Is kidney a new organ target in patients with obstructive sleep apnea? Research priorities in a rapidly evolving field

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Abstract

The bidirectional relationship between sleep disordered breathing and chronic kidney disease (CKD) has gained recently a lot of interest. Several lines of evidence suggest the high prevalence of coexistent obstructive sleep apnea (OSA) in patients with CKD and end-stage renal disease (ESRD). In addition, OSA seems to result in loss of kidney function in some patients, especially in those with cardio-metabolic comorbidities. Treatment of CKD/ESRD and OSA can alter the natural history of each other; still better phenotyping with selection of appropriate treatment approaches is urgently needed. The aim of this narrative review is to provide an update of recent studies on epidemiological associations, pathophysiological interactions, and management of patients with OSA and CKD or ESRD.

Keywords: obstructive sleep apnea, sleep-disordered breathing, chronic kidney disease, end-stage renal disease, positive airway pressure

Introduction

Obstructive sleep apnea (OSA) is characterized by patient inability to maintain upper airway patency during sleep, despite the presence of respiratory efforts, resulting in oxyhemoglobin desaturations, arousals and fragmented sleep architecture [1]. Diagnosis and treatment of obstructive sleep apnea (OSA) are receiving increasing medical attention [2]. Treatment of OSA that results in normalizing sleep stages pattern could reduce the risk of cardiovascular disease (CVD), minimize the effects of OSA on daily activities [3], resulting in the decrease of daytime sleepiness and improvement of patients' quality of life [1]. Efforts have been made to predict the risk of OSA with simple tools in order to discriminate high from low risk patients and thus improve appointment scheduling in sleep laboratories [2]. There is substantial evidence that OSA can be a comorbidity in patients diagnosed with a number of disorders, namely [4-6], but other disorders are frequently found in association with OSA [4], thus suspicion for OSA may arise when managing these diseases [4]. Specifically, there is a growing interest of the bidirectional relationship between OSA and chronic kidney disease (CKD) [7]. Prevalence of moderate-severe OSA is estimated as high as 9% in women and 17% in men aged 50-70 [8], while the prevalence of CKD in the general population is between 11 and 13% [9]. CKD is characterized as kidney damage or decreased kidney function, defined as glomerular filtration rate (GFR)<60 mL/min/1.73 m^2, for at least 3 months irrespective of the cause [10]. Both diseases share common risk factors and are strongly associated comorbidities, such as metabolic syndrome (obesity, systemic hypertension, diabetes, dyslipidemia) and CVD [3,4,7]. For these reasons, these two conditions deserve concurrent medical attention, when evaluating patients having either OSA or CKD [11].

Coexistence of OSA and CKD: Different sides of the same coin

The first reports dated back to 1985 when Millman et al. found that patients with end-stage renal disease (ESRD) showed a high risk for OSA [12]. Since then, a growing body of evidence has been gathered about the association between OSA and CKD from various epidemiological points of view (OSA in CKD, CKD in OSA, OSA in ESRD), and with different study designs (case series, cross-sectional, cohort studies and randomized controlled trials - RCTs), as well as studies on the effects of OSA on renal function in animal models [7,13,14]. Nevertheless, there is significant heterogeneity of the existing studies in terms of outcomes, which often leads to contradictory results. Among studies that assess the risk for CKD or ESRD in OSA, some considered the degree of OSA severity in terms of apnea-hypopnea index (AHI), while others also analyzed the level of nocturnal hypoxemia, namely the time spent with oxyhemoglobin below 90% (TST<90%) or the oxygen desaturation index (ODI). With respect to renal endpoints, most existing studies have investigated the effects of OSA on estimated GFR (as assessed by different formulas, namely the Modification of Diet in Renal Disease-MDRD, the Chronic Kidney Disease Epidemiology Collaboration-CKD-EPI, or the Cockcroft-Gault formula), and on the degree of albuminuria, while recent studies have also attempted to explore latent kidney disease by measurement of serum or urine biomarkers (e.g., Cystatin C, Neutrophil Gelatinase Associated Lipocalin-NGAL, Interleukin-18). Concerning treatment effects of either disease on the course to the other one, the current evidence suggests a beneficial role of nocturnal hemodialysis and peritoneal dialysis on the resolution of apneas and the reduction of AHI [15–18], whereas the role of treatment with positive airway pressure (PAP) in terms of kidney outcomes remains controversial. In the present article, we review the evidence on the

interactions between OSA and kidney disease in the form of questions that have clinical and research relevance in this field.

Are CKD and ESRD considered as risk factors for OSA development?

Accumulating data indicate a higher risk of OSA development in patients with reduced kidney function [19]. Specifically, cross-sectional studies have revealed an increased prevalence of concomitant OSA in both CKD and ESRD populations receiving dialysis [13]. Nicholl and colleagues have found that prevalence of sleep apnea increased alongside eGFR decline, as did also occurrence of nocturnal hypoxia [19]. Additionally, Sakaguchi et al. [20] demonstrated an inverse correlation between eGFR and AHI, after adjusting for confounders (age, body mass index - BMI, eGFR, diabetes, and CVD), and in particular a 10 ml decrease in eGFR increased the odds of having OSA by 42%. In a recent cross-sectional study on US Veterans with CKD stages 3-4 [21], prevalence of OSA was 39%, and age, BMI and diabetes were associated with increased odds of coexistent OSA independently of confounding factors. Several other studies have shown a remarkably high prevalence of OSA ranging from 67% to almost 94% among non-dialyzed patients with CKD [22–24]. With regard to ESRD population, the data on the association with OSA are stronger, and most studies including dialyzed patients, have reported prevalence of concomitant OSA above 50% (ranging from 40% to almost 80%) [8,19,22,25–28]. Interestingly, in a recent meta-analysis, the adjusted odds ratio (OR) for sleep apnea among the CKD and ESRD population was 1.961 (95% CI 1.702–2.260), while male sex, presence of diabetes and lower BMI were independent correlates of coexistent OSA [13]. Concerning BMI paradox, the authors suggested that patients with advanced CKD are often characterized by weight loss and malnutrition

state and thus rostral fluid shift between dialysis sessions could have an important role on the pathophysiology of OSA development.

Finally, prevalence rates of OSA were compared in relation to dialysis treatment. Earlier reports had shown that occurrence of sleep apnea was equally frequent in patients with ESRD, irrespective of the form of dialysis treatment (peritoneal dialysis-PD or hemodialysis-HD) [29,30]. Nonetheless, recent findings contradict this knowledge. Specifically, in a recent retrospective cohort study, male ~~and not female~~ patients on PD showed higher risk of OSA compared those on HD [31]. Possible explanations are the greater intra-abdominal pressure and the poorer ultrafiltration capacity in patients receiving PD [31].

Should clinicians assess kidney function in OSA patients? The role of comorbidities

Clearly, there is no affirmative evidence to support assessment of kidney function in all patients with OSA. Nevertheless, there are several epidemiological studies that attempted to answer this question and explore predictors (e.g., sleep parameters, anthropometrics, comorbidities etc.) that might correlate OSA with loss of kidney function in comparison to non-OSA individuals. Most published data point out on varying degrees of associations between OSA and CKD (defined as eGFR<60 mL/min/1.73m^2 with any CKD formula), and this fact depends, partly, on whether included individuals came from the general population or the sleep laboratories and whether they were studied cross-sectionally, retrospectively or longitudinally [13]. Cross-sectional studies performed in samples from sleep laboratories have shown a higher risk of prevalent CKD in patients diagnosed with OSA compared to those

without sleep apnea [32–34], while others have found increasing prevalence of OSA in line with declining eGFR [~~35,36~~ **34,35**]. Two cross-sectional studies have underscored the associations between OSA related-nocturnal hypoxia and CKD. In the first study, Marrone et al. have shown that minimum oxyhemoglobin saturation during sleep independently predicted prevalent eGFR<60 mL/min/1.73m^2 in a large European cohort of prospectively enrolled patients with suspected OSA [37]. In the other study, evaluating individuals recruited from the MESA cohort, sleep apnea-specific hypoxic burden (which represents an elegant marker of severity of sleep apnea associated hypoxia) was associated with a higher prevalence of moderate to severe CKD [38]. Lastly, prospective studies have additionally underlined the effect of OSA and OSA-related nocturnal hypoxemia on the rapid loss of kidney function. Specifically, Ahmed et al. demonstrated an accelerated decline of kidney function in patients with nocturnal hypoxia , defined as ≥12% of nocturnal monitoring with oxygen saturation <90%, compared to controls without it (OR 2.89; 95% CI 1.25-6.67) [39]. Additionally, several studies recruiting participants from the general population demonstrated varying effects of OSA on kidney function decline [40–44]. In the cross-sectional Hypnolaus cohort study, worsening CKD stage, from no CKD to CKD stage 3, was associated with higher prevalence of moderate to severe sleep disordered breathing (SDB) [40]. However, at multivariate analysis SDB correlated neither with CKD stage nor with eGFR quartile. In another cross-sectional study of randomly selected community-dwelling ambulatory men analyzing data from the Australasian MAILES study, significant associations between OSA and CKD (predominantly of mild stages) were observed, while no association of CKD was found with indices of nocturnal hypoxia [44]. Importantly, all longitudinal studies revealed some impact of OSA on renal outcomes [39,45–49],

except one [41]. In the latter study, prevalence of sleep apnea was low and participants at baseline had normal eGFR.

Interestingly, the most recent longitudinal study, using data from the Sleep Health Heart Study (i.e. 1,525 community-based adults without previous CKD), has reported that severe OSA predicted the risk of incident CKD (stage 3 or higher), over an average follow-up of 19 years, with coexistent obesity mediating the association [50]. Finally, in patients affected by diseases associated with increased CKD risk, such as systemic hypertension [51], diabetes [52], obesity and metabolic syndrome [53], the risk of poor renal outcomes is further increased by comorbid OSA.

Which are the main pathophysiological factors that could contribute to OSA development in CKD and ESRD populations and vice versa?

According to the present evidence, development of OSA in CKD/ESRD patients is related to three main pathogenic mechanisms, which can all coexist and alternate at the same time (Figure 1). First, there are altered chemoreflex responses in patients with ESRD [54]. Metabolic acidosis that frequently occurs in ESRD promotes hyperventilation and hypocapnia, followed by increases in chemosensitivity and instability of breathing during sleep, leading ultimately to fall of partial pressure of carbon dioxide below "apneic threshold" and creating a vicious cycle of hyperventilation and apneas [55,56]. Second, narrowed pharyngeal area is present in ESRD patients due to hypervolemia and rostral shift of excess body fluid in supine position at night [57,58]. Fluid accumulation in the neck predisposes to upper airway collapsibility, while pulmonary congestion stimulates lung J receptors which promote instability of breathing control [59,60]. Finally, impaired function of upper airway

muscles secondary to myopathy and neuropathy [61,62], could explain OSA development in CKD patients.

Conversely, pathogenesis of kidney function decline in patients with OSA is multifactorial (Figure 2). Nocturnal hypoxia appears to be the cornerstone of this interaction [39]. Scientific reports have proposed the "chronic hypoxia hypothesis" which supports a role of chronic hypoxia as a triggering factor of renal injury and a final pathway to end-stage renal disease [63]. In OSA during apneic events there is significant burden of hypoxic episodes which can trigger renal hypoxia and tubulointerstitial fibrosis resulting in CKD [37,39,64]. In addition, experimental data corroborate the evidence that intermittent hypoxia (IH) can damage the kidneys causing glomerular hypertrophy, increased expression of growth factors, expansion of mesangial matrix and finally lead in cellular apoptosis [65]. Moreover, IH impairs natriuretic and diuretic responses to fluid overload, and it is responsible for development of hypertension and kidney damage in rats [66].

Other mechanisms are also responsible for the development of CKD in OSA patients. Importantly, up-regulation of intrarenal RAS is one of these mechanisms [67]. Notably, Angiotensin II (AngII), the major effector of RAS, is mainly produced in bloodstream by the effects of angiotensin-converting enzyme (ACE) on Angiotensin I, but ACE can be found also in kidneys and heart tissues. An experimental study has found heightened activity of intrarenal RAS (as shown by reduced renovascular sensitivity in response to AngII infusion) in patients with OSA compared with control obese subjects, especially in those with severe nocturnal hypoxemia [67]. Of particular interest, additional evidence comes from an earlier study evaluating the role of PAP therapy on renal hemodynamics which demonstrated altered renal RAS responses at baseline and improvements following amelioration of OSA with PAP [68]. Additional mechanisms

known to promote kidney function loss are the overactivity of sympathetic nervous system [69,70] and endothelial dysfunction [71] which are present in OSA patients and improved or attenuated after application of CPAP [68,72–74]. Moreover, frequent coexistence of comorbid OSA in patients with systemic hypertension [51,75], diabetes [52,76,77], obesity [78], and metabolic syndrome [53] can accelerate kidney function loss resulting in a higher risk of CKD development or progression to worse stages. In specific, the confounding effect of OSA in never treated hypertensive patients can elicit more profound kidney damage, as indicated by the urinary albumin excretion (UAE), compared to those without OSA [75], while AHI has been recognized as a significant correlate of UAE in hypertensive patients with OSA [51].

In addition, recent retrospective data indicate that comorbid OSA with diabetes is associated with a higher risk of CKD than OSA alone [79]. In a cross-sectional study, severity of OSA is related to a higher risk of albuminuria (a marker of kidney injury) in patients with diabetes, [76]. Of particular interest is the special contribution of REM related OSA in the interaction between diabetes and risk of CKD [80]. As already shown, REM-OSA can have distinct features from NREM-OSA regarding cardiometabolic and neurocognitive endpoints [81,82]. In the context of CKD, AHI in REM sleep, and not in NREM, showed independent correlations with the risk of CKD in a group patients with diabetes, underlining the specific effects of REM sleep in OSA patients as predictor of worse kidney outcomes [80]. Finally, special attention should be paid on the relationships between REM-AHI and associated hypertension [83], as this sleep stage may be highly relevant to risk of development of CKD in OSA patients. The latter holds promise for further research in future studies.

Is OSA clinically apparent in CKD and ERSD populations?

A typical presentation of OSA is that of a male patient, with signs of visceral adiposity, and complaints of loud snoring, witnessed apneas during sleep, unrefreshing sleep and daytime sleepiness [1]. Nevertheless, these features are not frequently encountered in the CKD and ESRD populations, who demonstrate rather unspecific characteristics. In the study of Beecroft et al. [84], patients with ESRD and OSA were characterized by lower BMI and smaller neck circumference than the OSA individuals with normal renal function. Another observation was that symptoms suggestive of OSA were less likely to be present in the ESRD population compared with the OSA population without renal failure [84]. Likewise, excessive daytime sleepiness (EDS) and other OSA-related symptoms were less prevalent in the CKD population with OSA than in OSA patients without CKD [85]. It should be noted that while CKD and ESRD patients often complain of EDS [86,87], this is neither sensitive nor specific for identifying OSA in this patient population, similar to patients with stroke [88], heart failure [89] or hypertension [90]. In fact, fatigue might be mistakenly regarded as EDS, which is another common complaint in patients with kidney failure [91]. Interestingly, OSA screening tools, namely the Berlin, STOP-BANG, and the adjusted neck circumference questionnaire (i.e., the sum of patient's neck circumference, history of hypertension, snoring, and nocturnal choking), failed to accurately identify suspected OSA in a cohort of subjects with CKD and ESRD [92]. Thus, where the risk of OSA is high, an objective sleep evaluation should be performed, preferably an attended one at the sleep laboratory, as per the recommendations of the American Academy of Sleep Medicine [93].

Despite the atypical presentation of sleep disordered breathing in CKD patients, sleep quality is another issue to consider, which is often impaired in this specific population.

In a recent ESADA report, objective sleep quality, as noted in polysomnographic studies, was influenced by OSA severity ~~of~~ but not by CKD severity [94]. This finding highlights the importance of an adequate control of SDB in CKD to improve sleep quality. In summary, clinicians should have a low threshold to perform sleep studies in CKD and ESRD patients, especially when clinical suspicion of OSA is high.

Does OSA result in adverse outcomes and poorer survival in patients with CKD and ESRD?

Mortality risk is higher in patients with impaired kidney function, compared to the general population, and it is highest in patients under dialysis, whose mortality rate approaches 20% per year [95,96]. Mortality risk in these patients is frequently associated with cardiovascular morbidity, which progressively increases with the decline of kidney function [97]. Likewise, OSA is associated with increased risk of CV morbidity and all-cause mortality [98]. Whether co-occurring OSA could result in worse morbidity and mortality in individuals with CKD and ESRD was addressed by research in recent years. This is important since OSA can be effectively treated with CPAP and thus OSA-related complications can be attenuated or even prevented [1]. A recent study enrolling 180 patients with advanced CKD and ESRD on dialysis [28] with a median follow-up duration of 9 years, revealed no statistically significant effect of AHI on OSA mortality, whereas nocturnal hypoxic indices, namely the mean oxygen saturation and the percentage of time spent while sleeping with oxygen saturation below 90%, were major predictors of death. Other studies have also revealed additive effects of OSA on CV mortality and all-cause mortality in patients with CKD and ESRD [25,99–103]. Interestingly, in a retrospective cohort study evaluating 40 OSA patients

for 10 years, a higher survival rate was noted in individuals treated with fixed CPAP as compared to other PAP modalities, and a benefit was also observed in patients with a high compliance to PAP treatment [103]. Finally, a recent meta-analysis summarized the existing data regarding the impact of OSA on mortality risk in CKD and ESRD patients. Specifically, this study evaluating the risk of mortality in patients with CKD/ESRD and SDB (obstructive and central sleep apnea were included), showed that patients with CKD/ESRD and SDB were exposed at a higher risk of death, with an estimated OR of 2.092, compared to patients with CKD alone [104]. Surprisingly, individuals with CKD and SDB did not have a higher number of cardiovascular events compared to patients with CKD only. An explanation for this unexpected result lies in the fact that one of the three studies that were analyzed, which had the highest number of included patients, found a decreased occurrence of CV events in CKD/SDB versus CKD [102], thus blunting the pooled results of the other two positive studies [99,100]. To further elucidate this, one should consider the role of ischemic preconditioning during episodes of IH, as those seen during apneic events [105,106]. Previous evidence shows that hypoxic preconditioning may blunt the effects of ischemia-reperfusion injury associated with ischemic events [101], and thus presence of SDB in CKD population may have served beneficial in terms of CV events. Another speculation for this unexpected outcome is that adherence to preventive measures in the context of CVD might have been better in patients suffering from both diseases, namely CKD and SDB.

What is the role of ESRD treatment in pathogenesis of OSA?

A growing body of research has focused on the role of nocturnal dialysis in patients with ESRD and coexistent OSA. Specifically, studies evaluating the effects of fluid overload and ventilatory chemoreflex responsiveness in ESRD patients have shown positive results regarding OSA severity. In the seminal study of Hanly and Pierratos [15], switching from a conventional to a nocturnal hemodialysis regimen resulted in marked improvements in AHI and in nocturnal oxygenation of patients with OSA and ESRD. Later on, investigators observed that these findings could be due to a decrease in chemoreflex responsiveness, a key element of OSA development in the ESRD population [108]. Other studies have highlighted the role of rostral fluid shift as a mechanism for OSA development in the ESRD population [59,60]. Interestingly, the shift from conventional to nocturnal peritoneal dialysis resulted in improved fluid and uremic clearance, increased upper airway volume and reduced AHI [17,18], as did also removal of excess body fluids by ultrafiltration. [109].

Following kidney transplantation, the kidney function is restored, while hydration status is also improved in patients with ESRD. Regarding kidney transplant and occurrence of OSA, most studies showed that OSA prevalence decreased and its severity improved after kidney transplantation [110–115], while others did not reveal any impact on OSA outcomes [116–118], with even similar prevalence rates of OSA both in patients in transplant waiting list and in those having received a kidney transplant [119]. In the first context, a previous study has shown that prevalence of SDB in kidney transplant recipients was similar to that observed in the general population, i.e. up to 22%, while severity of SDB was associated with BMI [112]. In addition, a recent prospective study has demonstrated an improvement in OSA severity at 6 months post-transplantation, which correlated with reductions in fluid overload and body water. Longitudinal studies in patients after kidney transplant showed an increase in OSA

severity over time, underscoring that increases in body weight can cancel ~~the~~ any beneficial effects of kidney transplant on the SDB evolution in this specific population[115,118].

In summary, alternative approaches such as nocturnal dialysis and intensive removal of excess body water have shown benefit on attenuating the risk of development of OSA, whereas more data are needed in order to firmly clarify whether OSA improves or not in the long term after kidney transplantation.

Is treatment with PAP effective on preventing kidney function decline?

Continuous PAP (CPAP) is the optimal treatment for patients with OSA as it effectively resolves respiratory events by keeping the airway patent during sleep [1]. Currently, there is a growing interest on whether CPAP exerts protective effects on the evolution of kidney function decline [120,121]. So far, studies (retrospective and prospective observational or RCTs), assessing either the rate of eGFR decline or the degree of albuminuria, were divided into those including patients with established CKD or individuals without preexisting kidney disease [7]. In a recent study, using longitudinal data from the ESADA cohort over an average follow-up of 541 days [122], treatment with *fixed* CPAP attenuated the annual rate of eGFR decline over auto-adjusting CPAP or no treatment in patients with OSA (n=1807), underlining that fixed CPAP attenuated the progressive reduction of eGFR over time. The latter finding could derive from a more effective blunting of sympathetic nervous system hyperactivity during sleep by fixed CPAP, which could counteract endothelial dysfunction [123–125], a distinct characteristic which is highly relevant in hypertensive OSA-related kidney damage [51]. In the same context, in a retrospective cohort study assessing 40 OSA patients,

application of fixed CPAP protected from eGFR decline after 3 years compared with other PAP modalities [103]. Nevertheless, the protective effect of CPAP did not remain significant after 8 years [103]. A RCT to answer the question on possible differences in the effects of fixed or automatic CPAP on sympathetic activity is under way [126].

Adherence to CPAP treatment is another issue to consider when assessing the kidney function in OSA patients. Specifically, in a retrospective study including CKD patients with stages 3 to 5 and coexistent OSA [127], OSA patients with CPAP use of more than 4h per night showed a slower eGFR decline than patients with CPAP use less or equal to 4h per night [127]. Moreover, influence of CPAP on renal function was reported in three experimental studies including OSA patients without previous CKD. In the earlier study [128], investigators measured direct parameters of glomerular function, such as the glomerular filtration, the renal plasma flow and the filtration function in OSA patients with normal or high glomerular filtration rate before and after short term application of CPAP. They found that untreated OSA patients demonstrated a "glomerular hyperfiltration state" at baseline, which was improved after effective treatment with CPAP for one week [128]. Similarly, in a recent study enrolling OSA patients without diabetes, systemic hypertension or CKD, treatment with CPAP blunted the enhanced pre-treatment activity of renal RAS and improved parameters of glomerular filtration [68]. In the last experimental study enrolling otherwise healthy OSA patients, one month of CPAP treatment resulted in enhanced renal hemodynamics and improved response to angiotensin II in women but not in men, indicating that in women CPAP preferentially downregulated renal RAS activity [129]. On the contrary, in the only RCT published so far [130], enrolled patients with moderate and severe OSA and pre-existing CVD were allocated to CPAP plus standard therapy or to usual care only. The study failed to show any significant effect of CPAP on the rate of eGFR

decline compared with the usual care group after a median follow-up of 4.4 years. Nevertheless, the study had several limitations, as it was underpowered to detect differences in eGFR, the average CPAP use was low, while enrolled subjects were on maximum reno-protective treatment medications and their baseline characteristics were of normal kidney function, leaving little place to any potential beneficial effect of CPAP. Most of the studies evaluating the role of CPAP on albuminuria have reported beneficial effects of CPAP on urinary albumin excretion [131,132], especially when patients had good CPAP compliance [133–135]. Finally, the results from a pilot RCT [136], including patients with CKD stages 3 and 4 and concomitant severe OSA randomized to receive CPAP and usual care versus usual care only, showed no benefits of CPAP over the group of standard care in the change in eGFR and albuminuria after 12 months of follow-up. Of note, a trend towards slower eGFR change was observed only in those patients with a lower risk of CKD progression [136]. In summary, the existing data report some benefit of CPAP on the rate of kidney function decline .with observational studies highlighting the role of CPAP in terms of either eGFR or albuminuria, whereas the results from the only RCT [130] and a recent meta-analysis [137] did not corroborate these findings.

Is there any degree of latent kidney disease in OSA patients?

Strategies to improve screening of CKD in OSA patients are the object of an ongoing interest and several biomarkers have been proposed towards this approach [138]. Among them, Cystatin C, a novel marker of renal function, currently provides the best evidence. Cystatin C–based GFR equations outperform creatinine-based formulas in obese CKD patients [139], while Cystatin C levels may also predict the risk of CKD

development, CVD and death [140]. In a cross-sectional study, involving newly diagnosed OSA patients without other comorbidities and apparently normal renal function, serum Cystatin C levels were increased in OSA patients compared with controls, suggesting latent kidney dysfunction [141]. Similar findings were reported in another study which showed that individuals with severe OSA had the highest levels of serum Cystatin C levels compared with controls and mild and moderate OSA [142]. Other studies [143,144] have included OSA patients who had comorbid conditions such as diabetes and hypertension, that might have influenced Cystatin C levels regardless of OSA. Another biomarker is neutrophil gelatinase-associated lipocalin (NGAL), which is considered to reliably estimate renal function independently of GFR changes and a potential biomarker of both acute kidney injury and CKD [145]. In a recent study enrolling otherwise healthy OSA patients who underwent measurements of serum NGAL and Cystatin C, both kidney biomarkers were elevated in OSA patients compared to controls, suggesting a latent degree of declined kidney function [138]. Likewise, in a prospective study involving newly diagnosed patients with OSA [146], several markers of acute kidney injury (i.e., IL-18, Cystatin C and NGAL) correlated with the AHI, while after 6 months on treatment with CPAP, IL-18 levels and albuminuria significantly decreased. Other biomarkers have been assessed in OSA and showed correlations with kidney injury but they need to be evaluated in larger studies [147].

Research priorities in future studies and the need for collaboration between sleep and renal scientific societies. A call to action

An increasing body of evidence is currently suggestive of mutual associations between OSA and CKD/ESRD. On the one hand, clinicians should screen for coexistent OSA in CKD and ESRD patients due to its high prevalence in this patient population, while on the other hand assessment of kidney function to all patients with OSA could not be currently suggested. Nevertheless, a proportion of OSA subjects with severe nocturnal hypoxemia and/or presence of cardiometabolic comorbidities seem to be more affected by faster loss of kidney function. Additionally, gender differences may impact differently on CKD outcomes, with most of the studies ~~except for one [37],~~ showing that men present more rapid loss of kidney function than women, whereas women may show better response with CPAP therapy on renal hemodynamics than men. These OSA phenotypes deserve closer monitoring of kidney function and adequate control of both OSA and its related comorbidities. Moreover, influence of OSA and ESRD treatment on the occurrence of the other disease is another field of research with promising results so far. Specifically, intensification of dialysis treatment or initiation of alternative approaches (e.g., nocturnal sessions) has proven useful in reversing apneas and reducing the severity of OSA, while the application of fixed and not auto-titrating CPAP might slow the rate of eGFR decline. Importantly, some research points need to be addressed with special attention in future studies. First and foremost, CKD and OSA and their associated endpoints should follow homogeneous definitions across studies. Secondly, there should be more appropriate selection of patients, and CKD patients should be enrolled at milder stages 1 to 3, to clarify the role of OSA on the evolution of kidney function at reversible levels. Additionally, there is an increasing need for easily applied biomarkers that would aid in identification of OSA patients who are exposed at higher risk for poorer kidney function. Moreover, it is rather impossible to objectively assess all CKD patients for coexistent OSA, and thus future research should

also focus on selecting the most sensitive tests for screening purposes in everyday practice. Ultimately, some characteristics of OSA patients (female gender, severe nocturnal hypoxia, cardiometabolic comorbidities etc.) should be taken into consideration when assessing the effect of CPAP treatment on CKD outcomes.

In conclusion, the need for collaboration between sleep and renal societies is more and more growing, as this action would lead to a better understanding of the interaction between OSA and CKD and be translated into improved patients' outcomes.

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