Sleep Disorders in Chronic Kidney Disease

25

Rosa Maria De Santo

Before You Start: Facts You Need to Know

- More than 80 % of patients with ESRD on dialysis lack the benefits of a refreshing sleep. Sleep complaints include insomnia, daytime somnolence, delayed sleep onset, frequent awakenings, restless legs syndrome (RLS), periodic limb movements in sleep (PLMS), obstructive sleep apnea syndrome (OSAS), central sleep apnea (CSA), frequent nightmares, sleepwalking, and narcolepsy.
- The dialysis schedule has a significant influence on sleep quality. Patients dialyzed in the morning shift reported a shortest nocturnal sleep and worst sleep efficiency than those treated in the afternoon (like a disease of shift workers). The best and longest sleep is achieved in the night immediately after dialysis. Total sleep time (TTS) tends to decrease with the time distance from hemodialytic treatment being minimal in the night with the longest interdialytic interval. The worst sleepers are the patients on hemodialysis with medically intractable hyperparathyroidism and in need of surgery.
- Disordered sleep occurs in association with depression, pain, hypertension, cardiovascular events, low quality of life (QOL), and mortality.
- Even successful renal transplantation does not restore poor sleep to normalcy.
- Hypertension and the use of antihypertensive drugs have an independent role in the genesis of poor sleep.
- Awareness of sleeping disorders in patients with ESRD is preliminary to any intervention to improve their QOL. Patients with the worst sleep score have a 16 % higher mortality risk than that in good sleepers.
- Patients with a disordered sleep use more health resources.

25.1 Introduction

Sleep quality has been extensively studied in patients with end-stage renal disease (ESRD). A vast literature exists; however, the exact knowledge of the pathophysiological mechanisms is still lacking, and therapy is limited to the worst cases. Sleeping pills are rarely prescribed but are used by patients who also make use of various herbals.

R.M. De Santo
Italian Institute for Philosophical Studies,
20 Salita Scudillo, Parco La Collinetta,
Naples 80131, Italy
e-mail: bluetoblue@libero.it

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In contrast to the huge amount of data on sleep disorders in ESRD, data on sleep disorders in chronic kidney disease (CKD) are limited due to the recent onset of interest in the topic. The data available, however, provide stringent evidence for the existence of a disordered sleep with CKD, which will be discussed in this chapter.

25.2 Sleep Disorders in CKD: Definitions

Short definitions of the principal and most frequent sleep disorders encountered in CKD are given as a guide to identifying the vastness of this under-recognized burden affecting patients with many losses and dependences.

Insomnia is defined by experts as repeated complaints of unsatisfactory sleep, despite having adequate opportunity for sleep. The complaints can consist of difficulty initiating or maintaining sleep, waking up too early, and/or having unrefreshing sleep. Additionally, daytime consequences such as fatigue and lack of energy, impairment of concentration or memory, social or vocational dysfunction, or disturbances in mood or motivation must follow disturbed sleep. Chronic insomnia is generally defined as lasting at least 30 days [1].

Restless legs syndrome (*RLS*) is a sensorimotor disorder characterized by an almost irresistible urge to move one's legs or, more rarely, one's arms. RLS is usually associated with disagreeable leg sensations that are exacerbated during inactivity and have a profound impact on sleep. It is diagnosed by interview and based on the presence of the following criteria: (1) an urge to move the limbs, usually accompanied or caused by uncomfortable and unpleasant feelings in the limbs; (2) rest or inactivity precipitates or worsens symptoms; (3) getting up or moving improves the sensation; and (4) the urge to move or unpleasant sensations are only present or are worse in the evening or night. RLS is a common cause of sleep disorder in CKD [1].

Periodic limb movements in sleep (*PLMS*) are stereotyped, repetitive movements that primarily involve the legs. Each movement lasts from 0.5 to 5.0 s and occurs in regular intervals of 20–40 s during episodes that may last from minutes to almost all night. Many normal sleepers have such movements without ill effects. Periodic limb movement disorder (PLMD) is only diagnosed as a clinical condition when the PLMS (or their associated short arousals) exceed the norms for age and cause an otherwise unexplainable insomnia and/or excessive daytime fatigue [1].

Sleep apnea (*SA*) is an intermittent interruption of air flow during sleep, at the level of nose and mouth. It may be obstructive (OSA), central (CSA), or mixed (MSA).

Obstructive sleep apnea syndrome (*OSAS*) is characterized by repetitive partial or complete upper airway obstructions during sleep that cause apneas and hypopneas. A diagnosis of OSAS requires at least 15 obstructive events (apneas, hypopneas, and respiratory event-related arousals) per hour of sleep or greater than 5 such episodes per hour in a patient who reports excessive sleepiness, insomnia, and gasping during sleep or has a bed partner who reports loud snoring, breathing interruptions, or both during the patient's sleep [1].

Central sleep apnea syndrome (*CSAS*) consists of repetitive diminished or absent (10 s or less) respiratory efforts due to the failure of central respiratory centers to signal to breathe. This can result from the inability of the medulla and carotid chemoreceptors to correctly sense O_2 and CO_2 blood concentrations or in the inability of newly oxygenated blood to get from the lungs to these sensory centers (e.g., by impaired cardiac output). In contrast to OSAS, where arousals are typically required to terminate the apnea, CSAs often end gradually, when the signal to breathe returns. CSAs often cause arousals from sleep [1].

Excessive daytime sleepiness (*EDS*) interferes with daytime functioning. EDS can manifest itself as a tendency to fall asleep during normal waking hours when unstimulated (e.g., when driving long distances or when reading). EDS is objectively diagnosed when the average sleep latency on the multiple sleep latency test drops to $\leq$8 min. EDS and hypersomnia are currently used interchangeably [1].

Sleep quality is defined as one's satisfaction of the sleep experience, integrating aspects of sleep initiation, sleep maintenance, sleep quantity, and refreshment upon awakening [2].

Cognitive behavioral therapy focuses on addressing factors that contribute to the

persistence of insomnia: (1) conditioned arousal, (2) identifying and eliminating habits that were developed in an effort to improve sleep but have become ineffective, and (3) reducing sleep-related worry and other sources of heightened arousal [3].

25.3 Prevalence and Predictors of Sleep Disorders in CKD

Evidence obtained in cross-sectional studies indicates that disordered sleep occurs very early in the natural course of chronic kidney disease and may affect the lives of 89.5 % of patients with a mean eGFR of 58.6 ml/min within 4 weeks following the first diagnosis of CKD [4]. One of three patients received hypnotic drugs. Longitudinal studies [5, 6] in turn suggest that blood pressure control may be a key element in the prevention and cure of sleep disorders.

Sabbatini et al. [5] performed a 3-year longitudinal study. Patients who completed the study had baseline mean creatinine clearance of 45 ml/min and a mean diastolic blood pressure of 95.2 mmHg and were using 1.36 antihypertensive drugs a day. Sixty-two percent of patients suffered from poor sleep. At completion of the study (3 years), there was an additional loss of creatinine clearance (13.25 ml over baseline), and the mean arterial blood pressure averaged 103.7 mmHg. The use of hypotensive drugs significantly increased to 1.78 ± 1.10, and 97.5 % were poor sleepers (Fig. 25.1). Since progression of kidney disease was accompanied by worsening sleep quality, pharmacological intervention to treat sleep disorders seemed appropriate.

A 4-year longitudinal study in early-CKD patients, eGFR 84 ± 21.1 ml/min/1.73 m^2, disclosed that 1 month after receiving CKD diagnosis, 85.5 % of patients were poor sleepers [6]. Sleep habits improved with time by accurate control of blood pressure with various hypotensive drugs. Also, the score of Beck Depression Inventory (BDI) improved with time. The use of hypnotic drugs also reduced over time (Table 25.1).

Thus, the high prevalence of poor sleepers in early-stage CKD is viewed as a marker of the process of coping with the idea of a chronic disease associated with lifelong dependencies and

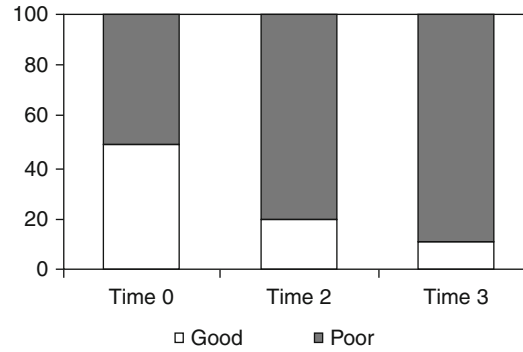

Fig. 25.1 Percent distribution of good (*white columns*) and poor (*dark columns*) sleepers during the time course of the study. *$p < 0.001$ vs Time 2 and Time 0 (minimum value) (Reprinted with permission from Sabbatini et al. [5])

Table 25.1 Longitudinal follow-up (4 years) of patients with early-stage CKD

	Baseline	2 years	4 years
Pts, no	220	210	200
eGFR, ml/min	84.1 ± 21.1	86.3 ± 22.10	83.7 ± 9.6
SBP, mmHg	139.6 ± 12.1	132.2 ± 10.7*	131.9 ± 10.7*
DBP, mmHg	83.9 ± 111	78.1 ± 8.7	77.9 ± 8.8*
On hypotensive drugs (%)	80	81.9	80.5
PSQI <5 (%)	15.5	19.0	50*+
BDI <11 (%)	36.4	50*	70*+
On hypnotics (%)	30 %	26.3	15.0*+

Source: Data from De Santo et al. [6]
*$p < 0.001$ vs basal +$p < 0.001$ vs. 2 years
eGFR estimated glomerular filtration rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PSQI* Pittsburgh Sleep Quality Index, *BDI* Beck Depression Inventory

losses. This explains the high percentage of patients needing sleeping pills, a number that exceeds the percentage observed in patients on hemodialysis. A chronic disease potentially amenable to dialysis, or at best, to renal transplantation, is the disrupting event to which patients must adapt. So the time of diagnosis is crucial for the kidney patient, since they must generate and develop a coping mechanism.

25.3.1 Is Pain a Determinant of Poor Sleep in CKD?

Cohen et al. [7] studied pain, sleep disorders, and quality of life in predialysis patients (eGFR 33.4 ± 23.7 ml/min) along with 61 general medical outpatients (eGFR 71.9 ± 26.7 ml/min ($p < 0.0001$). A total of 55.2 % of CKD patients had disordered sleep, which correlated with poorer quality of life, perception of pain, illness burden, and social support but was not associated with eGFR. In CKD patients, both the prevalence of sleep disturbances and pain were similar to those observed in general medical outpatients. Unfortunately, blood pressure was not measured—a rare occurrence in studies on CKD patients—and no reference was made available about the use of antihypertensive drugs.

25.3.2 Restless Leg Syndrome (RLS)

A 10.9 % prevalence of RLS was reported [8] in CKD patients (eGFR 41.6 ± 19 ml/min, range 10–86) and was compared to healthy control subjects (3.3 % ($p < 0.01$)). In CKD, the prevalence of hypertension was 91.8 % and that of anemia was 38.8 %. Patients with RLS used more benzodiazepines. A total of 86.9 % of the patients in this study were on drugs active on the cardiovascular system; however, it is not known whether hypertension was under control and, if so, by which drug. Independent predictors of RLS were sex (female) and percent transferrin saturation. Statistically significant findings show that patients with RLS had longer sleep latency, lower total sleep time, took more and longer naps, were more likely to be insomniacs, and had more daytime sleepiness. In multivariate analysis, RLS was independently associated with CKD. The study suggests that physicians caring for CKD patients with RLS should recognize female gender and iron deficiency as important indications.

25.3.3 Sleep Disordered Breathing (SDB)

Home polysomnographic studies [9] in CKD patients with eGFR <40 ml/min/1.73 m^2 (CKD 4 and 5), healthy controls, and HD (conventional three times a week) disclosed that severe sleep disordered breathing was highly prevalent not only in HD but also in CKD. Males were at higher risk of SDB. Potential pathophysiological mechanisms and mediators were increased pharyngeal cross-sectional area and abdominal circumference, overhydration, metabolic acidosis, and high levels of proinflammatory cytokines, C-reactive protein, and triglycerides. The study suggests that nephrologists should have a high index of suspicion of the diagnosis and treatment of SDB in CKD. In CKD patients in stages 3–5 and who have a mean eGFR of 24.9 ± 10.6 ml/min who completed the self-reported Kidney Disease Quality of Life Instrument (KDQOL), the prevalence of poor sleepers was 57 % in the study of Kumar et al. [10]. Self-reported daytime sleepiness was associated with a higher risk of mortality prior to ESRD and with a lower quality of life and several modifiable symptoms. The prevalence of poor sleep was comparable to that in HD patients in the Dialysis Outcomes and Practice Patterns Study Program (DOPPS). Poor sleep was associated with lower age, pain, dyspnea, depressive symptoms, nausea, cramps, and itching. A group of 382 patients was restudied after 1 year, but no correlation was seen between delta changes in sleep quality (SQ) and delta changes in eGFR. The data indicate the necessity to give great attention to pain, dyspnea, depression, nausea, cramps, itching, and daily sleepiness in patients with CKD grades 3–5. The study also points to a wider utilization of the KDQOL to screen unsuspected sleep disturbances by just asking the patients to complete the questionnaire.

In a study of the Kaiser Permanente cohort [11], SA was investigated for over 1,102,089 persons (61.37 % F) aged >18 years, 37.11 % hypertensive, 15.67 % with diabetes, and 3.45 % with congestive heart failure (CHF). The prevalence of SA was 2.54 %, a figure closer to the 2 % in females in the normal population than to the 4 % of males. A high risk for SA was found for eGFR <60 ml/min/1.73 m^2 when compared to persons with normal kidney function. The risk was not eliminated by controlling for hypertension, diabetes, and CHF.

In Japan, the prevalence of obstructive sleep apnea (OSA) was studied on 100 consecutive in-hospital CKD patients (mean eGFR of 28.5 ml/min/1.73 m^2), 80 % of whom were hypertensive [12]. The prevalence of OSA was 65 %. In univariate analysis, an association was found between AHI and eGFR, which persisted in multivariate analysis. The finding was explained by narrowing airway dimensions, enhanced chemoresponsiveness, and an effect on BP through heightened sympathetic nerve tone, which in turn activates the renin-angiotensin-aldosterone systems and leads to hyperfiltration. In addition, it was speculated that OSA promotes oxidative stress, micro-inflammation, and endothelial dysfunction leading to renal ischemia, CKD progression, and cardiovascular disease. Every 10 ml/min/1.73 m^2 decrease in eGFR is associated with a 42 % increased risk for OSA.

25.3.4 The Poor Sleep of Old Persons with CKD5

Data in patients aged 82 ± 6.6 years with the lowest GFR not treated with dialysis (11.2 ± 2.8 ml/min) disclosed a prevalence of disordered sleep in 41 %, of restless leg syndrome in 48 %, and of pain in 58 % [13].

25.3.5 Is Sleep Disordered Breathing a Risk for CKD?

The prevalence of CKD defined as eGFR <60 ml/min/1.73 m^2 was evaluated in 1,624 persons undergoing in-hospital polysomnography (PSG) and compared with that in 7,454 age- and sex-matched persons from the general population [14]. The prevalence of CKD was 30.9 % in the group with OSA and 9.1 % in the general population ($p < 0.0001$). In contrast with the screened population, the prevalence of CKD was inversely related to Beck Depression Inventory (BDI). The prevalence of CKD in the population in nondiabetic, non-hypertensive people was 5 %, whereas in diabetic and hypertensive persons, it was 13.8 %. Unfortunately, blood pressure and blood glucose were not studied in the OSA group. The study suggests the value of investigating renal function in non-obese patients with OSA on and off CPAP in order to prevent progression to ESRD.

A group of 158 consecutive patients, aged 61.2 ± 12.7 years, referred for full-night-observed-in-hospital PSG, was stratified according to the presence of sleep apnea [15]. After examination, a total of 25 persons were apnea-free and their eGFR averaged 94.67 ml/min/1.73 m^2, whereas in those with apnea, eGFR averaged 84.57 ml/min/1.73 m^2 ($p < 0.037$). All patients were stratified according to eGFR in CKD groups. Sleep apnea was present in 86 % of persons in CKD1, 80 % in CKD2, and 94 % in CKD3 (differences not statistically significant). Statistically significant results show, however, that the number of central sleep apneas (CSA) in CKD3 averaged 5.9 ± 12.2, six times greater than in patients with GFR >60 ml/min (averaging only 1.0 ± 2.1) (Fig. 25.2). In patients with central sleep apnea, then, eGFR must be calculated for appropriate treatment and improved outcomes.

Non-hypertensive nondiabetic OSA patients studied by in-hospital overnight PSG showed a prevalence of 18 % for CKD1-2 and 14 % prevalence of urine albumin-to-creatinine ratio (UACR) >30 mg/g. AHI was an independent risk factor for both CKD1-2 and UACR [16].

These studies indicate that patients with SDB are at risk of CKD. This, obviously, renders the measurement of plasma creatinine concentration mandatory in all patients with SDB.

25.3.6 Lessons from Population-Based Studies

Inadequate sleeping (<6 h per night) differed by CKD severity in a population-based study [17].

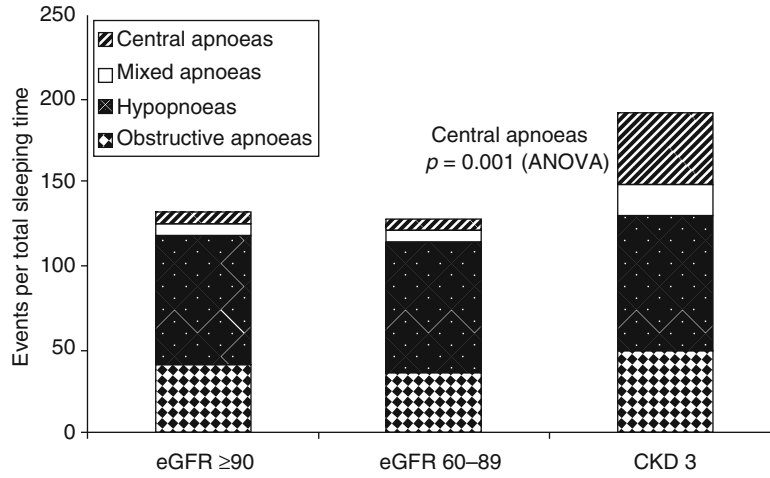

Fig. 25.2 Respiratory event per total sleep time (Reprinted with permission from Fleischmann et al. [15])

Sleeping pills use, legs symptoms, and nocturia also differed according to CKD severity. After adjustment for age, sex, race/ethnicity, obesity, diabetes, and cardiovascular disease, the prevalence of sleep-related problems remained higher in people with CKD 1 and 2 relative to no CKD. Primary care providers should know that nearly 9 % of the US adult population reported using sleep pills 5 or more times a month, although few of these reported having a prescription for sleep aid, indicating that the most sleeping aids used are available over-the-counter. Patients with moderate to severe CKD reported more frequent use of sleeping pills. Thus, providers of primary care should not forget to ask about the use of herbal, off-label, and over-the-counter drugs for sleep to ensure their patients' safety and prevent kidney-related complications. In patients with moderate CKD who used a prescription sleep aid, nearly 25 % were using medications contraindicated for kidney disease, likely because their physicians were unaware of their disease.

25.3.7 Reviewing the Topic of Poor Sleep in CKD

Sleep disorders in non-dialyzed CKD patients have been thoroughly followed up [18, 19]. Sim et al. [18] mainly focused on the relation of SA to CKD and point to a complex interaction of two disease processes where hypertension may represent an intermediary variable as depicted in Fig. 25.3, showing the overlapping of SA, CKD, and hypertension. Apnea per se may induce hypertension which in turn may cause CKD. Strong emphasis must be given to focal segmental glomerular sclerosis (FSGS) in sleep apnea (a disease characterized by renal hypoperfusion and ischemia), increased vascular endothelial growth factor (VEGF) levels, and reduced concentrations of nitric oxide. Patients with FSGS should be studied and treated according to the rules valid for the general population, namely, treatment of obesity, changes of lifestyles, adoption of an appropriate sleep position, and the use of medication. Control of blood pressure is also recommended to achieve target levels. Proteinuria and increased blood glucose must be also treated. Finally, one should not neglect that poor sleep exacerbates three risk factors for CKD (Fig. 25.4): hypertension, type 2 diabetes mellitus, and obesity [19].

25.3.8 Is Melatonin Circadian Rhythm Important?

In hemodialysis patients, the nocturnal melatonin rise associated with sleep propensity is absent. In CKD patients (mean GFR 50 ± 30 ml/min), the time course of melatonin concentration [20] varied according to renal function; those with highest GFR had the highest melatonin concentration

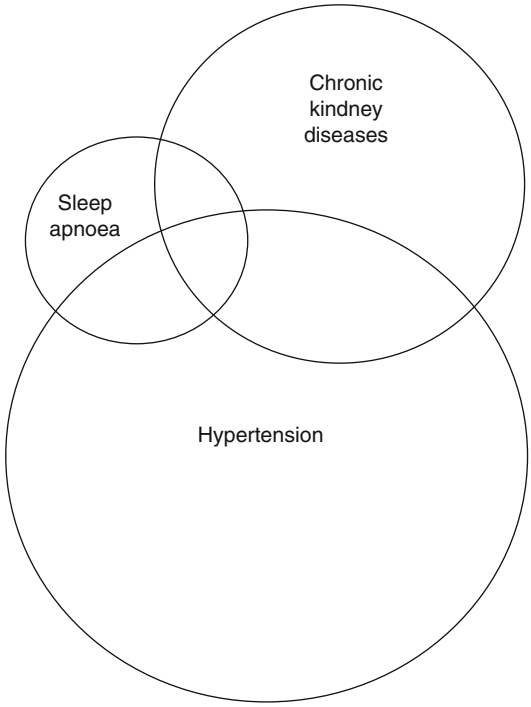

Fig. 25.3 Overlapping of CKD, hypertension, and sleep apnea (Reprinted with permission from Sim et al. [18])

and those with the lowest GFR had also the lowest melatonin (Fig. 25.5). In addition, the amplitude of the melatonin rhythm correlated with GFR (Fig. 25.6), as was the case for total melatonin production. The relation is not age and gender dependent. Melatonin is, however, under the influence of anemia, acidosis, and suppressed N-acetyltransferase (NAT)—which are markers of CKD—as well as beta-blockers and benzodiazepines, drugs frequently used by kidney patients. Acidosis and anemia are among the features of CKD, a condition which occurs with NAT suppression. In addition, beta-blockers are fundamental drugs to treat blood pressure, and benzodiazepines are used to treat insomnia. The same authors have reported that exogenous melatonin administration, in daytime hemodialysis patients characterized by absent nocturnal melatonin rise, caused a recovery of the melatonin rise and an improvement of subjective and objective sleep measurements in a placebo-controlled crossover study. The melatonin studies suggest that more research is needed in experiments with CKD persons following exogenous melatonin

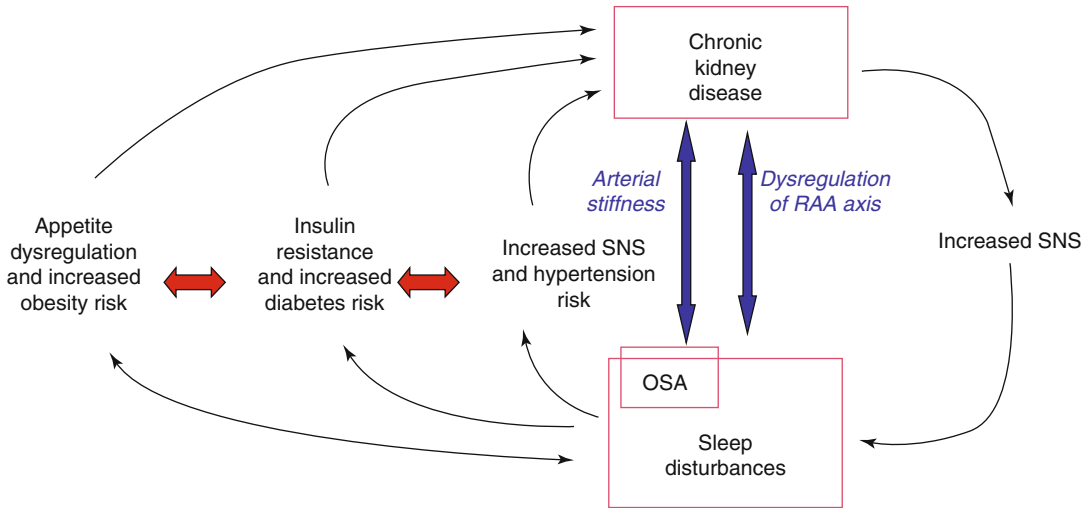

Fig. 25.4 Putative mechanisms linking sleep disturbances with CKD progression. *RAA* renin-angiotensin-aldosterone, *OSA* obstructive sleep apnea, *SNS* sympathetic nervous system activity (Reprinted with permission from Turek et al. [19])

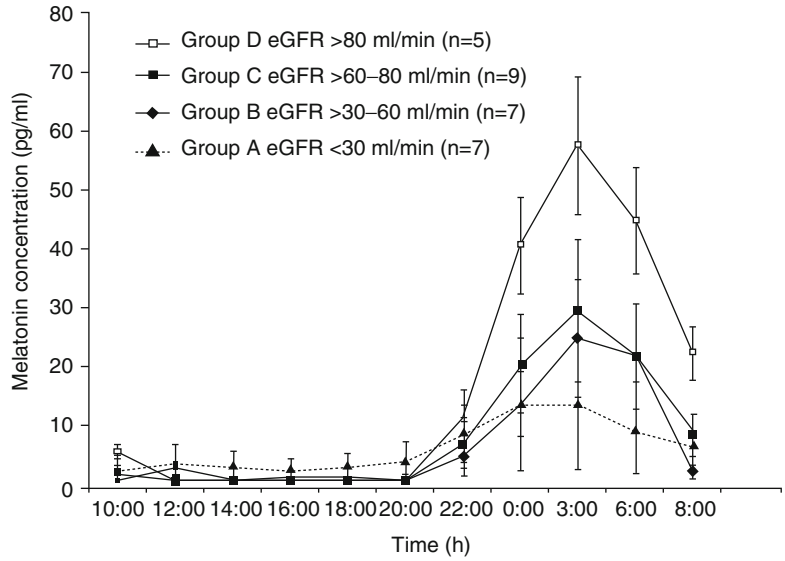

Fig. 25.5 Time course of melatonin concentration according to eGFR (Reprinted from Koch et al. [20] by permission of Oxford University Press)

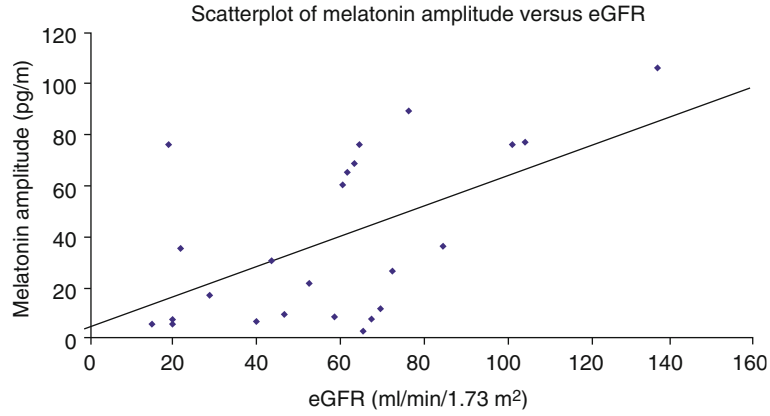

Fig. 25.6 Melatonin amplitude vs. eGFR in patients with melatonin rhythm (Reprinted from Koch et al. [20] by permission of Oxford University Press)

administration to mimic the endogenous melatonin rhythm.

25.4 Diagnosis and Therapy of Sleep Apnea

25.4.1 In the General Population

In a statement paper of the American Heart Association and of the American College of Cardiology [21], the whole topic has been reviewed in order to scrutinize (1) the pathophysiological components of OSA, (2) the activation of cardiovascular disease components, and (3) cardiovascular diseases. Table 25.2 differentiates central and obstructive sleep apnea.

25.4.2 In CKD Patients

OSA has negative influence on disease outcomes in various branches of clinical medicine including ESRD and CKD. It increases the utilization of health services, lowers the quality of life, and increases mortality. In CKD patients, sleep apnea deteriorates with nephron loss since it activates (Fig. 25.7) the sympathetic nervous system, the angiotensin-aldosterone system, cardiovascular hemodynamics, and the generation

Table 25.2 Sleep, signs, diagnosis, and therapy of obstructive sleep apnea (OSA) and central sleep apnea (CSA)

	Obstructive sleep apnea	Central sleep apnea
Sleep	Apnea Hypersomnolence Nocturia Snoring	Apnea Cheyne-Stokes respiration
Signs	Behavioral changes Enlarged neck size Headache in the morning Hypertension Male gender Obesity Reduced section of pharyngeal airway Sexual dysfunction Weakness	Cheyne-Stokes respiration during awakening Male gender Older age Heart failure Mitral regurgitation, atrial fibrillation Hyperventilation with hypocapnia
Diagnosis	Berlin questionnaire Epworth Sleepiness Scale 24-h Blood pressure recording Overnight oximetry In-hospital PSG +ECG monitoring Unattended PSG (?)	24-h Blood pressure recording Overnight oximetry In-hospital PSG Unattended PSG (?)
Therapy	Body weight loss, No alcohol No sedatives Positional therapy CPAP Surgery on uvula, tonsils, trachea	Strict control of heart failure CPAP Supplemental oxygen

Source: Data from Somers et al. [21]

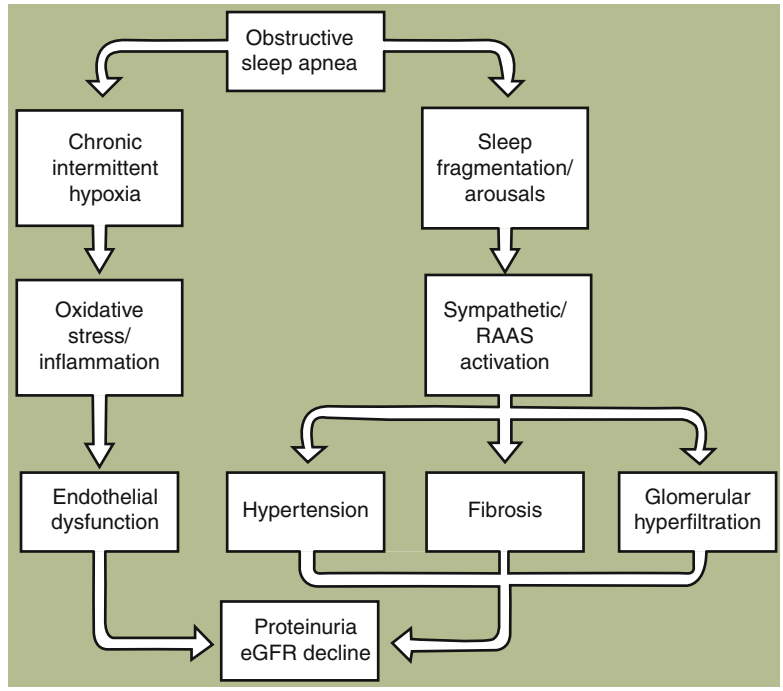

Fig. 25.7 Impact of obstructive sleep apnea on CKD (Reprinted with permission from Adeseun and Rosas [22])

of free radicals. The latter, in turn, triggers endothelial dysfunction, inflammation, platelet aggregation with thrombosis, increased negative intrathoracic pressure, atherosclerosis and fibrosis, insulin resistance, age and body mass index (BMI) independent hypertension, renal damage, proteinuria, CKD progression, nocturia, and increased blood atrial natriuretic peptide (ANP) concentrations [22].

Although there are no guidelines for sleep disorders in CKD, indications for treatment exist at least for SA [23]. It is known that SA and hypertension are associated. In addition, SA is a risk for CKD patients. SA and CKD are associated with a higher risk of hypertension. SA is a risk for mortality and progression of CKD because of the detrimental effects of anoxia, which also promotes tubulointerstitial lesions. Finally, the respiratory adaptation to metabolic acidosis may produce hypocapnia. Much can also be learned from available data in CKD patients following renal transplantation in whom SA may develop de novo (i.e., transplantation may represent a risk for SA). Steroids are, in fact, associated with increased body weight, total body water, total body sodium, and obesity. All of these may have a causal role for SA in these patients. Therefore, newer sleep complaints after renal transplantation should stimulate awareness for SA. Physicians should also be aided by the fact that proteinuria with SA improves after treatment of SA.

Psychiatric/psychological assessment and intervention are recommended; PSG is the gold standard for diagnosis and may help to differentiate between central and obstructive SA. It becomes mandatory in hypertensive patients with suspected SA. PSG also has a role to control the effects of therapy. PSG is associated with overnight assessment of electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), respiratory parameters and electrocardiogram (ECG), pulse oximetry, and noninvasive measurements of CO_2 blood levels.

In patients with SA and early CKD, with/without proteinuria, a renal biopsy may help in disclosing glomerulomegaly and the lesions of focal segmental glomerular sclerosis leading to hyperfiltration. Nasal continuous airway positive pressure (nCPAP) is the therapy of choice in moderate sleep apnea. It reduces daytime sleepiness, improves quality of life (QOL), and reduces the rate of cardiovascular accidents. Surgery, including tracheostomy, may be needed. Additional rules may be found in a recent paper of Kuhlmann et al. [23], where indications on signs, diagnosis, and therapy are available (Table 25.3).

Table 25.3 Therapy for obstructive sleep apnea

No evidence for effectiveness
Reduce body weight
Abstain from alcohol and drinks containing caffeine
Caveats
Tranquilizers induce and intensify obstruction
Beta-blockers are usable in the absence of bradycardia
Oxygen may prolong apnea periods
Evidence for effectiveness
Avoid supine sleeping
Lateral and abdominal sleeping reduces sleep apneas (aids may be needed)
Diuretics
Nasal CPAP reduces hypertension and daytime sleepiness
Side effects of CPAP
Hypoventilation, acute cardiac insufficiency, and a 25 % prevalence of rhinitis may make CPAP intolerable
Noncompliance is associated with increased mortality risk

Source: Data from Somers et al. [21]

For patients who cannot adapt/or refuse nCPAP, pharmacological treatment of the sympathetic overactivity may represent the last resort in managing the high risk carried by SDB, and clinical trials are warranted [24].

25.5 The Management of RLS/PLMS

RLS/PMLS occur with sympathetic hyperactivity, increased blood pressure and pulse rate, heart disease, and stroke, due to a dopaminergic deficit which is the primary target of dopaminergic therapy [25]. We know that RLS may not

increase through CKD 1–5, with the exception of diabetic patients, and is always associated with daytime sleepiness. Its pathophysiology is unknown but at a certain extent is related to iron deficiency. We also know that it improves after renal transplantation. In CKD, the prevalence of PLMS, in comparison with normal population (prevalence of 3–4 %), is increased by a factor of ten. Dopaminergic mechanisms have been identified.

Patients are recommended to abstain from alcohol and nicotine and to adopt specific physical exercises. In cases associated with depletion of body iron stores, a repletion is mandatory. Dopamine, dopamine receptor agonists, anticonvulsants, and opioids may be used. Benzodiazepines and various central depressants of the nervous system may however depress the respiratory drive and negatively affect the patency of the airways. Drugs must be dosed—when necessary—according to kidney function. For benzodiazepines and various central depressants of the nervous system, patients may have reduced capability in decreasing respiratory drive and also see effects to the patency of the airways. Drugs must be dosed—when necessary—according to kidney function.

25.6 Nephrologist's Role in the Work-up and Therapy of Sleep Disorders in CKD

For the American Academy of Sleep Medicine, sleep is a vital and necessary function, and sleep needs (like hunger and thirst) must be met. Sleep disorders are associated with low quality of life and impaired social and occupational functioning, are a risk for depression, and increase health care utilization. There are no specific guidelines for diagnosis management of sleep disorders in CKD (Box 25.1). However, the status of the art has reached a niveau that allows to appropriately assist the insomniac CKD patients (Box 25.2).

Nephrologists have a driving role for diagnosis (Box 25.3) which can be made either by means of clinical interviews or using sleep logs and/or questionnaires. The Pittsburgh Sleep Quality Index [26] has provided convincing results and is easy to handle. There are 19 questions with seven "component" scores. A global PSQI >5 has an 89.6 % sensitivity and 86.5 % specificity. Polysomnography (the gold standard) is usually performed on a single night and

Box 25.1. Relevant Guidelines

No guidelines are available for sleep disorders in CKD; however, relevant information is available in various papers which deal with insomnia, restless legs syndrome, and sleep apnea:

Insomnia

1. 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;4:487–504.

Restless Legs Syndrome and Periodic Limb Movement Disorder

2. Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults – an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses. Sleep. 2012;35:1039–62.

Sleep Apnea

3. Sim JJ, Rasgon SA, Derose SF. Managing sleep apnoea in kidney diseases. Nephrology. 2010;15:146–52.

Antidepressants

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in a sleep laboratory, which may not be indicative of normal sleep patterns. Actigraphy is a valid noninvasive method measuring sleep parameters at home and over multiple days. It is complementary to PSG. Hypnotics in CKD are used sparingly; however, the highest usage was reported in early-CKD patients immediately after receiving a diagnosis of chronic kidney disease. Recently, electrostimulation of leg extensors in ESRD reduced pain and improved QOL and quality of sleep [27].

Nephrologists, before asking for the help of the sleep specialist, should be aware that hemoglobin concentration and systolic and diastolic blood pressure must be kept within targets and pain cured according to WHO ladders. This is a prerequisite to the cure of the disordered sleep which is detailed in Box 25.4.

Box 25.2. What the Guidelines Say You Should Do

- Clinical assessment must be achieved through self-administered questionnaires, at-home sleep logs, symptoms checklists, psychological screening tests, and bed partner interviews. The Pittsburgh Sleep Quality Index has been translated into 56 languages. Actigraphy is becoming of age. Polysomnography is the gold standard.
- Sleep hygiene (caffeine, alcohol, nicotine) must be checked and followed up.
- If pain coexists, specific drugs must be given.
- Cognitive behavioral therapy is the first approach.
- Hypnotics have a role.
- nCPAP is an effective therapy for apnea.
- For RLS, start with iron replacement therapy. Medications include low-potency opioids, dopamine agonists, and gabapentin.

Box 25.3. The Role of the Nephrologists in the Work-up of Sleep Disorders in CKD

- CKD patients usually complain of their sleep problems and ask for help. Usually they complain of difficulties in initiating and maintaining sleep, early waking up, and unrefreshing sleep, which causes stress. The nursing staff is the most frequent target of these complaints. Sometimes, either the bed partner, family members, accompanying persons, or the patients hosted in the same hospital bedroom disclose RLS, PLMS, snoring, and OSAS.
- Nephrologists may get a direct insight in the sleeping problems by listening to the patient's narrative.
- The use of the PSQI may help.
- Daytime sleepiness with inability to maintain wakefulness may cause accidents.
- OSA may cause reduction of renal function.
- In the case that a sleep problem emerges, it might be appropriate to look for the coexistence of depression by using the Beck Depression Index (BDI). BDI is structured on 21 items. Each question is scored from 0 to 3. In the general population, a BDI score of 11 or greater indicates depression. In CKD, the cutoff for depression is score >14.
- In case of snoring, an overnight pulse oximetry—now easily available in any hospital—will monitor SaO_2. Further decision to proceed to PSG should be made in association with the sleep expert in the hospital.

Box 25.4. Therapy of Sleep Disorders in CKD

- Hemoglobin should be kept within the targets.
- Strict blood pressure control by low salt intake and drugs may have a beneficial effect.
- Be aware that beta-blockers have negative effects on sleep.
- Pain requires treatment according to WHO suggestions.
- Cognitive behavioral therapy is an effective nonpharmacological therapy which can improve the quality of sleep and decrease fatigue.
- The use of bright light (1,000 lux) may be appropriate in the old patients.
- Melatonin administration carries no risk and potentially may help circadian resynchronization.
- For insomnia, hypnotics must be used. The general practitioners and nephrologists, for unknown reasons, make a spare use of them which causes underdosage. The sleep specialist should advise for appropriate dosage and length of treatment. Benzodiazepines induce sleep, reduce sleep latency, and suppress REM and slow-wave sleep, but their effect is unwarranted. Non-benzodiazepine hypnotics should be preferred. Zolpidem is effective and does not cause apnea. The antidepressant mianserin may be advantageous as sleep inducer; however, a guide to use antidepressant is provided by European Renal Best Practice (See Box 25.1) [4].
- In presence of RLS and PMLS correct iron deficiency, forbid alcohol and smoking. L-dopa, and dopamine receptor agonists, anticonvulsants, and opioids may be used. Benzodiazepines may decrease the respiratory drive and also reduce airway patency. Drugs must be dosed—when necessary—according to renal function.
- OSAS may require nasal CPAP (i.e., delivering compressed air), which is not always tolerated.
- Daytime sleepiness renders patients unable to maintain wakefulness and is a reason for indoor and outdoor accidents.

Before You Finish: Practice Pearls for the Clinician

- SA in CKD is now considered a warning and deteriorates with the severity of nephron loss. The concept may be extended to all causes of disordered sleep in CKD.
- RLS is an important source of sleep disruption in CKD patients.
- Wake and sleep functions should be viewed as a vital sign: every patient should be asked about sleep and daytime alertness. Any complaint should be taken seriously and not simply attributed to the underlying renal disease and/or medications.
- Impaired quality of sleep impairs quality of life in CKD patients.
- A clinical suspicion of non-refreshing sleep should be followed by further assessment.
- Questionnaires are the cheapest and most easily available at every bedside. The PSQI is a good instrument. Actigraphy is simple and coming of age. PSG is the gold standard.
- The kidney specialist and the sleep specialist must interact to solve sleep problems in CKD.
- Awareness of sleep problems in CKD patients is the starting point to improve their QOL.
- Sleeping medications (usually benzodiazepines) are used with a warning for patients with SA..Nasal CPAP is the therapy of choice for severe SA.
- Poor sleep quality is associated with lower QOL and risk of pre-ESRD mortality.

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