

Insomnia in Patients With Chronic Kidney Disease

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Summary: Insomnia and poor self-perceived sleep are very common in patients with chronic kidney disease (CKD). Poor sleep is associated with fatigue, sleepiness, impaired daytime functioning, impaired health-related quality of life, and increased morbidity and mortality. Many illness- and treatment-related factors (metabolic changes, inflammation, altered sleep regulatory mechanisms, symptoms and complications of CKD, comorbid conditions, medications, and renal replacement therapies) may disturb sleep and contribute to the high prevalence of insomnia in this patient population. Accordingly, the approach to both diagnosing and treating this condition is quite complex. Although sleep-related problems are very important for patients with CKD, they largely are under-recognized and undertreated. Very few intervention trials provide an evidence base to support treatment decisions in this particular patient population. With this review we hope to increase awareness of insomnia among professionals involved in the management of patients with CKD and to provide guidance in recognizing and treating this important condition.

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Sleep disorders (insomnia, restless legs syndrome [RLS], and obstructive sleep apnea [OSA]) and poor self-perceived sleep are very common in patients with chronic kidney disease (CKD), both in patients on maintenance dialysis,¹⁻¹⁰ among patients with earlier stages of CKD,^{2,11-18} and in kidney transplant (KT) recipients,¹⁹⁻²⁵ as well. These problems affect 30% to 80% of patients, depending on the specific patient population. Insomnia symptoms (inability to fall asleep, frequent and/or prolonged awakenings, early morning awakening, and insufficient amount and/or quality of sleep) are very frequent complaints in the dialysis unit. Both specific sleep disorders and poor self-perceived sleep are associated with fatigue, sleepiness, impaired daytime functioning, impaired health-related quality of life (QoL), and increased morbidity and mortality.^{17,19,25-39} Still,

sleep problems largely are under-recognized and undertreated in these patient populations.

Many illness and treatment-related factors (anemia, hyperphosphatemia, medications, dialysis related factors, and so forth) and comorbid conditions may contribute to the increased prevalence of insomnia in patients with CKD. In addition, demographic, lifestyle-related, and psychosocial factors and other sleep disorders, such as RLS, periodic limb movements in sleep (PLMS), and OSA, which also are frequent among patients with CKD, also may cause or contribute to insomnia.

Systematic use of screening questions about sleep problems should be part of the regular assessment of patients with CKD. In patients with sleep problems, both the diagnostic and the treatment approach should consider the potential underlying factors and efforts should be made to correct the potentially reversible ones. All patients may benefit from health education about sleep hygiene. Persistent and unexplained sleep problems and the suspicion of specific sleep disorders should prompt a referral to a sleep specialist for systematic and comprehensive assessment and treatment recommendation.

Very few studies among patients with CKD have used the specific diagnosis of insomnia as a case definition. Instead, the correlates or consequences of short sleep duration or poor self-reported/self-perceived sleep have been assessed and reported. Although these categories certainly overlap with insomnia, the distinction is important because these questions or questionnaires usually overestimate the prevalence of insomnia. Rigorous epidemiologic studies are needed to assess the prevalence and significance of insomnia among patients with CKD. In this review, we use the phrases *poor sleep* and *insomnia* interchangeably when describing the results of studies in CKD populations. Furthermore, very few intervention trials have provided an evidence base to support treatment

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decisions in this particular patient population. This is particularly concerning given the very high prevalence and potentially debilitating consequences of this condition. The goal of this review is to increase awareness of insomnia among professionals involved in the management of patients with CKD and to provide guidance in recognizing and treating this important condition.

DEFINITION OF INSOMNIA

The International Classification of Sleep Disorders (ICSD) is the most widely used classification system for sleep disorders. The third edition of the ICSD (ICSD-3) was published in 2014 and includes seven major categories of sleep disorders, one of which is insomnia.⁴⁰ Sleep disorders also are classified by two additional systems, the International Classification of Diseases⁴¹ and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders.⁴² The classification of sleep disorders by these systems is largely parallel.

Based on the ICSD-3, insomnia is present when all three of the following criteria are met: (1) the patient complains of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early; (2) the earlier-described sleep difficulties occur despite adequate opportunity and circumstances for sleep; and (3) the sleep problem produces deficits in daytime function.

Short-term insomnia (also called *adjustment insomnia*, *acute insomnia*, *stress-related insomnia*, or *transient insomnia*) lasts for fewer than 3 months based on the ICSD-3. In chronic insomnia (earlier terminology also called this *primary* and *secondary insomnia*, *comorbid insomnia*) symptoms occur at least three times per week for 3 months or more and are not related to an inadequate opportunity for sleep or an inappropriate sleep environment. Although short-term insomnia could improve spontaneously or resolve without specific treatment, chronic insomnia may develop from acute onset because of bad sleep habits or anxieties about sleep (eg, “I will never sleep well again”). In other cases, insomnia may be caused by chronic problems interfering with sleep (eg, pruritus, chronic pain).

SIGNIFICANCE OF INSOMNIA

Insomnia is associated with impaired daytime functioning. Thus, fatigue, mood disturbances or irritability, reduced motivation, or reduced energy may occur as a result of poor sleep. Additional behavioral problems, such as hyperactivity, impulsivity, or aggressivity, also may result from insomnia. Poor sleep also may lead to impaired attention or concentration, social or vocational/educational dysfunction, and an increased risk of errors or accidents. Finally, insomnia is associated with impaired QoL,⁴³ increased health care use,⁴⁴ risk of comorbidities,⁴⁵ and also an increased risk of mortality²⁶ in the general population.

The presence of insomnia has been shown repeatedly to be associated with impaired QoL, both in patients on maintenance dialysis, KT recipients, and also in patients with earlier stages of CKD.^{5,36} In a large cohort study, patients with poor sleep achieved significantly lower QoL scores.³⁶ Insomnia also is associated with impaired self-reported cognitive functions.⁴⁶

A complex bidirectional association between insomnia and depression as well as anxiety has been reported repeatedly.^{24,36,47–50} Insomnia is a significant source of stress^{32,51} and patients with insomnia often are anxious.⁴⁸ Insomnia is one of the main symptoms of psychological distress, and, importantly, it also may be a precursor to depression.

Fatigue is a debilitating symptom that affects 60% to 97% of patients on maintenance dialysis and up to 84% of CKD stage 5 patients.^{52–57} Fatigue has a considerable effect on QoL and is viewed as being more important than survival by some patients.⁵⁸ Poor self-reported sleep quality has been associated with fatigue in both patients on maintenance dialysis,¹⁷ after KT,¹⁹ and with earlier stages of CKD.^{17,53–55}

Several studies have shown an association between insomnia/poor sleep and increased mortality among patients with end-stage kidney disease (ESKD).^{5,35,36} In the Dialysis Outcomes and Practice Patterns Study the risk of mortality was 16% higher in patients with poor sleep quality after adjusting for important co-variables (age, race, sex, comorbid conditions, physician-diagnosed depression, hemoglobin level, albumin-corrected serum calcium level, serum albumin level, serum phosphorus level, body mass index, smoking status, Kt/V (Kt/V is used to quantify dialysis adequacy, where K is dialyzer clearance of urea, t is dialysis time and V is volume of distribution of urea, approximately equal to patient’s total body water), and years on dialysis).³⁶ The mechanism by which insomnia may increase mortality is not clear. One possible explanation is that insomnia is linked to increased cardiovascular risk. In the general population, evidence has suggested that insomnia is associated with cardiovascular risk factors, including hypertension and heart rate variability.^{26,59,60} This relationship may be complex and several factors (depression, comorbidity, and so forth) should be considered. In addition, insomnia may be caused by OSA,^{61–63} RLS, or PLMS, which also are related to increased cardiovascular risk, although the link between insomnia versus OSA and PLMS has not been established clearly. Insomnia also may be linked to increased systemic inflammation, which has been associated with both ESKD and poor cardiovascular outcomes.^{47,64}

EPIDEMIOLOGY OF INSOMNIA

The reported prevalence of poor sleep/insomnia among patients with CKD ranges from 20% to 70%.^{5,32,47,65–69}

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