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SLEEP AND SLEEP APNEA AT THE EXTREMES (D GOZAL, SECTION EDITOR)

Sleep Apnea and the Kidney

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Abstract

Purpose of Review There are some uncertainties about the interactions between obstructive sleep apnea (OSA) and chronic kidney disease (CKD). We critically reviewed recent studies on this topic with a focus on experimental and clinical evidence of bidirectional influences between OSA and CKD, as well as the effects of treatment of either disease.

Recent Findings Experimental intermittent hypoxia endangers the kidneys, possibly through activation of inflammatory pathways and increased blood pressure. In humans, severe OSA can independently decrease kidney function. Treatment of OSA by CPAP tends to blunt kidney function decline over time, although its effect may vary. OSA may increase cardiovascular complications and mortality in patients with end-stage renal disease (ESRD), while it seems of little harm after renal transplantation. Excessive fluid removal may explain some of the improvements in OSA severity in ESRD and after transplantation.

Summary Severe OSA and CKD do interact negatively, mainly through hypoxia and fluid retention. The moderate mutually interactive benefits that treatment of each disease exerts on the other one warrant further studies to improve patient management.

Keywords Sleep-disordered breathing · Renal function · Hemodialysis · Kidney transplantation · CPAP

Introduction

Both obstructive sleep apnea (OSA) and chronic kidney disease (CKD) are common in the general population [1, 2]. An interrelationship between the two diseases is increasingly recognized, but interdisciplinary approaches to their treatment are highly variable, since both are usually managed by different medical specialists. Despite the fact that the evidence gathered from clinical and epidemiological observations conducted so far still leave some room to uncertainty about independent interrelations between OSA and CKD, there is a large body of biological data that support the plausibility of these interactions.

On the one hand, OSA is associated with intermittent hypoxemia, increased blood pressure and sympathetic activity, obesity, and metabolic alterations [3], all of which may endanger renal integrity and lead to increased albumin excretion and accelerated decline in glomerular filtration rate (GFR) over time. These mechanisms could lead to an increased incidence of CKD and to a more rapid trajectory towards end-stage renal disease (ESRD) in OSA patients. On the other hand, uremia and metabolic acidosis associated with renal dysfunction may increase chemoreceptor reactivity and destabilize breathing patterns, predisposing patients to both obstructive and central apnea. Besides, fluid retention due to inefficient glomerular filtration may be followed by rostral fluid shift when assuming a recumbent posture, leading to decreased cross-sectional pharyngeal area and obstructive apneas, or, particularly in patients with cardiac disease, to interstitial lung edema, hyperventilation, and central apneas [4].

Nowadays, the attention of physicians managing patients with OSA is mainly directed to symptoms and possible cardiovascular complications, and to a much lesser extent to the possible kidney involvement. Actually, the importance of addressing renal effects of OSA is not entirely clear. Renal consequences of OSA are less known than cardiovascular complications. Besides, direct evidence of the independent detrimental effects of untreated OSA, and of benefits of OSA

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treatment, on the kidneys is less strong compared to data obtained in animal experiments. As nephrologists are concerned, screening and treatment of OSA in CKD and ESRD have not entered general clinical practice yet.

In this review, we summarize recent data obtained in animal models on the pathogenesis of CKD in OSA, highlight the current evidence that may support a direct influence of OSA on kidney function, and try to account for the uncertainties and contradictory interpretations found in the current literature. In addition, we will examine the clinical implications of sleep-disordered breathing (SDB) in patients with renal disease, paying particular attention to those with ESRD or receiving transplantation. We will illustrate the present knowledge on the effects of dialysis and transplantation on SDB, as well as of OSA treatment on kidney function, which are topics still requiring extensive investigation.

Evidence of Renal Damage in Experimental Models of OSA

OSA typically causes intermittent hypoxia (IH) during sleep. Several studies in mouse and rat models assessed the impact of IH on the kidney. A major advantage of animal models is the possibility to study the effects of IH without the confounding variables occurring in human OSA, but the IH models do not provide data on the effects of intermittent hypercapnia associated with IH in OSA. One study assessed the effects of IH and IH associated with hypercapnia and suggested a possible protective effect of CO_2 on inflammatory markers, but duration of exposure was short, warranting further study [5•].

Acute exposures to IH caused minimal or no pathological changes and increased renal blood flow and GFR [6]. Conversely, chronic IH was associated with evidence of glomerular and tubular damage [6, 7]. The pathological findings included an increase in glomerular area, expansion of mesangial matrix, and increased apoptosis [7, 8]. As for functional changes, increased albuminuria [7] and reduced renal flow, GFR, and sodium transport were found after chronic IH exposures [6].

The molecular mechanisms involved in IH-induced renal injury are complex, with involvement of several pathways, such as the receptor for advanced glycation end-product (RAGE) [9] and its ligand, the high-mobility group box 1 protein (HMGB1) [5, 9], toll-like receptor 4 (TLR-4) [10], oxidative stress [11•] and the NLRP3 inflammasome [12]. Blockade of such pathways resulted in decreased tubular damage, collagen deposition and apoptosis, lower release of inflammatory cytokines, and blunted albuminuria [9, 10, 11•, 12].

Chronic IH exposure causes hypertension in rodents [8, 13]. The studies on kidney function did not always monitor blood pressure during chronic IH, raising the question about the confounding contribution of hypertension to kidney damage. In a complex experimental model of alanine-induced CKD followed by exposure to chronic IH, blocking endothelin (ET)-a and ET-b receptors prevented hypertension but not tissue injury [14••]. Conversely, Angiotensin 1–7, which counters the effect of Angiotensin-2, was found to blunt the effects of chronic IH on renal sympathetic activity, inflammation, and fibrosis [8]. Moreover, recent studies in which telmisartan and losartan were administered during chronic IH exposure suggested protective effects of these drugs on kidney injury [15, 16]. More studies are clearly needed to understand to what extent IH-induced kidney damage may be at least partly mediated by hypertension.

Epidemiology of the Association Between OSA and CKD

Despite unquestionable evidence of risk factors for CKD in OSA, the presence of confounders makes an independent link between the two conditions difficult to demonstrate in human patients. These confounders include advanced age, obesity, and especially comorbidities like arterial hypertension and diabetes mellitus. Therefore, one important requirement for epidemiological studies on OSA and CKD is a large sample of subjects in order to adjust for multiple confounders. In addition, ideally, the sample sizes of subjects with CKD, OSA (from mild to severe), and healthy controls should be adequately balanced, which is difficult to obtain. In fact, studies performed in general population samples, while showing little or no selection bias in subjects' recruitment, predominantly included healthy subjects, and the few OSA patients in the sample had a mild disease with little nocturnal hypoxemia. Conversely, studies on patients with suspected OSA included subjects with worse risk factors for CKD and more severe hypoxemia, with higher probability to show significant effects of OSA on renal function, but low applicability of results to the general population.

In the last several years, large epidemiological studies have been published. Among recent cross-sectional studies on the general population, a significant increase in the prevalence of SDB, considered as apnea/hypopnea index (AHI) $\geq$ 15/h of total sleep time (hrTST), was observed from non-CKD to CKD stages 1–2 to CKD stage 3 subjects in the HypnoLaus cohort in Swtizerland; however, CKD stage and estimated GFR (eGFR) quartile did not independently predict SDB [17]. The other available cross-sectional study observed a significant effect of AHI on CKD prevalence but, unsurprisingly, no effect of nocturnal hypoxemia: in fact, hypoxia among the recruited subjects was very mild [18•]. The longitudinal study on the general population in the Wisconsin cohort found that both the decline in eGFR and CKD incidence were similar in subjects with and without sleep apnea. However, patients with

sleep apnea, defined as AHI ≥ 15/hrTST, were few (90/855 subjects) and oxygen saturation values were not reported [19].

Among investigations on subjects with suspected sleep apnea, one longitudinal study demonstrated that an increased rate of decline in eGFR occurred when ≥ 12% of sleep time was spent with oxygen saturation (SaO_2) < 90% [20••], a threshold uncommon in significant proportions of subjects of general population samples. Accordingly, a multicenter cross-sectional study on a sleep laboratory population found that lowest nocturnal SaO_2 independently predicted eGFR < 60 ml/min/m^2 [21•]. Both these studies did not find any independent effect of AHI as a risk factor for CKD.

Finally, some recent longitudinal studies analyzed data taken from registries, with the advantage of including very large number of patients with diagnosed sleep apnea and controls. Common pitfalls of these studies are that no polysomnographic data were available, and information on continuous positive airway pressure (CPAP) prescription, when available, was not associated with data on actual CPAP use. Nevertheless, these studies agreed that OSA is likely to be a risk factor for the kidneys since it was associated with faster annual decline in eGRF [22•] and higher incidence of CKD [23–25] and of ESRD [26•].

Altogether, most epidemiological studies support an independent association between OSA and CKD. This association primarily involves patients with severe OSA, while it is much more uncertain for mild cases of sleep apnea. So far, attention has been paid mainly to the possible importance, as risk markers, of classic polysomnographic variables, i.e., AHI and hypoxemia parameters. Future studies may explore roles of other factors that are often altered in OSA, like 24-h blood pressure profile or insulin sensitivity.

Sleep Apnea and ESRD

Sleep apnea is common in patients with CKD, and its prevalence progressively increases with CKD severity [27]. Patients with ESRD show the highest prevalence, possibly because in ESRD, some risk factors for SDB, such as fluid retention and high chemoresponsiveness, are more common and severe than in milder CKD. ESRD patients with OSA have higher BMI and neck circumference than those without OSA [28–30], but they are thinner compared to typical OSA patients seen in sleep laboratories, and more rarely report typical OSA symptoms, like heavy snoring or excessive daytime sleepiness [31–33]. ESRD patients report poor sleep quality, but periodic leg movements [34] rather than SDB [35, 36] likely play a role.

However, several observations suggest that sleep apnea may be detrimental also in patients with ESRD (Table 1). One effect of occurrence of SDB in ESRD may be an overnight decrease in systolic and diastolic myocardial function [37••], as already observed in patients with heart failure [38]. Improvement of SDB, obtained with reduction in body fluids by plasma ultrafiltration, may blunt such deterioration [37••]. Recent studies have shown that, in the long term, OSA may increase cardiovascular and all-cause mortality in middle-aged ESRD patients [39, 40]. This effect was not demonstrated in older patients who, rather the opposite, showed a lower risk of all-cause death, myocardial infarction, and ischemic stroke when they had been diagnosed with OSA [41]. This is in agreement with observations in other populations reporting a lower coronary and mortality risk, if not an advantage, in elderly OSA patients [42, 43]. Mortality risk in middle-aged ESRD patients was related to nocturnal hypoxemia, and not to AHI [40], as already found in a previous small study [44].

Fluid Overload, Dialysis, and Sleep-Disordered Breathing

Rostral shift of fluids when assuming the recumbent posture has been identified as an important determinant of apnea in patients with ESRD. In these patients, overnight change in leg fluid volume correlated with apnea/hypopnea time in acute studies [45]. Over an average 8-month time period, it was observed that remission of nephrotic syndrome was associated with a reduction in AHI that was attributed to remission of limb edema [46]. Two more recent studies found that patients with a high AHI had a higher extracellular fluid volume in non-dialysis days [47] and a higher interdialytic weight gain [48].

Patients undergoing hemodialysis acutely reduce fluid retention and, at the same time, remove uremic toxins thus improving their metabolic status. Interestingly, if in a non-dialysis day ESRD patients are submitted to plasma ultrafiltration, leading to fluid removal without alterations in acid base balance or plasma metabolic components, their AHI decreases proportionally to the reduction in extracellular fluid volume [49•]. Such data strongly support a major role of fluid removal as responsible for the beneficial effect of dialysis on SDB. However, only minor, non-significant changes in AHI have been reported between nights preceding and following dialysis [28, 32, 50••]. One recent study showed that changes in obstructive AHI after dialysis were correlated to changes in fluid overload but confirmed that the average difference in AHI between nights before and after dialysis was not significant [51].

Different results have been reported with a stable change in dialysis regimen. After transition from conventional (three-diurnal sessions per week) to nocturnal (six nights per week) [50••], as well as from continuous ambulatory peritoneal dialysis to nocturnal dialysis [52], AHI significantly improved, with decrease in both central and obstructive apneas. Nocturnal dialysis, besides better reverting physiological perturbations of uremia [53], more effectively decreases sympathetic activity than conventional dialysis [54]. The lower

Table 1 Recent studies on effects of sleep apnea in patients with end stage renal disease (ESRD)

Authors	No. of subjects recruited	Sleep apnea diagnosis	No. of subjects with OSA	Follow-up duration	Outcomes
Tuohy et al. [41]	184,217 patients ≥ 67 years old starting hemodialysis	Diagnosis based on ICD-9 criteria in the 2 years before starting hemodialysis	15,121 SDB	Mean 1.6 years	SDB associated with lower risk of all-cause death, myocardial infarction and ischemic stroke; no effect on atrial fibrillation
Kerns et al. [39]	558 incident hemodialysis patients, mean age 56	Chart reviews of clinical medical records available in the year prior to dialysis initiation	66 OSA	Mean 23.2 months	OSA associated with all-cause and cardiovascular mortality and with sudden cardiac death
Inami et al. [37••]	15 ESRD patients	Polysomnography	6 OSA 2 CSA	1 day (evening to morning, and night pre-post plasma ultrafiltration)	Sleep apnea associated with overnight decrease in systolic and diastolic function in ESRD; improved SDB after body fluid removal
Jhamb et al. [40]	Stage 4–5 CKD ($n = 88$) and ESRD ($n = 92$), mean age 54	Polysomnography	45 mild 42 moderate 41 severe predominantly obstructive sleep apnea	Median 9 years	Relationships of mortality with nocturnal hypoxemia, but not with AHI

sympathetic activity could be associated with a greater decrease in chemoresponsiveness, which, in turn, could contribute to the improvement in SDB [55].

Children on dialysis show poor sleep quality [56–58] and prevalence of sleep-disordered breathing is estimated around 40% [56, 59]. One study reported higher AHI in patients compared to controls [58], but another study in children on automatic peritoneal dialysis found mild SDB in children with ESRD [57]. In summary, positive effects of dialysis on SDB in adult patients with ESRD are likely, but their mechanisms and the effects of pediatric ESRD are still incompletely understood.

Kidney Transplant and Sleep Apnea

After kidney transplantation, reversal of uremia and fluid overload could be expected to improve pre-existing sleep apnea. However, inconsistent results have been reported about the effects of transplantation on sleep apnea [60, 61]. Most of the studies were on small case series and did not adequately take into account factors such as OSA severity before transplantation, reduction in fluid overload, or change in body weight after transplantation. One recent, relatively large, controlled study on patients with a pretransplant AHI ≥ 15/hrTST demonstrated that after transplantation, AHI decreased proportionally to the decrease in fluid overload, although an increase in body fat tended to blunt the change in AHI [62••].

Evidence of unfavorable effects of sleep apnea in transplanted patients is scant (Table 2). It relies mainly on a paper showing that subjects transplanted after 2008 who were diagnosed with sleep apnea had a higher risk of graft loss, although their risk of death with functioning graft was not increased [63]. Three other studies, while confirming the lack of any influence of OSA [64, 65•], or risk of OSA [66], on mortality in transplanted patients, did not find any effect of OSA on rate of decline in eGFR [64] or in return to dialysis or retransplantation [65•]. Harmlessness of sleep apnea after transplantation has been hypothesized to be a consequence of the denervation of the transplanted kidneys, which may blunt apnea-induced sympathetic overactivation [64, 65•]. According to another theory, ischemic preconditioning due to recurrent apneas could determine long-term benefits in transplanted patients [65•], as already hypothesized for ischemic cardiac disease [42].

In transplanted children, 61% of the sample showed evidence of OSA that was moderate-severe in 38.5% and associated with uncontrolled hypertension. However, SDB was likely to be overestimated, since prevalence of obesity and metabolic abnormalities tended to be higher in children undergoing PSG compared to children refusing participation to the study [67].

Effects of CPAP Therapy on Kidney Function

CPAP is the therapy of OSA that more fully prevents occurrence of SDB. Its main limitation is related to variable adherence to its use, which leaves some patients incompletely

Table 2 Effects of sleep apnea in patients receiving kidney transplant

Authors	No. of subjects recruited	Sleep apnea diagnosis/ risk	No. of subjects with sleep apnea	Follow-up duration	Outcomes
Szentkiralyi et al. [66]	823 adults	Berlin questionnaire after transplant	226	Median 66 months	OSA risk was associated with graft loss in females, but did not influence all-cause mortality
Fornadi et al. [64]	100 adults	Polysomnography after transplant	18 mild 11 moderate 14 severe	Median 75 months	No effect of AHI or of OSA diagnosis on rate of decline of eGFR or on all-cause mortality and time to death
Lubas et al. [63]	322 adults	Medical records documenting sleep apnea before transplant of after transplant before graft loss	60	Up to 20 years	Sleep apnea did not influence mortality with functioning graft but was associated with higher risk of graft loss in patients transplanted after 2008
Tiwari et al. [65•]	4014 adults	Medical records documenting sleep apnea	415 diagnosed before transplant 117 diagnosed after transplant	Median 6.1 years	No influence of sleep apnea on acute kidney rejection, return to dialysis, re-transplantation or mortality

treated. Its favorable effects on patients' symptomatology are undiscussed, whereas benefits on other health aspects, like cardiovascular and metabolic manifestations, are small and still controversial [68].

CPAP therapy is associated with a reduction in common risk factors for CKD, which could warrant an improvement in kidney function. CPAP prevents nocturnal oxygen desaturations, slightly decreases blood pressure [69], and reduces renal RAS activity [70] and circulating inflammatory markers including IL-18, a marker of acute kidney injury [71].

All uncontrolled studies support a benefit of CPAP on both albumin excretion and GFR. The decrease in albumin excretion was evident in morning, but not in evening, urine samples, suggesting that SDB exerts acute detrimental effects that may be prevented by treatment [72]. Good compliance to CPAP therapy is necessary for a reduction in albuminuria to occur [73, 74]. Small studies addressing GFR consistently found benefits of CPAP therapy, as shown by decreased glomerular hyperfiltration [70, 75], blunted decline in eGFR [76], or even increase in eGFR [77]. One large multicenter cohort study compared changes in eGFR over time in patients who were untreated or treated by auto-CPAP or by fixed CPAP. While in the first two groups, a larger eGFR decline was observed in the patients who had a longer follow-up, eGFR remained substantially unchanged irrespective of follow-up duration in those treated by fixed CPAP. The changes in eGFR after fixed, but not after auto-CPAP, significantly differed from the changes after no OSA treatment [78•]. In contrast, the only RCT published so far on the effects of CPAP reported that mean changes in eGFR over time were small and did not significantly differ between patients under usual care or CPAP treatment [79•]. However, even in this study, a non-significant trend to a better evolution of eGFR with CPAP was observed.

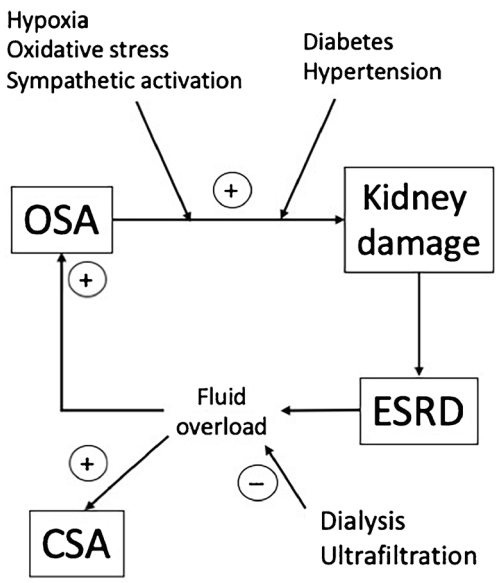

Fig. 1 Summary of the mechanisms by which OSA can worsen chronic kidney disease (CKD) and end-stage renal disease (ESRD) can cause sleep-disordered breathing. OSA: obstructive sleep apnea. CSA: central sleep apnea

A large interindividual difference in changes in eGFR after CPAP, which emerged in different studies [78•, 79•], may make it difficult to clearly demonstrate independent effects of CPAP. Age of the patients, baseline CKD function and OSA severity, duration of follow-up, comorbidities, drug therapies, and type of CPAP treatment are some of the factors that can influence the variability in eGFR time course. Discordant results and highly variable interindividual differences have been also reported for blood pressure changes after CPAP, and only meta-analyses on a high number of studies have been able to consistently demonstrate that CPAP decreases blood pressure, although by a small extent [69]. Similarly, we

believe that a high number of studies with many patients would be necessary to definitely demonstrate benefits of CPAP treatment on kidney function.

Conclusions

Experimental studies underpin the existence of biologically relevant interactions between OSA and CKD. In animals, the role of intermittent hypoxia as a factor endangering kidney function is evident, although it is still unclear to what extent the changes observed in kidney structure and function may be at least partly mediated by underlying increased blood pressure. The results of human studies are summarized in Fig. 1. Epidemiological studies have confirmed the detrimental effect of OSA on kidney function and on prognosis of patients with ESRD, which is more evident when OSA is severe. On the other hand, excessive fluid retention causes or worsens OSA in CKD, especially in ESRD. Many still poorly known factors, in addition to hypoxia and fluid overload, may come into play in the interaction between OSA and CKD, enhancing, or blunting, their effects. Among these factors, blood pressure levels and 24-h profile could have a prominent role, which deserves further careful studies. Effects of treatment of OSA or CKD on the other disease seem on average rather weak. Some confounders and interacting factors that could reduce the benefits of treatment are known, but the effects of OSA therapy remain incompletely understood and poorly predictable. Studies aimed at better understanding the complex effects that dialysis and kidney transplantation may exert on respiratory function during sleep, as well as of the mechanisms through which CPAP influences renal function, would be extremely useful to improve patients' management.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest relevant to the article.

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