Sleep Apnea as a Cardiorenal Risk Factor in CKD and Renal Transplant Patients

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Key Messages

- In CKD patients, the prevalence of SA parallels the severity of renal dysfunction.
- SA in predialysis CKD and in ESKD patients predicts a high risk for cardiovascular disease and death.
- Volume expansion is the main factor underlying SA in these populations.
- Renal transplantation is the most effective treatment of SA in ESKD, but this disturbance re-emerges on long-term observation in these patients.

Keywords

Sleep apnea · Chronic kidney disease · End-stage kidney disease · Cardiovascular risk · Chronic kidney disease progression · Mortality

Abstract

Background: Chronic kidney disease (CKD) is a public health priority of increasing concern worldwide. Sleep apnea (SA) of moderate-to-severe degree has a 3–9% prevalence in women and 10–17% in men in the general population. **Summary:** In CKD patients, the prevalence of SA parallels the decline of the GFR being 27% in CKD patients with a GFR of >60 mL/min/1.73 m² and 57% in patients with end-stage kidney disease (ESKD). In the early CKD stages, fluid overload is probably the sole risk factor for SA in this population. At more severe CKD stages, disturbed central and peripheral chemosensitivity and the accumulation of uremic toxins might contribute to SA. Still, there is no direct evidence supporting this hypothesis in human studies. Observational studies coherently show that SA is a risk factor for CKD inci-

dence and CKD progression as well as for cardiovascular disease and death in this population. However, there is no randomized clinical trial testing continuous positive airway pressure or other interventions documenting that attenuation of SA may have a favorable effect on renal and cardiovascular outcomes in CKD and ESKD patients. However, most likely, the causal nature of the association between SA and cardiorenal outcomes remains unproven. Renal transplantation is the most effective treatment of SA in patients with ESKD, but this disturbance re-emerges on long-term observation in this population. However, after renal transplantation, SA does not seem to be a predictor of adverse health outcomes.

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Introduction

Chronic kidney disease (CKD) is a public health priority of increasing concern [1], and projections to 2040 by the global burden of disease study rank CKD as the 5th

Fig. 1. Two typical examples of central and obstructive apneas. Central apnea is characterized by the lack of respiration (no airflow in the 1st trace and no thoracic and abdominal excursions in traces 3 and 4) and by a decline in O₂ saturation (last trace). Obstructive apnea is characterized by a decline in O₂ saturation simultaneous with amplified thoracic and abdominal excursions underlying a respiratory effort against an obstructed upper airway.

cause of death on a world scale [2]. Demographic and socioeconomic factors play a major role in the ascendancy of CKD among chronic noncommunicable diseases.

Sleep apnea (SA) is a condition characterized by episodes of hypoxia, sleep fragmentation, and excessive daytime sleepiness which impacts working activities and increases the risk for road traffic accidents. Studies at population level show that 3–9% of women and 10–17% of men have a moderate-to-severe SA [3]. Furthermore, SA – particularly the obstructive type – is much frequent in obesity and type 2 diabetes [4], which are the 2 most common causal risk factors for CKD [1], and sleep apnea is exceedingly frequent in the CKD population [5].

In this narrative review, we describe the SA phenotype and the pathophysiology of this condition in CKD and end-stage kidney disease (ESKD) patients. We then focus on the evidence that SA is a risk for CKD and cardiovascular disease as well as mortality in the same population. We conclude by discussing new data about the evolution of SA after renal transplantation, which is the most effective treatment of SA in ESKD.

Sleep Apnea Phenotype in CKD and ESKD Patients

In a study based on polysomnography and the relationship between renal function and SA, the prevalence of moderate-to-severe SA in CKD patients was 27% in CKD patients with a GFR of >60 mL/min/1.73 m² and 57% in patients with ESKD [6]. Polysomnographic studies allow the subdivision of SA into 3 types: obstructive (OSA), central (CSA), and mixed (MSA). OSA is characterized by intermittent narrowing or obstruction of the oropharynx and/or of the hypopharynx. CSA is diagnosed when there is no airway obstruction and is typified by the lack of inspiratory effort during apneic episodes (Fig. 1). OSA and CSA episodes coexist in some patients as MSA. In a meta-analysis of 8 studies by Nigam et al. [7], the prevalence of CSA among CKD patients was 9.6%. However, this estimate was highly variable (between 0 and 75%) among the 8 studies. In a well-designed epidemiologic survey in 6 hemodialysis centers in Switzerland [8], the prevalence of CSA was 4% which is close to an estimate (7%) made by Beecroft in a Canadian hemodialysis unit [9]. The average

Fig. 2. Risk factors for cardiovascular disease and for CKD in sleep apnea (see main text). (↑), increase; (↓), decrease; NO, nitric oxide; CKD, chronic kidney disease.

number of CSA episodes in 45 hemodialysis patients in a multicenter study in Western Pennsylvania did not exceed that in a well-matched sample of the general population [10]. Overall, OSA largely outweighs CSA both among predialysis and dialysis patients.

Pathophysiology and Risk Factors of Sleep Apnea in CKD and in ESKD Patients

In the early CKD stages, fluid overload – an alteration present in about 40% of hypertensive patients with mild-to-severe CKD [11] – is probably the sole risk factor for SA in this population. Fluid redistribution during supine overnight resting from the legs to the rostral parts of the body is an essential factor contributing to SA in diseases associated with volume expansion [12]. Pharyngeal and hypopharyngeal edema during sleep engenders or aggravates the obstruction of the upper airway, thereby triggering or worsening SA. Stage 1–3 CKD patients with resistant hypertension and SA manifest a significant reduction of the apnea-hypopnea index (AHI) after diuretic therapy, which goes along with the overnight change in leg fluid volume [13]. At more severe stages of CKD, other causal factors may contribute to the propensity to SA in these patients. In theory, uremic neuropathy might in-

crease the collapsibility of the upper airway during sleep [14]. Increased central and peripheral chemosensitivity may destabilize respiratory control in hemodialysis patients [9]. The accumulation of uremic toxins has been implicated in SA in ESKD patients, but there is no direct evidence supporting this hypothesis. Fluid overload is more common in hemodialysis patients than in CKD patients. Thus, the relevance of fluid overload in the pathogenesis of SA in ESKD cannot be overemphasized [15, 16], and this risk factor is the sole well-established causal risk factor for SA in the ESKD population.

Repeated episodes of airway occlusion in OSA and interruption of respiration in CSA trigger cycles of hypoxemia (low % O₂ saturation) and carbon dioxide retention. Cyclical hypoxemia and hypercapnia impinge upon cardiac parasympathetic and sympathetic activity [17]. Hypoxemia increases sympathetic tone and activates the renin-angiotensin-aldosterone system. On the other hand, oxidative stress, inflammation, and hypercholesterolemia (see below) reduce nitric oxide (NO) bioavailability via the endogenous NO inhibitor asymmetric dimethylarginine [18]. These effects eventually raise blood pressure and heart rate also beyond the nocturnal sleep [17]. The prevalence of hypertension in SA is about 50, and 83% of patients with treatment-resistant hypertension are affected by SA [19]. Sympathetic overactivity surges and the consequenc-

es of these alterations, including hypertension, insulin resistance, and endothelial dysfunction, have multiple detrimental effects on the cardiovascular system [20] and the kidney [21]. SA impinges upon cardiovascular and renal health by an overlapping set of risk factors (Fig. 2). Furthermore, the relationship between SA and renal function is bidirectional because the eGFR is reduced among individuals with SA, particularly in those with CSA [22].

Sympathetic overactivity and its sequels, apart other relevant mechanisms in SA, are implicated in cardiovascular and renal damage. Hypoxemia augments free radical production and alters endothelial function [23]. Furthermore, oxidative stress increases vascular smooth muscle proliferation and platelet activation and aggregation [24], which generate a risky milieu for the vascular system [25] whose effects extend to the kidney [26].

As alluded to before, insulin resistance is a well-established consequence of sympathetic overactivity [27]. Insulin resistance is a hallmark in obesity and diabetes, 2 conditions also characterized by high sympathetic activity [28, 29]. However, the link between this alteration and OSA is largely independent of obesity [30] and type 2 diabetes [31]. While the metabolic effects of insulin resistance – including hyperglycemia, dyslipidemia, and other abnormalities – are central to the proatherogenic milieu in diabetes and obesity, the same alteration in itself does not directly damage the arterial wall [32].

The effect of SA on the cardiovascular system is also mediated by the mechanical and neuroendocrine consequences of this alteration. In purely mechanical terms, excessive negative pleural and intrathoracic pressures during inspiration against an obstructed upper airway reduce right atrial pressure which, in turn, augments venous return to the heart [33]. Because the function of the 2 ventricles is strictly interrelated, the increase in right ventricular end-diastolic volume by the increased venous return determines a reduction in left ventricular stroke volume. On the other hand, excessive reduction in intrathoracic pressure during inspiration increases ventricular transmural pressure and consequently ventricular afterload [34]. Repeated episodes of nocturnal hypoxemia by OSA and CSA cause pulmonary vasoconstriction and arrhythmia and reduce by a direct mechanism of ventricular contractility and diastolic relaxation [27]. High aldosterone secondary to the activation of the renin-angiotensin system triggered by sympathetic overactivity, the increased left ventricular afterload, and wall stress, coronary heart disease and the amplification of the risk of myocardial infarction [35], and pulmonary vasoconstriction all concur to more than double the risk for heart failure in SA [36].

Sleep Apnea as a Cardiorenal Risk Factor

Heart failure, coronary heart disease, and arrhythmia [37] are the main factors underlying the high risk for cardiovascular events and death, including sudden death, in patients with SA [38]. Furthermore, independently of hypertension and other risk factors, SA per se doubles the risk for incident stroke [39]. Even though the association between SA and the risk for cardiovascular events is robust, the causal nature of these associations remains uncertain. A recent meta-analysis of intervention trials in patients with SA failed to show a benefit of continuous positive airway pressure (CPAP) on the incidence of these events [40]. However, to adequately investigate this fundamental question, large, long-term studies warranting adequate CPAP adherence are needed, which makes such studies very hard to perform.

As alluded to before, SA is traditionally held as a risk factor for incident CKD and CKD progression [41]. Full et al. [42] have recently re-examined the incident risk for CKD by SA in the 1,525 participants in the Atherosclerosis Risk in Communities (ARIC) study who completed in-home polysomnography assessments. In this study, during 19 years of follow-up, the presence of severe OSA adjusted for demographics and lifestyle behaviors predicted a 51% excess risk of incident CKD (stage 3 or higher). However, this excess risk attenuated to a mere, non-significant, 7% after adjustment for body mass index. On the other hand, in a Canadian study in 858 adults referred for diagnostic testing for SA, the presence of nocturnal hypoxemia predicted a 2.89 higher risk of accelerated renal function loss after adjustment for potential confounders, including the BMI. In chronic obstructive pulmonary disease, hypoxemia goes along with glomerular hyperfiltration [43]. In 2 relatively small studies in OSA patients, nocturnal hypoxemia associated with hyperfiltration and CPAP improved this alteration [44, 45]. A recent meta-analysis of 6 cross-sectional studies and 2 retrospective case-control studies, including 8,795 participants, underlined the strong association between OSA and CKD [5]. However, the nature of this link (causal vs. noncausal) remains uncertain. Obesity is a strong confounder for the interpretation of the incident risk of CKD by OSA in the general population [42]. Studies investigating the relationship between OSA and CKD progression rate are too small to allow definitive conclusions. Until now, just 1 randomized clinical trial tested the effect of CPAP on renal function, a substudy of the SAVE (Sleep Apnea Cardiovascular Endpoints) trial [46]. In this substudy, CPAP did not modify the rate of

eGFR loss or the urinary albumin-to-creatinine ratio. Furthermore, CPAP adherence did not influence either of these renal outcomes.

The Risk of Death and Cardiovascular Events of Sleep Apnea in CKD and ESKD Patients

The first study describing a link between SA as measured by nocturnal pulse oximetry and cardiovascular events in ESKD patients is now 20 years old [47]. Nocturnal hypoxemia alters the circadian BP profile [48] and associates with altered sympathovagal balance [49] and concentric left ventricular hypertrophy [50] in ESKD. Very sparse evidence, summarized in a meta-analysis by Tang et al. [51], shows that patients with CKD and various sleep disorders (including SA, periodic limb movement, or altered sleep duration/quality) have a 47% excess risk of death. In a recent cohort study based on polysomnography in 180 stage 4–5 CKD patients (92 on dialysis), nocturnal hypoxemia, but not the AHI, associated with the risk of death independently of other risk factors, including the BMI [52]. In a study in 558 incident hemodialysis patients (average age, 56 years) in the Baltimore area, past diagnosis of SA was associated with a higher risk of sudden death in analyses adjusted for demographics factors, comorbidities, and BMI but not with all-cause or cardiovascular mortality. In contrast, an extensive study in elderly patients (average age, 77 years) with a past diagnosis of SA initiating dialysis in the USA ($n = 15,121$), SA was weakly associated with lower, rather than higher, risk of death and cardiovascular events [53]. A weakness of these 2 studies based on administrative databases is the fact that the past diagnosis of SA was not confirmed with a new polysomnographic study after starting regular dialysis treatment. The causal nature of the association between SA and mortality and cardiovascular disease in predialysis CKD and ESKD patients remains much uncertain because no randomized clinical trial tested the effect of interventions targeting SA on these outcomes in this population.

Treatment of Sleep Apnea in CKD and ESKD Patients and the Evolution of Sleep Apnea after Renal Transplantation

CPAP is the golden standard treatment of SA. As discussed, treatment of fluid overload mitigates SA in stage 1–3 CKD patients with SA and resistant hypertension

[13] and the association between rostral volume shift has been confirmed in hemodialysis patients [16]. Of note, long nocturnal hemodialysis [54] and long, cyclical-assisted, nocturnal peritoneal dialysis [51] – two treatments that facilitate fluid overload removal – both improve SA in ESKD patients. Restored renal function after transplantation corrects fluid overload, uremic toxicity, and other factors. However, at 5 years posttransplantation, about 1/3 of renal transplant patients are again volume expanded [55], and there is a surge of obesity posttransplantation [56]. A recent long-term longitudinal study registered a progressive worsening of SA, which went along with the increase in BMI in renal transplant patients [57]. Furthermore, analyses in the database of the same study showed that independently of Framingham risk factors and the BMI and the GFR, repeated measures of the AHI were directly associated with 24-h, daytime and nighttime systolic BP. Thus, SA is per se a risk factor for hypertension in renal transplant patients [58].

Lubas et al. [59] investigated the relationship between SA and graft survival time and death with graft loss in a historical cohort, single-center study of 322 renal transplant patients who lost their graft or died with a functioning graft during follow-up. In patients transplanted between 2009 and 2017, SA was associated with a 2.61 higher risk of a composite endpoint (graft loss or cardiovascular-related death with a functioning graft). In contrast, an opposite association (a 37% risk reduction) was observed during the first decade of observation (1997–2008). Misclassification of SA during the first decade was very likely, and therefore, this study remains substantially inconclusive. In a study in 822 renal transplant patients based on the Berlin questionnaire, a weak surrogate marker of SA [60], a high score of this questionnaire predicted graft loss in women but not in men [61]. Another cohort study, including 100 renal transplant recipients, found no association between SA and adverse clinical outcomes, including mortality and the rate of GFR loss [62]. In another study, including 404 renal transplant patients with a pretransplantation diagnosis of SA and 117 with a de novo diagnosis of SA posttransplantation, this alteration failed to predict mortality and graft loss [63]. Renal denervation mitigates OSA [64], but no study has tested the effect of this intervention on SA in CKD and in ESKD patients.

For this reason, the apparent lack of harmful effects of SA posttransplantation has been attributed to the denervation of the transplanted kidneys [62, 63] or a highly hypothetical ischemic preconditioning effect of apneic episodes [63]. Overall, the critical question of whether SA

predicts adverse clinical outcomes in renal transplant patients needs extensive, well-designed, long-term cohort studies based on polysomnography. Whether SA is harmful in renal transplant patients remains an unresolved question.

Conclusions

In CKD patients, the prevalence of SA parallels the severity of renal dysfunction and predicts a high risk for cardiovascular disease and death. Volume expansion is the main factor underlying SA in this population. Renal transplantation is the most effective treatment of SA in ESKD, but this disturbance re-emerges on long-term observation in these patients.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Carmine Zoccali planned the review and made the literature search. He wrote the first version of the review. The other authors added additional scientific information and gave suggestions for improving the clarity of the manuscript. All authors approved the final version of the manuscript.

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