Sleep Disorders in CKD: A Review

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Sleep disorders are highly prevalent in patients with chronic kidney disease (CKD) but are often underrecognized. The most common sleep disturbances in people with CKD include insomnia, sleep apnea syndrome, restless legs syndrome, and periodic limb movement disorder. The presence of sleep disorders in CKD can further worsen the burden of high morbidity and mortality in a patient population with already high mortality rates. The detection and management of sleep disorders in patients with CKD are often challenging because the classic symptoms of sleep disorders (poor concentration, daytime sleepiness, and insomnia) overlap with CKD symptomatology. The treatment of one symptom may have a negative impact on others; hence treatment of these disorders is challenging and may need to be individualized and modified based on the response to treatment and the development of adverse effects. However, treatment of sleep disorders may have significant clinical benefits, leading to improved health-related quality of life. This Review presents an overview of sleep disorders in patients with CKD, with emphasis on relevant pathophysiology, diagnosis and treatment strategies.

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Introduction

Sleep disorders are highly prevalent in patients with chronic kidney disease (CKD) and have a profound effect on quality of life.[1,2] The impact of sleep disorders is increasingly recognized across all stages of kidney disease, including those persons with early CKD and also those persons with kidney failure receiving kidney replacement therapy (dialysis or kidney transplant). The reported prevalence of sleep disorders is 36% to 59% among those with CKD stages 3-4,[3,4] 25% to 80% in patients receiving dialysis,[5-7] and 8% to 46% in kidney transplant recipients.[4,8] The most common sleep disturbances include insomnia, sleep apnea syndrome, restless legs syndrome (RLS), and periodic limb movement disorder (PLMD). These disorders frequently overlap, and the treatment of one may have a negative impact on others; hence treatment of these disorders is challenging and may need to be individualized and modified based on the response to treatment and the development of adverse effects. This Review summarizes the current knowledge on the epidemiology, pathogenesis, clinical sequelae, and treatment options of these CKD-associated sleep disorders.

Insomnia

According to the *International Classification of Sleep Disorders*, Third Edition (ICSD-3), insomnia is characterized by the presence of all 3 of the following criteria: (1) difficulty initiating sleep, maintaining sleep, or waking up too early; (2) sleep difficulties occur despite adequate opportunity and circumstances for sleep; and (3) the problem negatively impacts daytime functioning.[4] ICSD-3 classifies insomnia into short-term (duration < 3 months), and chronic (≥3 months). Patients suffering from insomnia often have difficulty functioning during the day, poor health-related quality of life (HRQoL),[2,9,10] increased health care costs,[11] poor work performance, fatigue,[12] depression,[13] and increased mortality.[14-17]

The reported prevalence of insomnia is 36% to 59% in patients with CKD not on dialysis,[4,18] 25% to 80% in patients on dialysis,[4,5,19] and 8% to 46% in kidney transplant recipients[8,20] in comparison with 10% to 15% in the general population.[21]

Pathogenesis

Factors causing insomnia are complex, with multiple pathophysiological, biochemical, psychological, lifestyle, and treatment-related factors having been identified (Fig 1).

Metabolic Factors

Anemia and iron deficiency are associated with insomnia in patients on dialysis.[22] The metabolic consequences of CKD, including calcium and phosphate dysregulation and hyperparathyroidism, are reportedly associated with insomnia. Insomnia in patients with severe hyperparathyroidism improved after parathyroidectomy.[23,24] Uremic pruritus,[25] muscle cramps, neuropathic pain, and chronic bone pain also have a negative impact on sleep.[2] Systemic inflammation is common among patients with CKD, and inflammatory mediators (interleukin-1β, interleukin-6, interleukin-18, tumor necrosis factor α, and C-reactive protein) may alter sleep quality, but the relationship is controversial.[26,27]

Medications

The side effects of medications commonly used in patients with CKD, such as β-agonists and antagonists, antidepressants, diuretics, and immunosuppressive medications, may include insomnia.[8,28,29]

Physical and Psychological Symptoms

One important contributor to poor sleep is the high burden of chronic, undermanaged pain seen in CKD.[1,2,30] Depression, anxiety, and worry about disease, financial, and family issues (including sexual dysfunction) can further impair sleep. Several studies have shown strong,

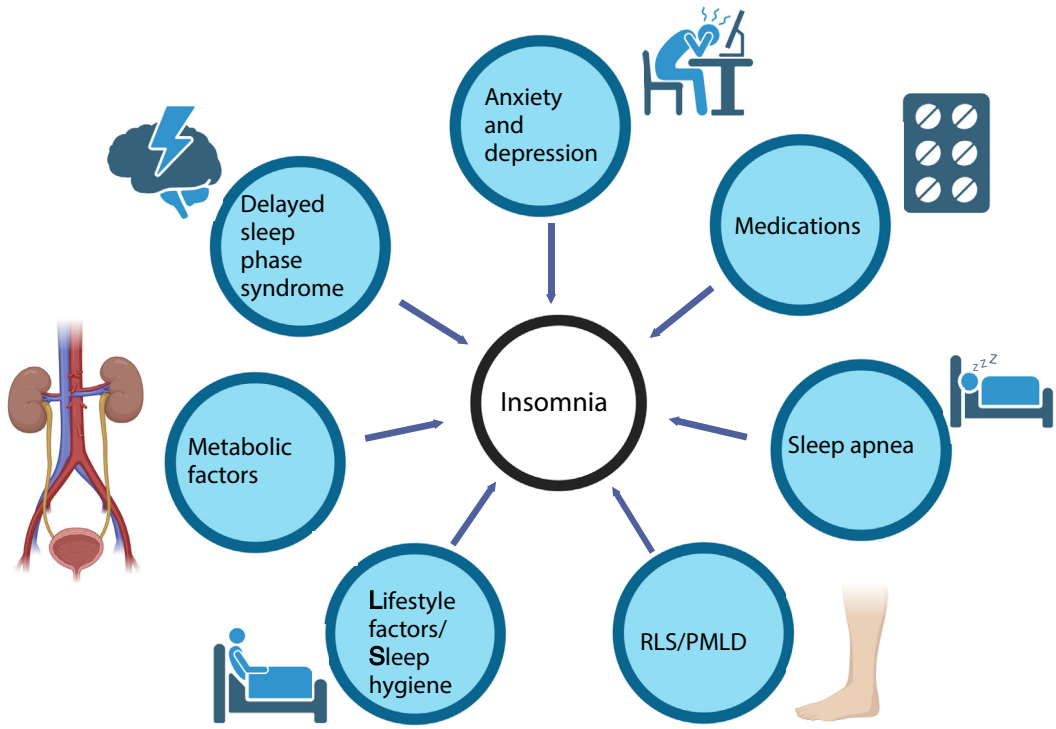

Figure 1. Factors contributing to insomnia in patients with chronic kidney disease. Abbreviations: PLMD, periodic limb movement disorder; RLS, restless legs syndrome.

bidirectional associations between insomnia and depression in patients on hemodialysis or peritoneal dialysis.[22,31]

Lifestyle-related Factors

Dialysis timing may impact insomnia. Patients on dialysis during early morning or late-night shifts have higher rates of insomnia than patients undergoing dialysis in the afternoon.[32] Sleep hygiene-related behaviors such as napping during the day or inactivity during waking hours have also been associated with insomnia in CKD[18] and might help to explain the relationship between insomnia and dialysis timing.[33]

Disturbance in the Circadian Rhythm

The pineal hormone melatonin plays an important role in circadian sleep-wake rhythm. In a healthy person, melatonin levels are low during the day and high at night. However, several studies have shown alteration in the diurnal variation of melatonin in those with CKD or on dialysis. Study findings vary, with some showing reduced levels while others show significant accumulation of both melatonin and active metabolites.[34-37]

Diagnosis

Insomnia is a clinical diagnosis. The assessment of insomnia begins with a detailed sleep history to identify the specific sleep problem, sleep habits, bedtimes and wakeup times, and issues around sleep hygiene. Concerns may range from difficulty falling asleep, waking early, excessive daytime somnolence, unusual leg movements, or features of breathing difficulty at night and often result in objective sleep disruptions (documented with polysomnography), poor subjective sleep quality, and impaired daytime functioning. A sleep diary can document symptoms, which can help with developing a management plan within the framework of formal assessment. Validated screening tools (Pittsburgh Sleep Quality Index,[38] Athens insomnia scale,[39] and Insomnia Severity Index[40]) can help in detecting insomnia. Actigraphy and polysomnography are not essential for diagnosing insomnia, but they can help in excluding other sleep disorders causing insomnia such as sleep apnea and RLS.

Treatment

The treatment goals of insomnia focus on improving subjective and objective sleep quality and preventing daytime sleepiness and fatigue, thereby improving daytime functioning. Both nonpharmacologic and pharmacologic measures are considered for treating insomnia in the general population. Those measures may also be considered for treating insomnia in patients with CKD. The initial assessment may point to a need for simple modifications to the sleep environment that were previously overlooked and may help set realistic patient expectations. In addition to reviewing sleep hygiene recommendations, identification and treatment of sleep-influencing symptoms, such as

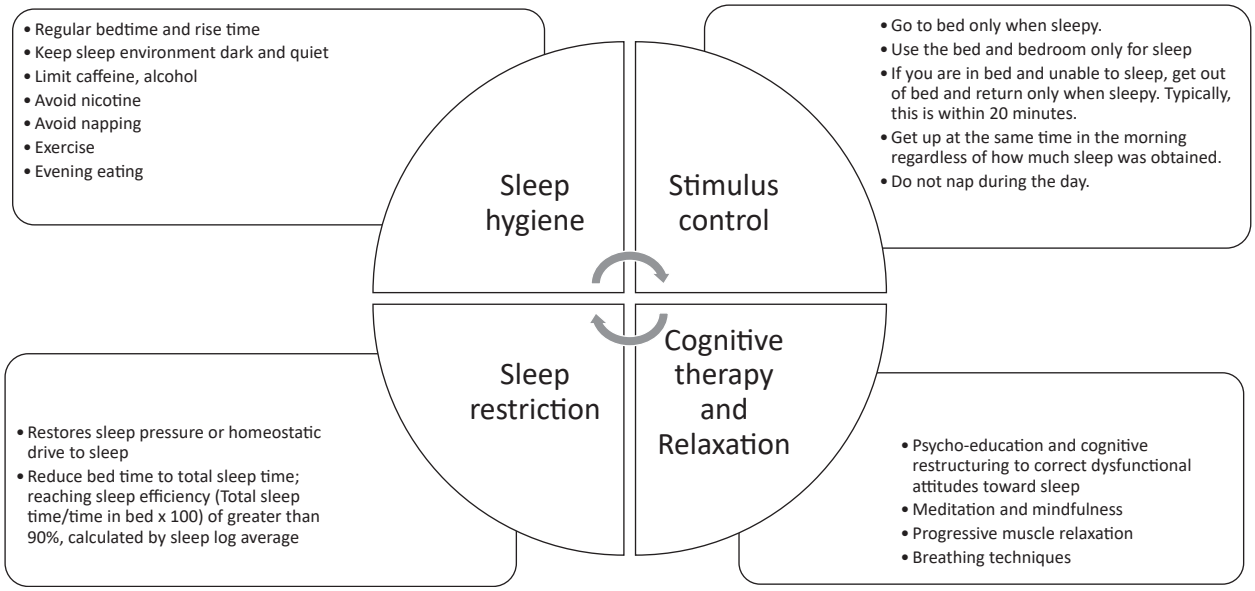

Figure 2. Components of cognitive behavioural therapy for insomnia (CBT-I).

pain, pruritus, depression, or anxiety, may improve insomnia. Because small improvements in daytime functioning may be seen, patients could be encouraged to participate in more exercise, allowing further improvement in sleep quality.[41] Pharmacologic treatment is mostly indicated for short-term insomnia. Long-term medication use to treat chronic insomnia is not favored, although it might be necessary in certain situations.

Nonpharmacologic Treatment

A comprehensive assessment of sleep behaviors using a sleep diary can identify simple modifications of sleep environment or hygiene that had not previously been noted. It may also help set realistic patient expectations of sleep. Symptoms of pain and anxiety must be addressed early as they can limit the success of other interventions. Cognitive behavioral therapy for insomnia (CBT-I) is the recommended first-line therapy in the general population and can be delivered in person or virtually.[42,43] A preference for CBT-I or other behavioral therapies over medication as initial therapy has been endorsed in clinical practice guidelines of the American Academy of Sleep Medicine,[44] the British Association for Psychopharmacology,[45] the American College of Physicians,[42] and the European Sleep Research Society.[46] The components of CBT-I include sleep hygiene, sleep restriction, stimulus control therapy, cognitive therapy, and relaxation (Fig 2). However, the effectiveness may be lower in patients receiving dialysis.

In a recently published small trial of 126 individuals with mild to moderate insomnia receiving dialysis who were randomized to trazadone, CBT-I (delivered virtually), or placebo, there was little difference between the groups.[47] Although sleep scores were numerically better in the CBT-I group, the difference was not statistically or clinically significant. The trazadone group appeared to have a higher risk of cardiovascular hospitalization, although small differences in baseline comorbidity may have contributed to this finding.

Increasing physical activity during waking hours is another approach to improving sleep. In older adults, exercise and tai chi improved symptoms.[48] A systematic review and meta-analysis by Valera et al[41] found aerobic exercise to be associated with improved sleep quality in people with CKD, with the majority of evidence derived from people on hemodialysis. Mindfulness-based interventions may also improve sleep and daytime symptoms in people with insomnia,[46,49,50] but we have no data about the impact of mindfulness on insomnia symptoms in patients with kidney disease.

Pharmacologic Treatment

The American College of Physicians recommends that clinicians use a shared decision making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacologic therapy in adults with chronic insomnia disorder in whom CBT-I alone was unsuccessful. The commonly used pharmacologic treatments for insomnia are nonbenzodiazepine Ω-receptor agonists ("Z-drugs": eg, zolpidem, zaleplon, zopiclone, and eszopiclone); benzodiazepine-receptor agonists (eg, temazepam, lorazepam, triazolam), melatonin and melatonin receptor agonists (eg, ramelteon), dual orexin receptor antagonists (eg, suvorexant), and histamine H1 receptor antagonist (low-dose doxepin). The use of other sedating medications for insomnia might be considered for patients who do not have an adequate therapeutic response to first-line medications and these include trazodone, mirtazepine, and gabapentin.

Table 1. Commonly Used Medications for Insomnia in Patients With Kidney Disease

Drug	Evidence Study	Methods	Participants	Key Findings	Side-Effect Profile	Recommendation
Z drugs						
Zaleplon	Sabbatini et al, 2003[111]	Randomized crossover study; zaleplon vs placebo	10 HD patients	Higher sleep quality, reduced sleep latency, but duration of sleep was not modified.	Low	Short-term use
Zolpidem	Dashti-Khavidak et al, 2011[112]	Randomized crossover study; zolpidem vs clonazepam	23 HD patients	Clonazepam improved PSQI more than zolpidem.	Higher side effect profile for clonazepam compared with zolpidem	Avoid benzodiazepines; zolpidem can be considered for short-term use.
Benzodiazepines	Winkelmayer et al, 2007[113]	Retrospective cohort study of US incident HD patients	3,690 incident HD patients	Benzodiazepine or zolpidem use is common in dialysis patients and associated with greater mortality.	15% increase in mortality risk	Advisory against use due to mortality risk, especially if used concurrently with opioids
	Muzaale et al, 2020[114]	Retrospective cohort of incident HD patients in US	69,368 HD patients	Codispensing of opioids and short-acting benzodiazepines is common in dialysis patients and associated with a higher risk of death.		
Melatonin	Koch et al, 2008[115] (EMSCAP study)	Randomized crossover study; melatonin vs placebo	24 HD patients	Melatonin resulted in an improvement of subjective and objective sleep parameters, as well as a recovered nocturnal melatonin rhythm.	Low	Short-term use
	Russcher et al, 2013[35] (MELODY study)	RCT; melatonin vs placebo	67 HD patients	No improvement in sleep quality and quality of life at 12 mo follow-up; high dropout rate.	Low	Inconclusive data; may be used for short-term benefit
	Yousef et al, 2022[116]	RCT; melatonin vs placebo	60 HD patients	Improvement in total score of PSQI Insomnia Severity Index, subjective sleep quality, and daytime dysfunction.	Low	Short-term use
Trazadone	Mehrotra et al, 2024[47]	RCT; CBT-I, trazadone vs placebo	126 HD patients	No statistically significant difference in the effectiveness of 6 wk of CBT-I or trazodone compared with placebo.	Higher incidence of side effects for trazadone	Use with caution

Abbreviations: CBT-I, Cognitive Behavioural Therapy-Insomnia trial; HD, hemodialysis; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trial.

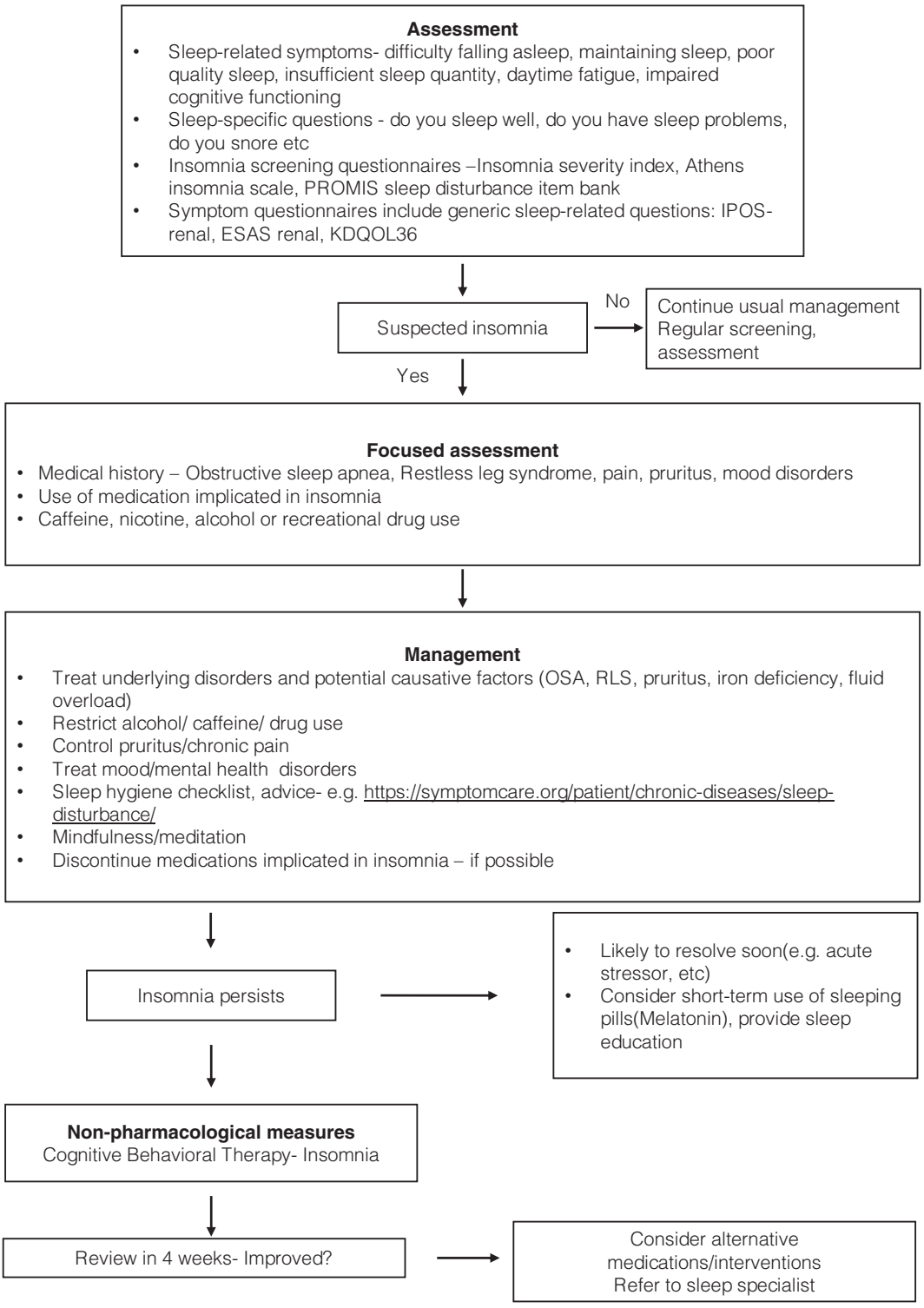

Figure 3. Approach to diagnosis and treatment of insomnia. Abbreviations: ESAS, Edmonton Symptom Assessment Scale; KDQOL36, Kidney Disease and Quality of Life; OSA, obstructive sleep apnea; PROMIS, Patient-Reported Outcomes Measurement Information System; RLS, restless legs syndrome.

Although a variety of medications are commonly used in the management of chronic insomnia, there have been no appropriately designed studies to evaluate their safety and efficacy in patients with kidney failure. Melatonin has been formally studied in patients on hemodialysis, but results remain inconclusive. Harms associated with melatonin are low. Although other pharmacologic treatments are often used, they must be

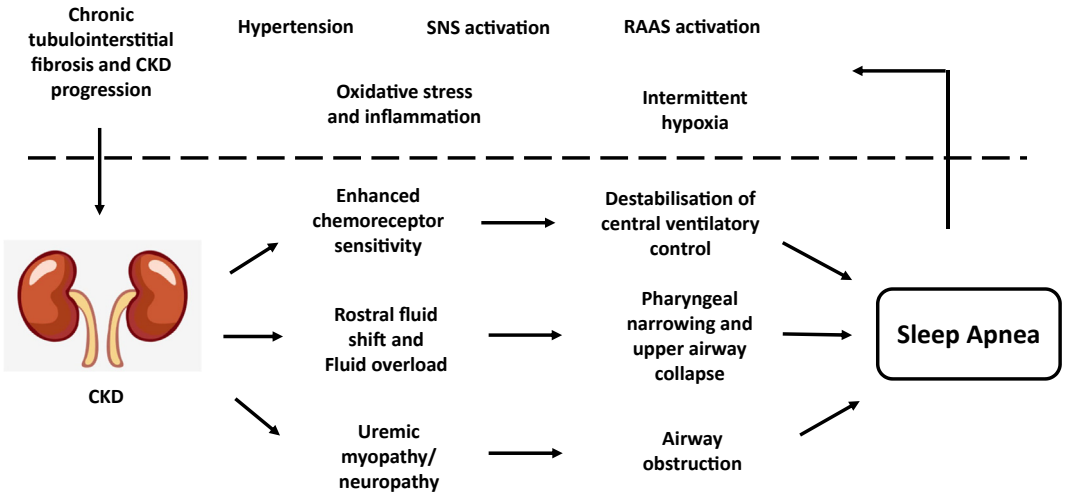

Figure 4. The complex bidirectional relationship between sleep apnea and chronic kidney disease. Abbreviations: CKD, chronic kidney disease; SNS, sympathetic nervous system and RAAS, renin-angiotensin-aldosterone system.

used with caution and preferably for short intervals only. Safety and efficacy data for these medications are limited in the dialysis and CKD population, and interactions and side effects are common. Commonly used medications along with their evidence for use are listed in Table 1.

Kidney Replacement Therapy

In patients with insomnia, it remains unclear if a change in dialysis modality can result in improved sleep. A systematic review that examined the effects of nocturnal hemodialysis on sleep parameters documented a significant improvement in sleep apnea after switching from conventional hemodialysis to nocturnal hemodialysis, although there did not seem to be a net benefit in overall subjective sleep quality.[51-53] This may be because nocturnal hemodialysis can disrupt sleep in some patients due to technical difficulties with the mode of dialysis (eg, alarms or discomfort due to body or arm positions), as well as to anxiety about receiving dialysis during the night. Novak et al[8] showed that the prevalence of insomnia was lower in transplant than wait-listed patients. A recent study also showed sleep quality was more likely to improve among males after kidney transplantation.[29]

We summarized our perspective on the diagnosis and treatment of insomnia in Figure 3.

Sleep Apnea Syndrome

Sleep apnea is defined as intermittent episodes of partial or complete interruption of respiratory airflow during sleep. Sleep apnea leads to sleep fragmentation, excessive daytime sleepiness, cognitive impairment, and impaired HRQoL. There are 2 types of sleep apnea: obstructive sleep apnea (OSA), which occurs due to intermittent closure of the upper airway during sleep, and central sleep apnea (CSA), which occurs due to intermittent loss of respiratory drive. An apneic episode is defined as the absence of airflow for 10 seconds or greater, and a hypopneic episode is the decrease in airflow by 50% for 10 seconds or decreases by 30% if there is an associated decrease in oxygen saturation or an arousal from sleep. The apnea-hypopnea index (AHI) is determined by the total number of apneas and hypopneas during sleep divided by the total number of hours of sleep. An AHI of 5-15 is considered mild and 15-30 as moderate apnea. An AHI of greater than 30 is classified as severe apnea.[54]

The reported prevalence of sleep apnea is 31% to 57% in early CKD, whereas a prevalence of 45% to 66% is reported in patients on dialysis[55-57] and 38% to 56% in kidney transplant recipients.[58,59]

Pathogenesis

Kidney disease may cause sleep apnea or worsen preexisting sleep apnea. There is often a component of both obstructive and central sleep apnea in patients with CKD. There are several proposed pathophysiologic mechanisms by which kidney disease could potentially contribute to sleep apnea. A combination of hypervolemia leading to upper airway collapse, increased chemoreceptor sensitivity causing central ventilatory instability,[60,61] and uremic myopathy leading to respiratory muscle fatigability[62] are implicated as important pathogenic factors (Fig 4).

Hypervolemia and rostral fluid shift from the legs overnight contributes to subsequent fluid accumulation in the neck, leading to pharyngeal narrowing by causing interstitial edema and/or increased fluid volume in the neck and peripharyngeal structures. This leads to increased upper airway collapsibility causing obstructive sleep apnea, and this may explain some of the observed improvements in sleep with nocturnal dialysis where volume control

Box 1. The International Restless Legs Syndrome Study Group criteria[93]

1. Urge to move the legs usually with unpleasant sensations in the legs; arms and other body parts are occasionally involved.
2. Symptoms begin or worsen during periods of rest or inactivity.
3. Symptoms partially or completely relieved by movement and as long as the activity continues.
4. Symptoms are worse during the evening or night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioural condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

occurs overnight.[63] Hypervolemia and pulmonary fluid accumulation may stimulate pulmonary irritant receptors, leading to a cycle of hyperventilation and apnea and predisposing to central sleep apnea.[64,65] Individuals with sleep apnea had a significantly higher total body extracellular fluid volume and segmental fluid volumes than those with no sleep apnea, and fluid removal by ultrafiltration reduces the apnea-hypopnea index of patients with kidney failure and sleep apnea, supporting the role of fluid overload as an important mechanism in the pathogenesis of sleep apnea in kidney failure.[66,67]

Studies have shown enhanced chemoreceptor sensitivity to hypercapnia in patients with kidney failure,[61] and a reduction in ventilatory sensitivity has been demonstrated among dialysis patients whose apnea improved when they were switched from conventional to nocturnal hemodialysis.[68] Among such patients, the reduction in ventilatory sensitivity correlated with a reduction in apnea severity, as reflected by a fall in the apnea-hypopnea index in all apneic patients.

Several investigators have explored the relationship between sleep apnea and the progression of CKD.[69] Intermittent hypoxia occurring due to sleep apnea can cause chronic intrarenal hypoxia,[70] oxidative stress, and inflammation along with activation of the sympathetic nervous system and renin-angiotensin-aldosterone system leading to intraglomerular hypertension and hyperfiltration,[71] eventually resulting in chronic tubulointerstitial fibrosis and the progression of kidney damage[72] (Fig 4). The repeated cycles of hypoxia/hypercapnia lead to sympathetically mediated vasoconstriction along with renin-angiotensin-aldosterone system activation leading to hypertension.[73,74] The nocturnal hypoxia and neurohumoral activation have been linked with the development of resistant hypertension,[75,76] left ventricular hypertrophy,[75] accelerated atherosclerosis, and increased cardiovascular mortality.[76]

However, studies in kidney transplant recipients did not directly confirm the association between OSA and CKD progression.[77,78]

Diagnosis

Because the prevalence of sleep apnea is high in patients with CKD, routine screening (eg, using the STOP-Bang questionnaire[79,80] or the Epworth Sleepiness Scale[80]) could be considered to identify patients who may benefit from further assessment. The definitive diagnosis of sleep apnea requires polysomnographic studies (either in laboratory testing or at home). The diagnosis of obstructive sleep apnea is confirmed if there are 15 or more obstructive respiratory events (apneas, hypopneas, or respiratory effort-related arousal per hour of sleep) or if there are 5 or more predominantly obstructive respiratory events (apnea/hypopnea/respiratory effort-related arousals) per hour of sleep, seen in a patient with 1 or more of the following: (1) sleepiness, fatigue, insomnia, or other symptoms; (2) waking up with breath holding, gasping, or choking; or (3) habitual snoring or breathing interruptions noted by a bed partner or other observer.[81]

Treatment

A number of behavioral interventions are recommended for sleep apnea. These include weight loss, exercise, positional therapy, and avoidance of alcohol and sedatives which are often prescribed for poor sleep. The American Academy of Sleep Medicine (AASM) recommends offering continuous positive airway pressure (CPAP) therapy to all patients who have been diagnosed with OSA.[81] CPAP keeps the pharyngeal airway open by delivering positive pressure through a nasal mask, which ameliorates nocturnal apneas and hypopneas, improves daytime somnolence, performance, and HRQoL,[82,83] and reduces blood pressure.[84] Oral appliances, such as mandibular advancement or tongue-retaining devices,[81,85] are sometimes used in patients with mild to moderate OSA who are intolerant of continuous positive airway pressure. Surgical procedures to correct airway obstruction, including maxillomandibular advancement and uvulopalatoplasty,[86] are usually used as a last option for selected patients who have an inadequate response or intolerance to CPAP and oral appliances.[81]

As discussed in the section on pathogenesis, fluid overload plays an important role in the pathogenesis of OSA in patients receiving dialysis. Hence, optimizing volume status by modifying ultrafiltration may help with counteracting rostral fluid shift and may lead to a reduction in OSA severity. Sleep apnea may be improved by changing the mode of kidney replacement therapy.[63,87-89] Nocturnal dialysis modalities that maximize nocturnal fluid removal may be favored.[67,88] In a small landmark study of nocturnal hemodialysis, changing from conventional 3 times weekly hemodialysis to nocturnal hemodialysis was associated with a significant reduction in the AHI.[87] Similarly, nocturnal cycler–assisted peritoneal dialysis may also reduce the prevalence and severity of sleep apnea compared with those treated with continuous ambulatory peritoneal dialysis.[88]

However, it is still controversial whether patients with sleep apnea should be converted from conventional

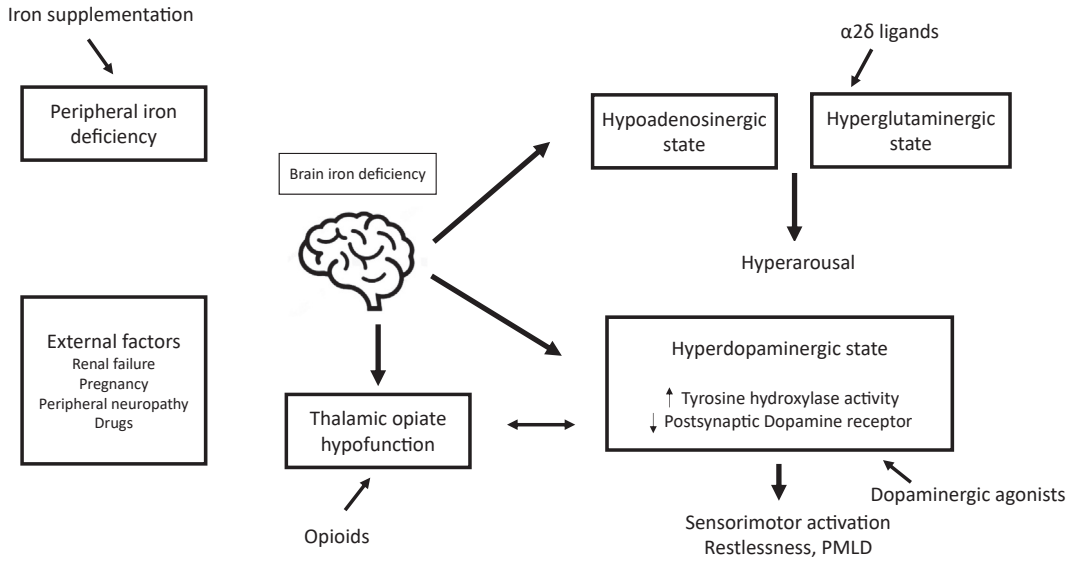

Figure 5. Pathogenesis of restless legs syndrome and the various therapeutic options. Abbreviation: PLMD, periodic limb movement disorder.

hemodialysis to nocturnal dialysis. A recent meta-analysis that included 6 single-arm studies, 1 observational study, and 2 randomized controlled trials (a total of 286 participants) concluded that a significant improvement in sleep apnea was observed by switching from conventional hemodialysis to nocturnal hemodialysis but a net benefit in overall subjective sleep quality was not seen.[51]

Kidney transplantation improves many aspects of well-being and health, including fluid overload, but has only shown resolution of sleep apnea in some patients.[90] A meta-analysis that included 8 prospective cohort studies with a total of 401 patients did not find a statistically significant effect on the apnea-hypopnea index, total sleep time, sleep efficiency, slow wave, or rapid eye movement after transplantation.[91]

Restless Legs Syndrome and Periodic Limb Movement Disorder

RLS, also known as Willis-Ekbom syndrome, is a sensorimotor movement disorder characterized by an irresistible need to move the legs. It is associated with limb discomfort and paresthesias, typically in the evening or early part of the night, which worsen during periods of inactivity and are transiently relieved by movement.[92,93] By contrast, PLMDs are sudden, repetitive, and highly stereotyped jerking leg movements occurring during sleep. These are seen in roughly 80% of patients with RLS. Around 60% to 70% of patients with RLS experience disrupted sleep, including difficulties in falling asleep, reduced total sleep time, and an increased number of awakenings with RLS symptoms.[94]

The reported prevalence of RLS in patients with CKD stages 3-4, those receiving dialysis, and those with a kidney transplant ranges from 9% to 37%,[95,96] 15% to 30%,[96,97] and 5% to 7%,[95,98] respectively.

Pathogenesis

The pathogenesis of RLS and PLMD in CKD is not clearly understood. Numerous studies have noted low iron availability in RLS.[99] Brain iron deficiency is a result of altered brain iron acquisition, and this is an important pathogenic factor in RLS.[100] The dopaminergic system is involved in the pathophysiology of RLS by causing a presynaptic hyperdopaminergic state, resulting in postsynaptic down-regulation of dopaminergic D2 receptors, leading to reduced dopaminergic signaling when dopamine levels are low in the evening due to the circadian dipping, and causing a relative nighttime dopamine activity deficit.[101,102] This is responsible for sensorimotor activation leading to periodic limb movements and restlessness.

In addition, there is a hyperglutaminergic state and hypoadenosinergic state, which is responsible for the hyperarousal and insomnia associated with RLS (Fig 5). Among the factors that increase the risk of RLS include medications (that patients with kidney failure frequently receive for relief of depression and psychological issues, pruritus, and gastroparesis), pregnancy, and peripheral neuropathy.[103]

Diagnosis

The diagnostic criteria for RLS were revised in 2014 adding a fifth criterion[93] (Box 1). Similarly, the *International Classification of Sleep Disorders*, Third Edition, has defined the diagnostic criteria of PLM disorder based on the presence of periodic limb movements of sleep of more than 15 periodic limb movements per hour in adults, and more

Table 2. Therapeutic Options in Restless Leg Syndrome

Drug	Dose, mg/d	Common Side Effects
α2δ Ligands		
Gabapentin	300-1,800 (CL_{cr} 30-49 mL/min, max dose 900; 15-29 mL/min, max dose 600; <15 mL/min, max dose 300)	Dizziness, somnolence
Pregabalin	50-450 (CL_{cr} 30-60 mL/min, max dose 75; <30 mL/min, max dose 25)	Fatigue
Dopaminergic agents		
Levodopa/carbidopa	100/25-600/150	Augmentation, contraindicated with a history of cardiac, pulmonary, or retroperitoneal fibrosis
Cabergoline	2-3	Contraindicated with cardiac valve abnormalities
Ropinirole	0.78-4.6	Augmentation, impulse control disorder, local site reaction
Rotigotine	2-3	Augmentation, impulse control disorder
Pramipexole	0.25-0.75 (CL_{cr} < 15 mL/min, max dose up to 0.5)	Augmentation, impulse control disorder
Opioids		
Oxycodone	5-40 (50% of dose when CL_{cr} < 30 mL/min)	Sleep-related respiratory problems
Iron therapy		
Oral iron preparations		
IV ferric carboxymaltose		
IV iron sucrose		Rare allergic reactions

Abbreviations: CL_{cr}, creatinine clearance; IV, intravenous; max, maximum.

than 5 periodic limb movements per hour in children, causing sleep problems that impact daytime functioning in the absence of any other sleep-related, psychiatric, or medical illnesses.[104] Polysomnography can be used to quantify periodic limb movements of sleep and serves as an indirect index of disease severity. Evaluation of iron stores with serum ferritin and transferrin saturation is recommended; iron deficiency should be treated.[105,106]

Treatment

Nonpharmacologic approaches for RLS management include cool dialysate, intradialytic aerobic exercise, aromatherapy massage, reflexology, acupoint therapy, and neuromuscular electrical stimulation. In a meta-analysis that included 24 randomized controlled trials with 1,252 dialysis patients, cool dialysate produced the largest RLS severity score reduction among the nonpharmacologic interventions.[107]

Multiple pharmacologic approaches have been used in RLS and are summarized in Table 2 and Figure 5. Before initiating treatment, a review of medications may be important to identify and potentially stop (if possible) drugs that may induce or worsen RLS (eg, domperidone, metoclopramide, nortriptyline, haloperidol, risperidone, etc). First-line therapies often include α2δ ligands (gabapentin and pregabalin) and dopaminergic agonists (eg, pramipexole, ropinirole, and rotigotine). Factors favoring dopamine agonists over the α2δ ligands as initial treatments include obesity, past or present moderate/severe depression, gait instability, disorders causing respiratory failure, and a history of substance use disorder. Over the past decade, the use of dopamine agonists has declined because they are associated with a high incidence of "augmentation" (dopamine agonist-induced worsening of RLS symptoms) and may worsen impulse control disorders when used long term.

A meta-analysis that looked at various treatment strategies for RLS in patients with kidney failure treated with dialysis concluded that gabapentin was the most potent pharmacologic treatment to reduce RLS severity.[107] Opioids are considered a second-line therapy for RLS and are used when symptoms are refractory to other treatments or in the case of associated severe pain disorder requiring opioids. Finally, kidney transplantation is associated with significant improvement or disappearance of the symptoms of RLS and PLMD.[98,108-110]

Summary

Sleep disorders are common in patients with CKD and kidney failure, and can be complicated to manage. Future research is required to better understand the complex relationship between sleep and kidney disease, to test standard treatments in CKD patients, and to develop novel therapies for sleep disorders to improve the quality of life, morbidity, and mortality in this high-risk population.

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References

1. Cohen SD, Patel SS, Khetpal P, Peterson RA, Kimmel PL. Pain, sleep disturbance, and quality of life in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2007;2(5):919-925. doi:10.2215/CJN.00820207
2. Elder SJ, Pisoni RL, Akizawa T, et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2008;23(3):998-1004. doi:10.1093/ndt/gfm630
3. Tu CY, Chou YH, Lin YH, Huang WL. Sleep and emotional disturbance in patients with non-dialysis chronic kidney disease. *J Formos Med Assoc*. 2019;118(6):986-994. doi:10.1016/j.jfma.2018.10.016
4. Tan LH, Chen PS, Chiang HY, et al. Insomnia and poor sleep in CKD: a systematic review and meta-analysis. *Kidney Med*. 2022;4(5):100458. doi:10.1016/j.xkme.2022.100458
5. Hui DS, Wong TY, Ko FW, et al. Prevalence of sleep disturbances in chinese patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. *Am J Kidney Dis*. 2000;36(4):783-788. doi:10.1053/ajkd.2000.17664
6. Walker S, Fine A, Kryger MH. Sleep complaints are common in a dialysis unit. *Am J Kidney Dis*. 1995;26(5):751-756. doi:10.1016/0272-6386(95)90438-7
7. Hsu CY, Lee CT, Lee YJ, et al. Better sleep quality and less daytime symptoms in patients on evening hemodialysis: a questionnaire-based study. *Artif Organs*. 2008;32(9):711-716. doi:10.1111/j.1525-1594.2008.00593.x
8. Novak M, Molnar MZ, Ambrus C, et al. Chronic insomnia in kidney transplant recipients. *Am J Kidney Dis*. 2006;47(4):655-665. doi:10.1053/j.ajkd.2005.12.035
9. Mucsi I, Molnar MZ, Rethelyi J, et al. Sleep disorders and illness intrusiveness in patients on chronic dialysis. *Nephrol Dial Transplant*. 2004;19(7):1815-1822. doi:10.1093/ndt/gfh130
10. Iliescu EA, Coo H, McMurray MH, et al. Quality of sleep and health-related quality of life in haemodialysis patients. *Nephrol Dial Transplant*. 2003;18(1):126-132. doi:10.1093/ndt/18.1.126
11. Novak M, Mucsi I, Shapiro CM, Rethelyi J, Kopp MS. Increased utilization of health services by insomniacs—an epidemiological perspective. *J Psychosom Res*. 2004;56(5):527-536. doi:10.1016/j.jpsychores.2004.02.007
12. Jhamb M, Liang K, Yabes J, et al. Prevalence and correlates of fatigue in chronic kidney disease and end-stage renal disease: are sleep disorders a key to understanding fatigue? *Am J Nephrol*. 2013;38(6):489-495. doi:10.1159/000356939
13. Paparrigopoulos T, Theleritis C, Tzavara C, Papadaki A. Sleep disturbance in haemodialysis patients is closely related to depression. *Gen Hosp Psychiatry*. 2009;31(2):175-177. doi:10.1016/j.genhosppsych.2008.09.016
14. Kim HW, Heo GY, Kim HJ, Kang S-W, Park JT, Lee E. Insomnia in patients on incident maintenance dialysis and the risk of major acute cardio-cerebrovascular events and all-cause mortality. *Nephrol Dial Transplant*. 2023;39(5):830-837. doi:10.1093/ndt/gfad231
15. Fitzpatrick J, Kerns ES, Kim ED, et al. Functional outcomes of sleep predict cardiovascular intermediary outcomes and all-cause mortality in patients on incident hemodialysis. *J Clin Sleep Med*. 2021;17(8):1707-1715. doi:10.5664/jcsm.9304
16. Brekke FB, Waldum B, Amro A, et al. Self-perceived quality of sleep and mortality in Norwegian dialysis patients. *Hemodial Int*. 2014;18(1):87-94. doi:10.1111/hdi.12066
17. Unruh ML, Buysse DJ, Dew MA, et al. Sleep quality and its correlates in the first year of dialysis. *Clin J Am Soc Nephrol*. 2006;1(4):802-810. doi:10.2215/CJN.00710206
18. Ogna A, Forni Ogna V, Haba Rubio J, et al. Sleep characteristics in early stages of chronic kidney disease in the HypnoLaus Cohort. *Sleep*. 2016;39(4):945-953. doi:10.5665/sleep.5660
19. Mucsi I, Molnar MZ, Ambrus C, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. *Nephrol Dial Transplant*. 2005;20(3):571-577. doi:10.1093/ndt/gfh654
20. Eryilmaz MM, Ozdemir C, Yurtman F, Cilli A, Karaman T. Quality of sleep and quality of life in renal transplantation patients. *Transplant Proc*. 2005;37(5):2072-2076. doi:10.1016/j.transproceed.2005.03.084
21. Morin CM, Jarrin DC. Epidemiology of insomnia: prevalence, course, risk factors, and public health burden. *Sleep Med Clin*. 2022;17(2):173-191. doi:10.1016/j.jsmc.2022.03.003
22. Pai MF, Hsu SP, Yang SY, Ho TI, Lai CF, Peng YS. Sleep disturbance in chronic hemodialysis patients: the impact of depression and anemia. *Ren Fail*. 2007;29(6):673-677. doi:10.1080/08860220701459642
23. Virga G, Stanic L, Mastrosimone S, Gastaldon F, da Porto A, Bonadonna A. Hypercalcemia and insomnia in hemodialysis patients. *Nephron*. 2000;85(1):94-95. doi:10.1159/000045638
24. Esposito MG, Cesare CM, De Santo RM, et al. Parathyroidectomy improves the quality of sleep in maintenance hemodialysis patients with severe hyperparathyroidism. *J Nephrol*. 2008;21(suppl 13):S92-S96.
25. Pisoni RL, Wikström B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2006;21(12):3495-3505. doi:10.1093/ndt/gfl461
26. Chiu YL, Chuang YF, Fang KC, et al. Higher systemic inflammation is associated with poorer sleep quality in stable haemodialysis patients. *Nephrol Dial Transplant*. 2009;24(1):247-251. doi:10.1093/ndt/gfn439
27. Yang JY, Huang JW, Chiang CK, et al. Higher plasma interleukin-18 levels associated with poor quality of sleep in peritoneal dialysis patients. *Nephrol Dial Transplant*. 2007;22(12):3606-3609. doi:10.1093/ndt/gfm231

28. Van Gastel A. Drug-induced insomnia and excessive sleepiness. *Sleep Med Clin*. 2018;13(2):147-159. doi:10.1016/j.jsmc.2018.02.001
29. Knobbe TJ, Kremer D, Eisenga MF, et al. Sleep quality, fatigue, societal participation and health-related quality of life in kidney transplant recipients: a cross-sectional and longitudinal cohort study. *Nephrol Dial Transplant*. 2024;39(1):74-83. doi:10.1093/ndt/gfad148
30. Novak M, Shapiro CM, Mendelssohn D, Mucsi I. Diagnosis and management of insomnia in dialysis patients. *Semin Dial*. 2006;19(1):25-31. doi:10.1111/j.1525-139X.2006.00116.x
31. Bornivelli C, Aperis G, Giannikouris I, Paliouras C, Alivanis P. Relationship between depression, clinical and biochemical parameters in patients undergoing haemodialysis. *J Ren Care*. 2012;38(2):93-97. doi:10.1111/j.1755-6686.2012.00259.x
32. Sabbatini M. Insomnia in maintenance haemodialysis patients. *Nephrol Dial Transplant*. 2002;17(5):852-856. doi:10.1093/ndt/17.5.852
33. Sheshadri A, Kittiskulnam P, Johansen KL. Higher physical activity is associated with less fatigue and insomnia among patients on hemodialysis. *Kidney Int Rep*. 2019;4(2):285-292. doi:10.1016/j.ekir.2018.10.014
34. Koch BC, van der Putten K, Van Someren EJ, et al. Impairment of endogenous melatonin rhythm is related to the degree of chronic kidney disease (CREAM study). *Nephrol Dial Transplant*. 2010;25(2):513-519. doi:10.1093/ndt/gfp493
35. Russcher M, Koch BC, Nagtegaal JE, et al. Long-term effects of melatonin on quality of life and sleep in haemodialysis patients (Melody study): a randomized controlled trial. *Br J Clin Pharmacol*. 2013;76(5):668-679. doi:10.1111/bcp.12093
36. Karasek M, Szuflet A, Chrzanowski W, Zylinska K, Swietoslawski J. Decreased melatonin nocturnal concentrations in hemodialyzed patients. *Neuroendocrinol Lett*. 2005;26(6):653-656.
37. Lüdemann P, Zwernemann S, Lerchl A. Clearance of melatonin and 6-sulfatoxymelatonin by hemodialysis in patients with end-stage renal disease. *J Pineal Res*. 2001;31(3):222-227. doi:10.1034/j.1600-079x.2001.310305.x
38. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4
39. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. *J Psychosom Res*. 2000;48(6):555-560. doi:10.1016/s0022-3999(00)00095-7
40. Bastien C. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(4):297-307. doi:10.1016/s1389-9457(00)00065-4
41. Valera S, Diz JC, Rey-Fernandez B, Gonzalez-Devesa D, Garcia-Fresneda A, Ayan C. Efficacy of physical exercise on sleep quality in patients with chronic kidney disease: a systematic review and meta-analysis. *Sleep Breath*. 2024;28(1):381-392. doi:10.1007/s11325-023-02891-4
42. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/M15-2175
43. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Med clinical practice guideline. *J Clin Sleep Med*. 2021;17(2):255-262. doi:10.5664/jcsm.8986
44. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
45. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol*. 2010;24(11):1577-1601. doi:10.1177/0269881119855343
46. Riemann D, Espie CA, Altena E, et al. The European Insomnia Guideline: an update on the diagnosis and treatment of insomnia 2023. *J Sleep Res*. 2023;32(6):e14035. doi:10.1111/jsr.14035
47. Mehrotra R, Cukor D, McCurry SM, et al. Effectiveness of existing insomnia therapies for patients undergoing hemodialysis. *Ann Intern Med*. 2024;177(2):177-188. doi:10.7326/M23-1794
48. Siu PM, Yu AP, Tam BT, et al. Effects of tai chi or exercise on sleep in older adults with insomnia: a randomized clinical trial. *JAMA Netw Open*. 2021;4(2):e2037199. doi:10.1001/JAMA-networkopen.2020.37199
49. Rash JA, Kavanagh VAJ, Garland SN. A meta-analysis of mindfulness-based therapies for insomnia and sleep disturbance moving toward processes of change. *Sleep Med Clin*. 2022;17(3):329-353. doi:10.1016/j.jsmc.2022.06.002
50. Wang YY, Wang F, Zheng W, et al. Mindfulness-based interventions for insomnia: a meta-analysis of randomized controlled trials. *Behav Sleep Med*. 2020;18(1):1-9. doi:10.1080/15402002.2018.1518228
51. Li L, Tang X, Kim S, Zhang Y, Li Y, Fu P. Effect of nocturnal hemodialysis on sleep parameters in patients with end-stage renal disease: a systematic review and meta-analysis. *PLoS One*. 2018;13(9):e0203710. doi:10.1371/journal.pone.0203710
52. Unruh ML, Larive B, Eggers PW, et al. The effect of frequent hemodialysis on self-reported sleep quality: Frequent Hemodialysis Network Trials. *Nephrol Dial Transplant*. 2016;31(6):984-991. doi:10.1093/ndt/gfw062
53. Culleton BF, Walsh M, Klarenbach SW, et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA*. 2007;298(11):1291-1299. doi:10.1001/JAMA.298.11.1291
54. American Academy of Sleep Med Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*. 1999;22(5):667-689. doi:10.1093/sleep/22.5.667
55. Pisano A, Zoccali C, Bolignano D, D'Arrigo G, Mallamaci F. Sleep apnoea syndrome prevalence in chronic kidney disease and end-stage kidney disease patients: a systematic review and meta-analysis. *Clin Kidney J*. 2024;17(1):sfad179. doi:10.1093/ckj/sfad179
56. Jamwal J, Qadri SM, Siraj F, Shah S. Prevalence of obstructive sleep apnea in patients with chronic kidney disease: a hospital-based study. *Sleep Breath*. 2023;27(5):1703-1708. doi:10.1007/s11325-022-02764-2
57. Huang H-C, Walters G, Talaulikar G, et al. Sleep apnea prevalence in chronic kidney disease—association with total body water and symptoms. *BMC Nephrol*. 2017;18(1):125. doi:10.1186/s12882-017-0544-3
58. Tandukar S, Hou S, Yabes J, et al. Does kidney transplantation affect sleep and fatigue in patients with kidney disease? *Transplant Direct*. 2019;5(6):e461. doi:10.1097/TXD.0000000000000895
59. Daabis R, El-Gohary E. Sleep apnea in kidney transplant patients: clinical correlates and comparison with pretransplant patients. *Egypt J Chest Dis Tuberc*. 2012;61(4):453-458. doi:10.1016/j.ejcdt.2012.08.013
60. Langevin B, Fouque D, Léger P, Robert D. Sleep apnea syndrome and end-stage renal disease. *Chest*. 1993;103(5):1330-1335. doi:10.5664/jcsm.4946

61. Beecroft J. Enhanced chemo-responsiveness in patients with sleep apnoea and end-stage renal disease. *Eur Respir J*. 2006;28(1):151-158. doi:10.1183/09031936.06.00075405
62. Tarasuik A, Heimer D, Bark H. Effect of chronic renal failure on skeletal and diaphragmatic muscle contraction. *Am Rev Respir Dis*. 1992;146(6):1383-1388. doi:10.1164/ajrccm/146.6.1383
63. Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane PA, Hanly PJ. Pharyngeal narrowing in end-stage renal disease: implications for obstructive sleep apnoea. *Eur Respir J*. 2007;30(5):965-971. doi:10.1183/09031936.00161906
64. Elias RM, Chan CT, Paul N, 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):937-944. doi:10.1093/ndt/gfs473
65. Yumino D, Redolfi S, Ruttanaumpawan P, 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):1598-1605. doi:10.1161/circulationaha.109.902452
66. 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. doi:10.1183/13993003.01789-2016
67. Lyons OD, Chan CT, Yadollahi A, Bradley TD. Effect of ultrafiltration on sleep apnea and sleep structure in patients with end-stage renal disease. *Am J Respir Crit Care Med*. 2015;191(11):1287-1294. doi:10.1164/rccm.201412-2288OC
68. Beecroft JM, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Decreased chemosensitivity and improvement of sleep apnea by nocturnal hemodialysis. *Sleep Med*. 2009;10(1):47-54. doi:10.1016/j.sleep.2007.11.017
69. Beaudin AE, Raneri JK, Ahmed SB, et al. Risk of chronic kidney disease in patients with obstructive sleep apnea. *Sleep*. 2022;45(2):zsab267. doi:10.1093/sleep/zsab267
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(2):e0192084. doi:10.1371/journal.pone.0192084
71. Kinebuchi S-I, Junichiro Satoh M, et al. Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome. *Clin Sci*. 2004;107(3):317-322. doi:10.1042/CS20040074
72. 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. doi:10.1378/chest.14-0596
73. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA*. 2000;283(14):1829. doi:10.1001/JAMA.283.14.1829
74. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342(19):1378-1384. doi:10.1056/NEJM200005113421901
75. Zoccali C, Benedetto FA, Mallamaci F, et al. Left ventricular hypertrophy and nocturnal hypoxemia in hemodialysis patients. *J Hypertens*. 2001;19(2):287-293. doi:10.1097/00004872-200102000-00016
76. Watanabe Y, Tanaka A, Furuhashi K, Saito S, Maruyama S. Mortality and cardiovascular events in patients with chronic kidney disease and sleep apnea syndrome. *Front Med (Lausanne)*. 2022;9:899359. doi:10.3389/fmed.2022.899359
77. Fornadi K, Ronai KZ, Turanyi CZ, et al. Sleep apnea is not associated with worse outcomes in kidney transplant recipients. *Sci Rep*. 2014;4:6987. doi:10.1038/srep06987
78. Szentkiralyi A, Czira ME, Molnar MZ, et al. High risk of obstructive sleep apnea is a risk factor of death censored graft loss in kidney transplant recipients: an observational cohort study. *Sleep Med*. 2011;12(3):267-273. doi:10.1016/j.sleep.2010.08.012
79. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology*. 2008;108(5):812-821. doi:10.1097/ALN.0b013e31816d83e4
80. Rosenthal LD, Dolan DC. The Epworth Sleepiness Scale in the identification of obstructive sleep apnea. *J Nerv Ment Dis*. 2008;196(5):429-431. doi:10.1097/NMD.0b013e31816ff3bf
81. Epstein LJ, Kristo D, Strollo PJ Jr, et al; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5(3):263-276. doi:10.5664/jcsm.27497
82. Campos-Rodriguez F, Queipo-Corona C, Carmona-Bernal C, et al. Continuous positive airway pressure improves quality of life in women with obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*. 2016;194(10):1286-1294. doi:10.1164/rccm.201602-0265OC
83. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;375(10):919-931. doi:10.1056/NEJMoa1606599
84. Dhillon S, Chung S, Fargher T, Huterer N, Shapiro C. Sleep apnea, hypertension, and the effects of continuous positive airway pressure. *Am J Hypertens*. 2005;18(5):594-600. doi:10.1016/j.amjhyper.2004.11.031
85. Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med*. 2015;11(7):773-827. doi:10.5664/jcsm.4858
86. Zaghi S, Holty J-EC, Certal V, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea: a meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2016;142(1):58-66. doi:10.1001/JAMAoto.2015.2678
87. 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):102-107. doi:10.1056/NEJM200101113440204
88. Tang SCW, Lam B, Ku PP, et al. Alleviation 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):2607-2616. doi:10.1681/ASN.2005090936
89. Tang SC, Lam B, Lai AS, et al. Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance. *Clin J Am Soc Nephrol*. 2009;4(2):410-418. doi:10.2215/CJN.03520708
90. Beecroft JM, Zaltzman J, Prasad R, Meliton G, Hanly PJ. Impact of kidney transplantation on sleep apnoea in patients with end-stage renal disease. *Nephrol Dial Transplant*. 2007;22(10):3028-3033. doi:10.1093/ndt/gfm309
91. Kanbay M, Ureche C, Copur S, et al. Kidney transplantation: a possible solution to obstructive sleep apnea in patients with end-stage kidney disease. *Sleep Breath*. 2023;27(5):1667-1675. doi:10.1007/s11325-023-02803-6
92. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord*. 1995;10(5):634-642. doi:10.1002/mds.870100517

93. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. *Sleep Med*. 2014;15(8):860-873. doi:10.1016/j.sleep.2014.03.025
94. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord*. 1997;12(1):61-65. doi:10.1002/mds.870120111
95. Lin Z, Zhao C, Luo Q, Xia X, Yu X, Huang F. Prevalence of restless legs syndrome in chronic kidney disease: a systematic review and meta-analysis of observational studies. *Ren Fail*. 2016;38(9):1335-1346. doi:10.1080/0886022X.2016.1227564
96. Safarpour Y, Vaziri ND, Jabbari B. Restless legs syndrome in chronic kidney disease—a systematic review. *Tremor Other Hyperkinet Mov (NY)*. 2023;13:10. doi:10.5334/tohm.752
97. Novak M, Winkelman JW, Unruh M. Restless legs syndrome in patients with chronic kidney disease. *Semin Nephrol*. 2015;35(4):347-358. doi:10.1016/j.semnephrol.2015.06.006
98. Molnar MZ, Novak M, Ambrus C, et al. Restless legs syndrome in patients after renal transplantation. *Am J Kidney Dis*. 2005;45(2):388-396. doi:10.1053/j.ajkd.2004.10.007
99. Allen RP, Earley CJ. The role of iron in restless legs syndrome. *Mov Disord*. 2007;22(suppl 18):S440-S448. doi:10.1002/mds.21607
100. Connor JR, Ponnuru P, Wang X-S, Patton SM, Allen RP, Earley CJ. Profile of altered brain iron acquisition in restless legs syndrome. *Brain*. 2011;134(4):959-968. doi:10.1093/brain/awr012
101. Manconi M, Garcia-Borreguero D, Schormair B, et al. Restless legs syndrome. *Nat Rev Dis Primers*. 2021;7(1):80. doi:10.1038/s41572-021-00311-z
102. Gonzalez-Latapi P, Malkani R. Update on restless legs syndrome: from mechanisms to treatment. *Curr Neurol Neurosci Rep*. 2019;19(8):54. doi:10.1007/s11910-019-0965-4
103. Bliwise DL, Zhang RH, Kutner NG. Medications associated with restless legs syndrome: a case-control study in the US Renal Data System (USRDS). *Sleep Med*. 2014;15(10):1241-1245. doi:10.1016/j.sleep.2014.05.011
104. Sateia MJ. International classification of sleep disorders—third edition: highlights and modifications. *Chest*. 2014;146(5):1387-1394. doi:10.1378/chest.14-0970
105. Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney Dis*. 2004;43(4):663-670. doi:10.1053/j.ajkd.2003.11.021
106. Trotti LM, Becker LA. Iron for the treatment of restless legs syndrome. *Cochrane Database Syst Rev*. 2019;1(1):CD007834. doi:10.1002/14651858.CD007834.pub3
107. Chen JJ, Lee TH, Tu YK, et al. Pharmacological and non-pharmacological treatments for restless legs syndrome in end-stage kidney disease: a systematic review and component network meta-analysis. *Nephrol Dial Transplant*. 2022;37(10):1982-1992. doi:10.1093/ndt/gfab290
108. Beecroft JM, Zaltzman J, Prasad GV, Meliton G, Hanly PJ. Improvement of periodic limb movements following kidney transplantation. *Nephron Clin Pract*. 2008;109(3):c133-c139. doi:10.1159/000145456
109. Molnar MZ, Szentkiralyi A, Lindner A, et al. Restless legs syndrome and mortality in kidney transplant recipients. *Am J Kidney Dis*. 2007;50(5):813-820. doi:10.1053/j.ajkd.2007.08.003
110. Winkelmann J, Stautner A, Samtleben W, Trenkwalder C. Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. *Mov Disord*. 2002;17(5):1072-1076. doi:10.1002/mds.10231
111. Sabbatini M, Crispo A, Pisani A, et al. Zaleplon improves sleep quality in maintenance hemodialysis patients. *Nephron Clin Pract*. 2003;94(4):c99-c103. doi:10.1159/000072493
112. Dashti-Khavidaki S, Chamani N, Khalili H, et al. Comparing effects of clonazepam and zolpidem on sleep quality of patients on maintenance hemodialysis. *Iran J Kidney Dis*. 2011;5(6):404-409.
113. Winkelmayer WC, Mehta J, Wang PS. Benzodiazepine use and mortality of incident dialysis patients in the United States. *Kidney Int*. 2007;72(11):1388-1393. doi:10.1038/sj.ki.5002548
114. Muzaale AD, Daubresse M, Bae S, et al. Benzodiazepines, codispensed opioids, and mortality among patients initiating long-term in-center hemodialysis. *Clin J Am Soc Nephrol*. 2020;15(6):794-804. doi:10.2215/CJN.13341019
115. Koch BC, Nagtegaal JE, Hagen EC, et al. The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (EMSCAP study). *Br J Clin Pharmacol*. 2009;67(1):68-75. doi:10.1111/j.1365-2125.2008.03320.x
116. Yousef EA, El Wasify MA, Baddor AA, Sobh MA-E. Study of exogenous melatonin as a treatment modality for sleep and psychiatric disorders in hemodialysis patients. *Saudi J Kidney Dis Transplant*. 2022;33(1):1-15. doi:10.4103/1319-2442.367802