27 Sleep Disorders in Chronic Kidney Disease

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Before You Start: Facts you Need to Know

- Sleep disorders are common in patients with chronic kidney disease (CKD) and affect nearly all patients in end-stage kidney disease (ESKD) on dialysis treatment.
- The worst sleep quality and quantity occur in the night of the longest interdialytic interval and in patients awaiting morning dialysis. However, sleep disorders in CKD and ESKD are largely under-recognized, overlooked and their treatment is far from optimal.
- The interest for the quality and quantity of sleep in patients with ESKD emerged immediately after the introduction of dialysis therapy and has grown extensively as indicated by the number of papers on the topic. We know that 80–100% of patients with ESKD on maintenance dialysis lack the benefits of a refreshing sleep. They sleep poorly and their sleep is characterized by delayed sleep onset (DSO), frequent awakenings (FA), excessive daily sleepiness (EDS), restless leg syndrome (RLS), sleep disordered breathing (SDB), nightmares (NM), and sleepwalking (SW).
- Insomnia is the first prioritized symptom in dialyzed patients who experience day–night reversal.
- The disordered sleep occurs with impaired neurocognition, depression, pain, cardiovascular events, low quality of life (QoL), and mortality and is associated with lower health related quality of life (HRQoL).
- A disordered sleep is also observed in children and adolescents treated with various dialysis modalities.
- Even successful renal transplants do not fully cure sleep disorders because of the impact of steroids, overweight, obesity, fluid and sodium retention, and diabetes.
- Many toxins including urea, phosphate, anemia, and PTH have been incriminated.
- The worst sleepers are the patients on dialysis with medically intractable hyperparathyroidism needing surgery. Their sleep significantly improves after parathyroidectomy.
- Hypertension and the use of antihypertensive drugs have an independent role in the genesis of poor sleep.
- The diagnosis of poor sleep is now included in the work-up of patients on maintenance dialysis. Polysomnography (PSG) has emerged as the gold standard but questionnaires still play a role. Actigraphy is coming of age because of its simplicity.
- Sleep disorders because of their impact on functional capacity are still an important med-

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ical burden in patients with ESKD and cause more health services utilization, thus increasing the expenditures for a disease already plagued by high costs.
- Therapy is still in its infancy but cognitive behavioral therapy (CBT) is coming of age.

27.1 Introduction

Sleep is a recurrent dynamic process that affects every body function for nearly one-third of the day and has a housekeeping role. It regulates metabolism and immunologic functions [1].

Sleep has been studied extensively since antiquity [2, 3] starting with *Homeric Poems* (750–723 BC). In *Iliad* (XIV, 270) sleep was located in the Isle of Lemnos where even Juno flew to visit the brother of death to induce sleep to Zeus. Hesiod (floruit c.700 BC), wrote: "*Nix bore hateful Moros (doom) and black Ker (destiny) and Thanatos (death) she bore Hypnos and the tribe of Oneroi*" (*Theogony* 211–212). For Heraclitus of Ephesus (floruit 504–1 BC): "in sleep sense-channels are closed, so that the mind is prevented from growing together with what stays outside." For Parmenides of Elea (c515/510 BC-450 BC): "sleep was due to a reduction of organic heat," whereas for Diogenes of Apollonia (floruit 440–430 BC) sleep was "caused by a moistening of the air-soul." Alcmeon of Croton (510–440 BC) thought that it was caused "by confinement of blood to large blood vessels, whereas waking is brought about by re-diffusion." For Anaxagoras (500/497–428 BC): "sleep was a process unrelated to the soul and entirely due to the body exhaustion of physical energy." For Empedocles (492–432 BC): "Sleep depends on a moderate cooling of the warmth in the blood, it depends on the separation of the element fire." For Plato (429–347 BC): "Sleep begins when the light is turned off. The dark supervenes, the eyes are shut and keep internally the fire of the light. Light meets with its dissimilar, the darkness." Whereas for Aristotle (384–322 BC): "Sleep was a deprivation of waking, and there was no perception (*De somno et vigilia)*."

The problem of how long one can sleep is well recorded in the Quran (610 AD), Surah XVIII, 8–26. The narrative addresses the Seven Sleepers of Ephesus and the famous Grotto. "*Dost thou consider that the Companions of the Cave, and al Rakim, were one of our signs and a great miracle? they said, O Lord, grant us mercy from before Thee, and dispose our business for us to a right issue. Wherefore we struck their ears so that when the young men took refuge in the Cave, they slept in the Cave for a great number of years: then we awakened them … that they might ask questions of one another. One of them said, How long have ye tarried here? They answered, We have tarried a day, or part of a day. Others said: Your Lord best know the time ye have tarried And they remained in their Cave 300 years and 9 years over.*"

Poor sleep of short duration may cause obesity, diabetes mellitus, hypertension, myocardial infarction, ictus as well as loss of attention and memory. Sleeplessness (5 h or less per night) is associated with a 30% reduction of estimated glomerular filtration rate (eGFR) and incident CKD (eGFR <60 mL/minx 1.73 m^2 of BSA [4, 5]. In the last 30 years, several studies have demonstrated that 20–80% of patients with end stage kidney disease (ESKD) have sleep disturbances [6, 7] that are partly corrected by kidney transplantation, the cheapest, most successful, and long-lasting treatment. Sleep disorders in ESKD include insomnia (I), restless leg syndrome (RLS), periodic limb movements in sleep (PLMS), and obstructive sleep apnea (OSA). A recent systematic review [8] and meta-analysis of 3708 articles published in the period between January 1, 1990 and September 18, 2018 on a total of 45,716 patients either on CKD or treated with hemodialysis (HD), peritoneal dialysis (PD), and transplantation (TX), identified 93 articles (62 on poor sleep, related to 21,180 patients and 31 on insomnia related to 17,010 patients. Prevalence of poor sleep was 59% in CKD, 68% in HD, 67% in PD, and 46% in TX. Correspondent prevalence for insomnia was 48% in CKD, 46% in HD, 61% in PD, and 26% in TX (Fig. 27.1).

The first report on sleep disorders in CKD was published by the group of Charles Mion in

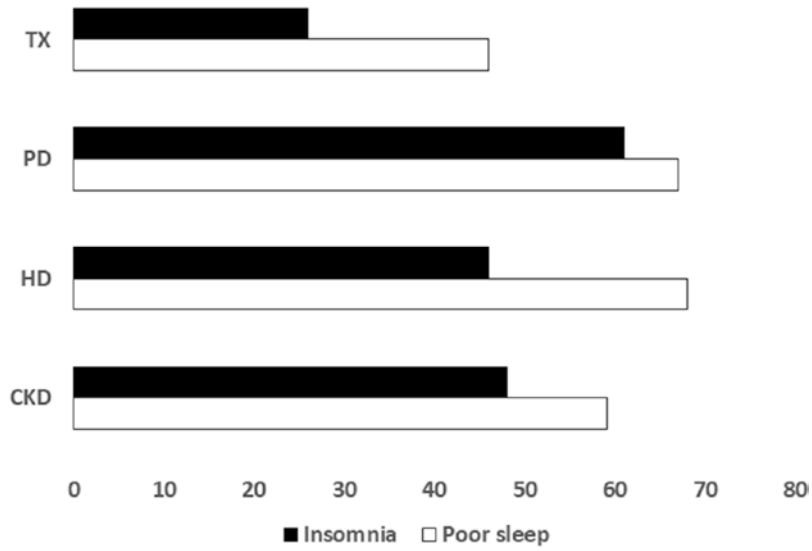

Fig. 27.1 Sleep disorders in CKD. A global perspective. Compiled from data of Tan L-H et al. [8]

Montpellier. A disorder of the sleep architecture was present in all stages. The early studies were not published in nephrological journals. However, in 1981 the term "Psychonephrology" was coined by Norman B. Levy [9, 10].

27.2 Sleep Disorders and their Effects in CKD

Sleep disorders (SD) in chronic kidney disease (CKD) are insomnia (I), sleep apnea syndrome (SAS), central sleep apnea (CSA), restless leg syndrome (RLS), and periodic limb movements (PLMS). They cause fatigue (FA), excessive daytime sleepiness (EDS), impaired day time function (DTF), impaired health-related quality of Llife (HRQoL), increase morbidity and mortality.

In the general population the prevalence of insomnia (difficulty in falling asleep and staying asleep and early morning awakenings) is 4–29%. Sleep disorders are common in chronic kidney disease (CKD) needing dialysis and were described for the first time in 1970, just 7 years after Belding Hibbard Scribner (1921–2001) made maintenance hemodialysis (HD) possible. A 41–85% prevalence of SD has been demonstrated in adult patients on HD and on peritoneal dialysis (PD). However, some recent data point to a higher prevalence (80–100%).

In the study of Merlino et al. [11]—a major study in the history of sleep disorders in end stage kidney disease—enrolling 832 HD and PD patients, SD were present in 80.2%, as insomnia (69.1%), RLS (18.4%), SAS (23.6%), excessive daytime sleepiness (EDS) (11.8%), possible narcolepsy (1.4%), sleepwalking (2.1%), nightmares (13.3%), and possible rapid eye movement (REM) behavior disorder (RBD) (2.3%) as shown in Fig. 27.2.

The worst sleep is experienced by aged patients and is typical in the nights during the longest dialytic interval and in the early morning shift. Insomnia may be associated with pain, itching, poverty, and dialysis vintage. It causes anxiety and stress, depresses the immune system, and is a risk for cardiovascular disease.

Sleep quality and quantity were linked to dialysis shift in 1997 [12]. We were able to characterize this link by means of a 14-day questionnaire compiled by patients treated three times a week by hemodialysis either in the morning or in the afternoon [13]. It was possible to demonstrate that early shifts are associated with poor sleep. We also characterized the sleep of 4 representative nights (A, B, C, D): Night A (after dialysis), night B (before dialysis), night C (neither pre-

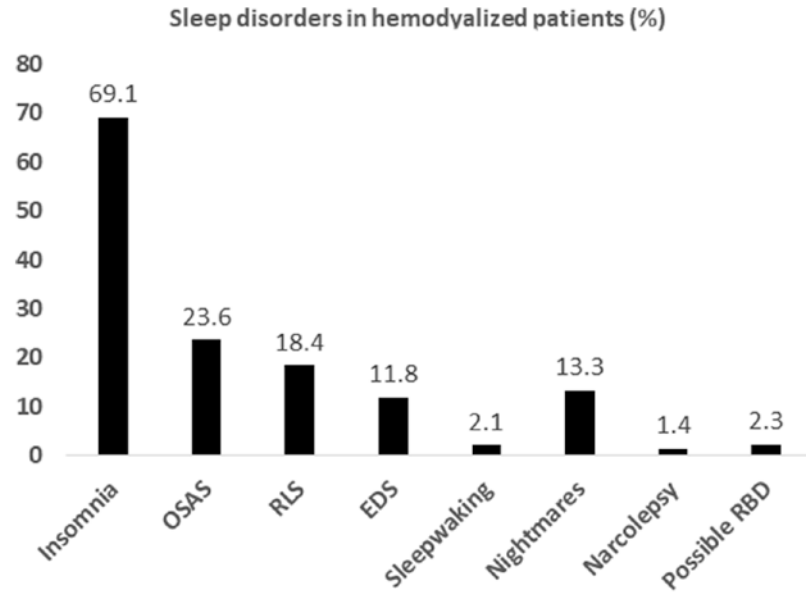

Fig. 27.2 Prevalence of sleep complaints in the historical study of Merlino G et al. [11]

ceded nor followed by dialysis). For example, Saturday night for those dialyzed on Monday–Wednesday–Friday), night D (the night of the longest interdialytic interval, for example, Sunday for those dialyzed on Monday–Wednesday–Friday). Sleep duration declined significantly from night A to night B, to nights C and D, more for those dialyzed in the morning. Sleep efficiency declined also from night A to night B, to nights C and D.

Pain is common in ESKD and is a burden even in early stage CKD. Its prevalence is in the range of 41.4–69% and is associated with higher prevalence of insomnia and of depression, burden of illness and life satisfaction, and, in addition, the Pittsburgh Sleep Quality Index (PSQI) correlates negatively with bodily pain.

PTH has been variably associated with sleep disorders since it causes bone disease and pain. In our experience patients with medically intractable hyperparathyroidism are among the worst sleepers. Sleep ameliorates following parathyroidectomy (Tables 27.1 and 27.2) [14].

Sleep disorders in HD patients predict quality of life and mortality risk, as it emerged in the DOPPS study where poor sleepers, in comparison with good sleepers, had a 16% higher relative risk of death [15]. It seemed safe to explain everything in terms of losses and dependencies associated with dialysis [16] as outlined in Table 27.3. However, SD were not cured by a successful kidney transplantation [17].

Table 27.1 Sleep disorders in hemodialyzed patients of comparable age, women/men ratio, BMI, dialysis vintage, Kt/v, needing and not needing parathyroidectomy. Compiled from data in R.M. De Santo et al. [14]

Category	Needing PTX	Not needing PTX	*p*
PTH, pg/mL	1300 ± 248.5	253 ± 52.4	<0.001
Serum phosphate, mg/dL	6.53 ± 0.46	5.03 ± 0.58	<0.001
SBP, mmHg	139 ± 4	131 ± 8	<0.001
DBP, mmHg	83 ± 4	73 ± 5	<0.001
On antihypertensive drugs %	100	63.8	<0.001
Charles comorbidity index	6.55 ± 0.62	5.27 ± 8.3	<0.001
PSQI	11.9 ± 1.4	6.91 ± 1.7	<0.001
Sleeping hours	5.08 ± 1.4	7.1 ± 0.8	<0.01
Daily naps	1.9 ± 1.6	3.6 ± 1.3	<0.01
Insomniacs, %	72.7	38.6	<0.001
No disturbances, %	4.54	28.4	<0.01

Table 27.2 Effects of parathyroidectomy on sleep disorders in hemodialyzed patients. Data before surgery (no. 40) and 3 years after (no. 36). Compiled from data in R.M. De Santo et al. [14]

Category	Before PTX	Three years after PTX	*p*
PTH, pg/mL	1278 ± 230	45 ± 2	<0.001
SBP, mmHg	138.1 ± 10.4	130.4 ± 6.8	<0.01
DBP, mmHg	83.1 ± 10.4	79.6 ± 8.9	<0.01
PSQI	11.9 ± 1.6	7.0 ± 1.2	<0.01

Table 27.3 Uremia associated losses and dependencies. Based on data of M Fabrazzo and RM De Santo [16]

Losses
Loss of urinary function
Loss of the capacity to concentrate
Loss of workplace
Loss of the freedom to select or to find a job
Loss of the role in the family
Loss of the family dynamics
Loss of the role in social relationship
Loss of quality of life
Loss of the sense of femininity
Loss of menstruation
Loss of the capability of having an orgasm
Loss of the sense of masculinity
Loss of erectile function
Loss of libido
Loss of capability to set constructive goals
Loss of good mood
Loss of life expectancy
Loss of capability of practicing a sport
Loss or limitation in mobility
Loss of freedom in selecting beverages
Loss of body weight
Loss of muscle mass
Loss of body imaging
Loss of skin color
Loss of weight stability
Loss of sleep hours
Dependencies
On dialysis staff
On physicians
On medications
On family
On a machine
On dialysis shifts
On dialysis calendar

27.3 Sleep Disorders in CKD Not Needing Dialysis

In predialysis CKD (creatinine clearance 29.96 ± 10.93 mL/min) Iliescu et al. 2004 were the first to disclose a 53% prevalence of disordered sleep by means of Pittsburgh Sleep Quality Index (PSQI). The prevalence matched that for hemodialysis patients studied at that time. The paper did not disclose any difference between patients with creatinine clearance lower or greater than 17.8 mL/min but identified depression as the only significant predictor of poor sleep [18].

The prevalence of poor sleepers was 14% at eGFR of 25.5 mL/min in the study of Kurella et al. [19]. In the latter study 34% of subjects with ESKD, 27% of subjects with advanced CKD, and 14% of subjects with mild to moderate CKD had sleep maintenance disturbances ($P = 0.05$). Thirteen percent of subjects with ESKD, 11% of subjects with advanced CKD, and no subjects with mild-moderate CKD had complaints of daytime somnolence ($P = 0.03$). The conclusion was that sleep disorders are common in CKD and ESKD particularly in those with lower eGFR.

In a study of Parker et al. [20], a total of 8 CKD patients were studied. The estimated GFR was 14.5 ± 7.2 mL/min (range 5.4–28.8 mL/min). They were compared to patients on HD who had less total sleep time, less REM sleep, longer sleep latency, more arousal, more apneas, and more PLMD. CKD patients had normal sleep latency but poorer functional and psychological status. It was concluded that sleep disorders in CKD have etiologies that are different from those on HD. Functional and psychological factors probably prevail in CKD, intrinsic disruption in HD treatment.

Sleep disorders, however, occur very early [21, 22] in CKD. In a study on sleep disorders in people with newly diagnosed CKD (eGFR 58.6 ± 44.4 mL/min), the prevalence of sleep disorder was 89.5% [21]. The prevalence of reported sleep complaints—shown in Fig. 27.3—was not associated with factors considered responsible for sleep disor-

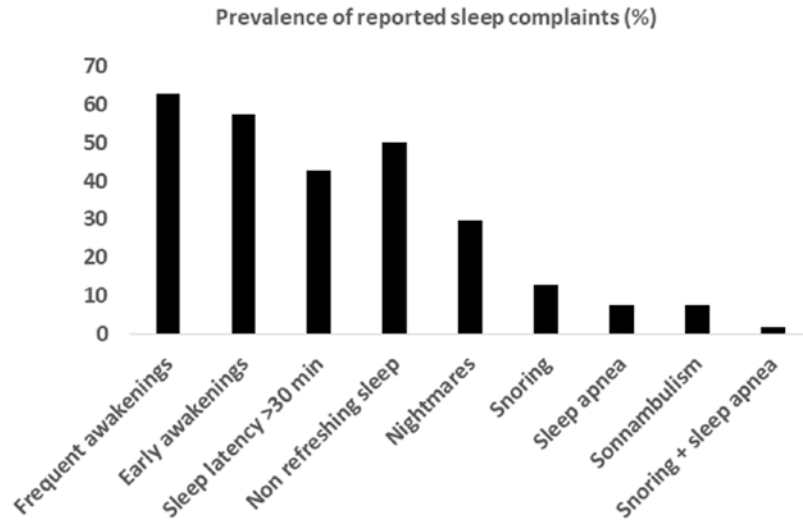

Fig. 27.3 Prevalence of sleep complaints at the time of CKD diagnosis. Compiled from data of De Santo RM et al. [21]

ders in maintenance hemodialysis [21]. The data suggested that the intrusion of a chronic disease in the life of patients with early CKD might be the triggering event for sleep disorders. Conversely, stress must be regarded as a more common precipitating factor than insomnia since more than seven out of 10 poor sleepers recall specific stressful experiences and also point to an inefficient coping mechanism. The lack of an association between comorbidities and sleep disorders suggested that in early CKD, sleep disorders are a marker of insufficient elaboration of coping with a chronic disease, usually viewed as associated with life-long constraints. From studies utilizing the narrative in CKD patients it has emerged that initial discovery of kidney disease is a disrupting event, so as Kjeerans and Maynooth say [23] the patients need "to create meaning and to re-establish cohesion in their lives. It means that discovering that you are affected by a chronic disease with unpredictable time course, with many potential comorbidities, is a deconstructing event. Thus, people who during their healthy days do not care where their kidneys are, start asking questions to physicians, friends, neighbors and patients on dialysis or receiving a kidney transplant. Thus, they learn that they will be needing a lot of medication and will probably end up attached to a machine and less probably receive a transplant. The latter appears a remote possibility, an impossibility" [21]. Indeed, the moment dialysis becomes essential [5, 6] a patient is faced with the irrefutable fact that recuperative powers have limits and there awaits a bleak future with loss of autonomy. Dialysis creates a radical shift of focus from the inside to outside oneself. The unpredictability of kidney disease which is made clear at the time of diagnosis has been appropriately defined as an act holding someone hostage. So it is important that the narrative be focused and extensive in the early days of the disease [22].

A 3-year longitudinal study by Sabbatini et al. [24] suggested that progression of kidney disease is accompanied by a progressive worsening of SD, but an independent association was not demonstrated. By contrast, in our laboratory, hypertension was associated with SD in HD and CKD patients. The association disappeared in the 4-year longitudinal study where systolic and diastolic blood pressure, under a tight control, fell within target values in CKD. In that study depression correlated with sleep quality in logistic regression analysis [25].

27.4 Restless Leg Syndrome and Periodic Limb Movements of Sleep

It is a common neurological sensory-motor disorder manifesting with unpleasant nocturnal sensation in the lower limbs that is relieved by

movements. It may be felt in the muscle mass or in the skin. It affects 5–15% of the general population. The condition is characterized by an urge to move the legs (rarely also the arms) and by a peculiar and unpleasant sensation of paresthesias, deep in the legs.

The sensation appears during periods of rest or inactivity, particularly in the evening and at night and is typically relieved by movement. Paresthesias may be exceedingly unpleasant and give rise to severe sleep disturbances with sleep fragmentation, daytime sleepiness, and fatigue. The deep sensation is felt within the lower extremities. It has been defined as aching, burning, cramping, crawling, creeping, itching, pulling, and tingling. The sensation may also be felt in the thighs and sometimes in the feet. The disagreeable long-lasting sensation is usually felt prior to sleep onset and causes an almost irresistible urge to move legs and causes disrupted sleep and excessive daytime sleepiness. RLS may be unilateral but commonly is bilateral and symmetrical, RLS may be continuous or intermittent. Patients walk to get relief (Night-walker's syndrome [26]).

Patients affected by RLS have higher scores for major depressive disorders, dysthymic disorders, anxiety, depression, minor depressive disorders. They have worse scores for day time sleepiness, sexual dysfunction, and social functioning as well. RLS is associated with impaired neurocognition and attention and higher mortality. It may appear at any age between 5 and 80 years but is more frequent in people aged 45 years or more with a family history of the disease. In 50% of the patients there is a positive family history. Physical examination is normal [13, 27].

Eighty to ninety percent of patients with RLS have Periodic Limb Movements of Sleep (PLMS). The latter is a distinct entity positively associated with age. As pointed out by the American Sleep Disorder Association, 34% of the cases occur in patients older than 60 years. The prevalence of PLMD may be as high as 70% [28] and as important as RLS in terms of sleep disorder. Brain iron deficiency has been identified as a causative factor since iron is a cofactor for dopamine production in the brain.

Diagnosis is based on polysomnography, the levodopa/carbidopa test (25 mg of levodopa/100 mg carbidopa) and by the Criteria of the RLS Study Group that includes the urge to move legs, an uncomfortable sensation, improved by motion and exacerbated by lying down. Treatment includes use of dopamine agonists effective but not long-lasting, gabapentin or pregabalin (calcium channel alpha-2-delta ligands that require renal adjustment). Acupuncture, pneumatic compression, near-infrared light may be helpful. RLS is very common in CKD patients requiring hemodialysis (prevalence 6–62%). In a recent study by Lamanna et al. [28], the prevalence of RLS was 31% and was associated with risk of cardiovascular events and deaths. Nocturnal hypertension and inflammation were discussed as potential independent risk factors.

In nondialyzed patients (eGFR 26.8 ± 9.2) a prevalence of RLS of 37.1% was reported by Markou et al. [29]. In patients with eGFR >15 mL/min it was 25%, whereas in those with eGFR<15 mL/min it was 45.4%. Daytime sleepiness was worst in patients with RLS [29].

In a case control study of Merlino et al. [30] in CKD patients not needing dialysis, the prevalence of RLS was 10% and 3.3% in controls. In a study by Lee et al. [31] in patients with eGFR>60 mil/min, CKD patients with eGFR <60 mL/min and patients on dialysis RLS emerged common and important source of sleep disruption in the whole spectrum of kidney disease. In fact, the prevalence of RLS was 18.9% in patients with eGFR>60 mL/min, 26% in CKD patients with eGFR <60 mL/min, and 26% in patients on maintenance hemodialysis (Fig. 27.4).

RLS in CKD patients has been associated with a statistically significant increase in sleep latency, non-refreshing sleep, leg movements during sleep, poor memory and with a poor sleep as indicated by a PSQI >5. CKD patients with RLS have difficulties in initiating and maintaining sleep. However, RLS is associated with kidney disease, but not with the severity of the disease and in multivariate analysis was predictor of poor sleep.

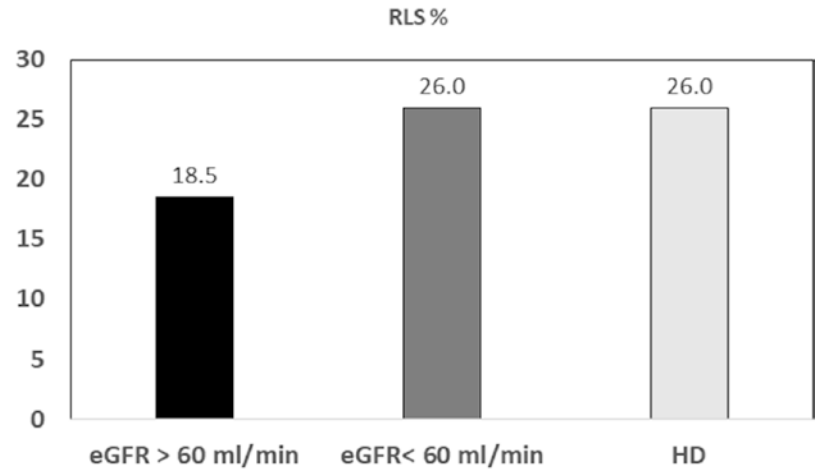

Fig. 27.4 Prevalence of RLS in the whole spectrum of kidney disease. Compiled from data of Lee J et al. [31]

The study did not disclose differences in daytime sleepiness between mild and severe CKD groups.

Transplantation normalizes RLS, but it deteriorates again with graft failure. In many studies the prevalence of RLS after transplantation falls in the range of the general population. However, many studies have reported a high prevalence of RLS in patients receiving a kidney graft.

27.5 Sleep Apnea

Sleep apnea syndrome (SAS) is a chronic sleep disorder causing repeated cessation of breath for 10 s or more, during sleep. It is characterized by loud snoring, breathlessness, waking, and daytime sleepiness. Hypopnea is a 50% reduction in airflow for 10 s or more or a decrease of 30% of airflow associated with increased desaturation or arousal from sleep. The apnea–hypopnea index (AHI) is calculated by dividing the number of apnea-hypopneic episodes for the hours of sleep. An index of 5–10 indicates mild apnea, an index of 15–30 indicates moderate apnea, and an index >30 indicates severe apnea.

The prevalence of SA in the general population is 3–10% in women and 10–17% in men. Prevalence may be higher in persons with obesity and diabetes.

Sleep apnea may be obstructive, central, mixed. Apnea accompanied by respiratory effort—obstructive sleep apnea (OSA)—is typical in CKD, whereas central sleep apnea (CSA) without respiratory effort is underreported. It causes cognitive impairment, decreased daytime functioning and is associated with depression, hypertension, left ventricular hypertrophy, cardiovascular morbidity and mortality. In CKD it is caused by (1) increased ventilatory threshold and/or higher sensitivity to hypercapnia and (2) a rostral fluid shift in reclined position of fluid from legs to the neck that increases collapsibility of the upper way. There is correlation between leg fluid volume and neck circumference.

OSA increases the risk of kidney injury and impairs kidney function. It is found in 1 out of 4 patients with eGFR <60 mL/min, in 4 out of 10 with ESKD, and in more than 6 out of 10 patients on HD or continuous ambulatory peritoneal dialysis (CAPD). The prevalence of CSA is in the range of 9–75%. Nocturnal hemodialysis and cyclic-assisted nocturnal peritoneal dialysis cure OSA that also benefits of compressive stockings.

The link between CKD and OSA is driven by (1) chemoreflex responsiveness and (2) pharyngeal narrowing [32, 33], as reported in Fig. 27.5. Metabolic acidosis causes hyperventilation and hypocapnia. The latter enhances chemoreceptor sensitivity that (1) destabilizes respiratory control during sleep, (2) reduces PCO2 below the apneic threshold, and (3) impairs chemoreflex control. Pharyngeal narrowing is brought about

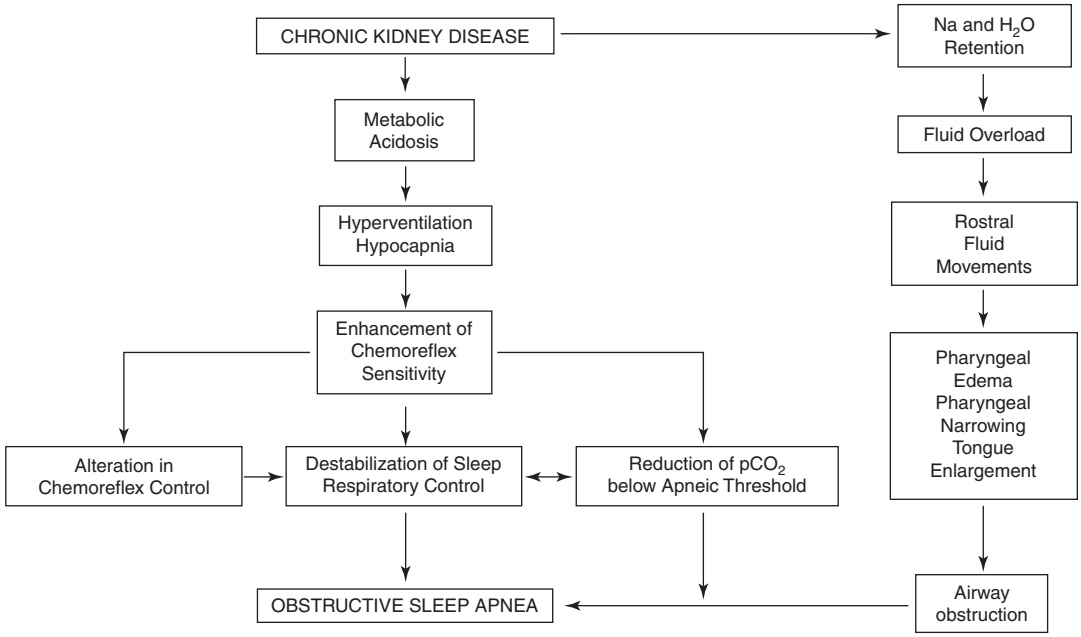

Fig. 27.5 Relation between CKD and OSA. Modified from Abuyassin B et al. [32]

by sodium and water retention and fluid overload and is characterized by narrowing and/or increased thickness of pharyngeal musculature and by tongue enlargement that leads to significant reduction of naso-pharyngeal volume, oropharyngeal volume, and hypopharyngeal volume.

The link between OSA (Fig. 27.5) and CKD is driven by hypoxia, leading to RAAS activation, increased sympathetic tone, hypertension, inflammation, oxidative stress, and excessive negative intrathoracic pressure. Hypoxia causes renal tissue hypoxia that leads to tubulointerstitial injury, renal vasculature damage, and apoptosis that are associated with functional impairment. CKD is the end effect. Oxidative stress causes an increase in asymmetric dimethylarginine that by inhibiting nitric oxide synthase reduces nitric oxide availability. Hypoxia also activates the RAAS and causes endothelial dysfunction, increases the sympathetic tone, causes hypertension, increases insulin resistance, and the atherogenic milieu and ends in CKD. CKD is also mediated by increased right atrial pressure, increased atrial natriuretic peptide that leads to hyperfiltration.

Volume overload has a pivotal role in edema formation in upper airway, leading to oropharyngeal narrowing. Hypervolemia also causes an increase in quantity of overnight rostral fluid shift from the legs during sleep. This is valid for the general population and much more for fluid retaining condition like heart failure and ESKD and causes changes in neck circumference as well as of apnea-hypopnea time (AHT) as demonstrated by Elias [34].

In a study by Sakaguchi et al. in non-obese CKD patients—mean eGFR of 31 mL/min per 1.73 m^2, the decline in GFR was three to fourfold faster in persons with mild-to-severe nocturnal hypoxia (NH), than in persons with no or mild NH (Fig. 27.6). That longitudinal study points to NH as an independent risk factor for fast GFR decline in CKD [35].

There were great expectations on the impact of kidney transplantation on OSA following the papers by Langevin et al. and Auckley et al. [36, 37]. But it soon became evident that transplanta-

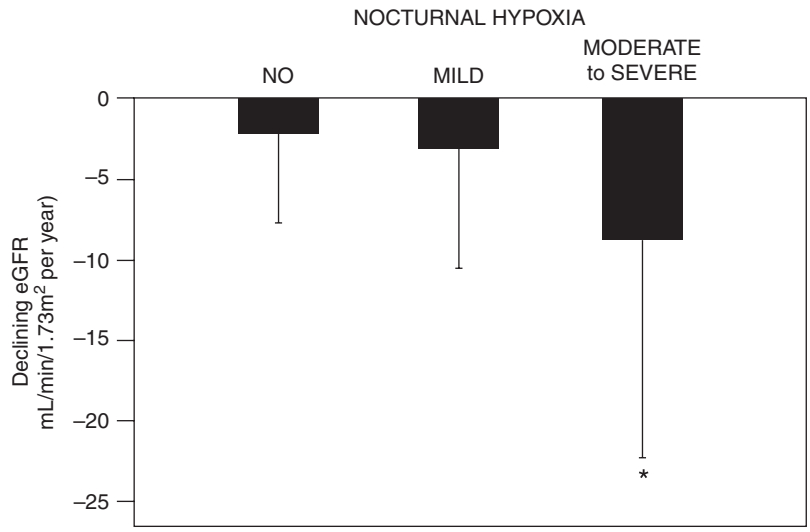

Fig. 27.6 eGFR losses caused by nocturnal hypoxia. (Modified from Sakaguchi Y et al. [35])

tion improved but did not normalize sleep disturbances [37]. Recent studies confirm partial benefits as attested in the study by Valentina Forni Ogna [38]. In kidney transplanted patients with sleep disordered breathing, a strong association was found with 24 h, daily and nocturnal systolic blood pressure by Mallamaci et al. [39]. The group in Reggio Calabria demonstrated that those hypertensive patients were not at higher risk of mortality. They may have been protected by the denervation.

27.6 Sleep Apnea Syndrome as a Trigger of CKD

The relation of OSAS and CKD is bidirectional (Fig. 27.7), there is high frequency of OSAS in CKD but also high prevalence of CKD with OSAS. The link is explained by the chronic hypoxia hypothesis introduced in 1998 by Fine, Orphanides, and Norman that is in good keeping with population and experimental data in humans [40–42]. The hypothesis explains how glomerular injury is transferred to the interstitium and causing scarring and loss of renal function. The primary glomerular disease leads to restriction of postglomerular flows in affected glomeruli and injury of peritubular capillaries causing a hypoxic milieu that maintains inflammation and the fibrotic response of tubulo-interstitial cells that extends to unaffected capillaries, nephrons, and glomeruli. The end effect is a reduction in the number of peritubular capillaries (the hallmark of chronic kidney disease) through enhancement of antiangiogenic factors and the contemporary suppression of proangiogenic factors.

Persons with OSAS carry an increased cardiovascular risk (systemic hypertension, atrial fibrillation, coronary artery disease, stroke). In addition, they may have mild CKD and/or proteinuria that is more common at night. There is a relation between severity of OSAS and loss of kidney function that is independent of hypertension although nearly 50% of people with OSAS may have hypertension. Renal biopsy has disclosed glomerulomegaly and focal segmental glomerulosclerosis [42–45].

Continuous positive airway pressure (CPAP) administered to patients with obstructive sleep apnea syndrome reduces renal plasma flow, filtration fraction, renal vascular resistance, activity of RAAS, and proteinuria. RAAS inhibition is superior to CPAP in reducing BP but not in improving excessive daily sleepiness. Administration of an aldosterone antagonist may reduce fluid retention and supine enlargement of neck circumference and remain a therapeutic

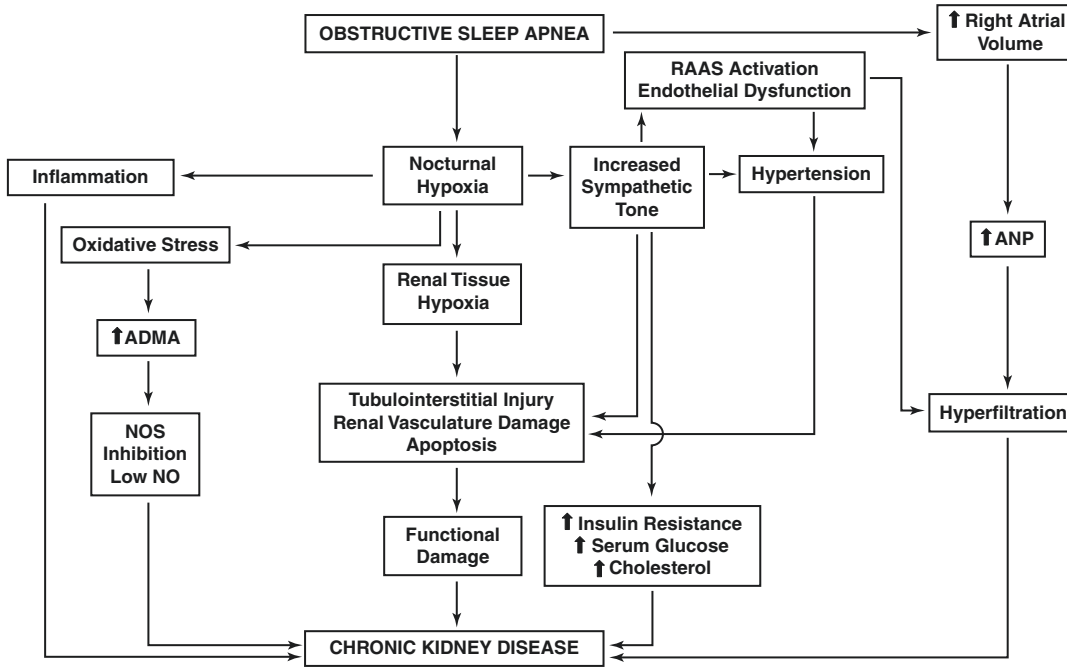

Fig. 27.7 Bidirectional relation of OSA and CKD. Modified from Abuyassin B et al. [32]

option when CPAP is not feasible. An association of CPAP and anti-aldosterone drugs is a possibility that deserves to be explored.

27.7 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) that affects 10–12% of the general population is more prevalent (60–70%) in dialyzed patients. It is characterized by inability to stay alert during the day resulting in sleepiness or unintentional dosing during active and passive daily activities, thus indicating that there is a day/night sleep reversal that is a principal indicator of the uremic status.

The pathogenesis is multifactorial and includes: (1) uremia per se, (2) subclinical encephalopathy, (3) abnormal melatonin metabolism, (4) tyrosine deficiency (dopamine production), (5) production of inflammatory cytokines, (6) changes in body temperature rhythm caused by dialysis, (7) effect of dialysate temperature on sleep, (8) coexistence of sleep apnea. It is improved by nocturnal hemodialysis and by transplantation.

27.8 Alexithymia and Sleep Disorders in CKD

Alexithymia is a personality trait that reflects difficulties in affective self-regulation that was introduced to medical literature by Peter E. Sifneos in 1996 [46]. A major contribution to our understanding of alexithymia comes from studies carried out by Fukunishi starting in 1989 [47]. As reported by R.M. De Santo et al. in 2010 [14], alexithymia incorporates difficulties in distinguishing between feelings and the physical sensations of emotional arousal, limited marginal process, and an externally oriented cognitive style. It has been associated with physical and mental health problems, substance abuse disorders, and mortality in the general population where a prevalence of 4–13% has been reported. It is considered a potential way of dealing with disease-generated stress. Alexithymia scores are correlated with sleep complaints in community samples. The correlation is dependent on depression because it disappears when the contribution of depression is partialled out by multiple regression [14]. That study was one of the 3 prospective

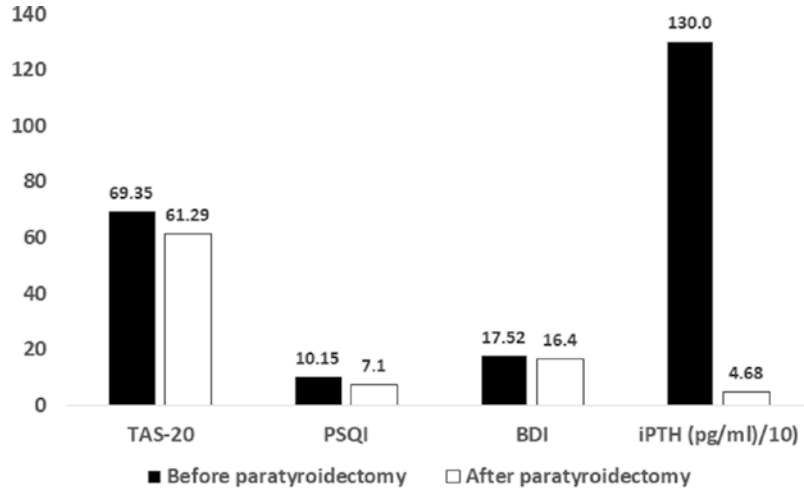

Fig. 27.8 Alexithymia, sleep disorders, PTH, and depression in patients with insuppressible hyperparathyroidism before and after parathyroidectomy. Compiled from data De Santo RM et al. [14]

studies characterized as bearing many strengths and no limitations among 23 studies amenable to meta-analysis in hemodialysis patients [48] and 1 of the 24 papers subjected to systematic review and peer analysis on the more general problem of sleep complaints and alexithymia [49].

De Santo et al. [14] performed a study on 80 HD patients not requiring parathyroidectomy (iPTH 353 ± 52.4 pg/mL) and 40 HD patients with insuppressible hyperparathyroidism needing parathyroidectomy (iPTH 1299.6 ± 248.5 pg/mL). They measured the degree of alexithymia with the Toronto alexithymia scale (TAS-20), sleep disorders with the 19-item Pittsburgh sleep quality index (PSQI) that identifies good sleepers and poor sleeper. The Beck depression inventory (BDI) was used to measure depression, comorbidities were evaluated by the Charles comorbidity index (CCI). Patients with insuppressible hyperparathyroidism had significantly higher TAS-20, higher PSQI, CCI, systolic and diastolic blood pressure, and higher BDI. In 40 patients needing parathyroidectomy, 32 had a BDI score ≥ 15 and BDI correlated directly with iPTH. Patients with insuppressible hyperparathyroidism after surgery had significantly lower TAS-20, PSQI, iPTH, and BDI, as indicated in Fig. 27.8.

There is a renewed interest in detecting alexithymia in CKD patients because it carries the risk of lack of adherence to dietary and medication plans. Inflammation has been assigned a causative role [50, 51] in a study on 170 HD patients probably malnourished (68.9% were poor sleepers, 65.3% alexithymia, 28% depressed, 21% with excessive daytime sleepiness).

27.9 Putative Determinants of Sleep Disorders in CKD

A list of nearly fifty putative determinants for SD in chronic kidney disease needing or not HD therapy [13, 52] have been grouped in: 1. Demographic factors, 2. Lifestyle related factors, 3. Disease related factors, 4. Psychological factors, 5. Treatment related factors, and 6. Socioeconomic factors. Important factors emerged: Age in group 1; cigarette smoking and obesity in group 2; GFR, anemia, PTH, calcium concentrations, neurotransmitters production, hypertension and antihypertensive drugs, bone pain, hypoxemia, and pruritus in group 3; depression, perceived quality of life, and disease intrusiveness in group 4; the dialysis team, the shift, the day of the weekly treatment schedule, albumin and C-reactive protein concentrations, comorbid conditions, losses and dependencies of a dialysis-dependent life emerge in group 5; poverty and living in urban environment emerge in the last group (Fig. 27.9).

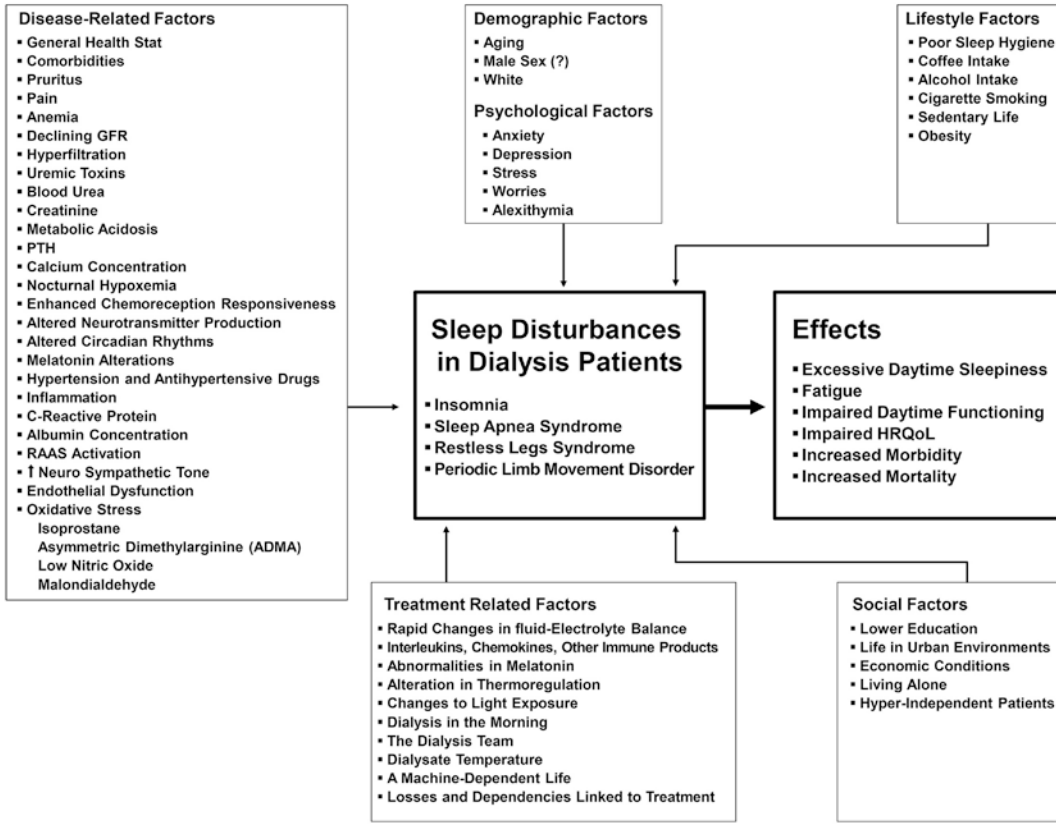

Fig. 27.9 Putative determinants of sleep disorders in CKD. Modified from Parker KP [52] and De Santo RM et al. [13, 22]

27.10 Mild Cognitive Impairment and Sleep Disorders in CKD

27.10.1 Mild Cognitive Impairment

The term mild cognitive impairment (MCI) was introduced to medical literature in 1988 by Reisberg et al. [53], and it took 11 years to become a very important syndrome that it now is [54]. According to De Carli it can be considered the transition phase between healthy cognitive aging and dementia [55] and is a syndrome defined by a "cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life" [56]. It affects attention, memory, language skills, visuospatial performance, executive functions, and inhibitory control.

As soon as dialysis became a widespread procedure worldwide, intellectual and emotional patterns were found to be impaired in hemodialyzed patients [57]. Dementia incidence rates (DIR) were progressively higher with lower eGFR: from 6.56/1000 person-years in persons with eGFR 90–104 mL/min to 30.28/1000 person-years in those with eGFR <30 mL/min. As many as 10% of dementia cases could be attributed to eGFR <60 mL/min/1.73m^2, a proportion higher than that attributed to other dementia risk factors such as cardiovascular disease and diabetes [58]. However, in the last few years MCI and dementia became the most important topic related to quality of life in CKD patients including those in ESKD, those receiving a kidney transplantation or just presenting with albuminuria.

Albuminuria associated with worse score of executive functioning and increased white matter hyperdensity volumes in older persons [59]. Albuminuria is a risk factor for MCI and dementia as demonstrated by cross-sectional and long-term studies. It is speculated that kidney and brain have in common microvascular similarities that render them prone to endothelial dysfunction driven by oxidative stress and inflammation. In a recent review [60] it was stressed that although the exact substrate of MCI and dementia is still under investigation, available experimental data indicate that elevated albuminuria and low glomerular filtration rate are associated with significant neuroanatomical declines in hippocampal function and gray matter volume. Thus, albuminuria may be critical in the development of MCI and its progression to dementia [60].

Furthermore, low eGFR as well as albuminuria has been associated with decreased volumes of hippocampus and gray matter and decreased cortical thickness in human and experimental studies in mouse. The association between MCI may be driven by elevated systolic blood pressure, increased arterial stiffness, older age, oxidative stress [61, 62].

The high prevalence of MCI (Table 27.4) is already present in the early stage of CKD (stage 3) and is nearly doubled (62%) in advanced stages of CKD (stage 4 and 5) [61–65]. In patients treated with hemodialysis, few have normal cognitive function [61, 62, 66]. Peritoneal dialysis seems to offer some advantages [61, 62, 67, 68]. Even kidney transplantation, the best treatment in terms of quality and quantity of life and costs for the society does not normalize cognition scores [69] but improves it significantly. The prevalence of cognitive impairment was 58.0%. Multivariable linear regression demonstrated that older age, male sex, and absence of diabetes were associated with lower Montreal Cognitive Assessment (MoCA) scores. Estimated GFR was not associated with level of cognition. The logistic regression analysis confirmed the association of older age with cognitive impairment. In other studies, transplanted patients did not score better than on HD patients [69–71].

It should be added that patients with sleep disordered breathing (SDB) have poor cognition scores for global cognitive function, immediate and delayed verbal memory, working memory, attention, and psychomotor speed. However, it has been shown that improvements are obtained with CPAP [68]. Table 27.1 also shows that in all categories the risk of dementia in MCI-CKD was very much higher than in the general population.

Finally, it should be stressed that few studies that have explored cognitive function in Stage 1 and 2 in elderly CKD have disclosed that these stages are not asymptomatic and are associated with significant impairment of speed of processing and attention [69].

In recent but classical study, Viggiano et al. [61, 62] reviewed the morphological, functional, and pathogenetic features of MCI-CKD. In MCI-CKD tractography disclosed internal capsule demyelination, whereas MRI disclosed deep white matter demyelination, EEG showed impaired cortical synchronization at delta frequencies. They also disclosed that animal models of CKD with MCI show sleep disorders but normal cerebral architecture, however difference exists between MCI in the general population and

Table 27.4 Data point out the burden of MCI and dementia in chronic kidney disease. Mainly based on recent but classical works of D Viggiano et al. [61, 62]

Population	Prevalence of MCI	Prevalence of dementia	References
Healthy	11–26%	13%	[61, 62]
Early CKD, stage 3	15.6–31%	Unknown	[61, 62]
Late CKD, stage 4, 5	25–62%	Unknown	[61–65]
Hemodialysis	26–73.6%, 87.7%	8–37%	[61, 62, 66]
Peritoneal dialysis	28.6–68.6%	4–33%	[61, 62, 67, 68]
Transplantation	58%	7–22%	[61, 62, 69]

MCI-CKD, the latter identified as a distinct "renocerebral syndrome" not overlapping with the former.

Two hypotheses have been proposed to explain MCI and dementia in CKD [70]. A vascular hypothesis based on cardiovascular risk factors (diabetes mellitus, hypertension, cerebrovascular disease) and a neurodegenerative hypothesis based on uremic toxins. Probably the explanation is in a combination of both. Risks include general factors, cardiometabolic factors, neuropsychiatric comorbidities, impairment of the glymphatic system, the uremic factors including toxins, genetic factors, factors causing endothelial dysfunction, neuroinflammation, neurodegeneration, dialysis driven factors causing cerebral edema or associated with drop in mean blood pressure and cerebrovascular flows (Table 27.5).

Diagnosis is based on polysomnography (EEG for characterizing NREM and REM sleep, electrooculography, electromyography, respiratory patterns, pulse oximetry) and by respiratory cannula on the assessment of sleep apnea. The use of an accelerometer allows assessment of hands tremor.

Actigraphy allows monitoring of motor activity and posture. Examination of retinal vessels might be of immediate clinical value for sleepiness but there is no agreement on its value.

A lot can be learned by assessing KDQoL-CF (as screening), Pittsburgh Sleep Quality Index, the Montreal Cognitive Assessment (MoCa) that has a sensitivity of 80–100% and a specificity of 50–76% and by single leg standing Time (SLST).

Sequential MRI and spectroscopy of the left hippocampal area, brain tractography (diffusion tensor imaging) to investigate demyelination of

Table 27.5 Risk factors and molecular mechanisms for MCI and dementia in CKD. Modified from DM Kelly, M Rothwell [71], and D Viggiano et al. [61, 62]

A. Risk factors for MCI and dementia
General factors
Advanced age
Education
Occupational attainment
Smoking
Cardiometabolic risk factors
Hypertension
Stroke
Small vessel disease
Diabetes mellitus
Obesity
Neuropsychiatric comorbidities
Depression
Sleep disorders
Beta-amyloid deposition
Genetic factors
Dialysis factors
1 Toxins causing brain edema
(a)Urea
(b) Newly generated osmolytes
2 Altered cerebral blood flow
(a) Reduced cerebral blood flow with "cerebral stunning"
(b) Drop in mean arterial pressure

Table 27.5 (continued)

B. Mechanisms for MCI and dementia
Reduction of brain extracellular spaces (glymphatic system) mediated by
Diabetes
Hypertension
Sleep disorders
Endothelial dysfunction mediated by
Asymmetric dimethyl arginine (ADMA)
FGF23
Hippuric acid
Neuropeptide Y
Neuroinflammation mediated by
CRP
Fibrinogen
IL-6
IL-1ℓ
TNF
Indoxyl sulfate
P-cresyl sulfate
Neurodegeneration mediated by
IL-1ℓ
Summary of uremic (neuro)toxins possibly involved in MCI
Uric acid
Phosphate
PTH
Homocysteine
Indole-3-acetic acid
Asymmetric dimethyl arginine (ADMA)
FGF23
Hippuric acid
Neuropeptide Y
CRP
Fibrinogen
IL-6
IL-1ℓ
TNF
Indoxyl sulfate
P-cresyl sulfate

Box 27.1 Mild Cognitive Impairment (MCI) in CKD

- MCI-CKD is a distinct "renocerebral" entity not overlapping with MCI in general population [61, 62, 71].
- Tractography discloses internal capsule demyelination, MRI deep white matter demyelination, EEG impaired cortical synchronization at delta frequencies.
- The patient is not aware of her/his MCI and may be reported by caregivers/family or may be suspected when a patient becomes confused with prescriptions and misses dates for consultation or therapies.
- MCI-CKD may be a cause of exclusion from unattended dialysis programs.
- Explore QoL indices, assess the Pittsburgh Sleep Quality Index, explore the Montreal Cognitive Assessment, workup the existence of sleep disorders by Polysomnography, explore the neurotoxin status and biomarkers of inflammation.
- No specific therapy exists but all suggestions for optimization of usual therapy should be followed up.

the internal capsule, CT/MRI imaging of white matter, fMRI for cerebral blood flow may help to follow up MCI starting with CKD stage 3.

Nephrologists should know that 90% of CKD patients are not aware of their MCI and a lot may be learned through patient's own narratives and by reports of spouses, family members, and caregivers. They should also be aware that MCI may interfere with taking medicines and may cause inability for programs of unattended dialysis (Box 27.1).

27.10.2 Cognitive Dysfunction and Sleep Disorders in CKD

It is now evident that the prevalence of sleep disorders and cognitive impairment is very high in CKD patients needing dialysis or not and affects their lives. The prevalence of cognitive impairment is 10–40% in CKD, 70–87% in HD patients, and 27–67% in peritoneal dialysis. The association of sleep disorders and cognitive impairment represents a further burden. Cognitive impairment (verbal memory, working memory, attention) has been associated with a sleep disordered breathing in CKD stages 4–5. In addition, memory problems have been disclosed in HD patients in whom cognitive impairments predict mortality. In a prospective study—not utilizing polysomnography—in PD patients [20], the prevalence of sleep disorders was 65.5% and that of possible narcolepsy 4.7%. Sleepwalking and nightmares in the same cohort were identified as risk factors for impaired delayed memory.

Presently cognitive impairment and sleep disorders may be seen as manifestations of brain dysfunction driven by an incompletely mosaic of factors that includes anemia, uremic toxins, PTH, inflammation, malnutrition, instable hemodynamics, and derangements in fluid volume and electrolytes. The structural equivalents are represented by lesions of hippocampus, small-vessels ischemic brain disease and deep and white matter demyelination.

Older patients or those with cerebrovascular lesion should be screened using the Montreal Cognitive Assessment to explore executive functions. If cognitive impairment is present, more specialized tests should be used under guidance of a geriatrist or a neurologist and/or a specialist of imaging [71]. For accurate evaluation refer to strategies employed in research [71–73]. In mild-moderate CKD with albuminuria, using angiotensin converting enzyme inhibitors and angiotensin receptor blockers and achieving strict blood pressure control are recommended. In dialyzed patients cooling dialysate temperature and more efficient removal of small molecules have not provided benefits. New experimental strategies are coming of age [72].

Physicians must be aware that [61, 62, 71]:

- No therapy exists.
- Treating the cardiovascular risks is mandatory but not enough.
- Mediterranean diet provides unproved benefits although people on Mediterranean diet score better on cognitive function.

- Supplementation of vitamin B, folate, vitamin D, vitamin E is ineffective but necessary if their levels are below normal.
- Use of polyunsaturated fatty acids did not meet expectation.
- Hemodialysis is ineffective.
- Peritoneal dialysis is probably better, transplantation improves the outcome.
- Obesity and isolation should be reduced if present.
- Physical activity should be optimized, and cognitive training prescribed.
- CPAP is mandatory in the presence of sleep apnea.
- Control of hyperparathyroidism is crucial both for sleep improvement and the toxin burden.
- Anti-inflammatory drugs have great promise (use of colchicine improved MCI).
- Use of plasma exchange + albumin supplementation reduced dementia progression by 61% in 1 year.
- Use of everolimus—a protein kinase inhibitor of m-TOR—may protect the glymphatic functions.
- Use of erythropoietin is certainly beneficial.

Transplantation is a great option since it improves the cognitive impairment that becomes evident within 1 year and is stable over the years. The improvement is due to restoration of kidney function that also favors optimal clearance of drugs and avoids the stress of dialysis and its associated hemodynamic changes and the risk of coagulation. In patients with cognitive impairment physicians should favor more frequent medical control and family shared decision, avoid polypharmacy and sedative medications, improve sleep hygiene, treat depression, increase social support, favor mental stimulation and exercise [70].

27.11 Impairment of the Melatonin Clock in CKD

Among the many factors associated with the disordered sleep in CKD, melatonin has been studied extensively also because of its circadian rhythm and the efficacy of its use in clinical practice.

Melatonin, a pineal hormone, is a determinant of the sleep-wake rhythm. It is nearly undetectable in blood during daytime and starts rising in the evening and the secretion peaks at night. In CKD, Koch et al. [74] were the first to show a correlation between impaired GFR and decrease in melatonin rhythm and production (Fig. 27.10) that is blunted at night.

These authors promoted the use of melatonin at bedtime (3 mg) that is well tolerated, free of untoward effects, and effective in improving the disordered sleep. Melatonin improves sleep quality by reducing sleep onset latency, increasing total sleep time and sleep efficiency, and reducing sleep fragmentation that in turn results in a more refreshing sleep. However, the favorable effect was not confirmed after a long-lasting use (3 years). But there might be reasons for this and some have been reviewed by Russcher et al. [2] who suggested melatonin accumulation in CKD as well as a possible downregulation of the melatonin receptor.

There are many reasons for utilizing melatonin in CKD: (1) the antioxidant properties, (2) the anti-inflammatory action, (3) the improvement of the dipping profile in essential hypertension, (4) the excessive daytime sleepiness in uremia, (5) the impairment of the beta-adrenergic system, (6) anemia, (7) the lack of erythropoietin [74, 75].

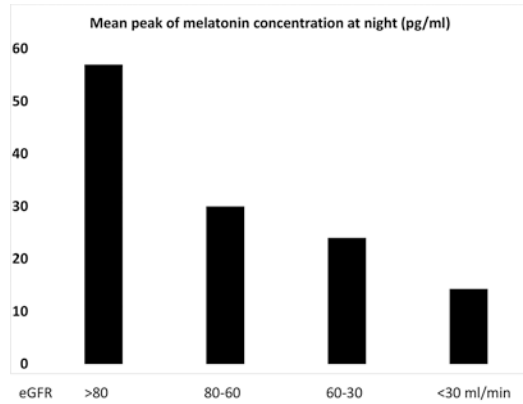

Fig. 27.10 Peak melatonin concentration at night. Modified from Koch BC et al. [74]

27.12 Management of Sleep Disorders in CKD

Treatment of pruritus and pain is preliminary. Pruritus affects up to 84% of dialysis patients but also patients with CKD. It may be continuous, discontinuous, may last months or years, and affect symmetrical areas of the body especially at night. It shall be treated topically by hydrating skin 2–3 times a day. Phototherapy (Type B UV light) has been used with success, but it did not pass the test of a controlled trial. Gabapentin (100 mg/after dialysis) has achieved good results. Promising results have achieved with oral and intravenous opioids and sertraline. There is no place for antihistamines since the central transmission of itch occurs via a non-histaminergic path [76].

27.12.1 Insomnia

Pharmacological approaches are the first line paying strong attention to sleep hygiene that reflects healthy habits, behaviors and environmental factors that promote improved sleep: going to bed just to sleep, avoiding caffeine, and reading in bed. If insomnia is chronic, cognitive behavioral therapy (CBT-I) is added.

Benzodiazepine receptor agonist of the non-benzodiazepine class is used for insomnia. They are known as the Z drugs (eszopiclone, zaleplon, zolpidem, zopiclone) that usually do not require adjustment for kidney failure. Treatment shall start with low dose and titrated monitoring adverse effects. Zaleplon has been investigated in a randomized double-blind placebo controlled study with amelioration of sleep quality [76].

Melatonin (3 mg before sleep) improved the quality of sleep in dialysis patients in short-term and long-term studies. Cooling the dialysate reduces sleep latency. More frequent hemodialysis improves sleep apnea [76].

27.12.2 Restless Leg Syndrome

Lifestyle changes include avoiding caffeine, nicotine, and alcohol, promoting exercise and resistance training. Pharmacological treatment starts with drugs affecting the dopamine pathways. Levodopa has been shown to be effective in reducing RLS but has been without effect on sleep quality and quantity. The non-ergoline dopamine receptor agonists ropinirole, pramipexole, and rotigotine (transdermal) have been used with success in short-term studies although associated with fatigue, lightheadedness, and nausea and frequently associated with augmentation (worsening of symptoms). Ropinirole has been proved effective in decreasing RLS and ameliorating sleep quality. Pramipexole also reduced the severity of RLS without adverse effects. Identical benefits have been achieved by transdermal rotigotine [76].

Second line drugs for RLS are gabapentinoids. Gabapentin (inhibitor of glutamate release) given at a dose of 100–300 mg after dialysis thrice a week reduced RLS severity, ameliorated general health, and reduced pain and was more effective than levodopa and significantly reduced pruritus [76]. Opioids too are coming of age. There are reasons to give intravenous iron that have not been confirmed. Aerobic exercise associated with low dose of the dopamine agonists ropinirole during dialysis gave very favorable results in reducing RLS [76].

27.12.3 Sleep Apnea

CPAP is the cost-effective mainstay of medical treatment for OSA [77]. It holds the potential for preventing and treating OSA in CKD.

Six months CPAP in obese patients with OSAS significantly improved eGFR (+20 mL/min/1.73 m^2) from 84 ± 13.1 mL min to 104.2 ± 19.0 mL/min ($p < 0.00001$). In addition, AHI was the most important independent predictor of eGFR [78]. However, a year of CPAP failed to improve CKD patients with eGFR at 38.4 + 1.5 mL/min × 1.73m^2, but the study provided some evidence that CPAP slowed the decline in eGFR in patients with a lower risk of CKD progression [3]. Thus, many studies are ongoing to address its effectiveness.

CPAP has been used successfully in patients with sleep apnea on hemodialysis since 1991, has

been effective in peritoneal dialysis, and has been recognized as an effective method [79] and recognized "the first line treatment in HD patients with OSA" [80, 81].

27.13 Assessing Effectiveness of Interventions

In a study aiming to assess the effectiveness of interventions to improve sleep quality in adults and children with CKD, or with ESKD treated with dialysis, or with transplantation [82], the real value of the whole armamentarium at our disposal was analyzed. Table 27.6 lists 15 intervention procedures utilized in clinical practice to improve CKD-related sleep disorders.

For relaxation there is very little evidence for effects on sleep quality and anxiety, depression, fatigue, and evidence for quality of life. Exercise improved sleep quality (very low certainty evidence), decreased fatigue and depressive symptoms according to Zung Self-Rating Depression Scale (moderate certainty evidence). Acupressure improved sleep latency scale, sleep efficiency and fatigue (moderate certainty evidence), total sleep time (low certainty evidence), sleep quality and depression (very low certainty evidence). Cognitive behavioral therapy improved sleep quality (very low certainty evidence). Single studies showed improved total sleep time, sleep efficiency, anxiety, quality of life. Effects on depressive symptoms were also observed (moderate certainty evidence). Sleep hygiene education improved sleep latency (very low certainty evidence), total sleep time, sleep efficiency, and sleep disturbance (moderate certainty evidence) but had no effect on fatigue, pain, and quality of life.

Table 27.6 Interventions for improving sleep quality in CKD [82]

1. Relaxation, progressive muscle relaxation, nurse-led breathing, mindfulness, Benson relaxation technique
2. Exercise (aerobic exercise, exercise during hemodialysis, yoga-based exercise, resistance exercise)
3. Acupressure
4. Cognitive behavioral therapy
5. Sleep hygiene education
6. Telephone support
7. Reflexology
8. Music at bedtime and during hemodialysis
9. Massage
10. Light therapy
11. Aromatherapy
12. Dopaminergic agonists (rotigotine and ropinirole)
13. Gabapentin
14. Melatonin
15. Dialytic modalities (CAPD, APD, nocturnal dialysis)

Telephone support improved [83] sleep quality, but had no effect on fatigue, pain, and quality of life. Reflexology caused slight improvement of sleep quality (moderate certainty evidence). However, Unai, Balci, and Akpinar showed improvement of fatigue [84]. Music during hemodialysis [85] improved sleep quality, total sleep time, and sleep disturbance. Music at bedtime outperformed music during hemodialysis at improving sleep latency, total sleep time, and sleep disturbance. Abdominal massage improved sleep quality, pain, and quality of life. Light therapy improved sleep latency but had no effect on sleep efficiency or depressive symptoms, whereas aromatherapy improved sleep quality, total sleep time, sleep efficiency, and sleep disturbance [86].

Rotigotine and ropinirole were also studied. When giving Rotigotine to patients requiring hemodialysis, Dauvilliers (2016) found improvement of total sleep time and sleep efficiency. Rotigotine also improved periodic limb movements and RLS symptoms [87]. Ropinirole and levodopa were given to 11 patients on maintenance hemodialysis with RLS in the course of an open randomized control trial. Levodopa improved RLS scores by 33%. Ropinirole was superior since it ameliorated RLS scores by 73.5% [88].

Gabapentin was compared with dopaminergic agonist levodopa. Improvement was observed for sleep latency and sleep disturbance with gabapentin. Melatonin for 30 weeks improved sleep quality [89].

No difference in sleep quality was seen between patients treated with continuous ambulatory peritoneal dialysis and with automated peritoneal dialysis. However, nocturnal dialysis is associated with poor sleep quality.

The study was unable to find suitable data for children and to provide evidence for adverse effects of therapies.

Before You Finish: Practice Pearls for the Clinician

- Sleep disorders in CKD are amenable to cures.
- Optimal blood pressure control must be achieved.
- Sleep hygiene should be optimized.
- Pharmacological therapy is feasible for insomnia and restless legs syndrome.
- Melatonin has a role in the therapy of insomnia, but in chronic treatments can lose efficacy.
- Compressive stockings may reduce fluid rostral movements at night.
- CPAP is the mainstay for OSA.
- Nocturnal hemodialysis and automated cyclic peritoneal dialysis are feasible options.
- Cognitive behavioral therapy is coming of age.

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