Chronic kidney disease in patients with obstructive sleep apnea. A narrative review

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Summary

Prevalence of both chronic kidney disease (CKD) and obstructive sleep apnea (OSA) is continuously increasing. Moreover, the prevalence of OSA increases as kidney function declines and is higher among patients with end-stage renal disease (ESRD). In addition, OSA is recognized as a potential nontraditional risk factor for development and progression of CKD. Continuous positive airway pressure (CPAP) plays a pivotal role in the management of OSA, eliminating patients' symptoms and improving their quality of life. Recent studies suggested that CPAP treatment may have beneficial effects on kidney function among patients with OSA. This narrative review summarizes the existing knowledge on the association between CKD and OSA, with emphasis on the epidemiology, the pathophysiology of the development of CKD in OSA and vice versa, as well as the effect of CPAP on renal function.

Keywords

chronic kidney disease; continuous positive airway pressure; kidney function; nocturnal hypoxia; obstructive sleep apnea

Abbreviations	
AHI	apnea hypopnea index
ACR	albumin to creatinine ratio
AngII	angiotensin-II
APAP	autoadjusting positive airway pressure
ASV	adaptive servo-ventilation
BMI	body mass index
BP	blood pressure
cIMT	carotid artery wall intima-media thickness
CG	Cockcroft-Gault
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease-epidemiology collaboration
CPAP	continuous positive airway pressure
CSA	central sleep apnea

CVD	cardiovascular disease
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
ESADA	european sleep apnea database
ESRD	end stage renal disease
ERPF	effective renal plasma flow
FF	filtration fraction
GFR	glomerular filtration rate
HD	hemodialysis
HR	hazard ratio
HTN	hypertension
IH	intermittent hypoxia
MDRD	modification of diet in renal disease
NSAID	nonsteroidal anti-inflammatory drug
MSNA	muscle sympathetic nerve activity
ODI	oxygen desaturation index

OR	odds ratio
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
P/C	protein to creatinine concentration ratio
PRA	plasma renin activity
PD	peritoneal dialysis
PSG	polysomnography
RAAS	renin angiotensin aldosterone system
RAS	renin angiotensin system
REM	rapid eye movement
RPF	renal plasma flow
SaO_2	oxyhemoglobin saturation
SMD	standardized mean difference
SNS	sympathetic nervous system
SDB	sleep disordered breathing

1. Introduction

Chronic kidney disease (CKD) constitutes a global health problem with high medical, social and financial impact. Patients with CKD have poor prognosis with high mortality rates and often report low quality of life [1]. The prevalence of CKD is increasing globally and it is estimated at approximately 10%-13% [2]. According to Kidney Disease: Improving Global Outcomes (KDIGO), CKD is defined as kidney damage with or without reduced glomerular filtration rate (GFR) or decreased kidney function with GFR<60 mL/min/1.73m^2 for ≥3 months [3]. Declining kidney function is related to cardiovascular morbidity and mortality, higher hospitalization rates and increased risk of death [4].

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of partial or complete upper airway obstruction during sleep, leading to intermittent hypoxia, frequent arousals, sleep fragmentation and daytime symptoms like excessive daytime sleepiness which is associated with traffic accidents and reduced work productivity [5–7]. Recent data show that 3 to 9% of women and 10 to 17% of men have an AHI≥15/h [8]. OSA is associated with systemic inflammation, endothelial dysfunction and increased risk of cardiovascular morbidity and mortality [9,10]. Moreover, OSA is related to clusters of metabolic syndrome and type 2 diabetes, the latter being considered a common cause of CKD nowadays together with systemic hypertension [11,12].

In patients with end stage renal disease (ESRD) OSA is frequently diagnosed, with currently estimated prevalence rate of up to 57% [13,14]. On the other hand, nocturnal hypoxia may impair kidney function and could ultimately lead to CKD [15,16]. Thus OSA may also represent a novel risk factor for CKD development and the latter, either

latent or established, should be taken into consideration in the management of OSA [17,18].

This review article aims to summarize current knowledge on the development of CKD in OSA patients and the development of OSA in patients with CKD and ESRD, focusing on epidemiology, pathogenetic mechanisms and the effect of CPAP on kidney function.

2. Epidemiology of kidney function decline in OSA

Occurrence of CKD in OSA has been explored in samples of subjects from various types of populations (general population, suspected or diagnosed OSA). Variable renal outcomes (protein excretion, eGFR, CKD), methods to estimate GFR (MDRD, CG, CKD-EPI, cystatin, Mayo), and experimental designs (cross-sectional or longitudinal) have been used. Generally, all studies accounted for the possible influence of hypertension and diabetes as confounders, or excluded subjects with these diseases. A few studies dealt with the association between OSA and CKD in diabetic subjects, as summarized in a recent excellent review [19].

Table 1 summarizes the existing literature on CKD in OSA. A few cross-sectional studies were done on general population samples. Two of them included both men and women [20,21], while four included only men [22–25]. In the Cleveland Family Study cohort, Faulx et al [20] found a significant correlation between albumin/creatinin ratio (ACR) adjusted for sex and race (aACR) and AHI. Subjects with AHI >30 showed lower GFR, higher aACR and higher prevalence of microalbuminuria compared to subjects with mild or no OSA, even after adjustment for hypertension and diabetes. Canales et al published three studies in community dwelling men ≥65 years old (MrOS cohort). In the first study [23] on 508 subjects, an eGFR<60 was associated with sleep

disordered breathing (SDB), defined as a RDI≥15, only when it was estimated by the Mayo Clinic, but not by the MDRD or the CG formula. In the second study [22] on 2696 subjects, either using the MDRD or the Mayo Clinic formula, the lowest quartile of eGFR was associated with RDI only in subjects aged <72 years, but the association was confounded by their higher BMI. In the last study [24], ACR and microalbuminuria, defined as ACR >30mg/g, were measured in 507 subjects and correlated with time spent at oxyhemoglobin saturation (SaO_2)<90% but not with RDI. Ogna et al [21], in the HypnoLaus cohort, assessed the association between SDB and CKD, evaluated by polysomnography (PSG) and ACR and eGFR, respectively. Although prevalence of AHI≥15 and ≥30 increased with worse CKD stages and lower eGFR, neither CKD stage or eGFR was associated with SDB at multivariate analysis. Similar measurements of ACR and eGFR were done by Adams et al in their cohort of community-dwelling ambulatory men (MAILES study) [25]. After adjustment for several possible confounders, significant associations were found between CKD and AHI or respiratory arousal index, but not with hypoxemia indices.

Other cross-sectional studies evaluated eGFR in subjects with suspected OSA. Iseki at al [26] compared 1,624 patients with AHI>5 with 7,454 - and gender-matched control subjects. Prevalence of CKD, defined as eGFR<60, was higher in the OSA group compared to controls (30.5% vs 9.1%, p<0.001), but AHI did not correlate with presence of CKD in the OSA population after adjusting for confounders. Fleischmann et al [27] reported that prevalence of RDI >5 and mean RDI were similar among groups with eGFR ≥90, 50-89 and 30-59, but the last group included more subjects with NYHA ≥3 who showed high prevalence of central rather than obstructive apneas. In the study by Kanbay et al [28] mean eGFR decreased progressively with increasing OSA severity, and eGFR was independently predicted by AHI and arterial hypertension.

Uyar et al [29] studied 634 OSA and 62 control subjects, and found no difference in eGFR between the two groups. Finally, in the multicentre ESADA cohort [30], Marrone et al reported that lowest nocturnal oxygen saturation, but not AHI, was an independent predictor of eGFR <60.

Protein or albumin excretion was evaluated in patients with suspected or diagnosed OSA. Early cross-sectional studies found slightly positive relationship between urine protein to creatinine ratio (P/C) and AHI (Iliescu et al [31]) or were negative (Casserly et al [32], Mello et al [33]). Moreover, a P/C >0.2 was uncommon in all studies [31-33]. More recent studies measuring albumin excretion reported a positive relationship between OSA severity and ACR. Daskalopoulou et al [34] reported a higher ACR in OSA patients compared to controls, especially in urine samples obtained after sleep. The difference in ACR between pre- and post-sleep samples was especially marked in OSA patients with non-dipping blood pressure. CPAP acutely decreased morning, but not evening ACR. In the study by Bulcun et al [35] ACR, but not eGFR, was higher in the patients and linearly correlated to nocturnal hypoxemia. Furthermore, microalbuminuria, defined as ACR>20 in men and >30 in women, was more common in OSA patients than controls. The only study in children with OSA [36] found similar ACR values in mild OSA (AHI 1-5, n=71), moderate-severe OSA (AHI>5, n=27) and control (AHI<1, n=31) groups, but moderate-severe OSA patients showed a higher risk of elevated ACR compared to controls. Log ACR was independently predicted by Log ODI and respiratory arousal index.

Finally, some longitudinal studies evaluated changes in eGFR or incidence in CKD in male and female subjects with OSA. Ahmed et al [15] studied 858 patients referred for suspected sleep apnea and followed on average for 2.1 years. Decline in eGFR >4 ml/min/1.73 m^2/year was independently associated with at least 12% of

nocturnal time spent at SaO_2 <90%, but not with RDI ≥15 or ≥30. In a cohort of over 3 million US veterans followed for a median time of 7.4 years, subjects with OSA showed about a three-fold higher risk of incidence of eGFR<60 and a high risk of rapid deterioration of kidney function, defined as a decrease in eGFR ≥5 ml/min/1.73 m^2/year [37]. Three studies from Taiwan [17,38,39], retrospectively examined the National Health Insurance registry for incidence of CKD (any stage) in newly diagnosed OSA patients compared to age- and sex-matched controls. Mean follow-up duration ranged between 3.9 and 5.2 years. In all these studies, incidence of CKD was significantly higher in OSA subjects, even after considering potential confounders. A subgroup of 277 subjects from the Three City-Study cohort, who were ≥65 years at baseline and were followed for 11 years, was studied by ambulatory PSG [40]. Among these subjects a high AHI, but not indices of hypoxemia, was associated with eGFR decline in the follow-up period. Recently Canales et al [41] analyzed eGFR decline in the Wisconsin Sleep cohort, followed for an average of 13.9 year, and - contrary to all other longitudinal studies - found a worse eGFR decline in subjects without OSA than in those with OSA at baseline, while incidence of CKD (eGFR <60) or progression to a worse stage was similar in both groups.

In summary, the epidemiological studies published so far have provided a variety of different indications about the relationship between OSA and CKD. Differences in characteristics of subjects under study, samples size, and study design may at least partly account for some apparently conflicting results. In studies in the general population, the number of subjects with severe OSA can be expected to be small, and the role of hypoxemia was often not analyzed, probably because it was mild in the vast majority of cases, or when analyzed, it was not significant; the frequency of apnea events appeared to play some role in the relationship between OSA and renal

impairment. Studies with large sample sizes and including patients from sleep laboratories were more likely to demonstrate a role of hypoxemia [15,30]. In most cases, albumin excretion, but not total protein excretion, was found to be associated with OSA. Cross-sectional studies on eGFR gave variable results, but sample sizes were frequently small. Conversely, results of longitudinal studies were more consistent in demonstrating some effect of OSA on eGFR decline or OSA incidence, with the exception of one study [41], probably due to the mild respiratory disorders found in a general population sample. Interestingly, in all studies that included OSA subjects both with and without CPAP prescription [37,39,41], a higher renal risk was found in patients without CPAP. However, no compliance data were available, and it is likely that untreated patients had more a more severe disease than OSA patients who were not prescribed treatment.

3. Pathophysiology of CKD in OSA

Nocturnal hypoxia

Hypoxia is a major factor in the development and progression of CKD. The kidneys physiologically receive a high blood flow, and are susceptible to tissue hypoxia due to a low oxygen tension, particularly in the renal medulla [42]. Intrarenal hypoxia may trigger the pathogenetic cascade in the development of CKD. As an initiator factor of CKD, glomerular injury promotes microvascular distortion and creates a hypoxic environment. Hypoxia predisposes to a vicious cycle of inflammation, myofibroblast differentiation, apoptosis of the peritubular endothelial cells, and extracellular matrix accumulation leading to renal fibrosis [43].

Hypoxia during sleep is common in OSA, and could promote kidney dysfunction, as suggested by studies that found an association between severity of hypoxemia and

urine protein or albumin excretion [31,35], eGFR [30], or rate of eGFR decline [15,16] in OSA patients. However, sleep hypoxemia in OSA is typically intermittent, and it remains unclear whether its role as a CKD risk factor may be mainly exerted directly through exposure to low oxygen tensions, or indirectly through enhancement of oxidative stress and inflammatory activation. Studies, addressing whether sustained hypoxia impacts renal function differently from intermittent hypoxia would be important in order to fill this knowledge gap.

Activation of renin-angiotensin-system

Another well-defined mechanism in the pathogenesis of CKD is the up-regulation of renal renin-angiotensin system (RAS) activity, with or without influence on circulating renin-angiotensin-aldosterone system (RAAS) [44]. The RAAS modifies the vascular tone, amplifies the effects of the sympathetic nervous system, and regulates body water and salt homeostasis [45]. Of note, OSA is related to activation of the RAAS and its components, which in turn predispose to resistant hypertension and kidney disease [46–48].

One study [49] comparing patients mostly affected by OSA with and without resistant hypertension found lower plasma renin and higher aldosterone in the hypertensive patients, and among them, a correlation between aldosterone and both AHI and percentage of sleep time spent at SaO_2<90% [49]. Zalucky et al [50] published an important study on the pathophysiology of kidney dysfunction in OSA by evaluating renal hemodynamics before and after infusion of angiotensin II (AngII) in obese OSA patients. Moderately and severely hypoxic OSA patients were compared to obese controls with no OSA and no nocturnal hypoxemia. Effective renal plasma flow and filtration fraction responses to AngII infusion were lowest in the severely hypoxemic

patients and highest in the normoxemic controls, even after adjusting for confounding factors, including age, sex and BMI. This finding was interpreted as enhanced renal RAAS related to hypoxia independent of obesity, which is another known renal risk factor [51,52]. A recent meta-analysis documented increased levels of serum angiotensin II and aldosterone in OSA, at least when it is associated with hypertension [53].

Increased tone of sympathetic nervous system

Over-activity of the sympathetic nervous system (SNS) has a central role in the pathogenesis and progression of CKD [54], and OSA is associated with increased sympathetic activity. Repeated sympathetic activation occurs during sleep apneas, and contributes to post-apneic increases in blood pressure and heart rate. However, increased sympathetic tone in OSA patients is also evident during wakefulness, as shown by measurements performed with microneurography on the peroneal nerve [55,56] and by catecholamines determinations [57]. Long-term OSA treatment is associated with decreased catecholamines and sympathetic nervous discharge [58,59]. Thus, sympathetic overactivity could be another important mechanism of kidney harm in OSA.

Endothelial dysfunction

Accumulating evidence indicates that sleep apnea is associated with endothelial dysfunction [60]. Bruno et al. demonstrated impaired endothelium-dependent vasodilation and renal vasodilating capacity in patients with OSA compared to healthy controls, even in the absence of risk factors for cardiovascular disease [61]. Similarly, another study reported reduced flow-mediated dilation and higher renal resistance index

and systolic/diastolic ratio in OSA patients without comorbidities and with preserved renal function compared to controls, which improved significantly after one month-CPAP [62].

Role of coexistent OSA in patients at risk of CKD due to common diseases

Hypertension (HTN) is one of the most common causes of CKD and favors progression to ESRD [63]. ~~[64]~~**.** In addition, diabetes mellitus (DM) is globally the leading cause of CKD and progression to ESRD.

It is well established that OSA and HTN frequently coexist, especially in individuals with resistant HTN [65–67]. OSA is recognized as a cause of increased BP both during wakefulness and sleep [**add**]. Moreover, OSA has been recognized as an independent risk factor for glucose intolerance, insulin resistance, poor glucose control and DM [70–72]. Therefore, the association of OSA with an increased occurrence of CKD may be partly mediated by its effects on BP and metabolic control. However, even among hypertensive and diabetic patients, a detrimental effect of OSA on the kidneys has been demonstrated independent of coexisting diseases.

Hypertension, OSA and CKD

In a cross-sectional study on hypertensive patients with and without OSA, albumin excretion was found to be higher in OSA+ than OSA- patients [68]. Moreover, at multivariate analysis, ACR correlated with the severity of sleep apnea independently of other risk factors ($r=0.35$; $p<0.001$).

In another study on OSA and non-OSA hypertensive patients [69], subjects with OSA showed higher 24-h urinary albumin excretion. At multivariate analysis, AHI correlated with urine albumin excretion independently of blood pressure and other

components of metabolic syndrome. However, eGFR wsa similar OSA and non-OSA patients.

Diabetes, OSA and CKD

Tahrani et al. [73] examined whether OSA is associated with diabetic nephropathy and with more severe decline in kidney function in 224 patients, 144 with type 2 DM and OSA, 80 with type 2 DM and no OSA. An independent effect of OSA on the prevalence of diabetic nephropathy was observed. In a 2.5 year follow-up period, eGFR declined more rapidly in the patients with than in those without OSA, while OSA and baseline AHI remained independent predictors of study-end eGFR measurements. Another cross-sectional study [74] investigated the effect of sleep apnea and nocturnal hypoxemia on CKD in obese diabetic patients. In patients diagnosed with OSA, eGFR<60mL/min was present in 22.7% and 13.3%, based on the MDRD and CKD-EPI equations respectively. After adjustment for age, BMI and other potential confounders, severity of OSA, expressed by AHI, alongside with duration of hypoxemia during sleep (% sleep time with SaO_2<90%) were inversely correlated to eGFR. In the cross-sectional study by Nishimura et al. [75] analyzing severity of SDB and albuminuria in DM patients, severity of SDB was associated with albuminuria, independently of traditional risk factors

Those results were corroborated by a recent meta-analysis [19]. In four studies, a moderate contribution of OSA to CKD development among individuals with DM was demonstrated. Besides, a significant association between the percentage of time spent at oxygen saturation<90% and diabetic nephropathy (DN) was noted in two of the included studies [19].

4. OSA in CKD and ESRD

Epidemiology

OSA is highly prevalent among patients with CKD and ESRD. An association between OSA and ESRD was first reported in 1985 [76]. Among 29 male patients on hemodialysis, 12 had symptoms suggestive of SDB, and OSA was confirmed in 6 out of the 8 patients studied by polysomnography (PSG).

Some studies, summarized in Table 2, evaluated the prevalence of OSA in CKD patients. Some studies were conducted in patients not dialyzed (Markou et al. [77], Sakaguchi [79], Tanaka [81]) other in patients on dialysis (Unruh [78]), while one study examined both groups and controls (Roumelioti et al [80]). Overall, the studies agree on a high prevalence of OSA in patients with CKD, although the studies were performed in relatively small samples. Positive correlations between CKD severity and OSA severity were reported by all studies. ~~in assessed the prevalence of OSA in 35 non-dialyzed stable CKD patients without major cardiovascular comorbidities. Polysomnography showed OSA in 19 patients, with an average AHI of 9.9±1.7 events/h. In the subgroup of non-diabetic patients (n=25), AHI was correlated to creatinine clearance, and an eGFR <15 was associated with higher AHI.~~

~~Unruh et al. [78] compared 46 patients on hemodialysis (HD) with 137 matched subjects from the Sleep Heart Health Study. A significant higher risk of severe SDB in HD was found in the patients compared with the control group even after adjustment for CVD and diabetes.~~

~~In 100 non-dialysis CKD patients, OSA (AHI>5/h) was found in 65% of the sample, with almost one-third classified as having moderate or severe OSA [79]. At multivariate analysis, likelihood for OSA increased by 42% for each 10ml/min decrease in eGFR.~~

~~In the study by Roumelioti et al. [80] in patients with advanced CKD (n=89), patients on HD (n=75) and controls (n=224), prevalence of severe SDB was higher in the CKD and ESRD groups than in controls (22.5% vs 25.7% vs 11.5% respectively). with a 2.4 higher risk for severe SDB in the patients.~~

~~In another study by Tanaka et al. [ref], including 100 non-dialysis CKD patients, OSA was found to be overall highly prevalent (95 patients) as it was severe OSA (39%).~~

Nicholl and colleagues investigated whether prevalence of OSA and nocturnal hypoxia increased when kidney function declines [13] in 254 patients. Three groups were classified based on eGFR according to CKD-EPI equation [81]: eGFR≥60 mL/min (controls, n=55), eGFR<60 mL/min but not on dialysis (CKD group, n=124), and eGFR<60 mL/min on dialysis (ESRD group, n=75). Loss of kidney function was associated with increased prevalence of both OSA (eGFR≥60: 27%; CKD: 41%; ESRD: 57%; p=0.002) and nocturnal hypoxia (eGFR ≥60: 16%; CKD: 47%; ESRD: 48%; p<0.001).

A recent meta-analysis [82] in non-dialysis CKD patients resulted in a pooled prevalence of OSA at 38% (95% CI, 21%□70%). The prevalence of OSA according to sleep questionnaires was 10%, while according to sleep studies it raised to 56%. In advanced CKD stages (eGFR<30ml/min) the prevalence of mild, moderate and severe OSA was 19%, 34%, and 37% respectively.

Pathophysiology

Increased ventilatory chemoreflex responsiveness

Metabolic acidosis is frequently observed in patients with CKD and ESRD, and reductions in $PaCO_2$ levels may serve as a compensatory mechanism [83]. Patients with CKD and ESRD may develop OSA through alterations in chemoreflex responsiveness

as a consequence of metabolic acidosis and uremia, leading to hypocapnia and respiratory control destabilization during sleep [84]. During NREM sleep, respiratory drive is under chemoreflex control, and ventilation is markedly influenced by alterations in $PaCO_2$ levels [66, 67]. In this sleep state, hyperventilation, due, e.g., to an arousal, can bring $PaCO_2$ under an "apneic threshold" and destabilize breathing, leading to a vicious circle of apneas and short intervals of hyperventilation [87,88].

Commentato [OM1]: 85-86?

Beecroft and colleagues have investigated these phenomena in 58 ESRD patients receiving HD or peritoneal dialysis (PD) [84]. Patients were classified into apneic (n=38, AHI≥10/h) and nonapneic (n=20, AHI<10/h) groups after polysomnographic evaluation, and both the peripheral and central chemoreflex responsiveness to $PaCO_2$ alterations were assessed. Compared to controls, OSA patients showed enhanced ventilatory sensitivity to hypercapnia during both hypoxic and hyperoxic tests (which reflect peripheral and central chemoreflex activity, respectively). At multivariate analysis AHI was a significant predictor of enhanced ventilatory sensitivity.

In agreement with these findings, parallel changes in chemoreflex responses and AHI were shown after shifting from conventional HD to nocturnal HD [89]. Based on results of PSG, patients were divided into OSA (n=17) and controls (n=7). Responders OSA patients were defined as patients showing a decrease in AHI >50% and/or a reduction to <15/events/h after shifting from conventional to nocturnal HD. In responders, such shift resulted in decreased ventilatory chemoreflex sensitivity to hyperoxic hypercapnia, whereas no change was observed in non-responders. Of note, in the entire group of OSA patients the change in chemoreflex sensitivity correlated with the change in AHI (r=0.528, p=0.029).

Fluid overload and fluid shift

OSA subjects tend to have narrow and hypotonic pharyngeal upper airway which may collapse at multiple sites [72, 73]. Interestingly, ESRD patients showed reduced pharyngeal cross-sectional area compared with controls with normal renal function, suggesting that ESRD may increase the likelihood of upper airway collapse during sleep [92]. CKD could also lead to OSA through pharyngeal narrowing due to rostral fluid shift in supine position during sleep. Rostral fluid shift during sleep from the legs to the neck may contribute to the pathogenesis of both OSA and CSA as it was shown in patients with heart failure [93].

Commentato [OM2]: 90,91?

A recent study investigated whether the presence of sleep apnea in ESRD patients was associated with higher extracellular fluid volume [94]. In total, 42 patients with ESRD on HD were studied. PSG on the night following a non-dialysis day was positive (AHI≥15/h) in 28 patients (sleep apnea group: 21 patients with OSA and 7 with CSA) and negative (AHI<15/h) in 12 patients (non-sleep apnea group). In the sleep apnea group, total body extracellular fluid volume was higher than in the non-sleep apnea group as were evening neck, thorax, and leg fluid volumes. A higher overnight change in leg fluid volume (p=0.048) was also observed. Of note, at multivariate analysis, extracellular fluid volume was correlated with the AHI (r=0.468, p=0.002) independently of other confounders. However, the sleep apnea group included more males and older subjects than the non-sleep apnea group, and both factors could predispose to an increased risk for OSA.

Another study, enrolled 23 patients with steroid-responsive nephrotic syndrome and lower limb edema, to evaluated whether nocturnal fluid shift increased the risk for OSA [95]. OSA (AHI>5/h) was diagnosed in 11 patients upon presentation and before

treatment initiation. After disease remission, AHI and RDI were reduced in OSA patients, in association with a decrease in total body fluid volume.

In another cross-sectional study, 20 ESRD patients underwent magnetic resonance imaging (MRI) the day before HD in order to assess fluid displacement from the legs and retention in the upper airway as a contributing factor for the development of OSA [96]. Seven patients had OSA (AHI≥15/h) based on PSG. Upper airway MRI was used to assess upper airway fluid accumulation. Both the internal jugular vein volumes and the upper airway-mucosal water content were correlated with the severity of OSA.

A role for rostral fluid accumulation in the upper airway at bedtime as a risk factor for OSA in ESRD patients is confirmed by the effects of conversion from conventional to nocturnal HD. The latter being associated with a decrease in AHI ($p=0.03$), and reduction of extracellular fluids [97]. Similarly, conversion from continuous ambulatory peritoneal dialysis to nocturnal peritoneal dialysis resulted in reduced prevalence of OSA ($p=0.016$), as it was demonstrated by a decrease in AHI [98].

In summary, OSA is highly prevalent among patients with CKD and especially ESRD, with estimates reaching up to 60%. Fluid overload and rostral fluid shift during supine position, as well as enhanced ventilatory sensitivity to hypercapnia, are important pathogenetic mechanisms of OSA in these populations.

5. Effect of treatment with CPAP on renal function

CPAP is the first line treatment for adult patients with moderate and severe OSA and for those with mild OSA and symptoms or complications of SDB [99]. Studies on the effects of CPAP on albuminuria or renal function highly differ in design, sample

size and treatment duration. The main results of the studies concerning effects of CPAP on renal function in OSA patients are summarized in Table 3.

Two small studies [101,102] evaluated changes in renal function after CPAP in patients who did not have a low GFR but could suffer from glomerular hyperfiltration. The latter is an abnormal increase in ~~(~~GFR~~)~~ or in the filtration fraction (the ratio of GFR to the effective renal plasma flow). In some situations, like pregnancy, it occurs naturally. Instead, in other situations, it may start as an adaptive mechanism to nephron loss and be followed by glomerular hypertension, glomerular sclerosis and, possibly, by the development of CKD [100]. Kinebuchi et al. [101] evaluated renal function before and after one week of CPAP. More specifically, the study included 27 patients with moderate to severe OSA, diagnosed with PSG, while 32 healthy kidney donors served as controls. Investigators examined whether glomerular hyperfiltration had been present in OSA, as evaluated by renal plasma flow (RPF), GFR and filtration fraction (FF), with the double clearance test of sodium thiosulphate and p aminohippurate, and if it was reduced after treatment with CPAP. Before the initiation of CPAP, FF was elevated in OSA patients compared to controls ($p<0.001$) and significantly associated with lowest SaO_2 at multiple regression analysis. In 21 patients treated for a week with CPAP, RPF increased~~,~~ and FF decreased. Thus, the use of CPAP, even for a short period, could reduce glomerular filtration overload. Additional evidence comes from the article of Nicholl et al. [102]. In their study, 20 OSA patients who were normotensive~~,~~ and did not have diabetes or CKD underwent evaluation of circulating and renal RAS activity after CPAP therapy and in response to AngII infusion. Treatment with CPAP reduced GFR, FF, plasma aldosterone and urinary protein excretion and increased RPF. Moreover, AngII challenge resulted in a greater decrease

in RPF in the post CPAP study (p=0.024), indicating that the kidney response to AngII was enhanced after CPAP and intrarenal RAS activity was effectively down-regulated.

Two other small studies evaluated effects of CPAP on eGFR in patients with various degrees of eGFR reduction at baseline. Koga et al [103] in 27 OSA patients free from cardiovascular disease observed significant reduction in serum creatinine and increase in eGFR after 3 months of treatment with CPAP. In a retrospective cohort study, Puckrin et al. demonstrated that compliance to CPAP treatment abated the decline of kidney function [104]. Forty-two patients with sleep apnea and concomitant CKD (stages 3-5) were divided into those who used CPAP for >4 h/night during >70% of nights (n=12 patients) and those with inadequate CPAP use, i.e. average use≤4 h/night on ≤70% of nights (n=30 patients). eGFR declined more slowly among patients with adequate CPAP use and this effect remained significant after adjustment for comorbidities and baseline eGFR. Interestingly, the group with higher CPAP use demonstrated a significant reduction in proteinuria.

Other studies addressed effects of CPAP on urinary albumin excretion Daskalopoulou et al. reported that morning albumin excretion measured in the immediately after CPAP decreased compared to the initial diagnostic study, and this effect remained stable up to 3 months after starting CPAP treatment (p<0.001) [34]. A similar reduction in morning albumin excretion was reported after one month of CPAP [105]. Chen et al [Medicine 2016 **to add**], reported that morning ACR decreased in OSA patients in subjects with good, but not in those with poor, compliance to CPAP after therapy for 6 months. A similar difference in the reduction in ACR between OSA patients compliant and non-compliant to therapy was observed by Matsumoto et al after CPAP therapy for 3 months [Ann AmTorac Soc 2016, **to add**].

Only one randomised controlled study has been published so far on long-term effects of CPAP on kidney function, which was a sub-study of the SAVE trial [106] on 200 patients without severe nocturnal hypoxemia followed up for a median period of 4.4 years. A small nonsignificant difference in eGFR was found between patients under CPAP or other treatment compared to patients with untreated OSA.

The ESADA study group recently examined the long term effect of CPAP use on renal function decline in a large sample of patients (n=1,807, median follow-up period of 541 days); in particular regarding the question of whether auto- or fixed CPAP may differ in the prevention of kidney disease among newly diagnosed OSA subjects [107]. Patients were divided into those who did not receive treatment (n=144), those who were treated with auto-adjusting PAP (APAP) (n=485) and those who received fixed CPAP (n=1,178). Fixed CPAP use resulted in a slight increase in eGFR values, which was significantly different from the change observed in the APAP group and in the untreated group. At multivariate analysis, fixed CPAP use independently predicted an increase in eGFR at follow-up, with a difference of 3.6 ml/min/1.73m^2 compared to the untreated group. The improvement observed with fixed CPAP was interpreted as a result of a greater reduction of sympathetic activity with fixed CPAP compared to APAP, as shown in previous studies [108,109].

A recent meta-analysis explored the efficacy of positive airway pressure on GFR in patients with SDB [110]. A total of 8 observational studies with 240 patients were included in the final analysis. Treatment duration ranged between 1 day and 12 months. In five studies patients received CPAP while in the remaining three studies patients received adaptive servo-ventilation (ASV) because of heart failure. Authors reported that treatment of SDB did not result in a significant impact on GFR [standardized mean difference (SMD) = 0.010, 95 % CI=−0.331 to 0.350, z=0.06,

p=0.956)]. Nevertheless, an increase in GFR was observed in patients older than 55 years (SMD = −0.283, 95 % CI=−0.518 to −0.047, z=2.35, p=0.019) and in patients treated for a least three months (SMD=−0.276, 95 % CI=−0.522 to −0.031, z=2.20, p=0.027). Of note, a trend towards significant increase in GFR was shown after treatment with ASV (SMD=−0.250, 95 % CI=−0.512 to 0.012, z=1.87, p=0.061).

Commentato [OM3]: I would skip this paper

In summary, despite a few studies support that treatment of OSA by CPAP has beneficial effects on the kidneys, some controversy still exists, and further stronger evidence is required to better clarify this issue. Large randomized trials are urgently needed and one has already been planned [111].

Conclusions

In summary, a new concept has been developed recently, that OSA may be a contributing factor for the development and progression of CKD. Thus, early recognition and treatment of OSA could potentially blunt progression to more advanced stages of CKD. The pathogenesis of the interaction between OSA and CKD is multifactorial, but nocturnal hypoxia appears to be the cornerstone of this process. Clinicians should be aware of this mutual association in order to investigate CKD patients for comorbid OSA, as well as OSA patients who are at risk for CKD. Further studies focusing on the role of CPAP, or on alternative OSA treatment modalities, in renal function are warranted, in order to recognize OSA patients who might benefit the most from the treatment of their disease.

Practice points

1. Recent data indicate an association between untreated obstructive sleep apnea and kidney function deterioration
2. The pathogenetic process through which obstructive sleep apnea contributes to chronic kidney disease development seems to be multifactorial, with nocturnal hypoxia possibly being the most prominent factor, interacting with other pathophysiological elements like renin angiotensin aldosterone system, sympathetic nervous system and endothelial dysfunction
3. Obstructive sleep apnea in the presence of diabetes mellitus and/or hypertension, augments the risk for chronic kidney disease development
4. Compliance to therapy with continuous positive airway pressure may have protective effects on renal function

Research agenda

1. Investigate the impact of obstructive sleep apnea on kidney disease in a latent stage and determine the role of treatment with continuous positive airway pressure
2. Review large prospective trials for specific phenotypes of obstructive sleep apnea associated with an increased risk for chronic kidney disease development (i.e. those with severe nocturnal hypoxemia, comorbid cardiovascular disease, obesity or diabetes) in order to highlight the importance of routine examination of renal function in patients with obstructive sleep apnea
3. Investigate the presence of other CKD-related sleep disturbances, such as periodic limb movements, due to their negative impact on cardiovascular outcomes in CKD and monitor closely these patients especially after treatment of obstructive sleep apnea with CPAP

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