

Self-assessed sleep quality in chronic kidney disease

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Abstract. *Background:* Although sleep complaints are commonly reported in persons with end stage renal disease (ESRD), little is known about the prevalence of sleep complaints in chronic kidney disease (CKD), and the relation of sleep quality to the severity of kidney disease. *Methods:* We administered the Kidney Disease Quality of Life (KDQOL) sleep scale to 156 subjects, 78 with ESRD and 78 with CKD. Glomerular filtration rate (GFR) was estimated using the six variable Modification of Diet in Renal Disease (MDRD) equation and used to stratify subjects with CKD as mild-moderate (GFR > 25 ml/min/1.73 m²) and advanced (GFR < 25 ml/min/1.73 m²). We used multivariable linear regression to determine independent predictors of KDQOL sleep scale scores. Higher scores indicate higher self-reported quality of sleep. *Results:* Median scores on the KDQOL sleep scale were 59 (interquartile range 40–80) in subjects with ESRD and 69 (interquartile range 53–80) in subjects with CKD ($P = 0.04$). Thirty-four percent of subjects with ESRD, 27% of subjects with advanced CKD, and 14% of subjects with mild to moderate CKD had sleep maintenance disturbances ($P = 0.05$). Thirteen percent of subjects with ESRD, 11% of subjects with advanced CKD, and no subjects with mild-moderate CKD had complaints of daytime somnolence ($P = 0.03$). There was no significant difference in the prevalence of sleep adequacy complaints in persons with ESRD versus CKD. In multivariable analyses, only age and ESRD status (vs. CKD) were significant predictors of lower KDQOL sleep scores. Among subjects with CKD, there was a significant direct association between estimated GFR and scores on the KDQOL sleep scale in non-African American subjects ($P = 0.01$). *Conclusions:* Sleep complaints are common in persons with CKD and ESRD and may be associated with the severity of kidney disease.

Key words: Chronic kidney disease, End stage renal disease, Sleep disturbance

Introduction

Sleep disturbances are common in persons with end stage renal disease (ESRD) and are associated with significant morbidity. Conditions such as sleep apnea, restless legs syndrome and periodic limb movements of sleep have been linked to elevated blood pressure, cardiovascular events and death [1–4]. In addition to specific sleep disorders, disturbances in sleep quality occur in up to 80% of persons with ESRD [5]. Sleep complaints, such as insomnia and daytime somnolence have been linked to lower self-reported quality of life [6].

Despite the significant impact of sleep disturbances, little is known about the correlates of sleep quality in persons with ESRD. Moreover, although sleep disturbances are thought to develop as chronic kidney disease (CKD) progresses towards ESRD, few studies have examined the prevalence or severity of sleep complaints in persons with CKD. Specifically, it is unclear whether the severity of kidney disease is directly related to poor sleep quality. Given the considerable adverse effects of sleep disturbances on clinical outcomes and quality of life, identifying the factors associated with poor sleep is an important goal. The objective of this study was to determine the

prevalence of sleep complaints and factors related to poor sleep quality in persons with CKD and ESRD. We hypothesized that self-reported sleep disturbance would vary directly with the severity of kidney disease.

Methods

Subjects

We recruited ambulatory subjects from three dialysis units and academic nephrology practices affiliated with the University of California San Francisco (UCSF) participating in a cross sectional study of cognitive function. These practices serve an ethnically and socioeconomically diverse population generally from within and around San Francisco. Subjects with ESRD received in-center hemodialysis three times per week, using ultrafiltration controlled machines, bicarbonate dialysate and high-flux polysulfone dialyzers. Subjects with CKD were eligible to participate if they had an estimated GFR <60 ml/min/1.73 m² on at least two occasions during the preceding 12 months. Subjects who had hearing impairments or were not fluent in English were excluded. Participation rates were $>95\%$ for screened subjects with ESRD. Potential subjects with CKD were screened by the treating nephrologist and referred to the study if eligible, thus participation rates were not determined for subjects with CKD. The UCSF Committee for Human Research approved the study and all subjects signed informed consent.

Sleep questionnaire

Participating subjects completed the Kidney Disease Quality of Life (KDQOL) four item sleep subscale. The KDQOL instrument is a self-administered questionnaire previously used in epidemiological studies to assess health related quality of life in persons with kidney disease [7]. The KDQOL sleep subscale was derived from the Medical Outcomes Study Sleep Scale, a validated measure of sleep quality in patients with chronic illnesses [8]. The KDQOL sleep subscale has been demonstrated to have high instrument reliability, and has been correlated with disability days, overall health, and other quality of life measures in persons with ESRD [9]. The sleep subscale consists

of four items corresponding to sleep maintenance disturbance, sleep adequacy, daytime somnolence, and global sleep quality: “Over the past 4 weeks how often do you (1) awaken during the night and have trouble falling asleep again, (2) get the amount of sleep you need, (3) have trouble staying awake during the day”? Each of the first three questions is answered on a qualitative 6-point scale ranging from “none of the time” to “all of the time.” A fourth question asks respondents to rate their overall quality of sleep on a 10-point scale. All four items are weighted equally, and scores reported on a scale of 0–100, with higher scores indicating higher self-reported quality of sleep. Questionnaires were completed with the aid of study personnel if patients had difficulty with self-administration (e.g., blindness).

Covariates

Clinical data were obtained from medical record review and subject interviews. The burden of comorbid conditions was assessed with the Charlson Comorbidity Index [10]. Depressive symptoms were assessed with the 12-item Geriatric Depression Scale (GDS) [11]. Blood pressure was measured at the beginning of a hemodialysis session for subjects with ESRD and during an office visit for subjects with CKD. Laboratory variables were collected within 1 month of questionnaire administration with the exception of parathyroid hormone (PTH), which was measured within 3 and 6 months for ESRD and CKD subjects, respectively. Glomerular filtration rate (GFR) was estimated using the six variable Modification of Diet in Renal Disease (MDRD) equation for subjects with CKD [12].

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or median with interquartile range and categorical variables were expressed as proportions. Between group comparisons were performed using Student's *t*-test, the Wilcoxon rank sum test, the χ^2 -test, or the Kruskal–Wallis test, where appropriate. Correlations among individual question scores and laboratory variables were examined using the Pearson product-moment coefficient. We used multiple linear regression to determine independent

Table 1. Selected subject characteristics

Characteristic	CKD (<i>n</i> = 78)	ESRD (<i>n</i> = 78)	<i>P</i> -value
Age (years)	63.8 ± 14.2	61.4 ± 14.3	0.29
Female (%)	23%	40%	0.02
Race			
Caucasian	55%	17%	< 0.001
Black	26%	53%	
Asian	17%	24%	
Other	2%	6%	
Charlson Comorbidity Index	4.8 ± 2.1	6.0 ± 2.8	0.004
Geriatric Depression Scale	3 ± 3	5 ± 3	< 0.001
Diabetes mellitus (%)	39%	54%	0.06
CAD (%)	35%	33%	0.82
CHF (%)	21%	50%	< 0.001
Stroke (%)	27%	21%	0.32
Benzodiazepine use (%)	9%	9%	0.92
Opiate use (%)	12%	21%	0.17
Antidepressant use (%)	18%	12%	0.26
Weight (kg)	78.7 ± 16.8	73.9 ± 29.3	0.23
Systolic BP (mm Hg)	136 ± 22	153 ± 26	< 0.001
Diastolic BP (mm Hg)	74 ± 13	82 ± 16	0.001
Time on dialysis (months)	–	36 (20–48)	–
KrU (ml/min)	–	1.0 ± 2.0	–
URR (%)	–	69.0 ± 6.8	–
eGFR (ml/min/1.73 m ²)	25.5 (18.7–35.3)	–	–
Creatinine (mg/dl)	3.1 ± 2.0	9.5 ± 3.6	< 0.001
BUN (mg/dl)	51.0 ± 22.6	61.9 ± 21.2	0.002
Albumin (mg/dl)	3.7 ± 0.5	3.7 ± 0.6	0.73
Hemoglobin (g/dl)	12.1 ± 1.5	11.9 ± 1.2	0.36
Calcium (mg/dl)	9.1 ± 0.8	9.3 ± 0.9	0.24
Phosphorus (mg/dl)	4.3 ± 1.2	5.6 ± 1.9	< 0.001
PTH (ng/l)	143 (71–262)	317 (198–501)	< 0.001

Note: Results are expressed as mean ± SD or median (interquartile range). To convert creatinine in mg/dl to μ mol/l multiply by 88.4, blood urea nitrogen (BUN) in mg/dl to mmol/l multiply by 0.357, albumin in g/dl to g/l multiply by 10, hemoglobin in g/dl to g/l multiply by 10, calcium in mg/dl to mmol/l multiply by 0.2495, phosphorus in mg/dl to mmol/l, multiply by 0.3229.

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; BP, blood pressure; KrU, residual urea clearance; URR, Urea reduction ratio; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; PTH, parathyroid hormone.

predictors of the degree of sleep disturbance. For the multivariable analysis, we considered variables associated with the KDQOL sleep subscale score on univariate analysis ($P < 0.10$) as well as selected multiplicative interactions. We fit models with and without the GDS, as sleep disturbance may lead to depression and *vice versa*. We also performed companion analyses stratifying subjects by CKD vs. ESRD status. Two-sided P -value < 0.05 were considered significant. All analyses

were performed with STATA version 8.0 (College Station, TX).

Results

We enrolled 160 subjects, 80 with ESRD and 80 with CKD. One hundred and fifty six subjects (98%) completed the KDQOL sleep subscale questionnaire. Selected subject characteristics are

shown in Table 1. Subjects with CKD had a median estimated GFR of 25.5 ml/min/1.73 m². Subjects with ESRD were more likely to be female and nonwhite. Subjects with ESRD had more extensive comorbid disease (by the Charlson Comorbidity Index), including specifically a significantly higher prevalence of congestive heart failure and depression. As expected, subjects with ESRD had higher systolic and diastolic blood pressure, and higher serum concentrations of creatinine, urea nitrogen, phosphorous and PTH. There was no significant difference in the use of sedating medications.

Figure 1 shows the distribution of KDQOL sleep subscale scores. Median scores on the KDQOL sleep scale were 59 (interquartile range 40–80) in subjects with ESRD and 69 (interquartile range 53–80) in subjects with CKD ($P = 0.04$). Total KDQOL sleep subscale scores were directly correlated with age ($r = 0.26$, $P = 0.0012$) and inversely correlated with serum creatinine ($r = -0.25$, $P = 0.0017$), potassium ($r = -0.18$, $P = 0.03$), phosphorus ($r = -0.17$, $P = 0.05$), and systolic ($r = -0.17$, $P = 0.03$) and diastolic ($r = -0.20$, $P = 0.013$) blood pressure. As expected, the KDQOL sleep subscale was inversely correlated with the GDS ($r = -0.40$, $P < 0.0001$).

Responses to individual questions were examined for subjects with ESRD and for subjects with CKD stratified by the median estimated GFR as advanced CKD (< 25 ml/min/1.73 m², $n = 36$) and mild-moderate CKD (> 25 ml/min/1.73 m², $n = 42$) (Figures 2a–c). Thirty-four percent of subjects with ESRD, 27% of subjects with advanced CKD, and 14% of subjects with mild to moderate CKD had sleep maintenance disturbances (“trouble falling asleep after awakening”) ($P = 0.05$). Thirteen percent of subjects with ESRD, 11% of subjects with advanced CKD, and no subjects with mild-moderate CKD had complaints of daytime somnolence ($P = 0.03$). Thirty-three percent of subjects with ESRD, 22% of subjects with advanced CKD, and 16% of subjects with mild-moderate CKD had complaints of sleep adequacy ($P = 0.11$).

Multivariable analyses

Among all subjects, we found CKD vs. ESRD status and age to be the only significant predictors of the KDQOL sleep score. Scores were significantly lower for subjects with ESRD ($P = 0.01$) and age modified the ESRD-sleep disturbance

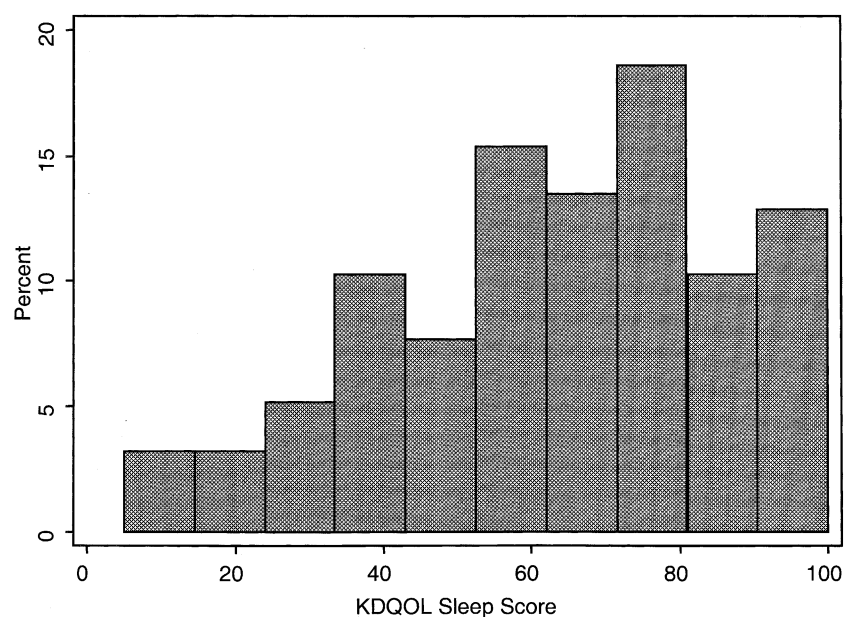


Figure 1. Distribution of Kidney Disease Quality of Life (KDQOL) sleep subscale scores in subjects with chronic kidney disease and end-stage renal disease.

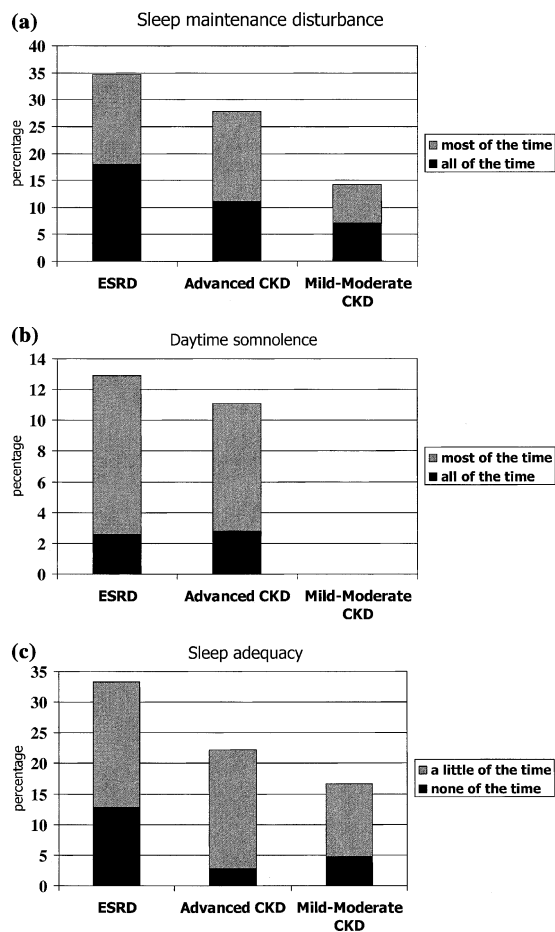


Figure 2a–c. Prevalence of sleep complaints for individual items from the Kidney Disease Quality Of Life (KDQOL) sleep subscale by severity of kidney disease.

relation (age \times ESRD interaction term $P = 0.03$). In other words, the difference in self-reported sleep disturbance among subjects with ESRD and CKD was prominent among younger subjects, and attenuated or absent among older subjects. For example, expected KDQOL sleep scores would be approximately 66 and 52 for persons with CKD and ESRD at 50 years of age, and 68 and 68 for persons with CKD and ESRD at 75 years of age. With additional adjustment for the GDS ($P < 0.0001$), ESRD and the age \times ESRD interaction terms remained significant, but the CKD-ESRD differences were attenuated (Table 2).

When we restricted our analysis to subjects with CKD, we found that subjects with lower estimated GFR had lower KDQOL sleep scores ($P = 0.01$) when adjusted for the significant

Table 2. Multivariable predictors of KDQOL sleep subscale score in subjects with end-stage renal disease and chronic kidney disease

Variable	$\beta \pm SE$	P -value
ESRD	-41.51 ± 16.31	0.01
Age	0.08 ± 0.18	0.67
ESRD \times Age	0.56 ± 0.25	0.03
Intercept	61.76 ± 11.75	< 0.0001

Note: Model $R^2 = 0.09$.

Abbreviations: β , linear regression coefficient; SE, standard error; ESRD, end-stage renal disease.

residual effect of African American race and the race \times GFR interaction. We estimated a 10 point difference in KDQOL sleep score per 15 ml/min/1.73 m² difference in estimated GFR among non-African American subjects with CKD and no relation between estimated GFR and KDQOL sleep score in African Americans. As with the full cohort, predictors of the KDQOL sleep score remained significant after adjustment for GDS, although the differences were attenuated.

Discussion

Sleep complaints are estimated to occur in 45–80% of ESRD patients and are associated with considerable morbidity and reduced quality of life [5, 6, 13, 14]. Despite the high prevalence of sleep complaints among persons with ESRD, few modifiable factors associated with poor sleep quality in ESRD patients have been identified. Previous studies have reported associations between sleep complaints and male sex [5, 15], caffeine intake [5, 16], and depression [17–19]. In a study of 694 hemodialysis patients, insomnia was present in 45% of subjects, and was associated with the length of time on dialysis and morning dialysis shift [13]. The associations among sleep quality and metabolic parameters associated with ESRD have been inconsistent. For example, restless legs syndrome was associated with higher serum concentrations of urea nitrogen and creatinine in one study [5], whereas daytime somnolence was associated with lower concentrations of urea nitrogen and creatinine in another [13]. Even less is known about sleep complaints in persons with CKD not yet on dialysis.

In the present study, the prevalence of sleep complaints ranged from 5 to 20% for all subjects with CKD, and 13 to 34% for subjects with ESRD. Sleep maintenance disruption was the most frequent complaint among both groups. Although there was no difference in self-assessed sleep adequacy, there was a significant, graded relation between the severity of kidney disease and the prevalence of sleep maintenance and daytime somnolence complaints. Moreover, estimated GFR was directly associated with KDQOL sleep score among non African-American subjects with CKD, even after accounting for depressive symptoms.

Only one previous study has examined sleep quality in persons with CKD. In a study of 120 CKD patients with creatinine clearances between 7 and 61 ml/min, 53% had poor sleep, defined as a Pittsburgh Sleep Quality Index (PSQI) > 5 [17]. Consistent with our findings, a history of depression was the only independent predictor of poor sleep in this cohort. There was no relation between creatinine clearance and global PSQI score, although there were significant correlations between serum urea nitrogen and creatinine concentration, and sleep efficiency. In our study, the association between estimated GFR and the KDQOL sleep score was attenuated after accounting for depressive symptoms. However, it should be recognized that many somatic complaints associated with depression overlap with those seen in CKD. Moreover, depressive symptoms may be the result of sleep disturbances in CKD and ESRD patients rather than the cause.

The factors contributing to the high prevalence of sleep complaints in CKD and ESRD remain unknown. Clinical conditions associated with sleep disorders in the general population, such as obesity, stroke, and congestive heart failure did not explain the association between ESRD and lower self-reported sleep quality in our study. In studies of elderly patients in the general population, African American race has been identified as a risk factor for lower self-assessed sleep quality and for sleep apnea [20–22]. In contrast, a study in elderly subjects with ESRD suggested African Americans were less likely to experience restless sleep [23]. We found a relation between estimated GFR and lower KDQOL sleep scores only among non-African American subjects. While this may reflect limitations due to sample size, it may also indicate

that the poor sleep quality is mediated by different factors among African American and non-African American individuals.

As with earlier studies, we failed to identify modifiable factors associated with poor sleep quality in persons with CKD and ESRD [6, 14, 17]. Specifically, factors associated with kidney disease including dose of dialysis, hemoglobin, or parathyroid hormone concentrations were not associated with sleep quality. Hypertension has been associated with sleep disorders in the general population and in patients with ESRD [1, 24, 25]. Elevated serum phosphorous concentrations have also been associated with poor sleep quality in a single study of dialysis patients [15]. Although we found modest correlations between the total KDQOL sleep score and systolic and diastolic blood pressure, serum phosphorous and serum potassium concentrations, these factors were not significant predictors of the KDQOL sleep score after adjustment for age and ESRD status. In our study, even models including depression explained less than 25% of the variance in KDQOL sleep scores. Thus, even after accounting for known and hypothesized predictors of poor sleep quality in persons with CKD and ESRD, the variation in self-assessed sleep quality remained largely unexplained.

There are several limitations of this study. We used a questionnaire rather than an objective measurement of sleep disturbance such as polysomnography. Nevertheless, the KDQOL sleep scale has been correlated with several health-related quality of life indicators, suggesting it is a valid measure of poor sleep quality in persons with kidney disease [9] and its components have been well validated in the general population [8]. Moreover, the KDQOL has been used in several epidemiological studies of kidney disease, facilitating comparisons of sleep complaints among different patient groups. Recruitment of subjects with CKD was not consecutive or population-based; therefore our results may not be generalizable to all CKD or ESRD patients. However in contrast to some prior studies, our study population was derived from multiple centers, and was ethnically and socioeconomically diverse. Finally, because of the small sample size, we had limited power to explore potential mediators of the association between estimated GFR and poor sleep.

In summary, sleep complaints are common in persons with ESRD and CKD, particularly those with lower estimated GFR. Further studies using objective and self-reported measures of sleep and sleep-related symptoms will be necessary to understand the burden of sleep disturbance in CKD. The KDQOL sleep scale may prove to be a useful screening tool in these studies.

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