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Review

A systematic review of sleep disorders in patients with chronic kidney disease undergoing hemodialysis

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Abstract. [Purpose] The purpose of this study was to conduct a systematic review of the available evidence on sleep disorders in patients with end stage renal disease (ESRD) undergoing hemodialysis (HD). [Subjects and Methods] Two independent reviewers performed a computer-assisted search of the MEDLINE, SciELO, LILACS, and BIREME Virtual Health Library medical databases from their inception to November 2015. [Results] One thousand one hundred twenty-six articles were found that met the inclusion criteria. Articles were excluded if they were not in English, the patients did not undergo HD, or the studies were not cross-sectional or clinical trials. After reading the full text, a further 300 studies were excluded because they did not use polysomnography. The remaining 18 studies with ESRD patients undergoing HD comprised 8 clinical trials and 10 cross-sectional studies. This systematic review followed the criteria outlined by the PRISMA declaration. [Conclusion] In this systematic review, a high prevalence of sleep disorders was observed in ESRD, including sleep-disordered breathing. This knowledge may enable health professionals to devise new strategies for the diagnosis and treatment of these patients, in order to reduce morbidity and mortality and improve their quality of life.

Key words: Sleep disorders, Chronic kidney disease, Hemodialysis

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INTRODUCTION

Currently, chronic kidney disease (CKD) is one of the most serious public health problems. Some recent epidemiological studies have suggested that approximately one million people with end stage renal disease (ESRD) undergo replacement therapy worldwide. The increased prevalence of CKD in the developed and developing countries threatens to become a global epidemic, as exemplified by the increased number of cases of diabetes mellitus and the increased life expectancy of the population[1)]. CKD severely affects patients' health, lifestyle and wellbeing, compromising their quality of life[2)]. According Ponngeon et al., CKD patients had "sedentary" and "inactive" levels of physical activity on dialysis and non-dialysis days, respectively[3)]. Silva and Marinho observed that the level of physical activity of most patients ESRD undergoing hemodialysis is poor and that most do not perform exercise regularly[4)]. The most common comorbidities observed in patients with CKD are diabetes mellitus type 2[1)], dyslipidemia, coronary heart disease, heart failure[5, 6)], hypertension[7, 8)], respiratory disorders[8, 9)], stress[10)], depression[10–12)], anxiety[13)], and obstructive sleep apnea (OSA)[14)].

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OSA is a major medical problem, estimated to affect up to 15–30% of male adults and up to 5–15% of female adults[15, 16]. It is characterized by repetitive obstructions of the upper airway during sleep, frequently causing oxygen desaturation. This induces frequent awakenings (arousals), resulting in fragmented sleep and excessive daytime sleepiness.

In Brazil, according to a recent epidemiological study conducted in São Paulo, an OSA prevalence of 24.8% in men and 9.6% in women was observed, based on an apnea-hypopnea index (AHI)≥15 events/h; for an AHI≥5 events/h, this prevalence increased to 40% in men and 26% in women[17]. In a recent study involving 2,121 individuals conducted in the city of Lausanne in Switzerland, a prevalence of 50% in men and 23% in women was observed, based on an AHI≥15 events/h[18]. In another study conducted by Oliveira et al., patients with neuromuscular disorders such as myasthenia gravis were observed to have a poor quality of sleep, excessive daytime sleepiness, presence of restless syndrome, and a high incidence of sleep-disordered breathing (SDB)[19].

The prevalence of sleep disorders among patients with CKD is 40–80%, which is higher than that among the general population. Among these sleep disorders, the presence of periodic leg movements during sleep and OSA has been highlighted[20].

The high prevalence (50%) of SDB in patients undergoing hemodialysis (HD) can be attributed to compromised upper airway stability (extracellular fluid volume overload)[21–23], ventilatory control instability (altered central and peripheral chemosensitivity), and reduced upper airway muscle tone (uremia)[24–28]. Risk factors of SDB in the general population, such as older age, male gender, obesity, smoking, increased neck circumference, and diabetes, are also prevalent in the CKD population[29].

SDB has been associated with increased cardiovascular risk, and may contribute to the morbidity and mortality of patients with advanced (stages 4 to 5) CKD or those undergoing HD[30].

Although numerous studies have shown that a substantial proportion of patients undergoing HD have sleep apnea, these studies were limited by the following factors: very small sample sizes[27, 31–34]; the use of partial channel polysomnography (PSG)[34–36]; the study of populations with limited generalizability to patients undergoing HD[37]; a selected subpopulation of patients undergoing dialysis, without sleep symptoms[38]; or study samples that were largely composed of symptomatic patients[26, 31, 39]. Hence, a better understanding of the prevalence and risk factors of SDB in CKD patients undergoing HD is critical. Therefore, a systematic review that can demonstrate the status of the knowledge is justified. This knowledge may enable health professionals, especially physiotherapists, to devise new strategies to reduce morbidity and mortality and improve the quality of life of CKD patients. The present study aimed to provide a thorough overview of the literature regarding the occurrence of sleep disorders in patients with ESRD undergoing HD.

SUBJECTS AND METHODS

Two independent reviewers performed a computer-assisted search of the MEDLINE, LILACS, and SciELO Virtual Health Library medical databases from their inception to November 2015. A combination of the following Medical Subject Headings (MeSH) were used in the search ("sleep" OR "sleep disorders" OR "obstructive sleep apnea") AND ("kidney dialysis" OR "hemodialysis" OR "dialysis").

The first stage of the search identified articles according to the title, abstract, and key words. In the second stage, the contents of the manuscripts were evaluated. Articles that involved patients >18 years old, having ESRD and undergoing HD, and that used overnight standard PSG for the diagnosis of sleep disorders, were included in the final analysis. This systematic review followed the criteria outlined in the PRISMA declaration[40].

RESULTS

One thousand one hundred twenty-six articles were identified that met the inclusion criteria. A total of 796 articles were excluded because they were not in English, the patients did not undergo HD, or the studies were not cross-sectional or clinical trials. After an evaluation of the full text, 312 studies were excluded, either because PSG was not performed or they were duplicated. The remaining 18 studies, comprising 8 clinical trials and 10 cross-sectional studies, were included for further examination (Fig. 1). The results and outcomes of all included studies are summarized in Tables 1 and 2 and are discussed below. Thus, a detailed analysis of 18 articles that used overnight PSG, which is considered the gold standard method for the diagnosis of sleep disorders, was conducted.

DISCUSSION

The aim of this study was to conduct a systematic review of studies showing the presence of sleep disorders in patients with ESRD undergoing HD.

The presence of sleep disorders, including SDB, Periodic Limb Movement Disorder (PLMD) and/or Restless Legs Syndrome (RLS), which compromise the quality of life and increase the morbidity and mortality rates of patients with CKD, has been documented in the literature[50–53]. Seventy percent of ESRD patients are believed to have some form of SDB[26, 39]. RLS is a common and extremely distressing problem experienced by many patients undergoing HD. It is a neurological condition characterized by an irresistible urge to move the legs and occurs more frequently during inactivity and at night[54, 55].

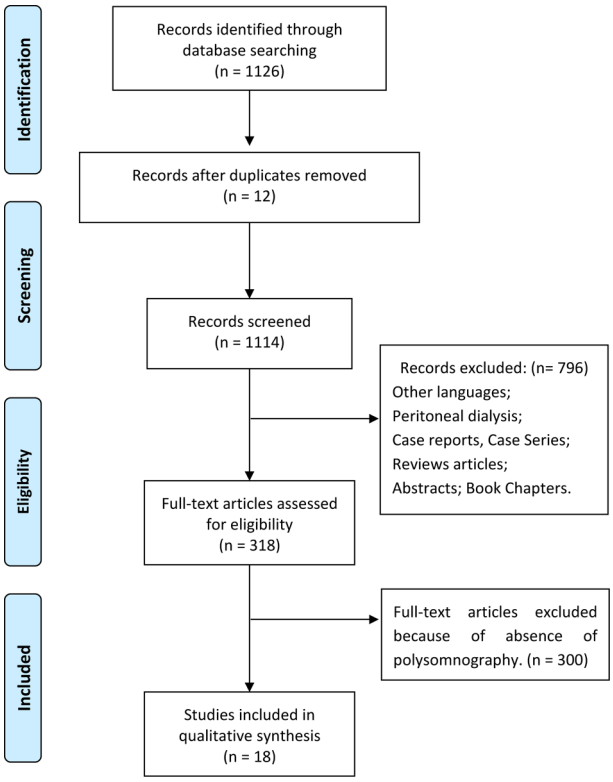

Fig. 1. Flowchart of the study

The prevalence of RLS in patients who are under treatment with HD varies across studies performed in broad geographical regions (6.6–68%), and recent studies using the International RLS Study Group criteria have suggested a prevalence rate of 33% in ESRD patients, which is greater than that in the general population[56].

Sleep fragmentation and sleep deprivation caused by RLS may contribute to cardiovascular complications and infections, often with poor prognosis in patients undergoing HD. According to the literature, patients undergoing HD have a poorer quality of sleep compared to the normal population. The presence of RLS and associated sleep disorders, such as daytime sleepiness, insomnia, and poor sleep quality, should be considered a problem that further impairs the quality of life of patients. Studies have demonstrated that 40–80% of ESRD patients undergoing HD suffer from poor sleep quality associated with a poor quality of life[57, 58]. Sleep disorders are usually associated with physical, behavioral, and psychological disorders that predispose to cognitive impairment, decline in social performance and interpersonal interactions, and depression[59].

SDB is very common among patients with CKD, especially those undergoing HD[36, 60]. Some studies have suggested OSA has a prevalence of 50–60% in ESRD patients[12, 61]. Depending on the methodology applied, approximately 50–80% of CKD patients have some form of SDB[26, 39]. OSA is 4 to 10 times more prevalent among CKD patients than in the general population[22, 49]. A more recent study conducted by Nicholls et al. involving 254 CKD patients showed a significant increase in the occurrence of SDB (predominantly OSA) which was related to impairment of renal function, with a prevalence of 57%[62].

This study utilized only studies performed using PSG, considered the gold standard for the diagnosis of sleep disorders. Despite the high prevalence of sleep disorders in the CKD population, there is limited scientific research on the topic, as evidenced by only as shown by 18 studies (10 cross-sectional studies and 8 controlled clinical trials) having been retrieved in this review. This is perhaps explained by the high cost of PSG examination, or by a lack of knowledge about the presence of sleep disorders in CKD population.

Other more viable diagnostic methods, such as pulse oximetry and specific validated sleep questionnaires, could be used as screening tools for the presence of SDB, aiding in the early diagnosis and choice of appropriate treatment with non-invasive ventilatory support.

Epidemiological studies have shown a strong and intrinsic relationship between CKD and OSA. ESRD contributes to the emergence and/or development of OSA due to factors such as metabolic acidosis, compromised sensitivity of chemoreceptors, uremic toxins, generalized muscle weakness, particularly of the dilator muscles of the pharynx, and narrowing of the upper airway due to fluid accumulation in the interdialytic period. It is known that OSA induces CKD due to increased blood pressure, oxidative stress, and repetitive hypoxia. Therefore, OSA is a major risk factor for CKD.

This systematic review verified the status of knowledge regarding the prevalence of sleep disorders in ESRD patients

Table 1. Cross-sectional studies that used overnight standard polysomnography for the diagnosis of sleep disorders in chronic kidney disease

Author. year	Title	Sample	Results	Conclusion
Hanly et al. 2001[36]	Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis	Patients who underwent both conventional HD and nocturnal HD (n=14)	AHI decreased during the nocturnal HD phase.	Nocturnal HD corrects SA associated with chronic renal failure.
Sanner et al. 2002[30]	Sleep-related breathing disorders impair quality of life in hemodialysis patients	ESRD patients who underwent HD (n=46)	Twenty-one patients had clinically significant sleep-related breathing disorders with a median AHI of 13.3 events/h.	Twenty-seven (22.7%) of the 119 patients had SA with subjective symptoms such as daytime somnolence and snoring.
Parker et al. 2003[37]	Daytime sleepiness in stable hemodialysis patients	ESRD patients who underwent HD (n=46)	Higher indices of SA and brief arousals correlated significantly with increased physiological, but not subjective, sleepiness.	Daytime sleepiness is common in HD patients, and may be severe despite the absence of obvious clinical risk factors.
Parker et al. 2003[33]	Nocturnal sleep, daytime sleepiness, and quality of life in stable patients on hemodialysis	ESRD patients who underwent HD (n=46)	Better sleep quality and less daytime sleepiness were associated with improved QOL in stable HD subjects.	Poor nocturnal sleep and increased daytime sleepiness are associated with decreased QOL in HD patients.
Jung et al. 2005[32]	Sleep apnea, coronary artery disease, and antioxidant status in hemodialysis patients	ESRD patients who underwent HD (n=26)	Coronary artery calcification is associated with the severity of SA.	Oxygen desaturation triggered by SA is associated with severe coronary artery disease.
Miskowiec et al. 2006[38]	Prevalence of sleep apnea syndrome in hemodialyzed patients with end stage renal disease	ESRD patients, assessed using PSG, on the night before HD (n=17) and on the night after HD (n=11)	Seven patients presented with SA on the 2 nights during the PSG.	HD does not change the prevalence of OSA in CKD.
Tada et al. 2007[39]	The predictors of central and obstructive sleep apnoea in haemodialysis patients	ESRD patients who underwent HD (n=30)	Forty-one patients presented with SA; 27 had SA with symptoms such as daytime somnolence and snoring.	There is a high prevalence of SA in HD patients. Good management of these factors might improve SA in HD patients.
Jung et al. 2010[16]	Nocturnal hypoxemia and periodic limb movement predict mortality in patients on maintenance hemodialysis	ESRD patients who underwent HD (n=30)	The median AHI and the PLM index were 22 and 36.9 events/h, respectively.	Nocturnal hypoxemia and periodic limb movement during sleep were associated with an increased risk of death in patients with ESRD.
Elias et al. 2012[40]	Rostral overnight fluid shift in ESRD renal disease: relationship with obstructive sleep apnea	ESRD patients who underwent HD (n=26)	The change in the leg fluid volume was correlated with the apnea–hypopnea time and neck circumference.	Nocturnal rostral fluid shift is associated with the severity of OSA in ESRD.
Elias et al. 2013[41]	Relationship of pharyngeal water content and jugular volume with severity of obstructive sleep apnea in renal failure	ESRD patients who underwent HD (n=20)	A positive correlation was found among the AHI, the internal jugular vein volume, and the upper airway mucosal water content.	Fluid overload increases the internal jugular vein volume and the upper airway mucosal water content, contributing to the pathogenesis of OSA in ESRD patients.

AHI: Apnea-hypopnea index; HD: hemodialysis; ESRD: end stage renal disease; SA: sleep apnea; QOL: quality of life; OSA: obstructive sleep apnea; CKD: chronic kidney disease; PLM: periodic leg movement

Table 2. Clinical trials that used overnight standard polysomnography for the diagnosis of sleep disorders in chronic kidney disease

Author. year	Title	Sample	Results	Conclusion
Parker et al. 2005[42]	Polysomnographic measures of nocturnal sleep in patients on chronic, intermittent daytime hemodialysis vs those with chronic kidney disease	ESRD patients who underwent HD (n=16) and the CKD patients (n=8)	Both groups had reduced total sleep time and sleep efficiency.	Sleep disorders of CKD patients and those receiving chronic, intermittent daytime HD may have different etiologies.
Lee et al. 2006[43]	A secondary analysis of racial differences in periodic leg movements in sleep and ferritin in hemodialysis patients	ESRD African–American patients who underwent HD (n=36); ESRD Caucasian patients who underwent HD (n=10)	African–American HD patients had higher ferritin and lower PLM than Caucasians.	PLM was less common in the African–American population, suggesting a differential genetic vulnerability.
Unruh et al. 2006[44]	Sleep apnea in patients on conventional thrice-weekly hemodialysis: comparison with matched controls from the sleep heart health study	ESRD patients who underwent HD (n=46) and the normal renal function group (n=137)	ESRD patients had a higher frequency of arousals per hour and AHI, and greater percentage of the TST below an oxygen saturation of 90%.	There was a strong association of HD with severe SDB and nocturnal hypoxemia independent of age, BMI, and a higher prevalence of chronic disease.
Beecroft et al. 2007[11]	Pharyngeal narrowing in end-stage renal disease: implications for obstructive sleep apnoea	ESRD patients who underwent HD (n=44) and the normal renal function group (n=41)	The pharynx was narrower in patients who underwent HD than in subjects with normal renal function.	A narrower upper airway can contribute to the pathogenesis of sleep apnea in dialysis-dependent patients.
Unruh et al. 2008[45]	Subjective and objective sleep quality in patients on conventional thrice-weekly hemodialysis: comparison with matched controls from the sleep heart health study	ESRD patients who underwent HD (n=46) and the normal renal function group (n=137)	There was no association between PSG sleep time and self-reported sleep time or between the ESS and the severity of SA in the HD population.	Kidney failure treated with thrice-weekly HD is significantly associated with poor subjective and objective sleep quality.
Enomoto et al. 2008[46]	Clinical characteristics of restless legs syndrome in end-stage renal failure and idiopathic RLS patients	Uremic RLS patients (n=15) and idiopathic RLS patients (n=20)	The PLM index was significantly higher in the uremic RLS group.	Uremic RLS appears to deteriorate faster and to become more severe than idiopathic RLS.
Loewen et al. 2009[47]	Sleep disruption in patients with sleep apnea and end-stage renal disease	ESRD patients who underwent HD (n=12) and a normal renal function group (n=18)	The prevalence of RLS LM-related arousals was higher in ESRD patients.	The co-existence of PLM is an additional source of sleep disruption in patients with ESRD and SA.
Roumelioti et al. 2011[48]	Sleep-disordered breathing and excessive daytime sleepiness in chronic kidney disease and hemodialysis	ESRD patients who underwent HD (n=75), the CKD group (n=89), and the normal renal function group (n=224)	Nocturnal hypoxemia was significantly elevated in the HD group compared with the CKD group.	Severe SDB and excessive daytime sleepiness are common among advanced CKD and HD patients.

ESRD: end-stage renal disease; HD: hemodialysis; CKD: chronic kidney disease; PLM: periodic leg movement; SDB: sleep disordered breathing; PSG: overnight standard polysomnography; ESS: Epworth sleepiness scale; SA: sleep apnea; RLS: restless legs syndrome; TST: total sleep time

undergoing HD. According to the studies analyzed, a high prevalence of PLMD, RLS, and OSA affecting the quality of sleep was observed, which in turn undermined the quality of life of these patients, leading to increased morbidity and mortality.

Thus, it is very important for healthcare professionals to recognize the signs and symptoms of sleep disorders in CKD patient population, both for accurate diagnosis and an appropriate therapeutic approach. For physical therapists, it is extremely important to identify SDB, particularly OSA, so they can institute treatment with continuous positive airway pressure.

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