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Sleep Disturbances as Nontraditional Risk Factors for Development and Progression of CKD: Review of the Evidence

Nicolas F. Turek, BA[1], **Ana C. Ricardo, MD, MPH**[2], and **James P. Lash, MD**[2]

[1]Sleep, Metabolism and Health Center, Department of Medicine, University of Chicago

[2]Section of Nephrology, Department of Medicine, University of Illinois at Chicago

Abstract

Despite the high prevalence and enormous public health implications of chronic kidney disease (CKD), the factors responsible for its development and progression remain incompletely understood. To date, only a few studies have attempted to objectively characterize sleep in CKD patients prior to kidney failure, but emerging evidence suggests a high prevalence of sleep disorders, particularly obstructive sleep apnea. Laboratory and epidemiologic studies have shown that insufficient sleep and poor sleep quality promote the development and exacerbate the severity of three important risk factors for CKD, namely hypertension, type 2 diabetes, and obesity. In addition, sleep disturbances might have a direct effect on CKD through chronobiological alterations in the renin-angiotensin-aldosterone system and sympathetic nervous system activation. The negative impact of sleep disorders on vascular compliance and endothelial function may also have also have a deleterious effect on CKD. Sleep disturbances may therefore represent a novel risk factor for the development and progression of CKD. Optimizing sleep duration and quality and treating sleep disorders may reduce the severity and delay the progression of CKD.

Index words

Sleep disorders; obstructive sleep apnea; chronic kidney disease

The prevalence of chronic kidney disease (CKD) has markedly increased over the past 10 years and this alarming trend is likely to continue.[1] Indeed, type 2 diabetes and hypertension are the two best established risk factors for CKD and the prevalence of both conditions is rapidly increasing, driven by the epidemic of obesity. Despite the public health implications of CKD, we have an incomplete understanding of the factors responsible for its development and progression. There is a wide inter-individual variability in the progression of CKD that remains poorly understood. Obesity, dyslipidemia, inflammation, and cigarette smoking are known risk factors[2] but they only partially account for individual differences in CKD progression.

Corresponding author: James P. Lash, MD, Section of Nephrology, MC 793, University of Illinois at Chicago, 820 South Wood Street, Suite 418W, Chicago, IL 60612-7315, jplash@uic.edu, Phone: 1-312-996-7729, Fax: 1-312-355-3992.

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In recent years, a limited number of studies have attempted to characterize sleep in predialysis CKD, and the emerging evidence suggests a high prevalence of sleep disorders, in particular sleep-disturbed breathing. There is substantial evidence indicating that insufficient sleep and poor sleep quality promote the development and exacerbate the severity of three important risk factors for CKD, namely type 2 diabetes, hypertension and obesity. Thus, sleep disturbances may play an *indirect* role in the development and progression of CKD. The plausibility of a *direct* adverse impact of sleep disturbances on CKD is supported by the fact that, under normal physiologic conditions, key hormones that regulate body fluid balance and blood pressure (BP) are exquisitely modulated by the sleep-wake cycle.[3–5] Furthermore, insufficient sleep and poor sleep quality, including obstructive sleep apnea (OSA), are associated with an elevation of daytime sympathetic nervous system activity, which is likely to have an adverse impact on CKD. Finally, there is an increasing body of evidence suggesting that OSA may contribute directly to the development of CKD and accelerate its progression.

The present review summarizes the evidence supporting a role for sleep disturbances as both direct and indirect non-traditional risk factors for the development and progression of CKD. Figure 1 illustrates the conceptual framework that guided this review.

ASSESSMENT OF SLEEP AND SLEEP DISORDERS

The temporal organization of sleeping and waking over the 24-hour cycle is controlled in part by an internal circadian clock and in part by a homeostatic mechanism that increases the pressure for sleep in proportion to the duration of prior wakefulness. Sleep itself oscillates between two separate states of markedly different brain activity, known respectively as Rapid Eye Movement (REM) sleep and non-REM (NREM) sleep. Normal sleep is characterized by a 90-min oscillation between NREM and REM stages. NREM sleep is divided into 4 stages. Stages 3 and 4 of NREM sleep are the deepest stages and are termed Slow Wave Sleep (SWS). Muscle tone inhibition and oneiric activity are characteristics of REM sleep.

The gold standard of assessing sleep is polysomnography (PSG), a method that combines an all-night recording of multiple-lead electroencephalogram (EEG) with measures of muscle tone and eye movements. The recordings are visually scored using standardized criteria to categorize whether the individual is awake or in stages 1, 2 3, 4 or REM sleep over each 30-sec interval.

Objective estimations of sleep duration and fragmentation may be obtained under ambulatory conditions by wrist actigraphy. Actigraphy monitors are devices the size of a wristwatch that use sensitive omnidirectional accelerometers to count wrist movements. Wrist actigraphy does not provide an assessment of sleep architecture, as it does not differentiate REM from NREM sleep.

Lastly, a number of validated questionnaires to assess sleep duration and quality have been developed. The most commonly used is the Pittsburgh Sleep Quality questionnaire.[6] The summary measure is the Pittsburgh Sleep Quality Index (PSQI). A global PSQI score above 5 is indicative of clinically significant poor sleep quality.

The most common form of sleep disturbance is insufficient sleep due to behavioral bedtime curtailment, an endemic condition in modern society. Self-reported sleep duration in Americans has decreased by 1.5 to 2 hours between 1960 and the beginning of the 21st century. In 2006, more than 30% of adults between 30 and 64 years of age reported sleep durations under 6 hours per night.[7] This curtailment of sleep is a sleep disorder in and of

itself in the sense that it produces both daytime and nighttime alterations of physiological systems.

Insomnia is the most common clinically recognized sleep disorder; the diagnostic criterion is a subjective complaint of difficulty in initiating or maintaining sleep for at least four weeks, to such an extent that daytime functioning is impaired. Prevalence of insomnia ranges from 7–50%,[8] and is associated with increased age, chronic medical illnesses, and psychological disorders.

OSA is an increasingly prevalent disorder that involves repetitive upper airway closures (apneas) or partial collapses (hypopneas) causing intermittent hypoxia and transient arousals that restore airflow but lead to sleep fragmentation and poor sleep quality. A clinical diagnosis of OSA is made when the number of apneas and hypopneas per hour (apnea-hypopnea index [AHI]) is ≥5. The major risk factor for OSA is obesity. In one study that used PSG to quantify the prevalence of sleep apnea in morbidly obese patients, 98% of the 51 participants had clinically diagnosable sleep apnea, while 33% had severe sleep apnea.[9] The treatment of choice for OSA is the administration of continuous positive airway pressure (CPAP), a non-pharmacological intervention that is highly efficacious in eliminating obstructive events.

Periodic limb movement disorder is a sleep disorder characterized by involuntary movements of the legs (or, less frequently, arms) that result in sleep fragmentation and may cause excessive daytime sleepiness.

PREVALENCE OF SLEEP DISORDERS IN CKD

There is ample evidence indicating a greater prevalence of sleep disorders in patients with end-stage renal disease (ESRD) than in people with normal kidney function.[10;11] In contrast, research on sleep disorders in earlier stages of CKD is a nascent field of inquiry, with the majority of studies relying on self-reported surveys rather than objective sleep measures. As a result, it is difficult to ascertain the prevalence of sleep disorders in non-dialysis-dependent CKD. Table 1 provides a summary of existing studies divided into three categories based on the methodology with which sleep disorders were diagnosed.

Studies based on questionnaires have provided widely different estimates of the prevalence of sleep disorders in CKD patients, ranging from 14% to 85% (Table 1). Furthermore, studies comparing CKD to non-CKD patients have reported inconsistent findings. For example, a study by Cohen et al[12] found no significant difference between the sleep of 92 CKD patients and 51 general medical outpatients assessed by the PSQI. In contrast, a study by De Santo et al[13] comparing 220 non-CKD patients with hepatitis C with 220 CKD patients found that 59.5% of hepatitis C controls suffered from poor sleep quality based on the PSQI versus84.6% of CKD patients. These somewhat disparate results call for a more objective, quantifiable and uniform methodology to estimate the prevalence of sleep disorders in CKD.

Few studies have used actigraphy to evaluate sleep disorders in non-dialysis-dependent CKD. Barmar et al[14] measured sleep using actigraphy in 36 non-dialysis-dependent patients with stages 4–5 of CKD and 51 hemodialysis patients. These investigators found that both groups had short and fragmented sleep and that both subjective and objective measures were worse in hemodialysis patients than in the CKD patients who were not undergoing hemodialysis. Agarwal et al[15] reported significantly lower sleep efficiency and higher sleep fragmentation in patients with CKD compared with those without CKD after adjusting for clinically relevant variables.

While PSG provides the most objective assessment of sleep to date, there has been no large systematic evaluation of sleep in CKD patients based on PSG. Fleischmann et al[16] examined 158 CKD patients who were already suspected of having SA and, using PSG as an objective measure, were able to document very high rates of SA (80% to 94%). A study by Markou et al[17] examined 35 patients with non-dialysis-dependent CKD and found a prevalence of sleep-distrubed breathing of 54.3% and of periodic limb movement disorder of nearly 30%. Using diagnostic codes to identify cases of SA, Sim et al[18] reported a higher risk for SA in patients with estimated glomerular filtration rate (eGFR) of 45–89 ml/min/1.73 m^2 as compared to patients with eGFR >90 ml/min/1.73m^2. In a cross-sectional analysis of registry data, Iseki et al[19] reported that 30.5% of patients with sleep-related breathing disorders have CKD.

The heterogeneity of these studies and the variability in the findings indicate that additional research on the prevalence of sleep disorders in CKD is needed. Nonetheless, the evidence summarized in Table 1 points to a greater prevalence of sleep disorders in patients with CKD than in the general population. These associations may be bidirectional (Figure 1). It is possible that kidney disease may actually promote the development of sleep disturbances. Excessive fluid volume, with a potential shift to the neck during recumbency, has been suggested as a potential mechanism promoting OSA in CKD.[20] Depression may be another factor in the pathway between CKD and poor sleep quality since patients with CKD and patients with sleep disorders both have an increased risk for depressive symptoms.[21;22] It is possible that there may be a cyclical effect whereby CKD negatively affects sleep, and sleep disorders negatively affect CKD.

DIRECT IMPACT OF SLEEP DISORDERS ON CKD

Overview

There are two lines of evidence in support of an adverse effect of sleep disorders on the development and progression of CKD. First, sleep has a major impact on key regulators of kidney function and BP and therefore, reduced sleep duration and quality could potentially have a negative impact on kidney function. Second, recent evidence points at OSA as an independent risk factor for CKD, with endothelial dysfunction and arterial stiffness in the causal pathway.

Sleep Disturbances and the Autonomic Nervous System

Reduced sympathetic activity and increased vagal tone during normal sleep, particularly during NREM sleep, are responsible for the nocturnal dipping of BP associated with sleep. In non-CKD patients, it is well recognized that sleep loss and sleep disorders, in particular sleep-disturbed breathing with its nocturnal hypoxemia and sleep fragmentation, lead to sympathetic nervous system stimulation and attenuation of the sleep-induced decrease in BP.[23–25] Furthermore, studies using microneurography have shown that OSA is associated with elevated daytime sympathetic nervous system activity, which can be corrected by successful CPAP treatment.[23] The impact of sleep disorders on the autonomic nervous system in CKD patients has not been extensively evaluated. A recent PSG study including stage 4–5 CKD as well as HD patients demonstrated that both groups of participants were unable to increase cardiac vagal tone during the transition from wakefulness to NREM sleep.[26] It is well documented that hyperactivation of the sympathetic nervous system is often present in patients with CKD and it has been postulated that this may be a risk factor for CKD progression due to its effects on BP and renal hemodynamics.[27] It is reasonable to speculate that further activation of the sympathetic nervous system due to sleep disorders would exacerbate this risk in patients with CKD.

Sleep and the Renin-Angiotensin-Aldosterone System

The 24-hour sleep/wake cycle in humans is intricately linked with homeostatic BP regulation.[28–31] As described above, normal sleep is accompanied by the so-called "dipping" of systolic and diastolic BP. A study by Charloux et al[29] that continuously recordedthe arterial BP of healthy volunteers using PSG identified this decrease in BP as the event that initiates a robust nocturnal elevation of plasma renin activity (PRA). Once sleep is initiated, sympatho-vagal balance is exquisitely modulated by the NREM-REM cycle, which is best quantified by assessing oscillations of EEG slow-wave activity using spectral analysis (Figure 2).[28] This oscillation drives an oscillation in PRA (Figure 3, upper panel)[3] and aldosterone (Figure 4, upper panel)[4] during sleep, with higher levels of PRA and aldosterone during SWS than during REM sleep. Both plasma renin and aldosterone exhibit these reproducible 24-hour variations, which are influenced by the timing, quantity and quality of sleep.[3;4] As shown in Figures 3 and 4 (lower panels), both PRA and aldosterone levels increase during nighttime and daytime sleep, and do not increase during a night of total sleep deprivation. Figure 5 shows the 24-hour profile of cardiac sympatho-vagal balance in healthy young participants after 6 days of bedtime restriction to 4 hours per night as compared to a fully rested condition.[25] It can be seen that sympathovagal balance is markedly elevated during most of the waking period, while the period of reduced activity during sleep is much shorter. These alterations are likely to have a direct adverse effect on the regulation of the renin-angiotensin-aldosterone system during wakefulness as well as during sleep. When sleep is shallow and fragmented, the nocturnal dipping of BP is absent or dampened and the sleep-related increase of renin and aldosterone are similarly affected.

A study by Sayk et al[31] showed that experimental SWS suppression reduced nocturnal BP dipping in healthy young adults. Thus, reduced sleep quality may decrease the normal nocturnal rise of PRA and aldosterone even if sleep duration is not affected, a fact of significant importance given the prevalence of poor sleep quality in patients with CKD. The relationship between sleep fragmentation caused by OSA and its subsequent effects on PRA have been well demonstrated in a study by Follenius et al,[5] in which participants with OSA were treated with CPAP and the subsequent fluctuations in PRA and aldosterone levels were measured. CPAP treatment was found to increase the nighttime PRA and aldosterone levels significantly, demonstrating that OSA was preventing the normal nocturnal regulation of these hormones. This chronobiological alteration in the activity of the renin-angiotensin-aldosterone system could play a role in CKD progression. Experimental models of kidney disease have shown that glomerular capillary hypertension, which is maintained largely by angiotensin-dependent mechanisms, ultimately leads to glomerular scarring and nephron dropout.[32]

OSA as a Direct Contributor to CKD Development and Progression

Specific features of OSA that are not present in other sleep disorders include intermittent hypoxia and re-oxygenation, nocturnal BP surges and nocturnal sympathetic activation. The cycles of hypoxia and re-oxygenation stimulate the formation of reactive oxygen species that promote inflammation and systemic endothelial dysfunction.[33;34] Endothelial dysfunction, inflammation, and oxidative stress all have adverse effects on kidney function.[35] A recent 6-year prospective study showed that endothelial dysfunction and inflammation predict the development of arterial stiffness in individuals without CKD.[36] Multiple studies have shown associations between OSA and arterial stiffness[37;38] and demonstrated that CPAP treatment of OSA can decrease arterial stiffness.[37] The association between OSA and arterial stiffness may have potential implications in CKD progression. A recent publication from the Multi-Ethnic Study of Atherosclerosis (MESA) reported that lower arterial elasticity was linearly and independently associated with faster kidney function decline.[39] It is speculated that reduced elasticity of major arteries can result in

microvascular damage and impair renal hemodynamics, and hence leads to compromised kidney function.

Early studies have suggested that patients with OSA have abnormalities in tubular function, leading to increased nocturnal natriuresis.[40;41] However, these studies were small and reported inconsistent findings. In contrast, there is limited but convincing evidence that OSA influences renal hemodynamics and that treatment with CPAP may ameliorate these effects. Kinebuchi et al[42] measured glomerular filtration rate (GFR) and renal plasma flow (RPF) in 27 patients with OSA before and after treatment with CPAP. After one week of treatment, GFR remained unchanged but RPF increased, which resulted in a small but significant decrease in filtration fraction. These findings are consistent with OSA-mediated vasoconstriction, which is attenuated by CPAP therapy.

A number of studies have investigated the link between OSA and proteinuria. Casserly et al[43] examined protein-creatinine ratios in 148 individuals referred for PSG and found no association between severity of OSA and proteinuria. These negative findings were contradicted by Faulx et al,[44] who performed an overnight PSG in 496 patients with mild-to-severe OSA and found that, after adjusting for body mass index (BMI), severe OSA (AHI≥30) was significantly associated with increased urine albumin excretion independently of GFR and of the presence of diabetes or hypertension. Glomerular endothelial dysfunction was proposed as the underlying mechanism for the elevated urinary albumin excretion. In another cross-sectional study, Tsioufis et al[45] compared 62 hypertensive patients with OSA and 79 hypertensive patients without OSA matched for age, sex, smoking status, BMI and 24-hour pulse pressure, and found that OSA was associated with a 57% elevation of albuminuria and that AHI was a significant predictor of albuminuria. In a subsequent study, Agrawal et al[46] performed PSG in 91 morbidly obese patients and found no differences in albuminuria in individuals with OSA (n=55) and without OSA (n=36), but detected a significant positive correlation between the severity of OSA and serum creatinine levels. Differences in these findings are likely related to differences in methodology and populations studied. Furthermore, it is difficult to assess the influence of OSA relative to that of obesity on CKD, despite statistical adjustment for BMI. Most likely, there is a complex interplay between these two factors and kidney function. Interestingly, however, an early small study[47] reported decreases in proteinuria with OSA treatment.

Based on the multiple negative effects of OSA on the systemic and renal vasculature, it is reasonable to speculate that OSA may be an independent risk factor for CKD progression. However, this association needs to be evaluated in a prospective study.

INDIRECT IMPACT OF SLEEP DISORDERS ON CKD: EFFECTS ON KNOWN RISK FACTORS

Overview

Research on the relationship between sleep, cardio-metabolic risk and endocrine function has become a fast growing topic in the last 10 years. Insufficient sleep and/or poor sleep quality have been shown to promote the risks of hypertension, type 2 diabetes and obesity, suggesting that sleep disturbance may be an important indirect contributor to both the development and progression of CKD. The following summarizes the associations that have been found between sleep and cardio-metabolic function that may be important in CKD.

Sleep disturbances and hypertension

It is well established that hypertension is a major risk factor for the development and progression of CKD[2] and that BP control, particularly with an angiotensin converting

enzyme inhibitor or an angiotensin receptor blocker can attenuate the progression of CKD.[48;49] Short sleep, poor sleep and OSA can all promote the risk of hypertension or exacerbate its severity. In the Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study,[50] shorter sleep duration and lower sleep maintenance assessed by actigraphy significantly predicted higher daytime systolic and diastolic BP cross-sectionally, and there were more adverse changes in systolic and diastolic BP over five years after excluding patients taking anti-hypertensive medications and adjusting for age, race and sex. Short sleep duration also significantly predicted increased odds of incident hypertension (OR, 1.37; 95% CI, 1.05–1.78). In NHANES, short sleep duration by self-report also predicted the development of hypertension.[51] Further, a recent prospective study in older men showed that those with low amounts of SWS were more likely to develop hypertension.[52]

Several studies have demonstrated that poor sleep quality is associated with a blunting of the nocturnal dip in BP in participants with normal kidney function.[31;53] Correlations between objectively assessed sleep quality and BP dipping have actually been documented in CKD patients. Indeed, a study by Agarwal et al[53] used wrist actigraphy monitoring to demonstrate that the sleep fragmentation associated with nocturia in patients with CKD (eGFR <60mL/min per 1.73 m^2) was positively correlated with a blunted night-time BP drop; individuals with increased activity due to nocturia were shown to have a decreased dip in their night-time BP.

Lastly, OSA is a well-documented risk factor for hypertension. The prospective analysis of the Wisconsin Sleep Cohort Study showed an increased risk of developing hypertension nearly threefold higher for those with clinically significant OSA.[54] In addition, OSA has been independently linked to specific cardiovascular outcomes such as stroke, myocardial ischemia, arrhythmias, cardiovascular events, and all-cause mortality.[55] These findings suggest that sleep disorders, particularly OSA, might contribute to increased cardiovascular risk in patients with CKD.

Sleep Disturbances and glucose intolerance

A large body of laboratory and epidemiologic research on the relationship between sleep and glucose metabolism has demonstrated that sleep quality and quantity play an integral role in glucose regulation.[56–60] Specifically, experimentally reduced sleep quantity or increased sleep fragmentation have both been shown to significantly increase insulin resistance without appropriate compensation by increased insulin release in healthy participants. In a study by Spiegel et al,[56] healthy young men were restricted to 4 hours of sleep per night for 6 nights, which resulted in a decrease in glucose tolerance consistent with pre-diabetes. A recent meta-analysis of prospective studies examining the impact of short sleep duration or reduced sleep quality on the incidence of type 2 diabetes concluded that, after controlling for multiple confounders, short sleepers were 28% more likely to develop diabetes, whereas difficulty in initiating or maintaining sleep was associated with an even higher risk of diabetes.[58] A subsequent analysis of the National Institutes of Health-American Association of Retired Persons Diet and Health Study, which involved nearly 175,000 individuals, found that the relative risk of developing type 2 diabetes over the 5- to 10-year follow-up period was 46% higher in those sleeping 5 hours or less than in those sleeping 7 to 8 hours.[61] Furthermore, two prospective studies have found that the presence of OSA independently increases the risk of developing diabetes.[59;60]

There is also good evidence indicating that sleep disturbances exacerbate the severity of diabetes. A study by Knutson et al[59] demonstrated that in diabetic patients, reduced self-reported sleep duration and quality are significant predictors of poorer glycemic control. More recently, OSA was found to affect 53% to 87% of patients with diabetes and a “dose-

response" relationship between the severity of OSA and hemoglobin A1c levels was evidenced.[60] Lastly, the presence of insomnia in diabetic patients was found to be associated with markedly higher blood glucose levels.[62]

In summary, multiple studies have suggested that poor sleep quantity and quality are significant risk factors for type 2 diabetes, an important consideration for CKD in light of the close association between diabetes and CKD. The current data also indicate that sleep disturbances have an adverse impact on glycemic control in diabetic patients and would thus exacerbate this frequent co-morbidity of CKD.

Sleep and Obesity

Closely linked with the aforementioned association between sleep and diabetes is that of sleep and obesity. There is increasing evidence that obesity may be an independent risk factor for CKD and its progression to kidney failure and the need for dialysis.[63;64] In healthy lean young adults, curtailing sleep has an important impact on the neuroendocrine control of satiety and hunger, promoting excessive eating.[25] Leptin, a hormone that is an important satiety factor in mammals, was found to be decreased in patients whose sleep had been shortened, while levels of ghrelin, a hunger hormone, were markedly increased; as a consequence, hunger ratings increased, suggesting that reduced sleep quantity could promote weight gain. Sleep restriction in middle-aged overweight adults was indeed shown to increase food intake from snacks.[65] Further, when healthy volunteers who had had bedtimes restricted to 4 h per night for 5 nights were presented with ad libitum food, they ingested nearly 300 kcal more than when they had 8 h bedtimes.[66]

There is an abundance of epidemiologic studies showing an association between short sleep and elevated BMI, after controlling for multiple confounders. The impact of sleep quality on the risk of obesity has been explored in fewer studies, but all studies to date have had positive findings. The association between sleep and obesity is very relevant for CKD because of the high rate of obesity amongst patients with CKD and the emerging evidence that obesity, an inflammatory state, may in itself have an adverse impact on kidney function. Furthermore, obesity is the major risk factor for OSA and its cardio-vascular consequences, including the risk of hypertension and its deleterious effects on kidney function.

CONCLUSION

Research in the last decade has demonstrated that sleep disturbances promote the development and exacerbate the severity of three well-documented risk factors for CKD: diabetes, hypertension and obesity. Furthermore, a tight link between the renin-angiotensin-aldosterone axis and sleep has been demonstrated, and a plausible direct deleterious impact of OSA on kidney function has been proposed. Taken together, these findings strongly suggest that sleep disturbances may represent a novel risk factor for the progression of CKD. Identifying and treating sleep disorders may have a therapeutic benefit in CKD.

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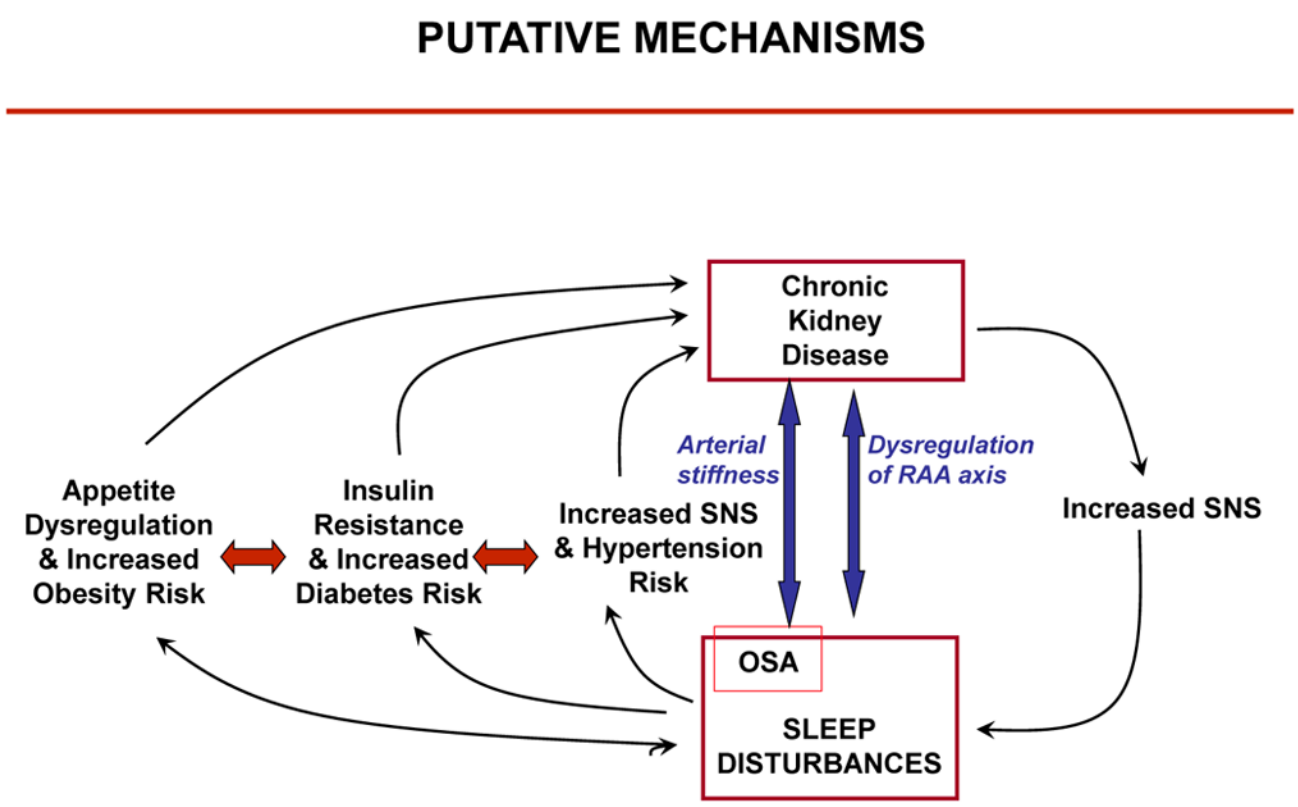

Figure 1.
Putative mechanisms linking sleep disturbances and progression of CKD. Abbreviations: SNS, sympathetic nervous system activity; OSA, obstructive sleep apnea.

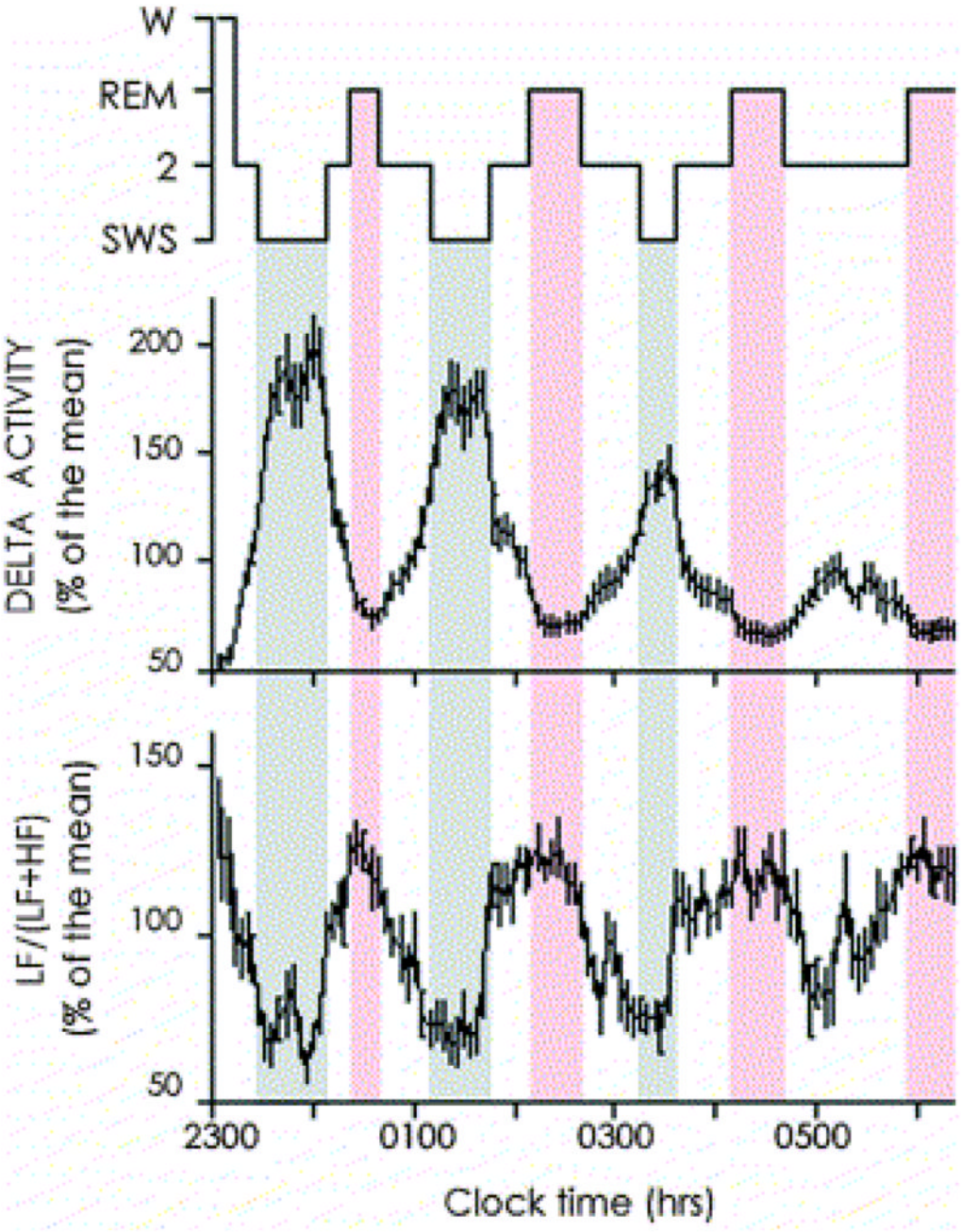

Figure 2.

Inverse relationship between the intensity of NREM sleep, assessed by EEG spectral activity in the delta frequency band (top), and cardiac sympatho-vagal balance, assessed via spectral analysis of heart rate variability. Recordings were obtained in healthy young adults. Values reported are mean ± standard error of the mean. Reproduced from Brandenberger et al[28] with permission from the International Federation of Clinical Neurophysiology

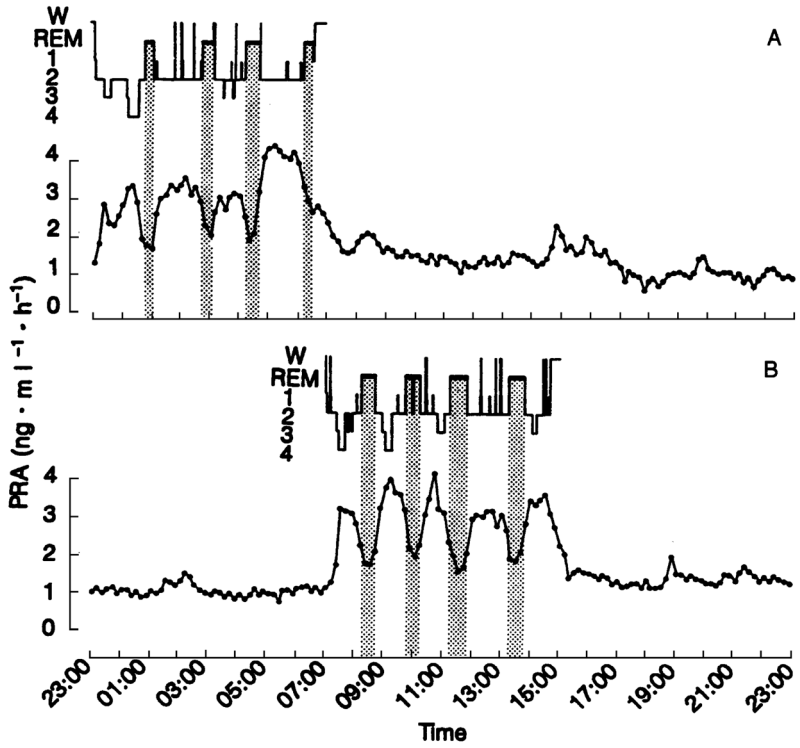

Figure 3.

24-hour profile of plasma renin activity (PRA) in an apparently healthy young adult studied once with sleep at the usual nocturnal time (A) and once with sleep deprivation during the night and recovery sleep in the daytime (B). The shaded area indicates REM stages . Reprinted from Brandenberger et al[3] with permission from Wolters Kluwer Health.

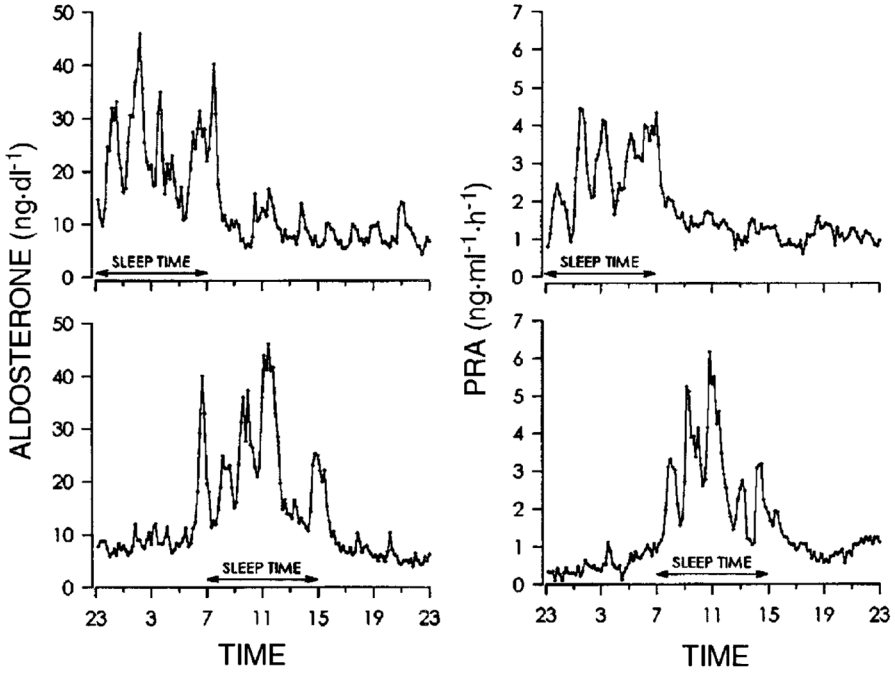

Figure 4.

24-hour profile of plasma aldosterone levels (left) and plasma renin activity (PRA; right) in an apparently healthy young adult studied once with sleep at the usual nocturnal time (upper panels) and once with sleep deprivation during the night and recovery sleep in the daytime (lower panels). Reproduced from Charloux et al[4] with permission from the American Physiological Society.[4]

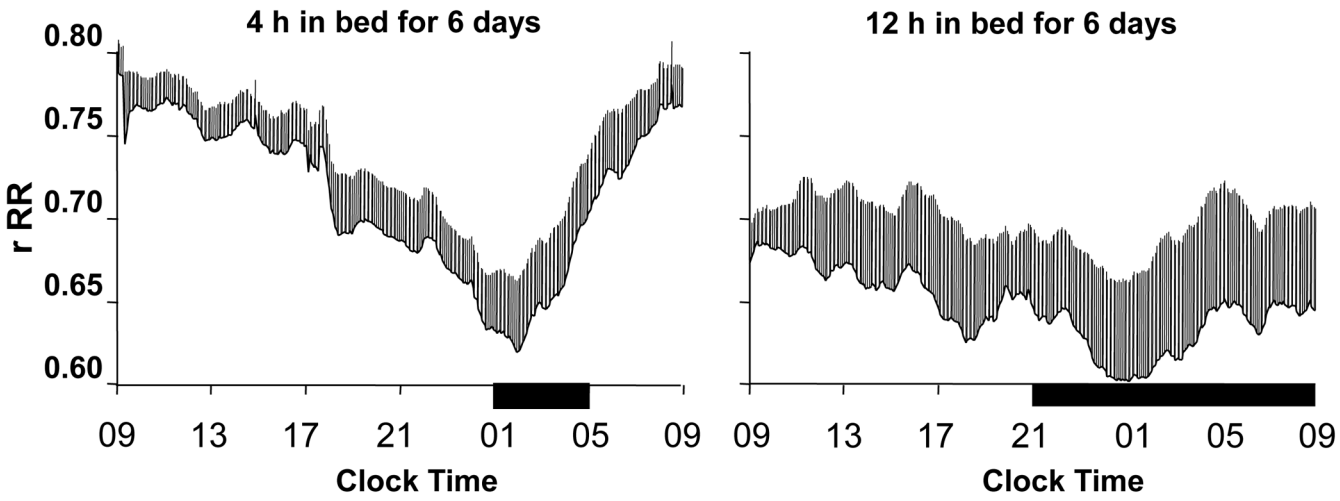

Figure 5.

Impact of sleep duration on cardiac sympathovagal balance. Mean (+standard error of the mean) 24-hour profiles of sympathovagal balance (estimated at 5-min intervals using the coefficient of autocorrelation of successive cardiac interbeat intervals rRR; E panels), when time in bed is 4 hours for 6 consecutive nights (left; mean total sleep time during night 6) or 12 hours for 6 consecutive nights (right; mean total sleep time during night 6). Particpants were 11 young healthy men. The black bars represent the sleep periods. Reproduced from Spiegel et al[25] with permission from the Endocrine Society.[25]

Table 1

Summary of Representative Sleep Studies in Non-dialysis-dependent CKD

Study	Participants	CKD Stage	Results
Diagnosed via questionnaire			
Iliescu et al, 2004[67]	120 CKD	2–5	prevalence of disordered sleep by PSQ[a]: 53%; no association with CCr
Kurella et al, 2005[68]	78 CKD; 78 HD	3–4	prevalence of disturbed sleep maintenance by KDQOL[b]: 14–27% in CKD, 34% in HD
Cohen et al, 2007[12]	92 CKD; 61 non-CKD	2–5	prevalence of disordered sleep by PSQ: 55% in CKD (NS difference with non-CKD)
Sabbatini et al, 2008[69]	78 CKD	3–5	prevalence of disordered sleep by PSQ: 50%; sleep quality worsened as eGFR declined over time, but association NS after adjusting for confounders
De Santo et al, 2008[70]	124 CKD	2–3	prevalence of insomnia by Sleep Disorders Questionnaire: 57%
Kumar et al, 2010[71]	673 CKD	3–5	prevalence of poor sleep quality by KDQOL: 57%; no association with eGFR
De Santo et al, 2010[13]	220 CKD; 220 Hep C	1–3	prevalence of disordered sleep by PSQ: 85% in CKD, 60% in Hep C
Plantinga et al, 2011[72]	1805 CKD; 7305 non-CKD	1–4	Prevalence of short sleep duration (≤6 h) by NHANES[f]: 43% in CKD1–2, 31% in CKD3–4, 37% in non-CKD
Diagnosed via wrist actigraphy			
Barmar et al, 2009[14]	36 CKD; 51 HD	4–5	Reduced sleep duration and efficiency in both CKD and HD but worse in HD
Agarwal et al,2011[15]	145 CKD; 116 HD; 19 Non- CKD	3	Lower sleep efficiency and higher sleep fragmentation in CKD vs non-CKD
Diagnosed via PSG			
Kimmel et al, 1989[73]	8 CKD; 20 HD	5	prevalence of sleep apnea: 73% in patients with sleep apnea symptoms (16/22)
Parker et al, 2005[74]	8 CKD; 16 HD	4–5	Reduced total sleep time and efficiency in CKD and HD but worse in HD
Markou et al, 2006[17]	35 CKD	3–5	prevalence of sleep apnea: 54%; of periodic limb movements: 29%; no association between AHI[c] and CCr
Fleischmann et al, 2010[16]	18 CKD; 140 non-CKD[e]	3	prevalence of sleep apnea[d]: 94% in CKD, 83% in non-CKD (NS)
Roumelioti et al,2011[75]	89 CKD; 75 HD; 224 non-CKD	4–5	Risk of severe sleep-disordered breathing significantly higher in CKD and HD vs non-CKD

[a] PSQ= Pittsburgh Sleep Questionnaire, threshold for disordered sleep is PSQ index > 5.

[b] KDQOL=Kidney Disease Quality of Life.

[c] AHI= Apnea-hypopnea index ≥5

[d] Sleep apnea defined as the respiratory disturbance index (RDI) > 5.

[e] non-CKD patients had been referred for sleep study

[f] the NHANES sleep quality questionnaire

Abbreviations: CCr, creatinine clearance; CKD, chronic kidney disease; Hep C, hepatitis C; HD, hemodialysis; NS, nonsignificant; PSG, polysomnography