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**Title:** Sleep Disturbance and Sleep-Disordered Breathing in Haemodialysis

**Running head:** Sleep-disordered breathing in haemodialysis

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**Abstract**

Sleep disturbance is one of the most common dialysis-related symptoms reported by haemodialysis patients. Poor sleep confers significant physical and psychological burden on patients with kidney disease and is associated with reduced quality of life and survival. More recent evidence also indicates that sleep-disordered breathing may be a risk factor for kidney injury.

Despite the high prevalence and the importance of sleep disturbance to patients with kidney disease, relatively few studies have addressed therapeutic interventions to improve patient outcomes for sleep disordered patients, and there is a lack of clinical guideline to aid patient management.

The purpose of this review is to describe the existing studies that have evaluated sleep disorders in the haemodialysis population, outline the current understanding of the pathophysiology of sleep-disordered breathing, and to discuss the role of haemodialysis modality in management of sleep-disordered breathing.

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Sleep disturbance is common in people with chronic kidney disease (CKD) [1], and the severity progresses when deteriorating kidney function necessitates dialysis [2]. Up to 80% of patients with End-Stage Kidney Disease (ESKD) experience sleep disturbance [3,4]. Although sleep disturbance may be associated with declining kidney function and uraemic syndrome [5,6], an increasing dose of standard dialysis treatment in the ESKD population itself does not improve the sleep quality of most patients [7].

The cause of disturbed sleep in haemodialysis patients can be considered as either intrinsic or extrinsic. Pain associated with dialysis treatment, such as chronic pain, cannulation pain or muscle cramping are common external factors that potentially cause sleep disturbance in haemodialysis patients [8,9]. Other uraemia-related problems such as accumulation of uraemic toxins and fluid may reduce sleep efficiency and cause sleep disturbance in patients on maintenance haemodialysis [2,10]. Specific types of sleep disorders in patients receiving dialysis include insomnia, restless leg syndrome (RLS), periodic limb movement disorder (PLMD) and sleep-disordered breathing (SDB) [11-13]. Each may represent different or overlapping clinical entities, with different pathophysiological mechanisms and clinical correlates. For example, anaemia, hyperphosphatemia, reduced melatonin levels and change in circadian rhythm are thought to be the main causes

of insomnia and RLS/PLMD [14-17], whilst upper airway oedema and destabilised ventilatory sensitivity are reported to cause the development of SDB in renal patients [18-20].

Sleep disturbance is one of the most prevalent and intense symptom burdens identified by patients with ESKD [21,22]. The consequences of sleep disorders such as fatigue and depression can profoundly impact patients' mental and physical function, cause poor quality of life (QoL) and adversely affect survival [9,23-26]. Short sleep duration not only is associated with rapid decline in kidney function [27], patients who have less sleep and more total arousals per hour of sleep experience a 50% higher mortality risk compared with those with less sleep disturbance [28].

Despite the significance and high prevalence of sleep disturbance, there is insufficient evidence for clinicians to manage this common symptom burden in the dialysis population [29]. In the absence of robust data to inform improvements in clinical care, patients who receive maintenance dialysis are likely to continue to experience poor QoL.

In this review, we first outline the overall prevalence and known risk factors of intrinsic sleep disturbances in ESKD patients. We then focus on SDB specifically and the relationship between SDB and kidney disease. Finally, we discuss the

proposed mechanism and the influence of dialysis treatment in ESKD patients with SDB.

A literature search was undertaken using the Ovid database, Embase and Medline from 1996 to the present. Keywords used included: sleep wake disorder, sleep, sleep-disordered breathing, sleep apnoea, kidney disease, renal replacement therapy, dialysis, or their corresponding synonyms in MeSH term, with limits on English language and adult (age ≥ 18 years). The focus of this review is on haemodialysis patients; hence the studies on peritoneal dialysis and transplant patients were excluded. There were a total of 546 papers, of which 104 were selected to be of relevance for this review.

**Sleep disturbance in haemodialysis patients: Prevalence and Terminology**

In the last decade, many studies have explored the high prevalence of sleep disturbances in haemodialysis patients (Table 1). Similar studies have been conducted in various countries around the world including Europe, Asia, and the Middle-East, and the common types of sleep disturbance/symptoms identified were insomnia, RLS, sleep apnoea and excessive daytime sleepiness. The overall prevalence of sleep disturbance in haemodialysis patients is between 49-98%.

There are several potential difficulties in interpreting prior literature. Firstly, the terminology used to describe sleep disorders has been inconsistent and not always based on consensus definitions. Some terms describe symptomology that is based on patient complaints. For example, sleep disturbance is used as a general term to describe poor sleep quality or interrupted sleep. Similarly, insomnia describes the symptom of an insufficient amount of sleep or not feeling rested after sleep. The International Classification of Sleep Disorders (ICSD) also includes daytime consequences, such as daytime sleepiness, mood swings or impairment of daytime function, as part of the overall constellation of insomnia [30].

In contrast, some terms describe specific pathophysiological abnormalities that cause symptomatic sleep disturbance. One good example is sleep apnoea, which is defined as a pause in breathing of 10 seconds or more during sleep that is often accompanied by reduction in blood oxygen saturation [31]. Clinically, there are

three types of sleep apnoea: Obstructive sleep apnoea (OSA); central sleep apnoea (CSA); and mixed sleep apnoea [30]. OSA is classified as ventilatory effort, observed by chest movement, but no airflow. CSA is characterised by decreased or absence of ventilatory effort that results in reduced or no airflow. Mixed sleep apnoea, is a clinical presentation of both OSA and CSA [32]. Due to the various clinical presentations associated with sleep apnoea, sleep-disordered breathing has been increasingly used in literature as a general term for all breathing dysfunctions occurring during sleep, which covers diagnoses such as OSA, CSA, as well as sleep-related hypoventilation or hypoxemia disorder [33].

Finally, some terms such as RLS, or PLMD are symptom-based but may reflect specific clinical entities. RLS describes the presence of an irresistible urge to move the legs prior to sleep onset, and the urge to move the legs is often the main reason for sleep disturbance [32]. Similar to RLS, PLMD presents with repetitive and highly stereotyped limb movement that occurs during sleep, but the movement is not limited to the lower limbs and can also be observed in the arms [34]. It is important to note that these disorders/clinical symptoms often do not exist alone. For example, patients who complain of insomnia may fulfil diagnostic criteria for OSA or RLS that lead to insomnia [35]. The cause of sleep disturbance is often complex and multifaceted, and may include psychological components [36], which can make the diagnosis of sleep disorder complicated.

**Existing screening and diagnostic tools**

The complexity of diagnosis and mix of symptomatic and diagnostic labels has led to the development of various screening and assessment tools. Commonly used tools include the Pittsburgh Sleep Quality Index (PSQI) [37], Epworth Sleepiness Scale (ESS) [38], Berlin Questionnaire [39], and the STOP-BANG [40] questionnaire. Each tool has a different purpose and functionality in identifying sleep problems. Although the majority of these tools are validated, it is important to understand their limitations and applicability, when used in the haemodialysis population. Table 2 summarises the most commonly used tools in terms of the number of items, the purpose, the domains measured and the validity.

The PSQI is a tool to distinguish a "good" sleeper from a "poor" sleeper [37]. Studies by Chen et al, Menon et al and Sabet et al used the PSQI to screen for sleep disorders in haemodialysis populations and the prevalence was consistently above 66% (range 66-73%) [12,41,42]. Whilst PSQI is a validated screening tool with excellent sensitivity (89.6%) and specificity (86.5%), it is not a diagnostic tool nor does it reflect sleep disorder severity [37]. Many studies have used PSQI to detect the prevalence of insomnia. However, this could potentially overestimate the significance of strictly defined insomnia. According to ICSD, there are three severities of insomnia: mild, moderate and severe. These are derived based on evidence of impaired daytime function [30]. Using PSQI alone could potentially include patients who experience a one-off bad night sleep with those who have significant daytime dysfunction as the result of constant poor sleep quality. Given

that sleep complaints can be subjective and many people with poor sleep quality/quantity do not experience significant daytime consequences [33], it is important for clinicians to know the severity of sleep disturbance to justify the need for clinical interventions.

The function of ESS is to assess the level of "sleepiness", with a high score (above 10 out of a total score of 24) indicating daytime sleepiness which is believed to be associated with poor sleep quality [38]. Although excessive daytime sleepiness often presents in adults with sleep disorders, it is important to note that there are other factors, such as advancing age, hormonal changes and the use of certain medications, which can also contribute to excessive daytime sleepiness without changing sleep patterns [43]. Renal patients, in particular, can present with some degree of daytime sleepiness irrespective of the presence or absence of sleep disorders due to underlying disease progression with anaemia, uraemic fatigue and depression, [44,45]. A study of 89 CKD patients not receiving haemodialysis (HD) (estimated glomerular filtration rate (eGFR) ≤ 40ml/min/1.73m2) and 75 HD-dependent patients used the ESS questionnaire to screen for excessive daytime sleepiness, found that almost all patients reported excessive daytime sleepiness, but this did not correlate with the severity of sleep disorder [46]. This finding highlights that excessive daytime sleepiness is a common subjective complaint present in patients with kidney disease, and that the use of ESS alone to assess a sleep disorder may overestimate the issue in this population.

In contrast to PSQI and ESS, Berlin and STOP-BANG questionnaires have been designed specifically for sleep-related disordered breathing. The Berlin questionnaire uses prominent risk factors for SDB such as snoring behaviour, daytime sleepiness and the presence of obesity and hypertension to assess the likelihood of SDB. Similarly, STOP-BANG screens for risk factors of SDB but has an additional emphasis on age, body mass index (BMI) and neck circumference. Both Berlin and STOP-BANG have high sensitivity to predict OSA when used in non-disease-specific adult populations (86% and 84% respectively) [39,40]. However, when tested in renal populations, although sensitivity remains high, specificity (compared with gold standard polysomnography), was only 52% (Berlin) and 64% (STOP-BANG) in the CKD group, and 51% and 75% respectively in the ESKD group [47].

There are a number of potential explanations for this result. Firstly, the prevalence of hypertension and elderly patients in CKD and ESKD populations is high [47], which can potentially reduce specificity. Additionally, the traditional correlates of SDB such as excessive daytime sleepiness and snoring behaviour present differently in patients with kidney disease; less snoring behaviour was observed in ESKD patients with OSA compared with OSA patients with normal kidney function [48,49]. This highlights a potential issue of using these questionnaire tools alone and the need for using objective measures to assess SDB in patients with kidney disease.

The gold standard for the diagnosis of SDB is polysomnography (PSG) [50]. PSG is an objective measure of sleep that records the total sleep time, the percentage of total sleep time in non-rapid eye movement (NREM) and rapid eye movement (REM) stages respectively, apnoea and hypopnea index (AHI) and sleep efficiency. There are five stages of sleep which can be divided into 2 main categories: NREM (stage 1-4) and REM (stage 5) [51]. The structure of sleep stages is described as sleep architecture [51]. Sleep efficiency is calculated by the sum of sleep stages divided by the total time in bed and multiplied by 100, with higher efficiency scores denoting better sleep [52]. PSG can be performed either at home or in-laboratory. Home-based PSG, also known as unattended portable monitoring, records oximetry, airflow, respiratory effort and is considered a good alternative when in-laboratory PSG is not feasible [53]. In-laboratory PSG monitors additional complex body functions including brain activity, eye movements, muscle activity or skeletal muscle activation, heart rhythm and oxygen levels during sleep, and from a technical point, is superior to home-based PSG [54]. The severity of SDB can be identified through AHI reported in a PSG. AHI is the total number of apnoea and hypopnea events during sleep divided by the total number of sleep hours [55]. AHI categorises sleep apnoea into three levels, with mild sleep apnoea defined as an AHI of 5-15/hour, moderate 15-30 and severe > 30 [55]. Parker et al is one of the few studies that have reported sleep quality of haemodialysis patients using an objective measure [56]. Sixteen HD and 8 CKD (stage 4-5 pre HD) patients were enrolled in the study, and both groups showed reduced total sleep

time (≤6 hours) and efficiency (mean: 77% in CKD group and 87% in HD group) compared with normative data in the same age group.

The total sleep time and sleep efficiency can also be objectively measured by actigraphy [57]. An actigraph is a device that can be worn by an individual to record movement. Although actigraphy does not provide comprehensive analysis of aspects of sleep patterns such as sleep architecture and AHI, it is recognised as clinically useful particularly in the evaluation of treatment outcomes [58]. Barmar et al studied 36 CKD (stage 4-5-pre HD) and 51 HD patients using a wrist actigraphy for 2 weeks, to document patients' total sleep time, sleep efficiency and fragmentation index. They found that although both groups had reduced total sleep time and efficiency, the HD group fared worse in all measures. Compared with the CKD group the total sleep time, sleep efficiency, and fragmentation index were 343 *vs*.410 (min), 71% *vs* 77% and 28.7 *vs* 24 respectively. Although this was a single-centred study with a small sample size, it suggests that dialysis patients have significant sleep impairment and that dialysis treatment does not ameliorate sleep problems [59].

**Risk factors for sleep-disordered breathing in haemodialysis patients**

In the general population risk factors for SDB include male gender, obesity, hypertension and neck circumference (>40 centimetres) [60,61]. Although similar risk factors are identified in the haemodialysis population [62,63], some of these

factors are not as pronounced nor as useful to screen for SDB in patients with ESKD.

Gender is a predisposed risk factor for a certain type of sleep disorder [64]. It is believed that differences in hormones, body fat and physical attributes can contribute to differences in sleep disorders. For example, insomnia is more female predominant due to changes in hormones (menstrual cycle or menopause), and sleep-disordered breathing is more often found in males due to larger pharyngeal length [65]. In the haemodialysis population, gender difference does not correlate to poor sleep quality [11,66,67], nor to the presence of SDB [63,68,69]. Tada et al assessed 119 ESKD patients and compared those with SDB (defined by oxygen desaturation index (ODI) more than 5) to those without (ODI less than 5); they found no differences in gender between the two groups [68]. A similar finding was reported by Pfister et al using ODI of 15 as a cut-off point [63]. Ogna et al further demonstrated that gender was a weak predictor of SDB in the haemodialysis population (OR: 0.72; CI: 0.12-4.20, P>0.2) and should not be used to screen for SDB in this population [69].

Obesity and, particularly, a large neck circumference are strong predictors of SDB in the general population [60]. Fat deposition in the tissues, particularly surrounding the upper airway (neck circumference) is believed to result in a smaller lumen and collapsible upper airway and considered a predisposition to

apnoea [70]. Several studies have reported positive correlations between high body mass index (BMI) and the development of SDB in haemodialysis patients [62,68,71,72]. However, a high BMI is not a perfect measure of excess fat, and certainly not a reflection of excess localised fat. In haemodialysis patients, the value of BMI is further affected by fluid overload and protein-energy wasting, whereby excess catabolism of muscle and fat occur as kidney disease progresses [73]. For this reason, neck circumference (>40cm) is increasingly recognised as a more predictive factor of SDB in the haemodialysis population [69]. In haemodialysis patients, an increased neck circumference is positively associated with fluid overload and severity of SDB [74,75]. Ogna et al described a positive association between less fluid overload (after a haemodialysis treatment) and a lower AHI in 12 haemodialysis patients ($r=0.49$, $p=0.04$) [75]. Lyons et al further supported the effect of fluid removal in 15 haemodialysis patients, and reported an ultrafiltration of 2.17 ± 0.45 litres in dialysis decreases AHI by 36% (AHI 43.8±20.3 to 28.0±17.7, $p<0.001$). Both studies indicate that haemodialysis treatment with fluid removal had impact on AHI, which supports the existing evidence that fluid accumulation may cause airway narrowing and symptoms of SDB in haemodialysis patients.

**Impact of SDB on kidney injury and patient outcomes**

Although most studies focus on the effect of renal disease in causing or

exacerbating sleep disorders [5,6,76-78], there is some evidence that SDB may itself contribute to renal disease and its outcomes. Hypoxia and hypercapnia, as the result of sleep apnoea, increase sympathetic neural tone and cause persistent hypertension [79], which can cause kidney injury. A large national study compared 43,434 individuals (8687 with sleep apnoea; 34,747 without sleep apnoea) and found that the risk of CKD development was 1.58 times greater in patients with sleep apnoea than in those without (adjusted HR 1.58, 95% CI: 1.29–1.94) [80]. This study did not exclude patients with hypertension and/or diabetes, which are the common comorbidities of CKD. There were more patients with hypertension and diabetes in the sleep apnoea cohort than the non-sleep apnoea cohort (20% vs 13%; 38% vs 24%, respectively, $P<0.001$), which may have confounded the study results. Chou *et al* analysed the relationship between the severity of sleep apnoea and kidney function of 40 individuals without hypertension or diabetes. AHI was used to assess the severity of sleep apnoea, and they found that higher AHI was independently associated with worse kidney outcomes, assessed by urine albumin to creatinine ratio ($\beta=0.26$, $P=0.01$, $R^2=0.17$) and eGFR ($\beta=0.32$, $P<0.01$, $R^2=0.32$) [81]. The study authors suggest that sleep apnoea is an independent risk factor for kidney injury and potentially a predictor of progression of kidney disease.

Although the relationship between severity of SDB and mortality remains unproven, there is some evidence that poorer sleep quality is associated with

worse mortality. Unruh *et al* found in 909 haemodialysis patients that a decline in sleep quality during the first year on dialysis was associated with shorter survival time compared with those who had stable or improved sleep quality (HR 1.44; 95% CI: 1.13-1.83, *P*=0.003) [24]. Benz et al also found that patients (n=29) with more sleep disturbance (quantified by PSG) had 50% less chance of survival compared to those with less sleep disturbance (*P*=0.007) [28].

**Proposed mechanisms for development of SDB in haemodialysis patients**

Fluid accumulation and disturbed respiratory drive are the two mechanisms that have been most frequently postulated for the high prevalence of SDB in haemodialysis patients (Figure 1). Excess fluid in these patients can redistribute to the upper airway when they lie down at night and cause pharyngeal narrowing and OSA [69,74,82-84]. Elias et al studied 20 haemodialysis patients using bioelectrical impedance to measure volume status and magnetic resonance imaging to record upper airway mucosal water content and internal jugular volume. They found that jugular volume and upper airway congestion were associated with worse apnoea (assessed by AHI), and together accounted for 72% of the variability in AHI scores [20]. Pharyngeal narrowing in the dialysis population was reported by Beecroft et al using an acoustic pharyngometer, HD patients (N=44) were found to have a smaller pharyngeal area when compared with a non-renal group (N=41) (3.04 vs 3.46 cm; *P*=0.033); and this difference was proposed to be the factor responsible for sleep apnoea in dialysis patients [85].

De-stabilised chemoreceptor responsiveness is another potential cause of SDB in haemodialysis patients [86]. Normal respiratory drive is regulated by the chemoreceptors base on the change of concentration in partial pressure of oxygen ($pO_2$), carbon dioxide ($pCO_2$) and pH of blood [87]. For example, when there is an increase in pCO2 leading to a decrease in pH, the chemoreceptors will detect the change and stimulate ventilation to maintain homeostatic regulation. When the chemoreceptors are hyperactive due to prolonged or uncorrected hypoxia or hypercapnia, instability and variability in respiratory control will occur and cause periodic breathing [88]. During normal NREM sleep, ventilation is predominately controlled by the chemoreceptors [89]; therefore, changes in chemoreflex sensitivity could cause sleep disturbance by promoting periodic breathing during sleep [19].

Beecroft et al confirmed increased chemoreflex sensitivity in HD patients by studying 58 chronic HD patients; 38 were apnoeic and 20 non-apnoeic as assessed by AHI. Chemoreflex responsiveness was measured by ventilatory sensitivity to $pCO_2$ level using the modified Read rebreathing technique [90], where participants were asked to perform voluntary hyperventilation for 5 mins and ventilation was measured from hypocapnia to hypercapnia. In this procedure, chemoreflex responses can be determined by the difference between ventilatory responses to $pCO_2$ at high constant O2 tension (isoxic hyperoxic) and low constant O2 tension (isoxic hypoxic) [91]. The total respiratory response consists of central and

peripheral chemoreflexes, and because the main trigger of peripheral chemoreceptors is the change of $pCO_2$ level at low constant O2 tension, when the test is performed during hyperoxia, the ventilatory response mainly reflects the activity of central chemoreflexes [90]. The difference between hyperoxic and hypoxic responses therefore represents the peripheral chemoreflex response [91]. They found that although all patients had the same ventilatory threshold; the apnoeic group showed higher ventilatory sensitivity during both isoxic hypoxia and hyperoxia compared with the non-apnoea group. This suggested that increased chemoreflex sensitivity (both central and peripheral) in HD patients can lead to destabilisation of respiratory control and result in sleep apnoea [18].

**The influence of dialysis treatment in SDB**

Although the mechanism responsible for increased chemoreflex sensitivity in dialysis patients remains unclear, chemoreflex responsiveness can be enhanced by metabolic acidosis [92]. Patients who require chronic haemodialysis are often acidemic prior to each dialysis treatment [93]. During a haemodialysis treatment, bicarbonate is used as a buffer system to restore normal blood pH levels. Loss of $CO_2$ throughout the dialysis treatment in theory will reduce the $CO_2$ level in the blood and cause hypoventilation [94]. Whether increasing dialysis intensity will exacerbate the apnoea episodes due to dialysis-induced hypoventilation, or improve the clinical symptom of SDB by reducing fluid retention and the sensitivity of the chemoreflex remains unclear.

Currently, the most common dialysis model is conventional haemodialysis which provides daytime treatment 3 times/week for 4 hours a day. Intensified dialysis modalities such as nocturnal haemodialysis (NHD) have been explored as a management approach for sleep apnoea [95]. In contrast to conventional dialysis, NHD delivers slow, frequent, and long dialysis treatment (6-7nights/week for 10-12 hours during the night), which has shown better efficacy in uraemia and fluid control [96,97]. Hanly et al compared the effect of conventional dialysis (4 hours daytime/3 times/week) and NHD (8hours/ 6-7nights/week) on AHI scores in patients with sleep apnoea. They found that the frequency of AHI was significantly reduced (from mean 25±25 to 8±8, P=0.03) when patients were switched to NHD from conventional HD [98]. NHD is positively associated with decreasing chemosensitivity and increasing pharyngeal size [99-101].

Nocturnal dialysis however, is a therapy, which is not viable for most haemodialysis patients. There is clearly a need to explore the effectiveness of dialysis treatment on SDB using more-widely available dialysis treatments. Currently there are no interventional studies comparing the effect of increasing dialysis dose on conventional haemodialysis and SDB, nor has any study investigated the effect of haemodiafiltration (HDF). Some studies indicate that HDF reduces all-cause mortality in HD patients as well as improving blood

pressure, fluid control, nutritional status and anaemia [102,103], all of which have been linked to sleep disturbance [104-106].

Clearance in standard HD is predominantly due to diffusion, which enables effective removal of low molecular weight molecules (< 500 Daltons (Da)) such as urea (60 Da) and creatinine (113 Da) [107]. This method however is less effective in removal of middle ( 0.5-600 kDa ) to large (>60 kDa) molecular weight molecules [108], which are considered to mediate many of the adverse effects of uraemia . HDF utilises convection which enables more effective removal of middle molecular weight molecules, including beta-2 microglobulin (11 kDa) and Leptin (16 kDa) [109,110]. Better clearance of these molecules may reduce chronic inflammation and alleviate symptoms of SDB [111-113] (Figure 1). High serum pro-inflammatory cytokine levels such as high-sensitivity C-reactive protein, serum interleukin-1β and leptin are commonly found in patients with OSA [114-119]. Although the mechanism linking OSA and inflammation is unclear [112], existing evidence suggests that systemic inflammation may be a contributing factor to the pathogenesis of OSA [112,120]. Increased inflammatory responses could potentially cause chemoreflex hypersensitivity by stimulating the carotid body where peripheral chemoreceptors are located [121]. It can also induce upper airway oedema and cause pharyngeal narrowing [85], both of which can exacerbate symptoms of SDB. HDF may be a good alternative in managing sleep disturbance, particularly in SDB [111].

## Conclusion and future direction

The true prevalence of sleep apnoea and overall sleep disorders is difficult to ascertain due to the lack of a standard definition and methodology. However, it is quite clear that sleep disorders are common in both HD-dependent and non-HD requiring kidney patients; they have a detrimental impact on patients' quality of life; and are associated with poor survival. More studies on the management of sleep disorders are required to improve health outcomes in patients with kidney disease; especially studies investigating sleep disorders with objective markers and robust outcome measures. The mechanisms behind the improvement of sleep apnoea in ESKD patients on nocturnal dialysis and other dialysis models should be explored in future studies.

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**Table1. Summary of previous studies on prevalence of sleep disorder in haemodialysis patients**

| Study | Study Design | Limitations | Screening Tool | Population | Sample size | Prevalence |
|---|---|---|---|---|---|---|
| Walker et al 1995[122] | Single centre Observational study | Single centre study<br><br>Non-validated screening tool<br><br>No objective assessment | 1.Unspecified questionnaire contains 19 questions | Canada | N= 54 | 1. 83% (Insomnia)<br>66% (EDS) |
| Chen et al 2006[12] | Observational cross-sectional study | No criteria for diagnosis of common sleep disorders<br><br>No objective assessment | 1. PSQI<br>2. ESS<br>3. Berlin | Taiwan | N= 700 | 1. 66% (Insomnia)<br>2. 17.8% (EDS)<br>3. 15% (OSA) |
| Merlino et al 2008[11] | Multicentre Observational study | No objective assessment | 1. Ohayon method<br>2. IRLSSG<br>3. Berlin<br>4. ESS<br>5. ICSD<br>6. Hatoum's | Italy | N= 883 | 1. 69% (Insomnia)<br>2. 18% (RLS)<br>3. 23% (OSA)<br>4. 11% (EDS)<br>5. 1.4% (narcolepsy)<br>6. 2% (sleep-walking) |
| Elder et al 2008[123] | Retrospective review | Retrospective | 1. KDQOL-SF-36 | France<br>Germany<br>Italy | N= 17034 | 49% (Sleep disorder) |

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|---|---|---|---|---|---|---|
| | | Not using a sleep specific questionnaire<br><br>No objective assessment | | Japan<br>Spain<br>UK<br>US | | |
| Sabry et al 2010[13] | Single centre Observational study | Single centre study<br><br>No objective assessment | 1. Ohayon method<br>2. IRLSSG<br>3. ESS<br>4. ICSD<br>5. Berlin<br>5. Hatoum's | Egypt | N= 88 | 1. 65% (Insomnia)<br>2. 42% (RLS)<br>3. 27% (EDS)<br>4. 16% (Narcolepsy)<br>5. 31% (OSA)<br>6. 3.4% (sleep-walking) |
| Al-Jahdali et al 2010[4] | Observational Cross-sectional study | Single centre study<br><br>No objective assessment | 1. ICSD<br>2. IRLSSG<br>3. ESS<br>4. Berlin<br>5. PSQI | Saudi Arabia | N= 227 | 1. 60% Insomnia<br>2. 46% (RLS)<br>3. 63% (EDS)<br>4. 67% (OSA)<br>5. 98% (Poor sleep quality) |
| Ibrahim et al 2011 [66] | Observational Cross-sectional study | No objective assessment | 1. AIS<br>2. IRLSSG<br>3. Berlin | Egypt | N= 264 | 1. 57% (Insomnia)<br>2. 56% (RLS)<br>3. 21% (OSA) |
| Sabet et al 2012[42] | Observational Cross-sectional study | Single centre study | 1. PSQI | Iran | N= 61 | 73% (Sleep disorders) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | No criteria for diagnosis common sleep disorder | | | | |
| Menon et al 2015[41] | Observational Cross-sectional study | Single centre study<br><br>No criteria for diagnosis common sleep disorder | 1. PSQI | India | N= 126 | 67% (sleep disorders) |

Table 1. PSQI: Pittsburgh sleep quality index, IRLSSG: The international restless legs syndrome study group, ESS: Epworth sleepiness scale, ICSD: International classification sleep disorder, KDQOL-SF-36: Kidney disease quality of life-short form-36, AIS: Arthens insomnia scale, EDS: Excessive daytime sleepiness, OSA: Obstructive sleep apnoea, RLS: Restless leg syndrome,

**Table2. Summary of commonly used screening and assessment tools**

| Questionnaire | Purpose | Domains | Sensitivity | Specificity | Consideration when used in CKD/ESKD patients |
|---|---|---|---|---|---|
| PSQI | Measures sleep quality and sleep habits | Sleep duration, latency and difficulty. Use of sleep medication and daytime function. | 89.6% [37] | 86.5% [37] | No validation in CKD population or community sample. |
| ESS | Measures level of sleepiness | Likelihood of falling sleep | Dependent on the diagnosis, when used to predict OSA (with AHI 5 as cut-off), the sensitivity is reported between 46-66% [124,125]. However, the internal consistency is reported high (Cronbach's alpha statistic=0.88), and considered a reliable tool for measuring daytime sleepiness [126] | | Not validated in CKD population.<br>Not suitable for patients with cognitive impairment. |
| Berlin | Measures risk of sleep apnoea | Severity of snoring, daytime function and history of high blood pressure | 86% (to predict RDI* greater than 5) [39] | 77% (to predict RDI* greater than 5) [39] | Focuses on the traditional risk factors for sleep apnoea such as snoring and daytime sleepiness. These symptoms are not pronounced in CKD/ESKD patients with sleep apnoea. [48,49] |
| STOP-BANG | Measures risk of obstructiv | Observed snoring and stop breathing, daytime function, | 87% (to predict AHI | 31% (to predict AHI | Focuses on the traditional risk factors for sleep apnoea such as snoring and daytime sleepiness. |

| | | | | | |
|---|---|---|---|---|---|
| | e sleep apnoea | high blood pressure and body mass index | greater than 15) [40] | greater than 15) [40] | These symptoms are not pronounced in CKD/ESKD patients with sleep apnoea. [48,49] |

Table 2. PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale: RDI: respiratory disturbance index (average number of apnoeas, hypopneas and respiratory event–related arousals events, AHI: apnoea-hypopnea index (average number of apnoeas and hypopneas events), OSA: obstructive sleep apnoea, CKD: Chronic kidney disease, ESKD: End stage kidney disease

**Figure1. Proposed mechanism for development of SDB in haemodialysis patients**