

**Review**

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# The Triad of Sleep Apnea, Hypertension, and Chronic Kidney Disease: A Spectrum of Common Pathology

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Sleep apnea · Resistant hypertension · Chronic kidney disease · Volume overload

**Abstract**

Obstructive sleep apnea (OSA), hypertension, and chronic kidney disease (CKD) are different entities and are generally managed individually most of the time. However, CKD, OSA, and hypertension share many common risk factors and it is not uncommon to see this complex triad together. In fact, they share similar pathophysiology and have been interlinked with each other. The common pathophysiology includes chronic volume overload, hyperaldosteronism, increased sympathetic activity, endothelial dysfunction, and increased inflammatory markers. The combination of this triad has significant negative impact on the cardiovascular health, and increases the mortality and morbidity in this complicated group of patients. On one hand, progression of CKD can lead to the worsening of OSA and hypertension; similarly, worsening sleep apnea can make the hypertension difficult to treat and enhance the progression of CKD. This review article highlights the bidirectional interlink among these apparently different disease processes which share common pathophysiological mechanisms and emphasizes the importance of treating them collectively to improve outcomes.

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**Introduction**

Obstructive sleep apnea (OSA) continues to be one of the most difficult to manage medical problems causing a significant impact on the individual's health and health-care expense. As per 2005 National Sleep Foundation pool, 1 in 4 Americans is at risk for developing OSA with increasing risk until the age of 65 [1]. The classic Wisconsin Sleep Cohort

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study reported that approximately 2% of the women and 4% of the men in the middle age meet the minimal diagnostic criteria for OSA, and in the general population 9% of men and 4% of the women have moderate to severe OSA [2]. OSA is associated with daytime hypersomnolence, poor quality of life, increased overall morbidity and mortality [3, 4]. At the same time, OSA is independently associated with hypertension [5]. Multiple mechanisms have been proposed to explain the negative impact of OSA on cardiovascular hemodynamics including hypertension, heart failure, and increased risk of coronary artery disease [5]. Recent evidence suggests that there is a bidirectional relationship between OSA and chronic kidney disease (CKD). CKD increases the risk of OSAs, while OSAs hasten the progression of CKD [6]. Kraus and Hamburger [7] reported that 50–70% patients with end-stage renal disease (ESRD) have OSA. CKD, OSA, and hypertension share many risk factors and it is not uncommon to see this complex triad together, making the management more challenging. The purpose of this review is to summarize the evidence supporting the complex interrelationship between OSA, CKD, and hypertension and how that should affect our management in treating this patient population.

### OSA, Hypertension, and CKD

OSA is defined as “transient partial or complete upper airway obstruction during sleep, leading to loud snoring and increased daytime somnolence” [8]. An obstructive episode is defined as >10-s cessation of respiratory airflow, associated with intermittent hypoxia [9]. The apnea-hypoxia index (AHI) is used to diagnose OSA. AHI >5 per hour is usually sufficient to consider someone as having OSA. AHI is also a useful marker to grade the severity of OSA and to guide the management of OSA [8].

A history of loud snoring, apneic episodes during sleep, and daytime somnolence often leads to the diagnosis of OSA [10–12]. The presentation of OSA in CKD usually lacks the typical features of OSA including loud snoring, apneic episodes, and daytime somnolence, which leads to the underdiagnosis of OSA in this patient population [13]. Features associated with CKD such as chronic fatigue, uremia or side effects of medications may overshadow the complaint of subjective sleepiness, and the increased sympathetic activity in the setting of volume overload may hinder the development of excessive sleepiness [14]. Approximately 50% of the patients with ESRD have OSA, making it common among this patient group [15]. Sakaguchi et al. [16] reported a high prevalence of OSA in nondialysis CKD patients; they found moderate to severe OSA in these patients as compared to mild to moderate OSA in the control group. In a large and contemporary cohort of more than 3 million US veterans, a diagnosis of incident OSA was associated with higher mortality, coronary artery disease, stroke, and CKD along with faster decline of kidney function [17]. In another retrospective cohort study from Taiwan of >4,600 incident patients with sleep apnea, the investigators showed a 1.94-fold increase in the incidence of CKD, as well as a 2.2-fold increase in the incidence of ESRD [18]. Markou et al. [19] measured AHI in patients with stable CKD (creatinine clearance <40 mL/min) and found that the severity of AHI correlates with urea concentration and creatinine clearance. Similarly, Fleischmann et al. [20] found that the patients with GFR <60 mL/min/1.73 m<sup>2</sup> have a high tendency to develop OSA. Similarly, one study showed that the severity of metabolic acidosis in patients with CKD is significantly associated with the severity of the OSA [21]. Both CKD and OSA share the same major risk factors including diabetes and hypertension, making it difficult to determine the direct relationship between CKD and OSA. This combination is also frequently associated with hypertension, suggesting a common pathophysiology which drives all the 3 diseases together.

## Pathological Mechanisms Linking OSA with Hypertension and CKD

Many mechanisms have been proposed to explain the complex relationship between the triad of OSA, hypertension, and CKD. Episodes of intermittent hypoxia occur in association with OSA and likely contribute to the pathogenesis of hypertension [22]. OSA has also been associated with diastolic dysfunction and increased left ventricular (LV) mass index which, besides increases in afterload, is also the result of episodes of repetitive hypoxemia during sleep [23, 24]. In one study, the authors found that the LV mass index was correlated with AHI and AHI was an independent risk factor for LV hypertrophy [25]. In another study of normotensive versus hypertensive subjects with or without OSA, both the LV mass index and percentage of LV hypertrophy had similar increases in normotensive OSA and patients with hypertension and no OSA, with a significant further increase in the LV mass index and percentage of LV hypertrophy in subjects with OSA and hypertension [26]. In a recent study of 74 nonobese Japanese male OSA patients, it was shown that severe OSA itself may contribute directly to LV diastolic dysfunction [27]. Increased transmural pressure, which is caused by excessive negative intrathoracic pressure during apneic episodes may be a contributory factor, as well as an increase in central blood pressure (BP) [27]. In another study, Abdel-Kader et al. [28] found an association between OSA with resistant hypertension in patients with ESRD and nondialysis CKD, and non-CKD patients. They found that the patients with OSA and treatment-resistant hypertension had advanced kidney disease. Furthermore, 30% of the patients with CKD had resistant hypertension, and 25% of them had severe OSA. Besides episodes of apnea, other major mechanisms linking them together are thought to be volume overload, secondary hyperaldosteronism, increased sympathetic activity, vasoconstriction, and increased inflammatory markers.

### *Volume Overload*

It has been thought that volume overload is one of the most likely causes of treatment-resistant hypertension and difficult to manage OSA in CKD and ESRD patients. In the recumbent position during sleep, volume may be shifted from the lower extremities to the upper parts of the body causing the worsening of peripharyngeal edema leading to the worsening of OSA. Bucca et al. [29] used aggressive diuretic therapy in patients with OSA and heart failure, and they found a significant improvement in AHI with the improved volume status. Similarly, Beecroft et al. [30] found 12% decreased pharyngeal cross-sectional area in a CKD patient as compared to the control group. Elias et al. [31] investigated the role of overnight fluid shift in patients with OSA and ESRD. They concluded that the amount of volume shift is directly related with the episodes of apnea and that the redistribution of volume overload could make the OSA worsen, which can be treated with aggressive volume removal. In another study of 20 ESRD patients on thrice weekly HD, the investigators found that the greater the upper airway mucosal water content and internal jugular vein volume, the higher the AHI [32]. Hypertension in CKD is multifactorial, volume overload and renin-angiotensin-aldosterone system (RAAS) activation being the 2 most important mechanisms, making BP difficult to control in these patients [33]. Many studies have shown that the intensive dialysis techniques in patients with ESRD on dialysis can decrease the severity of OSA and can allow better control of BP. Additionally, the ultrafiltration guided by bioimpedance may provide a practical way of achieving a fair volume status in these patients and better volume control would be extremely helpful in the management modalities in these patients [34].

### *Increased Sympathetic Tone*

Patients with OSA have high sympathetic activity during sleep [35]. The mechanism behind this finding is unclear but can be secondary from the increased chemo-reflex drive

[34]. They are also found to have increased heart rates and increased BP variability [35–37]. This increased sympathetic outflow can be hypoxia driven in these patients because studies of some animal models have suggested that OSA-induced hypoxia can increase the sympathetic outflow which will lead to vasoconstriction, leading to resistant hypertension and worsening renal function [37]. The uncontrolled BP can further worsen the kidney function, and worsening kidney function can further aggravate OSA. In a pig model of OSA, Linz et al. [38] showed that renal sympathetic denervation can prevent postapneic increase in the BP, suggesting an association between the increased sympathetic tone, OSA, and resistant hypertension. A study comparing functioning renal transplants with matched controls in the general population did not show any difference in the prevalence of sleep breathing disorder in the 2 groups [39]. Another interesting finding observed in renal transplant patients is that there was no association between the presence of OSA and the rate of decline in graft function in prevalent kidney transplant recipients [40]. Though the study was small and underpowered, one might speculate that since the transplanted kidney is denervated, it is protected from sympathetic overactivation [40].

#### *RAAS Activation*

Aldosterone excess plays an important role in the complicated pathophysiology linking OSA, resistant hypertension, and progression of CKD. Increased vascular resistance due to increased sympathetic outflow during night-time from the hypoxic events of OSA leads to the activation of RAAS, which will subsequently increase the plasma aldosterone level [37]. Increased plasma aldosterone has been shown to be associated with glomerulosclerosis, renal fibrosis, and progression of CKD [41]. Various observational studies showed that the increased aldosterone levels are associated with resistant hypertension and severity of OSA [42, 43]. Hyperaldosteronism may be a key link between resistant hypertension and OSA, leading to the progression of CKD. As all these studies are observational, more prospective trials are needed to establish this bidirectional relationship, which can be a novel target for the management of patient with OSA, treatment-resistant hypertension and CKD.

#### *Endothelial Dysfunction*

Intermittent hypoxia from OSA during the night leads to the release of endothelin. It is a potent vasoconstrictor, which is another contributor towards resistant hypertension in OSA [44]. In OSA, the determination of endothelial function includes functional evaluation of vascular response by accessing changes in the blood flow in response to the endothelium-dependent vasodilators or hypoxemia [45]. Lattimore et al. [46] used intra-arterial acetylcholine and sodium nitroprusside to assess endothelial function in 10 subjects with moderate OSA and found that treatment with continuous positive airway pressure (CPAP) improved endothelial function. The subjects had detailed forearm vascular reactivity studies before and after 3 months of CPAP treatment. After CPAP therapy, endothelium-dependent dilation to acetylcholine was significantly increased, and resting NO production was also higher. This is a potential mechanism which improves systemic and vascular function in patients with OSA treated with CPAP. Many animal models have been shown to develop resistant hypertension after exposure to intermittent hypoxia [47, 48]. OSA-induced intermittent hypoxia leads to the production of increased inflammatory markers such as serum C-reactive protein, IL-6, and TNF- $\alpha$  [49–51]. Similarly, hypoxia increases reactive oxygen species and oxidative stress markers [52]. The combination of severe vasoconstriction, increased inflammatory markers and increased reactive oxygen species leads to the progression of the CKD in patients with OSA [53].

### *OSA and Proteinuria*

Many studies have shown that urinary albumin-creatinine ratio is an independent risk factor associated with the severity of OSA [54–56]. Faulx et al. [54] have shown that the severity of OSA is significantly associated with increased urine albumin excretion. Similarly, in a case study of 2 patients with severe OSA, it was shown that proteinuria could be corrected by treating the OSA with CPAP [57]. Excessive proteinuria can also hasten the progression of CKD due to its toxic effects on glomeruli and tubules. Worsening renal function will increase the severity of OSA, which will increase the degree of proteinuria.

### *Inflammatory and Oxidative Stress in OSA, CKD, and Resistant Hypertension*

It has been shown that the repeated collapse of the airway in OSA leads to a cyclic alteration in arterial oxygenation (hypoxia/reoxygenation phenomenon). This cyclic variation in the arterial oxygenation has been shown to be the major cause of oxidative burst of neutrophils, thus creating a systemic inflammatory and oxidative state [49–52]. Similarly, irrespective of the cause of renal disease, there is strong evidence that both acute and chronic inflammatory states exist in patients with CKD and ESRD. Hypoalbuminemia, malnutrition, atherosclerosis, etc. are thought to be the inflammatory mediator in this patient population. Both OSA and CKD put the patient at high risk for systemic inflammatory and oxidative stress, which has a negative impact on the cardiovascular health, and increase the mortality and morbidity in this complicated group of patients. Møller et al. [58] reported disturbed 24-h BP profile in patients with OSA. They also observed elevated heart rates in this patient population. The severity of hypoxemia during night-time was demonstrated to be the main stimulus for RAAS activation leading to abnormal heart and BP profile, with strongly negative impact on the cardiovascular morbidity and mortality. To summarize, OSA, treatment-resistant hypertension and progression of CKD have common pathogenic associations, including volume overload, excessive RAAS activation, hyperaldosteronism, endothelin-derived vasoconstriction, increased inflammatory and reactive oxygen markers, and excessive proteinuria.

## **Treatment**

### *Positive Airway Pressure Therapy*

OSA can be treated with positive airway pressure therapy, either CPAP or BIPAP. CPAP remains the most widely used therapy for OSA and remains the gold standard treatment. CPAP delivers compressed air to the patient, which prevents the collapse of the upper airway, thus preventing the hypoxic episodes during the night. It has been shown that proper use of CPAP can reduce the nocturnal apneic episodes, which can improve resistant hypertension and overall cardiovascular prognosis [59]. By better control of hypertension, CPAP can also reduce the glomerular hyperfiltration, thus slowing the progression of the CKD [60]. Logan et al. [61] published a small study of 11 patients with resistant hypertension. They showed that nightly use of CPAP for 2 months was associated with significant decrease in both systolic and diastolic BP. CPAP improves baseline endothelial NO release and stimulates endothelium-dependent vasorelaxation in the systemic circulation [45]. In a clinical study of 27 patients with OSA, the investigators measured the glomerular function and the short-term effect of CPAP, and found that OSA patients were generally in a condition of glomerular hyperfiltration, and filtration fraction significantly decreased after 1 week of CPAP therapy [62]. It has also been shown that plasma brain natriuretic peptide and urinary meta-adrenaline levels have been reduced with the regular use of CPAP [63]. The above-mentioned studies suggest that the proper use of CPAP can effectively control the BP, thus reducing the cardiovascular risks and slowing the progression of CKD.

### *Role of Renal Replacement Therapy*

In patients with ESRD on HD, intensive dialysis techniques have been shown to improve the severity of OSA [64–66]. Hanly et al. [64] have shown significant improvement in OSA of the patients who were switched from conventional HD to nocturnal HD. In a recent study in thrice-weekly HD patients, Lyons et al. [67] performed isolated ultrafiltration on a nondialysis day in patients with AHI >20 and found that the AHI decreased by 36% without affecting uremia, reinforcing the notion that fluid removal by UF attenuates sleep apnea without altering the uremic status. In a study of patients on peritoneal dialysis (PD), patients performing nocturnal PD using a cycler had lower AHI during sleep compared to patients undergoing CAPD [68]. Using bioelectrical impedance analysis, it has been shown that the total body water content is significantly lower during NPD than CAPD during sleep [68, 69]. Thus, preventing hypervolemia in the patients with ESRD can significantly improve OSA and resistant hypertension. Further, renal transplant in patients with ESRD has been associated with significant improvement of OSA. Thus, preventing hypervolemia in the patients with ESRD can significantly improve OSA and resistant hypertension. In a trial where a sleep study was performed before and after transplant, there was a significant decrease in AHI in OSA patients after transplant [70]. In another study, renal transplantation was found to ameliorate sleep disturbances and lead to improvement of sleep architecture [71].

### *Antihypertensive Therapy*

Fluid displacement from the lower extremities to the upper body during sleep is strongly associated with OSA in hypertensive patients, and it has been shown that intensified diuretic therapy reduces the apnea-hypopnea index along with overnight change in leg fluid volume as well as neck circumference [72]. In one study, the investigators evaluated the changes in the severity of OSA in patients with resistant hypertension after treatment with spironolactone and found that with treatment, the AHI and hypoxic index, weight, and clinic and ambulatory BP were significantly reduced [73]. Though ACE inhibitors are used frequently in OSA patients, there are case reports of ACE inhibitors worsening OSA due to upper airway inflammation, so they should probably be stopped if they cause a cough [74].

## **Conclusions**

OSA is found more frequently in patients with CKD than in healthy individuals. Difficult to control hypertension is highly prevalent in this patient population. There are multiple mechanisms contributing to a complicated relationship between OSA, hypertension, and CKD. Enough evidence is available showing appropriate treatment of OSA can improve BP control and slow the progression of CKD. Therefore, OSA should be carefully investigated in patients with CKD and treatment-resistant hypertension. Referral should be made to conduct a sleep study for timely diagnosis and treatment of OSA, when clinically suspected. When diagnosed with OSA, patients should be appropriately counseled regarding the use of CPAP and importance of compliance with the therapy. Appropriate dry weight should be determined in patients with ESRD on hemodialysis, and dialysis treatment should be tailored to prevent volume overload and subsequent worsening of OSA and hypertension. More intense hemodialysis and use of night-time cycler in PD patients for optimal ultrafiltration to maintain euvolemia is recommended when ESRD patients have difficult to control OSA and hypertension.

### Author Contributions

F.A. and K.C. contributed to the structure, content, and discussion of the manuscript.

### Disclosure Statement

F.A. and K.C. declare no conflict of interest.

### References

- Hiestand DM, Britz P, Goldman M, Phillips B: Prevalence of symptoms and risk of sleep apnea in the US population: results from the national sleep foundation sleep in America 2005 poll. *Chest* 2006;130:780–786.
- Young T, Palta M, Dempsey J, et al: The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–1235.
- Foley DJ, Monjan A, Simonsick EM, Wallace RB, Blazer DG: Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. *Sleep* 1999;22(suppl 2):S366–S372.
- He J, Kryger MH, Zorick FJ, Conway W, Roth T: Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. *Chest* 1988;94:9–14.
- Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D’Agostino RB, Newman AB, Lebowitz MD, Pickering TG: Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *Sleep Heart Health Study*. *JAMA* 2000;283:1829–1836.
- Ozkok A, Kanbay A, Odabas AR, Covic A, Kanbay M: Obstructive sleep apnea syndrome and chronic kidney disease: a new cardiorenal risk factor. *Clin Exp Hypertens* 2014;36:211–216.
- Kraus MA, Hamburger RJ: Sleep apnea in renal failure. *Adv Perit Dial* 1997;13:88–92.
- Adeseun GA, Rosas SE: The impact of obstructive sleep apnea on chronic kidney disease. *Curr Hypertens Rep* 2010;12:378–383.
- Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–689.
- American Academy of Sleep Medicine: International Classification of Sleep Disorders. Diagnostic and Coding Manual American Academy of Sleep Medicine, ed 2. Westchester, American Academy of Sleep Medicine, 2005.
- Guilleminault C, Bassiri A: Clinical features and evaluation of obstructive sleep apnea-hypopnea syndrome and the upper airway resistance syndrome; in Kryger MH, Roth T, Dement WC (eds): Principles and Practices of Sleep Medicine. Philadelphia, Elsevier, 2005, pp 1043–1052.
- Kuhlmann U, Bormann FG, Becker HF: Obstructive sleep apnoea: clinical signs, diagnosis and treatment. *Nephrol Dial Transplant* 2009;24:8–14.
- Ozkok A, Kanbay A, Odabas AR, Covic A, Kanbay M: Obstructive sleep apnea syndrome and chronic kidney disease: a new cardiorenal risk factor. *Clin Exp Hypertens* 2014;36:211–216.
- Nicholl DDM, Ahmed SB, Loewen AHS, et al: Clinical presentation of obstructive sleep apnea in patients with chronic kidney disease. *J Clin Sleep Med* 2012;8:381–387.
- Unruh ML: Sleep apnea and dialysis therapies: things that go bump in the night? *Hemodial Int* 2007;11:369–378.
- Sakaguchi Y, Shoji T, Kawabata H, et al: High prevalence of obstructive sleep apnea and its association with renal function among nondialysis chronic kidney disease patients in Japan: a cross-sectional study. *Clin J Am Soc Nephrol* 2011;6:995–1000.
- Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, Arah OA, Ma JZ, Lu JL, Sim JJ, Streja E, Kalantar-Zadeh K, Kovesdy CP: Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax* 2015;70:888–895.
- Lee YC, Hung SY, Wang HK, et al: Sleep apnea and the risk of chronic kidney disease: a nationwide population-based cohort study. *Sleep* 2015;38:213–221.
- Markou N, Kanakaki M, Myrianthefs P, et al: Sleep-disordered breathing in nondialyzed patients with chronic renal failure. *Lung* 2006;184:43–49.
- Fleischmann G, Fillafer G, Mattereder H, et al: Prevalence of chronic kidney disease in patients with suspected sleep apnoea. *Nephrol Dial Transplant* 2010;25:181–186.
- Tada T, Kusano KF, Ogawa A, et al: The predictors of central and obstructive sleep apnoea in haemodialysis patients. *Nephrol Dial Transplant* 2007;22:1190–1197.
- Dewan NA, Nieto FJ, Somers VK: Intermittent hypoxemia and OSA: 515 implications for comorbidities. *Chest* 2015;147:266–274.
- Bradley D, Hall MJ, Ando S, Floras JS: Hemodynamic effects of simulated obstructive apneas in humans with and without heart failure. *Chest* 2001;119:1827–1835.

- 24 Somers VK, Dyken ME, Clary MP, Abboud FM: Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96:1897–1904.
- 25 Damy T, Paulino A, Margarit L, Drouot X, Stoica M, Vermes E, Gueret P, Adnot S, Rande JL, D’Ortho MP, Hittinger L: Left ventricle remodelling is associated with sleep-disordered breathing in non-ischaemic cardiopathy with systolic dysfunction. *J Sleep Res* 2011;20(pt 1):101–109.
- 26 Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G: Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. *Chest* 2007;131:1379–1386.
- 27 Usui Y, Takata Y, Inoue Y, Tomiyama H, Kurohane S, Hashimura Y, Kato K, Saruhara H, Asano K, Shiina K, Yamashina A: Severe obstructive sleep apnea impairs left ventricular diastolic function in non-obese men. *Sleep Med* 2013;14:155–159.
- 28 Abdel-Kader K, Dohar S, Shah N, et al: Resistant hypertension and obstructive sleep apnea in the setting of kidney disease. *J Hypertens* 2012;30:960–966.
- 29 Bucca CB, Brussino L, Battisti A, et al: Diuretics in obstructive sleep apnea with diastolic heart failure. *Chest* 2007;132:440–446.
- 30 Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane PA, Hanly PJ: Pharyngeal narrowing in end-stage renal disease: implications for obstructive sleep apnea. *Eur Respir J* 2007;30:965–971.
- 31 Elias RM, Bradley TD, Kasai T, et al: Rostral overnight fluid shift in end-stage renal disease: relationship with obstructive sleep apnea. *Nephrol Dial Transplant* 2012;27:1569–1573.
- 32 Elias RM, Chan CT, Paul N, Motwani SS, Kasai T, Gabriel JM, Spiller N, Bradley TD: Relationship of pharyngeal water content and jugular volume with severity of obstructive sleep apnea in renal failure. *Nephrol Dial Transplant* 2013;28:937–944.
- 33 Campese VM, Mitra N, Sandee D: Hypertension in renal parenchymal disease: why is it so resistant to treatment? *Kidney Int* 2006;69:967–973.
- 34 Shamsuzzaman S, Gersh B, Somers V: Obstructive sleep apnea: implications for cardiac and vascular disease. *J Am Med Assoc* 2003;290:1906–1914.
- 35 Narkiewicz K, Montano N, Cogliati C, Van De Borne P, Dyken E, Somers V: Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998;98:1071–1077.
- 36 Narkiewicz K, Pesek C, Kato M, Phillips B, Davison D, Somers V: Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. *Hypertension* 1998;32:1039–1043.
- 37 Dempsey JA, Veasey SC, Morgan BJ, O’Donnell CP: Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47–112.
- 38 Linz D, Mahfoud F, Schotten U: Renal sympathetic denervation suppresses postapneic blood pressure rises and atrial fibrillation in a model for sleep apnea. *Hypertension* 2012;60:172–178.
- 39 Mallamaci F, Leonardi D, Tripepi R, Parlongo G, Catalano C, Tripepi G, Castronovo V, Ferini-Strambi L, Zoccali C: Sleep disordered breathing in renal transplant patients. *Am J Transplant* 2009;9:1373–1381.
- 40 Fornadi K, Ronai KZ, Turanyi CZ, Malavade TS, Shapiro CM, Novak M, Mucsi I, Molnar MZ: Sleep apnea is not associated with worse outcomes in kidney transplant recipients. *Sci Rep* 2014;4:6987.
- 41 Greene EL, Kren S, Hostetter TH: Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest* 1996;98:1063–1068.
- 42 Pratt-Ubunama M, Nishizaka M, Boedefeld R, Cofield S, Harding S, Calhoun D: Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest* 2007;131:453–459.
- 43 Gonzaga C, Gaddam K, 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.
- 44 Faller V: Hypoxia induces endothelin gene expression and secretion in cultured human endothelium. *J Clin Invest* 1991;88:1054–1057.
- 45 Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK: Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000;102:2607–2610.
- 46 Lattimore JL, Wilcox I, Skilton M, Langenfeld M, Celermajor DS: Treatment of obstructive sleep apnoea leads to improved microvascular endothelial function in the systemic circulation. *Thorax* 2006;61:491–495.
- 47 Brooks D, Horner R, Kozar L, Render-Teixeira C, Phillipson E: Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 1997;99:106–109.
- 48 Belaidi E, Joyeux-Faure M, Ribuot C, Launois S, Levy P, Godin-Ribuot D: Major role for hypoxia inducible factor-1 and the endothelin system in promoting myocardial infarction and hypertension in an animal model of obstructive sleep apnea. *J Am Coll Cardiol* 2009;53:1309–1317.
- 49 Ryan S, Taylor CT, McNicholas WT: Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 2005;112:2660–2667.
- 50 Kato M, Roberts-Thomson P, Phillips BG, et al: Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000;102:2607–2610.
- 51 Dursunoglu N, Dursunoglu D: Obstructive sleep apnea syndrome, endothelial dysfunction and coronary atherosclerosis (in Turkish). *Tuberk Toraks* 2005;53:299–306.
- 52 Yamauchi M, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Suzuki T, Kimura H: Oxidative stress in obstructive sleep apnea. *Chest* 2005;127:1674–1679.
- 53 Fasset RG, Venuthurupalli SK, Gobe GC, et al: Biomarkers in chronic kidney disease: a review. *Kidney Int* 2011;80:806–821.



- 54 Faulx MD, Storfer-Isser A, Kirchner HL, Jenny NS, Tracy RP, Redline S: Obstructive sleep apnea is associated with increased urinary albumin excretion. *Sleep* 2007;30:923–929.
- 55 Tsioufis C, Thomopoulos C, Dimitriadis K, Amfilochiou A, Tsiachris D, Selima M, Petras D, Kallikazaros I, Stefanadis C: Association of obstructive sleep apnea with urinary albumin excretion in essential hypertension: a cross-sectional study. *Am J Kidney Dis* 2008;52:285–293.
- 56 Ursavas A, Karadag M, Gullulu M, Demirdogen E, Coskun F, Onart S, Gozu RO: Low-grade urinary albumin excretion in normotensive/non-diabetic obstructive sleep apnea patients. *Sleep Breath* 2008;12:217–222.
- 57 Sklar AH, Chaudhary BA: Reversible proteinuria in obstructive sleep apnea syndrome. *Arch Intern Med* 1988;148:87–89.
- 58 Møller DS, Lind P, Strunge B, Pedersen EB: Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. *Am J Hypertens* 2003;16:274–280.
- 59 Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD: Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003;348:1233–1241.
- 60 Kinebuchi S, Kazama JJ, Satoh M, et al: Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome. *Clin Sci (Lond)* 2004;107:317–322.
- 61 Logan A, Tkacova R, Perlikowski S: Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. *Eur Respir J* 2003;21:241–247.
- 62 Kinebuchi S, Kazama JJ, Satoh M, Sakai K, Nakayama H, Yoshizawa H, Narita I, Suzuki E, Gejyo F: Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome. *Clin Sci (Lond)* 2004;107:317–322.
- 63 Kita H, Ohi M, Chin K, Noguchi T, Otsuka N, Tsuboi T, Itoh H, Nakao K, Kuno K: The nocturnal secretion of cardiac natriuretic peptides during obstructive sleep apnoea and its response to therapy with nasal continuous positive airway pressure. *J Sleep Res* 1998;7:199–207.
- 64 Hanly PJ, Pierratos A: Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 2001;344:102–107.
- 65 Tang SC, Lam B, Ku PP, Leung W, Chu C, Ho Y, Ip M, lai K: Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cyclor-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 2006;17:2607–2616.
- 66 Tang SC, Lam B, Lai AS, Pang CB, Tsa WK, Khong PL, Ip MS, lai KN: Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance. *Clin J Am Soc Nephrol* 2009;4:410–418.
- 67 Lyons OD, Chan CT, Yadollahi A, Bradley TD: Effect of ultrafiltration on sleep apnea and sleep structure in patients with end-stage renal disease. *Am J Respir Crit Care Med* 2015;191:1287–1294.
- 68 Tang SC, Lam B, Ku PP, Leung WS, Chu CM, Ho YW, Ip MS, Lai KN: Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cyclor-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 2006;17:2607–2616.
- 69 Tang SC, Lam B, Lai AS, Pang CB, Tso WK, Khong PL, Ip MS, Lai KN: Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance. *Clin J Am Soc Nephrol* 2009;4:410–418.
- 70 Lee JJ, Kim GS, Kim JA, Kim SJ, Kang JG, Kim GH, Jung HH: Improvement of sleep-related breathing disorder in patients with end-stage renal disease after kidney transplantation. *Clin Transplant* 2011;25:126–130.
- 71 Rodrigues CJ, Marson O, Togeiro SM, Tufik S, Ribeiro AB, Tavares A: Sleep-disordered breathing changes after kidney transplantation: a polysomnographic study. *Nephrol Dial Transplant* 2010;25:2011–2015.
- 72 Kasai T, Bradley TD, Friedman O, Logan AG: Effect of intensified diuretic therapy on overnight rostral fluid shift and obstructive sleep apnoea in patients with uncontrolled hypertension. *J Hypertens* 2014;32:673–680.
- 73 Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM, Calhoun DA: Spironolactone reduces severity of obstructive sleep apnea in patients with resistant hypertension: a preliminary report. *J Hum Hypertens* 2010;24:532–537.
- 74 Cicolin A, Mangiardi L, Mutani R, Bucca C: Angiotensin-converting enzyme inhibitors and obstructive sleep apnea. *Mayo Clin Proc* 2006;81:53–55.