REVIEW ARTICLES

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Obstructive Sleep Apnea and Kidney Disease: A Potential Bidirectional Relationship?

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Chronic kidney disease (CKD) is associated with high mortality rates and heavy economic and social burdens. Nearly 10% of the United States population suffer from CKD, with fatal outcomes increased by 16–40 times even before reaching end-stage renal disease. The prevalence of obstructive sleep apnea (OSA) is between 3% and 7% in the general population, and has increased dramatically during the last 2 decades along with increased rates of obesity. However, the prevalence of OSA is much greater in patients with CKD. In addition, aggressive dialysis improves OSA. The current literature suggests a bidirectional association between CKD and OSA through a number of potential pathological mechanisms, which increase the possibility of both diseases being possible risk factors for each other. CKD may lead to OSA through a variety of mechanisms, including alterations in chemoreflex responsiveness, pharyngeal narrowing due to fluid overload, and accumulation of uremic toxins. It is also being increasingly recognized that OSA can also accelerate loss of kidney function. Moreover, animals exposed to intermittent hypoxia suffer histopathological renal damage. Potential mechanisms of OSA-associated renal dysfunction include renal hypoxia, hypertension, endothelial dysfunction, activation of the sympathetic nervous system, and increased oxidative stress.

Commentary: A commentary on this article appears in this issue on page 845.

Keywords: sleep apnea, kidney function, hypertension, endothelium, oxidative stress

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Chronic kidney disease (CKD) severely affects a patient's health, lifestyle, and well-being. Diabetes and hypertension are the leading causes for the increased prevalence of CKD.[1] The silent nature of CKD is of considerable concern as well, particularly during the early stages of disease progression. Nearly 10% of the United States population suffer from CKD.[2] The global prevalence of CKD is estimated to be between 8% and 16%.[3] There was a high number of deaths (90,118 patients) associated with end-stage renal disease (ESRD) in 2009 in the United States.[2] In fact, individuals with CKD are 16 to 40 times more likely to die from cardiovascular diseases and other comorbidities before ESRD.[2,4] The prevalence of CKD in Canada (12.5% for 2007–2009) is similar to that in the United States.[5] The economic burden of CKD is troublesome as well, since the total expenditure for CKD management in the United States reached $45.5 billion in 2011, constituting 18% of total Medicare expenditure,[6] and the annual cost of medical care per CKD patient was $19,752 in 2008 in the United States.[7] Based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI), CKD is defined as either kidney damage or having an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for ≥ 3 months.[8]

Sleep apnea is characterized by repeated episodes of apnea and hypopnea during sleep,[9–11] while obstructive sleep apnea (OSA) is characterized by upper airway collapse during sleep, and is by far the most common type of sleep apnea.[12] Most studies estimate the prevalence of sleep disordered breathing to be between 3% and 7%, depending on the definition of the disease.[13–18] The number of patients with OSA in the United States is estimated at 15 million.[19] However, some believe that these rates may be an underestimate, since rates of obesity, which is a major risk factor for OSA, has been steadily increasing over recent decades. Estimates based on current weight trends suggest that moderate-to-severe sleep disordered breathing occurs in 10% in men between 30 and 49 years old, and up to 17% in men aged 50 to 70 years old.[20] The association between obesity and OSA is illustrated by data from Saudi Arabia where there are high rates of obesity[21] that results in one in 3 middle-aged males and 4 in 10 middle-aged females being at increased risk of developing OSA.[22,23] However, these data are based on the Berlin questionnaire stratification for risk of OSA, which can falsely exaggerate prevalence of OSA. Of note, OSA is generally underappreciated, with 93% of women and 82% of men with moderate-to-severe sleep apnea not being clinically diagnosed.[24–27]

Accumulating data suggest a bidirectional relationship between OSA and CKD. That is, CKD likely confers an increased risk of OSA, and OSA may in turn increase the risk of renal injury. We undertook a search of the medical literature published between 1980 and 2014, using the PubMed, EMBAASE, and OVID databases for articles published in English, and included the following keywords: chronic kidney disease, obstructive sleep apnea, epidemiology or pathophysiology, or their corresponding synonyms in MeSH terms. Our search yielded a total of 275 papers, of which we selected 124 to be of interest for this review.

Table 1—Occurrence of OSA in patients with CKD.

Author	Subjects	Diagnostic Method / Sleep Apnea Threshold	Main Findings
Millman[28]	29 males on hemodialysis	Polysomnography	4% with positive sleep apnea symptoms 6 of 8 had sleep apnea
Kimmel[29]	26 patients with ESRD	Polysomnography Disordered breathing events ≥ 30 per session	Sleep apnea symptomatic group (22): sleep apnea found in 7% Sleep apnea asymptomatic group (4): none had sleep apnea (p < 0.02)
Nicholl[36]	254 patients (nephrology clinic)	Ambulatory sleep recorder Respiratory disturbance index ≥ 15	Sleep apnea (predominantly obstructive) in (eGFR ≥ 60 mL/min) group (55): 27% Sleep apnea in CKD (eGFR < 60 mL/min, not on dialysis) group (124): 41% Sleep apnea in ESRD on hemodialysis group (75): 57% (p = 0.002) Nocturnal hypoxia found in 50% of CKD and ESRD (p < 0.001)
Markou[128]	35 dialysis independent CKD patients	Polysomnography AHI ≥ 5	Sleep apnea (mainly obstructive) found in 54.3% In non-diabetic subjects, AHI correlated with: Urea (r = 0.608, p = 0.001) Creatinine clearance (r = −0.50, p = 0.012)
Sakaguchi[129]	100 dialysis independent CKD patients	Type 3 portable monitor AHI ≥ 5	OSA found in 65% Multivariate logistic regression analysis: A decrease by 10 mL/min/1.73 m^2 in eGFR associated with a 42% increase in odds of the likelihood of OSA (p = 0.02)

CKD AS A POTENTIAL RISK FACTOR FOR OSA

Epidemiology

Patients with ESRD have an increased prevalence of OSA. In a survey of male patients undergoing hemodialysis, 41% (12 of 29) had positive symptoms of sleep-related breathing disorders. A follow-up investigation of 8 of these patients using all-night polysomnography confirmed that 6 patients had OSA.[28] Another relatively small study confirmed the association between kidney disease and sleep apnea in 26 patients with ESRD, in which 22 patients were symptomatic of sleep apnea and 16 patients from the symptomatic group had a confirmed diagnosis of sleep apnea.[29] Several recent epidemiological studies affirm the association between CKD and resultant sleep apnea.[30–34] Some authors suggest that sleep apnea occurs in at least 50% to 60% of CKD patients with ESRD,[32,35] and the prevalence of sleep apnea in CKD patients is 10 times higher than the prevalence of sleep apnea in the general population.[34] **Table 1** summarizes the outcomes of a number of epidemiological studies relating to OSA in CKD patients.

More recent data on the occurrence of sleep apnea in CKD comes from Nicholl and colleagues, who studied sleep apnea in different categories of CKD patients.[36] They stratified 254 patients from a nephrology clinic into 3 categories based on their kidney function: (1) eGFR ≥ 60 mL/min, (2) CKD with eGFR < 60 mL/min and not on dialysis, and (3) ESRD on hemodialysis. Their data revealed significant increases in the occurrence of sleep apnea (predominantly obstructive) that was related to declining kidney function, with the prevalence of sleep apnea being 57% in the ESRD group, 41% in the CKD patients not on dialysis, and 27% in the patients with eGFR ≥ 60 mL/min. They concluded that the high incidence of nocturnal hypoxia in CKD with ESRD patients could contribute to both the loss of kidney function and increased cardiovascular risk. Despite the statistically significant association between declining kidney functions and nocturnal hypoxia, it should be noted that CKD and ESRD patients were significantly older and presented with other risk factors for sleep apnea such as hypertension and diabetes. An important consideration in studies reporting a high incidence of sleep apnea in CKD patients is the presence of multiple comorbidities that can also contribute to the occurrence of sleep apnea as well.[37,38]

Pathological Mechanisms

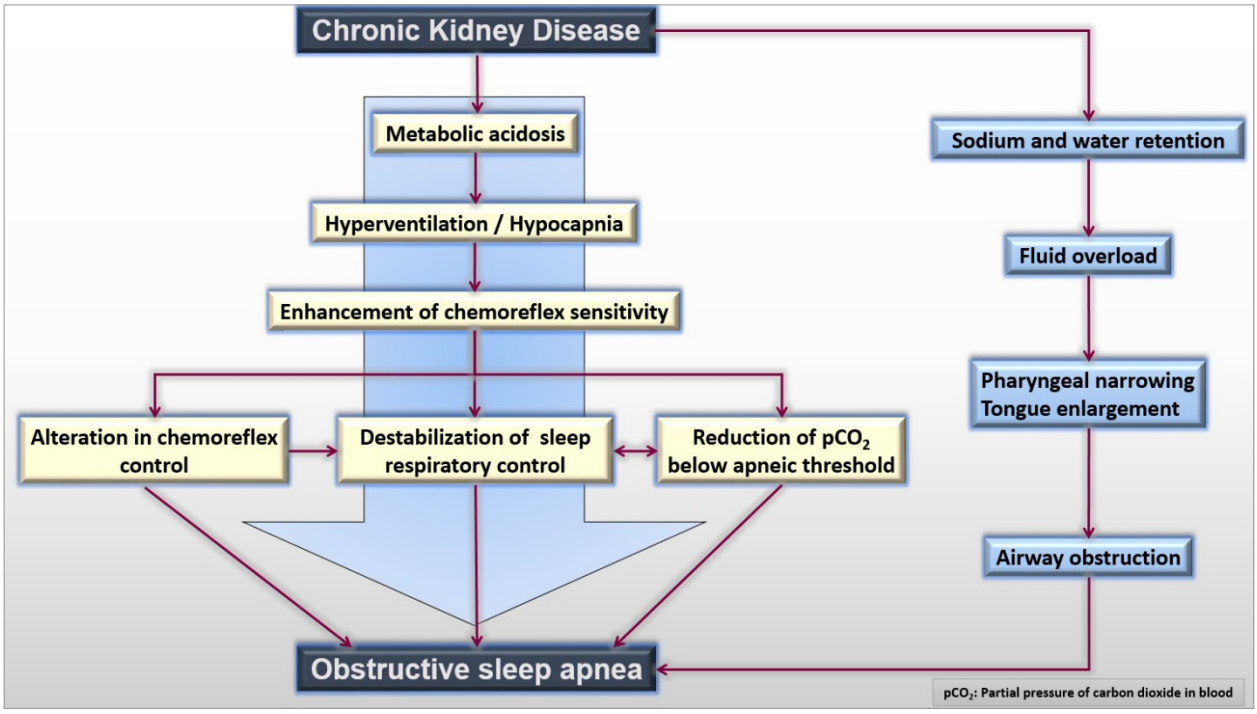
Epidemiological studies highlight an increased risk of OSA in patients with CKD. The exact mechanisms of kidney disease-induced OSA are not yet fully elucidated. However, there are several proposed mechanisms that describe the pathophysiology of CKD-related sleep apnea.

Chemoreflex Responsiveness

Chemoreflex control is the predominant drive of respiration during NREM sleep.[39] Both peripheral and central chemoreflexes may have crucial roles in the pathophysiology of various diseases including sleep apnea.[40] In fact, the instability of ventilatory control during sleep is a distinguishing feature in the pathophysiology of central sleep apnea.[41,42] However, altered chemoreflex responsiveness can also contribute to OSA by leading to increased controller gain of the respiratory system and breathing instability (**Figure 1**).[39–40]

Alterations in chemoreflex responsiveness occur in patients with ESRD[43] and could partially explain the pathophysiological mechanisms linking CKD to sleep apnea, particularly through

Figure 1—Potential mechanisms linking CKD to OSA.



metabolic acidosis and accumulation of uremic toxins, which are considered consequences of progressive CKD.[44–45] Metabolic acidosis enhances peripheral chemosensitivity, causing marked alterations in the ventilatory recruitment threshold of pCO_2 and ultimately predisposing central or OSA.[39,46–47] It is thought that hypocapnia (reduced pCO_2 levels), a respiratory compensatory mechanism during metabolic acidosis, enhances chemoreceptor sensitivity to CO_2, thus altering chemoreflex control, and ultimately destabilizing respiratory control during sleep by decreasing pCO_2 levels below the apneic threshold.[37–39,41,48–51] On the other hand, chemoreflex sensitivity is markedly altered by hypercapnia.[52] The central and peripheral chemoreflex responsiveness to arterial CO_2 was studied in 58 patients with ESRD,[39] where patients were stratified based on their polysomnography-measured apnea-hypopnea index ([AHI] averaged frequency of apnea and hypopnea per sleeping hour) into non-apneic (n = 20) or apneic (n = 38) groups, who mostly (89%) had obstructive respiratory symptoms. Compared to non-apneic group, a significant increase in chemoreflex sensitivity to hypercapnia (measured by ventilatory sensitivity to arterial CO_2) was found in apneic patients during isoxic-hypoxia and hyperoxia states. Nevertheless, multiple linear regression analysis identified AHI as a positive predictor for hypoxic and hyperoxic ventilatory sensitivity. These results suggest that chemoreflex responsiveness is augmented in patients with ESRD and sleep apnea, and this may, at least partially, explain the pathophysiological association between the two disease states.

Pharyngeal Narrowing

OSA is partly due to lateral pharyngeal narrowing and/or increased thickness of the lateral pharyngeal muscular walls.[53–55] Some studies reported changes in pharyngeal morphology in ESRD, which may provide another mechanism for ESRD-related OSA. For example, the pharyngeal area is narrower in ESRD patients (3.04 cm^2) than that in subjects with normal renal function (3.46 cm^2).[56] Furthermore, changes in the pharyngeal cross-sectional area was assessed after conversion from conventional hemodialysis (4 h/day, 3 days/week) to nocturnal hemodialysis (8 h/night, 3–6 nights/week) in 24 ESRD patients, of whom 16 had AHI ≥ 15/h (predominantly obstructive).[57] There were significant increases in the average pharyngeal cross-sectional area at functional residual capacity (3.29 cm^2 vs 3.39 cm^2) and at residual volume (1.91 cm^2 vs 2.13 cm^2) ($p < 0.05$) after conversion to nocturnal hemodialysis, with a 19% (3 of 16) response rate (AHI reduced to 15/h) in apneic patients.

A crossover study of 38 patients with ESRD who underwent overnight polysomnography during either cycler-assisted nocturnal peritoneal dialysis or continuous ambulatory peritoneal dialysis reported that continuous ambulatory peritoneal dialysis doubled the prevalence of severe sleep apnea (AHI ≥ 15/h) (42.1% vs 21.1%), as well as the mean AHI (21.5 vs 9.6).[48] Volumetric magnetic resonance imaging (MRI) of the upper airway showed significant reductions in nasopharyngeal volume by 25.4%, oropharyngeal volume by 34%, and hypopharyngeal volume by 21.6% after conversion to continuous ambulatory peritoneal dialysis. There was also a significant increase in tongue volume by 8.22%. These results were in accordance with a 2.2-fold greater reduction in total body water with cycler-assisted nocturnal peritoneal dialysis, compared with continuous ambulatory peritoneal dialysis. Importantly, AHI correlated negatively with urea kinetics and also with peritoneal creatinine. These findings suggest that cycler-assisted nocturnal peritoneal dialysis alleviates sleep apnea secondary to improved fluid and uremic clearance.

Table 2—Occurrence of CKD in patients with OSA.

R	Subjects	Design	Diagnostic Method / Sleep Apnea Threshold	Main Findings
66	Sleep-related breathing disorder: 1,624 Control: 7,454	Retrospective cohort	Polysomnography AHI ≥ 5	Prevalence of CKD in the sleep-related breathing disorder: 30.5% Prevalence of CKD in control: 9.1% ($p < 0.001$) Adjusted odds ratio: 4.542 ($p < 0.0001$) AHI is not a significant determinant for CKD in sleep-related breathing disorder patients
67	Obese OSA: 55 None: 36	Cross-sectional	Polysomnography AHI ≥ 5	Serum creatinine in control group: 0.8 mg/dL Serum creatinine in OSA group: 0.9 mg/dL ($p = 0.013$) No major difference in albuminuria between groups
130	175	Cross-sectional Retrospective	Polysomnography AHI ≥ 5	Mean eGFR in negative group: 50 mL/min Mean eGFR in mild OSA (AHI = 5–15): 44.8 mL/min Mean eGFR in moderate OSA (AHI = 15–30): 40.8 mL/min Mean eGFR in severe OSA (AHI > 30): 38.8 mL/min $p < 0.001$ for trend

The effect of pharyngeal narrowing secondary to renal failure on sleep apnea can also be attributed to the fluid overload.[58] Applying positive pressure to the lower limbs when in a supine position significantly increases neck circumference and airflow resistance of the pharynx, thus affecting airflow to the lungs.[59] This mimics fluid overload status in patients with renal failure. Other mechanism include reduction in lung volume secondary to pulmonary edema, especially during sleep, which can reduce the upper airway size.[57]

Finally, uremic myopathy or neuropathy can directly affect the upper airway dilator muscles and so reduce the airway size,[60–61] although this mechanism has not been investigated in patients with ESRD.

ESRD Management and OSA

The potential impact of ESRD management on sleep apnea was elegantly shown in an intervention trial by Hanly et al. These investigators switched 14 ESRD patients (9 of 14 diagnosed with OSA) from conventional 3 times/week hemodialysis to 6–7 times/week nocturnal hemodialysis at home.[62] After 6–15 months, average AHI was reduced from 25 to 8 episodes/h of sleep ($p = 0.03$). The potential mechanisms of improvement in OSA symptoms were not evaluated in this study. An earlier case of 2 ESRD patients with severe OSA (AHI = 80) and central sleep apnea (AHI = 51) reported an absence of sleep apnea symptoms, with reductions in AHI to 9 and 5, respectively, after undergoing renal transplantation.[63]

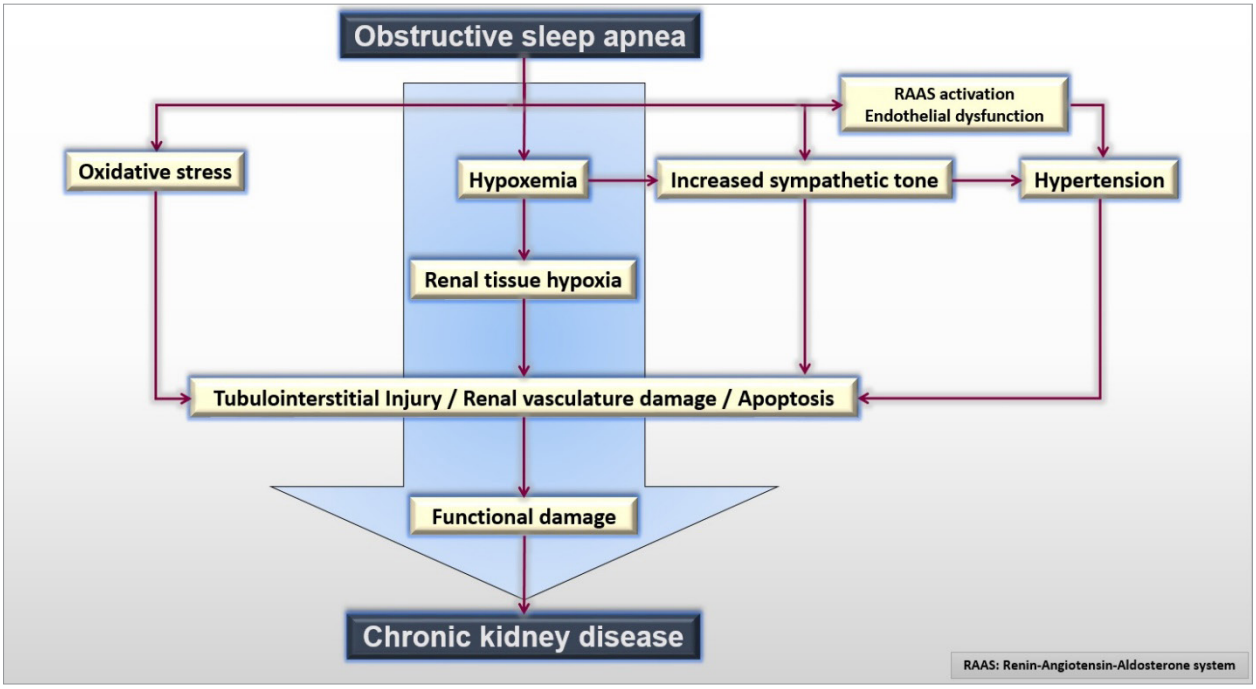
OSA AS A POTENTIAL RISK FACTOR FOR CKD

Epidemiology

Rates of CKD are greater in patients with OSA, raising the possibility that sleep apnea can contribute in CKD as well (**Table 2**). A major obstacle for investigating this unexpected consequence of sleep disordered breathing is the fact that patients with sleep apnea usually also present with several other comorbidities such as obesity, diabetes, and hypertension, which are also all risk factors for CKD.[64–65] An early study on the occurrence of CKD in patients with sleep disordered breathing took place in Okinawa, Japan, in a retrospective cohort fashion.[66] This investigation compared data of 1,624 patients diagnosed with sleep-related breathing disorder and with known estimated values of GFR, with 7,454 age- and gender-matched control subjects. Sleep related breathing disorder was defined as AHI > 5, and CKD as eGFR < 60 mL/min/1.73 m^2. The prevalence of CKD in the sleep disordered breathing group was 3 times greater than in controls (30.5% vs 9.1%), with an adjusted odds ratio of 4.542. Neither body mass index (BMI) nor AHI were significant determinants for CKD in the sleep disordered breathing group when other confounding variables were adjusted for. In fact, the prevalence of CKD decreased as BMI increased in the sleep disordered breathing group, causing the investigators to recommend screening for development of CKD in patients with sleep disordered breathing. However, these results should be interpreted with caution since several risk factors for CKD, such as diabetes, hypertension, and metabolic syndrome, were not defined in the subjects. In addition, all subjects were recruited from a single center in retrospective fashion, and the possibility of selection bias could not be eliminated.

The effect of OSA on kidney function was also examined in a cross-sectional study of 91 morbidly obese subjects who underwent polysomnography tests prior to bariatric surgery.[67] Thirty-six subjects had no OSA (AHI < 5), while the 55 remaining patients suffered from OSA (AHI ≥ 5). Of note, the average level of serum creatinine was significantly higher in the OSA group (0.9 mg/dL vs 0.8 mg/dL) from a statistical point of view, suggesting that the increased severity of OSA in obese adults was associated with higher serum creatinine levels. However, there were no differences in albuminuria between the groups, except when subjects were categorized

Figure 2—Potential mechanisms linking OSA to CKD.



based on the presence of hypertension. Generalizability of these results is not warranted, since the majority of the subjects were Caucasian females.

The presence of hypertension, diabetes, and old age present challenges when studying sleep apnea-induced CKD, leading some to investigate the likelihood of increased CKD in non-diabetic, non-hypertensive OSA patients.[68] In a group of polysomnography-screened subjects, 40 subjects met these criteria and were included in prospective analysis: 37 subjects presented with mild-to-severe OSA, of whom 5 subjects met the criteria for CKD. Multivariate stepwise linear regression analysis indicated that AHI and desaturation index were the only predictors for urine albumin-to-creatinine ratio and eGFR. The small sample size, gender (83% male), race (Asian), and the lack of control for some confounders affecting urine albumin-to-creatinine ratio were the main limitations of the study.

Pathological Mechanisms

The potential mechanisms of OSA-induced CKD are unclear. Most studies conclude that sleep related breathing disorder induces kidney injury or CKD indirectly through hypertension, oxidative stress, endothelial dysfunction, and hypoxemia-related activation of the sympathetic nervous and renin-angiotensin-aldosterone systems (**Figure 2**).[69–76]

Hypoxia

Renal tissue hypoxia plays an important role in the development of acute kidney injury and chronic kidney diseases. It is generally agreed that several mechanisms can aggravate renal hypoxia. Of these, hypoxemia has recently been suggested to be significantly associated with sleep apnea.[77] Kidneys are among the most richly perfused organs in the body since the kidneys receive nearly one-quarter of resting cardiac output.[78] On other hand, renal oxygen tension is relatively low secondary to low renal oxygen consumption, since less than 10% of the total oxygen passing through the kidneys is consumed.[78] The relatively low renal oxygen consumption compared to the high blood flow volume is mainly attributed to the unique structure and organization of the renal arterioles and venules within the cortex and medulla. The close contact and the parallel pathways of the renal arteries and veins, particularly within renal medulla, allows a countercurrent exchange of oxygen before its entry to the capillary bed. The availability of oxygen within renal tissues depends on renal blood flow, which is closely regulated to allow for a sustained GFR. Another essential factor determining intra-renal oxygen level is the renal cellular consumption of oxygen, which is determined by energy-requiring mitochondrial consumption and tubular electrolyte transportation processes. Therefore, in addition to reduced renal perfusion, renal tissue hypoxia can be attributed to increased tissue consumption as well.[79]

Tubulointerstitial injury is thought to be the final common pathway in ESRD. Moreover, recent data suggest that abnormal reductions of renal oxygen tension driven by renal hypoxia, particularly in the tubulointerstitium, also plays an important role In the early stages of kidney injury through several pathological mechanisms.[78–82] Renal hypoxia and tissue injury are related in a cyclic fashion. Renal hypoxia induces epithelial-mesenchymal trans-differentiation of the tubular cells and activates fibroblasts, which in turn plays a crucial role in the progression of renal interstitial fibrosis and damage of peritubular capillaries.[82,83] Trans-differentiated cells also stimulate the production of collagen I and α-smooth muscle actin.[79] As a result, tubular atrophy occurs and further impairment of oxygen supply is induced. In addition, chronic renal hypoxia induces

mitochondrial malfunction of the tubular cells and reduces energy production, eventually triggering apoptosis.[82] Ischemia-induced renal hypoxia constitutes one of the most common causes of acute kidney injury. Nevertheless, persistent renal tissue hypoxia post-acute kidney injury can contribute to the development of CKD as well.[84] On the other hand, hypoxemia represents a common and a direct pathway for the development of renal tissue hypoxia. A study in rabbits examined the cortical and the medullary oxygen delivery and consumption following systematic hypoxemia.[81] The rabbits' kidneys were denervated to avoid sympathetic renal vasoconstriction secondary to hypoxemia. Most organs respond to hypoxemia by increasing local blood flow to attenuate hypoxia-related tissue injury. However, renal blood flow did not increase in response to hypoxemia, even when arterial oxygen concentration was reduced by more than 50%. In addition, the oxygen tension of both renal cortical and medullary tissues fell significantly following arterial oxygen content reduction by 5% to 8%, which caused by a reduction of oxygen ventilation from 21% (room air) to 17%. Oxygen delivery was reduced rapidly following reduction in arterial oxygen content, while renal oxygen consumption was maintained until arterial oxygen fell by more than 40%. Interestingly, ventilation with 11% oxygen markedly reduced mean arterial pressure (−11 ± 3 mm Hg) and GFR (−36% ± 17%). These results led the authors to conclude that renal tissue hypoxia secondary to relatively mild hypoxemia has important implications for the progression of kidney disease.

The effect of nocturnal hypoxia on kidney function in humans was recently studied in 858 subjects referred for diagnostic testing of sleep apnea, and who were followed for an average of 2.1 years.[85] Assessments of sleep and oxygenation were objectively measured, and the severity of OSA was assessed based on the respiratory disturbance index score (averaged frequency of apnea, hypopnea, and respiratory effort-related arousal per sleeping hour). In this patient cohort, 44% had nocturnal hypoxia as defined by oxygen saturation < 90% for > 12% of nighttime monitoring. Compared to control subjects, patients with nocturnal hypoxia were at significant risk for accelerated kidney function loss (reductions in eGFR by ≥ 4 mL/min/1.73 m^2 per year), with an odds ratio of 2.89 (95% CI: 1.25–6.67) after adjustment for respiratory disturbance index, age, BMI, diabetes, and heart failure. However, severe OSA (respiratory disturbance index > 30) was not associated with increased risk of accelerated loss of kidney function using a multivariate adjusted model of logistic regression (OR: 1.68; 0.85–3.31).

Hypertension

The link between hypertension and CKD was first demonstrated at the early part of the 19th century. Hypertension has multitudinous effects in the kidney including nephrosclerotic glomerulopathy, diffuse glomerulosclerosis, renal interstitial fibrosis, glomerular and peritubular fibrosis, mesangial hypertrophy, and several other pathologies that all eventually lead to decreased GFR and CKD,[86] making hypertension the second most common cause of ESRD after diabetes. Experimental and epidemiological studies suggest a strong link between blood pressure and OSA. There is not only a high prevalence of OSA in hypertensive patients, but patients with OSA are at greater risk of developing incident hypertension over time.[87–90]

Hypertension is a standalone known risk for CKD, while OSA can induce resistant hypertension through various mechanisms that include activation of renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, and oxidative stress.[76]

A cross-sectional study compared albuminuria levels in hypertensive patients with and without OSA.[91] All recruited subjects had untreated hypertension (stage I or II). Urinary albumin excretion was significantly higher in the OSA-hypertensive group (by 57%), suggesting a pathophysiological linkage between OSA and dysfunctional kidney vasculature, particularly in hypertensive patients. Interestingly, albuminuria levels correlated significantly with the severity of OSA. However, no significant difference was seen in eGFR between hypertensive-OSA patients and those without OSA. In addition, albumin to creatinine ratio was determined using 2 consecutive morning urine samples, and not by the standard 24-h urine collection method.

Another cross-sectional study examined the association between resistant hypertension and OSA in non-dialysis dependent CKD and ESRD patients.[74] There was a strong association between resistant hypertension and severe OSA (AHI ≥ 30) in ESRD patients, but not in non-dialysis dependent CKD patients or in control non-CKD subjects. The results of this study might be limited by several constraints, including small sample size, use of unattended home polysomnography instead of in-lab polysomnography, and finally by not assessing essential factors that may contribute in resistant hypertension in these patients (such as volume status and aldosterone levels).

Additional evidence that links OSA, hypertension, and kidney disease comes from a recent study of 20 newly diagnosed normotensive non-diabetic OSA patients.[92] The investigators examined the role of the renin-angiotensin system in OSA-related loss of kidney function. Renal hemodynamics were measured at baseline and in response to angiotensin II infusion (3 or 6 ng/kg/min × 30 min), pre and post 1 month of continuous positive airway pressure (CPAP) therapy. Treatment with CPAP increased renal plasma flow, and significantly reduced filtration fraction (18.9% vs. 15.3%, p = 0.004), indicating reduced intraglomerular pressure. Nonetheless, short-term CPAP treatment significantly reduced plasma aldosterone levels (149 vs 109 pmol/L, p = 0.003) and urinary total protein excretion (61 vs 56 mg/day, p = 0.003). Renal plasma flow was significantly augmented in response to angiotensin challenge post-CPAP treatment, indicating decreased renal renin-angiotensin system activity. It remains unclear whether the effect of CPAP treatment can be sustained after discontinuation of treatment.

Increased Sympathetic Tone

The relationship between the sympathetic nervous system and kidney disease is well described. Despite the kidneys being a major source of afferent signals in the sympathetic nervous system, there is much evidence showing that sympathetic hyperactivity worsens kidney function and also leads to renal structural damage.[93–97] Factors that increase sympathetic activity include heart failure, smoking, hypercapnia, and hypoxia-related sleep disordered breathing.[98–100]

Somers and associates reported increased sympathetic activity in OSA patients.[101] Sympathetic nervous activity was

measured using direct multi-unit intraneural recordings of efferent sympathetic discharge to muscles and blood vessels and expressed as bursts/min or bursts/100 heart beats. Patients with OSA had significantly higher sympathetic activity during wakefulness in comparison with control subjects (59 bursts/min or 76 burst/100 heart beats vs 34 burst/min or 50 bursts/100 heart beats). Blood pressure and sympathetic activity gradually rose as sleep apnea progressed. Upon termination of apnea, sympathetic activity decreased while blood pressure continued to increase, reaching values as high as 240/130 mm Hg in some subjects.

The most common form of sleep disordered breathing is OSA, which has a prevalence of 1% to 3% in children.[102] The pediatric literature supports a causal relationship between OSA and increased autonomic nervous system activity, where it is reported that sympathetic tone is significantly increased in children with OSA, and that this can precede cardiovascular consequences.[102–103] In 70 children referred for sleep disordered breathing assessment due to snoring, 33 were diagnosed with primary snoring, 20 with mild OSA, and 17 with moderate to severe OSA. Urinary catecholamine levels were compared with those from 26 healthy control children.[103] The average levels of norepinephrine were higher in the combined OSA groups (29.2 vs 24.7 µmol/mol creatinine), as were levels of epinephrine (4.0 vs 2.2 µmol/mol creatinine) and dopamine (372.1 vs 293.3 µmol/mol creatinine). Linear regression analysis revealed significant associations between norepinephrine ($r = 0.32$) and epinephrine ($r = 0.27$) levels with AHI values.

Treatment with CPAP is a well-established form of OSA management. Importantly, CPAP treatment for sleep apnea decreases the OSA-related sympathetic hyperactivity.[104] Levels of muscle sympathetic nerve activity were reduced significantly by CPAP treatment (from 51 to 41 burst/min). There were no changes in heart rate or blood pressure when sympathetic activity was reduced by CPAP treatment in this study.

Oxidative Stress

An imbalanced production of reactive oxygen species (ROS) and the natural antioxidant defense mechanisms result in a status of oxidative stress, which mediates cellular damage in a number of conditions, including structural and functional changes in the kidney.[105–109] Markers of cellular oxidative stress include malondialdehyde (a lipid peroxidation end product), F2-isoprostanes, and lipid hydroperoxide.[108] On the other hand, sleep related breathing disorders, especially OSA, disrupt the balance between ROS removal and formation to initiate oxidative stress,[110–111] and thus constitute another indirect pathogenesis of sleep apnea-associated CKD.

Support for a role of oxidative stress comes from the finding that vitamin C reverses endothelial dysfunction secondary to OSA.[112] Patients with established atherosclerotic disease, but who were free of other cardiovascular risk factors were excluded from the trial, and there were no differences in the cardiovascular risk profiles between the OSA and control groups. Endothelial dysfunction was tested by intra-arterial infusion of acetylcholine (vasodilator that stimulates the release of endothelial nitric oxide) and measuring forearm blood flow. Changes in blood flow were reported as percentage changes from baseline flow. The maximal increase of forearm blood flow induced by acetylcholine was significantly higher in the control group (233.6% vs 148.7%), indicating endothelial dysfunction in the OSA group, particularly when changes in forearm blood flow negatively correlated with AHI. Additionally, forearm blood flow was measured after treatment with intra-arterial vitamin C, which resulted in a significant improvement in the acetylcholine response, leading the authors to conclude that microvascular endothelial dysfunction in OSA patients may result from increased oxidative stress.

Support for a role for oxidative stress also comes from measurements of isoprostanes, which are prostaglandin-like compounds produced by non-enzymatic free radical-catalyzed peroxidation of arachidonic acid.[113–117] Plasma levels as well as exhaled breath condensate were significantly higher when measured in the morning (i.e., after sleep) in patients with OSA compared to age- and weight-matched healthy obese subjects, while evening levels of 8-Isoprostanes were similar in both groups.[118] The positive correlation between morning levels of 8-isoprostane and AHI suggested an association between OSA and increased systemic and local levels of oxidative stress.

OSA MANAGEMENT AND KIDNEY FUNCTION

Treatment of moderate to severe OSA by CPAP positively affects kidney filtration by minimizing glomerular hyperfiltration, which is common in many renal disorders.[119–120] Kinebuchi et al. compared the filtration fractions of 21 patients with moderate-to-severe OSA before and after CPAP treatment, considering filtration fractions and renal plasma flows as indicators of glomerular hyperfiltration.[121] Short-term CPAP therapy significantly reduced hyperfiltration by increasing renal plasma flow and reducing the filtration fraction. Another recent study examined the effects of short-term CPAP treatment on kidney function in 27 men with polysomnography-diagnosed OSA ($AHI \geq 20$).[122] Three months of CPAP treatment decreased average serum creatinine levels (0.87 to 0.82 mg/dL), and increased average eGFR levels from 72.9 to 79.3 mg/dL; these changes were statistically significant but with unreported clinical benefits. Findings from this study are limited by the lack of a control group and adjustment for other potential confounders.

ANIMAL MODEL OF SLEEP APNEA-INDUCED RENAL DAMAGE

A mouse model of sleep apnea based on repeated exposures to episodes of intermittent hypoxia has allowed for laboratory investigations of proposed morbidities of sleep apnea,[123–124] including endothelial dysfunction, cardiovascular abnormalities, immunological disorders, and kidney diseases.[125–127] The epidemiological and cohort studies linking sleep apnea to kidney disease led Sun and colleagues to examine the effects of sleep apnea on renal function and morphology in a mouse model of intermittent hypoxia.[127] Animals were randomly assigned to either intermittent hypoxia or control groups and primary measures were collected after 3 days, and later at 1, 2, and 8 weeks. There were no changes in renal function as measured by 24-h urinary albumin, but levels of inflammatory mediators such as renal vascular cell adhesion molecule-1 (VCAM-1)

were increased after 8 weeks of intermittent hypoxia. Levels of pro-fibrotic cytokines such as intercellular adhesion molecule-1 (ICAM-1) and plasminogen activator inhibitor-1 (PAI-1) were also elevated at all measurement time points, suggesting ongoing inflammatory and renal fibrosis processes in the kidneys after acute and chronic exposure to intermittent hypoxia. Histopathological fibrotic renal damage due to chronic intermittent hypoxia was further confirmed by increased connective tissue growth factor measurements. Evidence for early oxidative stress was provided by increases in nuclear factor-erythroid 2-related factor 2 (Nrf2, an essential transcription factor in the defense against the cytotoxic effect of oxidative stress) expression 3 days after onset of intermittent hypoxia, but with a gradual reduction after 8 weeks in parallel with increases in malondialdehyde levels and renal apoptotic cell death. The authors concluded that acute intermittent hypoxia induces inflammatory responses and protective measures against oxidative stress, while chronic intermittent hypoxia caused histopathological damage including renal cell death and fibrosis.

SUMMARY

OSA and chronic kidney disease are potentially related in a bidirectional fashion. Epidemiological studies indicate a causal relationship between OSA and CKD, and experimental data further support the causal relationship between these diseases. End-stage renal disease likely contributes to the development of OSA, perhaps through mechanisms such as metabolic acidosis, changes in chemoreceptor sensitivity, uremic toxins, and pharyngeal narrowing due to fluid accumulation. Recent studies suggest that sleep apnea induces CKD through increases in blood pressure, oxidative stress, and renal hypoxia. In other words, OSA may be an unconventional risk for CKD.

There is clear evidence of an association between severity of OSA and extent of kidney damage. However, it should be noted that the majority of studies investigated the causal relation between CKD and OSA in dialysis-dependent patients, which may not necessarily provide details on these mechanisms in CKD patients not requiring dialysis. Additional studies are needed to investigate the clinical outcomes of aggressive treatment of OSA on renal dysfunction.

REFERENCES

1. Weiner E. Causes and consequences of chronic kidney disease: implications for managed health care. J Manag Care Pharm 2007;13:S1–9.
2. Centers for Disease Control and Prevention. Chronic kidney disease surveillance system. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services, 2011. http://www.cdc.gov/ckd. Accessed August 5, 2013.
3. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet 2013;382:260–72.
4. NIH Publication, No. 12-3895, June 2012, available at www.kidney.niddk.nih.gov.
5. Arora P, Vasa P, Brenner D, Iglar K, McFarlane P, Morrison H, Badawi A. Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey. CMAJ 2013;185:E417–23.
6. U.S. Renal Data System, USRDS 2013 Annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2013.
7. Calabrese D. Management of cardiovascular disease in chronic kidney disease: implications for managed care. Am J Manag Care 2011;17:S412–8.
8. National Kidney Foundation. KDOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 39:S1-S000, 2002 (suppl 1).
9. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–39.
10. Lurie A. Obstructive sleep apnea in adults: epidemiology, clinical presentation, and treatment options. Adv Cardiol 2011;46:1–42.
11. Lee W. Epidemiology of obstructive sleep apnea: a population-based perspective. Expert Rev Respir Med 2008;2:349–64.
12. American Sleep Apnea association – www.sleepapnea.org.
13. Punjabi N. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:136–43.
14. Brunetti L, Rana S, Lospalluti ML, et al. Prevalence of obstructive sleep apnea syndrome in a cohort of 1,207 children of southern Italy. Chest 2001;120:1930–35.
15. Amra B, Farajzadegan Z, Golshan M, Fietze I, Penzel T. Prevalence of sleep apnea-related symptoms in a Persian population. Sleep Breath 2011;15:425–9.
16. Meslier N, Vol S, Balkau B, et al. Prevalence of symptoms of sleep apnea syndrome. Study of a French middle-aged population. Rev Mal Respir 2007;24:305–13.
17. Endo Y, Suzuki M, Inoue Y, et al. Prevalence of complex sleep apnea among Japanese patients with sleep apnea syndrome. Tohoku J Exp Med 2008;215:349–54.
18. Sharma SK, Kumpawat S, Banga A, Goel A. Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India. Chest 2006;130:149–56.
19. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease. J Am Coll Cardiol 2008;52:686–717.
20. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of Sleep-Disordered Breathing in adults. Am J Epidemiol 2013;177:1006–14.
21. Badran M, Laher I. Obesity in arabic-speaking countries. J Obes 2011;2011:686430.
22. BaHammam AS, Alrajeh MS, Al-Jahdali HH, BinSaeed AA. Prevalence of symptoms and risk of sleep apnea in middle-aged Saudi males in primary care. Saudi Med J 2008;29:423–6.
23. Bahammam AS, Al-Rajeh MS, Al-Ibrahim FS, Arafah MA, Sharif MM. Prevalence of symptoms and risk of sleep apnea in middle-aged Saudi women in primary care. Saudi Med J 2009;30:1572–6.
24. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 1997;20:705–6.
25. Flemons WW, Littner MR, Rowley JA, et al. Home diagnosis of sleep apnea: a systematic review of the literature. Chest 2003;124:1543–79.
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;131:1379–86.
27. Hanly PJ, Ahmed SB. Sleep apnea and the kidney: is sleep apnea a risk factor for chronic kidney disease? Chest 2014;146:1114–22.
28. Millman RP, Kimmel PL, Shore ET, Wasserstein AG. Sleep apnea in hemodialysis patients: the lack of testosterone effect on its pathogenesis. Nephron 1985;40:407–10.
29. Kimmel PL, Miller G, Mendelson WB. Sleep apnea syndrome in chronic renal disease. Am J Med 1989;86:308–14.
30. Hallett M, Burden S, Stewart D, Mahony J, Farrell P. Sleep apnea in end-stage renal disease patients on hemodialysis and continuous ambulatory peritoneal dialysis ASAIO J 1995;41:M435–41.
31. Venmans BJ, van Kralingen KW, Chandi DD, de Vries PM, ter Wee PM, Postmus PE. Sleep complaints and sleep disordered breathing in hemodialysis patients. Neth J Med 1999;54:207–12.
32. Kraus MA and Hamburger RJ. Sleep apnea in renal failure. Adv Perit Dial 1997;13:88–92.
33. Fletcher EC. Obstructive sleep apnea and the kidney. J Am Soc Nephrol 1993;4:1111–21.
34. Hanly P. Sleep apnea and daytime sleepiness in end-stage renal disease. Semin Dial 2004;17:109–14.
35. Fleischmann G, Fillafer G, Matterer H, Skrabal F, Kotanko P. Prevalence of chronic kidney disease in patients with suspected sleep apnoea. Nephrol Dial Transplant 2010;25:181–6.
36. Nicholl DD, Ahmed SB, Loewen AH, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. Chest 2012;141:1422–30.

37. Perl J, Unruh ML, Chan CT. Sleep disorders in end-stage renal disease: 'Markers of inadequate dialysis?' Kidney Int 2006;70:1687–93.
38. Zoccali C, Mallamaci F, Tripepi G. Sleep apnea in renal patients. J Am Soc Nephrol 2001;12:2854–9.
39. Beecroft J, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Enhanced chemo-responsiveness in patients with sleep apnoea and end-stage renal disease. Eur Respir J 2006;28:151–8.
40. Kara T, Narkiewicz K, Somers VK. Chemoreflexes--physiology and clinical implications. Acta Physiol Scand 2003;177:377–84.
41. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. Chest 2007;131:595–607.
42. Chowdhuri S, Shanidze I, Pierchala L, Belen D, Mateika JH, Badr MS. Effect of episodic hypoxia on the susceptibility to hypocapnic central apnea during NREM sleep. J Appl Physiol 2010;108:369–77.
43. Burgess KR, Burgess EE, Whitelaw WA. Impaired ventilatory response to carbon dioxide in patients with chronic renal failure: implications for the intensive care unit. Crit Care Med 1994;22:413–9.
44. Pierratos A, Hanly PJ. Sleep disorders over the full range of chronic kidney disease. Blood Purif 2011;31:146–50.
45. Fein AM, Niederman MS, Imbriano L, Rosen H. Reversal of sleep apnea in uremia by dialysis. Arch Intern Med 1987;147:1355–6.
46. Plataki M, Sands SA, Malhotra A. Clinical consequences of altered chemoreflex control. Respir Physiol Neurobiol 2013;189:354–63.
47. Duffin J. Role of acid-base balance in the chemoreflex control of breathing. J Appl Physiol 2005;99:2255–65.
48. Tang SC, Lam B, Lai AS, et al. Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance. Clin J Am Soc Nephrol 2009;4:410–8.
49. Skatrud JB, Dempsey JA. Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. J Appl Physiol 1983;55:813–22.
50. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. Am Rev Respir Dis 1993;148:330–8.
51. Dempsey JA, Smith CA, Przybylowski T, et al. The ventilatory responsiveness to CO2 below eupnoea as a determinant of ventilatory stability in sleep. J Physiol 2004;560:1–11.
52. Jensen D, Wolfe LA, O'Donnell DE, Davies GA. Chemoreflex control of breathing during wakefulness in healthy men and women. J Appl Physiol 2005;98:822–8.
53. Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 1997;82:1319–26.
54. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 1995;152:1673–89.
55. Haponik EF, Smith PL, Bohlman ME, Allen RP, Goldman SM, Bleecker ER. Computerized tomography in obstructive sleep apnea. Correlation of airway size with physiology during sleep and wakefulness. Am Rev Respir Dis 1983;127:221–6.
56. Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane PA, Hanly PJ. Pharyngeal narrowing in end-stage renal disease: implications for obstructive sleep apnoea. Eur Respir J 2007;30:965–71.
57. Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Nocturnal haemodialysis increases pharyngeal size in patients with sleep apnoea and end-stage renal disease. Nephrol Dial Transplant 2008;23:673–9.
58. Mavanur M, Sanders M, Unruh M. Sleep disordered breathing in patients with chronic kidney disease. Indian J Med Res 2010;131:277–84.
59. Chiu KL, Ryan CM, Shiota S, et al. Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. Am J Respir Crit Care Med 2006;174:1378–83.
60. Kimoff RJ. Upper airway myopathy is important in the pathophysiology of obstructive sleep apnea. J Clin Sleep Med 2007;3:567–9.
61. Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D. Upper airway sensation in snoring and obstructive sleep apnea. Am J Respir Crit Care Med 2001;164:250–5.
62. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med 2001;344:102–7.
63. Langevin B, Fouque D, Léger P, Robert D. Sleep apnea syndrome and end-stage renal disease Chest 1993;103:1330–5.
64. Tada T, Kusano KF, Ogawa A, et al. The predictors of central and obstructive sleep apnoea in haemodialysis patients. Nephrol Dial Transplant 2007;22:1190–7.
65. Wolf J, Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences. Nutr Metab Cardiovasc Dis 2007;17:233–40.
66. Iseki K, Tohyama K, Matsumoto T, Nakamura H. High Prevalence of chronic kidney disease among patients with sleep related breathing disorder (SRBD). Hypertens Res 2008;31:249–55.
67. Agrawal V, Vanhecke TE, Rai B, Franklin BA, Sangal RB, McCullough PA. Albuminuria and renal function in obese adults evaluated for obstructive sleep apnea. Nephron Clin Pract 2009;113:c140–7.
68. Chou YT, Lee PH, Yang CT, et al. Obstructive sleep apnea: a stand-alone risk factor for chronic kidney disease. Nephrol Dial Transplant 2011;26:2244–50.
69. Adeseun GA, Rosas SE. The impact of obstructive sleep apnea on chronic kidney disease. Curr Hypertens Rep 2010;12:378–83.
70. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA. Autonomic neuropathy is linked to nocturnal hypoxaemia and to concentric hypertrophy and remodelling in dialysis patients. Nephrol Dial Transplant 2001;16:70–7.
71. Carpio C, Alvarez-Sala R, García-Río F. Epidemiological and pathogenic relationship between sleep apnea and ischemic heart disease. Pulm Med 2013;2013:405827.
72. Turek NF, Ricardo AC, Lash JP. Sleep disturbances as nontraditional risk factors for development and progression of CKD: review of the evidence. Am J Kidney Dis 2012;60:823–33.
73. Ursavas A, Karadag M, Gullulu M, et al. Low-grade urinary albumin excretion in normotensive/non-diabetic obstructive sleep apnea patients. Sleep Breath 2008;12:217–22.
74. Abdel-Kader K, Dohar S, Shah N, et al. Resistant hypertension and obstructive sleep apnea in the setting of kidney disease. J Hypertens 2012 30:960–6.
75. Di Murro A, Petramala L, Cotesta D, et al. Renin-angiotensin-aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism. J Renin Angiotensin Aldosterone Syst 2010;11:165–72.
76. Parati G, Ochoa JE, Bilo G, et al. Obstructive sleep apnea syndrome as a cause of resistant hypertension. Hypertens Res 2014;37:601–13.
77. Fanfulla F, Grassi M, Taurino AE, D'Artavilla Lupo N, Trentin R. The relationship of daytime hypoxemia and nocturnal hypoxia in obstructive sleep apnea syndrome. Sleep 2008;31:249–55.
78. Eckardt KU, Bernhardt WM, Weidemann A, et al. Role of hypoxia in the pathogenesis of renal disease. Kidney Int Suppl 2005;99:S46–51.
79. Palm F, Nordquist L. Renal tubulointerstitial hypoxia: cause and consequence of kidney dysfunction. Clin Exp Pharmacol Physiol 2011;38:474–80.
80. Nangaku M. Hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. Nephron Exp Nephrol 2004;98:e8–12.
81. Evans RG, Goddard D, Eppel GA, O'Connor PM. Factors that render the kidney susceptible to tissue hypoxia in hypoxemia. Am J Physiol Regul Integr Comp Physiol 2011;300:R931–40.
82. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol 2006;17:17–25.
83. Tang R, Yang C, Tao JL, et al. Epithelial-mesenchymal transdifferentiation of renal tubular epithelial cells induced by urinary proteins requires the activation of PKC-α and βI isozymes. Cell Biol Int 2011;35:953–9.
84. Legrand M, Mik EG, Johannes T, Payen D, Ince C. Renal hypoxia and dysoxia after reperfusion of the ischemic kidney. Mol Med 2008;14:502–16.
85. Ahmed SB, Ronksley PE, Hemmelgarn BR, et al. Nocturnal hypoxia and loss of kidney function. PLoS One 2011;6:e19029.
86. López-Novoa JM, Martínez-Salgado C, Rodríguez-Peña AB, López-Hernández FJ. Common pathophysiological mechanisms of chronic kidney disease: therapeutic perspectives. Pharmacol Ther 2010;128:61–81.
87. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle aged adults. N Engl J Med 1993;328:1230–5.
88. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 2001;19:2271–7.
89. Wolk R, Shamsuzzaman AS, Somers VK. Obesity, sleep apnea, and hypertension. Hypertension 2003;42:1067–74.
90. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
91. Tsioufis C, Thomopoulos C, Dimitriadis K, et al. Association of obstructive sleep apnea with urinary albumin excretion in essential hypertension: a cross-sectional study. Am J Kidney Dis 2008;52:285–93.
92. Nicholl DD, Hanly PJ, Poulin MJ, et al. Evaluation of continuous positive airway pressure therapy on renin-angiotensin system activity in obstructive sleep apnea. Am J Respir Crit Care Med 2014;190:572–80.

93. Ritz E, Amann K, Fliser D. The sympathetic nervous system and the kidney: its importance in renal diseases. Blood Press Suppl 1998;3:14–9.
94. DiBona GF. Nervous kidney. Interaction between renal sympathetic nerves and the renin-angiotensin system in the control of renal function. Hypertension 2000;36:1083–8.
95. Grisk O, Rettig R. Interactions between the sympathetic nervous system and the kidneys in arterial hypertension. Cardiovasc Res 2004;61:238–46.
96. Schlaich MP, Socratous F, Hennebry S, et al. Sympathetic activation in chronic renal failure. J Am Soc Nephrol 2009;20:933–9.
97. Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. Kidney Int 2004;65:1568–76.
98. Bradley TD, Floras JS. Sleep apnea and heart failure: Part I: Obstructive sleep apnea. Circulation 2003;107:1671–8.
99. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. J Hypertens 1997;15:1613–9.
100. Solin P, Kaye DM, Little PJ, Bergin P, Richardson M, Naughton MT. Impact of sleep apnea on sympathetic nervous system activity in heart failure. Chest 2003;123:1119–26.
101. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897–904.
102. Hakim F, Gozal D, Kheirandish-Gozal L. Sympathetic and catecholaminergic alterations in sleep apnea with particular emphasis on children. Front Neurol 2012;3:7.
103. O'Driscoll DM, Horne RS, Davey MJ, et al. Increased sympathetic activity in children with obstructive sleep apnea: cardiovascular implications. Sleep Med 2011;12:483–8.
104. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. Circulation 1999;100:2332–5.
105. Betteridge DJ. What is oxidative stress? Metabolism 2000;49:3–8.
106. Cheng J, Wang F, Yu DF, Wu PF, Chen JG. The cytotoxic mechanism of malondialdehyde and protective effect of carnosine via protein cross-linking/mitochondrial dysfunction/reactive oxygen species/MAPK pathway in neurons. Eur J Pharmacol 2011;650:184–94.
107. Forbes JM, Coughlan MT, Cooper ME. Oxidative stress as a major culprit in kidney disease in diabetes. Diabetes 2008;57:1446–54.
108. Tucker PS, Dalbo VJ, Han T, Kingsley MI. Clinical and research markers of oxidative stress in chronic kidney disease. Biomarkers 2013;18:103–15.
109. Galle J. Oxidative stress in chronic renal failure. Nephrol Dial Transplant 2001;16:2135–7.
110. Yamauchi M, Kimura H. Oxidative stress in obstructive sleep apnea: putative pathways to the cardiovascular complications. Antioxid Redox Signal 2008;10:755–68.
111. da Rosa DP, Forgiarini LF, Baronio D, Feijó CA, Martinez D, Marroni NP. Simulating sleep apnea by exposure to intermittent hypoxia induces inflammation in the lung and liver. Mediators Inflamm 2012;879419.
112. Büchner NJ, Quack I, Woznowski M, Stähle C, Wenzel U, Rump LC. Microvascular endothelial dysfunction in obstructive sleep apnea is caused by oxidative stress and improved by continuous positive airway pressure therapy. Respiration 2011;82:409–17.
113. Petrosino T, Serafini M. Antioxidant modulation of F2-isoprostanes in humans: a systematic review. Crit Rev Food Sci Nutr 2014;54:1202–21
114. Montuschi P, Corradi M, Ciabattoni G, Nightingale J, Kharitonov SA, Barnes PJ. Increased 8-isoprostane, a marker of oxidative stress, in exhaled condensate of asthma patients. Am J Respir Crit Care Med 1999;160:216–20.
115. Bauer J, Ripperger A, Frantz S, Ergün S, Schwedhelm E, Benndorf RA. Pathophysiology of isoprostanes in the cardiovascular system: implications of isoprostane-mediated thromboxane A2 receptor activation. Br J Pharmacol 2014;171:3115–31.
116. Basu S, Helmersson J. Factors regulating isoprostane formation in vivo. Antioxid Redox Signal 2005;7:221–35.
117. Badr KF, Abi-Antoun TE. Isoprostanes and the kidney. Antioxid Redox Signal 2005;7:236–43.
118. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. 8-Isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy. Chest 2003;124:1386–92.
119. Brenner BM1, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int 1996;49:1774–7.
120. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol 2012;8:293–300.
121. 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;107:317–22.
122. Koga S, Ikeda S, Yasunaga T, Nakata T, Maemura K. Effects of nasal continuous positive airway pressure on the glomerular filtration rate in patients with obstructive sleep apnea syndrome. Intern Med 2013;52:345–9.
123. Tagaito Y, Polotsky VY, Campen MJ, et al. A model of sleep-disordered breathing in the C57BL/6J mouse. J Appl Physiol 2001;91:2758–66.
124. Badran M, Ayas N, Laher I. Insights into obstructive sleep apnea research. Sleep Med 2013;15:485–95.
125. Cai J, Tuong CM, Zhang Y, et al. Mouse intermittent hypoxia mimicking apnoea of prematurity: effects on myelinogenesis and axonal maturation. J Pathol 2012;226:495–508.
126. Almendros I, Wang Y, Becker L, et al. Intermittent Hypoxia-induced changes in tumor-associated macrophages and tumor malignancy in a mouse model of sleep apnea. Am J Respir Crit Care Med 2014;189:593–601.
127. Sun W, Yin X, Wang Y, et al. Intermittent hypoxia-induced renal antioxidants and oxidative damage in male mice: hormetic dose response. Dose Response 2013;11:385–400.
128. Markou N, Kanakaki M, Myrianthefs P, et al. Sleep-disordered breathing in nondialyzed patients with chronic renal failure. Lung 2006;184:43–9.
129. 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.
130. Kanbay A, Buyukoglan H, Ozdogan N, et al. Obstructive sleep apnea syndrome is related to the progression of chronic kidney disease. Int Urol Nephrol 2012;44:535–9.

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