Prevalence and Correlates of Insomnia and Obstructive Sleep Apnea in Chronic Kidney Disease

Shahbaj Ahmad[1], Manan Gupta[2], Ravi Gupta[3], Mohan Dhyani[4]

[1]Departments of Nephrology, [2-4] Psychiatry and Sleep Clinic, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Doiwala, Dehradun, Uttarakhand, India

Abstract

Background: Poor sleep quality, insomnia, and restless legs syndrome (RLS) and sleep apnea are common in patients with chronic kidney disease (CKD). Clinical correlates of these problems are poorly understood. **Aims:** This study was to find out the prevalence and correlates of insomnia and subjects with 'high risk for obstructive sleep apnea (OSA)' in adults with chronic kidney disease. **Materials and Methods:** One hundred and four adults with CKD were included. Their demographic data, details regarding kidney disease and hemodialysis (HD) were recorded. Presence of insomnia and its severity was assessed. They were screened for sleep apnea using a validated questionnaire. **Results:** Average age was 54.17 (± 12.96) years. 89.4% had stage 5 nephropathy and 78.8% subjects were on regular HD. Males outnumbered females. Insomnia was reported by 35.5%. Among these, 50% had chronic insomnia. Insomnia subjects had higher prevalence of diabetes ($P = 0.01$) and depression ($P < 0.001$). Fifty-one percent subjects were at "high risk for sleep apnea". They had higher prevalence of diabetes ($P < 0.001$), coronary disease ($P = 0.02$), insomnia ($P = 0.008$), and experienced daytime symptoms of insomnia ($P < 0.001$). However, in the logistic regression, only male gender (odds ratio, OR = 13.59) and daytime symptoms of insomnia (OR = 7.34) were found to be associated with "higher risk for sleep apnea". **Conclusion:** Insomnia was prevalent in CKD. Nearly half of these patients are at high risk for sleep apnea and a third of them suffer from insomnia. Hence, these patients should be screened for sleep disorders.

Keywords: Chronic kidney disease, Hemodialysis, Insomnia, Obstructive sleep apnea

Address for correspondence: Dr. Ravi Gupta, Department of Psychiatry and Sleep Clinic, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Doiwala, 248-140, Dehradun, Uttarakhand, India. E-mail: sleepdoc.ravi@gmail.com

Introduction

Sleep problems are commonly seen in patients with chronic kidney disease (CKD). These problems vary in nature and range from insomnia, restless legs syndrome (RLS) to obstructive sleep apnea (OSA). Insomnia has been reported in nearly 60% of subjects on hemodialysis (HD), ranging from difficulty in falling asleep in nearly half of the patients to difficulty in sleep maintenance in a quarter of patients.[1] This is more than expected population prevalence of approximately 15%. Increasing age and RLS have been found to be associated with

insomnia in CKD patients.[1] One large multicentric study that included more than 11,000 patients on maintenance HD reported that nearly half of the subjects complained of poor quality of sleep.[2] Resultantly, these patients were prescribed various medications to induce sleep and to counteract daytime symptoms of insomnia.[2] Needless to mention, these medications might have adversely affected physiological functions in these patients. Besides that, through unknown mechanisms, poor quality sleep has been found to increase the risk of mortality among CKD patients.[2]

Sleep disorders are not just comorbid with CKD, rather, they may be pathophysiologically linked to this problem. Psychological as well as biological factors influence the sleep among CKD patients. From the psychological perspective, the CKD may be considered as a state of chronic stress that may adversely affects the quality of life across all domains.[3] As a result of chronic stress, a higher prevalence of anxiety and depression that has been reported in these patients should not be

surprising.[4,5] Stress, anxiety, and depression are well-known factors leading to insomnia — a common sleep problem — reported in CKD patients. On physiological level, the process of HD can influence neural mechanisms of sleep-wake cycle which are located in the brain by changing the homeostasis.[3] In addition, the circadian factors may also play a role in generation of sleep disorders in these subjects as dialysis shift can influence the zeitgebers. Together, all of these factors not only influence the secretion of melatonin, but also other cues associated with sleep-wake cycle.[3,6-9] Thus, quality of sleep often remains poor in patients undergoing HD. CKD patients are also prone to develop OSA as they are often in a state of fluid excess that can lead to upper airway narrowing by causing edema (vide infra). OSA is characterized by snoring, pauses in breath lasting at least 10 s and oxygen desaturation occurring during sleep.[10] Polysomnography is essential for its diagnosis.[10] Earlier studies have reported that nearly a third of the CKD patients have comorbid OSA.[11] Beecroft *et al.*,[12] suggested that a narrow upper airway could be responsible for the OSA in these patients. This narrowing is thought to be caused by fluid excess and consequent upper airway edema as already mentioned.

Earlier studies have used a variety of measures to examine the sleep problems in CKD patients. These measures include questionnaires, for example, Pittsburg Sleep Quality Index (PSQI), and objectives measures viz., actigraphy or polysomnography.[1,3,13] Each of these methods had some limitations. For example, PSQI cannot diagnose insomnia; rather, it measures the quality of sleep. Quality of sleep cannot be equated with insomnia as diagnosis of insomnia takes into account both qualitative (sleep quality) and quantitative (duration of at least 1 month) dimensions in addition to the impaired daytime functioning.[10] Similarly, actigraphy data may not give us a real estimate of insomnia as majority of subjects with CKD and HD suffer from RLS and periodic limb movement disorder.[3,13] Although, polysomnography is a gold standard tool for diagnosis of OSA, its utility as a diagnostic tool in insomnia is limited; since, sleep perception is a subjective phenomenon. This could be one reason why subjective and objective assessments of sleep quality and duration do not match in insomnia subjects.[14] In total, a number of different measures have been used to assess sleep problems and all of them had some limitation.

Despite the availability of extensive literature discussed so far, our understanding regarding causation or association of sleep problems in CKD patients is limited. In one study, insomnia has been found to be associated with anemia, RLS, anxiety, and depression; but this study did not use the multivariate logistic model and hence interdependence of these variables could not be

established.[15] Furthermore, Merlino *et al.*,[16] assessed prevalence of a number of sleep disorders in CKD patients and found that age, alcohol, smoking, diabetes, polyneuropathy, and dialysis-shift had predicted the occurrence of sleep disorders in patients undergoing HD. Thus, earlier studies have attributed sleep problems to different factors in these patients. In total, previous studies differed in their methodologies and this could be one reason that they had provided conflicting results.[1,3,13,15,16]

Thus, the present study was planned to address prevalence and correlates of insomnia and OSA in subjects with CKD. In this study we used the standard diagnostic criteria for insomnia proposed by American Academy of Sleep Medicine.[10] Although polysomnography would have been a better choice for the diagnosis of OSA, yet owing to financial constrains OSA was screened using a validated questionnaire.[17,18]

Materials and Methods

This study was conducted in the nephrology clinic and dialysis unit of a tertiary care institute. Permission from the institutional ethics committee was obtained beforehand. All consecutive patients presented with the CKD as per standard criteria were included.[19] These criteria required any structural or functional damage to the kidney persisting for at least 3 months. They were explained regarding the objectives and rationale of this study and written informed consent was sought. However, subjects with major neurological deficit, known psychiatric disorder, abusing tobacco, or alcohol in past 6 months, those with craniofacial abnormalities, those suffering from acute exacerbation of chronic obstructive pulmonary disease (COPD), uncontrolled hypothyroidism, and congestive heart failure were excluded from the study. None of these subjects was diagnosed with sleep disorders previously and they were not taking antidepressants or antipsychotics. Subjects younger than 18 years were also excluded from the study.

Information regarding their demographic data and duration of CKD were sought. Details regarding diabetes mellitus, hypertension, coronary artery disease (CAD), stroke, hypothyroidism, and COPD were collected through their medical records. Status of HD and their latest reports of blood parameters, for example, hemoglobin, serum creatinine, serum albumin, serum phosphorus, and serum calcium were also collected through medical records. Estimated glomerular filtration rate (eGFR) was calculated using Cockroft-Gault formula.[20]

An open interview regarding sleep duration and sleep quality was conducted. Frequency of sleep disturbance

was also noted. Family history of sleep problems was also gathered.

Insomnia was diagnosed when a person met following criteria:[10]

a. Quality of sleep: At least one of the following: (i) difficulty in falling asleep, (ii) difficulty in staying asleep, (iii) awakening at least 1 h earlier than usual wake time, and (iv) nonrefreshing sleep or complained of "not getting deep sleep"

b. Duration and frequency: These complaints should have been present for at least one month on most of the nights.

c. They should have experienced at least one daytime symptom of insomnia like poor concentration, fatigue, lethargy.

Whenever any person did not meet duration criteria for the insomnia, but reported symptoms from criteria A and C as mentioned earlier, for at least 2 nights a week, he was considered to be suffering from transient insomnia.[21] Severity of insomnia was assessed using Hindi version of Insomnia Severity Index.[22,23]

Diagnosis of depression was made according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria using structured interview.[21]

OSA was screened using STOP-Bang questionnaire.[17] This questionnaire includes eight items that collect information regarding snoring, daytime tiredness, observed pauses in breath, hypertension, body mass index (BMI), age, neck circumference, and gender. We have done a slight modification in the BMI criteria of this questionnaire as the available literature has lowered the cut-off values of BMI to 25 for the obesity in Asian population.[24] Moreover, earlier work from India has suggested that Indian population with a BMI of 25 or more was at increased risk for OSA.[25] Physical examination was done that included measurement of weight, height, and neck circumference. Neck circumference was assessed with a nonelastic measuring tape at the level of cricothyroid. Height and weight were used to calculate BMI. Subjects obtaining a score of more than 3 on this questionnaire were considered having high risk for OSA.

Statistical analysis

Analysis was done using Statistical Packages for Social Sciences (SPSS) v 17.0 software (Chicago, IL). Descriptive statistics was calculated for the whole of the group. Continuous variables were presented as mean and standard deviation. Chi-square test was applied to compare proportion across groups. Independent sample *t*-test was used to compare means between the groups.

All the variables that reached statistical significance were analyzed in a model using binary logistic regression.

Results

A total of 126 subjects were screened for exclusion criteria. Twenty-two subjects were excluded because of various reasons mentioned under exclusion criteria. Hence, 104 subjects with CKD were finally included in this study. Their demographic and clinical data has been depicted in [Table 1]. Age of these subjects ranged between 22 and 85 years and 20.2% subjects had BMI greater than 25.

Both groups with and without HD were comparable with regards to comorbidities, for example, diabetes, hypertension, CAD, stroke, and COPD.

Males outnumbered females (60.6% males vs 39.4% females). Male and female groups were comparable with respects to age (male: 56 years vs 51.34 years in females), BMI, and prevalence of comorbidities, for example, CAD, diabetes, hypertension, hypothyroidism and stroke. However, males had larger neck circumference as compared to females (38.34 ± 3.39 cm in males vs 34.42 ± 2.91 cm in females; $t = 6.01$; $P < 0.001$). Gender did not affect the duration of CKD. A higher number of females were dialysis dependent as compared to the males (92.7 vs 69.8%; $\chi^2 = 7.76$; $P = 0.004$). They were also undergoing dialysis more frequently (2.12 ± 0.84 per week vs 1.63 ± 1.19 per week in males; $t = -2.26$; $P = 0.02$).

Insomnia

Insomnia fulfilling International Classification of Sleep Disorders-2 (ICSD-2) criteria[10] was reported by 35.5% of

Table 1: Demographic and clinical data of subjects

Variables	
Age (in years)	54.17±12.96
BMI	21.05 ± 5.81
Comorbidities:	
Systemic hypertension	81.7%
Diabetes mellitus	43.3%
Coronary artery disease	13.5%
Hypothyroidism	9.6%
COPD	6.7%
Stroke	6.7%
Data regarding CKD:	
Duration (in months)	44.21±51.86
Stage 5 CKD (%)	89.4%
Hemodialysis (HD):	
Subjects on HD (%)	78.8%
Duration (in months)	17.78±22.34
Frequency of HD (per week)	1.82±1.09

BMI = Body mass index, COPD = Chronic obstructive pulmonary disease, CKD = Chronic kidney disease

the subjects. In addition, transient insomnia (<1 month duration) was reported by 4.8%. Thus, a total of 40.3% had insomnia. Among these, 76.2% complained of insomnia for three or more nights a week. Problems in sleep initiation were reported by 92.8% subjects and 85.71% subjects had problems in maintaining their sleep. Early morning awakening was reported by 57.14% subjects and lack of deep sleep was complained by 16.6% of the subjects. Fifty percent of the subjects with insomnia had insomnia lasting more than 6 months. Chi-square suggested that insomnia was associated with diabetes mellitus (57.1 vs 42.9% in nondiabetics; $P = 0.01$) and depression (64.3 vs 35.7% in nondepressed; $\chi^2 = 12.67$; $P < 0.001$). Other factors were not found to have a significant association with insomnia.

High risk for obstructive sleep apnea

High risk for OSA was found in 51% of the subjects. Male predominance was seen in the "high risk for OSA" group (83 vs 17% in females; $\chi^2 = 22.79$; $P < 0.001$). Chi-square analysis suggested that "high risk for OSA" group had higher prevalence of diabetes mellitus (62.3 vs 23.5% in low risk for OSA; $\chi^2 = 15.88$; $P < 0.001$), CAD (20.8 vs 5.9% in low risk for OSA; $\chi^2 = 4.93$; $P = 0.02$), daytime symptoms of insomnia (84.9 vs 43.1% in low risk for OSA; $\chi^2 = 19.78$; $P < 0.001$), insomnia (52.8 vs 27.5% in low risk for OSA; $\chi^2 = 6.96$; $P = 0.008$). Results of binary logistic regression analysis are shown in [Table 2]. The intercept only model classified only 51% cases; however, when other factors were included in the equation, it increased to 82%. High risk of OSA group scored higher on the insomnia severity index (7.5 vs 4.05 in low risk for OSA; $t = 2.36$; $P = 0.02$). All the factors included in STOP-Bang had significant association with the OSA, as they were the part of the diagnostic questionnaire. Surprisingly, CKD or HD related variables did not show any relation with insomnia and OSA.

Discussion

This study suggested that insomnia was frequent in CKD patients. More than a third of them suffered from insomnia and a half of them were "high risk for OSA". Difficulty in sleep initiation and sleep maintenance were common in insomnia group. Secondly, diabetes

mellitus and depression increased the chances of having insomnia. Thirdly, male gender and "daytime symptoms of insomnia" predicted "high risk for OSA". Lastly, sleep problems were unaffected by duration of CKD and status of HD.

Contrary to the present study where insomnia was seen in nearly one-third of subjects, earlier studies have reported a wide variation in prevalence of insomnia in CKD patients, ranging from 59-69%.[1,15,16] This difference could be attributed to methodological differences across studies (vide supra). Unlike previous studies, we used standard criteria for diagnosis of insomnia which excluded cases of transient insomnia. Hence, we were able to identify clinically relevant insomnia. Another reason for the lower prevalence of insomnia in this study could be inclusion of younger subjects as compared to earlier studies. Moreover, most of the subjects in this study were having stage 5 CKD. In an earlier study, subjects with stage 5 CKD have been found to have greater cognitive impairment as compared to stage 3 and 4 CKD.[26] Thus, lesser prevalence of insomnia in present study could be attributed to ignorance about sleep problems in presence of possible cognitive impairment secondary to depression and stage 5 CKD. Similar results, that is, underreporting of sleep problems by CKD patients has been described earlier, too.[12] Together, these factors could have resulted in a lesser prevalence of insomnia in present study.

Insomnia in CKD subjects could be attributed to a number of factors: Financial burden of therapy, comorbid depression and anxiety, and comorbid sleep disorders like RLS and OSA.[1,15] Financial burden was not an issue as most of the subjects included in this study were either state sponsored or had medical insurance facility. However, like earlier data, in this study, depression and diabetes were found to be associated with insomnia. Insomnia and depression have intricate relationship and insomnia increases the chances of developing depression.[27] Similarly, sleep disorders like insomnia, RLS, and OSA have been found to be associated with diabetes mellitus.[28] We found its association with diabetes, but owing to the cross-sectional nature of the study, we could not assess causality.

Nearly half of the subjects were screened positive for the "high risk for OSA" in this study. Previous studies have reported a prevalence of OSA ranging from 23-34% in CKD patients using Berlin questionnaire or polysomnography.[11,15,16] Higher rates of "high risk for OSA" in present study could be attributed to use of STOP-Bang questionnaire. This questionnaire had been reported to have highest sensitivity, while the Berlin's questionnaire was found to have the highest specificity for predicting the risk for moderate to severe OSA.[18]

Table 2: Factors associated with high risk for OSA				
Factors	B	Wald	Sig.	OR
Diabetes mellitus	−1.99	10.54	0.001	0.13
Male gender	2.61	17.50	0.000	13.59
CAD	−0.56	0.43	0.509	0.57
Insomnia	−0.34	0.30	0.579	0.71
Daytime symptoms of insomnia	1.99	9.88	0.002	7.34

OSA = Obstructive sleep apnea, CAD = Coronary artery disease, Sig. = Significance, OR = Odds ratio.

Thus, there are chances that present study could have resulted in overestimation of "high risk for OSA" because of inclusion of some false positive cases. On the other hand, studies using Berlin's questionnaire could have missed few true positive cases. Since the objective of the present study was to screen and not to diagnose the OSA, use of STOP-Bang questionnaire was justified.

In this study, male gender was found to increase the odds for "high risk for OSA" [Table 2]. Male gender, older age, obesity, and larger neck circumference were reported as risk factors for OSA in end-stage renal disease patients in an earlier study, which supported our results.[29] However, contradictory reports are also available and they did not find any link between male gender, age, and OSA in uremic patients.[16] This difference could be attributed to difference in the population included across studies. It is worth mentioning here that occurrence of OSA depends upon a number of factors including age, gender, BMI, neck circumference, central obesity, craniofacial anatomy, patency of upper airway, etc.[30,31] Varying prevalence and risk factors amongst the studies mentioned so far could be attributable to lack of control over these variables.

Similarly, subjects with "daytime symptoms of insomnia" had higher odds for being the "high risk for OSA". Hence, CKD subjects with these complaints should be specifically assessed for OSA. OSA is associated with frequent arousals and hence, it worsens the quality of sleep. This poor quality sleep is often perceived as insomnia to a number of patients. Besides that, insomnia could be an independent disorder which may co-occur in OSA patients with frequencies higher than general population.[32] In addition, RLS and periodic limb movement during sleep with arousals are not uncommon in CKD patients which worsens the quality of sleep, and these may co-occur with OSA.[13] Although we have not assessed for the RLS in present study; but considering the literature, we presume that this could also be one reason for the insomnia and daytime symptoms of insomnia in these subjects.

Like any other scientific study, this study also had some methodological limitations. First, the number of the subjects in CKD-without HD group was small. Second, we used a questionnaire to screen for OSA. Third, we did not take RLS into account which could have been an important contributory factor for the insomnia. Lastly, it was a cross-sectional study; hence, causation could not be established. Nonetheless, we identified insomnia according to standard criteria (ICSD-2) and frequency of the sleep problems was also taken into account while diagnosing transient insomnia. Further strength of the study lies in avoidance of potential confounders.

Conclusion

A high proportion of CKD patients suffer from insomnia and are at high risk for OSA. It may be difficult to differentiate between insomnia and OSA on clinical grounds as a number of other sleep disorders like RLS may also co-occur in these patients. Male patients with daytime symptoms of insomnia should be screened for OSA as these factors increased the odds of being in "high risk for OSA". Hence, due importance should be given to the sleep problems in these patients and daytime symptoms, for example, fatigue, lethargy, poor concentration, etc. should not be left unaddressed.

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