Manual Therapy, Posturology & Rehabilitation Journal
ISSN: 2236-5435

REVIEW

Obstructive sleep apnea in chronic kidney disease patients undergoing hemodialysis. Prevalence, severity, and treatment. A narrative review

Diego A. C. P. G. Mello[1], Israel R. Santos[2], Aline R. Danaga[3], João Pedro R. Afonso[1]; Ricardo S. Moura[1], Miriã C. Oliveira[1]; Carla N. S. Nunes[1], Shayra K. A. Souza[4]; Bruna M. R. Silva[4]; Max S. Sousa[4], Ezequiel F. Oliveira[5], Bruno C. Queiroz[6], Caroline F. Gonçalves[6]; Jéssica S. Tomei[6], Pamella Matiolli[6], Bruna A. P. F. Oliveira[7], Barbara O. Moura[8], Sergio R Nacif[9], Luis Vicente F. Oliveira[1].

[1]Human Movement and Rehabilitation master's degree and Doctorate Program, Evangelical University of Goiás (UNIEVANGELICA), Anapolis (GO), Brazil.
[2]Medicine School, Nove de Julho University (UNINOVE), São Paulo (SP) Brazil.
[3]Federal University of Alfenas (UNIFAL), Alfenas (MG), Brazil.
[4]Scientific Initiation Program, Evangelical University of Goiás (UNIEVANGELICA), Anapolis (GO), Brazil.
[5]Sleep Institute, Federal University of São Paulo (UNIFESP), São Paulo (SP), Brazil.
[6]Department of Physiotherapy, Faculdade Sudoeste Paulista (FSP), Avare (SP), Brazil.
[7]Policlin Hospital, São José dos Campos (SP), Brazil.
[8]Physiotherapy Course, Evangelical University of Goiás (UNIEVANGELICA), Anapolis (GO), Brazil.
[9]Hospital Servidor Público Estadual (HSPE), São Paulo (SP), Brazil.

Abstract:

Background: Chronic kidney disease (CKD), also known as chronic renal insufficiency (CRI), can be defined by a glomerular filtration rate (GFR) less than 60mL/min/1.73m^2 associated with an albumin-to-creatinine ratio greater than 30mg of albumin per 1g of creatinine. CKD is a significant factor leading to a decline in the quality of life, increased morbidity, and a substantial reduction in life expectancy. Currently, it is estimated that there are 3.9 million patients worldwide on renal replacement therapy for CKD. Recent data indicates that in the United States of America (USA), more than 500,000 people suffer from renal failure or insufficiency. In Brazil, epidemiological data is incomplete and outdated. In 2016, there were 122,825 patients in Brazil on renal replacement therapy. **Objectives:** This literature review aims to assess the prevalence, severity, and therapeutic recommendations for obstructive sleep apnea (OSA) in patients with CKD undergoing hemodialysis. **Methods:** A literature review was conducted using PubMed, Web of Science, and SciELO databases with keywords including "Obstructive Sleep Apnea", "Chronic kidney disease", "End-stage renal disease", "sleep disorders", "hemodialysis", "CPAP", "Continuous positive airway pressure", and "Physiotherapy." Only studies published in the last twenty years and in the English language were included. **Results:** Despite scientific evidence demonstrating a high prevalence of OSA in CKD patients undergoing hemodialysis, there are still a lack of studies examining the effects of Continuous positive airway pressure (CPAP) therapy on the clinical outcomes of these patients. In the scientific literature, only three randomized clinical trials were found that investigated the impact of CPAP therapy on improving kidney function. Consequently, there is a critical need for clinical studies to assess the effects of CPAP therapy in CKD patients undergoing hemodialysis. It is also essential to highlight the role of physiotherapy in managing sleep disorders and aiding in the adaptation and monitoring of patients undergoing CPAP therapy. **Conclusion:** This literature review concluded that more randomized controlled studies are necessary to better define the optimal therapy for OSA in CKD patients, with the goal of preventing a decline in GFR progression, reducing morbidity and mortality, and enhancing overall quality of life.

Keywords: Respiratory sleep disorders; obstructive sleep apnea; end-stage renal disease; hemodialysis; physiotherapy; continuous positive airway pressure; CPAP.

Corresponding author: Luis Vicente Franco Oliveira
E-mail: oliveira.lvf@gmail.com

Received: 22 Nov, 2022.
Accepted: 26 Apr, 2023.
Published: 27 Oct, 2023.

BACKGROUND

Chronic kidney disease (CKD), also known as chronic renal insufficiency (CRI), can be defined by a glomerular filtration rate (GFR) less than 60mL/min/1.73m^2 associated with an albumin-to-creatinine ratio greater than 30mg of albumin per 1g of creatinine. CKD is a significant factor leading to decline in the quality of life, increased morbidity, and substantial reduction in life expectancy. Currently, it is estimated that there are 3.9 million patients worldwide on renal replacement therapy for CKD[1, 2]. Recent data indicates that in the United States of America (USA), more than 500,000 people suffer from renal failure or insufficiency. According to the United States Renal Data System database in 2015, 124,411 new cases of end-stage renal disease (ESRD) were diagnosed, with an expected annual increase of 20,000 new cases, making it the ninth leading cause of death that year[2, 3].

In Brazil, epidemiological data is incomplete and outdated. In 1994, there were 24,000 patients with ESRD on renal replacement therapy, and by 2004, this number had risen to 59,153 patients. The annual incidence of CKD was 8%, with 18,000 new cases diagnosed in 2001. In 2004, the annual cost of the National Dialysis Program was R$1.4 billion Brazilian reais, and an estimated 1.5 million Brazilians were living with some degree of CKD[4]. In 2013, the prevalence of CKD in Brazil was 1.42%, rising to 2.68% among Brazilians aged 65 or older, with an estimated annual incidence of 119.8 cases per million inhabitants. In 2016, there were 122,825 Brazilians on renal replacement therapy[5]. In 2018, the estimated prevalence of patients on dialysis worldwide was approximately 298.4 per million inhabitants. The annual mortality among hemodialysis patients was 6.6% in Japan compared to 21.7% in the USA[3].

While individuals between the ages of 40 and 44 can expect to live for about another 40 years, those at the same age with CKD on hemodialysis can only expect about another 10 years of life[3]. CKD patients have a significantly higher prevalence of various comorbidities compared to the general population, including sleep disorders[6]. In a study conducted in 2018 in São Paulo, it was found that 73% of CKD patients on hemodialysis were found to have obstructive sleep apnea (OSA). Other studies have shown prevalence rates of up to 50% in this patient population[7, 8].

The presence of sleep-disordered breathing (SDB), OSA, or central sleep apnea (CSA) in CKD patients increases the risk of cardiovascular events and overall mortality, regardless of the modality of renal replacement therapy and even in non-dialytic patients[6, 7, 9, 10]. The presence of mixed sleep apnea can lead to a rapid decline in renal function in non-dialytic CKD patients, potentially resulting in stage alteration and the need for renal replacement therapy[9, 10]. SDB is characterized by episodes of hypopnea and/or apnea that lead to repetitive hypoxia, elevated cytokine levels, and increased blood pressure, resulting in peripheral insulin resistance. These changes are risk factors for CKD progression, as diabetes and systemic arterial hypertension (SAH) are the main causes of CKD worldwide[10, 11]. In addition to SDB, the presence of pruritus in cases of uremia and restless legs syndrome impairs sleep, compromises quality of life, and increases the risk of cardiovascular events, thereby increasing mortality in CKD patients[12, 13]. Despite sleep disorders being a risk factor for CKD progression, CKD is also a risk factor for the development of sleep disorders[6].

The high prevalence of SDB in patients with CKD on renal replacement therapy can be explained by uremic neuropathy and hypervolemia. A weight gain of more than 2kg between dialysis sessions is an independent risk factor for the development of SDB[6-8, 14]. Despite their considerable impact on the life expectancy and quality of life of dialysis patients, sleep disorders present clinically differently in these patients from the general population, making their diagnosis and treatment challenging. This literature review aims to assess the prevalence, severity, and therapeutic recommendations for OSA in patients with CKD undergoing hemodialysis.

METHODS

A literature review was conducted using PubMed, Web of Science, and SciElo databases with keywords including "Obstructive Sleep Apnea", "Chronic kidney disease", "End-stage renal disease", "sleep disorders", "hemodialysis", "CPAP", "Continuous positive airway pressure", and "Physiotherapy." Only studies published in the last twenty years and in the English language were included. In the scientific literature, only three randomized clinical trials were found that investigated the impact of CPAP therapy on improving kidney function.

Definition and classification

CKD, also known as Chronic Renal Insufficiency (CRI), is defined according to the Kidney Disease Improving Global Outcomes (KDIGO) Foundation Guidelines as morphological or functional renal alterations lasting for more than three months, associated with a GFR less than 60 mL/min/1.73m^2 and an albumin-to-creatinine ratio greater than 30 mg of albumin per 1g of creatinine. In stage G5 of the KDIGO classification, the patient is in ESRD, with a GFR of less than 15 mL/min/1.73m^2, requiring renal replacement therapy to survive[1, 2, 6].

A respiratory event is considered apnea in adults if there is a ≥50% reduction in airflow compared to the graphed baseline prior to the event, as measured using an oronasal thermal sensor and/or pressure cannula, positive pressure airflow device, or an alternative apnea sensor. This reduction must last for at least 10 seconds or more to be considered apnea. To be classified as hypopnea, there should be a 30% or greater reduction in respiratory airflow for at least ten seconds, accompanied by a decrease of four percent or more in oxygen saturation[15]. The Apnea-Hypopnea Index (AHI) per hour of sleep is used to classify the severity of sleep apnea based on the number of events. A normal index ranges from 0 to 5 events per hour, mild from 5 to 14.9 events/hour, moderate from 15 to 30 events/hour, and severe with more than 30 events/hour[6, 16].

Epidemiology

The prevalence of OSA and CSA in the general population varies according to sex and age, being more common in men and older people. For moderate to severe disorders, the prevalence is in the age group of 30 to 49 years, at 10% for men and 3% for women. In the age group between 50 and 70 years old, there is a 17% prevalence in men and 9% in female patients[17]. In the population with CKD, the prevalence of sleep disorders is significantly higher, and the prevalence increases according to the worsening of GFR. According to some studies, this prevalence varies from 50 to 73% in stage 5 patients according to KDIGO[1, 7, 8, 18, 19]. Patients with CKD with a GFR greater than 59mL/min/1.73m^2 have a prevalence of 27% for moderate to severe disorders, while patients with a GFR of 59 to 15mL/min/1.73m^2 have a prevalence of 41%, and in renal replacement therapy patients (GFR less than 15mL/min/1.73m^2) the prevalence rises to 57%. The influence of weight, age, sex, and comorbidities was excluded in the studied population, leaving CKD as the main influence[18, 20].

Sleep apnea as a risk factor for CKD and worsening renal function

According to the scientific literature, it is known that the presence of OSA can increase the risk of developing CKD and even lead to progressive impairment of renal function in these patients[6]. In a cohort study involving 6,866 patients, Lin et al., demonstrated that patients with OSA had an odds ratio of 1.37 for developing CKD, and they developed CKD earlier than patients without OSA[21]. In an intriguing cohort study involving three million veterans, Molnar et al., observed a strong association between OSA and CKD. According to the study, patients with OSA had about twice the odds of developing CKD compared to patients without OSA[22]. Besides increasing the risk of developing CKD, the presence of sleep disorders also raises the risk of worsening renal function.

In a prospective study of GFR with an 11-year follow-up, Jaussent et al., demonstrated that the presence of excessive daytime sleepiness (EDS) and periodic leg movements (PLM) increased the risk of worsening renal function by 1.7 and 2 times, respectively. In this study, Jaussent et al., showed that severe apnea increased the risk of worsening renal function independent of the presence of diabetes Mellitus, systemic arterial hypertension (SAH), smoking, body mass index (BMI), age, gender, and the presence of EDS[23]. The presence of EDS may result from reduced nighttime sleep duration, which can cause low-grade systemic inflammation, increasing the likelihood of worsening or developing cardiovascular disease and consequently worsening renal function[24]. In patients with SAH without CKD, the presence of OSA increased the risk of worsening GFR and progressing to CKD by 1.21 times more than in patients without OSA[25].

Sakaguchi et al., in a multicenter retrospective study, assessed the association between nocturnal hypoxia and the progression of CKD in patients classified as moderate and severe according to the KDIGO stages 3 and 4. Patients with a BMI above 25kg/m^2 were excluded to avoid obesity as a confounding factor. Among the patients involved in the study, those who had moderate to severe nocturnal hypoxemia (fifteen or more points on the oxygen desaturation index) experienced a three to four times faster decline in renal function[26].

Among the theories proposed, it is known that nocturnal hypoxia can lead to hyperactivation of the renin-angiotensin-aldosterone system (RAAS), which in turn can cause direct renal injury with increased glomerular pressure and worsening of renal function. This hyperactivation can be evidenced by the lack of an increase in effective renal plasma flow during the administration of angiotensin II tests in patients with OSA[27, 28]. The RAAS hyperactivation due to severe intermittent hypoxia (IH) (nighttime peripheral oxygen saturation below 90% due to OSA) leads to direct renal damage. Additionally, it results in SAH due to water and sodium retention[27-30].

Adding to this clinical picture of RAAS hyperactivation is the role of the sympathetic autonomic nervous system (SANS). In an interesting experimental study with rats, IH for approximately seven hours daily was shown to activate the SANS through carotid chemoreceptors, increasing the action of the RAAS through type 1 angiotensin II receptors[29].

Patients with IH nocturnal tend to have higher blood pressure levels, with the elevation being related to increased SANS activity that occurs both during sleep and wakefulness. This increase in blood pressure is related to peripheral vasoconstriction caused by the action of the SANS[6, 31, 32]. SAH associated with vasoconstriction causes damage to renal function through tubulointerstitial injury, as well as injury to the renal microvasculature (fibrosis of peritubular capillaries), resulting in mitochondrial impairment and apoptosis[30].

IH in renal tissue alone is capable of generating oxidative stress, with an increase in the production of oxygen-free radicals that cause tissue damage and endothelial dysfunction, stimulating the activation of fibroblasts leading to fibrosis of renal tissues, as well as hypertrophy of tubular epithelial cells and dilation of the glomerulus[30, 33, 34].

The paradox between CKD and OSA as cause and effect still persists, as OSA appears to be a risk factor for CKD development and a contributor to the worsening of CKD patients, but CKD is also a risk factor for the development of OSA[30]. According to various published studies, it is known that the prevalence of OSA in CKD patients undergoing renal replacement therapy is approximately 55%. It has also been demonstrated that when dialysis sessions (peritoneal or hemodialysis) are intensified, there is an improvement in the OSA condition with a reduction in the AHI. The same improvement is observed after kidney transplantation[7, 8, 19, 35-38]. Based on these data, it becomes clear that the clinical picture of CKD can be an independent cause of OSA.

Patients with CKD present a metabolic acidosis that stimulates bulbar chemoreceptors, leading to hyperventilation with hypocapnia, causing instability in central respiratory control due to a reduction in pCO_2 below bulbar activation levels. In association with central dysregulation and reduced chemosensitivity, there is sodium and water retention, both due to impaired renal excretion and hyperactivation of the RAAS, causing pharyngeal narrowing and an increase in tongue volume, leading to upper airway obstruction[30, 39]. The accumulated hypervolemia in the lower limbs during the day shifts to the chest and neck region when the patient assumes the supine position to sleep. The migration of excess extracellular fluid rostrally (from the lower limbs to the trunk, cervical region, and cranial pole) results in external compression of the upper airway, consequently reducing its caliber[39-42].

According to various studies, neck circumference is a predictive factor for the magnitude of OSA related to fat accumulation and/or hypervolemia[42-44]. The displacement of fluid from the lower limbs to the thoracic and cervical region also affects the extravascular lung space, stimulating capillary pulmonary receptors, leading to a cycle of hyperventilation and predisposing to OSA and especially CSA[40, 41, 43, 44]. Studies evaluating the diameter of the internal jugular vein using magnetic resonance imaging have shown that the greater the vein's distension (caused by increased intravascular volume), the worse the sleep apnea condition. Other markers that are also proportionally related to the magnitude of hypervolemia and consequently OSA include brain natriuretic peptide and cardiothoracic index, as well as the diameter of the inferior vena cava[40, 42, 44, 45].

The presence of uremic neuropathy in CKD patients reduces the sensitivity of the upper airways, increasing the likelihood of collapse and subsequent obstruction. Additionally, uremic myopathy contributes to a reduced exhaustion threshold of ventilatory muscles, leading to a decrease in the tone of these muscles, thereby contributing to sleep-related respiratory events[46, 47].

Despite the aforementioned, in a meta-analysis conducted by Kanbay et al., in 2023, the authors assessed the changes in polysomnographic (PSG) parameters in patients undergoing kidney transplantation and demonstrated that there was no improvement in the AHI, total sleep time, or rapid eye movement (REM) sleep time even after transplantation[48]. For CKD patients on peritoneal dialysis, who are older, male, have coronary artery disease, dyslipidemia, chronic obstructive pulmonary disease (COPD), or SAH, the risk of OSA is even higher[49].

Clinical picture of OSA in patients with CKD

Many CKD patients with OSA are not initially diagnosed. The symptoms of OSA that affect the population without kidney disease are generally not present in CKD patients. Furthermore, sleep-related symptoms are present in CKD patients whether they have OSA or not, with the exception of EDS. Symptoms such as EDS, snoring, choking or witnessed apnea, non-refreshing sleep, morning headache, and memory difficulties are more common in the population with OSA without CKD than in CKD patients. Therefore, CKD patients with coexisting OSA may initially go undiagnosed due to the absence of characteristic symptoms. Additionally, it should be noted that patients with ESRD have lower BMI and neck circumference values than OSA patients without CKD[50].

Both BMI and neck circumference are significant risk factors for the development of OSA and are used in screening questionnaires for OSA. However, these screening tools are less applicable in the CKD population[30, 50, 51]. Other factors that may contribute to masking the symptoms of OSA in CKD patients include the presence of various comorbidities, the use of various medications, and the typical symptoms of CKD itself, such as fatigue and poor sleep quality. Insomnia, PLM and, restless legs syndrome (RLS) are also common symptoms in CKD[13, 30, 50, 52, 53].

Given the high prevalence of sleep disorders in CKD, the scarcity of symptoms, and the ineffectiveness of screening questionnaires in this population, the use of highly sensitive diagnostic tests such as overnight polysomnography or cardiopulmonary sleep monitoring tests becomes important for detecting OSA, as it increases overall mortality and is a risk factor for cardiovascular events in CKD[7, 54].

The use of CPAP in CKD patients and its impact on kidney function

The use of CPAP is the first-line treatment for patients with moderate to severe OSA, effectively maintaining open airways during sleep and preventing hypopnea and apnea events[55,56]. Some studies have shown that using CPAP in stage 5 CKD patients for one week decreased renal plasma flow, which can be seen as a partial reversal of renal hyperperfusion, one of the contributing factors to declining eGFR in CKD[55, 56].

Moriya et al., in a retrospective study, correlated the ratio of creatinine to urinary N-acetyl-β-D-glucosaminidase (UNCR) with worsening oxygen desaturation index (ODI) in patients with OSA and CKD. Additionally, CPAP therapy was applied to patients with an AHI of 20 or higher. The use of CPAP reduced diastolic blood pressure, decreased UNCR, and maintained stable eGFR in these patients[57].

Rimke et al., initiated a randomized controlled clinical study applying CPAP therapy to CKD patients with OSA in the study group, in addition to standard therapy for other comorbidities and CKD, to assess changes in eGFR over one year of treatment and compare them to a control group[58]. The results of the study are not yet available. In a case report of a 51-year-old peritoneal dialysis patient, one year of CPAP use reduced EDS and improved sleep quality, cognitive ability, and quality of life, but no changes in blood pressure levels were evaluated[59]. Fu et al., published a meta-analysis in 2023 that assessed the use of CPAP in non-dialysis CKD patients using randomized clinical trials, a large sample (519 in total), and CPAP use for at least 4 hours per night[60]. The use of CPAP did not effectively modify eGFR.

In patients with OSA without impaired kidney function, the use of CPAP has been shown to reduce the overactivation of the RAAS, as evidenced by increased renal flow after angiotensin II administration, decreased serum aldosterone levels, and reduced proteinuria. Additionally, blood pressure levels in these patients decreased after 30 days of CPAP use[61]. Since OSA in CKD patients causes a gradual decline in kidney function, treating the respiratory disorder could prevent the progression of CKD caused by the respiratory disorder. An interesting study conducted by Marrone et al., compared the decline in eGFR in patients with untreated OSA, those treated with standard CPAP, and those treated with auto-adjustable CPAP[62]. After 541 days of follow-up, the authors found that the decline in eGFR was greater in the untreated and auto-adjustable CPAP-treated groups than in the standard CPAP-treated group.

There are few studies in the scientific literature that have assessed the effectiveness of CPAP in preventing or reducing the decline in eGFR in CKD patients. In a meta-analysis conducted in 2017, Chen et al., demonstrated that the use of CPAP therapy in CKD patients did not lead to a decline in eGFR[63]. When subgroups were evaluated, the authors observed a significant improvement in eGFR in patients aged 55 and older and those treated for 3 months or more. Conversely, in one arm of the SAVE (Sleep Apnea Cardiovascular Endpoints) study, patients with cerebrovascular or coronary artery disease, both with moderate to severe OSA, were randomized into two groups: one receiving standard treatment for the underlying disease and the other receiving standard treatment plus CPAP. The two groups were followed up for 4.4 years, with no difference in terms of eGFR decline, the albumin-to-creatinine ratio, or the number of severe renal complications. However, the study was not primarily designed to evaluate renal repercussions or complications. The study design also failed to include patients whose initial eGFR was normal, preventing the evaluation of OSA control as a protective factor against CKD progression[64].

In another study, Puckrin et al., compared CKD patients with eGFR less than 59 mL/min/1.73m^2 who used CPAP therapy[65]. Among the patients involved in the study, those who used CPAP for more than 4 hours per night and on more than seventy percent of nights showed a reduction in eGFR decline and worsening proteinuria compared to patients who used CPAP for shorter periods or less frequently.

FINAL CONSIDERATIONS

Despite the high prevalence of sleep disorders in CKD patients, the symptoms they may present are nonspecific and can complicate diagnosis. When diagnosed, CKD patients with OSA should be treated with CPAP, as there are studies demonstrating the stabilization of renal function and proteinuria in treated patients, although there is no randomized controlled trial providing clear evidence of the benefit of this therapeutic modality in maintaining renal function.

In contrast, there is evidence that intensifying dialysis therapy, especially with the use of nocturnal dialysis sessions, improves the respiratory status of these patients with a reduction in AHI. However, there are authors who disagree with this assertion, and such intervention requires resources and may generate long-term complications. Moreover, it is feasible only for patients already on dialysis.

According to the literature, there is a worldwide consensus that CPAP is the gold standard in the therapeutic approach to moderate to severe OSA. The effects of its use include improving cognitive function, daytime drowsiness, subjective sleep quality, mood, and health-related quality of life[66-68].

Patients with CKD have a high risk factor for cardiovascular disease, often progressing to ESRD. At this stage, the only therapeutic options are dialysis or kidney transplant, with significant financial implications for patients and the yours health conditions[69]. Given the high prevalence of CKD in the world population, it would be of great importance to identify new risk factors for the development of the disease and new clinical approaches. In this scenario, OSA, observed in up to 40% of patients with CKD[8], has contributed to the progression of the disease due to IH and sleep fragmentation caused by apneic events, as demonstrated in the scientific literature in experimental animal models[70] and also in studies involving patients[71].

Even with the scientific demonstration of the high prevalence of OSA in patients with CKD undergoing hemodialysis, there is still a lack of studies demonstrating the effects of CPAP therapy on the clinical evolution of these patients. In the scientific literature, only three randomized clinical trials were found that verified the effects of using CPAP on improving kidney function[58, 64, 72]. Therefore, clinical studies that show the effects of using CPAP in CKD patients undergoing hemodialysis are extremely necessary. It would be extremely important to draw attention to the role of physiotherapy in sleep disorders in the adaptation and monitoring of these patients undergoing CPAP therapy.

Through this literature review, it can be concluded that more randomized controlled studies are needed to better define the preferred therapy for OSA in patients with CKD, to prevent the progression of the fall in GFR, and consequently, reduce morbidity and mortality while improving the quality of life.

Author Contributions: Author Contributions: Conceptualization, DACPGM, IRS, ARD, SRN, and, LVFO; formal analysis, JPRA, SRN, IRS and, LVFO. funding acquisition, DACPGM, IRS and, LVFO. investigation, methodology, DACPGM , RSM, MCO, BMRS, MSS, CNSN, SKAS, IRS, and L.V.F.O. Data collect, ISR, ARD, JST, EFO, BCQ, CFG and, PM project administration, DACPGM, IRS and, LVFO supervision, SRN and IRS. writing—original draft, LLG, APLO, RABLM, MCO, GI, DACPGM, Writing—review and editing, IOS, GI, LFVO, BAPFO, BOM, and, RKP. All authors have read and agreed to the published version of the manuscript.

Funding: CNSN received grants from Coordenação de Apoio ao Pessoal de Nível Superior (CAPES/PROSUP); MCO, JPRA, and, RSM, received grants from Fundação de Amparo à Pesquisa (FAPEG), Goiás (GO), Brazil; SKAS, MSS and, BMRS received Scientific Initiation Grants, Evangelical University of Goiás (UNIEVANGELICA). L.V.F.O. received grants from Research Productivity, modality PQII; process no. 310241/2022-7 of Conselho Nacional de Desenvolvimento Científico e Tecnológico (local acronym CNPq), Brazil.

Financial Support: nothing to declare

Conflict of interest: The authors declare that they have no conflicts of interest

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59.
2. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, et al. US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2018;71(3 Suppl 1):A7.
3. Abbasi M, Chertow G, Hall Y. End-stage Renal Disease. Am Fam Physician. 2010;82(12):1512.
4. Romão Júnior, JE. Doença Renal Crônica: Definição, Epidemiologia e Classificação. J Bras Nefrol - nº 3 - Supl. 1 - Agosto de 2004. Braz. J. Nephrol., 2004, 26(3 suppl. 1).
5. Aguiar LK, Prado RR, Gazzinelli A, Malta DC. Factors associated with chronic kidney disease: epidemiological survey of the National Health Survey. Rev Bras Epidemiol. 2020;23:e200044.
6. Lin CH, Lurie RC, Lyons OD. Sleep Apnea and Chronic Kidney Disease: A State-of-the-Art Review. Chest. 2020;157(3):673-685.
7. Harmon RR, De Lima JJG, Drager LF, Portilho NP, Costa-Hong V, Bortolotto LA, et al. Obstructive sleep apnea is associated with interdialytic weight gain and increased long-term cardiovascular events in hemodialysis patients. Sleep Breath. 2018;22(3):721-728.
8. Nicholl DDM, Ahmed SB, Loewen AHS, Hemmelgarn BR, Sola DY, Beecroft JM, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. Chest. 2012;141(6):1422-1430.
9. Xu J, Yoon IY, Chin HJ. The effect of sleep apnea on all-cause mortality in nondialyzed chronic kidney disease patients. Sleep Med. 2016;27-28:32-38.
10. Kanbay A, Buyukoglan H, Ozdogan N, Kaya E, Oymak FS, Gulmez I, et al. Obstructive sleep apnea syndrome is related to the progression of chronic kidney disease. Int Urol Nephrol. 2012;44(2):535-9.
11. López-Novoa JM, Martínez-Salgado C, Rodríguez-Peña AB, López-Hernández FJ. Common pathophysiological mechanisms of chronic kidney disease: therapeutic perspectives. Pharmacol Ther. 2010;128(1):61-81.
12. Bello AK, Alrukhaimi M, Ashuntantang GE, Basnet S, Rotter RC, Douthat WG, et al. Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action. Kidney Int Suppl (2011). 2017;7(2):122-129.
13. Chavoshi F, Einollahi B, Sadeghniat Haghighi K, Saraei M, Izadianmehr N. Prevalence and sleep related disorders of restless leg syndrome in hemodialysis patients. Nephrourol Mon. 2015 Feb 24;7(2):e24611.
14. Lyons OD, Inami T, Perger E, Yadollahi A, Chan CT, Bradley TD. The effect of fluid overload on sleep apnoea severity in haemodialysis patients. Eur Respir J. 2017;49(4):1601789.
15. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated

Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597-619.

16. Daltro CH, Fontes FH, Santos-Jesus R, Gregorio PB, Araújo LM. Síndrome da apnéia e hipopnéia obstrutiva do sono: associação com obesidade, gênero e idade [Obstructive sleep apnea and hypopnea syndrome (OSAHS): association with obesity, gender and age]. Arq Bras Endocrinol Metabol. 2006;50(1):74-81.
17. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006-14.
18. Ogna A, Forni Ogna V, Haba Rubio J, Tobback N, Andries D, Preisig M, et al. Sleep Characteristics in Early Stages of Chronic Kidney Disease in the HypnoLaus Cohort. Sleep. 2016;39(4):945-53.
19. Chavoshi F, Einollahi B, Sadeghniat Haghighi K, Saraei M, Izadianmehr N. Prevalence and sleep related disorders of restless leg syndrome in hemodialysis patients. Nephrourol Mon. 2015;7(2):e24611.
20. Unruh ML, Sanders MH, Redline S, Piraino BM, Umans JG, Hammond TC, et al. Sleep apnea in patients on conventional thrice-weekly hemodialysis: comparison with matched controls from the Sleep Heart Health Study. J Am Soc Nephrol. 2006;17(12):3503-9.
21. Lin YS, Liu PH, Lin SW, Chuang LP, Ho WJ, Chou YT, et al. Simple obstructive sleep apnea patients without hypertension or diabetes accelerate kidney dysfunction: a population follow-up cohort study from Taiwan. Sleep Breath. 2017;21(1):85-91.
22. Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. Thorax. 2015;70(9):888-95.
23. Jaussent I, Cristol JP, Stengel B, Ancelin ML, Dupuy AM, Besset A, et al. Impact of sleep disturbances on kidney function decline in the elderly. Eur Respir J. 2016;47(3):860-8.
24. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32(12):1484-92.
25. Liu M, Heizhati M, Li N, Lin M, Gan L, Zhu Q et al. The relationship between obstructive sleep apnea and risk of renal impairment in patients with hypertension, a longitudinal study. Sleep Med. 2023;109:18-24.
26. Sakaguchi Y, Hatta T, Hayashi T, Shoji T, Suzuki A, Tomida K, et al. Association of nocturnal hypoxemia with progression of CKD. Clin J Am Soc Nephrol. 2013;8(9):1502-7.
27. Zalucky AA, Nicholl DD, Hanly PJ, Poulin MJ, Turin TC, Walji S, et al. Nocturnal hypoxemia severity and renin-angiotensin system activity in obstructive sleep apnea. Am J Respir Crit Care Med. 2015;192(7):873-80.
28. Hanly PJ, Ahmed SB. Sleep apnea and the kidney: is sleep apnea a risk factor for chronic kidney disease? Chest. 2014;146(4):1114-1122.
29. Fletcher EC, Bao G, Li R. Renin activity and blood pressure in response to chronic episodic hypoxia. Hypertension. 1999;34(2):309-14.
30. Abuyassin B, Sharma K, Ayas NT, Laher I. Obstructive Sleep Apnea and Kidney Disease: A Potential Bidirectional Relationship? J Clin Sleep Med. 2015;11(8):915-24.
31. Arabi Y, Morgan BJ, Goodman B, Puleo DS, Xie A, Skatrud JB. Daytime blood pressure elevation after nocturnal hypoxia. J Appl Physiol (1985). 1999;87(2):689-98.
32. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96(4):1897-904.

33. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. 8-Isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy. Chest. 2003;124(4):1386-92.
34. Poonit ND, Zhang YC, Ye CY, Cai HL, Yu CY, Li T, et al. Chronic intermittent hypoxia exposure induces kidney injury in growing rats. Sleep Breath. 2018;22(2):453-461.
35. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med. 2001;344(2):102-7.
36. Tang SC, Lam B, Ku PP, Leung WS, Chu CM, Ho YW, et al. Aleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. J Am Soc Nephrol. 2006;17(9):2607-16.
37. Kennedy C, Ryan SA, Kane T, Costello RW, Conlon PJ. The impact of change of renal replacement therapy modality on sleep quality in patients with end-stage renal disease: a systematic review and meta-analysis. J Nephrol. 2018;31(1):61-70.
38. Hui L, Benca R. The Bidirectional Relationship Between Obstructive Sleep Apnea and Chronic Kidney Disease. J Stroke Cerebrovasc Dis. 2021;30(9):105652.
39. Hanly PI, Ahmed SB. Sleep apnea and the kidney: is sleep apnea a risk factor for chronic kidney disease? Chest. 2014:146(4):1114-1122.
40. Elias RM, Chan CT, Paul N, Motwani SS, Kasai T, Gabriel JM, et al. Relationship of pharyngeal water content and jugular volume with severity of obstructive sleep apnea in renal failure. Nephrol Dial Transplant. 2013;28(4):937-44.
41. Yumino D, Redolfi S, Ruttanaumpawan P, Su MC, Smith S, Newton GE, et al. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. Circulation. 2010;121(14):1598-605.
42. White LH, Lyons OD, Yadollahi A, Ryan CM, Bradley TD. Night-to-night variability in obstructive sleep apnea severity: relationship to overnight rostral fluid shift. J Clin Sleep Med. 2015;11(2):149-56.
43. Elias RM, Bradley TD, Kasai T, Motwani SS, Chan CT. Rostral overnight fluid shift in end-stage renal disease: relationship with obstructive sleep apnea. Nephrol Dial Transplant. 2012;27(4):1569-73.
44. Jafari B, Mohsenin V. Overnight rostral fluid shift in obstructive sleep apnea: does it affect the severity of sleep-disordered breathing? Chest. 2011;140(4):991-997.
45. Tanaka A, Inaguma D, Ito E, Kamegai N, Kato A, Mizutani M, et al. Factors associated with severity of sleep apnoea syndrome in patients with chronic kidney disease. Acta Cardiol. 2017;72(4):440-445.
46. Kennedy C, Ryan SA, Kane T, Costello RW, Conlon PJ. The impact of change of renal replacement therapy modality on sleep quality in patients with end-stage renal disease: a systematic review and meta-analysis. J Nephrol. 2018;31(1):61-70.
47. Tarasuik A, Heimer D, Bark H. Effect of chronic renal failure on skeletal and diaphragmatic muscle contraction. Am Rev Respir Dis. 1992;146(6):1383-8.
48. Kanbay M, Ureche C, Copur S, Covic AM, Tanriover C, Esen BH, et al. Kidney transplantation: a possible solution to obstructive sleep apnea in patients with end-stage kidney disease. Sleep Breath. 2023.
49. Huang ST, Lin CL, Yu TM, Kao CH, Liang WM, Chou TC. Risk, Severity, and Predictors of Obstructive Sleep Apnea in Hemodialysis and Peritoneal Dialysis Patients. Int J Environ Res Public Health. 2018;15(11):2377.

50. Nicholl DD, Ahmed SB, Loewen AH, Hemmelgarn BR, Sola DY, Beecroft JM, et al. Clinical presentation of obstructive sleep apnea in patients with chronic kidney disease. J Clin Sleep Med. 2012;8(4):381-7.

51. Nicholl DD, Ahmed SB, Loewen AH, Hemmelgarn BR, Sola DY, Beecroft JM, et al. Diagnostic value of screening instruments for identifying obstructive sleep apnea in kidney failure. J Clin Sleep Med. 2013;9(1):31-8.

52. Sekercioglu N, Curtis B, Murphy S, Barrett B. Sleep quality and its correlates in patients with chronic kidney disease: a cross-sectional design. Ren Fail. 2015;37(5):757-62.

53. Unruh ML, Hartunian MG, Chapman MM, Jaber BL. Sleep quality and clinical correlates in patients on maintenance dialysis. Clin Nephrol. 2003;59(4):280-8.

54. Tang SC, Lam B, Yao TJ, Leung WS, Chu CM, Ho YW, et al. Sleep apnea is a novel risk predictor of cardiovascular morbidity and death in patients receiving peritoneal dialysis. Kidney Int. 2010;77(11):1031-8.

55. Voulgaris A, Marrone O, Bonsignore MR, Steiropoulos P. Chronic kidney disease in patients with obstructive sleep apnea. A narrative review. Sleep Med Rev. 2019;47:74-89.

56. Voulgaris A, Bonsignore MR, Schiza S, Marrone O, Steiropoulos P. Is kidney a new organ target in patients with obstructive sleep apnea? Research priorities in a rapidly evolving field. Sleep Med. 2021;86:56-67.

57. Moriya R, Hokari S, Ohshima Y, Suzuki R, Nagai A, Fujito N, et al. Continuous positive airway pressure treatment reduces renal tubular damage in patients with obstructive sleep apnea: A retrospective single-center cohort study. Sleep Med. 2023;106:106-115.

58. Rimke AN, Ahmed SB, Turin TC, Pendharkar SR, Raneri JK, Lynch EJ, et al. Effect of CPAP therapy on kidney function in patients with obstructive sleep apnoea and chronic kidney disease: a protocol for a randomised controlled clinical trial. BMJ Open. 2019;9(3):e024632.

59. Park KS, Chang JH, Kang EW. Effects of 12 months of continuous positive airway pressure therapy on cognitive function, sleep, mood, and health-related quality of life in a peritoneal dialysis patient with obstructive sleep apnea. Kidney Res Clin Pract. 2018;37(1):89-93.

60. Fu Y, Lin J, Chen L, Chen X, Chen Q. Meta-analysis of the effects of CPAP therapy on estimated glomerular filtration rate in patients with obstructive sleep apnea. Sleep Breath. 2023.

61. Nicholl DD, Hanly PJ, Poulin MJ, Handley GB, Hemmelgarn BR, Sola DY, et al. Evaluation of continuous positive airway pressure therapy on renin-angiotensin system activity in obstructive sleep apnea. Am J Respir Crit Care Med. 2014;190(5):572-80.

62. Marrone O, Cibella F, Pépin JL, Grote L, Verbraecken J, Saaresranta T, et al. ESADA Network. Fixed But Not Autoadjusting Positive Airway Pressure Attenuates the Time-dependent Decline in Glomerular Filtration Rate in Patients With OSA. Chest. 2018;154(2):326-334.

63. Chen LD, Lin L, Ou YW, Wu Z, Cai ZM, Wang TZ, et al. Effect of positive airway pressure on glomerular filtration rate in patients with sleep-disordered breathing: a meta-analysis. Sleep Breath. 2017;21(1):53-59.

64. Loffler KA, Heeley E, Freed R, Anderson CS, Brockway B, Corbett A, et al. SAVE (Sleep Apnea Cardiovascular Endpoints) Investigators. Effect of Obstructive Sleep Apnea Treatment on Renal Function in Patients with Cardiovascular Disease. Am J Respir Crit Care Med. 2017;196(11):1456-1462.

65. Puckrin R, Iqbal S, Zidulka A, Vasilevsky M, Barre P. Renoprotective effects of continuous positive airway pressure in chronic kidney disease patients with sleep apnea. Int Urol Nephrol. 2015;47(11):1839-45.

66. Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. Sleep 34:111-119, 2011

67. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. Chest 130:1772-1778, 2006.

68. Pressman MR, Benz RL, Schleifer CR, Peterson DD. Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. Kidney Int 43:1134-1139, 1993.

69. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet 2013;382: 260–272.

70. Abuyassin B, Badran M, Ayas NT, Laher I. Intermittent hypoxia causes histological kidney damage and increases growth factor expression in a mouse model of obstructive sleep apnea. PLoS One 2018;13:e0192084.

71. Nicholl DDM, Hanly PJ, Zalucky AA, Handley GB, Sola DY, Ahmed SB. Nocturnal hypoxemia severity influences the effect of CPAP therapy on renal renin-angiotensin-aldosterone system activity in humans with obstructive sleep apnea. Sleep (Basel) 2021;44:zsaa228.

72. Zamarrón E, Jaureguizar A, García-Sánchez A, Díaz-Cambriles T, Alonso-Fernández A, Lores V, Mediano O, et al. Continuous Positive Airway Pressure Effect on Albuminuria Progression in Patients with Obstructive Sleep Apnea and Diabetic Kidney Disease: A Randomized Clinical Trial. Am J Respir Crit Care Med. 2023;207(6):757-767.