Daytime sleepiness, also known as hypersomnolence, is common among patients receiving maintenance dialysis and following successful kidney transplantation. Sleepiness may be secondary to medical comorbid conditions, medication side effect, insufficient sleep syndrome, and sleep-disordered breathing or the result of a primary central disorder of hypersomnolence, such as narcolepsy. Unrecognized and untreated sleep disorders are associated with substantial morbidity and mortality among patients with end-stage kidney disease. Effective management of hypersomnolence can improve quality of life in patients with kidney disease. This review focuses on the principal causes of sleepiness in patients with end-stage kidney disease. Awareness of these disorders by treating nephrologists is crucial. This review provides a systematic approach to guide providers through the recognition, early diagnosis, and treatment of hypersomnolence, which is commonly encountered in this patient population. Areas of future research are also suggested.

Clinical Vignette
PJ is a 52-year-old woman with end-stage kidney disease (ESKD) in the setting of long-standing type 2 diabetes mellitus and hypertension who has been receiving in-center hemodialysis for the past 2 years. She reports chronic fatigue, difficulty concentrating, and trouble staying awake. She has been falling asleep while using the computer and recently received a formal warning at work. She states that she has fallen asleep at the dinner table and while talking on the telephone with friends. She usually retires to bed at 11:00 PM and falls asleep with the television on after midnight. She has 1 to 2 brief nocturnal awakenings and wakes up at 5:00 AM on dialysis days. On nondialysis weekdays, she wakes up at 10:00 AM to get to her part-time job. She sleeps until noon on weekends. On her last vacation, her sister commented about her loud snoring. She drinks 4 cups of coffee daily to stay awake. Dialysis has been going well, and last month’s delivered Kt/V was 1.4. Her diabetes is well-controlled with low-dose insulin, but her blood pressure remains elevated at 149/82 mm Hg despite good adherence to treatment with 3 antihypertensive agents. Her body mass index is 29 kg/m². She is currently active on the kidney transplant waiting list.

Introduction
Sleep concerns are common in patients with ESKD.1-3 Contributing factors include physiologic changes related to reduced kidney function, dialysis-related disruption in homeostatic sleep rhythm, poor sleep hygiene, and medication side effects.1-3 The prevalence of sleep disorders in patients receiving maintenance dialysis is reported to be as high as 80%.4 Sleep disorders may present with symptoms of sleepiness, also known as hypersomnolence, defined as an increased tendency to fall asleep. Conversely, trouble falling and/or staying asleep despite ample sleep opportunity is the hallmark of insomnia. Both hypersomnolence and insomnia often substantially affect the quality of life and overall health of patients requiring kidney replacement therapy. The approach to sleep disorders associated with insomnia symptoms, which include primary insomnia disorder, restless legs syndrome, and periodic limb movement disorder, is covered in a recent review in this journal.5 Of note, restless legs syndrome and periodic limb movement disorder contribute to unrefreshing sleep and fatigue and are generally considered to be causes of insomnia. However, some patients with these disorders will misclassify their tiredness and report sleepiness although they do not have an increased tendency to fall asleep or prolonged sleep time.

Given the high prevalence and significant impact of sleep disorders on health and well-being, it is important that providers recognize their symptoms (Box 1) and use a systematic approach to their evaluation and treatment (Fig 1). When available, collaboration with a sleep medicine physician is recommended. This review focuses on hypersomnolence and aims to provide an
approach to the patient with ESKD who presents with this disorder (Table 1).

**Approach to the Patient Presenting With Sleepiness**

The first consideration for a patient presenting with a report of sleepiness is to determine whether she or he is getting enough sleep (Fig 1). Insufficient sleep is defined as failure to obtain adequate sleep to maintain normal levels of alertness and wakefulness despite having sufficient sleep opportunities. The American Academy of Sleep Medicine and Sleep Research Society currently recommend at least 7 hours of sleep per night for adults. Patients receiving dialysis often experience reduced sleep quality and total sleep time compared with healthy individuals. The rate of disturbed sleep is reported to be as high as 52%, and daytime sleepiness has been observed in 67% of patients receiving dialysis. If the patient is sleep deprived, he or she must be encouraged to get more sleep to avoid negative consequences (Fig 1).

Chronic insufficient sleep not only negatively affects quality of life and cognitive function but can also have detrimental effects on metabolism and cardiovascular health. Sleep deprivation is associated with alterations in glucose metabolism and increased appetite stimulation by affecting the secretion of leptin and ghrelin, which may result in insulin resistance and obesity. Additionally, multiple investigators have found links between insufficient sleep and increased levels of inflammatory cytokines, most notably interleukin 6 and C-reactive protein. Insufficient sleep is also associated with increased risk for cardiovascular disease, including myocardial infarction, stroke, and angina. Given the already complex relationship between ESKD and cardiovascular disease, recognition of insufficient sleep and efforts to extend total sleep time are especially important in this population.

**Sleep and Dialysis**

Providers should consider whether patient reports of sleepiness are due to irregular sleep schedules, which may occur in patients who sleep during the day while receiving dialysis and report being unable to sleep at night, leading to a cycle of daytime sleepiness followed by a lack of nocturnal sleep onset. These patients may raise insomnia as a concern. Unlike patients with primary insomnia who have difficulty obtaining adequate hours of sleep when provided with ample opportunities and conditions for sleep, patients with irregular sleep schedules are able to obtain adequate sleep, albeit at inconvenient and undesired times. Furthermore, patients with primary insomnia will often overcompensate by spending extended periods awake in bed. A typical patient with insomnia spends 10 or more hours in bed but gets a mere 4 to 5 hours of fragmented sleep. In contrast, a patient who sleeps for 4 to 5 hours during dialysis and then is only able to sleep for 3 to 4 hours overnight is obtaining 8 hours of sleep in a 24-hour period. This latter pattern is related to inadequate sleep hygiene.

Hemodialysis can adversely affect sleep through direct and indirect mechanisms. Dialysis directly affects the production of melatonin, a hormone produced by the pineal gland to help promote sleep and maintain circadian rhythm. Several studies have demonstrated a lack of nocturnal melatonin surge in patients receiving daytime hemodialysis, which can contribute to sleep disturbance. Supplementation of exogenous melatonin in dialysis patients resulted in improved sleep quality in a randomized controlled trial. Hemodialysis has also been associated with delayed sleep onset and decreased nighttime sleep by increasing daytime sleep propensity. Exposure of blood to certain dialyzers activates an inflammatory pathway involved in the release of interleukin 1, which is associated with sleep induction. Furthermore, heat load from the dialysate may increase body temperature, triggering intrinsic cooling mechanisms that enhance daytime sleepiness. Indirect effects of early-morning dialysis treatment sessions on patients’ wake time and exposure to bright light contribute to a decrease in total sleep time. Patients assigned to the earliest and latest dialysis treatments exhibit the greatest sleepiness, as measured using the Epworth Sleepiness Scale (ESS). Similarly, patients receiving peritoneal dialysis experience reduced total sleep time and sleep fragmentation. However, the effect of melatonin suppression described in patients receiving hemodialysis is attenuated in patients receiving peritoneal dialysis. All these factors have the potential to contribute to excessive daytime sleepiness in patients with ESKD.

**Poor Sleep Hygiene**

Sleep quality is a multifactorial phenomenon influenced by various internal and external factors. The term sleep hygiene comprises a series of recommendations to promote better sleep quality that are summarized in Box 2. Attention to sleep hygiene is an integral component of behavioral therapy for sleep concerns. Poor sleep hygiene can make it more difficult for patients with ESKD to

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**Box 1. Factors Suggestive of a Sleep Disorder in Patients With Sleepiness and ESKD**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring</td>
</tr>
<tr>
<td>Witnessed apneas</td>
</tr>
<tr>
<td>Choking or gasping for air at night</td>
</tr>
<tr>
<td>Frequent spontaneous nocturnal awakenings</td>
</tr>
<tr>
<td>Morning headaches</td>
</tr>
<tr>
<td>Hypnagogic (ie, at sleep onset) or hypopomic (ie, upon awakening) hallucinations</td>
</tr>
<tr>
<td>Sleep paralysis</td>
</tr>
<tr>
<td>Cataplexy</td>
</tr>
<tr>
<td>Regular sleep time and duration that does not conform to desired sleep time</td>
</tr>
</tbody>
</table>

Abbreviation: ESKD, end-stage kidney disease.
fall asleep and obtain good-quality sleep at night. Dialysis-
related factors, such as early awakenings for and naps
during dialysis sessions can worsen nocturnal sleep quality
and quantity in patients with ESKD. Specifically, patients
may have trouble falling or staying asleep and report sleep
fragmentation with multiple spontaneous arousals of var-
iable duration throughout the night. Therefore, education
about proper sleep hygiene, including keeping a regular
sleep schedule and avoiding activities that promote
wakefulness while in bed (eg, watching television) may
improve quality of sleep and should arguably be a part of
routine dialysis patient education.

Returning to the patient described in the clinical
vignette, PJ is advised to increase her sleep amount so that
she gets at least 7 hours of sleep each day and improve her
sleep hygiene by choosing consistent daily bed and wake
times, avoiding afternoon naps, and reducing caffeine
intake after lunch.

**Common Causes of Sleepiness in Non–Sleep-
Deprived Patients With ESKD**

For individuals who are obtaining adequate sleep yet
report sleepiness, other causes of their hypersomnolence
should be considered (Fig 1). Common medical causes of
sleepiness despite adequate sleep duration within a 24-
hour period include anemia, hypothyroidism, mood dis-
orders, and medication effects (Table 2), and these factors
should be considered and treated. If sleepiness persists, a
more focused evaluation for sleep disorders is warranted.

Medical history and physical examination of the patient
presenting with hypersomnolence are useful. History
should include information about sleep habits, sleep duration, and caffeine intake (Box 3). The patient should complete an ESS.20 A total score greater than 10 indicates subjective sleepiness. Additional symptoms can be elicited based on the level of concern for a specific sleep disorder (Table 1). Questionnaires, such as the STOP-Bang, can assist with screening for obstructive sleep apnea (OSA).25 Physical examination should include assessment of blood pressure, body mass index, and neck circumference. These components of the examination can be easily performed to help risk stratify those at increased risk for OSA and suggest some of the more common causes of sleepiness commonly seen in patients with ESKD (Fig 1).

**Sleep-Disordered Breathing**

OSA occurs in the presence of repetitive partial or complete upper airway compromise during sleep, leading to reduced or absent airflow. These obstructive events may be associated with oxyhemoglobin desaturation and are often terminated by arousals. Patients with OSA present with snoring, daytime fatigue, and witnessed apneas at night. Many will report multiple nocturnal awakenings with nocturnal gasping and choking, which contribute to feeling unrefreshed on awakening despite adequate sleep duration.

The diagnosis of OSA may be further supported by determination of the STOP-Bang score.25 Although there are limited data for its validity in patients with ESKD, the

<table>
<thead>
<tr>
<th>Sleep Disorders</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient sleep syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Daily irrepressible need to sleep; short sleep time (for age); present for most days for ≥3 mo; extending total sleep time leads to improvements in symptoms; exclusion of other sleep disorders, medications, or medical disorder</td>
<td>Extension of total sleep time to ≥7 h per night, based on individual sleep needs</td>
</tr>
<tr>
<td>Poor sleep hygiene&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Inconsistent sleep/wake schedule; stimulating activities before bedtime; frequent naps; consumption of products that disrupt sleep; bright light exposure around bedtime; noisy or hot sleep environment</td>
<td>See Box 2</td>
</tr>
<tr>
<td>Sleep-disordered breathing: OSA and CSA</td>
<td>Daytime sleepiness despite adequate sleep amounts, witnessed apneas, snoring, or comorbid conditions (hypertension, mood disorder, CAD, stroke, CHF, atrial fibrillation, cognitive dysfunction, or T2DM); PSG (or HSAT) with AHI (or REI) ≥ 5 events/h</td>
<td>OSA: PAP; mandibular advancement devices; positional therapy; upper airway surgery; hypoglossal nerve stimulation CSA: optimize volume status, PAP therapy, consider ASV in appropriate patients</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Periodic irrepressible need to sleep; MSLT with sleep latency ≤ 8 min and ≥2 sleep onset REM periods; type 1 is presence of cataplexy; type 2 is absent cataplexy</td>
<td>Behavioral (scheduled naps, sleep hygiene); pharmacologic treatment directed at sleepiness (stimulants, sodium oxybate); pharmacologic treatment directed at cataplexy, if present (selective serotonin reuptake inhibitors, serotonin-norepinephrine uptake inhibitors, sodium oxybate)</td>
</tr>
<tr>
<td>Idiopathic hypersomnia</td>
<td>Periods of irrepressible need to sleep; lack of cataplexy; MSLT without 2 sleep-onset REM periods; MSLT with mean sleep latency ≤ 8 min; rule out other causes of hypersomnolence</td>
<td>Sleep hygiene, scheduled naps, stimulants</td>
</tr>
<tr>
<td>Circadian rhythm sleep disorders&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Misalignment in sleep and wake propensity that interferes with school, work, or social activities</td>
<td>Melatonin with light therapy, chronotherapy, hypnotics in jet lag or shift work disorder</td>
</tr>
<tr>
<td>Nonsleep disorders</td>
<td>Hypothyroidism, depression, CHF, rheumatologic diseases, vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency, stroke, neurodegenerative diseases, anemia</td>
<td>Targeted treatment for each disorder</td>
</tr>
</tbody>
</table>

**Table 1. Differential Diagnosis of Sleepiness/Hypersomnolence in Patients With ESKD**

**Box 2. Sleep Hygiene Recommendations**

- Keep constant daily sleep-wake schedule
- Avoid being in bed for activities other than sleeping or sex
- Avoid naps in the late afternoon (eg, after 3:00 PM)
- Avoid products that cause sleep disturbance (including alcohol, caffeine, nicotine)
- Avoid exercising within 3 h of bedtime
- Avoid large meals within 3 h of bedtime
- Maintain cool quiet environment for sleep
- Remove clocks from bedroom
- Avoid using electronics or watching television in bed

**Box 3. In Practice**

- Reference to additional resources and guidelines for sleep hygiene.

**Abbreviations:** AHI, apnea-hypopnea index; ASV, adaptive servo-ventilation; CAD, coronary artery disease; CHF, congestive heart failure; CSA, central sleep apnea; ESKD, end-stage kidney disease; HSAT, home sleep apnea test; MSLT, multiple sleep latency test; OSA, obstructive sleep apnea; PAP, positive airway pressure; PSG, polysomnogram; REI, respiratory event index; REM, rapid eye movement; T2DM, type 2 diabetes mellitus.

<sup>a</sup>Increased prevalence in patients with ESKD.

<sup>b</sup>Refer to Table 3 for different types of circadian rhythm sleep disorders.
STOP-Bang questionnaire is a well-validated OSA screening tool for use in obese individuals. A total score of 3 (ranging from 0–6) has sensitivity of 90.5% (95% confidence interval [CI], 86.2%–93.8%) and positive predictive value of 84.8% (95% CI, 80%–88.9%) in detecting all OSA, and sensitivity of 100% (95% CI, 95.5%–100%) in detecting severe OSA. In a small sample of patients with ESKD, the STOP-Bang score demonstrated 94% sensitivity and 29% specificity in detecting moderate OSA. Additional studies are needed to further assess its utility in this population.

A formal diagnosis of OSA is made using a polysomnogram or home sleep apnea test. During each study, respiratory events are noted and characterized. Determination of OSA involves identification of obstructive apneas (defined as cessation of airflow for at least 10 seconds despite continued respiratory effort) and obstructive hypopneas (defined as reduction of airflow by >30% of baseline for at least 10 seconds despite continued respiratory effort with a 3%–4% decrease in oxyhemoglobin desaturation or an arousal). The polysomnogram reports an apnea-hypopnea index (AHI), which refers to the total number of apnea and hypopnea events per hour of sleep. The home sleep apnea test provides a respiratory event index, which corresponds to the total number of respiratory events per hour of recording time. The respiratory event index in-home sleep apnea test is considered a surrogate for the AHI. Both studies can be used to diagnose OSA (≥5 events per hour) and aid in the determination of its severity (5–15, 16–30, and >30 events per hour for mild, moderate, and severe, respectively).

### Table 2. Medications That Can Contribute to Sleepiness in Dialysis Patients

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Opioids (ie, oxycodone, codeine)</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants (ie, gabapentin, pregabalin)</td>
</tr>
<tr>
<td></td>
<td>Muscle relaxants (ie, cyclobenzapirone)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Antihistamines (ie, diphenhydramine, brompheniramine, hydroxyzine)</td>
</tr>
<tr>
<td></td>
<td>Hypnotics (ie, zolpidem, eszopiclone)</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines (ie, alprazolam, temazepam, diazepam)</td>
</tr>
<tr>
<td></td>
<td>Atypical antidepressants (ie, trazodone, mirtazapine)</td>
</tr>
<tr>
<td>Depression/ anxiety</td>
<td>Benzodiazepines (ie, alprazolam, lorazepam)</td>
</tr>
<tr>
<td></td>
<td>Selective serotonin reuptake inhibitors (ie, paroxetine, citalopram)</td>
</tr>
<tr>
<td></td>
<td>Atypical antidepressants (ie, trazodone, mirtazapine)</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics (ie, quetiapine)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Antiemetics (ie, ondansetron, prochlorperazine)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>Antihistamines (ie, diphenhydramine, brompheniramine, hydroxyzine)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>ß-Blockers (ie, carvedilol)</td>
</tr>
<tr>
<td></td>
<td>Central α2-agonists (ie, clonidine)</td>
</tr>
</tbody>
</table>

### Box 3. Components of the History and Physical Examination in Sleepy Patients

**Sleep habits**
- Use of electronics (cell phone, television, tablets, computer)
- Caffeine intake
- Nicotine exposure
- Dinner within 3 h of bedtime
- Exercise within 3 h of bedtime
- Bedroom temperature and lighting

**Sleep history**
- Time to bed
- Sleep latency
- Frequency of nocturnal awakenings
- Nocturia
- Sleep latency after an arousal
- Awake time
- Duration and frequency of daytime naps
- Total sleep time in 24 h

**Physical examination**
- Body mass index (BMI) (>35 kg/m²)
- Neck circumference (≥17 in for men and ≥16 in for women)
- Blood pressure (SBP ≥ 130, DBP ≥ 90 mm Hg)

**Epworth Sleepiness Scale; assessment of sleepiness**

<table>
<thead>
<tr>
<th>Likelihood of falling asleep reported, on a scale of 0 (low) to 3 (high):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
</tr>
<tr>
<td>Watching television</td>
</tr>
<tr>
<td>Sitting, inactive in a public place</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
</tr>
</tbody>
</table>

**STOP-Bang Questionnaire: assessment of OSA risk**

<table>
<thead>
<tr>
<th>Each category, scored 0 (none) to 1 (present):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring: loud snoring</td>
</tr>
<tr>
<td>Tired: feeling fatigued or sleepy during the day</td>
</tr>
<tr>
<td>Observed: apneic episodes, choking/gasping episodes</td>
</tr>
<tr>
<td>Pressure: high blood pressure diagnosis</td>
</tr>
<tr>
<td>Body mass index &gt; 35 kg/m²</td>
</tr>
<tr>
<td>Age (&gt;50 y)</td>
</tr>
<tr>
<td>Neck circumference (male: ≥17 inches, female: ≥16 inches)</td>
</tr>
<tr>
<td>Gender: male</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; OSA, obstructive sleep apnea; SBP, systolic blood pressure.

Risk factors for OSA in the general population include obesity, male sex, older age, postmenopausal state, and African American race. Patients with ESKD are more likely to develop OSA, and the prevalence of OSA is reported to be as high as 57% in patients receiving dialysis compared to 6% to 17% in the general population. A variety of factors lead to the increased risk for...
OSA in this population. Patients with ESKD have narrower pharyngeal areas compared with patients with normal kidney function. Fluid status and rostral fluid shift in the supine position during normal sleep contribute to soft tissue edema in patients with OSA, and this physiology may be exaggerated in patients with ESKD. In addition, uremic myopathy and neuropathy can weaken the upper airway muscles and further reduce airway size. More frequent or longer dialysis sessions that lead to greater fluid removal, including nocturnal dialysis and peritoneal dialysis, have been shown to improve AHI in patients with ESKD and concomitant OSA.

Untreated OSA is associated with increased metabolic and cardiovascular morbidity and mortality. Hypoxia-induced increases in sympathetic tone have the potential to increase blood pressure through activation of the renin-angiotensin-aldosterone system, leading to persistent hypertension. In addition, hypoxia-induced free radical production and endothelial dysfunction may favor the development of atherosclerosis and fibrosis in the cardiovascular and renal systems. Additionally, untreated OSA has been linked to insulin resistance. More frequent obstructive events and hypoxia are associated with impaired glucose tolerance, and patients with OSA have higher fasting glucose levels. Therefore, recognition and treatment of OSA is especially important in the ESKD population, who are already at increased risk for negative cardiovascular and metabolic outcomes.

The myriad treatment modalities of OSA aim to normalize the AHI and oxygen saturation and improve sleep quality. Positive airway pressure, which maintains airway patency by using air pressure to stent the upper airway, is considered the first-line therapy for patients with moderate to severe OSA. Use of positive airway pressure has been shown to improve blood pressure in patients with OSA, especially those with resistant hypertension. The main limitation of this therapy is adherence, defined as more than 4 hours per night for at least 70% of 30 consecutive nights. Although no specific data exist regarding adherence in the ESKD population, non-adherence in the general population can range from 29% to 83%. Smaller nasal cross-sectional area, presence of claustrophobia, initial difficulty when trying out continuous positive airway pressure machines, and impediments when applying the mask (eg, upper extremity weakness) have been associated with worse adherence. Close follow-up in these subpopulations of patients is warranted to maximize adherence. Additional treatment modalities include positional therapy, mandibular advancement devices, and a variety of surgical procedures involving the upper airway, including implantation of a hypoglossal nerve stimulator. These treatments may be considered in patients who are intolerant of or decline positive airway pressure therapy. In addition, all patients with OSA should be counseled regarding diet and exercise because evidence supports weight loss as a successful treatment for OSA.

Central sleep apnea (CSA) refers to an abnormal central drive to breathe, leading to lack of breath initiation, and is less common than OSA. Unlike obstructive apneas, central apneas on polysomnogram or home sleep apnea testing are scored when there is a cessation of airflow for at least 10 seconds without associated respiratory effort. Although its prevalence in ESKD is not well studied, CSA has been associated with chronic kidney disease (CKD). In a cohort of patients screened for OSA, the odds ratio of central sleep apnea in those with versus without non–kidney replacement therapy–requiring CKD was found to be as high as 5.16; prevalence has been estimated at 10%. Fluid overload and pulmonary congestion, both common in patients with CKD, have been postulated to stimulate the vagal nerve, triggering central apneic events. Patients with CSA present similarly to those with OSA, and evaluation and management are focused on identifying and treating the root cause and, when necessary, providing standard modes of positive airway pressure therapy, often with a back-up rate. Adaptive servoventilation, which is an alternative form of positive airway pressure treatment that continuously monitors the patient’s breath-to-breath status and adapts the support provided accordingly, may be considered for treatment of CSA in the absence of significant heart failure.

It is important to recognize the clinical presentation of sleep-disordered breathing in patients with ESKD and earlier stages of CKD and provide appropriate diagnosis and treatment, which may include referral to a sleep specialist.

Primary Sleep Disorders as Causes of Sleepiness

Nephrologists should also be familiar with the primary sleep disorders that cause hypersomnolence in the general population but are not necessarily more common among patients with kidney disease. Narcolepsy is a central disorder of hypersomnolence caused by dysregulation of rapid eye movement (REM) sleep. This condition affects 1 in 2,000 to 3,000 people in the United States and often leads to significant impairment in quality of life. The prevalence of narcolepsy in those with ESKD is not well characterized but has been reported to be 1.4%. Patients with narcolepsy typically report excessive daytime sleepiness despite adequate sleep duration. Narcolepsy often presents in the second or third decade of life and may be associated with a decline in school or work performance and an increase in sleep-related motor vehicle accidents. Unlike patients with OSA or idiopathic hypersomnia, patients with narcolepsy feel refreshed upon waking from the nocturnal sleep period and particularly after short naps. Cataplexy, characterized by sudden episodes of partial or complete...
loss of muscle tone associated with extreme emotions, is a pathognomonic feature found in patients with narcolepsy type 1, distinguishing this sleep disorder from narcolepsy type 2. Patients can also experience a dreamlike state or paralysis during transition from sleep or wake, known as hypnagogic hallucinations and sleep paralysis, respectively.

Confirmation of the diagnosis requires an overnight polysomnogram, followed by a multiple sleep latency test, which consists of four 20-minute nap trials at set times over the day. The findings of a mean sleep-onset latency across all naps of less than 8 minutes, along with the presence of at least 2 sleep-onset REM periods, are consistent with a diagnosis of narcolepsy.

Treatment of narcolepsy uses short (15- to 20-minute) daytime naps and use of stimulant medications to address daytime sleepiness. In patients with narcolepsy type 1, additional treatment with REM sleep suppressant agents, such as selective serotonin reuptake inhibitors, to address cataplexy may be useful.

**Idiopathic Hypersomnia**

Idiopathic hypersomnia, also a central disorder of sleep-wakefulness, has not specifically been associated with kidney disease. The patient with idiopathic hypersomnia typically presents in adolescence with excessive sleepiness despite long sleep duration and does not feel refreshed upon awakening. The reported prevalence varies greatly (5%-47%). The clinical diagnosis is confirmed with a polysomnogram followed by a multiple sleep latency test that demonstrates a reduced sleep onset latency with fewer than 2 REM onsets during the nap.

Treatment of idiopathic hypersomnia can be difficult because the patients are less responsive to therapy as compared with those with narcolepsy. Behavioral treatments including sleep hygiene and scheduled naps are recommended, and stimulant therapy similar to those used in narcolepsy may be considered.

**Circadian Rhythm Sleep Disorders**

Circadian rhythm sleep disorders are a group of disorders caused by disruptions in endogenous circadian rhythm by external factors. The body’s circadian rhythm helps determine the timing and duration of sleep and wakefulness and promotes low and high sleep propensity states through core body temperature fluctuations and melatonin production. The circadian rhythm is controlled by a pacemaker in the suprachiasmatic nucleus of the brain and is regulated by multiple factors, most importantly light exposure, which promotes the circadian drive for wakefulness.

Patients with a circadian rhythm sleep disorder experience a shift in their body clock relative to normal 24-hour social and environmental schedules and may present with sleepiness and/or difficulty falling asleep, depending on the direction of the shift in their internal clock. The diagnosis is made by confirming altered sleep patterns by history, sleep diary, and/or actigraphy, which involves a device worn on the wrist that records movements used to estimate sleep timing. The different types of circadian rhythm sleep disorders and treatment options are detailed in Table 3.

**Clinical Vignette, Continued**

PJ improved her sleep hygiene by reducing electronics use before bed and decreasing afternoon caffeine intake. In addition, she adopted a sleep schedule of 9:30 PM to 5:00 AM daily. She went on to undergo successful deceased donor kidney transplantation. However, she returns to her nephrologist’s office 9 months later to report that although she has been doing generally well, she has started to feel more tired during the day compared to 3 to 4 months ago, despite sleeping 8 hours per night. She thinks she may be snoring more and has awakened gasping for air. She reports morning headaches and a 10-pound weight gain that she attributes to her increased appetite and attendance at more social events. Her ESS score is 12. Systolic blood pressure remains elevated on treatment with amlodipine, 10 mg, daily and carvedilol,
25 mg, twice daily. To better control her blood pressure, losartan, 25 mg, daily was recently added. Her immunosuppression regimen consists of tacrolimus, mycophenolate mofetil, and prednisone. Physical examination is notable for blood pressure of 147/83 mm Hg, body mass index of 30 kg/m², and neck circumference of 16 inches. Laboratory studies revealed serum creatinine level of 1.2 mg/L and hemoglobin level of 14.7 g/dL (increased from 12.5 g/dL 6 months ago).

A home sleep apnea test was performed, with a total recording time of 7 hours 5 minutes. The respiratory event index (a surrogate for AHI in home sleep studies) was 16 events per hour. The oxyhemoglobin saturation nadir was 78% and the time spent at arterial oxygen saturation < 90% was 10 minutes.

**OSA in the Kidney Transplant Recipient**

The home sleep apnea test reveals that PJ has developed moderate OSA, which is associated with considerable morbidity in this population. Large cross-sectional studies have reported an increased incidence (26%) and prevalence (27%) of OSA in kidney transplant recipients, while others have shown no significant differences in the occurrence of OSA in recipients of kidney transplants compared with healthy matched controls. The discrepancy in prevalence is also reflected in the varying reported effects of kidney transplantation on improvement in AHI and resolution of sleep apnea. In addition, the impact of kidney transplantation on sleep quality remains unclear.

Kidney transplant recipients with increased risk for OSA have worse baseline kidney function, higher prevalence of diabetes, and higher rates of graft loss. When compared with those without OSA, transplant recipients with OSA required more blood pressure medications and had significantly higher average systolic blood pressures despite receiving antihypertensive medications. In addition, OSA is associated with increased risk for atrial fibrillation and stroke-associated morbidity and mortality, even in patients without kidney disease. Although studies have not shown a consistent association between OSA and posttransplantation erythrocytosis, the authors’ experiences suggest that secondary polycythemia, or even normalization of hemoglobin level in a previously anemic patient, is often an early clue to the diagnosis of OSA. Secondary polycythemia in patients with OSA may be related to the severity of the oxyhemoglobin desaturation associated with respiratory events. Additionally, secondary polycythemia is also seen in patients with coexistent chronic hypoxia, such as those with substantial tobacco use or severe chronic obstructive lung disease. Increased production of erythropoietin through the hypoxia inducible factor pathway in hypoxic conditions mediates this secondary erythrocytosis. We recommend that kidney transplant recipients who report daytime sleepiness in association with weight gain and even mild erythrocytosis should undergo evaluation for OSA.

**Review of Clinical Vignette and Conclusions**

After reviewing the sleep study results, PJ’s nephrologist referred her to a sleep medicine specialist. For 2 months, she has been using autoadjusting continuous positive airway pressure with a pressure range of 5 to 15 cm water with a nasal mast interface for at least 5 hours nightly. Her ESS score is 6. Blood pressure has improved such that losartan treatment was discontinued; currently she remains on treatment with amlodipine and carvedilol.

Sleepiness is common among patients receiving dialysis and following successful kidney transplantation. In the absence of an obvious medical disorder or medication side effect, the report of sleepiness may be a marker of insufficient sleep syndrome, poor sleep hygiene, sleep-disordered breathing, a central disorder of hypersomnolence such as narcolepsy, or a circadian rhythm sleep disorder. Unrecognized and untreated sleep disorders are associated with substantial morbidity and mortality. Recognition and appropriate treatment of OSA in particular is of paramount importance in the kidney transplantation population. Amelioration of symptoms can often have a marked impact on quality of life in all patients with kidney disease. Nephrologists and other providers should be familiar with the presentation of these conditions and collaborate with sleep physicians, including referral when appropriate. Future research should focus on the reciprocal effects of kidney transplantation on OSA, the utility of secondary polycythemia as a marker of sleep-disordered breathing in kidney transplant recipients, and the mortality and morbidity benefit of treatment of OSA following kidney transplantation.

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References


