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Sleep disorders: Serious threats among kidney transplant recipients

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ABSTRACT

In patients with chronic kidney disease (CKD) and kidney transplant recipients who continue to have some degree of CKD, the prevalence of sleep-related disorders is very high. Common sleep disorders in both groups include insomnia, sleep-disordered breathing (SDB), restless legs syndrome (RLS), excessive daytime sleepiness (EDS), and others. Depending on the kidney graft function, some patients see sleep disorders resolve after kidney transplantation, while others continue to have persistent sleep disorders or develop new ones. Kidney transplant recipients (KTRs) are unique patients due to the presence of a single kidney, the use of immunosuppressive medications, and other comorbidities including obesity, a high risk of cardiovascular disease, malignancy, and the anxiety of losing their allograft. All of these factors contribute to the risk for sleep disorders. CKD and sleep disorders have a bidirectional relationship; that is, CKD may increase the risk of sleep disorders and sleep disorders may increase the risk of CKD. Obstructive sleep apnea (OSA) is the most common form of SDB and is known to alter renal hemodynamics. OSA leads to hypoxemia and sleeps fragmentation, which activates the sympathetic nervous system. This activates the renin-angiotensin-aldosterone system and ultimately alters cardiovascular hemodynamics. Sleep disorders may have deleterious effects on the kidney allograft and proper screening and management are important for both graft and patient survival.

Contents

Abbreviations: AHI, Apnea-hypopnea index; BMI, Body mass index; CKD, Chronic kidney disease; CKD-T, Chronic kidney disease after transplant; CSA, Central sleep apnea; EDS, Excessive daytime sleepiness; eGFR, Estimated glomerular filtration rate; ESRD, End-stage renal disease; KTR, Kidney transplant recipient; OSA, Obstructive sleep apnea; PLMD, Periodic limb movement disorder; RLS, Restless legs syndrome; SDB, Sleep-disordered breathing.

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1. Introduction

The Centers for Disease Control and Prevention in the United States has declared insufficient sleep a public health problem [1]. Sleep disorders have recently gained increasing attention due to their serious health consequences, such as depression, diminished quality of life, premature mortality, as well as major economic consequences (including increased health care utilization and lost productivity) [2]. Clearly, kidney transplant recipients (KTRs) can experience many of these same issues due to the nature of their underlying illness and the surgery itself [3,4]. However, despite the high prevalence of sleep disorders in patients with chronic kidney disease (CKD), there have been few investigations exploring how sleep disorders affect this patient population after a successful kidney transplant and those who redevelop CKD after transplantation (CKD-T).

Sleep disorders, especially insomnia and sleep-disordered breathing (SDB), are alarmingly common in patients with CKD [5,6]. In this review article, we will explore the various effects of kidney transplantation and immunosuppressive medications on sleep disorders and the effect of sleep disorders on KTRs and patients with CKD and CKD-T.

2. Common types of sleep disorders

Common sleep disorders seen in CKD or CKD-T patients include insomnia, sleep-disordered breathing, restless legs syndrome (RLS), periodic limb movement disorder (PLMD), excessive daytime sleepiness (EDS), sleepwalking, nightmares, narcolepsy and many more [7]. For the purposes of this paper, the discussion is limited to disorders with the highest prevalence in this patient population.

2.1. Insomnia

According to the International Classification of Sleep Disorders third edition, insomnia is present when patients complain of difficulty initiating or maintaining sleep or waking up too early despite adequate opportunities and circumstances for sleep, which produces deficits in daytime function [8]. Insomnia and poor self-perceived sleep are common in patients with CKD. These result in fatigue, excessive daytime sleepiness, poor daytime functioning, poor health-related quality of life, and increased morbidity and mortality. Illness and treatment-related factors like metabolic changes, altered sleep regulatory mechanisms, CKD symptoms and complications, medications, and renal replacement therapies may disturb sleep and contribute to the high prevalence of insomnia in this population [8]. In one study, the prevalence of insomnia was 86.5% among patients with CKD and the prevalence and severity of these symptoms increased as the CDK stage advanced [9]. Worsening CKD, or end-stage renal disease (ESRD), was directly correlated with worsening insomnia [10]. Various factors including elderly age, dialysis vintage and a higher level of parathyroid hormone level have been associated with insomnia in ESRD patients [11].

Insomnia may improve after kidney transplantation, although it may take years after transplantation to do so [12]. One study reported that the prevalence of insomnia in KTRs was similar to that observed in the general population and substantially less to the waitlisted dialysis population [13]. Persistent, chronic sleep deprivation due to insomnia leads to a general enhancement of markers for inflammatory activity [14]. Various studies have demonstrated a significant increase in specific inflammatory markers (e.g.,IL-6, TNF-α receptor 1, and C-reactive protein) in those who are chronically sleep deprived [15,16]. Chronic insomnia has been associated with significant decreases in the numbers of CD3+, CD4+ and CD8+ T cells, and reduced NK-cell responses [17,18]. The effects of insomnia in KTRs, particularly for graft and patient survival or rejections are understudied. However, given the overall effects of poor sleep quality on physical, psychological, social, and cognitive functions, insomnia is likely to have a detrimental effect on the kidney graft.

2.2. Restless leg syndrome

Essential diagnostic criteria for RLS include an urge to move legs with unpleasant sensations. These worsen during periods of rest and partially or totally resolve with movement, and are usually worse in the evening or night than during the day [19]. Approximately 25% of patients on dialysis have restless leg syndrome (RLS) symptoms when the international RLS diagnostic criteria are applied [20]. RLS may be linked with cardiovascular morbidity, decreased quality of life, sleep disturbance, and increased risk of death in patients with CKD [20]. Pharmacological agents are available to treat moderate to severe RLS; however, data specific to patients on dialysis with RLS are lacking [20]. The higher sensitivity of diagnostic criteria in the physical examination and patient history may be valuable for timely management [21]. In patients with CKD,RLS symptoms are associated with depression, which remained significant even after accounting for insomnia [22]. In the dialysis population, RLS is a very common problem and is associated with insomnia and excessive daytime sleepiness (EDS) [23]. The prevalence of RLS decreases after kidney transplantation but depends upon kidney allograft function [24]. Although a treatable condition, RLS has been associated with an increased risk of mortality in kidney transplant recipients [25].

2.3. Other sleep-related disorders

Periodic limb movements disorder (PLMD) are brief leg or arm jerks during sleep that are associated with negative physiological consequences, including cardiac acceleration, spikes in blood pressure, and cortical arousals [26]. Periodic limb movements disorder in sleep is common in patients with CKD and ESRD [27]. The great majority of patients with RLS will also demonstrate PLMD. A smaller proportion of patients with PLMD do not recognize symptoms of RLS while awake. PLMD is strongly and independently associated with mortality in CKD [28]. In one study, the prevalence of PLMD was lower in KTRs than in patients on the waiting list (27% and 42%, respectively), but the difference was not statistically significant ($p = 0.09$). Nevertheless, the prevalence of severe PLMD was significantly lower in KTRs ($p = 0.02$) compared to dialysis patients [29].

The International Classification of Sleep Disorders, third edition defines excessive daytime sleepiness (EDS) as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least 3 months [30]. Excessive daytime sleepiness is also common in patients with CKD and is estimated to be around 29% in CKD patients and 41% in patients on dialysis [31]. Excessive daytime sleepiness is the third most commonly reported sleep disorder in patients with ESRD, after insomnia and day/night sleep reversal [32]. Excessive daytime sleepiness is associated with sleep apnea, RLS, and insomnia, along with multiple other medical comorbidities [33]. Even after a transplant, there is a high prevalence of EDS, which has been associated with medication and immunosuppressive non-compliance, thus risking graft rejection [34]. Although common, the effects of day/night sleep reversal in patients with CKD or CKD-T is unknown.

Pruritus is also common in patients with CKD and ESRD. CKD associated pruritus is defined as itching that is directly related to kidney disease without another comorbid condition such as a comorbid liver or skin condition that includes itching [35]. Approximately 40% of patients with ESRD are affected with moderate to severe pruritus, and it has been associated with poor quality of life along with impaired sleep and increased mortality [36]. In a case series of three patients, Nigam etal. noted that sleep-related scratching can occur as a primary parasomnia, without known dermatologic or systemic precipitant, and without itching or scratching outside the sleep period [37]. These patients may benefit from an in lab polysomnogram with video recording or outpatient actigraphy along with the precise history of pruritus confined exclusively to sleep periods. This will help exclude parasomnias such as "sleep-related scratching" as the cause of nocturnal pruritus in such patients [38]. Even after kidney transplantation, pruritus remains substantially higher than in the general population and impacts the quality of life in these patients [39].

2.4. Sleep disordered breathing

Sleep-disordered breathing is a chronic condition in which partial or complete cessation of breathing occurs many times during sleep, resulting in waking symptoms of sleepiness or fatigue that interfere with a person's ability to function and reduces the quality of life [40]. The severity is based on the numbers of apnea or hypopnea episodes per hour during sleep, also called the apnea-hypopnea index (AHI) and is categorized as: mild (AHI = 5–14), moderate (AHI = 15–30), and severe (AHI > 30) [41]. Apnea is defined as a pause in respiration for >10 s and hypopnea is as a reduction in ventilation of at least 50% that results in a decrease in arterial saturation of 4% or more due to partial airway obstruction [42]. The AHI is the combined average number of apneas and hypopneas that occur per hour of sleep [43]. Obstructive sleep apnea (OSA) is the most common SDB, and is increasingly being seen due to the obesity epidemic. Another type of SDB, central sleep apnea, has increased prevalence among CKD patients.

2.4.1. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a disorder in which a person frequently stops breathing during his or her sleep due to the obstruction of the upper airway during sleep because of the inadequate motor tone of the tongue and/or airway dilator muscles [44]. Obstructive sleep apnea is the most common and clinically significant form of SDB [45]. OSA is underdiagnosed and underreported in the general population. [46]. OSA is reportedly associated with a higher risk of stroke, hypertension, diabetes mellitus, congestive heart failure, arrhythmias, metabolic syndrome, and fatal and non-fatal cardiovascular events [47–50].

It has been estimated that approximately 20% of adults with CKD have OSA, while the prevalence is as high as 50–90% among patients on dialysis [51–53]. In one study from Japan, the prevalence was as high as 65% among non-dialysis dependent CKD patients and decreased renal function was a predictor of OSA [54]. In another study from Australia, 55 of 57 patients with CKD stage IV and V had OSA. In the same study, an AHI ≥30/h or severe OSA was found in 66% of hemodialysis and 54% of non-dialysis participants [55]. In another study from the United States, even at early stage CKD with an estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m^2, the odds ratios for OSA was increased by 1.22 to 1.42 for each 15 ml/min decrease in the eGFR [56]. Long-term consequences of OSA include cardiovascular disease, hypertension, stroke, and a reduced quality of life [57,58]. In the Wisconsin sleep cohort (which had long-term follow up of 18 years), SDB was independently associated with an increased risk of mortality irrespective of age, sex, or body mass index (BMI) [59]. OSA appears to alter the renal hemodynamics and function in a harmful manner. Although the exact mechanism is unclear, it is speculated that the hypoxemia and sleep fragmentation from activates the sympathetic nervous system that in turn activates the renin-angiotensin-aldosterone system and alters cardiovascular hemodynamics. In addition, OSA results in the free radical generation and multiple deleterious processes (such as endothelial dysfunction, inflammation, platelet aggregation, atherosclerosis, and fibrosis), which predispose individuals with OSA to adverse cardiovascular events and likely renal damage [60]. Fletcher etal. observed that urinary excretion of norepinephrine and epinephrine was higher in patients with OSA than in the general population, even during waking hours [61]. In one study, AHI correlated with urea concentration, but interestingly, not with creatinine clearance [62]. Treatment with intensive dialysis therapies appears to decrease the frequency of apneic events [46].

OSA and CKD have a bidirectional relationship; CKD is a well-known risk factor for OSA, and OSA appears to be an important risk factor for the progression of CKD(Fig. 1). OSA has been linked to proteinuria, a manifestation of kidney problems and a risk factor for CKD progression. In one study of six patients with high-grade proteinuria and OSA, the authors reported improvement in proteinuria after surgical correction of OSA. In the four patients for whom follow-up data were available, three patients had complete resolution of nephrotic-range proteinuria and the fourth saw a marked reduction in proteinuria [63]. Similarly, Molnar etal. conducted a study of more than three million US veterans with eGFR ≥60 ml/min/1.73 m^2 and concluded that a diagnosis of incident OSA was associated with higher mortality, incident heart disease, stroke, CKD, and faster CKD progression [64]. OSA is also known to cause resistant hypertension [65]. OSA is an independent risk factor for perioperative pulmonary complications along with postoperative hypoxemia, intensive care unit transfers, and prolonged hospital stay [66,67]. Other complications of OSA are pulmonary hypertension, neurocognitive effects, depressed quality of life, motor vehicle accidents, awakening headache, childhood growth interruption, pregnancy-induced hypertension, fetal growth retardation, and disruption of the patients' bed-partners' sleep quality [68] (Table1).

There are few studies of OSA in kidney transplant recipients. In one case study of two ESRD patients with OSA, the syndrome disappeared completely after successful kidney transplantation [69]. Auckley etal. reported a similar finding in one patient with severe OSA [70]. Beecroft etal. conducted a similar study in 11 patients with OSA, with the hypothesis that sleep apnea would resolve after kidney transplantation. In this group, despite the restoration of good kidney function, there were no significant changes in AHI score (20.2 ± 15.1 pre-transplant vs. 23.5 ± 21.3 post-transplant). In the same study, out of 11 apneic ESRD patients, only three (30%) apneic ESRD patients had more than a 50% decrease in AHI score post kidney transplantation [71]. OSA in KTRs could be multifactorial and could be due to pre-existingOSA or new symptoms after kidney transplantation. In a large cross-sectional survey ('TransQoL-HU Study') of 841 kidney transplant recipients and 175 waitlisted patients, the Berlin Sleep Apnea Questionnaire was used to assess the risk of OSA. The prevalence of patients at high risk for OSA was similar in both the transplanted and waitlisted groups at 27% and 33% respectively [72]. In the same study, male gender, older age, lower educational status, worse kidney function, use of hypnotic drugs and comorbidities were independent predictors of OSA in kidney transplant recipients [72]. One small, underpowered study found that OSA was not associated with the progression of CKD-T or all-cause mortality in KTRs and the authors recommended further study to agree or disagree with their findings [45]. In another study, based on the Berlin questionnaire, high risk for OSA at baseline was an independent predictor of graft loss among female KTRs but for an unknown reason, not in male [73].

Obstructive sleep apnea provides the clinical model for chronic partial sleep loss, and OSA has also been associated with increased risk for surgical site infections, pneumonia, and other complications [74,75]. Dysregulation of sleep may affect the immune system, leading to increased risk of infections or rejections in kidney transplant recipients, although to the best of our knowledge, no studies have looked at this question directly. The exact mechanisms and effects of the OSA-

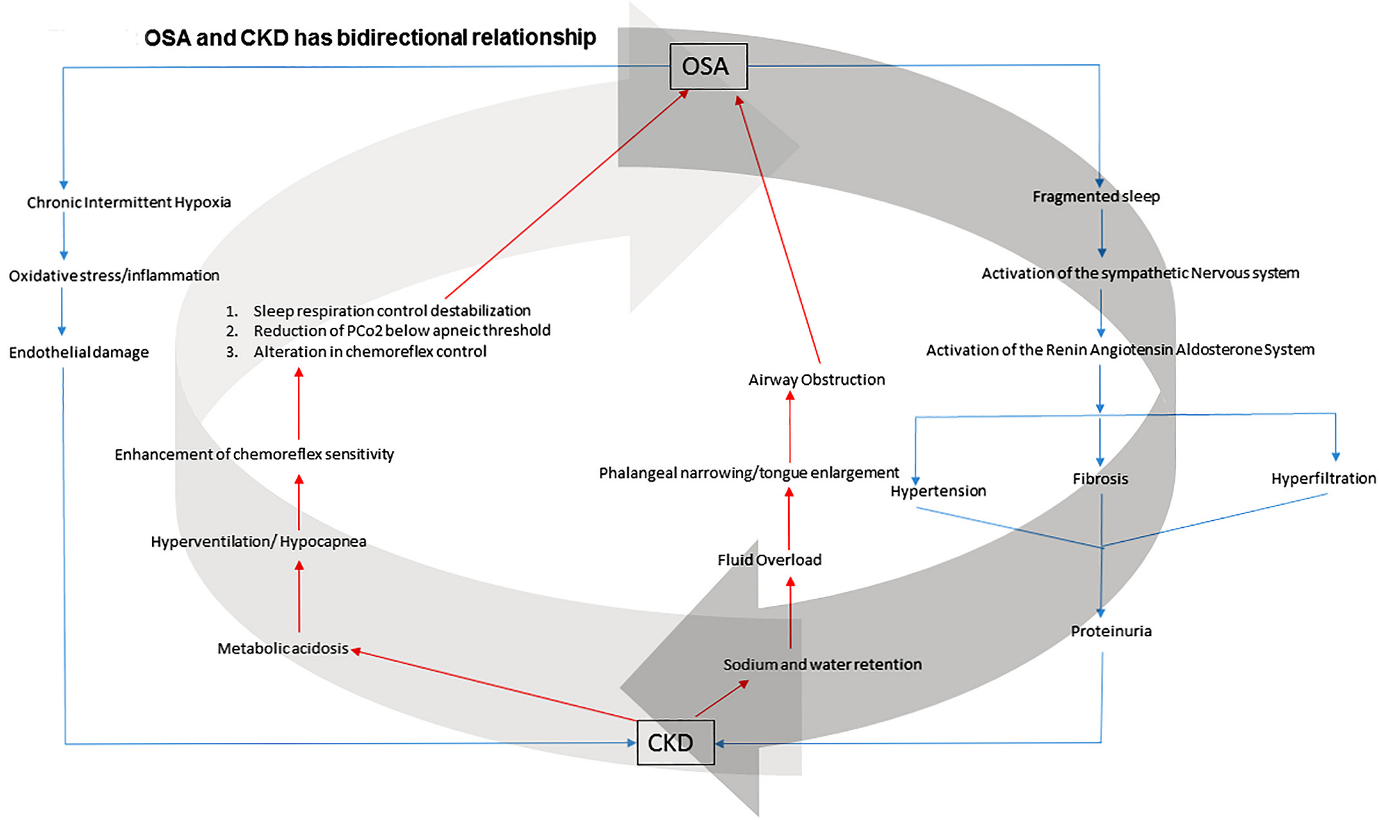

Fig. 1. Legend: Sleep apnea and CKD has a bidirectional relation.

induced renal disease in the kidney graft are understudied. Given the complex pathogenesis and adverse effect of OSA in the general population and in patients with CKD, it is suspected that OSA has deleterious effects on kidney graft and patient survival.

2.4.2. Central sleep apnea

Central sleep apnea (CSA) is characterized by a lack of drive to breathe during sleep, resulting in insufficient or absent ventilation and compromised gas exchange [76]. Chronic kidney disease is associated with central sleep apnea (CSA) [77], and the prevalence of CSA in CKD patients is estimated to be around 10%, ranging from 0 to 75% [78]. Compared to non-CKD patients, CSA is an independent risk factor for all-cause mortality [77]. The prevalence of congestive heart failure is estimated to be 65–70% in ESRD patients and increases greatly as the renal function deteriorates [79]. Patients with congestive heart failure and CKD are at much higher risk for CSA [80]. The mechanism of CSA in CKD is unknown. It has been proposed that it may result from fluid overload and pulmonary congestion, which activates lung vagal irritant receptors and stimulates hyperventilation and hypocapnia, leading to CSA [81,82]. Other putative risk factors for CSA include interstitial pulmonary edema, chronic metabolic acidosis, anemia, and compromised clearance of uremic toxins [83]. There are limited data related to CSA in kidney transplant recipients. It is speculated that CSA may improve post-transplant, depending upon graft function. Similarly, there are limited data about the effects of CSA on kidney graft function/survival.

Table 1
Common complications of obstructive sleep apnea.

Common Complications of OSA
Resistant hypertension
Peri and post-operative complications
Prolonged hospital stay
Pulmonary hypertension
Neurocognitive deficit
Depression
Reduced quality of life
Increased risk of motor vehicle accident
An awakening headache
Childhood growth interruption
Pregnancy-induced hypertension
Fetal growth retardation
Bed partner's sleep quality disruption

3. Effects of kidney transplantation on sleep disorders

For most patients with CKD, sleep disorders persist after transplantation or they develop a de novo sleep disorder. The prevalence of poor sleep quality in kidney transplant recipients ranges from 30% to 62% [84]. Sleep disorders in kidney transplant recipients could be multifactorial and may be due to the pre-existing sleep disorders or new symptoms after kidney transplantation. In addition to the physiological processes, anxiety about a new allograft and various other psychological issues may contribute to the sleep disorders experienced by KTRs at various time periods after transplant (Table 2). As healthcare providers, we should try to distinguish if sleep disorders are due to the medical or psychological factors for timely intervention (Table 3). In a large series of solid organ transplant recipients (predominately kidney) from the Swiss Transplant Cohort Study, they report 29% of patients with poor sleep quality at 3 years post-transplant period compared to 38% pre-transplant [85]. Some small studies have demonstrated improvement or resolution of sleep disorders and SDBpost-transplant, and others have shown no improvement or even worsening sleep quality. Larger studies and trials are needed as there is still a higher prevalence of poorly sleeping KTRs and the effects of poor sleep quality among them are undefined. Sleep quality and overall health-related quality of life

Table2
Common causes of sleep disorders in kidney transplant recipients.

Early phase	Later
Pre-Existing sleep disorder (OSA, restless leg syndrome etc.)	Development of new sleep disorder
Recent surgery	Deteriorating kidney function and advancing CKD
New medications adjustment and side effects	Co-morbidity, complications of CKD (bone disease, chronic pain, post-transplant anemia etc.)
Anxiety- uncertainty fear of rejection	Anxiety and uncertainty—fear of rejection
Adjustment to a new lifestyle	Obesity
Depression, delirium- guilt of taking organ	

due to poor sleep remain lower in KTRs compared to the general population [86].

3.1. Role of Immunosuppressive medications on sleep disorders

The majority of kidney transplant recipients are maintained on immunosuppressive medications, which are known to have sleep-related complications. Insomnia is the most frequently reported sleep-related side effect of steroids and immunosuppressive medications [87]. Corticosteroids are well-known to cause sleep disturbance, insomnia, and unpleasant dreams [88]. It is difficult to pinpoint which immunosuppressive medication is most likely to cause a sleep disorder, but commonly used maintenance immunosuppressive medications – tacrolimus, mycophenolate mofetil, and sirolimus – have a sleep disorder and insomnia listed in their side effect profile [89–91]. In one study of lung transplant recipients, higher cumulative exposure to the tacrolimus was associated with insomnia [92]. Poor sleep quality is common after kidney organ transplantation. It is important to note that while selecting immunosuppressive agents it is worthwhile to categorically study their effects on circadian disturbances and quality and quantity of sleep as consolidated restorative sleep is quintessential for better immune regulation. The severity of insomnia symptoms in KTRs is independently associated with a higher proportion of slow wave sleep and increased beta activity during REM sleep but not with other parameters of sleep architecture [93].

4. Various co-morbid condition associated with sleep disorders

Most of the sleep disorders described above cause poor quality sleep due to inadequate or fragmented sleep. Insufficient sleep duration has been linked with seven of the fifteen leading causes of death in the United States, including cardiovascular disease, malignant neoplasm, cerebrovascular disease, accidents, diabetes, septicemia and hypertension [1]. Various comorbid conditions not described below but associated with sleep disorders which could affect KTRs include gastroesophageal reflux disease, stroke, impaired insulin sensitivity, and hypertension [94–96].

4.1. Obesity after transplant and sleep disorders

Obesity is a common problem in both CKD patients and kidney transplant recipients. An estimated 60% of kidney transplant patients are overweight or obese at the time of transplant [97]. Additionally, most gain approximately 10% of their body weight in the first year after kidney transplant [98]. Post-transplant weight gain has been associated with a reduction in graft and patient survival [99]. Obesity is identified as the strongest risk factor for OSA, and weight loss has been shown to reduce the AHI [100]. Reilly-Spong etal. observed that obese transplant recipients are more than eight times as likely to have poor total sleep time than those who are not obese [84]. Beecroft etal. concluded that, despite the improvement of uremia, OSA was higher in kidney transplant recipients due to increased neck circumference and BMI [71]. Obesity is also a well-known risk factor for the progression of CKD [101]. Obese patients then are at high risk for both OSA and CKD-T progression.

Table3
Health care providers: Should distinguish medical vs psychological risk factors.

Pain	Depression
Pruritus	Anxiety
Tremors	Fear
Drugs	
Nocturia/bladder outlet obstruction	

4.2. Cardiovascular effects of sleep disorders

There is a temporal relation between sleep disorders and the occurrence of vascular events, cardiac arrhythmias, and sudden death [102]. Cardiac arrhythmias are common among patients with OSA, and the presence of complex tachyarrhythmias and bradyarrhythmias increase morbidity and mortality [103]. OSA is associated with myocardial ischemia (silent or symptomatic), acute coronary events, stroke, transient ischemic attacks, pulmonary hypertension, and heart failure [104]. Moderate to severe OSA is associated with a 6.2 fold increased risk of death compared to the general population without OSA [105]. Cardiovascular morbidity and mortality are significantly higher in kidney transplant recipients. Although cardiovascular mortality and events decrease after kidney transplant compared to ESRD, they remain two-fold higher compared to the general population [106,107]. By 2 years post-transplant, it is estimated that approximately 40% of recipients experience cardiovascular events, mainly related to congestive heart failure (CHF), the second most common cause of hospital admission for kidney transplant recipients after infection [108]. Kidney transplant recipients with sleep disorders are expected to have a higher incidence of cardiovascular events.

4.3. Infections and sleep disorders

There appears to be a complex relationship between sleep and immunity against infections. Studies have demonstrated sleep deprivation modifies various components of the immune system and conversely that sleep patterns are altered during infection due to the immune response [109]. In the general population, OSA has been associated with increased risk of pneumonia and surgical site infection following colectomy [74,75]. In a large cohort of 9697 participants, even early-stageCKD was associated with infection-related hospitalization and death [110]. Although the risk of infections specific to KTRs with sleep disorders is understudied, it is expected to be higher in those with sleep disorders compared to those without.

4.4. Cancer and sleep disorders

There is also a relationship between sleep disorders and cancer. It is estimated that the prevalence of sleep disorders is 30–75% among newly diagnosed or recently treated cancer patients, which is almost double than that of the general population [111]. There is some evidence of a link between sleep disorder and the risk of cancer in the general population. In one study, patients diagnosed with insomnia, parasomnia, and OSA were at increased risk of developing breast cancer [112]. In another large cohort of approximately 5.6 million individuals, OSA was associated with increased risk of pancreatic cancer, kidney cancer, and melanoma but was not associated with increased risk of metastasis or death [113]. However, another long-term follow up study found moderate to severe OSA was associated with increased risk of all-cause mortality along with increased cancer incidence and mortality [114]. The risk of cancer specific to patients with CKD-T is understudied but may well be higher in those with sleep disorders compared to without.

5. Screening questions for non-sleep medicine practitioners

Early risk assessments with proper questions and review of systems are key to assess the risk of sleep disorders in kidney transplant recipients. The six questions included in Table4, also called "I-S-N-O-R-E", when added to the standard review of systems, may help the non-sleep medicine practitioner identify at-risk patients who need an early referral for any positive response.

6. Discussion

Sleep-related problems are prevalent in CKD patients and in KTRs. The prevalence of common sleep disorders is summarized in Table5. Kidney transplant recipients are a unique subgroup of patients with CKD. They have gone through the extreme progression of CKDi.e., ESRD, and have received a kidney transplant [115,116]. Kidney transplantation is the preferred method of renal replacement therapy, although it is not a cure for ESRD. Kidney function may not regress to the non-CKD state after kidney transplantation, and most of the patients experience CKD after transplantation (CKD-T) [117]. Kidney transplant recipients are unique due to the presence of a single kidney, immunosuppressive medications, and other comorbidities (including obesity, a high risk of cardiovascular disease, malignancy, and the anxiety of losing their graft) and all factors pose a risk for sleep disorders. In one large study of >1600 patients comparing the deterioration of kidney function among CKD and CKD-T, the authors found there was a significantly higher rate of deterioration of kidney function among patients with CKD compared to CKD-T [118]. Nevertheless, patient survival was inferior among CKD-T, which offset the benefit of the slower rate of progression of CKD among KTRs due to other comorbidities.

Depending on the kidney graft function, some patients will have sleep disorders resolve after transplantation while others continue to have persistent sleep disorders or even develop new ones. This dynamic creates a bidirectional relationship whereby sleep disorders may increase the likelihood and severity of CKD, and CKD can increase the effects of sleep disorders. Although most data are from the general population or patients with CKD, the physiological and psychological effects of sleep disorders in KTRs put added stress on this group that is already under unique pressures in both regards.

Patients with any stage CKD, not only ESRD, are at an increased risk for cardiovascular events and mortality. The risk of death and cardiovascular events are increased independently in individuals who have less severely impaired kidney function and are not on dialysis compared to those who have preserved kidney function [119]. In recent years, there has been a significant improvement in the prevention of kidney rejection. Death with functional graft is the most common cause of graft failure and cardiovascular disease, infections, and malignancies are the leading causes of death among KTRs [90].

Table4
Screening questioner about sleep disorders: I-SNORE.

I-SNORE	
Insomnia	Do you have a hard time falling asleep or staying asleep?
Snoring	Does snoring disturb your sleep or the sleep of someone else?
Nocturnal behavior	Does nocturnal behavior disturb your sleep or the sleep of someone else?
Observed apnea	Have you ever been told that you stop breathing during sleep?
Restorative sleep	Do you feel that your sleep is not refreshing?
Excessive sleepiness	Do you sometimes feel sleepy or tired during the day even after your usual night's sleep?

Table5
Prevalence of common sleep disorders.

	General population	CKD/ESRD	Kidney transplant recipients
Sleep disordered breathing	6.5–31% [122]	50–90% [51–53]	~20% [123]
Insomnia	10–60% [124]	15–86% [9,13]	5–14% [13]
RLS	1.9–15% [125]	~25% [20]	1.8–23.5% [24]
PLMD	~4% [126]	~42% [29]	~27% [29]
EDS	5.1–29% [127]	29–41% [31]	~25% [4]

Cardiovascular disease and mortality decrease after kidney transplantation compared to being on dialysis but still remain higher than those of the general population. Risk of mortality is initially worse with kidney transplantation compared to dialysis; the risks are equal by 3–4 months post-transplant, and subsequently, there are long-term survival benefits to transplantation [120]. Overall, cardiovascular mortality is approximately two times higher in kidney transplant recipients compared to the general population [106,107]. After cardiovascular disease, infections are the second most common cause of death in kidney transplant recipients. The risk of infection is significantly higher after kidney transplantation than in the general population and is a common cause of morbidity and mortality. Urinary tract infection is the most common bacterial infection, which requires hospitalization in kidney transplant recipients [121].

Another common complication in kidney transplant recipients is a malignancy. The overall incidence of malignancy in kidney transplant recipients is 3–5 times higher compared to the general population, with skin cancer being the most common cancer [117]. Although sleep disorders in KTRs are understudied, they may have similar or even worse detrimental effects on patients survival compared to the general population or patients with CKD. Cardiovascular disease, infection, and malignancy, which are the top three causes of mortality in KTRs are also associated with sleep disorders in CKD or the general population.

7. Conclusion

Sleep disorders are major problems in KTRs. Proper screening and management may improve patient survival, slow down the progression of CKD-T, and prolong the much-needed graft survival, along with other medical, physical and psychosocial benefits to the recipients. Common sleep disorders seen in KTRs include insomnia, sleep apnea, RLS, PLMD, EDS. However, there is limited information about adverse effects of sleep disorders pertinent to the KTRs, and most of information on sleep disorders is based on studies on the general population or patients with CKD. But, if sleep disorders have detrimental effects on general population or patients with CKD, we believe it is reasonable to think they will have same or even worse effects on this special and unique group of patients with kidney transplant.

As healthcare providers, it is necessary for us to evaluate patients for sleep-related disorders by obtaining a proper history, physical examination, and reviewing the impact of prescribed medication. The addition of the "I-S-N-O-R-E" questions may help to identify patients at risk. Treating sleep disorders or a timely referral to a sleep specialist is crucial for KTRs. More studies are needed in this field.

Disclosure

The authors declare no conflicts of interest.

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