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REVIEW

Sleep disorders and chronic kidney disease

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Abstract

Sleep disorders have a profound and well-documented impact on overall health and quality of life in the general population. In patients with chronic disease, sleep disorders are more prevalent, with an additional morbidity and mortality burden. The complex and dynamic relationship between sleep disorders and chronic kidney disease (CKD) remain relatively little investigated. This article presents an overview of sleep disorders in patients with CKD, with emphasis on relevant pathophysiologic underpinnings and clinical presentations. Evidence-based interventions will be discussed, in the context of individual sleep disorders, namely sleep apnea, insomnia, restless leg syndrome and excessive daytime sleepiness. Limitations of the current knowledge as well as future research directions will be highlighted, with a final discussion of different conceptual frameworks of the relationship between sleep disorders and CKD.

Key words: Chronic kidney disease; End-stage renal disease; Renal replacement therapy; Hemodialysis; Kidney transplantation; Sleep initiation and maintenance disorders; Disorders of excessive somnolence; Intrinsic sleep disorders; Parasomnias; Restless legs syndrome; Sleep apnea; Dyssomnias; Circadian rhythm disorders; Melatonin

Core tip: Sleep disorders have a profound and well-documented impact on overall health and quality of life in the general population. In patients with chronic disease, sleep disorders are more prevalent, with an additional morbidity and mortality burden. The complex and dynamic relationship between sleep disorders and chronic kidney disease (CKD) remain relatively little investigated. This article presents an overview of sleep disorders in patients with CKD, with emphasis on relevant pathophysiologic underpinnings and clinical presentations.

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INTRODUCTION

Sleep disorders are prevalent in patients with chronic kidney disease (CKD) in particular those with end stage renal disease (ESRD)[1]. It has been reported that 80% of ESRD patients receiving dialysis report sleep complaints, with daytime sleepiness to be the most common reported symptom[2,3]. The reason for increased rates of sleep related issues and disorders in this population is likely multifactorial and will be discussed in this review. Sleep issues are not only related to decreased quality of life[4,5], but are also associated with increased health related risks[6], and mortality[1,7] in CKD.

BIOLOGICAL EFFECTS OF CKD ON SLEEP

Although it is commonly accepted that patients with CKD experience poor sleep quality, not much is known about the physiological mechanisms underlying this phenomenon. According to Hildreth, patients with CKD often exhibit sympatho-vagal imbalance due to baro-receptor reflex function impairment in which there is hyperactivity of the sympathetic nervous system and decreased vagal tone[8,9]. In healthy individuals, sleep is accompanied by a decrease in sympathetic activity and an increase in vagal tone that leads to a nocturnal dipping of blood pressure. However, patients who have sleep disorders resulting in hypoxemia and sleep fragmentation have been shown to have increased sympathetic nervous system stimulation and decreased parasympathetic activity, which results in a reduced fall in nocturnal blood pressure[10].

Blood pressure regulation by the autonomic nervous system during sleep also affects the renin-angiotensin-aldosterone system. As blood pressure decreases during the normal sleeping period, there is a reflexive increase in plasma renin activity and aldosterone. As an individual goes through cycles of rapid eye movements (REM) and non-REM (NREM) sleep, there are oscillations of cardiac sympatho-vagal balance and plasma renin levels. Plasma renin activity and aldosterone peaks during NREM sleep, more specifically stages 3 and 4, and dips during REM sleep. This oscillatory nature of PRA is absent in patients who experience a night of sleep deprivation[11]. However, decreased sleep duration is not the only factor affecting nocturnal PRA and aldosterone secretion. Sayk *et al*[12] showed that decreased sleep quality induced by suppressing slow-wave sleep (stages 3 and 4) also reduced nocturnal blood pressure dipping, which would affect the RAA system as well. It is believed that the lack of nocturnal blood pressure dipping is an important risk factor for progression of CKD[13]. Reducing nighttime blood pressure by means of carefully timed antihypertensive therapy in the evenings may reduce the risk of progression of CKD to ESRD[13].

CHRONOBIOLOGY OF MELATONIN IN CKD PATIENTS

Melatonin, a hormone secreted by the pineal gland, is responsible for the sleep - wake circadian rhythm. It is secreted in small amounts during the daytime but increases during the night, which correlates with the onset of nocturnal sleepiness. In a small cross sectional study comparing 30 ESRD patients undergoing hemodialysis (HD) and 20 healthy participants, nocturnal melatonin levels were significantly lower in patients with ESRD[13]. About 22 of the 30 patients also lacked the circadian rhythm in melatonin secretion. HD did not correct or improve melatonin concentrations. In another study by Karasek *et al*[14], melatonin concentrations released during the night did not improve with kidney transplantation, despite improvements in renal function. Sleep quality, as measured by actigraphy, did not significantly improve either.

CHANGES IN SLEEP ARCHITECTURE

Patients with ESRD typically exhibit poor sleep architecture as measured objectively on polysomnographic studies. In a comprehensive review, ESRD patients had short, fragmented sleep with total sleep times between 260-360 min[15]. Sleep efficiencies ranged between 66%-85% and time spent awake ranged from 77-135 min. Sleep latencies were reported between 10-30 min and REM latencies between 92-64 min. There was a pattern of increased stage 1 and stage 2 sleep while slow wave sleep and REM sleep were decreased. Daytime sleepiness is a parameter not measured by polysomnographic studies but is still considered an important marker of inadequate sleep. Multiple sleep latency tests (MSLT) objectively measure daytime sleepiness by having the patient take five scheduled naps throughout the day separated by 2-h breaks. Time to onset of sleep, also known as sleep latency, of less than 5 min is considered to be pathological and may be exacerbated by various sleep disorders. A study conducted by Parker *et al*[15] in 2003 also found that out of 46 ESRD patients, 46% had abnormal MSLTs. Another study conducted by Stepanski *et al*[16] on peritoneal dialysis patients reported a MSLT of 6.6 ± 3.7 min.

SLEEP APNEA

Sleep apnea is a chronic sleep disorder which causes repeated cessation of breath while a person is sleeping. Characteristics of sleep apnea include loud snoring, breathlessness, waking up from sleep, and daytime sleepiness. Prevalence in the general population is

approximately 2%-4%[17,18], compared to the prevalence in ESRD patients which is estimated between 50%-60%, through self-report questionnaires[18-20], and about 70%-80% of ESRD patients when based on polysomnography[17,19-21].

Sleep apnea is divided into three sub-types: Central sleep apnea (CSA), obstructive sleep apnea (OSA) or mixed[22]. While OSA is the most common form of sleep apnea in the ESRD population[18], CSA may be underreported in patients with ESRD, as it can only be diagnosed with polysomnography tests[21]. OSA causes repeated episodes of apneas, arousals, and loud snoring. In contrast to CSA, OSA is commonly recognized by an individual's bed partner. The most conclusive method of diagnosing OSA remains overnight polysomnography studies[21].

Sleep apnea in the ESRD can cause excessive sleepiness and cognitive impairment, diminishing daytime functioning. OSA is also commonly linked to depression, hypertension and increased cardiovascular morbidity and mortality[17,21,22].

Pathology

The direct relationship between sleep apnea and ESRD is not clear. However, several studies have examined "rostral fluid shift" as a possible mechanism in the pathogenesis of OSA in CKD patients[23,24]. Due to their reclined position overnight, excess fluid shifts from the legs towards the neck leading to upper airway restriction and collapse[23].

Thus, when CKD patients accumulate excess fluid in the neck due to rostral shift, upper airway "collapsibility" increases leading to high rates of OSA occurrences[23-25]. One study tested this theory by measuring the neck circumference (NC) and leg fluid volume (LFV) in ESRD patients with OSA[23]. The change in LFV correlated with significant change in NC, supporting the notion that leg fluid is displaced into the neck overnight. Another study conducted by Elias *et al*[24] confirmed the rostral fluid shift by measuring internal jugular vein volume (iJVVOL) and upper airway mucosal water content (UA-MWC). They found that greater iJVVOL and UA-MWC levels correlated to greater apnea-hypopnea index. Both studies concluded that fluid accumulation in the neck due to rostral shift predisposes ESRD patients to OSA.

Treatments

Similar to the general population, continuous positive airway pressure (CPAP) is the first line of treatment in CKD patients with OSA[22,26]. Other treatment modalities in the general population include the use of dental appliances, oral surgery, and treating underlying medical conditions (*e.g.*, obesity or hypothyroidism). These modalities have not yet been extensively studied in the CKD population.

Research has shown that conversion from conventional HD to nocturnal HD (NHD) reduces the occurrence of apneas. One suggested mechanism is that NHD aggressively removes more uremic toxins than conventional HD which may contribute to better sleep quality[26]. Studies that examined ESRD patients before and after conversion to NHD, found that NHD was effective in lowering the heart rate and reducing the frequency of apneas and hypoxemias in all of the patients[26,27].

INSOMNIA

Insomnia is the inability to fall asleep or stay asleep and is characterized by poor sleep quality and poor quality of life[21]. It is a common sleep disorder in the general population and is significantly more common in ESRD patients on HD. The prevalence of insomnia in the general population ranges from 4% to 29%[28]. Whereas in the ESRD population, approximately 50%-75% of ESRD patients experience symptoms of insomnia[28-30].

Clinical significance

Poor quality of sleep and lack of sleep reduces overall quality of life and may lead to a host of other complications including impaired immune system and risk for cardiovascular disease[21]. It is important to understand insomnia and its relationship associated with other complications in order to reduce mortality and improve quality of life and sleep in these patients.

Pathology

The causes of insomnia are both physiological and psychological and there are several factors that contribute to its onset. As compared to the general population, patients with inosomnia have higher rates of anxiety, stress and relatively poor self-concepts[31].

Insomnia is also commonly found in individuals with coexisting medical conditions. Other influences include low socioeconomic status, female gender, psychiatric conditions and conditions that cause chronic pain[4,21]. In ESRD patients, the risk of insomnia is higher than the general population due to the physical stress of their condition. Chronic pain is a common problem in patients on dialysis and is a leading cause of insomnia in this population[21]. Elder *et al*[4] examined factors that affect sleep quality in a worldwide self-report study in 11351 patients on dialysis. Data showed that reports of poor sleep quality increased with reports of higher, more severe degrees of pain.

Sabbatini *et al*[28] found dialysis shift time to be an important risk factor for the development of insomnia. Patients on dialysis during early morning shifts had higher rates of insomnia than patients on dialysis in the afternoon. Others have found that late night dialysis shifts play a role in insomnia as well[21]. Additionally, the prevalence of insomnia is much higher in elderly patients with ESRD and patients who have been on dialysis for longer periods of time[28].

Physiologically, individuals undergoing HD experience disturbances in the sleep-wake (circadian)

cycle[32]. As discussed earlier, the process of dialysis influences secretion of melatonin, which is responsible for the regulation of the circadian cycle. In one study, 73% of patients on dialysis had no identifiable circadian rhythm at all[14].

Additionally, high levels of parathyroid hormone (PTH) are linked to the prevalence of insomnia in patients with ESRD[4,28]. PTH is associated with renal bone disease and bone pain. In a study of 654 patients, patients on dialysis had substantially higher levels of PTH than control patients.

In summary, research suggests that chronic pain, stress, older age, dialysis shift, melatonin, and high PTH all play a role in the development of insomnia in ESRD patients, although the mechanisms are not yet fully understood.

Treatments

There are pharmacological and nonpharmacological means of treating insomnia. Research suggests that it may be most beneficial to first treat the underlying conditions, such as pain or depression.

Sedative antidepressants and anxiolytics are effective in individuals who suffer from depression, worry and insomnia, however there is little research supporting their safety and efficacy in ESRD patients.

Melatonin is recommended for regulation and improvement of the sleep-wake cycle in patients with insomnia. The rather limited evidence base in ESRD patients supports this. In short-term studies on maintenance HD patients[33,34], 3 mg of melatonin (administered at bedtime or 10 pm respectively) improved both subjective and objective sleep parameters, with no significant side effects reported. In one long-term study[35], despite not sustaining its efficacy at one year, melatonin use continued to be a safe and well-tolerated option.

In a recent critical summary of the existing body of evidence, Yang *et al*[36] systematically reviewed the literature on such non-pharmacological interventions in dialysis-dependent patients, and identified 12 randomized controlled trials and one prospective cohort study. Four intervention modalities were studied; cognitive behavioral therapy (CBT), acupressure, physical exercise and change of dialysis modality. None of the studies had a head to head design, and all RCTs were identified as having a high risk for bias, limiting their overall conclusion. They concluded that CBT for insomnia (CBTi) is helpful for patients on HD, and more studies are needed to further assess the potential of the other interventions.

From a cognitive behavioral perspective, acute insomnia is maintained through maladaptive coping strategies, resulting in a strong association between bed and arousal, not sleepiness. The core tenets of CBTi are stimulus control, sleep restriction, and sleep hygiene. CBTi usually starts with stimulus control, in which the association between bed and sleep is gradually re-established, by following a set of behavioral instructions that may include keeping a fixed wake-time, using the bedroom/bed only for sleep or sex, sleeping only in the bedroom, and leaving the bed when not able to sleep. In sleep restriction, the total sleep time (the average time spent actually asleep) is estimated, and a fixed wake-time is established. The patient is then instructed to limit their time in bed to the estimated total sleep time, gradually "rolling back" their bedtime by 15 min increments. Sleep hygiene describes a broad set of "good sleep habits" that include exercising regularly (but generally not before bedtime), avoiding excessive liquids, caffeine, nicotine and alcohol in the evening, ensuring that the bedroom is comfortable and noise-free, as well as adjusting the timing of meals and snacks relative to bedtime.

Classically, CBTi is carried out in 6-8 wk sessions, starting with clinical evaluation and baseline assessment utilizing a sleep diary, followed by these three components, with gradual titration of sleep restriction. Chen demonstrated the effectiveness of CBTi in patients with ESRD[36,37], but it is unclear from his publications how classic CBTi was adapted to the ESRD population.

Other studied techniques for insomnia include relaxation training, acupressure and physical exercise. Relaxation training can be a helpful adjunctive therapy in treating chronic insomnia[38,39]. It emphasizes progressive muscle relaxation and breathing exercises for the relief of chronic pain and insomnia. The Iranian group of Rambod *et al*[40] demonstrated that listening to an instructional relaxation audiotape for twenty minutes, twice a day, for 8 wk, after an initial training session, resulted in a statistically significant improvement of sleep quality in patients treated with HD, as measured by the Pittsburg Sleep Quality Index.

In acupressure, specific points along the pathways of energy are targeted, without using needles.

The evidence on the utility of acupressure and accupoint massage in ESRD patients with chronic insomnia is largely derived from three RCTs conducted by a Taiwan-based group[41-43], and two Iranian RCTs[44,45]. The methodological concerns of these studies have been documented[36,46], but acupressure may be a safe alternative therapy for insomnia.

Physical exercise has beneficial effects on slowing the decline of renal function[47-49]. In addition, aerobic or resistance exercise programs have been demonstrated to have moderately positive effects on sleep quality in the general population[50]. The evidence base on such effects in the ESRD population is scant yet promising, and thus should be interpreted cautiously[51-53]. Furthermore, little is described in the literature to guide the selection of ESRD patients for customized exercise interventions, or to ensure safety.

There is little that can be concluded about the treatment of insomnia in ESRD populations, however it is clear that more research is needed and that the

combination of pharmacological and nonpharmacalogical techniques are likely to work in tandem to provide the greatest relief to the patient.

RESTLESS LEG SYNDROME

Restless leg syndrome (RLS), also known as Willis-Ekbom syndrome, is a sensory-motor disorder manifested by unpleasant nocturnal sensations in the lower limbs that are relieved by movement. These sensations generally occur deep within the muscle of the leg, but patients occasionally report feeling them on the skin. Two-thirds of patients experience the sensation bilaterally; one-third of patients have unilateral symptoms. The most common site of symptoms is the upper calf, with 75% of patients reporting sensations there. About 80%-90% of RLS patients present with periodic limb movements of sleep (PLMS)[54-57].

Epidemiology

In the general population, symptoms most frequently appear after the age of 45, with 38% of sufferers report onset of symptoms before age 20. RLS is twice as common in females than in males. Family history of RLS is common; 63% of patients report at least one first degree relative with RLS. No monogenic cause has yet been found, but studies show six different genes that may play a role[58,59].

In HD patients, the prevalence of RLS is 20%-30%, compared to 3%-7% in the general population. In kidney transplant patients, the prevalence is close to 5%, approximately average for the general population[2,3,57,60,61].

Clinical significance

RLS impacts sleep, which can lower sleep quality and efficiency as well as overall quality of life. Untreated RLS is highly associated with depression, both in the general population and in patients with CKD. In addition, RLS is associated with higher mortality in ESRD patients.

Pathology

Brain iron dysregulation plays a role in RLS[54], possibly during transport across the blood brain barrier. Since iron is an essential cofactor in the production of dopamine, low iron levels could explain the changes in dopamine metabolism that occur in RLS. The syndrome is worsened by iron deficiency and symptoms are improved by iron supplementation. RLS sufferers show a drop in CSF ferritin levels throughout the night, while healthy controls do not. Circadian changes in brain iron status are what make this a circadian disease. Other possible factors associated with the condition are elevated serum calcium levels and PNS/CNS abnormalities[61,62]. ESRD patients may be particularly susceptible to acquiring RLS because peripheral neuropathy complicates and overlaps the picture of RLS.

Assessment

Diagnosis of RLS is based on the 2012 revised International RLS Study Group criteria[55]. These criteria include: Urge to move legs, usually because of an uncomfortable sensation; sensations are exacerbated when resting or lying down; urges and unpleasant sensations are at least partially relieved by motion, such as walking around; and symptoms cannot be accounted for by other medical issues or behavioral patterns. A levodopa test (50% improvement in symptoms after 25/100 mg of carbidopa/levodopa) can be used to help diagnose RLS, although not all patients respond to dopaminergic drugs. The PLMS Index - the number of leg movements per hour - can be recorded by polysomnography and is one measure used to assess severity of the syndrome.

Non-pharmacological treatments

Both aerobic exercise and resistance training have been shown to improve symptoms of RLS[54,63]. Improvement of sleep hygiene is also thought to have some beneficial effect. There have been no controlled studies on the effects of alcohol, nicotine, and caffeine, but these substances are thought to aggravate the condition. Small studies have shown that pneumatic compression devices, acupuncture, and near-infrared light can be helpful to RLS sufferers[54].

Pharmacological treatments

Dopamine agonists (DAs) are commonly considered to be the first pharmacological option, and they simultaneously address the symptoms of PLMS as well[54]. Although DAs are an effective initial treatment, they are only shown to be effective in the long term in 25% of patients. In addition, long-term use brings about a worsening of symptoms, known as augmentation, in a large percentage of patients. About 6%-17% of RLS patients who take DAs develop impulse control disorders. Correcting iron deficiency has been shown to improve RLS in HD patients[64]. Other pharmacological therapies include calcium channel alpha-2-delta ligands (gabapentin, and pregabalin), opioids, and iron therapy. Gabapentin, an alpha-2-delta ligand, is a good choice for patients with polyneuropathy in addition to RLS. In general, both and gabapentin and pregabalin appear to be helpful in improving sleep quality in ESRD patients with painful peripheral neuropathy. However, dosages of both medications need to be renally-adjusted, and side-effect profile has not been adequately described in CKD studies[65,66].

Augmentation

Augmentation refers to the severe exacerbation of RLS symptoms, sometimes up to 24 h a day, caused by the medication used to treat initial symptoms[67-70]. It is thought to be the result of pharmacological treatment, not a natural progression of the disease. This is a common complication seen in patients treated with

dopaminergic drugs. Augmentation is characterized by gradually earlier onset of symptoms, greater severity of symptoms, increasingly shorter periods of rest between symptoms, expansion of symptoms to upper limbs, and shorter periods of effectiveness of medication[54]. One study found prevalence of augmentation in patients treated with DAs to be as high as 76%[54]. Because of this, DAs should be prescribed only when necessary and patients' symptoms should be monitored closely.

Large, methodologically sound studies are still needed to further assess the effectiveness of both pharmacological and non-pharmacological treatment options, as well as the impact of different renal replacement modalities.

EXCESSIVE DAYTIME SOMNOLENCE

Excessive daytime somnolence (EDS) is defined as the inability to stay awake or alert throughout the course of the day, resulting in sleepiness or inadvertent dozing during passive (reading, watching television) or active (driving, conversation) daily activity.

Compared to the 10%-12% prevalence in the general population[71-73], EDS is significantly more common in CKD patients, especially those on HD[3,15,74,75]. Parker *et al*[15] estimated that two-thirds of their HD subjects listed daytime sleepiness as a main complaint. Moreover, one-third had abnormal levels of objective sleepiness, and an additional 13% showed pathological levels of sleepiness on the MSLT and the Epworth Sleepiness Scale (ESS).

Pathogenesis

Multiple factors may contribute to daytime sleepiness[15,76,77]. These factors include uremia, high prevalence of periodic limb movements and high prevalence of sleep apnea. Studies have shown all of these to be correlated with more severe daytime sleepiness. Other possible contributors include subclinical uremic encephalopathy, tyrosine deficiency (tyrosine being important for dopamine production), release of inflammatory cytokines during dialysis, high daytime melatonin levels, and change in body temperature rhythm. NHD may alleviate daytime sleepiness.

The approach to the assessment and treatment of EDS in CKD patients is generally the same as that to in the general population. An additional intervention is to switch to NHD[76]. One study assessing patients after kidney transplant found that three months after surgery ESS scores had dropped significantly[78].

CLINICAL RECOMMENDATIONS

While there is not sufficient data to make evidence-based recommendations, there is still a need for the practicing clinician to address sleep complaints in their patients with renal disease. Our recommendation is to first do an appropriate clinical assessment which may include a referral for a full evaluation including somnography, if sleep apnea is suspected. Clearly, patients with sleep apnea should be aggressively followed and encouraged to use their CPAP machines, as recommended. Patients with conventional insomnia or sleepiness should have their sleep hygiene evaluated. Often the most basic components of sleep hygiene are being neglected and relatively minor changes in the patients' behavior can lead to substantial sleep change. If this approach is not successful the clinician may then consider referral for cognitive behavior therapy or the limited use of sleep agents. While sleep difficulty is very common in renal patients, the nephrologist should be encouraged to utilize the expertise of colleagues trained in sleep medicine and employ a team approach to care.

CONCLUSION

In patients with ESRD, the identification, diagnosis and treatment of sleep disorders is complicated by the overlapping presentation with CKD and other commonly comorbid conditions. One approach to conceptualizing this relationship is to consider sleep disorders as secondary or end product of multiple concurrent and interactive processes[79]. Such processes include psychological disorders (depression, anxiety), lifestyle factors (coffee/nicotine use, sleep hygiene), treatment-related factors (timing of dialysis, daytime napping, production of cytokines, thermoregulatory changes, dialysis disequilibrium syndrome, disruptions in circadian rhythm, medication side effects) as well as intrinsic, ESRD-specific factors (anemia/OSA/RLS and other comorbidities, uremia, overall all health and quality of life, alterations in neurotransmitter production). This approach highlights the difficulty in separating sleep disturbances for either research or clinical purposes, and suggests that treatment of sleep disorders should be multi-layered and comprehensive.

An alternative simpler approach is to separate insomnia from concurrent medical/psychiatric comorbidities, and treat it as an independent co-occurring disorder[80,81]. While this approach lacks the richness of a multifactorial conceptualization, it more readily allows for the targeted study and treatment of sleep dysfunction in ESRD populations.

Clearly, the high rates of sleep apnea, insomnia, and RLS in ESRD populations necessitate larger well-designed clinical trials. Future research should attempt to explain the complex interrelationships between sleep and kidney disease, test standard treatments in ESRD communities and develop novel treatments for sleep disorders that can take the complex psychosocial and physiological burden HD presents.

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