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ORIGINAL PAPER

Patient-reported sleep difficulty and cognitive function during the first year of dialysis

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Abstract *Background* Research in the general population indicates that sleep fragmentation is detrimental for cognitive function, but little attention has been given to this issue in dialysis patients. We hypothesized that patients with self-reported persistent sleep difficulty would have an increased risk of scoring lower on a cognitive function measure at follow-up compared to their score at baseline.*Methods* Sleep difficulty and cognitive function were reported by a large national patient cohort near the start of dialysis and at a 9- to 12-month follow-up. Logistic regression was used to investigate the risk of scoring lower on a cognitive function measure at follow-up as a function of self-reported sleep difficulty, controlling for patients' sociodemographic, clinical and treatment characteristics, including depressed mood.*Results* At follow-up, cognitive function scores were lower among 35.8% of the cohort. Patients with self-reported persistent sleep difficulty had the lowest average cognitive function score. Men with reported persistent sleep difficulty, regardless of presence of depressed mood, had a significantly increased risk of a lower cognitive function score at follow-up. Women with reported persistent sleep difficulty as well as depressed mood had significantly increased risk of a lower cognitive function score.*Conclusion* The potential impact of sleep difficulty and depressed mood on the cognitive function of dialysis patients emphasizes the importance of evaluating and treating these risks and highlights the value of continued research to improve our understanding and management of these issues.

Keywords Cognitive function · Cohort study · Depression · Dialysis · Insomnia · Quality of life

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Introduction

Sleep disturbance and cognitive impairment are prevalent among dialysis patients, and both conditions have important implications for patients' quality of life [1–6]. Individuals who report sleep difficulty may experience fragmented, nonrestorative sleep, and studies conducted in the general population indicate that sleep fragmentation is detrimental for cognitive functioning [7–11]. For example, an investigation of insomnia and cognitive status among a large cohort of older community residents who participated in the Established

Populations for Epidemiologic Studies of the Elderly (EPESE) found that chronic insomnia independently predicted cognitive decline among older community dwelling persons [7].

Very little attention has been given to the possible association between sleep disturbance and cognitive function among dialysis patients. Williams et al. found that hemodialysis (HD) patients who reported a series of sleep difficulties also reported having more frequent problems with their perception and memory [12]. We found an association between sleep difficulty and cognitive function scores reported at the start of dialysis by a national cohort of patients who participated in the baseline phase of the Dialysis Morbidity and Mortality Study (DMMS) Wave 2 [13]. To date, however, there have been no published studies of dialysis patients that have investigated the potential association of sleep difficulty and cognitive function over time in this patient group.

In this study we used data that were originally collected to assess quality of life in DMMS Wave 2 patients near the initiation of dialysis treatment (baseline) and again after 9–12 months (follow-up) to investigate cognitive function scores at these same time-points in relation to reported sleep difficulty of these patients. We hypothesized that individuals with persistent sleep difficulty – i.e. reported sleep difficulty at baseline and follow-up – would have an increased risk of scoring lower on a cognitive function measure at follow-up than at baseline.

Methods

Study design and participants

The DMMS Wave 2 was a prospective inception cohort study of patients (Medicare and non-Medicare) who initiated end-stage renal disease (ESRD) therapy in 1996–1997 [14]. Incident patients were defined by their receiving any type of peritoneal dialysis (PD) or incenter HD at least once weekly for the first time. Patients were excluded if they were receiving intermittent dialysis treatment because of fluid overload or heart failure, if they were on home HD, if they had a previous transplant, or if they were less than 18 years of age. Patients treated by or training for PD on day 60 of ESRD and patients treated by HD on day 60 of ESRD were recruited. All enrolled patients provided written informed consent.

The 799 dialysis units included in the DMMS Wave 2 were a random selection of 25% of the units in the United States on the Master List of Medicare Approved Dialysis Facilities as of December 31, 1993; all new dialysis units opening after January 1, 1994 were also included. The U.S. 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 ending with 2 or 9. Of the 4024 patients who were enrolled in the study from March 1996 to December 1997, 3584 enrolled patients had a non-duplicate, non-zero ID 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 around day 60 of ESRD (baseline), and 2286 patients answered questions about sleep in the baseline questionnaire. This study includes 1194 patients who answered questions about sleep in the patient questionnaire both at baseline and at a 9- to 12-month follow-up. We used the patient characteristics that were available for the study cohort on the 2004 USRDS Core Standard Analysis File.

Patients who completed the DMMS Wave 2 patient questionnaire at baseline and follow-up were less likely to be black than were nonrespondents. However, there were no significant differences between respondents and nonrespondents in terms of age, gender, diabetic ESRD, baseline cardiovascular comorbidity, or dialysis modality (HD/PD).

Measures and data collection

DMMS Wave 2 data collection instruments are available in the Researcher's Guide to the

USRDS Database at http://www.usrds.org/research.htm. The patient questionnaire that was distributed to enrolled patients included scales from the Kidney Disease Quality of Life-Short Form (KDQOL-SF) instrument (http://www.gim.med.ucla.edu/kdqol/) and related questions. Patients were asked to complete the questionnaire within 30 days and to return the questionnaire in a sealed envelope identified only by study ID number. The protocol specified that patients should be asked to self complete the patient 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.

As a measure of sleep quality, patients were asked 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. The DMMS Wave 2 questionnaire also asked patients to rate the quality of their sleep during the last 30 days from 0 (poor quality) to 10 (high quality). After ratings were transformed to a 0–100 scale, patients who reported sleep difficulty rated their sleep quality significantly lower than patients who did not report sleep difficulty (46.9 ± 22.7 vs. 77.4 ± 18.8, respectively; $P < 0.0001$). We used the sleep difficulty indicator measure in this study rather than the 0–10 sleep quality rating because the wording to which patients responded in the former measure specified sleep problems that are consistent with many other studies that have investigated insomnia, while the sleep quality rating item does not have specific referents. Although patients were asked about their difficulty falling asleep, difficulty staying asleep, and/or early morning awakening, which are characteristic elements of insomnia [15], we use the term *sleep difficulty* rather than the term *insomnia* in this study because the DMMS Wave 2 questionnaire did not use the validated multi-item, multi-response measure that has been used to assess insomnia in epidemiologic studies such as the EPESE [7, 10].

Cognitive function was assessed by the KDQOL-SF cognitive function scale, i.e. the KDQOL-CF [16]. The KDQOL-CF includes three questions: ''During the past 4 weeks, did you react slowly to things that were said or done?'' ''Did you have difficulty concentrating or thinking?'' ''Did you become confused?'' Responses on a 6-point scale are weighted and transformed to a score ranging 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 [17] 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 alpha of 0.72.

Depressed mood was measured by two KDQOL items in the patient questionnaire: ''How much of the time during the last 30 days have you felt so down in the dumps that nothing could cheer you up?'' and ''How much of the time during the last 30 days 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. [18] we classified patients as reporting depressed mood if they had felt down in the dumps *or* if they had 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 based on feeling down in the dumps and 18.8% had depressed mood based on 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. [18]. Although 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 argue that this scale should not be construed as a scale of depressive symptoms [19], and we did not use it to assess depressed mood in this study.

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 for a patient's age, gender, education, dialysis modality, primary cause of ESRD, cardiovascular comorbidity, serum albumin, and hemoglobin; the patient him/herself was also a source of information for ascertainment of race. 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 for the date corresponding as closely as possible to the patient's DMMS Wave 2 study start date, i.e. information characterizing the patient at approximately day 60 of ESRD.

Statistical analysis

Baseline characteristics of the study cohort were summarized and presented as the mean ± standard deviation (SD) for continuous variables and by proportion for categorical variables. Mean (SD) KDQOL-CF scores at baseline and at follow-up were identified for patients in four sleep difficulty categories: no sleep difficulty reported at baseline or at follow-up; sleep difficulty reported at baseline only; sleep difficulty reported at follow-up only (new sleep difficulty); sleep difficulty reported at both baseline and follow-up (persistent sleep difficulty). Patient-reported sleep difficulty at follow-up (none, new, persistent) as a risk for reporting a lower cognitive function score at follow-up was assessed by univariable and multivariable logistic regression models. Covariates included in the multivariable logistic regression models were depressed mood (reported/not reported), age, race, education, diabetic ESRD, cardiovascular comorbidity, hemoglobin, serum albumin, and dialysis modality (HD/PD). Because the prevalence and patterns of sleep disturbance and depressed mood differ among men and women in the general population [7], these models were estimated separately for men and for women. Men and women who did not report sleep difficulty or depressed mood at follow-up were the reference group in these models.

Results

Baseline characteristics of the study cohort are summarized in Table 1. The mean age of the patient cohort was 58 ± 15 years. Approximately 55% of the cohort were men, and 26% were black. Almost one-third of the patients had completed less than 12 years of education. Diabetes was the primary cause of kidney failure for almost 43% of the cohort, and almost 60% had a history of one or more documented cardiovascular conditions at the start of treatment. Consistent with the design of the DMMS Wave 2, approximately equal proportions of the cohort began treatment on HD (54%) and PD (46%). Sleep difficulty was reported at baseline by 58% of the cohort. Depressed mood during the last 30 days (feeling down in the dumps and/or feeling downhearted and blue) was reported by almost 24% of the cohort. The average cognitive function score for the patient cohort at baseline, as measured by the KDQOL-CF, was 76.7 ± 21.7.

Table 1 Baseline characteristics of the DMMS Wave 2 study cohort (n = 1194)

Patient characteristic	Mean ± SD or percentage
Age at enrollment; years (mean ± SD)	58.0 ± 15.0
Male (%)	55.5
Black (%)	25.7
Educational status (%)	
< High school	30.9
≥ High school	69.1
Diabetic end-stage renal disease (ESRD) (%)	42.8
Cardiovascular comorbidity (%)	58.4
Hemoglobin; g/dl (mean ± SD)	10.6 ± 3.6
Serum albumin; g/dl (mean ± SD)	3.5 ± 0.6
Hemodialysis (HD) (%)	53.9
Sleep difficulty (%)	58.5
Depressed mood (%)	23.9
Kidney Disease Quality of Life-Cognitive Function (KDQOL-CF) score (mean ± SD)	76.7 ± 21.7

Table 2 Mean (±SD) KDQOL-CF scores of dialysis patients at baseline and follow-up in relation to their reported sleep difficulty at these same time-points

	Baseline KDQOL-CF score	Follow-up KDQOL-CF score
No sleep difficulty at baseline or follow-up (n = 256)	83.4 (18.9)	84.1 (19.2)
Sleep difficulty at baseline only (n = 140)	73.0 (23.6)	79.0 (21.3)
New sleep difficulty: follow-up only (n = 193)	80.3 (19.7)	78.2 (23.0)
Persistent sleep difficulty: baseline and follow-up (n = 504)	72.7 (22.2)	74.6 (21.6)

Mean KDQOL-CF scores at baseline and follow-up are shown in Table 2 in relation to the level of sleep difficulty reported by patients at baseline and follow-up. At follow-up, the average KDQOL-CF score of patients who did not report sleep difficulty at baseline or follow-up was 10 points higher than the average KDQOL-CF score of patients who reported sleep difficulty at both time points. The latter group, patients who reported persistent sleep difficulty, had the lowest average KDQOL-CF score. The average KDQOL-CF scores of patients who reported sleep difficulty at baseline but did not report it at follow-up showed the greatest increase over time (6 points). On the other hand, patients who did not report sleep difficulty at baseline but did report sleep difficulty at follow-up – i.e., the ''new'' sleep difficulty category – were the only group for whom the average KDQOL-CF score was lower at follow-up than it was at baseline.

Overall, KDQOL-CF scores were lower at follow-up than at baseline among 35.8% of the cohort, with similar rates among men (37.4%) and women (33.8%). The mean (±SD) and median score declines on the KDQOL-CF scale from baseline to follow-up were –19.9 (±15.1) and –13.1, respectively. Among patients who scored lower on the KDQOL-CF at follow-up compared to baseline, 31% had scored >60 at baseline but scored ≤60 at follow-up, a change that may be indicative of a developing global cognitive impairment [16].

Odds ratios (ORs) for reporting a lower KDQOL-CF score at follow-up are shown in Table 3 for men and women, classified by reported sleep difficulty and depressed mood at follow-up. Compared to non-depressed men who did not report sleep difficulty, men with persistent sleep difficulty had a significantly increased risk for reporting a lower cognitive function score at follow-up, independent of depressed mood [in the absence of depressed mood: adjusted OR: 1.70; 95% confidence interval (95%CI):1.03–2.80;in the presence of depressed mood: adjusted OR: 2.17; 95%CI: 1.08–4.34]. Compared to non-depressed women who did not report sleep difficulty, persistent sleep difficulty was associated with a significantly increased risk for reporting a lower cognitive function score at follow-up among women who reported depressed mood (adjusted OR: 2.16; 95%CI: 1.03–4.55).

Discussion

Sleep difficulty may be associated with neurocognitive change over time in patients on dialysis. With the exception of women who did not report depressed mood, data from the DMMS Wave 2 incident patient cohort supported the hypothesis that persistent sleep difficulty independently increased the risk for patient-reported lower cognitive function scores after approximately 1 year on dialysis. The analyses were adjusted for sociodemographic (age, gender, race, education), clinical (diabetes, cardiovascular comorbidity, hemoglobin, serum albumin), and treatment modality (HD/PD) covariates as well as for patient-reported depressed mood.

Our findings showed the same pattern as those reported for a cohort of community-dwelling persons aged 65+ studied by Cricco et al. using data from the EPESE [7]. Cricco et al. suggested that an association between chronic insomnia and cognitive decline observed in non-depressed men but not in non-depressed women could reflect a gender difference in the nature or quality of sleep disturbance [10]. In the general population, polysomnographic data indicate that women may have less objectively disturbed sleep than men [20]. Thus, men may have a higher threshold than women for reporting sleep complaints, and men who report sleep difficulty may therefore have

Table 3 Odds ratios (ORs) among men and women for decrease in KDQOL-CF score at follow-up in relation to sleep difficulty and depressed mood reported at follow-up

	Number of respondents	Number (%) with decreased KDQOL-CF score	OR (univariable) (95% CI)	OR (multivariable) (95% CI)[a]
Men *without* depressed mood				
No sleep difficulty (reference group)	177	49 (27.7%)	1.00	1.00
Sleep difficulty: new	88	34 (38.6%)	1.64 (0.96, 2.82)	1.41 (0.75, 2.69)
Sleep difficulty: persistent	201	80 (39.8%)	1.73* (1.12, 2.67)	1.70* (1.03, 2.80)
Men *with* depressed mood				
No sleep difficulty	25	9 (36.0%)	1.47 (0.61, 3.54)	1.62 (0.53, 4.93)
Sleep difficulty: new	13	8 (61.5%)	4.18* (1.30, 13.89)	3.45 (0.86, 13.86)
Sleep difficulty: persistent	66	33 (50.0%)	2.61* (1.46, 4.68)	2.17* (1.08, 4.34)
Women *without* depressed mood				
No sleep difficulty (reference group)	146	49 (33.6%)	1.00	1.00
Sleep difficulty: new	73	23 (31.5%)	0.91 (0.50, 1.66)	0.73 (0.37, 1.47)
Sleep difficulty: persistent	151	39 (25.8%)	0.69 (0.42, 1.14)	0.70 (0.40, 1.21)
Women *with* depressed mood				
No sleep difficulty	25	12 (48.0%)	1.83 (0.78, 4.30)	1.70 (0.68, 4.21)
Sleep difficulty: new	13	8 (61.5%)	3.17 (0.98, 10.20)	3.14 (0.70, 14.07)
Sleep difficulty: persistent	50	24 (48.0%)	1.83 (0.95, 3.51)	2.16* (1.03, 4.55)

*$P < 0.05$

[a] Multivariable model included sleep difficulty, depressed mood, age, race, education, diabetic ESRD, cardiovascular comorbidity, hemoglobin, serum albumin, and dialysis modality (HD/PD)

significantly more disturbed sleep than women who report sleep difficulty. No polysomnographic data relevant to this interesting issue are currently available for dialysis patients.

A mechanistic basis for potential cognitive decline among dialysis patients in relation to poor sleep remains uncertain. There is a substantial database suggesting that loss of sleep may impact behavioral performance and cognition. For example, experimental studies have shown that sleep deprivation in young adults produces deficits in neurobehavioral performance suggestive of frontal lobe dysfunction [21]. In support of this, Drummond et al. used functional magnetic resonance imaging to demonstrate metabolic changes in the prefrontal cortex following prolonged sleep deprivation [22]. Similar results have been noted with positron emission tomography in the prefrontal and posterior parietal cortex and thalamus [23]. Whether these findings can be extrapolated to the dialysis population with chronically poor sleep is not yet known, but several epidemiologic surveys of chronic insomniac populations have shown that consistently poor sleep is associated with the subjective experience of decreased concentration and difficulty with work performance and memory [24, 25]. Psychometric data from several studies of older persons have also documented such deficits [26, 27]. Further studies are required to define precisely how sleep difficulty, especially persistent sleep difficulty, may be associated with decreased cognitive functioning in dialysis patients.

Our primary interest was to explore the potential association of sleep difficulty with the cognitive function score of the patients. In addition to effects associated with sleep difficulty, the data clearly showed that depressed mood also increased patients' risk for cognitive function score decline. We obtained similar results when we repeated the analysis after defining depressed mood as being present at baseline as well as at

follow-up. Poor sleep and depressed mood may form an interrelated complex of symptoms [10, 28]. Gul et al. note that sleep is invariably affected in patients with depression and that the pathophysiology of depression shares a number of neurotransmitters with sleep [29]. Among both men and women in our study, patients with persistent sleep difficulty were twice as likely to report depressed mood at follow-up compared to patients without persistent sleep difficulty.

Several limitations of our study must be noted. Our study cohort consisted of patients who answered questions about sleep in the DMMS Wave 2 patient questionnaire both at baseline and at follow-up. Of the patients who completed the patient questionnaire at baseline, 47% did not complete the follow-up assessment for a number of reasons, including death ($n = 454$), transplantation ($n = 149$), or loss to follow-up ($n = 482$).

Potential limitations of the measures available for use in this study must also be acknowledged. 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 which could impact cognitive function. The measure of sleep difficulty was a shortened version of sleep questions used in previous epidemiologic research and had not been directly validated at the time of the study. Although there is substantial evidence from the work of other investigators that the KDQOL-CF [16] and the measure of depressed mood [18] that we used in this study are reasonable tools for research in the dialysis population, they provide estimates rather than a definitive assessment of the constructs of cognitive function and depressed mood.

Finally, no information on prescribed sleep medications was obtained in the DMMS Wave 2 follow-up. Our analysis of the baseline DMMS Wave 2 data indicated that patients who reported sleep difficulty were more likely to have prescriptions for sleep medication in their medical record [13]. In addition, having been prescribed sleep medications independently predicted a lower baseline KDQOL-CF score [13], and it is possible that prescribed sleep medication may be a marker for the presence of more severe sleep difficulty in a patient. It is also possible that some sleep medications themselves negatively impact cognitive functioning [30].

The strength of our study is the availability of data from a large and varied multicenter national cohort of patients. Although the KDQOL-CF cannot be viewed as a global test of cognition, the three questions that make up the KDQOL-CF subscale reflect cognitive issues that are likely to significantly impact on the daily functioning and well-being of the patients. Of the patients whose KDQOL-CF subscale score declined between baseline and follow-up, more than 80% reported that they were reacting slowly to things and that they had difficulty concentrating or thinking, while almost 60% said that they had become confused in the past 4 weeks. Thus, most of the patients whose scores declined reported that they were having difficulties with cognitive performance in daily activities.

Sleep disorders, depressed mood, and cognitive impairment may be overlooked and underestimated in the dialysis treatment setting [3, 4, 18]. Recent reviews have focused on pharmacologic and nonpharmacologic approaches for the treatment of insomnia and depressed mood in dialysis patients [29, 30]. Clinical evaluation followed by interventions targeting insomnia should improve the quality of life of dialysis patients [30]. Because sleep and depressed mood are likely to be closely associated, treating depression may reduce the morbidity associated with sleep disturbances [29]. Our finding that sleep difficulty as well as depressed mood were associated with lower cognitive function scores at follow-up in a large dialysis cohort adds increased importance to the necessity of evaluating dialysis patients for these risks and highlights the value of continued research to address these issues.

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