

Central Sleep Apnea in Renal and Endocrine Disease



Kimihiko Murase, MD, PhD^a, Owen D. Lyons, MBBChBAO, MCPI^{b,c,d,e,*}

KEYWORDS

• Central sleep apnea • Chronic kidney disease • Hypervolemia • Acromegaly • Hypothyroidism

KEY POINTS

- Central sleep apnea (CSA) is prevalent, though often under-recognized, in conditions such as chronic kidney disease (CKD) and endocrine conditions such as acromegaly and hypothyroidism.
- End-stage renal disease (ESRD) is characterized by fluid overload predisposing to ventilatory control instability and CSA, while in acromegaly and hypothyroidism, changes in hormonal status can lead to direct effects on ventilatory control stability, predisposing to CSA.
- The presence of CSA in CKD may have a negative impact on kidney function mediated through the actions of intermittent hypoxia on the kidney medulla.
- In CKD and ESRD, optimization of fluid volumes through more intensified renal replacement therapy can attenuate CSA severity.
- In acromegaly and hypothyroidism, biochemical correction of the underlying hormonal imbalance can abolish CSA.

INTRODUCTION

Central sleep apnea (CSA) is a disorder characterized by a lack of drive to breathe during sleep. Rare in the general population, it is most commonly seen in patients with heart failure, but is also prevalent, though often under-recognized, in conditions such as chronic kidney disease (CKD), acromegaly and to a lesser extent hypothyroidism. CKD, especially end-stage renal disease (ESRD), similar to heart failure, is characterized by fluid overload, which can predispose to ventilatory control instability and subsequent development of CSA, while in endocrine diseases such as acromegaly and hypothyroidism, changes in hormonal and biochemical status can lead to direct effects on ventilatory control stability, predisposing to

CSA. While there is a relative paucity of data compared to obstructive sleep apnea (OSA), there is evidence to suggest CSA may have an impact on morbidity and mortality in CKD, driven by the deleterious impact of intermittent hypoxia on kidney pathology. This article aims to review the prevalence, pathophysiology, diagnosis, and treatment of CSA in these disparate conditions.

DEFINITIONS AND DIAGNOSIS

CKD, defined by a glomerular filtration rate (GFR) less than 60 mL/minute/1.73 m² or the presence of pathologic evidence of kidney damage with a preserved GFR for ≥ 3 months.

ESRD, an advanced form of CKD, occurs when kidney function has deteriorated to an extent that

^a Department of Advanced Medicine for Respiratory Failure, Kyoto University Graduate School of Medicine, Kyoto University, Kyoto, Japan; ^b Department of Medicine, University of Toronto, Toronto, Canada; ^c Department of Medicine, Women's College Hospital, Toronto, Canada; ^d Women's College Research Institute, Toronto, Canada; ^e Sleep Research Laboratory, KITE-UHN, Toronto, Canada

* Corresponding author. Division of Respiriology, Women's College Hospital, 76 Grenville Street, Toronto, Ontario M5S 1B2, Canada.

E-mail address: owen.lyons@wchospital.ca

Abbreviations	
AHI	apnea–hypopnea index
ASV	adaptive servo-ventilation
BPAP	bilevel positive airways pressure
CAPD	continuous ambulatory peritoneal dialysis
CHD	conventional hemodialysis
CKD	chronic kidney disease
CSA	central sleep apnea
ESRD	end-stage renal disease
GFR	glomerular filtration rate
GH	growth hormone
IGF-1	insulin-like growth factor-1
NHD	nocturnal hemodialysis
NPD	nocturnal peritoneal dialysis
ODI	oxygen desaturation index
OR	odds ratio
OSA	obstructive sleep apnea
PSG	polysomnography
RRT	renal replacement therapy

renal replacement therapy (RRT) in the form of chronic dialysis or transplant is required.

GFR, mathematically derived entity based on patient’s serum creatinine, age, sex, and race, calculated by using one of several validated formulas.

Acromegaly, a rare disorder caused by the excessive production of growth hormone (GH), typically from a benign pituitary adenoma, after skeletal growth is complete. It results in the gradual enlargement of bones, cartilage, organs, and soft tissues, particularly in the hands, feet, and face.

Hypothyroidism, a disorder in which the thyroid gland does not produce sufficient thyroid hormones (T3 and T4), usually due to an issue with the thyroid gland itself or more rarely due to pituitary or hypothalamic failure.

Apnea, defined as the absence of tidal volume for at least 10 seconds. *Hypopnea*, defined as a decrease in the tidal volume of 30% for at least 10 seconds that is accompanied by at least a 3% decrease in oxygen saturation or is terminated by an arousal from sleep, as measured on overnight polysomnography (PSG).¹

Obstructive or Central: Apneas are classified as obstructive if they are accompanied by inspiratory effort against the occluded pharynx, and central if they are not. Hypopneas are classified as obstructive if there are signs of upper airway flow limitation, or central if there are no such signs.

Apnea–hypopnea index (AHI), PSG measurement of sleep apnea severity. It is the average number of apneas and hypopneas per hour of sleep; sleep apnea can be classified as absent (AHI <5), mild (AHI 5–< 15), moderate (AHI 15–< 30) or severe (AHI ≥ 30).²

PaCO₂, the partial pressure of carbon dioxide in arterial blood.

Apnea threshold, the threshold level of PaCO₂ required to stimulate breathing.

CENTRAL SLEEP APNEA AND CHRONIC KIDNEY DISEASE

CKD is very common with 10% to 16% global prevalence.^{3,4} Patients with CKD have increased morbidity and mortality, and this worsens as kidney function declines. ESRD in particular is associated with very high mortality, morbidity, and increased use of health care resources.^{5,6} Compared to the general population, patients with CKD have a high prevalence of sleep-related breathing disorders including both OSA and CSA. In contrast to OSA which is characterized by repetitive pharyngeal collapse during sleep, CSA is characterized by a lack of drive to breathe during sleep,^{7,8} with central apneas and hypopneas arising from complete or partial reductions in central neural outflow to the respiratory muscles during sleep.^{1,2}

The presence of sleep apnea in CKD has been associated with poor sleep quality, poor quality of life, and increased cardiovascular risk, further contributing to the burden of heightened morbidity and mortality. However, although highly prevalent in CKD, sleep apnea, whether obstructive or central, remains under-recognized and under-diagnosed.

Prevalence, Presentation and Diagnosis of Central Sleep Apnea in Chronic Kidney Disease

There are several limitations in our understanding of true prevalence rates of CSA in CKD. Studies to date have been heterogenous in terms of the patient cohorts studied and also in the type of diagnostic tool used to diagnose sleep apnea, varying from in-lab PSG to a variety of different home sleep study diagnostic devices. Many research studies fail to differentiate between obstructive and CSA, instead using nonspecific terminology such as *sleep apnea* or *sleep-disordered breathing*. Further complicating this issue is that in patients with CKD there is significant night-to-night variability in both overall sleep apnea severity but also the predominant type of sleep apnea, obstructive or central, particularly in patients on dialysis, in whom there is marked night-to-night variability in fluid volume status. The implication of this is that a traditional one-night sleep study may not accurately capture the true burden of disease. It is estimated that compared to the general population, in which the

prevalence of CSA is less than 1%, the prevalence of CSA is high in CKD is $\sim 10\%$.^{9,10} Furthermore, central events and mixed apneas are also commonly seen in CKD patients with predominantly obstructive events, and thus classified as OSA, and the prevalence rates of moderate–severe OSA in CKD range from 25% to 57% depending on the severity of the underlying kidney disease.^{11–15} The increased prevalence of CSA in CKD is not explained by age or comorbidities, suggesting that the underlying kidney disease itself might be the main cause.^{12,16,17}

The presence of CSA in CKD/ESRD is often not clinically apparent. Similar to heart failure patients with CSA, typical symptoms are of sleep fragmentation and daytime fatigue/tiredness rather than overt excessive sleepiness.^{18,19} These symptoms are common and nonspecific in CKD patients, who often have other sleep disorders, such as restless legs syndrome and/or insomnia, which along with comorbid disease such as anemia and the underlying kidney disease itself, can lead to poor sleep and daytime tiredness, masking the presence of CSA.^{20–22} It is not surprising therefore that there are no prediction scores or questionnaires to help identify the potential presence of CSA in CKD. Given the high prevalence of CSA and the fact it may not be clinically apparent, it has been suggested that diagnostic testing with overnight PSG should be considered in all patients with CKD, particularly in more advanced stages of disease.

Pathophysiology of Central Sleep Apnea in Chronic Kidney Disease

A growing body of evidence supports the concept of a bidirectional relationship between sleep apnea and CKD, in that the presence of OSA, and possibly CSA, can contribute to an accelerated decline in kidney function in patients with CKD, and in the later stages of disease, ESRD contributes to the pathogenesis of both OSA and CSA.

Central sleep apnea as a risk factor for worsening kidney function

There is a substantial body of evidence to support the role of OSA in accelerating decline in kidney function, through various pathophysiological mechanisms including intermittent hypoxia, increased negative intrathoracic pressure swings, and cortical arousals leading to sympathetic nervous system activation, hypertension, inflammation, oxidative stress and activation of the renin–angiotensin–aldosterone system.^{23–30} CSA does not lead to increased negative intrathoracic pressure swings, given that central apneas/hypopneas occur in the presence of a patent airway,

and is not associated with the same degree of cortical arousals as OSA, however, it does lead to intermittent hypoxia. While CSA is far less prevalent than OSA in the earlier stages of CKD, its presence can lead to worsening kidney function, mediated through intermittent hypoxia, which is of particular importance given the susceptibility of the kidney medulla to hypoxia.^{23,31} While the kidneys receive about 25% of cardiac output, renal oxygen tension is relatively low due to low renal oxygen consumption. Intermittent hypoxia has been shown, in animal models of sleep apnea, to lead to kidney injury with histologic damage, characterized by glomerular hypertrophy, mesangial matrix expansion and increased cellular apoptosis.³² Intermittent hypoxia has also been shown to activate the renin–angiotensin system in animal and human studies.^{30,33,34} This in turn can lead to increased hypertension, hyperfiltration, and renal inflammation and fibrosis, leading to worsening CKD.³⁵

In a prospective cross-sectional study of 7700 individuals from the European Sleep Apnea Database cohort the overnight minimum oxygen saturation was found to be an independent predictor of the presence of CKD, with a 2% higher probability of CKD for every unit decrease in the minimum oxygen saturation.³⁶ Another prospective study of more than 800 patients that followed changes in GFR over 2 years, of whom approximately 20% had CKD at baseline, showed that those with hypoxia (defined as $\geq 12\%$ of the recording time with oxygen saturation $< 90\%$) had a higher risk (odds ratio [OR]) 2.89 (1.25–6.67) of rapid loss of kidney function (that is, estimated glomerular filtration rate [eGFR] decline $\geq 4\text{ ml/minute/1.73 m}^2$ per year) after adjustment for sleep apnea severity and other recognized risk factors for CKD progression.³⁷ In a study of 161 patients with stage 3 to 4 CKD, GFR decline was 3- to 4-fold faster in patients with a 4% oxygen desaturation index (ODI) ≥ 15 compared with those with a 4% ODI less than 15, after adjustment for confounders.³⁸

The role of chronic kidney disease/end-stage renal disease in the pathogenesis of central sleep apnea

Pathophysiological mechanisms related to the underlying CKD/ESRD that can lead to CSA include hypervolemia, altered chemosensitivity and possibly uremia-induced myopathy (Fig. 1).

While it has been postulated that uremia-induced neuropathy or myopathy may play a role in the pathogenesis of both OSA and CSA, there are actually very little data regarding their role in the pathogenesis of CSA in ESRD. Uremic

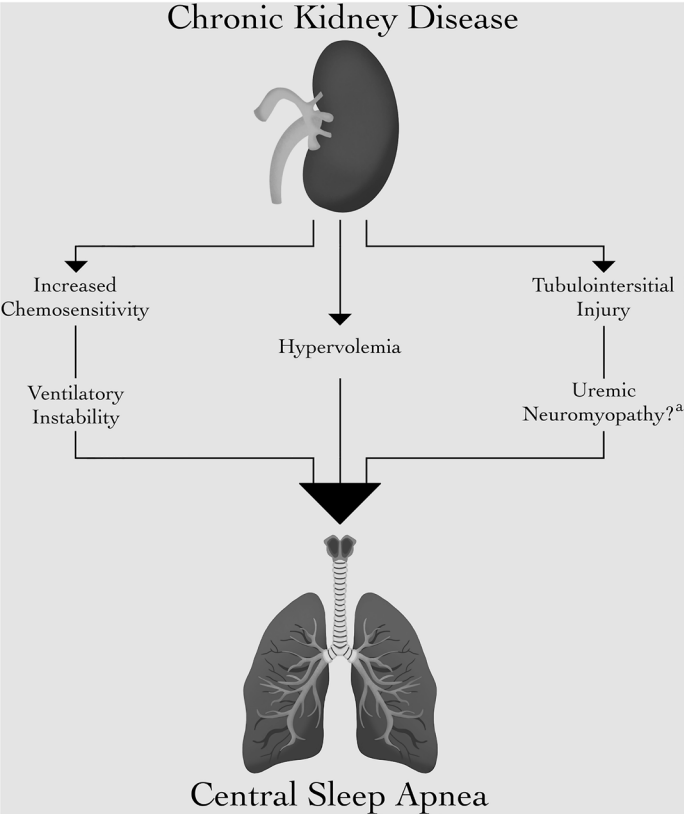


Fig. 1. Pathophysiological mechanisms promoting CSA in patients with ESRD. In CSA, the upper airway remains patent. ESRD-associated hypervolemia can lead to pulmonary congestion, similar to what is observed in heart failure, another condition in which CSA is common. This congestion leads to alterations in chemical feedback loop mechanisms to the respiratory center, which can in turn trigger cycles of hyperventilation alternating with central apneas or hypopneas. ^aWhile it has been postulated that uremic neuromyopathy may play a role in pathogenesis of sleep apnea, there is little data to support this.

myopathy increases fatigability of the respiratory muscles, including the diaphragm.³⁹ However, while this may contribute to a degree of hypoventilation it is not clear whether it leads to CSA and as such the concept of the role of uremic myopathy in the pathogenesis of CSA remains a hypothesis.

There is, however, a substantial body evidence to support the role of hypervolemia and altered chemosensitivity in the pathogenesis of both OSA and CSA in ESRD, similar to as in heart failure, which is also characterized by fluid overload and high prevalence of both types of sleep apnea.^{40–42} Central apneas occur during sleep when the PaCO₂ decreases to less than the apnea threshold. Similar to heart failure patients with CSA who chronically hyperventilate causing hypocapnia with PaCO₂ closer to the apnea threshold than normal,^{43,44} it has been shown that ESRD patients with CSA also have low-normal PaCO₂.⁴⁵ During sleep, any transient increase in ventilation for any reason, for example, an arousal, leads to a decrease in the PaCO₂ below the apnea threshold causing a central apnea. Fluid overload and nocturnal rostral fluid shift from the legs contributes to accumulation of fluid in the neck and chest.^{40–42} Fluid accumulation in

the lungs stimulates pulmonary irritant receptors causing chronic hyperventilation and leading to CSA by promoting cycles of hyperventilation and apnea.^{42,46}

The role of hypervolemia in the pathogenesis of CSA in CKD is supported by findings from observational studies. In a cross-sectional study of patients with CKD who were not receiving dialysis and had a body mass index of 24 ± 3.9 kg/m², brain natriuretic peptide levels and cardiothoracic ratio were significantly higher in those with severe sleep apnea than in those without sleep apnea.⁴⁷ Among patients with ESRD on conventional hemodialysis (CHD), those with moderate–severe sleep apnea had a greater total body extracellular fluid volume (>2 L) than those with mild or no sleep apnea and in a multivariate analysis, the total body extracellular fluid volume was the only factor that was independently and directly associated with sleep apnea severity (r = 0.47, P = .002).¹² Other studies have shown that interdialytic weight gain greater than 2 kg and the degree of fluid overload posthemodialysis are independent predictors of sleep apnea severity in patients with ESRD on CHD.^{48,49} Increased ventilatory sensitivity to hypercapnia has also been shown

to correlate with CSA severity in patients with ESRD.⁵⁰ Furthermore, transition from CHD to nocturnal hemodialysis (NHD) reduced ventilatory sensitivity, which was associated with a decrease in CSA severity.⁵¹

Impact of Central Sleep Apnea on Morbidity and Mortality in Chronic Kidney Disease/End-stage Renal Disease

The evidence base linking CSA with morbidity and mortality in CKD is quite limited.

One prospective study of 180 patients with CKD followed over 9 years, in whom just more than half had ESRD, showed that although sleep apnea severity, as measured by AHI, was not associated with increased mortality when adjusted for confounders, measures of overnight hypoxic burden—a higher proportion of sleep time with oxygen saturation less than 90% and lower mean oxygen saturation—were significantly associated with higher mortality hazard ratio (HR), 1.4; 95% confidence interval (CI), 1.1–1.7; $P = .007$ for every 15% higher proportion of time with low oxygen saturation, and HR, 1.6; 95% CI, 1.2–2.1; $P = .003$ for every 2% lower mean oxygen saturation).⁵² In a recent large retrospective cohort study of the United States Renal Data system, of more than 600,000 patients, the presence of CSA was associated with an increased risk of stroke (adjusted relative risk [aRR] 1.69, 95% CI = 1.28–2.23) and increased mortality (adjusted hazard ratio [aHR] 1.42, 95% CI 1.29–1.56) though the methodology likely led to under-recognition of the presence of CSA with a reported prevalence of only 0.1%.^{53,54}

Treatment of Central Sleep Apnea in Chronic Kidney Disease

Positive airway pressure (PAP) therapy for central sleep apnea in chronic kidney disease

There is a paucity of evidence-based guidelines to inform treatment of CSA in CKD or ESRD. A meta-analysis of 8 studies, that included patients with both OSA and CSA, treated with continuous positive airway pressure (CPAP), bilevel positive airways pressure (BPAP) or adaptive servo-ventilation (ASV) showed no overall change in GFR before and after PAP treatment in patients with sleep apnea.⁵⁵ However, in a subgroup analysis of the data, longer PAP usage duration and increased age were associated with significant improvements in GFR.⁵⁵ There are no CKD-specific data to guide treatment of CSA for subjective improvement in terms of sleep quality or overall quality of life. Recent 2025 American Academy of Sleep Medicine (AASM) guidelines

on treatment of CSA reflect the lack of evidence, with conditional recommendations based on low certainty evidence for the use of CPAP or ASV for treatment of CSA in CKD, and conditional recommendation based on very low certainty evidence for BPAP with a backup rate.⁵⁶ PAP therapy can be challenging in all patients but can be particularly so in CKD and especially ESRD patients given the burden of their underlying kidney disease, the burden of treatment, and the impact of comorbidities including other sleep disorders such as restless leg syndrome and insomnia.²²

Impact of intensification of renal replacement therapy on central sleep apnea severity

A meta-analysis of 9 studies that evaluated the impact of RRT modality on sleep apnea severity showed that intensive RRT was superior to conventional RRT in AHI reduction (OR 0.66, CI 95% 0.51–0.84, $P < .001$) and sleep quality improvement.⁵⁷ In patients with ESRD, intensification of dialysis treatment, either by conversion from CHD to NHD, or from continuous ambulatory peritoneal dialysis (CAPD) to nocturnal peritoneal dialysis (NPD), has been shown to reduce sleep apnea severity.^{58,59} In a study of 14 patients with ESRD on thrice-weekly CHD, conversion to NHD reduced AHI from 25 ± 25 to 8 ± 8 ($P = .03$).⁵⁸ While fluid volumes were not measured in this study, a more recent study evaluated the impact of fluid removal on sleep apnea severity using ultrafiltration. The study included 15 individuals on CHD with moderate–severe sleep apnea (including OSA and CSA) and showed a 36% reduction in AHI after fluid removal during a single ultrafiltration session with average volume removed of 2.2 L. Uremic and metabolic status were unchanged.⁴⁵ In those subjects with CSA, the AHI decreased by 40% from 60.4 ± 16.7 to 36.0 ± 19.1 ($P = .003$). The study also showed a correlation between AHI reduction and the decrease in total body fluid volume ($r = 0.567$; $P = .027$) and a reduction in thoracic fluid volume of approximately 500 mL ($P < .001$) postultrafiltration as measured by bioelectrical impedance. Furthermore transcutaneous CO₂ levels also normalized with the decrease in fluid volume, suggesting a decrease in respiratory drive and possibly improved ventilatory stability.⁴⁵ In a study of patients with ESRD on CAPD, conversion to NPD led to a reduction in prevalence of sleep apnea from 33.3% to 4.2%, in association with a reduction in total body water from 35.1 ± 7.35 L to 32.8 ± 7.37 ($P = .004$), further highlighting the important role of hypervolemia in the pathogenesis of sleep apnea ESRD.

Summary

CSA is far more common in CKD than the general population and its presence has potential significant impact for morbidity and mortality, mediated through intermittent hypoxia. As CKD progresses, CSA is even more common, underpinning the concept of a bidirectional relationship between the disorders, with hypervolemia playing an important role in CSA pathogenesis. Given the increased prevalence of CSA in CKD and its potential impact on outcomes, there should be a low threshold to proceed with diagnostic testing for CSA in this population. While PAP therapy still plays an important role in terms of treatment options there are practical barriers to adherence. Optimization of fluid volume status by conversion to NHD or NPD can attenuate sleep apnea severity, in some cases obviating the need for PAP therapy.

CENTRAL SLEEP APNEA AND HYPOTHYROIDISM

Hypothyroidism is a relatively common endocrine disorder with prevalence rates of biochemical (subclinical) hypothyroidism occurring in 4% to 5% of the population, with overt clinical hypothyroidism occurring in 0.3%–0.4%.⁶⁰ It is a disorder in which the thyroid gland does not produce sufficient thyroid hormones (T3 and T4), usually due to an issue with the thyroid gland itself or more rarely due to pituitary or hypothalamic failure. OSA occurs in approximately 20% to 25% of patients with hypothyroidism, thought to be possibly due to narrowing of the upper airway secondary to deposition of mucopolysaccharides and protein extravasation into the tissues, while CSA is far less common and is associated with more severe cases, which were more common historically than currently.^{61,62}

Thyroid hormones are important to ensure normal sensitivity of chemoreceptors and deficiency of thyroid hormones may manifest with blunted ventilatory responses, with subsequent correction of the deficiency with exogenous thyroxine leading to normalization of the ventilatory response and attenuation of CSA severity.^{61–63} Interestingly, women seem to be more vulnerable to the effect of hypothyroidism on ventilatory drive.⁶²

CENTRAL SLEEP APNEA AND ACROMEGALY

Acromegaly is a rare endocrine disorder, with reported prevalence of 122 cases/10⁶ persons. It is caused by excessive secretion of GH and insulin-like growth factor-1 (IGF-1), usually from a benign pituitary hormone⁶⁴ and results in the

gradual enlargement of bones, cartilage, organs, and soft tissues, particularly in the hands, feet, and face. Soft tissue hypertrophy in the upper airway can lead to OSA, and the prevalence of OSA is reported to be as high as 60%.^{65–67} Interestingly, CSA, though less common than OSA, is prevalent and has been reported to occur in 5% to 10% of cases.⁶⁸ It has been shown that acromegalic patients with CSA have increased GH and IGF-1 levels compared with their counterparts with OSA.⁶⁸ Furthermore, measures of ventilatory responsiveness correlate with GH levels.⁶⁸ It is thought that GH and IGF-1 directly sensitize the central chemoreceptors leading to ventilatory instability. Identification of CSA in patients with acromegaly is important as it is a condition associated with increased cardiovascular risk of hypertension, arrhythmias and cardiomyopathy. Biochemical control of acromegaly with either surgical resection or somatostatin analogs may lead to a reduction in CSA severity. If there is persistence of CSA, PAP therapy with CPAP or ASV can be used.⁵⁶

SUMMARY

CSA is often under-recognized in endocrine conditions such as acromegaly and hypothyroidism. In both conditions, hormonal changes seem to play a role in leading to ventilatory instability and subsequent CSA. While relatively rare, the presence of CSA is associated with poorer outcomes in these conditions. While biochemical correction of the underlying hormonal imbalance with surgery or medication often leads to a resolution of CSA, PAP therapy can be considered if CSA persists.

CLINICAL CARE POINTS

- Given the increased prevalence of CSA in CKD and its potential impact on morbidity and mortality, clinicians should have a low threshold for screening for its presence.
- PAP therapy plays an important role in treatment of CSA but in patients with CKD/ESRD, adherence to treatment can be a problem due to the impact of co-morbid disease, insomnia and other factors.
- Before considering PAP therapy for treatment of CSA in ESRD, consideration should be given to optimization of fluid volume status by intensification of dialysis, which may obviate the need for PAP therapy.
- While CSA is rare in endocrine diseases, clinicians should be aware that its presence can be associated with increased mortality.

REFERENCES

- Berry RB, Brooks R, Gamaldo CE, et al, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Version 2.4, 2017, American Academy of Sleep Medicine. *J Clin Sleep Med* 2017;13(5):665–6.
- AASM. 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;22:667–89. <https://doi.org/10.1378/chest.97.1.27>.
- Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* (London, England) 2013;382:260–72.
- Xie Y, Bowe B, Mokdad AH, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int* 2018;94:567–81.
- Daratha KB, Short RA, Corbett CF, et al. Risks of subsequent hospitalization and death in patients with kidney disease. *Clin J Am Soc Nephrol* 2012;7:409–16.
- Klarenbach SW, Tonelli M, Chui B, et al. Economic evaluation of dialysis therapies. *Nat Rev Nephrol* 2014;10:644–52.
- Yumino D, Bradley TD. Central sleep apnea and Cheyne-Stokes respiration. *Proc Am Thorac Soc* 2008;5:226–36.
- Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* (London, England) 2014;383:736–47.
- Donovan LM, Kapur VK. Prevalence and characteristics of central compared to obstructive sleep apnea: analyses from the sleep heart health study cohort. *Sleep* 2016;39:1353–9.
- Nigam G, Pathak C, Riaz M. A systematic review of central sleep apnea in adult patients with chronic kidney disease. *Sleep Breath* 2016;20:957–64.
- Nicholl DDM, Ahmed SB, Loewen AHS, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. *Chest* 2012;141:1422–30.
- Lyons OD, Inami T, Perger E, et al. The effect of fluid overload on sleep apnoea severity in haemodialysis patients. *Eur Respir J* 2017;49:1601789. <https://doi.org/10.1183/13993003.01789-2016>.
- Roumelioti ME, Buysse DJ, Sanders MH, et al. Sleep-disordered breathing and excessive daytime sleepiness in chronic kidney disease and hemodialysis. *Clin J Am Soc Nephrol* 2011;6:986–94.
- Markou N, Kanakaki M, Myrianthefs P, et al. Sleep-disordered breathing in nondialyzed patients with chronic renal failure. *Lung* 2006;184:43–9.
- 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.
- Unruh ML, Sanders MH, Redline S, et al. Sleep apnea in patients on conventional thrice-weekly hemodialysis: Comparison with matched controls from the sleep heart health study. *J Am Soc Nephrol* 2006;17:3503–9.
- Beecroft JM, Pierratos A, Hanly PJ. Clinical presentation of obstructive sleep apnea in patients with end-stage renal disease. *J Clin Sleep Med* 2009;5:115–21.
- Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998;97:2154–9.
- Bradley TD, Floras JS. Sleep apnea and heart failure: part II: central sleep apnea. *Circulation* 2003;107:1822–6.
- Sekercioglu N, Curtis B, Murphy S, et al. Sleep quality and its correlates in patients with chronic kidney disease: a cross-sectional design. *Ren Fail* 2015;37:757–62.
- Unruh ML, Hartunian MG, Chapman MM, et al. Sleep quality and clinical correlates in patients on maintenance dialysis. *Clin Nephrol* 2003;59:280–8.
- Lyons OD. Sleep disorders in chronic kidney disease. *Nat Rev Nephrol* 2024;20:690–700.
- Sun W, Yin X, Wang Y, et al. Intermittent hypoxia-induced renal antioxidants and oxidative damage in male mice: hormetic dose response. *Dose Response* 2012;11:385–400.
- Brooks D, Horner RL, Kozar LF, et al. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Investig* 1997;99:106–9.
- Horner RL, Brooks D, Kozar LF, et al. Immediate effects of arousal from sleep on cardiac autonomic outflow in the absence of breathing in dogs. *J Appl Physiol* 1995;79:151–62.
- Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Investig* 1995;96:1897–904.
- Yokoe T, Minoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 2003;107:1129–34.
- Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 2005;112:2660–7.
- Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive

- oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* 2002;165:934–9.
30. Zalucky AA, Nicholl DDM, Hanly PJ, et al. Nocturnal hypoxemia severity and renin-angiotensin system activity in obstructive sleep apnea. *Am J Respir Crit Care Med* 2015;192:873–80.
 31. Evans RG, Goddard D, Eppel GA, et al. Factors that render the kidney susceptible to tissue hypoxia in hypoxemia. *Am J Physiol Regul Integr Comp Physiol* 2011;300:R931–40.
 32. Abuyassin B, Badran M, Ayas NT, et al. Intermittent hypoxia causes histological kidney damage and increases growth factor expression in a mouse model of obstructive sleep apnea. *PLoS One* 2018;13:e0192084. <https://doi.org/10.1371/journal.pone.0192084>.
 33. Fletcher EC, Bao G, Li R. Renin activity and blood pressure in response to chronic episodic hypoxia. *Hypertension* 1999;34:309–14.
 34. Foster GE, Hanly PJ, Ahmed SB, et al. Intermittent hypoxia increases arterial blood pressure in humans through a Renin-Angiotensin system-dependent mechanism. *Hypertension* 2010;56:369–77.
 35. Hanly PJ, Ahmed SB. Sleep apnea and the kidney: is sleep apnea a risk factor for chronic kidney disease? *Chest* 2014;146:1114–22.
 36. Marrone O, Battaglia S, Steiropoulos P, et al. Chronic kidney disease in European patients with obstructive sleep apnea: the ESADA cohort study. *J Sleep Res* 2016;25:739–45.
 37. Ahmed SB, Ronksley PE, Hemmelgarn BR, et al. Nocturnal hypoxia and loss of kidney function. *PLoS One* 2011;6:e19029. <https://doi.org/10.1371/journal.pone.0019029>.
 38. Sakaguchi Y, Hatta T, Hayashi T, et al. Association of nocturnal hypoxemia with progression of CKD. *Clin J Am Soc Nephrol* 2013;8:1502–7.
 39. Tarasuk A, Heimer D, Bark H. Effect of chronic renal failure on skeletal and diaphragmatic muscle contraction. *Am Rev Respir Dis* 1992;146:1383–8.
 40. Elias RM, Chan CT, Paul N, et al. Relationship of pharyngeal water content and jugular volume with severity of obstructive sleep apnea in renal failure. *Nephrol Dial Transplant* 2013;28:937–44.
 41. 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;27:1569–73.
 42. Yumino D, Redolfi S, Ruttanaumpawan P, et al. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. *Circulation* 2010;121:1598–605.
 43. Naughton M, Benard D, Tam A, et al. Role of hyper-ventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis* 1993;148:330–8.
 44. Hanly P, Zuberi N, Gray R. Pathogenesis of Cheyne-Stokes respiration in patients with congestive heart failure. Relationship to arterial PCO₂. *Chest* 1993;104:1079–84.
 45. Lyons OD, Chan CT, Yadollahi A, et al. Effect of ultra-filtration on sleep apnea and sleep structure in patients with end-stage renal disease. *Am J Respir Crit Care Med* 2015;191:1287–94.
 46. Anastassov GE, Trieger N. Edema in the upper airway in patients with obstructive sleep apnea syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;86:644–7.
 47. Tanaka A, Inaguma D, Ito E, et al. Factors associated with severity of sleep apnoea syndrome in patients with chronic kidney disease. *Acta Cardiol* 2017;72:440–5.
 48. Harmon RR, De Lima JGG, Drager LF, et al. Obstructive sleep apnea is associated with interdialytic weight gain and increased long-term cardiovascular events in hemodialysis patients. *Sleep Breath* 2018;22:721–8.
 49. Ogna A, Forni Ogna V, Mihalache A, et al. Obstructive sleep apnea severity and overnight body fluid shift before and after hemodialysis. *Clin J Am Soc Nephrol* 2015;10:1002–10.
 50. Beecroft J, Duffin J, Pierratos A, et al. Enhanced chemo-responsiveness in patients with sleep apnoea and end-stage renal disease. *Eur Respir J* 2006;28:151–8.
 51. Beecroft JM, Duffin J, Pierratos A, et al. Decreased chemosensitivity and improvement of sleep apnea by nocturnal hemodialysis. *Sleep Med* 2009;10:47–54.
 52. Jhamb M, Ran X, Abdalla H, et al. Association of sleep apnea with mortality in patients with advanced kidney disease. *Clin J Am Soc Nephrol* 2020;15:182–90.
 53. Acree L, Waller J, Bollag W, et al. Sleep apnea in end-stage renal disease patients: impact on cardiovascular and neurological outcomes. *J Postgrad Med* 2024;70:36–42.
 54. Prabu P, Acree L, Waller JL, et al. Sleep apnea in end-stage renal disease patients: risk factors and mortality. *J Investig Med* 2023;71:465–70.
 55. Chen LD, Lin L, Ou YW, et al. Effect of positive airway pressure on glomerular filtration rate in patients with sleep-disordered breathing: a meta-analysis. *Sleep Breath* 2017;21:53–9.
 56. Badr MS, Khayat RN, Allam JS, et al. Treatment of central sleep apnea in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2025;21:2181–91.
 57. Kennedy C, Ryan SA, Kane T, et al. The impact of change of renal replacement therapy modality on sleep quality in patients with end-stage renal disease: a systematic review and meta-analysis. *J Nephrol* 2018;31:61–70.

58. 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.
59. Tang SC, Lam B, Ku PP, et al. Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 2006;17:2607–16.
60. Wyne KL, Nair L, Schneiderman CP, et al. Hypothyroidism prevalence in the United States: a retrospective study combining national health and nutrition examination survey and claims data, 2009-2019. *J Endocr Soc* 2022;7:bvac172. <https://doi.org/10.1210/jeendo/bvac172>.
61. Millman RP, Bevilacqua J, Peterson DD, et al. Central sleep apnea in hypothyroidism. *Am Rev Respir Dis* 1983;127:504–7.
62. Ladenson PW, Goldenheim PD, Ridgway EC. Prediction and reversal of blunted ventilatory responsiveness in patients with hypothyroidism. *Am J Med* 1988;84:877–83.
63. Zwillich CW, Pierson DJ, Hofeldt FD, et al. Ventilatory control in myxedema and hypothyroidism. *N Engl J Med* 1975;292:662–5.
64. Aagaard C, Christophersen AS, Finnerup S, et al. The prevalence of acromegaly is higher than previously reported: changes over a three-decade period. *Clin Endocrinol* 2022;97:773–82.
65. Colao A, Ferone D, Marzullo P, et al. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 2004;25:102–52.
66. Davi MV, Dalle Carbonare L, Giustina A, et al. Sleep apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. *Eur J Endocrinol* 2008;159:533–40.
67. Vannucci L, Luciani P, Gagliardi E, et al. Assessment of sleep apnea syndrome in treated acromegalic patients and correlation of its severity with clinical and laboratory parameters. *J Endocrinol Investig* 2013;36:237–42.
68. Grunstein RR, Ho KY, Berthon-Jones M, et al. Central sleep apnea is associated with increased ventilatory response to carbon dioxide and hypersecretion of growth hormone in patients with acromegaly. *Am J Respir Crit Care Med* 1994;150:496–502.