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Chronic Kidney Disease and Sleeping Disordered Breathing (SDB)

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Abstract

The outlines of the current manuscript are: 1. Re-establish the link between hypertension and SDB including prevalence, mechanism, and reversal of process (i.e. improvement in hypertension with improvement in SDB), why it is important-cardiovascular mortality with numbers. 2. Re-establish the link between hypertension and CKD including same points as above. Then ask if both CKD and SDB are combined, what happens to hypertension and cardiovascular mortality. 3. Lastly, talk about links between CKD and SDB on how each process feeds on the other and is a growing, common problem.

Keywords

Chronic kidney disease; sleep apnea; hypertension; dialysis; overnight fluid shift

INTRODUCTION

Sleep disorders are highly prevalent in patients with chronic kidney disease (CKD), although remain under-recognized [1, 2]. The most common sleep disorders that affect this population are insomnia, restless leg syndrome, periodic limb movements of sleep, and sleeping disordered breathing (SDB). Among all these sleep disorders, SDB, and particularly sleep apnea, is recognized worldwide as having impact on mortality and cardiovascular events. In recent years, the literature suggests that various medical specialties are taking great interest in sleep disorders.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

Sleep apnea can be defined as consecutive reduction (hypopnea) or cessation (apnea) of breathing during sleep with consequent hypoxemia. The number of episodes of apneas and hypopneas during sleep are quantified by the apnea-hypopnea index (AHI), which classifies the sleep apnea into mild (between 5 and 15 episodes per hour (/hr) of sleep), moderate (between 15 and 30 episodes/hr of sleep) and severe (more than 30 episodes/hr of sleep). There are primarily two types of sleep apnea namely obstructive sleep apnea (OSA) and central sleep apnea (CSA).

SDB is described in more than 50% of patients with CKD [2, 3], which is substantially higher than the described prevalence in the general population [4]. The reasons for this high prevalence are still being debated. However, several reasons might help explain, at least partially, this high prevalence. First, comorbidities as hypertension and diabetes are the global leading causes of CKD and are associated with high prevalence of SDB. Second, patients with CKD present more inflammation, which is also implicated in the pathogenesis of SDB [5]. Lastly, but not less important, patients with CKD are prone to have hypervolemia, with consequent overnight fluid shift, another potential mechanism already described in the pathogenesis of SDB [6–10]. It is proposed that “uremia” itself might contribute somehow to this increased prevalence, as suggested by case reports that have pointed to the alleviation of sleep apnea following kidney transplant [11, 12]. In addition, the dialysis dose was implicated in the pathogenesis of SDB [13, 14], suggesting a role of uremic toxins in this sleep disease. Taken together, the presence of comorbidities, inflammation and hypervolemia may contribute to the high prevalence of SDB in this population.

In addition to the high prevalence of SDB in CKD population, the importance of the recognition of this sleep disorder is its association with cardiovascular mortality in this population [15, 16]. Several reports in the literature are corroborating to this: risk of atrial fibrillation in patients with left ventricular systolic dysfunction [17], the snoring *per se* increasing the risk of heart failure and mortality [18], increasing mortality risk in patients with CKD on hemodialysis [15] and peritoneal dialysis [16] and increasing mortality risk associated with hypoxemia [19].

To that end, although SDB is highly prevalent and may increase mortality risk in patients with CKD, the diagnosis is still under estimated. The reasons that lead to under-diagnosis may be related to the lack of knowledge of sleep disorders by nephrologists, the absence of specific clinical factors that facilitate the diagnosis, and the need for additional tests, that may not always be available. To address this, this chapter will review several aspects of the SDB in patients with CKD, in an effort to summarize the growing body of literature in this field.

PRESENTATION OF SDB IN CKD POPULATION

Patients with CKD exhibit symptoms of SDB at much lower frequency compared to those without CKD, making recognition of this disorder difficult despite higher frequency compared to the general population [20–22]. The presence of snoring, witnessed apnea, daytime sleepiness, unrefreshing sleep and morning headaches are significantly less frequent

in patients with OSA with CKD compared to those without CKD [21]. Moreover, these symptoms identified on screening questionnaires appear to be noted at similar frequency in patients with CKD even without OSA. Hence, the standard screening questionnaires appear to have no diagnostic power amongst patients with CKD. Agarwal *et al.* have reported significant lower sleep efficiency and higher sleep fragmentation in patients with CKD [23]. This implies different characteristics rather than absence of sleep related symptoms in patients with CKD.

More recently, there has been a growing interest in understanding the bidirectional relationship between CKD and sleep apnea. Not only is there higher incidence of sleep apnea in patients with CKD, but also sleep apnea is thought to contribute to progression of CKD. This is mediated by intra-renal hypoxia [24, 25] and activation of RAS [21] as primary mechanisms. In addition, OSA is known to have an impact on insulin resistance, onset of diabetes [26, 27], hypertension [28], and obesity [29], all of which are known risk factors for CKD [2].

DIAGNOSIS

Most individual signs and symptoms have limited utility in determining the likelihood of sleep apnea, and no clinical feature is sufficiently sensitive or specific to confirm or exclude the diagnosis. A variety of clinical prediction scores have been evaluated using common signs and symptoms of SDB relating to snoring, observed apneas, body mass index, age, neck circumference, gender and sleepiness, that are easily obtained and interpreted. Unfortunately, their sensitivity is generally much higher than their specificity and they are more useful for decreasing the chance of having SDB. Examples of such questionnaires include the STOP-Bang questionnaire, the sleep apnea clinical score (SACS), and the Berlin questionnaire. Their sensitivity and specificity range from 80 to 86% and 46 to 56% respectively, when OSA is defined as an AHI > 5 events per hour [30–32].

The diagnosis of SDB is based upon the presence or absence of related symptoms, as well as the frequency of respiratory events during sleep as measured by polysomnography (PSG). Full night, attended, in-laboratory polysomnography is considered the gold-standard diagnostic test for SDB. Out-of-center sleep testing is an alternative for patients without comorbidities and in whom there is a high probability of SDB.

During PSG, the patient sleeps while being connected to a variety of monitoring devices that record physiologic variables. Monitoring includes electroencephalogram, electro-oculogram, chin electromyogram, respiratory effort, and airflow measurements. PSG, although considered the gold standard for the diagnosis of SDB, is expensive and time consuming. In addition, night-to-night variability makes it possible for a single study to underestimate the severity of SDB. Therefore, it is reasonable to consider repeating the baseline PSG if there is a strong clinical suspicion for SDB with a negative PSG [33].

According to the International Classification of Sleep Disorders, 3rd ed, published in 2014 by The American Academy of Sleep Medicine, the diagnosis of obstructive sleep apnea is confirmed if there are five or more predominantly obstructive respiratory events (obstructive

and mixed apneas, hypopneas, or RERAs) per hour of sleep (for polysomnography) or recording time (for OCST) in a patient with one or more associated symptoms or comorbidities or if there are 15 or more predominantly obstructive respiratory events per hour of sleep or recording time.

CSA diagnosis requires five or more predominantly central apneas and/or central hypopneas per hour of sleep in a PSG study in a patient with one or more associated symptoms and this finding could not be better explained by another concurrent sleep disorder or a certain medication use such as opioid [34, 35].

CENTRAL AND OBSTRUCTIVE SLEEP APNEA IN CKD POPULATION

A proportion of patients appear to exhibit features of both types (OSA and CSA), a condition often described as mixed apnea. OSA occurs due to intermittent closure of the upper airway during sleep and CSA occurs due to intermittent loss of respiratory drive.

Daytime sleepiness, moodiness, irritability, lack of concentration, memory impairment, morning headaches, history of hypertension, type 2 diabetes mellitus, cardiovascular disease, cerebrovascular disease, or renal disease are common features of SDB.

There is a high prevalence of SDB in hemodialysis patients [36, 37], and OSA is the predominant type affecting approximately 75% of the cases [38]. The prevalence of CSA appears to be higher among patients who are elderly, male, or have certain comorbid conditions as left ventricular dysfunction, stroke or CKD. In patients on dialysis as well as in patients with congestive heart failure (CHF), fluid overload and pulmonary congestion activate lung vagal irritant receptors and stimulate hyperventilation and hypocapnia, which induces central apnea [39, 40]. Atrial fibrillation, CHF, and metabolic acidosis might have an important role in the occurrence of CSA in hemodialysis patients [38].

IMPACT OF RENAL REPLACEMENT THERAPY ON SDB

As the kidney function declines, the prevalence of SDB increases [21], such that patients on dialysis have the highest prevalence of this sleep disorder. Both SDB (mainly obstructive) and hypoxemia are more frequent in patients on hemodialysis than non-dialysis CKD patients [20].

The reported prevalence of SDB in patients under conventional hemodialysis and peritoneal dialysis are usually >50% [41, 42]. New methods with intensified dialysis regimens that change frequency and duration of sessions have been proposed in order to optimize the uremic parameters as well as fluid control. These new renal replacement therapies include short daily dialysis (1.5–2hours, 5–6 times a week), long hemodialysis, usually during nocturnal period (6–8hours, 5–6 times a week), and nocturnal peritoneal automated dialysis. Brief overview of impact of these on SDB is described below:

Short Daily Dialysis

One study demonstrated a prevalence of OSA of 33.3% in patients receiving short daily dialysis as compared to 53.3% of patients receiving conventional hemodialysis ($p=0.083$)

[13]. Authors found that higher dialysis dose correlates with lower risk for obstructive sleep apnea. It is important to note that this was a non-randomized observational study.

Nocturnal Long Hemodialysis (NHD)

Hanly *et al.* demonstrated that this modality of dialysis was associated with a significant improvement of sleep apnea, by switching fourteen patients who were undergoing conventional hemodialysis to nocturnal hemodialysis (eight hours during each of six or seven nights a week) [43]. Patients underwent PSG at baseline and again 6 to 15 months later on one night when they were undergoing nocturnal hemodialysis and on another night when they were not. Authors showed that the conversion from conventional hemodialysis to nocturnal hemodialysis was associated with a reduction in the frequency of apnea and hypopnea from 25 ± 25 to 8 ± 8 events per hour of sleep ($p=0.03$). They also showed that the AHI measured on nights when they were not undergoing nocturnal hemodialysis was greater than that on nights when they were undergoing nocturnal hemodialysis, but it still remained lower than it had been during the period when they were undergoing conventional hemodialysis ($P=0.05$).

Nocturnal Automatic Peritoneal Dialysis

The conversion from continuous ambulatory peritoneal dialysis (CAPD) to nocturnal automatic peritoneal dialysis (NPD) was associated to an improvement of sleep apnea [44]. The authors showed that the prevalence of an AHI>15 events per hour of sleep was 21.1% and 41.1%, while on CAPD or NPD, respectively. In addition, authors demonstrated by magnetic resonance imaging that there was a reduction in pharyngeal volume and an increase in the minimal pharyngeal cross-sectional area after conversion from CAPD to NPD. The imaging findings along with the differences in the bioimpedance spectroscopy measurements of third-spaced fluid of CAPD and NPD patients helped authors conclude that better volume status and possibly, better uremic control helps improve SDB in these patients.

INFLUENCE OF SDB IN OUTCOMES

Sleep apnea has been widely recognized as a risk factor for cardiovascular morbidity and mortality. There have been small studies evaluating the direct relationship of sleep apnea with some suggestion of increased mortality amongst CKD and end-stage renal disease (ESRD) patients [16, 45]. The reason for this are likely compounding effects of kidney disease over established relationships of OSA with hypertension [28], atrial fibrillation [46, 47], coronary artery disease [48, 49], stroke [50] amongst other precursors of cardiovascular mortality. Sleep apnea is also known to increase oxidative stress, inflammation and possibly atherosclerosis [51–54]. Further concern regarding is corroborated from studies by Zoccali *et al.* who have shown relationship of nocturnal hypoxemia with left ventricular hypertrophy and high rate of incident cardiovascular complications in patients on dialysis [55]. Further studies are necessary to independently evaluate impact of SDB on mortality amongst patients with kidney disease.

SDB significantly impairs cognitive performance especially, attention, memory and executive function in the general population [56, 57]. Kang *et al.* have recently evaluated the

cognitive performance in CKD patients with appreciable impact on cognitive function, most prominently verbal memory [58]. Unfortunately, OSA and various sleep disorders that impact sleep quality also markedly impair quality of life amongst patients with kidney disease [59–62]. Effect of OSA on renal function has been discussed previously. See “Presentation of SDB in CKD”³

TREATMENT

The objectives of therapy are to improve signs and symptoms of OSA, ameliorate sleep disturbances, and normalize the apnea hypopnea index and oxyhemoglobin saturation levels.

Continuous positive airway pressure (CPAP) is considered the modality of choice for treatment of SBD, which has been shown to improve mortality in the general population [63, 64]. However, the compliance of CPAP is not satisfactory. Decreased adherence can lessen the potential benefits of positive airway pressure devices therapy. It is estimated that 20 to 40 percent of patients do not use their positive airway pressure device and many others do not use it all night, every night [65]. As an alternative, oxygen therapy was tested in a population of 40 individuals on peritoneal dialysis which appears to be effective in decreasing hypopneas and central apneas by ameliorating the oxygen desaturation [66].

Although OSA has been associated with increased cardiovascular risk and mortality in CKD patients [16], to our knowledge, no studies have demonstrated improvement in mortality with treatment of OSA amongst patients with ESRD. The treatment of sleep apnea in this population is extrapolated from results obtained from the general population. It is plausible to consider that, patients with CKD as having high risk of mortality and therefore may derive greater benefit from CPAP therapy. Nevertheless, studies confirming this benefit are lacking. Until further evidence emerges, it is prudent to suggest behavior modification such as weight loss, exercise, and avoidance of alcohol and/or medications with effects on the central nervous system as well as offer CPAP therapy to all patients.

CONCLUSIONS

This chapter has summarized the importance of recognizing SDB among patients with CKD, emphasizing the association of this sleep disorder with cardiovascular risk and mortality in this population. The future challenge is to verify if the treatment would change the prognosis through randomized studies. Until then, it seems reasonable to recognize the importance of a diagnosis and treatment of SDB in CKD patients, based on the already demonstrated benefit for the general population with normal renal function. In addition, for these patients on dialysis, until further evidence emerges, ultrafiltration goals should be individualized and optimized.

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