Sleep disordered breathing in patients with chronic kidney disease

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The prevalence of sleep-disordered breathing (SDB) in the advanced chronic kidney disease (CKD) patient population has been estimated to be more than 50 per cent. SDB is associated with episodic upper airway obstruction or cessation of breathing during sleep leading to repetitive episodes of hypoxaemia, hypercapnia, and sleep fragmentation, activation of the sympathetic nervous system, endothelial dysfunction, oxidative stress, and inflammation. Clinical consequences of this disorder may include excessive daytime sleepiness, depressed mood, cognitive impairment, hypertension, as well as increased risk for cardiovascular disease and metabolic dysregulation. SDB may also contribute substantially to the daytime sleepiness, poor quality of life, and high rate of cardiovascular disease in CKD patients. Although the causal links between CKD and SDB remain speculative, there are multiple factors related to fluid overload and azotaemia that may contribute to the increased propensity to SDB. Renal transplantation, nocturnal automated peritoneal dialysis and nocturnal haemodialysis have been found to be associated with a reduction in the severity of SDB when compared to conventional forms of dialysis. Nocturnal dialysis modalities may facilitate further understanding of the pathophysiology of SDB as well as provide therapeutic alternatives for patients with both kidney failure and SDB. SDB is an important but often overlooked public health problem in the CKD patient population. Early diagnosis and treatment of SDB may provide better quality of life and attenuate the cardiovascular risk of morbidity and mortality in these patients.

Key words Chronic kidney disease - end-stage renal disease haemodialysis - sleep disordered breathing

Introduction

The prevalence of chronic kidney disease (CKD) is increasing worldwide, and there is increasing evidence linking sleep-disordered breathing (SDB) with kidney disease. CKD describes patients with a chronically decreased glomerular filtration rate (GFR) or other evidence of kidney damage. There are different levels of CKD, which provide the basis of an international classification system1 (Table). CKD is associated with the inability to excrete waste products, control serum electrolytes, secrete or excrete hormones, handle the daily dietary and metabolic acid load, and maintain fluid balance. In the United States, the incidence and prevalence of advanced CKD requiring renal replacement therapy has doubled in the past ten years2. The true prevalence of CKD is unknown in India due to lack of a renal registry but some community-based population studies have reported the prevalence of kidney failure to be between 0.16 and 0.79 per cent3. The potential importance of sleep disordered breathing
in the CKD population is highlighted by the worldwide mortality in end stage renal disease (ESRD) patients as high as 20 per cent per annum and the leading cause of mortality and morbidity in this patient population is cardiovascular disease. One of the risk factors for cardiovascular disease in the general population is SDB\(^3,5\) and the high rate of SDB in the CKD population may contribute to the burden of cardiovascular disease found in this population.

While the prevalence of SDB in the general population is 5-12 per cent using an apnoea hypopnoea cut off of greater than 15, several studies in the advanced CKD patient population have shown a much higher prevalence; ranging from 18 to 80 per cent\(^6-10\). The most precise estimates in the US ESRD population demonstrate that SDB is four times more prevalent in patients with advanced CKD on haemodialysis than in the general population and several studies have demonstrated a higher risk in patients with milder CKD\(^11-13\). Most investigators have outlined the potential for CKD to contribute to SDB, however, it is also possible that there is bi-directional causality such that SDB also contributes to the progression of kidney disease\(^7,14-16\). Given the high prevalence and severe consequences of untreated SDB in the CKD population. The clinical diagnosis, treatment, and pathophysiology of SDB in the context of CKD are reviewed. Also, the disease-targeted treatment of SDB in advanced CKD will be assessed and the extent to which novel dialysis therapies and kidney transplantation improve SDB in this patient population will also be examined.

**Definition of SDB**

Various definitions of SDB have been employed across studies in CKD, making a unified description of the distribution and determinants of SDB difficult in this high-risk population. SDB refers to an abnormal respiratory pattern (apnoeas, hypopnoeas, or respiratory effort related arousals) or an abnormal reduction in gas exchange (hypoventilation) during sleep. Some studies in CKD have relied on questionnaires and/or pulse oximetry to investigate SDB\(^17\). However, these techniques are neither sufficiently sensitive nor specific. At best, they may provide only a rough estimate of the prevalence of SDB. Moreover, they do not determine the type of SDB. SDB can be obstructive, central, or mixed. An obstructive apnoea is characterized by a period of absent or nearly absent air flow for at least 10 sec despite persistent inspiratory efforts. Central apnoea reflects absent airflow for at least 10 sec in conjunction with absent inspiratory efforts\(^18\). Primary Central Sleep Apnoea is defined as five or more central apnoeas per hour of sleep in association with patient report of either excessive daytime sleepiness or frequent arousals and awakenings during sleep or awakening short of breath\(^19\). Mixed apnoea reflects an initial interval during which there is no inspiratory effort (i.e., central apnoea pattern) and a subsequent interval during which there are obstructed breathing efforts. In general, hypopnoea reflects a reduction in airflow that does not reach the criterion for an apnoea and lasting at least 10 sec. Additional criteria that have been used include oxyhaemoglobin saturation and arousal. It is not feasible to distinguish obstructive from central hypopnoeas without quantitative measure of inspiratory effort such as esophageal pressure, diaphragm EMG or calibrated inductance plethysmography\(^18,20\). Although an updated definition of hypopnoea has been recently modified by the American Academy of Sleep Medicine\(^18\), the existing literature is inconsistent\(^21,22\). The apnoea-hypopnoea index (AHI) is the total number of apnoeas and hypopnoeas during sleep divided by the total number of sleep hours. SDB is mild if the AHI is 5-15, moderate if 15-30, and severe if >30. Most studies in CKD have used an AHI cut-off of 10-15/h\(^21-23\) to diagnose SDB in their patients, while others have used a higher AHI measure of >30/h\(^24\). In addition to PSG (polysomnography) performed for studies, epidemiologic reports have demonstrated a higher risk of SDB in CKD using billing codes for sleep apnoea and positive airway pressure devices\(^12\). These inconsistent definitions and methods have influenced the interpretation of study findings and may lead to disparate conclusions on the prevalence and predictors of SDB in CKD.

**Clinical features, diagnosis and treatment of SDB in CKD**

SDB in CKD may not be recognized by clinicians either due to the shared symptom complex between

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**Table. Stages of chronic kidney disease**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate

**Source:** Ref. 1

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**Reference**

\(^1\) Ref. 1

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**Definition of SDB**

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**Clinical features, diagnosis and treatment of SDB in CKD**

SDB in CKD may not be recognized by clinicians either due to the shared symptom complex between
uraeemia and SDB or the lack of association between the normal risk factors for SDB in the setting of CKD. The presentation of SDB in patients with CKD differs in that bed-partners report apnoeas during sleep less frequently, snoring is less intense and patients are often not overweight. Unlike the general population, obesity and hypertension are not consistently associated with SDB in dialysis patients. This is probably related to the unique role of uraemic toxins, volume overload, and autonomic dysfunction in promoting SDB among the advanced CKD patient population. The association between SDB and daytime sleepiness is weaker in the CKD population.

While questionnaires and oximetry have been used in the general population for screening, there has not been strong evidence supporting their use for clinical care in the CKD population. In order to facilitate prioritization of patients for diagnostic studies, investigators have attempted to identify the clinical features that are most useful in estimating the probability that a patient had SDB by comparing scores on self-reported disease-specific questionnaires with objective PSG data. The Berlin questionnaire, for example, has been validated against PSG in the general population. Scoring high risk patients using the Berlin questionnaire had a sensitivity of 0.86 and specificity of 0.77. Flemons et al. investigated the likelihood ratios for a SDB clinical prediction rule. Predictors of SDB included neck circumference, hypertension, habitual snoring, and bed partner reports of nocturnal gasping/choking respirations. A SDB clinical score of less than 5 had a likelihood ratio of 0.25 and a corresponding post-test probability of 17 per cent, while a score of greater than 15 had a likelihood ratio of 5.17 and post-test probability of 81 per cent. The use of pulse oximetry may provide the opportunity to screen the high risk CKD population with limited costs. However, other studies have challenged the use of overnight oximetry alone in the diagnosis of SDB as it was found to be either a sensitive or a specific test for SDB, but not both. In sum, there is currently no evidence-based strategy for screening CKD patients for SDB.

The gold standard for the diagnosis of SDB is still an overnight in-laboratory PSG including monitoring of the electrooculogram, electroencephalogram (EEG), submental electromyogram, oral airflow by thermistors and nasal airflow by recording pressure fluctuations at the nares, Chest wall (rib cage and abdominal) movement, usually by inductance plethysmography to reflect ventilatory effort, oxygen saturation, electrocardiogram (ECG), body position and video. Disadvantages of PSG include the need for specialized equipment and personnel which engenders high cost and limited availability. Portable monitoring refers to the diagnostic evaluation of SDB outside a conventional sleep laboratory. It has evolved as an alternative to PSG because it is convenient, relatively accurate, and less costly. Fewer physiologic variables are measured using portable monitors compared to PSG, but the use of portable monitors can be performed in the patient’s home or in a hospital room without a technician to attend the study. The American Academy of Sleep Medicine has recommended that portable monitors should only be used for the diagnostic evaluation of suspected SDB when patients have a high pre-test probability of having moderate to severe SDB and have no co-morbid medical or sleep disorders. This recommendation limits the use of portable monitors in dialysis patients, for whom it is otherwise an attractive option given the convenience of scheduling studies around their dialysis treatments.

Many sleep specialists advocate initiation of treatment for SDB when the AHI is greater than 15 events per hour, or the AHI is between 5 and 14 events per hour with associated clinical sequelae. Clinical sequelae may include excessive sleepiness, impaired neurocognitive function, mood disorders, insomnia, and/or cardiovascular disease (e.g., hypertension, ischaemic heart disease, and stroke). Although lifestyle management such as weight loss, cessation of smoking and avoiding caffeinated drinks and alcohol is recommended, evidence of their effectiveness is lacking in patients with CKD. The mainstay of medical treatment is continuous positive airways pressure (CPAP) which introduces positive pressure to the upper air passages via a nasal interface, face mask or specialized oral appliance. About 20 to 40 per cent of patients will not use CPAP, and others do not use it throughout the entire night. In the general population, treatment of SDB with CPAP has been shown to improve vigilance, cognition, sexual performance, quality of life and also to restore nocturnal blood pressure dipping. Pressman et al. studied the effect of CPAP on eight ESRD patients with SDB and demonstrated an improvement in nocturnal oxygenation as well as daytime alertness. Larger studies are required to evaluate the efficacy of CPAP treatment for CKD population.
Pathophysiology of SDB in the CKD patients

The aetiology of SDB among patients with the advanced CKD patients is likely multifactorial and may be due to ventilatory instability, volume overload, upper airway narrowing, older age, and other co-morbidities such as diabetes. Obstructive SDB is the predominant type in the general population, as well as in the CKD patients. Earlier studies in the CKD patients undergoing haemodialysis demonstrated a distribution of both central and obstructive SDB. Here, it is important to recognize the possible role of acetate, once a commonly used buffer for haemodialysis. It favours development of intradialytic hypoxaemia through hypoventilation and ventilation-perfusion changes. Jean et al. assessed the influence of buffer, acetate or bicarbonate, on sleep and ventilation. Central apnoea occurred more frequently during the night following acetate dialysis and obstructive apnoeas were not different. The respiratory drive operates mainly under chemoreflex control. Effective ventilatory rhythmogenesis in the absence of stimuli associated with wakefulness is critically dependent on chemoreceptor stimulation secondary to PCO2 during non rapid eye movement (NREM) sleep. However, increased chemoresponsiveness associated with ESRD can increase loop-gain promoting destabilization of central respiratory control and contributing to SDB.

Patients with CKD may also develop SDB through mechanisms that promote upper airway occlusion during sleep. CKD patients are vulnerable to fluid overload which could contribute to pharyngeal narrowing by causing increased fluid volume in the neck and peripharyngeal structures. In a study by Chiu et al., a significant increase in neck circumference and pharyngeal resistance was found with only 0.5 l of fluid shift in healthy patients during recumbency. Most of the CKD patients on conventional haemodialysis require an average of 2 to 3 l of ultrafiltration per thrice-weekly dialysis session. Beecroft et al. showed that the pharynx is narrower in patients with CKD on haemodialysis when compared to those with normal renal function, which may contribute to the upper airway occlusion and thereby to SDB in dialysis patients. Another potential cause of pharyngeal narrowing is upper airway dilator muscle dysfunction secondary to neuropathy or myopathy associated with either chronic uraemia or the underlying cause of CKD, such as diabetes mellitus.

Clinical impact of SDB on CKD patients

Similar to findings in the general population, SDB is associated with impaired quality of life in CKD patients on dialysis. SDB causes excessive daytime sleepiness which has been linked to hazardous driving and may contribute to poorer vocational and rehabilitation potential in CKD patients. SDB has been linked with markers of cardiovascular disease in CKD. SDB in those with CKD disrupts the normal NREM sleep, attenuates the vagal modulation of heart rate, with a predominance of the sympathetic nervous system. Increased cardiac and peripheral adrenergic drive may help explain why nocturnal hypoxaemia has been associated with left ventricular hypertrophy, hypertension and increased cardiovascular events in the haemodialysis population. Jung et al. demonstrated both an association between the severity of SDB and coronary calcification scores and an association of nocturnal hypoxia with decreased total antioxidant status in patients on haemodialysis. A significant positive correlation between obstructive AHI and coronary atherosclerotic plaque volume, even in the absence of significant oxygen desaturation was shown by Turmel et al. in non-CKD patients suggesting a role of sleep fragmentation itself in atherosclerosis.

Impact of the mode of dialysis therapy on SDB in CKD

While conventional forms of dialysis have not been shown to reduce SDB, the conversion from daytime to nocturnal dialysis has been associated with reduced SDB among both haemodialysis and peritoneal dialysis patients. Nocturnal haemodialysis patients undergo overnight home dialysis (6-7 times per week) and it has been associated with improvements in several cardiovascular risk factors including hypertension, left ventricular hypertrophy, as well as impaired left ventricular systolic function. Chan et al. showed that higher heart rates and impaired vagal and augmented sympathetic heart rate modulations during sleep in ESRD patients are normalized by nocturnal haemodialysis (NHD). Hanly et al. demonstrated that conversion from CHD to NHD was associated with reduction in AHI in patients with sleep apnoea (Fig. 1). Of the 14 patients were studied, seven had AHI>15. In these seven patients, the AHI significantly decreased from 46 ± 19 to 9 ± 9 per hour.

Thus improvement in SDB from nocturnal haemodialysis is likely related to both better toxin clearance and ultrafiltration. Beecroft et al. found that the conversion from thrice-weekly haemodialysis to NHD was associated with an increase in the pharyngeal
no significant relationship was found between change in lung volumes or BMI and the pharyngeal size. Previous work from the same group has shown that chemoreflex responsiveness is decreased in patients following conversion from thrice-weekly haemodialysis to NHD. Increased chemoresponsiveness is associated with propensity for increased loop-gain and ventilatory instability; therefore, if NHD reduces chemosensitivity, it should dampen loop-gain, improve ventilatory stability and thereby NHD should contribute to reducing SDB.

While nocturnal haemodialysis was associated with improvement in SDB, nocturnal peritoneal dialysis (NPD) was also associated with attenuation in the severity of SDB. Tang et al. compared the effect of the timing and delivery of peritoneal dialysis on SDB. They recruited 23 NPD (nocturnal cycler assisted PD) and 23 CAPD patients. The prevalence of SDB with AHI>15 was 52 per cent for NPD and 91 per cent for CAPD patients. They also studied 24 incident peritoneal dialysis patients who underwent PSG study during mandatory NPD while awaiting their turn for CAPD training. A second PSG was done after they were established on CAPD. Prevalence of SDB was significantly lower with NPD (4.2%) than CAPD (33.3%). AHI markedly increased from 3.4 ± 1.34 during NPD to 14.0 ± 3.46 during CAPD (P<0.001). One contributor to the improvement in SDB may be that NPD reduced total body water based on their bioelectrical impedance analysis.

Renal transplantation and sleep disordered breathing

Similar to nocturnal haemodialysis, improved clearance of uraemic toxins after successful renal transplant would be expected to alleviate SDB. However, with the exception of two case reports describing reversal of SDB after transplantation, other studies have failed to show significant benefit. Beecroft et al. reported that kidney transplantation was associated with a significant reduction in blood urea nitrogen and serum creatinine without significant changes in AHI. Only 3 of the 11 patients with SDB improved. Whilst the authors found no significant correlation of responders with BMI and co-morbid conditions, the role of steroids/ immunosuppressive protocol was not investigated. SDB may contribute to the high prevalence of sleep-related complaints in this patient population. Since cardiovascular disease remains the leading cause of mortality in renal transplant patients and sleep complaints are prevalent in transplant patients, further research is required to determine the extent to which kidney transplantation may improve SDB.

Conclusion

SDB is highly prevalent in patients with CKD where it may contribute to the cardiovascular disease, adding a significant burden to the substantial morbidity and mortality found in this population. As outlined in Fig. 2, the optimal approach to managing SDB in patients with CKD remains under study. The screening for the disorder and appropriate referral for sleep studies in high risk individuals is vital, but the best approach remains to be demonstrated and depends on

Long-term implications of SDB treatment in ESRD

- Need To Diagnose and Monitor
  - History and Physical Exam
  - Polysomnography
- Informed treatment selection
  - Kidney Transplantation
  - Nocturnal Dialysis
  - Use of CPAP
- Treatment Effects
  - Improved daytime functioning
  - Improved BP and LVH

Fig. 2. Implications of sleep-disordered breathing (SDB) treatment in CKD. PSG, polysomnography; CPAP, continuous positive airways pressure; LVH, left ventricular hypertrophy.
local resources. A careful history and exam should be performed and then the next diagnostic steps should be considered. Oximetry alone is not an acceptable screening tool and a negative portable monitor study does not exclude the diagnosis of SDB. In addition to the usual therapy of SDB such as CPAP in CKD patients with dialysis-dependent kidney failure, clinicians may consider both nocturnal forms of dialysis as well as aggressive management of volume status. Larger studies are needed to further elucidate the aetiology of SDB in CKD and its impact on mortality and morbidity in this patient population. It may be that patients with CKD would benefit from disease-specific treatments of SDB.

**Conflict of interest:** Mark Sanders is a scientific consultant to Philips-Respironics which manufactures devices used to monitor sleep, diagnose and treat Sleep-Disordered Breathing and non-invasive ventilation. Consistent with this, he is a co-inventor of BiPAP®, manufactured by Philips-Respironics and has a financial interest in this brand and related technologies by Philips Respironics. In the past, he received research support from Respironics and was on their Speakers Bureau. In the past he was on advisory panels for Sanofi and Cephalon. Mark Unruh has research support from Baxter Healthcare, Dialysis Clinics Inc., and a Norman S. Coplon Award from Satellite Healthcare.

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**References**


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