± 245 ng/mL, respectively; $P < 0.01$). However, there was no significant difference in the plasma renin level between the two groups (0.47 ± 0.15 vs. 0.63 ± 0.21 ng/mL·h, respectively). Most of the patients in the experimental group of the present study had mild OSAHS, and the sample size was small. However, the patients in the experimental group had moderate to severe OSAHS, making our results more credible.

Our study also confirmed the effect of CPAP in reducing the aldosterone level in patients with T2DM complicated by moderate to severe OSAHS and demonstrated the effect of CPAP on aldosterone secretion. We found that the plasma aldosterone and renin levels declined significantly after CPAP intervention. The mechanism may be related to the reduction of aldosterone levels by the CPAP ventilator, which improves ventilation and reduces sleep interruption, reduces sympathetic excitability, and increases insulin sensitivity. The aldosterone level is also correlated with the severity of OSAHS[14]; this suggests that sleep fragmentation and repeated arousal induce stress, which stimulates the release of adrenocorticotrophic hormone (ACTH) and ultimately elevates the aldosterone level. This is consistent with our observation that the aldosterone level was decreased after CPAP treatment in patients with OSAHS. Saarelainen et al.[15] performed a study involving 11 men with OSAHS with an average age of 47 years, BMI of 36 kg/m^{2}, AHI of 55/h, and no drug history. After 3 months of CPAP treatment, the plasma aldosterone level in the morning was measured. The 24-hour blood pressure and heart rate were both significantly decreased. The average nocturnal blood pressure was associated with the plasma aldosterone level, suggesting that effective CPAP treatment improves sympathetic nerve excitability and attenuates stress levels. Barcelo et al.[14] found that after CPAP treatment, the aldosterone level was significantly decreased ($P = 0.012$) in patients with moderate to severe OSAHS, which is consistent with the results of our study.

Few previous studies have evaluated the 24-hour urinary aldosterone levels before and after CPAP treatment. In this study,

we found no significant difference in the 24-hour urinary aldosterone levels before and after CPAP treatment, suggesting that the release of aldosterone may be affected by many factors such as the RAAS and levels of ACTH, potassium, vasopressin, and dopamine. The RAAS and ACTH synergistically regulate the 24-hour pulse wave of aldosterone.[16] The RAAS plays a major role during the night, when the plasma cortisol concentration is low. The high daytime cortisol concentration controls the pulse amplitude of aldosterone. The urinary aldosterone level reflects changes in the 24-hour plasma aldosterone level. In addition to the nocturnal sleep duration and sleep disruption, daytime feeding, activity, and mood swings can affect cortisol secretion and thereby alter the aldosterone level. Therefore, even if nocturnal CPAP therapy improves the sympathetic nervous system via its effect on the RAAS, daytime activities result in non-significant differences in 24-hour urinary aldosterone.

Notably, no correlation was found between the AHI and plasma renin, aldosterone, and 24-hour urinary aldosterone levels in our study. The relationship between the AHI and aldosterone is inconclusive. Previous studies on the relationship between the AHI and aldosterone levels mostly focused on patients with resistant hypertension. Pratt-Ubunama et al.[17] performed a study of 84 patients with OSAHS; 60 had resistant hypertension (experimental group) and 24 did not (control group). The plasma aldosterone level in the experimental group was positively and significantly correlated with the AHI (rho = 0.44, $P = 0.0002$). However, no correlation between renin and the AHI was observed. The aldosterone level was significantly lower in the control than experimental group (5.5 vs. 11.0 ng/dL, respectively; $P < 0.05$), but there was no correlation between the plasma aldosterone level and the renin level and AHI. High aldosterone levels can cause water and sodium retention, promote the transfer of body fluids from blood vessels to the tissue space (especially around the neck), and increase airway resistance; they also tend to cause OSAHS due to airway collapse. The present study also suggests that there is a threshold effect in aldosterone-induced organ damage because the control group failed to reach the threshold level. Similar results were reported by Gonzaga et al.[18] We found no correlation between the AHI and plasma renin, aldosterone, or 24-hour urinary aldosterone levels. This was likely because all patients in our study had non-resistant hypertension, and they did not meet the standard or threshold level of hyperaldosteronism.

In conclusion, we evaluated the status of the RAAS in patients with concurrent T2DM and moderate to severe OSAHS and assessed the role of CPAP for the first time. Previous studies have reported the limited role of the urinary aldosterone levels before and after CPAP treatment. The morning plasma aldosterone level only reflects the impact on nocturnal sleep. However, the 24-hour urinary aldosterone level can be used to monitor the average level of daily plasma aldosterone. Although the final result showed no significant differences in the pre- and post-treatment levels, the implications are clinically significant. A limitation of our study is the small sample size (only 40 patients), which may have been a consequence of the low prevalence of T2DM complicated by severe OSAHS.

ORCID iD

Jie Zhang (iD) https://orcid.org/0000-0002-6958-7562

References

1. Bonsignor MR and Zito A. Metabolic effects of the obstructive sleep apnea syndrome and cardiovascular risk. *Arch Physiol Biochem* 2008; 114: 255–260.
2. Levy P, Bonsignore MR and Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J* 2009; 34: 243–260.
3. Lam JC and Ip MS. An update on obstructive sleep apnea and the metabolic syndrome. *Curr Opin Pulm Med* 2007; 13: 484–489.
4. Hein MS, Schlenker EH and Patel KP. Altered control of ventilation in streptozotocin-induced diabetic rats. *Proc Soc Exp Biol Med* 1994; 207: 213–219.
5. Grassi G, Seravalle G, Dell'Oro R, et al. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. *J Hypertens* 2003; 21: 1761–1769.
6. Catena C, Lapenna R, Baroselli S, et al. Insulin sensitivity in patients with primary aldosteronism: a follow-up study. *J Clin Endocrinol Metab* 2006; 91: 3457–3463.
7. Lastra-Lastra G, Sowers JR, Restrepo-Erazo K, et al. Role of aldosterone and angiotensin II in insulin resistance: an update. *Clin Endocrinol* 2009; 71: 1–6.
8. Bochud M, Nussberger J, Bovet P, et al. Plasma aldosterone is independently associated with the metabolic syndrome. *Hypertension* 2006; 48: 239–245.
9. Hannemann A, Meisinger C, Bidlingmaier M, et al. Association of plasma aldosterone with the metabolic syndrome in two German populations. *Eur J Endocrinol (Oslo)* 2011; 164: 751–758.
10. Kidambi S, Kotchen JM, Grim CE, et al. Association of adrenal steroids with hypertension and the metabolic syndrome in Blacks. *Hypertension* 2007; 49: 704–711.
11. Sim JJ, Yan EH, Liu IL, et al. Positive relationship of sleep apnea to hyperaldosteronism in an ethnically diverse population. *J Hypertens* 2011; 29: 1553–1559.
12. Moller DS, Lind P, Strunge B, et al. Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. *Am J Hypertens* 2003; 16: 274–280.
13. Maillard D, Fineyre F, Dreyfuss D, et al. Pressure-heart rate responses to alpha-adrenergic stimulation and hormonal regulation in normotensive patients with obstructive sleep apnea. *Am J Hypertens* 1997; 10: 24–31.
14. Barcelo A, Pierola J, Esquinas C, et al. Relationship between aldosterone and the metabolic syndrome in patients with obstructive sleep apnea hypopnea syndrome: effect of continuous positive airway pressure treatment. *PLoS One* 2014; 9: 84362.
15. Saarelainen S, Hasan J, Siitonen S, et al. Effect of nasal CPAP treatment on plasma volume, aldosterone and 24-h blood pressure in obstructive sleep apnoea. *J Sleep Res* 1996; 5: 181–185.
16. Charloux A, Gronfier C, Lonsdorfer-Wolf E, et al. Aldosterone release during the sleep-wake cycle in humans. *Am J Physiol* 1999; 276: 43–49.
17. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, et al. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest* 2007; 131: 453–459.
18. Gonzaga CC, Gaddam KK, Ahmed MI, et al. Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. *J Clin Sleep Med* 2010; 6: 363–368.