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Sleep Disorders Associated with Chronic Kidney Disease

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1. Introduction

Twenty-six million American adults have Chronic Kidney Disease (CKD). Chronic Kidney Disease is defined as kidney damage for 3 or more months with or without decreased GFR. Chronic Kidney Disease is divided into five stages, from Stage 1 to Stage 5. End-Stage renal disease is the 5th stage of CKD when dialysis is needed to sustain life. Sleep disorders are common and under recognized in advanced stages of Chronic Kidney Disease. Sleep disorders affect the quality of life and may also increase cardiovascular morbidity and mortality.

Subjective sleep complaints are reported by more than 50% of patients on Hemodialysis (HD) (1). Common organic sleep disorders in patients with CKD include Sleep Apnea Syndrome (SAS), Periodic Limb Movement Disorder (PLMD) and Restless Leg Syndrome (RLS). These disorders are more common in the dialysis population than in the general population. When dialysis patients with a sleep disorders were studied objectively in sleep laboratory, 53% to 75% were found to have sleep apnea, which is higher than general population (2-4%) (2). Sleep disorders in CKD patients have been linked to increased incidences of cardiovascular disease including coronary artery disease, left ventricular hypertrophy and hypertension. (3, 4, 5, 6). Heart disease is the major cause of death in patients with CKD (www.kidney.org). In fact most patients who have advanced CKD and are not on dialysis are more likely to die from heart disease before they start dialysis.

Daytime somnolence resulting from sleep disorders may lead to diminished quality of life and cognition (7, 8). PLMD is associated with increased mortality in patients with ESRD. (49). Early diagnosis and treatment may improve quality of life.

2. Subjective complaints in dialysis patients

Subjective sleep complaints are common in dialysis patients and include difficulty initiating and maintaining sleep, problems with restless, jerking legs, and/or day time sleepiness. Sleep disorders are very inconvenient for the patients and affect their activities of daily living. Most patients believe that relief of these symptoms would improve subjective quality of life. A large number of dialysis patients take sleep-inducing medications. Sleep complaints are more common in elderly patients on dialysis than in younger patients and

male patients are more likely to have sleep complaints than women (10). Caucasian patients have a higher prevalence of restless legs syndrome than African American (1, 10). Subjective complaints are also high in patients with increased caffeine intake, pruritis, bone pain, cigarette use, and premature discontinuation of dialysis (1). As in general population, increased stress, anxiety, depression, and worry are also associated with poor subjective sleep quality in dialysis patients (10-12).

3. Factors contributing to sleep disturbances (Figure 1)

No consistent relationship has been detected between subjective sleep complaints of poor sleep and Blood Urea Nitrogen (BUN), Creatinine, or Kt/V (see glossary) (1, 11, & 13). Anemia has been associated with complaints of poor sleep with improvement after treatment with recombinant erythropoietin (14). Mild hypercalcemia has also been associated with increased frequency of subjective insomnia (15). Frequent napping during day time dialysis may also be a factor which contributes to fragmented sleep at night.

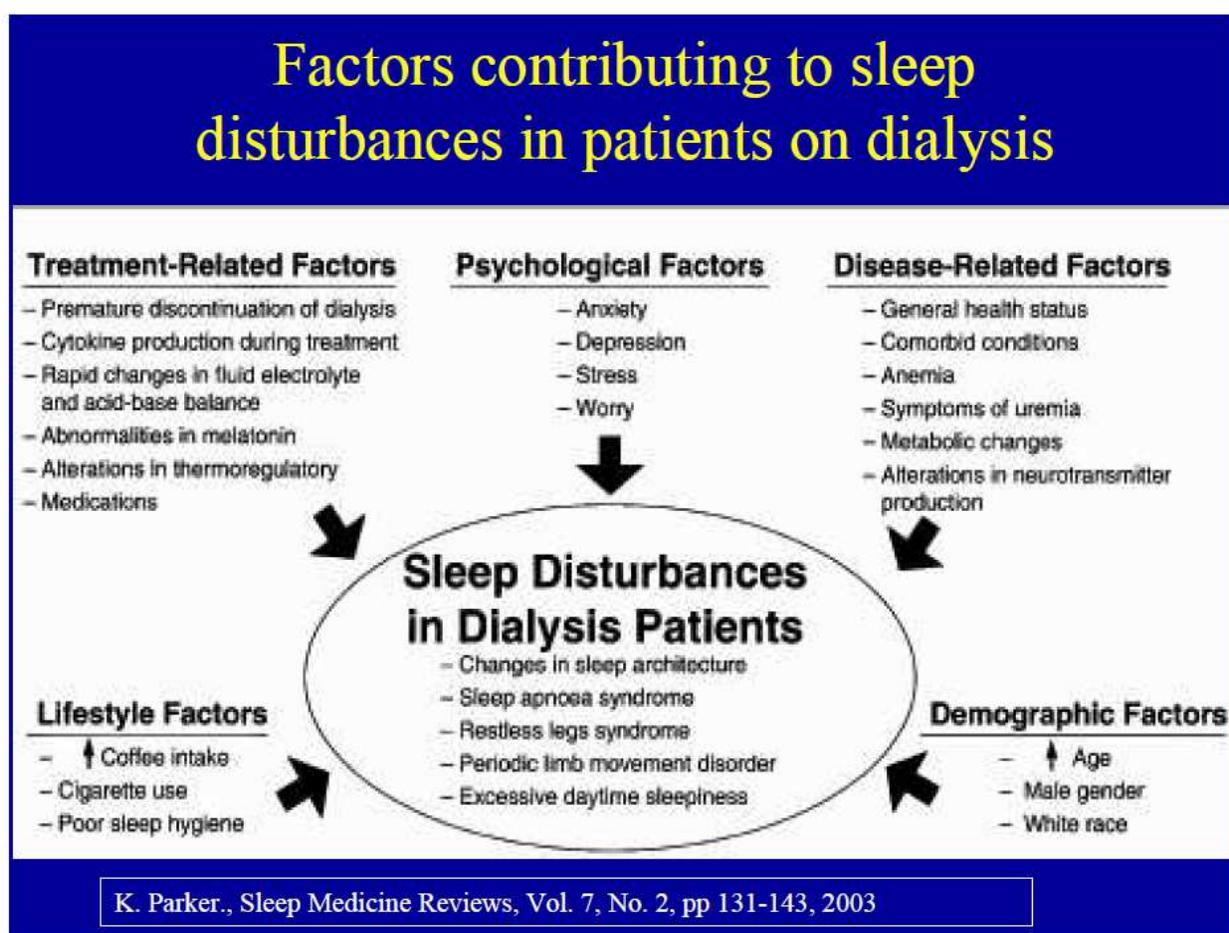


Fig. 1. Factors associated with sleep disturbances.

Nocturia, one of the earliest symptoms of kidney disease may also lead to reduced sleep due to frequent awakening. Untreated sleep apnea has also been linked to nocturia. Most of the awakenings attributed to nocturia by patients are attributable to sleep disorders, particularly sleep apnea (63).

4. Changes in sleep architecture

Nocturnal sleep of patients on dialysis is short and fragmented with total sleep time ranging between 260 and 360 minutes. Sleep efficiency is between 66% and 85% with a large amount of wakeful time (77-135 min), and numerous arousals (25-30/h of sleep) (16-18). Patients have increased patterns of Stage I and Stage II sleep, decreased slow wave (deep sleep), and REM sleep (17, 18). Thus dialysis patients have both reduced quantity and quality of sleep. Changes in sleep patterns in advanced CKD patients who are not on dialysis are similar to patients on dialysis (21)

5. Sleep Apnea Syndrome (SAS)

Sleep apnea is classified as obstructive (OSA) due to intermittent closure of the upper airway or central due to intermittent loss of respiratory drive or both (mixed). More than 50% of patients with ESRD have sleep apnea (7, 19). Prevalence appears to be similar in advanced CKD patients who are not on dialysis and those treated with peritoneal or hemodialysis (7, 20). Sleep Disordered Breathing (SDB) is observed with similar frequency in dialysis dependent and dialysis independent CKD patients. Sleep apnea in CKD patients is more frequently obstructive (21).

6. Pathogenesis-figure 2

Sleep apnea in patients with ESRD is mostly obstructive but several observers have reported features of both obstructive and central sleep apnea (16,31). Sleep apnea is caused by both impaired central ventilatory control and upper air way occlusion during sleep. Enhanced ventilatory sensitivity to hypercapnea correlates with apnea severity (22). Conversion from conventional Hemodialysis (CHD) to nocturnal Hemodialysis (NHD) has been associated with reduced severity of sleep apnea due to reduction in ventilatory sensitivity to hypercapnea(31). Upper airway occlusion can be caused by fluid overload and interstitial edema in the upper air way (23). Displacement of fluids from the lower limbs increases neck circumference and pharyngeal resistance and reduces upper air way cross sectional area, contributing to the pathogenesis of obstructive sleep apnea (OSA). Pharyngeal cross sectional area in patients on CHD was smaller than the control, suggesting that this may predispose to upper airway occlusion during sleep (22). Conversion from CHD to NHD is associated with an increase in pharyngeal cross sectional area, possibly due to improve fluid removal(31). Conversion from continuous ambulatory peritoneal dialysis (CAPD) to nocturnal peritoneal dialysis has been shown to reduce the frequency of sleep apnea (24). Upper airway dilator muscle dysfunction due to neuropathy or myopathy associated with chronic uremia or the underlying cause of renal disease such as diabetes mellitus can cause narrowing of pharyngeal muscles (31). There could also be some role for oxidative stress, inflammatory cytokines and middle molecules, all elevated in ESRD in the development of ventilatory instability and or upper airway occlusion, but this has not been established (66).

The apnea -hypopnea index (AHI) is an index used to assess the severity of sleep apnea based on the total number of complete cessations (apnea) and partial obstructions (hypopnea) of breathing occurring per hour of sleep found during polysomnography. Patients with advanced CKD not on dialysis who are non-diabetic are predisposed to more severe AHI as compared to patients with less advanced CKD (25). In patients with diabetes no such association was found probably due to the fact that diabetes itself may be an

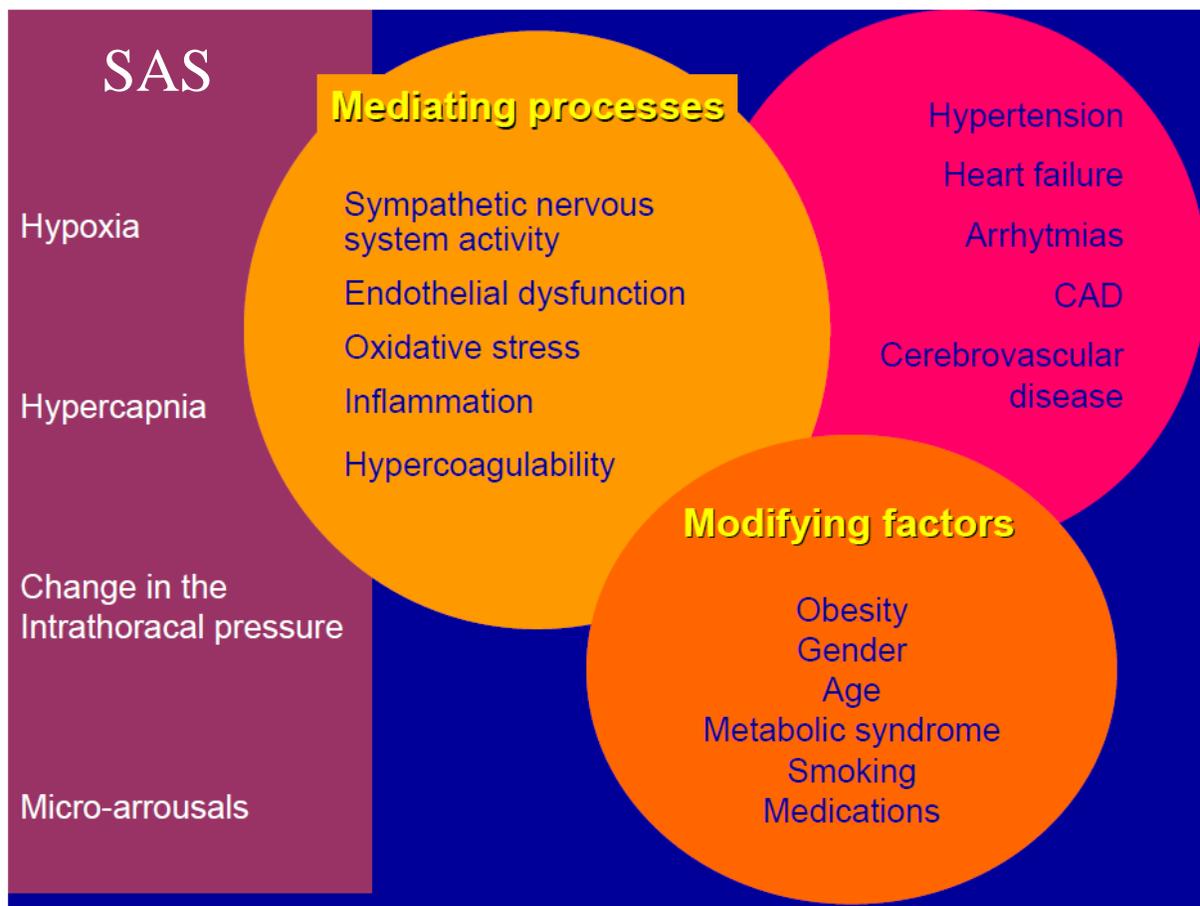


Fig. 2. Pathogenesis of sleep Apnea Syndrome (SAS).

overriding factor for the development of sleep apnea (25). It was also found that AHI index correlated weakly with urea level in all patients, but not with creatinine clearance.

Obesity is not required for ESRD patients to develop sleep apnea. Snoring is less intense in patients with CKD who have sleep apnea than in patients with sleep apnea with normal renal function (67).

7. Clinical significance

Sleep apnea worsens the symptoms of CKD such as daytime fatigue, sleepiness, and impaired neurocognitive function. Hypoxemia during sleep is associated with nocturnal hypertension, left ventricular hypertrophy, impaired sympathovagal balance, and increased risk of cardiovascular complications including death (68-69). Sleep apnea may exacerbate the infectious complications common in ESRD patients because sleep disruption and deprivation degrade immune function (26). Severe sleep apnea is an independent predictor of graft loss among female kidney transplant patients (27).

8. Diagnosis

Subjective sleepiness can be assessed with a number of simple scales, such as the Epworth Sleepiness Scale (ESS) or the Stanford Sleepiness Scale. The ESS is a self-administered

questionnaire with 8 questions and is more commonly used. It provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The ESS asks people to rate, on a 4-point scale (0 - 3), their usual chances of dozing off or falling asleep in 8 different situations or activities that most people engage in as part of their daily lives. The total ESS score is the sum of 8 item-scores and can range between 0 and 24. The higher the score, the higher the person's level of daytime sleepiness. Most people can answer the ESS, without assistance, in 2 or 3 minutes. (www.sleepfoundation.org).

Although the characteristic features of sleep apnea may be absent, a history of snoring, witnessed apnea during sleep, and day time sleepiness are suggestive of sleep apnea. Objective diagnostic testing includes home ambulatory monitoring which records air flow, snoring, respiratory movement, oxygen saturation, and heart rate.

Polysomnography (PSG), also known as a sleep study is a nocturnal, laboratory- test used in the diagnosis of Sleep Apnea Syndrome (SAS). It is often considered the standard for diagnosing OSAS, determining the severity of the disease, and evaluating various other sleep disorders that can exist with or without OSAS. PSG consists of a simultaneous recording of multiple physiologic parameters related to sleep and wakefulness. It generally includes monitoring of the patient's airflow through the nose and mouth, blood pressure, heartbeat as measured by an electrocardiograph, blood oxygen level, EEG wave patterns, eye movements (EOG), and the movements of respiratory muscles and limbs (EMG).

Polysomnography can be performed in a sleep laboratory or center and includes comprehensive monitoring of respiration, sleep stages and leg movements. Polysomnography is used to quantify the Apnea-Hypopnea Index (AHI). AHI is an index used to assess the severity of sleep apnea based on the total number of complete cessations (apnea) and partial obstructions (hypopnea) of breathing occurring per hour of sleep. These pauses in breathing must last for at least 10 seconds and be associated with a 3% or greater decrease in oxygenation of the blood. To determine AHI, add the total number of apnea events, plus hypopnea events and divide by the total number of minutes of actual sleep time, then multiply by 60. For example:

Apnea + Hypopnea divided by actual sleep time, then multiply by 60

200 apneas, 200 Hypopneas (400 Total Events)

420 Minutes Actual Sleep Time (7 hours x 60)

Divide 400 by 420 = .95 x 60 = 57 AHI (Severe OSA)

In general, the AHI can be used to classify the severity of disease (mild 5-15, moderate 16-30, and severe greater than 30).

Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) can be considered for the evaluation of day time sleepiness. MSLT is used to measure the time elapsed from the start of a daytime nap period to the first signs of sleep, called sleep latency. The test is based on the idea that the sleepier people are, the faster they will fall asleep. The MWT is a daytime polysomnographic procedure which quantifies wake tendency by measuring the ability to remain awake during sleep conducive circumstances. The test isolates a person from factors that can influence sleep such as temperature, light, and noise. Furthermore, the patient is also advised to not take any hypnotics, drink alcohol, or smoke before or during the test. After allowing the patient to lie down on the bed, the time between lying down and falling asleep is measured and used to determine one's daytime sleepiness.

9. Treatment

Sleep apnea should be treated if the patient has symptoms such as fragmented sleep and day time sleepiness or significant oxygen desaturation. In patients without sleep related symptoms who have PSG suggestive of severe sleep apnea, consideration should be given to treat patients with severe disease (Apnea/hypopnea index >30), since sleep apnea of this severity has been associated with increased cardiovascular morbidity and mortality. Sleep apnea should also be treated if it is exacerbating co-existing medical condition such as hypertension, myocardial ischemia, and respiratory failure or nocturnal hypoxemia.

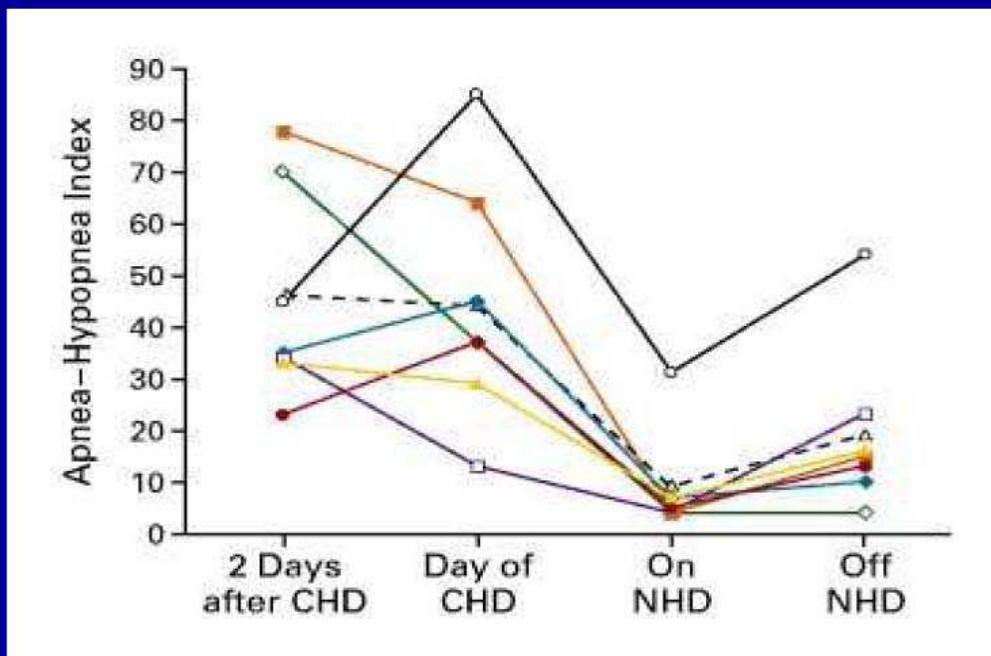
Management of sleep apnea includes treatment of any underlying medical conditions such as obesity or hypothyroidism, correction of aggravating factors such as use of alcohol or sedatives close to the bedtime. Continuous Positive Airway Pressure (CPAP) is a method of respiratory ventilation used primarily in the treatment of sleep apnea. The CPAP machine delivers a stream of compressed air via a hose to a nose mask, full-face mask, or hybrid, splinting the airway (keeping it open under air pressure) so that unobstructed breathing becomes possible, therefore reducing and/or preventing apneas and hypopnea. Pressman and Benz first reported in 1993 that CPAP improves both OSA and central apnea in ESRD patients, suggesting that CPAP eliminates the repetitive cyclical pattern of apnea followed by deep breathing, then followed by another central apnea.(28) The degree of hypopnea following apnea may be a function of the magnitude of respiratory drive necessary to overcome upper air way occlusion at the end of apnea. By preventing air way collapse, CPAP probably eliminates the deep breathing that results in hyperventilation and then lowered respiratory drive, thus setting the stage for next central sleep apnea. Also high levels of CPAP are successful in treatment of central sleep apnea due to the fact that central sleep apnea probably occurred following passive airway closure, which in turn caused stimulation of mucosal sensory receptors and reflex apnea. (28)



Fig. 3. CPAP Machine and Mask.

Sleep apnea is not corrected by conventional hemodialysis or peritoneal dialysis. Apnea frequency has been reduced by the use of bicarbonate rather than acetate based dialysate (29). Intensive daily dialysis has been shown to resolve sleep apnea in one critically ill patient (30). Nocturnal Hemodialysis(see glossary) that enables patients to receive hemodialysis 6-8 hours per night for 6 nights has been shown to improve sleep apnea (31). (Figure 4) Improvements are usually more significant in patients with more severe sleep apnea.

SAS and Nocturnal Home Hemodialysis



Hanly PJ, Pierratos A. *N Engl J Med* 2001; 344(2): 102-107.

Fig. 4. Improvement of Sleep Apnea with Nocturnal Hemodialysis.

Although case reports have indicated correction of sleep apnea after successful kidney transplantation (32), preliminary results from case series suggest that sleep apnea resolves only in a minority of patients after kidney transplantation (33). The administration of branched chain amino acids has shown improvement in apnea index in one patient, although the mechanism and implications are not understood. (34).

10. Restless leg syndrome and periodic limb movement disorder

Restless leg syndrome (RLS) is a disorder characterized by sensation that usually occurs prior to sleep onset and causes an almost irresistible urge to move the legs, resulting in delayed sleep onset and disrupted sleep (35). RLS may be idiopathic or secondary to other conditions such as pregnancy, rheumatoid arthritis or uremia. Almost 80% of patients with RLS also have periodic limb movement disorder (PLMD), a condition characterized by episodic limb movements associated with nocturnal awakening and disrupted sleep.

RLS has been reported in 14-23% in patient on CHD and 20-57% in CKD patients (21, 36). The prevalence of PLMD is greater than 50% in CHD and CAPD(see glossary) population (1, 2, 35-38). RLS has also been reported to be 4.5% in transplanted patients. The prevalence of RLS is significantly lower in transplant patients than in patients on maintenance dialysis. Declining renal function is associated with increasing prevalence of RLS.

RLS and PMLD may be equally important as sleep apnea in patients with CKD. RLS severity score has been correlated to self perceived sleep problems, nocturnal awakening,

delayed sleep onset latency, decreased total sleep time, increased use of sleep medications and self reported nocturnal leg movements (36). Polysomnographic studies of dialysis patients with RLS and or PLMD showed increase in sleep latency, Stage 1 and Stage 2 sleep, and decreased total sleep time and efficiency (38-41).

11. Pathophysiology

The pathophysiological mechanisms involved in RLS and PLMD are not very clear. Anemia, iron, and vitamin deficiencies, disturbance in peripheral and central nervous system (CNS) functioning and musculoskeletal abnormalities have all been proposed. It is likely that alteration of dopamine activity in the nervous system plays a role (42-43).

Correction of anemia by treatment with erythropoietin has been associated with reduction in the frequency of PLMD, improvement in sleep quality and day time alertness (44). Iron deficiency probably plays a dual role in that it causes anemia and is also a co-factor in the metabolism of dopamine in the brain. Treatment with intravenous iron is associated with a significant improvement in RLS and PLMD(45). Peripheral neuropathy, secondary to uremia or the underlying cause of renal disease such as diabetes may also predispose to develop RLS and or PLMD. Data regarding the clinical and laboratory correlation of RLS and PLMD is inconsistent. Higher predialysis urea and creatinine levels have been associated with increase RLS complaints in one study (1) but no relationship was detected in others (36, 41). Higher intact parathyroid hormone(PTH) levels has been found in dialysis patients with PLMD vs. those without the disorder(46), but lower levels have been noted in uremic patient with RLS in comparison without symptoms(47).

12. Diagnosis/Clinical significance

RLS is diagnosed clinically. PLMD is diagnosed objectively with polysomnography, which reveals periodic, involuntary movements of the legs during sleep.

PLMD can be identified on a polysomnogram by examining spiked activity coming from the electromyogram (EMG), which measures muscle movement during sleep. Specifically, anterior tibialis recording is usually sufficient in detecting the periodic limb movement episodes. Periodic limb movements typically last 0.5-5 seconds in duration and usually occurs approximately every 20-40seconds. The severity is described in terms of leg movement per hour of sleep (periodic limb movement index, PLMI). PLMI >5 is considered abnormal. Additionally, the examination of EEG test results will indicate micro-arousals, which can also lead to a diagnosis. PLMD can occur independently of RLS, and is more common with advancing age (35). RLS is almost always associated with PLMD, but PLMD can occur in the absence of RLS.

RLS is associated with difficulty initiating sleep, poor sleep quality, and impaired health quality of life (48) (FIGURE-5). RLS has been associated with depression. PLMD has been associated with increased mortality in patient with ESRD (49).

13. Treatment

General treatment measures include reducing potential exacerbating factors such as excess caffeine, alcohol, nicotine, medical conditions (anemia, iron deficiency), and medications

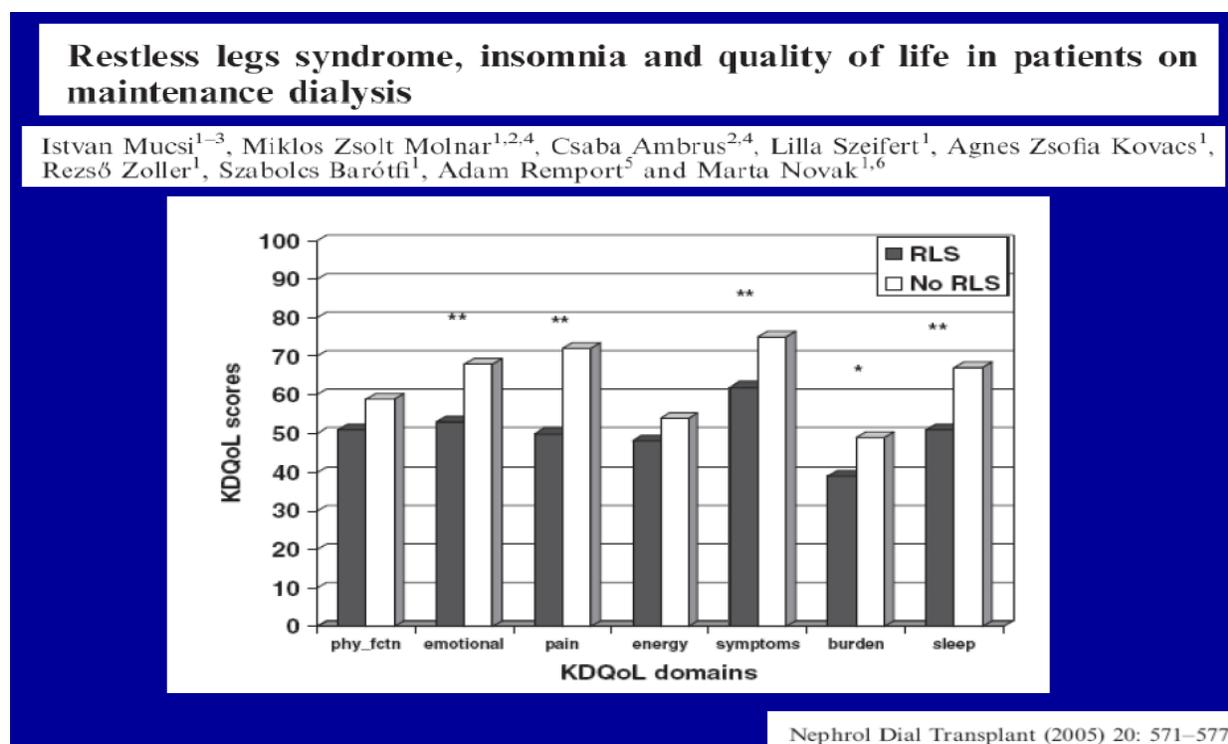


Fig. 5. RLS, Insomnia and quality of life in patients on maintenance dialysis.

(tricyclic antidepressants, Serotonin reuptake inhibitors, dopamine antagonists). Medical therapy includes L-Dopa and dopamine agonists such as pramipexole and ropirinoles (64). These medications are favored over benzodiazepines. Gabapentin can also be used as an alternative. The frequency of PLMD is not affected by switching from CHD to NHD (28). Kidney transplantation has been associated with an improvement in both RLS and PLMD in several small studies (50, 51).

14. Excessive day time sleepiness

Excessive day time sleepiness (EDS) has been described in dialysis patients. Seventy-seven percent of patients on CAPD reported taking day time naps and 51% reported falling asleep unintentionally (46). The **Multiple Sleep Latency Test (MSLT)** is a sleep disorder diagnostic tool. It is used to measure the time elapsed from the start of a daytime nap period to the first signs of sleep, called **sleep latency**. The test is based on the idea that the sleepier people are, the faster they will fall asleep. The test consists of four or five 20-minute nap opportunities that are scheduled about two hours apart. The test is often performed after an overnight sleep study. During the test, data such as the patient's, EEG, muscle activity, and eye movements are monitored and recorded. The entire test normally takes about 7 hours. In one study, 44 HD patients were studied. Potential subjects with other major chronic conditions or those with medications known to have CNS effects were excluded from the study. In addition, to exclude those with obvious causes of EDS, subjects with a history suggestive of SAS, RLS and PLMD were also excluded. All subjects underwent polysomnography along with MSLT. One third of patients of the subjects had MSLT scores consistent with abnormal sleepiness (mean sleep latency <8min). High AHI was significantly associated with lower MSLT score, but explained only 10% of the variance in MSLT score, suggesting that

additional factors play an important role in the expression of day time sleepiness in this group (65).

Benz et al reported the effects of hematocrit normalization with recombinant erythropoietin on the sleep of 10 HD patients (44). All subjects underwent an initial nocturnal polysomnogram, with seven completing a 40 minutes MWT the next day. Tests were repeated after normalization of hematocrit. Treatment resulted in a significant reduction of nocturnal periodic limb movements and improvement on the MWT.

SAS, RLS and PLMD are prevalent in patients with advanced kidney disease and could explain EDS, but some studies suggested that other factors related to renal disease or its treatment may contribute to EDS (52, 53).

Mild elevations of BUN and creatinine in renal failure patients have been associated with increased slow wave activity in the waking EEG and abnormalities in cognitive function, which may explain the susceptibility of patients with advanced renal disease to sleepiness (54). Elevation of parathyroid hormone has been associated with increased waking EEG slow wave activity in uremic animals and stable dialysis patient (55). The metabolites of creatinine may inhibit GABA responses (in mouse neurons) and may interfere with neurotransmissions necessary for sleep to occur. These changes may destabilize the wakeful state by increasing day time sleepiness propensity and decreasing nocturnal sleep (56).

Treatment with dialysis may also predispose patients to sleepiness. Abnormal production of interleukin-1, TNF-alpha, factor S can increase somnolence (57, 58). Rapid removal of these sleep inducing substances has also been postulated as the cause for fragmented nocturnal sleep and resulting day time sleepiness and fatigue in one study on patients on CAPD (59). Dialysis also results in rapid change in electrolytes, acid base balance and serum osmolarity which may decrease arousal and alertness (60). Treatment with dialysis may also disrupt the circadian pattern sleepiness due to inappropriately timed elevation of serum melatonin in response to the hemoconcentration (61) or from change in rhythm of body temperature (62). Medications such as antihypertensive and antidepressants may also contribute to the EDS in CKD patients.

15. Summary

- Sleep complaints and disorders are common in patients with CKD whether on dialysis or not and are characterized by difficulty in initiating and maintaining sleep, restless/jerking legs, and daytime sleepiness.
- Polysomnographic studies have demonstrated that dialysis patients have overall decreased quantity and quality of sleep, suggesting that behavioral interventions such as sleep hygiene and the appropriate use of medications may be helpful.
- Most common sleep disorders in CKD patients include SAS, RLS, and PLMD.
- SAS has been effectively treated with CPAP in patients with chronic kidney disease and ESRD. Switching from CHD to NHD may also be useful.
- RLS and PLMD are also very common and are associated increased mortality in patients on dialysis. Treatments include correcting anemia, iron deficiency and dopamine agonists.

- Day time sleepiness is common in patients with ESRD and patients with CKD not on dialysis.
- Sleep disorders have negative impacts on overall quality of life in patients with kidney diseases and may affect rehabilitative potential of treatment.

16. Glossary of dialysis-related terms

Blood Urea Nitrogen (BUN) is the blood test used to measure nitrogen in the form of Urea, which is the by product from protein metabolism produced in liver and removed by kidney

Dialysate-the fluid used in dialysis, typically with a lower solute concentration than the blood, into which metabolic waste and excess electrolytes diffuse.

Hemodialysis(HD)-a process of removal of fluid and solutes through a semi-permeable membrane into dialysate by passing the blood through an artificial kidney. Hemodialysis is most commonly delivered to patients three times a week for three to four hours (Conventional Hemodialysis-CHD), but may also be given more slowly across the day or night (Nocturnal Hemodialysis-NHD).

Nocturnal Hemodialysis (NHD). Nocturnal hemodialysis or nightly hemodialysis is a form of hemodialysis which is done at home by the patient or a family member when the patient is sleeping at night. Most patients dialyze five to seven nights a week, anywhere from six to 12 hours, on average for eight hours.

Peritoneal Dialysis (PD)-the process of removal of fluid and wastes from the body using the semi-permeable membrane of the peritoneum for the diffusion and osmosis,

Continuous Ambulatory Peritoneal Dialysis (CAPD)-continuous dialysis process that involves infusion of fluid into peritoneum, a prolonged dwell period for dialysis and drainage. The procedure typically involves four exchanges of fluid daily.

Kt/V is a way of measuring dialysis adequacy. Kt/V is defined as the dialyzer clearance of urea (**K**, obtained from the manufacturer in mL/min, and periodically measured and verified by the dialysis team) multiplied by the duration of the dialysis treatment (**t**, in minutes) divided by the volume of distribution of urea in the body (**V**, in mL), which is approximately equal to the total body water.

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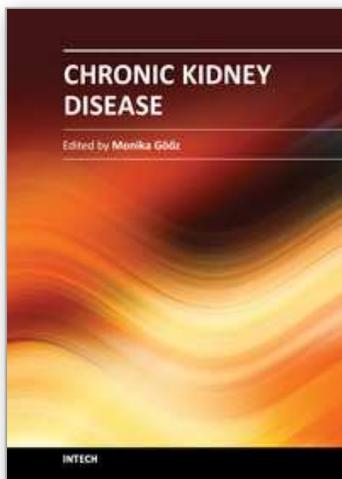
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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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