

Association of Sleep Difficulty with Kidney Disease Quality of Life Cognitive Function Score Reported by Patients Who Recently Started Dialysis

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Sleep disorders are associated with impaired cognition in the general population, but little attention has been given to the potential association between sleep and cognitive function in the dialysis population. This study investigated reported sleep difficulty and cognitive function scores in a national cohort of patients who initiated maintenance hemodialysis and peritoneal dialysis. The cognitive function scale of the Kidney Disease Quality of Life instrument (KDQOL-CF), which measures aspects of cognitive ability that are important for daily functioning (perceived reaction time, ability to concentrate, and tendency to become confused), was used. The study population included 2286 patients who responded to a questionnaire at baseline in the US Renal Data System Dialysis Morbidity and Mortality Study Wave 2. Reported sleep difficulty was associated in a univariate manner with lower KDQOL-CF score. In a multivariable regression analysis that controlled for age, gender, race, education, diabetic ESRD, cardiovascular comorbidity, smoking, hemoglobin, serum albumin, prescribed sleep medications, dialysis modality, pre-ESRD care, bodily pain, and depressed mood, the association of sleep difficulty with KDQOL-CF score remained significant ($P < 0.0001$); the association also was significant in a multivariable analysis that was restricted to hemodialysis patients and included adjustment for Kt/V ($P = 0.001$). Depressed mood and sleep medication prescription predicted a lower KDQOL-CF score, and higher educational level and less bodily pain predicted a higher KDQOL-CF score. Increased understanding of links among sleep difficulty, management of sleep difficulty, and cognitive function could benefit multiple dimensions of dialysis patients' quality of life and daily functioning.

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Dialysis patients have increased risk for impaired cognitive function (1–4), and brain function affects many aspects of an individual's life. There is increasing evidence from experimental and epidemiologic studies in the general population that sleep quality is associated with cognitive function (5–9). Although pervasive sleep difficulty has been documented widely among dialysis patients (10–14), we identified only one study that considered the potential association of sleep difficulty with cognitive function. The Kidney Outcomes Prediction and Evaluation (KOPE) Study of approximately 240 hemodialysis (HD) patients asked respondents to indicate whether they experienced a series of sleep difficulties: Trouble falling asleep, waking up during the night, waking up too early, usually feeling tired in the morning, feeling tired this morning, usually having restless sleep, and having restless sleep last night. In univariate analyses, patients who reported each of these sleep difficulties also reported having more frequent problems with perception and memory

than did patients who did not report sleep difficulties, and in a multivariate analysis, waking up too early was associated independently with more frequent problems with perception and memory (15).

In this study, we used questionnaire responses from a large national cohort of HD and peritoneal dialysis (PD) patients to investigate the association of reported sleep difficulty and individuals' scores on the cognitive function scale of the Kidney Disease Quality of Life-Short Form (KDQOL-SF) instrument. Kurella *et al.* (16) termed this scale the KDQOL-CF and concluded that it is a valid instrument for *estimating* cognitive function in renal patients and a useful tool for comparing cognitive function among various patient groups in epidemiologic studies. Information that is provided by the KDQOL-CF cannot be equated with information that is provided by neuropsychological testing, but the scale does tap aspects of cognitive function that have a direct impact on individuals' ability to carry out daily activities and thus their quality of life. We hypothesized that patients who reported sleep difficulty would score lower on the KDQOL-CF than those who did not report sleep difficulty.

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Materials and Methods

Study Design and Participants

The Dialysis Morbidity and Mortality Study (DMMS) Wave 2 was a prospective inception cohort study of patients (Medicare and non-Medicare) who initiated ESRD therapy in 1996 to 1997 (17). Incident

patients were defined by receipt of any type of PD or in-center HD at least once weekly for the first time. Patients were excluded when they were receiving intermittent dialysis treatment because of fluid overload or heart failure or when they were on home HD, when they had had a previous transplant, or when they were younger than 18 yr. Patients who were treated by or training for PD on day 60 of ESRD and patients who were treated by HD on day 60 of ESRD were recruited. All enrolled patients provided written informed consent.

The 799 dialysis units that were included in the DMMS Wave 2 were a random selection of 25% of the units in the United States that were on the Master List of Medicare Approved Dialysis Facilities as of December 31, 1993; all new dialysis units that opened after January 1, 1994, also were included. The US Renal Data System (USRDS) Coordinating Center (then located at the University of Michigan) directed the study. All eligible incident PD patients were included, and 20% of eligible HD patients were included by selecting only those with social security numbers that ended with 2 or 9. Of the 4024 patients who were enrolled in the study March 1996 to December 1997, 3584 patients had a non-duplicate, nonzero identification number and available demographic and modality status data; had not received a transplant at the time of first ESRD service; and had not received their first ESRD service before 1996 or after 1997. Approximately 60% of these patients completed a patient questionnaire near day 60 of ESRD. From patient characteristics that were available for the study cohort on the 2004 USRDS Core Standard Analysis File, patients who completed the questionnaire, compared with nonrespondents, were less likely to have diabetic ESRD and were more likely to have completed a higher level of education, but there were no significant differences between respondents and nonrespondents in race, gender, age, or cardiovascular comorbidity. Consistent with the DMMS Wave 2 study design, approximately equal numbers of patients were treated by HD and PD. Our study includes 2286 patients who answered questions about sleep in the patient questionnaire.

Measures and Data Collection

DMMS Wave 2 data collection instruments are available in the Researcher's Guide to the USRDS Database (<http://www.usrds.org/research.htm>). Patients were asked to complete the questionnaire within 30 d and to return the questionnaire in a sealed envelope identified only by study identification number. The protocol specified that patients should be asked to self-complete the questionnaire at the dialysis unit, but patients who were unable to complete the questionnaire because of reading or vision impairments could receive assistance from a dialysis unit staff member or a family member.

The DMMS Wave 2 questionnaire asked patients to indicate yes or no to the statement, "I sleep less at night, for example, wake up too early, don't fall asleep for a long time, awaken frequently." We classified patients who answered yes to this statement as reporting sleep difficulty. Insomnia is characterized by difficulty falling asleep, difficulty staying asleep, and/or early morning awakening (18), all of which are captured by the DMMS Wave 2 questionnaire item. Because a validated measure of insomnia was not included in the DMMS Wave 2, we refer to sleep difficulty rather than to insomnia in this study. The DMMS Wave 2 questionnaire did not include the full KDQOL-SF sleep scale or the items that were used to assess insomnia in epidemiologic studies such as the Established Populations for Epidemiologic Studies of the Elderly (8). The DMMS Wave 2 questionnaire did ask patients to rate the quality of their sleep during the past 30 d from 0 (poor quality) to 10 (high quality), which is one item in the KDQOL-SF sleep scale. Patients who reported sleep difficulty rated their sleep quality significantly lower than did patients who did not report sleep difficulty (46.7 ± 23.2 versus 76.9 ± 18.9 ; $P < 0.0001$).

The KDQOL-CF, the measure of cognitive function in this study, includes three questions: (1) During the past 4 wk, did you react slowly to things that were said or done? (2) Did you have difficulty concentrating or thinking? (3) Did you become confused? Responses on a six-point scale are weighted and transformed to a score that ranges from 0 to 100, with higher scores indicating better self-assessed cognitive function. Kurella *et al.* (16) compared KDQOL-CF scale scores of a small sample of HD patients with these same patients' scores on the Modified Mini-Mental State Examination (19) and concluded that the KDQOL-CF is a valid instrument for estimating cognitive function in patients with ESRD. The KDQOL-CF demonstrated adequate internal consistency in the DMMS Wave 2 data, with an α of 0.72.

The patient questionnaire also was the source of information for measures of bodily pain, depressed mood, and pre-ESRD care. The bodily pain scale, one of the eight generic health status measures included in the KDQOL-SF instrument, asks, "How much bodily pain have you had during the last 30 d?" (six-point response scale) and, "During the last 30 d, how much did pain interfere with your normal work (including work both outside the home and housework)?" (five-point response scale). Patient responses are weighted and transformed to a score that ranges from 0 to 100, with higher scores indicating better quality of life in terms of pain experience. The bodily pain scale had an internal consistency of 0.83 in the DMMS Wave 2 data.

Depressed mood was measured by two KDQOL items: (1) How much of the time during the last 30 d have you felt so down in the dumps that nothing could cheer you up? (2) How much of the time during the last 30 d have you felt downhearted and blue? The six possible responses to these questions were 1, none of the time; 2, a little of the time; 3, some of the time; 4, a good bit of the time; 5, most of the time; and 6, all of the time. Consistent with research conducted by Lopes *et al.* (20), we classified patients as reporting depressed mood when they indicated that they had felt down in the dumps or felt downhearted and blue a good bit of the time or more often. Using this definition, 16.1% of patients in our study had depressed mood on the basis of feeling down in the dumps and 18.8% had depressed mood on the basis of feeling downhearted and blue, which was virtually identical to the 16.6 and 18.5% endorsement of these same items, respectively, in the cohort of dialysis patients studied by Lopes *et al.* (20). The five-item generic mental health scale of the KDQOL-SF that has been used by other investigators as a measure of depression was included in the DMMS Wave 2 questionnaire. Kimmel and Peterson (21) argued that this scale should not be construed as a scale of depressive symptoms, however, and we did not use it to assess depressed mood in this study.

Information about pre-ESRD care was obtained in the DMMS Wave 2 by an item with structured response categories that asked, "Prior to starting regular dialysis, when did you first receive medical attention from a kidney specialist (nephrologist)?" We defined early referral for care by a nephrologist as 4 mo or more before dialysis treatment start, consistent with previous research (22).

A medical questionnaire was completed by dialysis unit personnel who abstracted data from medical records, billing records, dialysis logs, patient rosters, hospital records, and personal physician records as information sources. The medical questionnaire was the source of information about patients' age, gender, education, dialysis modality, primary cause of ESRD, cardiovascular comorbidity, current smoking status, serum albumin, hemoglobin, sleep medications, and Kt/V (HD patients); for ascertainment of race, the patient also was a source of information. Cardiovascular comorbidity was defined by documentation of any of the following conditions in the patient's medical records: Coronary heart disease/coronary artery disease, acute myocardial infarction, cardiac arrest, cerebrovascular accident/stroke, peripheral

vascular disease, and congestive heart failure. Abstractors were instructed to record laboratory data and medications for a date that corresponded as closely as possible to the DMMS Wave 2 study start date (*i.e.*, information that characterized the patient at approximately day 60 of ESRD).

Statistical Analyses

Baseline characteristics of patients who reported sleep difficulty ($n = 874$) and patients who did not report sleep difficulty ($n = 605$) were compared by t test (continuous variables) and χ^2 analysis (categorical variables). The association of reported sleep difficulty with KDQOL-CF score was investigated in a standard multivariable linear regression analysis, controlling for age, gender, race, education, diabetic ESRD, cardiovascular comorbidity, smoking status, hemoglobin, serum albumin, prescribed sleep medications, dialysis modality (HD/PD), early referral to a nephrologist, bodily pain score, and depressed mood. A total of 1495 of 2286 patients had information available for all covariates and were included in this analysis. A second linear regression analysis that included Kt/V as an additional covariate was conducted for HD patients who had information available for all covariates ($n = 719$).

Results

Table 1 shows characteristics of the study cohort by reported sleep difficulty. Patients who reported sleep difficulty scored lower on the KDQOL-CF than patients who did not report sleep difficulty (73.1 ± 22.3 versus 81.2 ± 20.1). In addition, patients who reported sleep difficulty were less likely to have completed high school, were more likely to have sleep medication prescriptions in their medical record, were more likely to be on HD, reported more pain, and were more likely to report depressed mood compared with patients who did not report sleep

difficulty. No significant differences in age, gender, race, diabetic ESRD, cardiovascular comorbidity, smoking status, hemoglobin, serum albumin, or early referral to a nephrologist were evident between patients who reported sleep difficulty and those who did not report sleep difficulty. In addition, there was no difference in the mean serum phosphate levels of patients who reported sleep difficulty and patients who did not report sleep difficulty (5.6 ± 2.3 versus 5.7 ± 4.7 mg/dl; $P = 0.68$).

In a multivariable analysis that included all patients who were on HD and PD and had information for all covariates (Table 2), reported sleep difficulty was associated independently with a lower KDQOL-CF score. Sleep difficulty resulted in a reduction of approximately 4.4 points in cognitive function score. Depressed mood and sleep medication prescription also predicted a lower KDQOL-CF score. Having a higher educational level predicted a higher KDQOL-CF score. The analysis also indicated a significant association between bodily pain score and KDQOL-CF score (higher score, *i.e.*, less pain, was associated with a higher KDQOL-CF score). In a multivariable analysis that was restricted to patients who were on HD and included Kt/V as an additional covariate (Table 2), the findings were similar except that sleep medication prescription was not a significant predictor of lower KDQOL-CF score using the $P < 0.05$ criterion.

When we investigated the listing in patients' medical records of medications that may be used in treatment of insomnia as discussed by Novak *et al.* (14), we found that temazepam, lorazepam, and Benadryl composed approximately 76% of the listed medications. Medications that composed the remainder

Table 1. Patient baseline characteristics, by reported sleep difficulty^a

Patient Characteristic	Sleep Difficulty Reported ($n = 1383$)	No Sleep Difficulty Reported ($n = 903$)	P
Age at enrollment (yr; mean [SD])	58.2 (15.2)	58.6 (15.6)	0.54
Male (%)	54.5	52.6	0.37
Black (%)	26.9	25.2	0.37
Educational status (%)			0.04
less than high school	32.9	28.6	
high school or more	67.1	71.4	
Diabetic ESRD (%)	43.2	41.5	0.42
Cardiovascular comorbidity ^b (%)	60.2	59.0	0.58
Current smoking (%)	15.6	13.0	0.09
Hemoglobin (g/dl; mean [SD])	10.6 (3.7)	10.6 (3.6)	0.62
Serum albumin (g/dl; mean [SD])	3.5 (0.6)	3.5 (0.6)	0.62
Sleep medication(s) (%)	10.8	7.2	0.004
HD (%)	55.8	44.1	<0.0001
Kt/V (HD patients; mean [SD])	1.2 (0.4)	1.2 (0.3)	0.13
Early referral (%)	66.9	66.2	0.72
Bodily pain score (mean [SD])	55.5 (28.6)	66.3 (27.1)	<0.0001
Depressed mood (%)	31.4	17.0	<0.0001
KDQOL-CF score (mean [SD])	73.1 (22.3)	81.2 (20.1)	<0.0001

^aESRD, end-stage renal disease; HD, hemodialysis; KDQOL-CF, Kidney Disease Quality of Life-Cognitive Function.

^bHistory of one or more of the following: Coronary heart disease/coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, acute myocardial infarction, and cardiac arrest.

Table 2. Multivariable predictors of KDQOL-CF score

Variable	Full Sample (n = 1495)		HD Only (n = 719)	
	$\beta \pm SE$	P	$\beta \pm SE$	P
Sleep difficulty	-4.4 ± 1.0	<0.0001	-5.1 ± 1.6	0.001
Depressed mood	-12.4 ± 1.2	<0.0001	-12.2 ± 1.7	<0.0001
Bodily pain score	0.2 ± 0.02	<0.0001	0.1 ± 0.03	<0.0001
Higher educational level	4.9 ± 1.1	<0.0001	5.7 ± 1.6	0.0002
Sleep medication	-4.3 ± 1.7	0.01	-3.7 ± 2.5	0.13
Older age	-0.6 ± 1.1	0.60	-0.1 ± 1.8	0.96
Male	0.1 ± 1.0	0.95	0.1 ± 1.6	0.97
Black	-1.5 ± 1.2	0.21	-2.8 ± 1.7	0.10
Diabetic ESRD	0.6 ± 1.1	0.59	0.2 ± 1.6	0.90
Cardiovascular comorbidity	-1.5 ± 1.1	0.17	-3.2 ± 1.7	0.06
Current smoking	-0.4 ± 1.5	0.80	-0.3 ± 2.3	0.89
Hemoglobin	-0.04 ± 0.1	0.76	-0.1 ± 0.2	0.65
Serum albumin	-0.1 ± 0.9	0.87	0.5 ± 1.4	0.73
HD	1.4 ± 1.0	0.18	—	—
Kt/V	—	—	-1.1 ± 1.9	0.57
Early referral	0.6 ± 1.1	0.55	0.3 ± 1.5	0.85

were clonazepam (Klonopin), flurazepam (Dalmane), triazolam (Halcion), trazodone, estazolam (ProSom), and zolpidem.

Discussion

Almost 60% of the patients in our study cohort reported sleep difficulty, which generally is consistent with findings of other investigators who have studied sleep quality among dialysis patients using validated measures (10–12). As we hypothesized, lower KDQOL-CF scores were observed among patients who reported sleep difficulty. There is a substantial database suggesting that loss of sleep may have an impact on behavioral performance and cognition (23). Experimental studies have shown that sleep deprivation in young adults produces deficits in neurobehavioral performances that are suggestive of frontal lobe dysfunction (24), and using functional magnetic resonance imaging, Drummond *et al.* (25) demonstrated metabolic changes in prefrontal cortex after prolonged sleep deprivation as well. Similar results have been noted with positron emission tomography in prefrontal and posterior parietal cortex and thalamus (26). In addition, data that were reported recently from the Study of Osteoporotic Fractures (SOF) indicate that sleep fragmentation, more than total amount of sleep, may be detrimental for cognitive functioning (9).

Psychomotor efficiency and processing speed, attention and working memory, and learning efficiency are brain function domains that are described as characteristically fluid rather than remaining relatively stable over time. Fluid domains are influenced by disease status. It is of interest that Jassal *et al.* (4) recently reported marked improvement in neuropsychological test scores of the attention and working memory domain in patients who converted from standard thrice-weekly HD to nocturnal HD. Other researchers have reported improvements in aspects of sleep quality in patients who converted from standard HD to nocturnal HD (27), and it is tempting to spec-

ulate that improved sleep quality, a variable that was not discussed by Jassal *et al.* (4), might mediate the association that those investigators found between more frequent HD and improvement in patients' cognitive functioning.

Patients for whom insomnia medications were listed scored lower on the KDQOL-CF, independent of whether they reported sleep difficulty. Kurella *et al.* (16) found an independent association between benzodiazepine use and lower KDQOL-CF score in chronic kidney disease and prevalent HD patients. Medications that are described as efficacious in treating insomnia also may be associated with a number of adverse effects, including impairment in daytime cognitive and psychomotor performance (14). It is important to note that the medications identified in the data may have been prescribed for problems other than sleep, such as anxiety or restless legs. In addition, other medications that patients may have been taking, such as antihypertensives, could be associated with both sleep and perceived memory.

Depressed mood and bodily pain score also were independent predictors of the KDQOL-CF score. Although Murray *et al.* (3) did not find an association between depression and cognitive impairment in HD patients who were 55 yr and older, an association between depression and cognitive status has been reported in other studies of dialysis patients (16,28). The direction of the association between depression and cognitive function is not known, but it has been recommended that evaluation for the presence of depression should be part of all neuropsychological evaluations of patients who are on dialysis (2).

Depressed mood, pain, and poor sleep may form an interrelated complex of symptoms, as Foley *et al.* (7) found in a national survey of older adults in the United States and as Davison *et al.* (29) found in a study of 205 HD patients in Canada. Davison *et al.* (29) noted that sleep disturbance in patients who experience pain may serve to increase pain sen-

sitivity and create a self-perpetuating cycle of sleep disruption, increased pain, and depression.

As Table 2 indicates, higher educational level was associated independently with higher KDQOL-CF scores, as Kurella *et al.* (16) also showed. The recent study by Murray *et al.* (3) of 338 HD patients who were 55 yr and older and completed neuropsychological testing in at least two different cognitive domains found that individuals with >12 yr of education had reduced risk for severe cognitive impairment. Educational status has been found to influence the results of cognitive testing in the general population as well (30,31).

Our study was limited by the measures that were available to us. The measure of sleep difficulty that we used was a shortened version of sleep questions that were used in previous epidemiologic research and had not been validated directly, although we did find that the measure was associated significantly with patients' 0 to 100 rating of their sleep quality. In addition, the DMMS Wave 2 data did not contain information about daytime sleepiness, sleep apnea, periodic limb movements, and restless legs symptoms, all of which are known to be associated with impaired nocturnal sleep quality in renal patients and could have an impact on cognitive function.

Although there is substantial evidence from the work of other investigators that the KDQOL-CF (16) and the measure of depressed mood (20) that we used in this study are reasonable tools for research in the dialysis population, they provide estimates rather than definitive assessment of the constructs of cognitive function and depressed mood. We are not able to judge the completeness or accuracy of the listing of medications by DMMS Wave 2 abstractors. In addition, the standard of practice for pharmacologic management of transient and chronic insomnia may have changed significantly since the DMMS Wave 2 was conducted.

The strength of our study is the availability of data from a large and varied multicenter national cohort of patients. Although the KDQOL-CF scale by no means provides a global test of cognition, it may have usefulness as a measure for cognitive status screening (16). Equally important, the questions that make up the KDQOL-CF reflect cognitive issues that are important for patients' daily functioning and well-being. Approximately 60% of DMMS Wave 2 respondents said that reacting slowly and having difficulty concentrating had been problems for them during the past 30 d, issues that have an impact on ability to perform a job and make decisions. In this sense, the KDQOL-CF can be said to have ecologic validity, a characteristic of outcome measures that should be important to sleep researchers (5). With regard to generalizability of the findings, patients who answered the questionnaire had a higher educational level than did nonrespondents. The data indicated that both sleep difficulty and lower cognitive function scores were more likely to characterize patients with a lower educational level; therefore, the data presented here may understate the extent of sleep difficulty and impaired cognitive functioning among incident dialysis patients.

Mahowald and Cramer Bornemann (32) recently commented that the bad news is that sleep complaints are ubiquitous in chronic renal failure, but the good news is that most wake/

sleep complaints are diagnosable and treatable. The first step is to query the patient about nocturnal sleep quality and daytime alertness (32,33). Complaints of sleep difficulty can be evaluated by having patients keep sleep diaries or by collecting information about wake/sleep patterns *via* actigraph, a wristwatch-like device that records movement (32). Possible contributing conditions then must be identified, especially restless legs syndrome, periodic leg movements during sleep, sleep apnea, and depression (33,34). Long-term insomnia also may be "learned" behavior that requires behavioral and/or pharmacologic treatment (32). Behavioral treatments include sleep restriction, sleep consolidation, sleep hygiene, and cognitive behavioral therapy. Mahowald and Cramer Bornemann (32), as well as Novak *et al.* (14), recommend consideration of newer nonbenzodiazepine medications (*e.g.*, zaleplon, zolpidem, eszopiclone) for use in renal patients.

Numerous vascular risk factors, as well as nonvascular risk factors such as sleep disorders, potentially influence the results of cognitive testing in dialysis patients (2). Additional studies are needed, especially studies that include standardized measures of sleep quality and cognitive functioning. Novak *et al.* (14) noted that there is an almost complete lack of pharmacologic studies in renal patients who report insomnia. Increased understanding of links among sleep difficulty, management of sleep difficulty, and cognitive function could benefit multiple dimensions of dialysis patients' quality of life and daily functioning.

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None.

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