Correlates and Outcomes of Fatigue among Incident Dialysis Patients

Manisha Jhamb,* Christos Argyropoulos,† Jennifer L. Steel,‡ Laura Plantinga,§ Albert W. Wu,§ Nancy E. Fink,§ Neil R. Powe,§ Klemens B. Meyer,‖ and Mark L. Unruh,† for the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study

**Department of Medicine, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania; †Renal-Electrolyte Division, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; ‡Department of Surgery and Psychiatry, University of Pittsburgh School of Medicine; §Department of Epidemiology, Johns Hopkins University, Baltimore Maryland; and ‖Division of Nephrology, Tufts Medical Center, Boston, Massachusetts*

Background & objectives: Fatigue is a debilitating symptom experienced by patients undergoing dialysis, but there is only limited information on its prevalence and its association with patient outcomes. This study examines the correlates of self-reported fatigue at initiation of dialysis and after 1 yr and assesses the extent to which fatigue was associated with health-related quality of life and survival.

Design, setting, participants, & measurements: A longitudinal cohort of 917 incident hemodialysis and peritoneal dialysis patients who completed the CHOICE Health Experience Questionnaire (CHEQ) participated in the study. Fatigue was assessed using the SF-36 vitality scale. Known predictors of fatigue including sociodemographic and psychosocial factors, dialysis-related factors, biochemical variables including inflammatory markers, comorbidities, and medications were used as covariates.

Results: A low vitality score was independently associated with white race, higher Index of Coexistent Disease score, higher body mass index, lack of physical exercise, antidepressant use, and higher C-reactive protein levels (CRP). A lower vitality score was strongly associated with lower SF-36 physical functioning, mental health, bodily pain scores, and decreased sleep quality (all $P < 0.001$) at baseline. Among surviving participants, higher serum creatinine at baseline was associated with preserved vitality at 1 yr. Patients with the highest baseline vitality scores were associated with longer survival (hazard ratio 0.75; 95% CI 0.58 to 0.96, $P = 0.03$).

Conclusions: The findings of this study demonstrate that ESRD patients experience profound levels of fatigue and elucidate its correlates. Also, the association of fatigue with survival may have significant implications for this population.

Clin J Am Soc Nephrol 4: 1779–1786, 2009. doi: 10.2215/CJN.00190109

Many end-stage renal disease (ESRD) patients experience debilitating fatigue. Fatigue, which can be conceptualized on a continuum from extreme tiredness to high energy (1,2), has been reported to affect 60% to 97% of chronic dialysis patients (3–8). Fatigue is important to patients, as 94% of surveyed dialysis patients would accept more frequent hemodialysis if it would increase their energy, whereas only 19% would exchange more frequent treatments for a 3-yr increase in survival (7).

Despite the high prevalence of fatigue in ESRD, we know little about its correlates, severity, and clinical implications (9). Cytokines have been found to be potential mediators of fatigue in cancer (10,11), but their role in ESRD patients is not known. We examine the relationship of fatigue to clinical and laboratory factors including cytokines in a prospective study of a diverse, national population of incident peritoneal dialysis (PD) and hemodialysis (HD) patients. We use vitality score as a surrogate for measurement of fatigue, with low vitality score indicating more fatigue. We first examine the predictors of fatigue at the initiation of dialysis treatment in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study, and then determine the factors related to longitudinal change in vitality. Lastly, we examine the relationship of fatigue with health-related quality of life (HRQOL) and survival.

Materials and Methods

Study Design and Population

The study participants were a subpopulation of patients enrolled in CHOICE. CHOICE is a national, prospective cohort study of incident HD and PD patients. From October 1995 to June 1998, 1041 (767 HD and 274 PD) patients were enrolled from 81 dialysis clinics associated with Dialysis Clinic, Incorporated (DCI, Nashville, TN), New Haven CAPD

Received January 13, 2009. Accepted August 27, 2009.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Mark Unruh, University of Pittsburgh Medical Center, Renal-Electrolyte Division, 3550 Terrace Street, A909 Scaife Hall, Pittsburgh, PA 15261. Phone: 412-647-2561; Fax: 412-647-6891; E-mail: unruh@pitt.edu

ISSN: 1555-9041/411–1779

(New Haven, CT), and the Hospital of St. Raphael (New Haven, CT). All study participants were incident kidney failure patients initiating outpatient dialysis, 18 yr or older, English or Spanish language speakers, and gave informed consent. Patients were enrolled a median of 45 d from initiation of chronic dialysis (98% within 4 mo).

There were a total of 917 participants who responded to the CHOICE Health Experience Questionnaire (CHEQ) and completed at least the items regarding vitality. Participants who did not respond to the CHEQ ($n = 113$) or who had incomplete information on vitality items ($n = 11$) were excluded. Of the 917 patients, 714 had complete data on all the variables adjusted for in the models. Of these, nine patients with body mass index (BMI) of greater than or equal to 50 were excluded from multivariable regression analysis as outliers. Thus, the remaining 705 participants were included in the adjusted models.

The study protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board and the institutional review boards of the participating clinical centers.

Fatigue Assessment

The development of the CHEQ has been described previously (12). The instrument includes the SF-36 vitality scale questions, which measure the continuum of fatigue (13). The SF-36 vitality scale has good psychometric properties and internal consistency reliability in people with ESRD (12). A higher score reflects more vitality and less fatigue. Patients were also asked about the number of good waking hours they had ("In the past 4 wk, on an average day, how many good waking hours did you have?").

Baseline Data Collection

Demographic characteristics, primary cause of kidney failure, and date of first chronic dialysis were ascertained from the Centers for Medicare and Medicaid Services Medical Evidence Form (Form 2728). Data regarding health behaviors were collected from the baseline questionnaire. The average values for serum albumin, creatinine, phosphate, and hematocrit during the 3 mo surrounding study enrollment were calculated. The single C-reactive protein (CRP) and interleukin 6 (IL-6) measurements were performed at a median time from enrollment to serum collection at 3.0 mo (94% within 6 mo). Serum CRP, an acute-phase protein, was measured by using a colorimetric competitive enzyme-linked immunosorbent assay (ELISA, Coefficient of variation [CV] 8.9%). Plasma fibrinogen was measured by using an automated clot-rate assay (CV 2.9%). IL-6, a proinflammatory cytokine, was measured in serum by an ultrasensitive ELISA method (CV 7%). Comorbidity was measured by the Index of Coexistent Disease (ICED) (14). Medication profiles were obtained by review of electronic order entry records provided by the clinics. Dialysis modality at baseline was defined as the modality used the majority of time within 90 d of study enrollment.

Health-Related Quality of Life Domains

The SF-36 has been extensively evaluated both in the general and the ESRD populations (12,15). To limit the number of comparisons, only the associations of vitality scores with SF-36 physical functioning, mental health, and bodily pain scores were examined, as these were *a priori* thought to be related to fatigue. The range for all scales is from 0 to 100, with higher scores indicating better health. To define sleep quality, scores were assigned to responses for the three questions in the CHEQ instrument assessing sleep initiation (how often did you have trouble falling asleep?), sleep maintenance (how often did you awaken during your sleep time and have trouble falling asleep again?), and sleep adequacy (how often did you get enough sleep to feel rested upon waking in the morning?). On the CHEQ sleep quality scale, a higher score on a scale of 0 to 100 reflects better sleep quality. The sleep quality scale has demonstrated adequate internal consistency and reliability as measured by the Cronbach α of 0.75, and its construct validity was described previously (16).

Selection of Covariates

Factors previously found to be associated with fatigue in the general population and among dialysis patients were considered as covariates (9,17). These included: demographics (age, gender, race, education, marital status, and employment) (18,19); lifestyle factors (current smoking, alcohol consumption, and physical exercise); dialysis treatment-related factors (mode of dialysis, dose of dialysis, cause of ESRD); laboratory factors (hematocrit, serum albumin, creatinine, phosphate) (20–23); psychologic factors (SF-36 mental health score, used to assess the role of psychologic well-being) (8,24); comorbid disease (ICED score) (9); sleep disorders (16,25,26); and inflammatory markers (CRP, IL-6, fibrinogen) (27–29).

Statistical Analyses

Patients were grouped into four categories based on approximate baseline vitality quartiles. Baseline demographic, socioeconomic, and laboratory factors are described as means and SD for continuous variables and as frequency distributions for categorical variables. Statistical significance of the differences between vitality category groups was tested using the Kruskal–Wallis test for continuous variables and χ^2 tests for categorical variables. Continuous variables that were not normally distributed in the cohort (CRP, IL-6) were transformed to normality by applying a logarithmic (Box-Cox) transformation. All analyses were performed using the software R (30). Univariate analysis was done for the association of fibrinogen and IL-6; however, to avoid problems with multicollinearity, these were not included in the same models with CRP.

We created a linear regression ANCOVA model to identify factors independently associated with the raw vitality score at the onset of chronic outpatient dialysis therapy, since the proportional odds assumptions for ordinal logistic regression to examine the vitality quartiles were not satisfied. Model selection was based on those variables found to have a relationship ($P < 0.10$) to vitality in bivariate analysis, and included major demographic factors.

In longitudinal analysis, we defined a statistically significant individual change in vitality as a change in score exceeding two standard errors of measurement (SEM) of vitality score at baseline (31). We calculated the SEM as $SD \times \sqrt{1 - R}$, where SD is the SD of the baseline domain score and R is the vitality internal consistency reliability (32). Patients who died during the follow-up year were excluded from the analysis. We examined differences in change in vitality using multivariable logistic regression.

The relationship of baseline vitality scores to survival was assessed using multivariable Cox proportional hazard regression models. Patients with baseline vitality score in the highest quartile (score >55) were compared with those with vitality score ≤ 55. The vitality score was dichotomized into highest level compared with all other levels since we found that several of the lower quartiles violated proportionality. Patients who received transplants, who were lost to follow up, and who remained enrolled at the close of the study (December 31, 2004) were censored at the time of those events. Survival regressions were stratified by baseline modality of dialysis and ICED score and used the robust variance method to account for the cluster effect of dialysis centers (33). The survival time was started at 1 yr for the

survival model examining the relationship of change in vitality in the first year with survival.

Results

Patient Characteristics by Vitality

The range of vitality scores among these incident dialysis patients was 0 to 100 with mean being 40.9 ± 22.5 SD. Table 1 shows patient characteristics and compares patients by approximate quartiles of the vitality score. Patients with worse fatigue (lower vitality scores) were more likely to be white, had more severe comorbid diseases (higher ICED score), did not do physical exercise, had lower serum creatinine, and minimally lower serum albumin. A significant number of patients with lower vitality reported using benzodiazepines and antidepressants more often and had fewer "good waking hours." Poor vitality was significantly related to elevated levels of markers of inflammation such as CRP and IL-6 ($P = 0.01$ for both) but not to fibrinogen ($P = 0.81$). Those with low vitality at baseline also reported a significantly lower baseline HRQOL in the domains of mental health, physical functioning, bodily pain, and sleep quality.

Independent Predictors of Vitality

In multivariable linear ANCOVA analysis, nonwhite race (including African American and other races) was associated with higher adjusted vitality scores at the initiation of dialysis (Table 2). Higher ICED score, higher BMI, physical exercise, antidepressant use, and higher CRP levels were found to be significantly associated with lower baseline vitality, but age, gender, mode of dialysis (HD *versus* PD), serum albumin, and creatinine were not (Table 2). Although BMI was found to be statistically significant, the magnitude of change in vitality per unit change in BMI was small.

Longitudinal Changes in Vitality

Among the participants who completed the CHEQ questionnaire at 1 yr, 464 had complete data for all the variables included in the longitudinal analysis. Patients who had lower serum creatinine values at baseline were more likely to experience decline in vitality (Table 3). African American patients were less likely to experience decline in vitality. Age, gender, albumin, BMI, physical exercise, CRP, ICED score, use of antidepressants, and mode of dialysis were not associated with change in vitality (Table 3).

Association of Vitality with Survival

During a median follow-up period of 1065 d, there were 425 deaths in the cohort of 705 patients who completed a baseline CHEQ in CHOICE and for whom complete information regarding predictors of vitality were available. Patients with baseline vitality score in the highest quartile (score >55) were compared with those with vitality score ≤55. As shown in Figure 1, a higher vitality score was associated with a lower hazard of death (Crude HR: 0.64; 95% CI 0.49 to 0.84, $P < 0.001$). The strength of the relationship between vitality and survival was attenuated but remained statistically significant after adjusting for age, gender, race, BMI, creatinine, albumin, CRP, dialysis modality, and antidepressant use (HR: 0.75; 95% CI 0.58 to 0.96, $P = 0.03$). The proportionality assumption was evaluated by examining the scaled Schoenfeld residuals (*p*-value for nonproportionality was 0.67) (34). Neither the magnitude, nor the significance of these associations was modified when physical exercise was included as a covariate in the model (data not shown).

We further analyzed the effect of change in vitality over 1 yr on survival. The median survival for those with a decline in vitality at 1 yr was 3.0 yr, as compared with 3.8 yr for those with stable or improved vitality. Also, a decline in vitality in the first year of dialysis was associated with an increased crude risk of death. Compared with patients who reported stable or improved vitality at 1 yr, patients who reported a decline in vitality had a higher risk of death (HR 1.41; 95% CI 1.06 to 1.89, $P = 0.02$), after adjusting for age, gender, race, use of antidepressants, dialysis modality, albumin, creatinine, log CRP, BMI, and baseline vitality quartile.

Discussion

Our findings confirm that ESRD patients experience profound levels of fatigue (8,18,22,), as underscored by average vitality scores among these incident dialysis patients (40.9 ± 22.5 SD), which is well below a community-based average score (60.9 ± 20.9) (15). Furthermore, the profound severity of fatigue in this population is underscored by the average vitality scores of these ESRD patients, which is lower than 12 of the 13 norms from chronic health conditions and has similar severity to patients with clinical depression (15). These results also indicate the complex correlates of fatigue, some of which (*e.g.*, poor sleep quality) may be amenable to intervention. Our study has the strength of representing a racially and geographically diverse population of incident dialysis patients that is similar in age (mean 57.9 *versus* 61.1 yr), gender (males 54.2% *versus* 53.3%), and race (whites 66.9% *versus* 62.0%) distribution to United States Renal Data System samples (35). We also adjusted for a number of potential confounders shown to be associated with fatigue in previous studies, thus limiting potential bias. After adjustment for multiple cofactors, we found a significant association between CRP levels (a marker of inflammation) and low baseline vitality. Such associations are not surprising, since chronic inflammatory states are linked to fatigue and to lack of energy in other chronic conditions. The importance of fatigue was highlighted by a strong association of lower vitality scores with poor self-reported sleep quality and increased bodily pain. Such association does not necessarily imply causality but indicates the complex and interdependent relation between these domains and their influence on the overall HRQOL. Examining the association of vitality with survival revealed that lower vitality at baseline and decline in vitality over 1 yr were both independently associated with a higher risk of death.

A finding with significant implications for the dialysis patients is the association of baseline vitality and longitudinal declines of vitality with survival. These associations, which occurred independent of the patient's age, serum albumin, and state of inflammation (assessed by the CRP levels), are consistent with data from the DOPPS study and several other small

Table 1. Characteristics of incident patients with ESRD by vitality levels[a]

Characteristic	Lowest Vitality (Scores ≤25)	>25 to ≤40	>40 to ≤55	Highest Vitality (Scores >55)	Overall	*P*
N	272 (29.6%)	197 (21.5%)	237 (25.8%)	211 (23.0%)	917	
Vitality score	14.1 ± 8.4	34.8 ± 4.0	49.7 ± 3.9	71.1 ± 10.4	40.9 ± 22.5	<0.001
Age (*n* = 917)	57.3 ± 15.2	59.2 ± 15.1	59.1 ± 13.8	56.1 ± 14.7	57.9 ± 14.8	0.08
Male (*n* = 917)	136 (27.9%)	104 (21.3%)	130 (26.7%)	117 (24.0%)	487 (53.1%)	0.60
Race (*n* = 917)						<0.001
White (*n* = 621)	200 (32.2%)	148 (23.8%)	153 (24.6%)	120 (19.3%)	621 (67.7%)	
Black (*n* = 254)	64 (25.2%)	44 (17.3%)	75 (29.5%)	71 (27.9%)	254 (27.7%)	
Others (*n* = 42)	8 (19.1%)	5 (11.9%)	9 (21.4%)	20 (47.6%)	42 (4.6%)	
Less than high school (*n* = 906)	78 (30.1%)	51 (26.0%)	70 (27.0%)	60 (23.2%)	259 (28.6%)	0.82
Unemployed (*n* = 917)	11 (28.9%)	8 (21.0%)	7 (18.4%)	12 (31.6%)	38 (4.1%)	0.54
Married (*n* = 914)	148 (29.2%)	119 (23.4%)	128 (25.3%)	112 (22.1%)	507 (55.5%)	0.45
Cause of renal failure (*n* = 917)						0.16
Diabetes	134 (31.9%)	84 (20.1%)	108 (25.8%)	93 (22.2%)	419 (45.7%)	
Hypertension	41 (25.6%)	29 (18.1%)	51 (31.8%)	39 (24.4%)	160 (17.5%)	
Glomerulonephritis	40 (25.2%)	36 (22.6%)	39 (24.5%)	44 (27.6%)	159 (17.3%)	
Other	57 (31.8%)	48 (26.8%)	39 (21.7%)	35 (19.6%)	179 (19.5%)	
Hemodialysis (*n* = 917)	200 (29.3%)	155 (22.5%)	176 (25.5%)	158 (22.9%)	689 (75.1%)	0.61
Comorbidity (*n* = 916)						<0.001
ICED 0 to 1	66 (20.3%)	60 (18.4%)	103 (31.6%)	97 (29.7%)	326 (35.6%)	
ICED 2	116 (35.8%)	68 (21.0%)	80 (24.7%)	60 (18.5%)	324 (35.4%)	
ICED 3	89 (33.5%)	69 (25.9%)	54 (20.3%)	54 (20.3%)	266 (29.0%)	
Current smoker (*n* = 910)	49 (35.5%)	33 (23.9%)	32 (23.2%)	24 (17.4%)	138 (15.2%)	0.15
Current alcohol (*n* = 655)	27 (26.5%)	23 (22.5%)	29 (28.4%)	23 (22.5%)	102 (15.6%)	0.93
Physical exercise (*n* = 900)	34 (17.8%)	32 (16.8%)	55 (28.8%)	70 (36.7%)	191 (21.2%)	<0.001
BMI (kg/m^2; *n* = 852)	27.8 ± 7.4	26.9 ± 6.8	26.6 ± 5.9	27.2 ± 7.1	27.1 ± 6.9	0.48
Number of good waking hours (*n* = 835)	9.9 ± 9.1	9.8 ± 4.7	12.2 ± 14.7	14.5 ± 31.8	11.5 ± 17.5	<0.001
Benzodiazepines (*n* = 917)	38 (43.2%)	26 (29.5%)	16 (18.2%)	8 (9.1%)	88 (9.6%)	<0.001
Antidepressants (*n* = 917)	47 (37.9%)	36 (29.0%)	26 (21.0%)	15 (12.1%)	124 (13.5%)	<0.01
Albumin (mg/dl; *n* = 894)	3.6 ± 0.4	3.7 ± 0.4	3.6 ± 0.4	3.7 ± 0.3	3.6 ± 0.4	0.01
Creatinine (mg/dl; *n* = 896)	7.1 ± 2.7	7.1 ± 2.4	7.3 ± 2.6	7.6 ± 2.3	7.3 ± 2.5	<0.01
Hematocrit (*n* = 889)	32.2 ± 3.9	32.2 ± 3.4	32.8 ± 4.3	32.4 ± 4.0	32.5 ± 4.1	0.32
Phosphate (mg/dl; *n* = 895)	5.2 ± 1.4	5.2 ± 1.3	5.3 ± 1.4	5.2 ± 1.3	5.2 ± 1.3	0.91
Kt/V (*n* = 628)	1.3 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	0.76
CRP (mg/l; *n* = 790)	9.1 ± 12.7	7.9 ± 9.4	8.4 ± 12.8	6.4 ± 9.9	8.4 ± 12.5	<0.01
Fibrinogen (mg/dl; *n* = 714)	371.1 ± 121.6	368.0 ± 101.1	380.7 ± 129.2	374.5 ± 129.7	375.3 ± 121.9	0.81
IL-6 (pg/ml; *n* = 789)	7.4 ± 9.3	6.7 ± 7.4	7.8 ± 11.6	6.7 ± 11.5	7.3 ± 10.4	0.005
Sleep quality (*n* = 903)	51.1 ± 22.4	54.6 ± 19.7	61.7 ± 21.9	66.6 ± 21.1	58.2 ± 22.2	<0.001
Mental component summary (MCS) (*n* = 867)	38.6 ± 10.6	45.1 ± 10.0	49.1 ± 9.5	54.8 ± 8.9	46.4 ± 11.5	<0.001
Physical component summary (PCS) (*n* = 867)	27.5 ± 7.8	30.2 ± 8.7	33.1 ± 9.0	41.1 ± 8.9	32.6 ± 10.0	<0.001
Bodily pain (BP) (*n* = 914)	44.4 ± 25.7	50.4 ± 24.4	58.2 ± 26.2	74.2 ± 23.8	56.3 ± 27.5	<0.001

[a]χ^2 for categorical variables and Kruskal-Wallis for continuous variables.
n = 917 (participants who responded to the CHEQ questionnaire and completed items regarding vitality at the initiation of dialysis).

Table 2. Baseline characteristics independently associated with vitality scores by multiple linear regression using ANCOVA

Characteristic	Adjusted Mean Difference	*F* statistic	*P* value
Age (per 10 yr)	0.07	0.04	0.84
Gender (male *versus* female)	1.54	2.03	0.16
Race (*versus* White)		7.16	<0.001
Black	4.78		
Other	8.71		
Mode of dialysis (PD *versus* HD)	−0.10	0.002	0.97
ICED score (*versus* ICED ≤1)		6.83	<0.01
ICED = 2	−4.70		
ICED = 3	−5.32		
BMI (kg/m^2)	−0.30	6.06	0.01
Physical exercise	−8.30	17.52	<0.001
Using antidepressants	−7.84	11.48	<0.001
Albumin (mg/dl)	3.06	2.28	0.12
Creatinine (mg/dl)	0.14	0.15	0.70
Log CRP	−0.57	6.05	0.01

n = 705 (714 participants had complete information on all the variables included in the model, out of these nine participants with BMI ≥ 50 were excluded as outliers).

Table 3. Baseline factors associated with worsening of vitality at 1 yr[a]

Characteristic	Adjusted Odds Ratio (95% CI)	*P* value
Age	0.99 (0.97 to 1.01)	0.29
Gender (male *versus* female)	0.73 (0.40 to 1.31)	0.29
Race (*versus* white)		0.02
Black	0.43 (0.21 to 0.88)	
Other	0.36 (0.10 to 1.25)	
Mode of dialysis (PD *versus* HD)	1.85 (0.92 to 3.72)	0.09
ICED score (*versus* ICED ≤ 1)		0.88
ICED = 2	1.04 (0.54 to 2.01)	
ICED = 3	0.87 (0.43 to 1.78)	
BMI (kg/m^2)	1.02 (0.97 to 1.07)	0.50
Physical exercise	1.65 (0.85 to 3.18)	0.14
Using antidepressants	0.91 (0.38 to 2.20)	0.84
Albumin (mg/dl)	0.74 (0.35 to 1.57)	0.44
Creatinine (mg/dl)	0.84 (0.72 to 0.98)	0.03
Log CRP	0.90 (0.69 to 1.19)	0.47

[a]Adjusted for baseline vitality score.
n = 464 (includes participants who completed the CHEQ questionnaire at 1 yr and had complete information on all the variables included in the model).

studies that have demonstrated that HRQOL predicts survival in ESRD patients (36–38). One can postulate the existence of a pathogenic inflammatory factors common to fatigue and decreased survival to explain these finding. Otherwise, one may consider fatigue as a protean manifestation of the "residual syndrome" due to uremic toxins in patients undergoing renal replacement (39). To provide empiric evidence for this assertion, further studies should be undertaken that combine longitudinal assessments of dialysis patients and measurements of molecular biomarkers associated with uremic toxicity (40).

Notwithstanding such explanations, fatigue is a common manifestation of multiple co-existent conditions and health states, most of which are not unique to dialysis. The observation that obese people had lower vitality replicates a relationship that is known to exist in the general population (41,42). Obesity has also been related to lower HRQOL in patients with chronic medical and psychiatric conditions in the Medical Outcomes Study (43). More recently it was shown that obesity is related to lower HRQOL (although not vitality specifically) in ESRD patients in the Dialysis Morbidity and Mortality Study

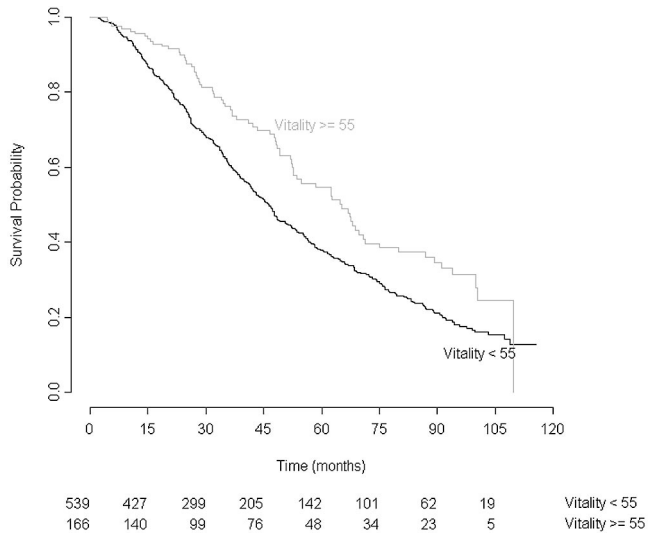

Figure 1. Cumulative survival among incident dialysis patients by vitality score ($P < 0.001$ by log-rank test), $n = 705$.

(DMMS) Wave 2 (44). Our study replicates this observation and calls for additional research to examine the impact of targeted interventions on the quality of life and survival of dialysis patients (45).

Inflammatory markers like IL-1, IL-6, CRP, and Tumor Necrosis Factor (TNF)-α have been studied extensively in cancer-related fatigue (11). High levels of CRP have also been shown to correlate with poor physical performance and muscle strength in myocardial infarction survivors and elderly people (46,47). Studies among ESRD patients have also shown that elevated levels of pro-inflammatory cytokines are linked to an increase in energy expenditure, mortality, and lower functional status (27,48,49). However, this study also provides evidence that fatigue in dialysis patients may be independently associated with other factors in addition to inflammation, for example, the presence of obesity, or the comorbidity burden present at the time the patient is started on renal replacement.

Although we found a negative correlation of antidepressant use and baseline vitality in our study, we cannot distinguish a cause-and-effect relationship. The significant relationship may suggest an underlying direct correlation of depression with fatigue, as has been shown in previous studies (8). However, it may also be due to modulation of norepinephrine, serotonin, and/or dopamine-receptor activity by antidepressants (especially tricyclic antidepressants), which can cause somnolence, insomnia, and muscular weakness (50). In addition, the scales used to measure mental health and fatigue are moderately correlated in general. Further work is needed toward defining this intricate relationship between depression and fatigue, and may uncover other factors amenable to intervention.

Our current finding that incident African American dialysis patients report more vitality and less loss of vitality over time than do non-African Americans supports the position that race is a useful construct in understanding the adaptation to dialysis treatment and that further exploration of racial differences in this response may be informative. In a cross-sectional analysis of the DMMS Wave 2, incident African American dialysis patients had better vitality scores. However, the differences were attenuated in this study after adjustment for patients' sociodemographic and clinical characteristics (51). We have previously reported that in adjusted models, prevalent African American HD patients have higher scores on the Index of Well-Being and Kidney Disease Quality of Life scale, and perceived lesser burden of disease as compared with whites (19). For scales reflecting symptoms and effects of kidney disease, sleep quality, and the Physical Component Summary, non-African Americans experienced significantly greater decline in scores with increasing comorbidity (19).

There are several limitations to our study. First, we did not measure the patients' quality of life and vitality before initiation of dialysis. This may have attenuated or caused us to miss the change in vitality that patients experienced at the initiation of dialysis. Second, when examining the distribution of vitality in our sample, we found that 32 patients reported a score of zero at baseline. Due to this inherent floor effect and clustering of more people toward a lower vitality score, the SF-36 scale may fail to fully capture the full range of fatigue severity in the dialysis population. Future work should consider instruments with measurement of more severe fatigue, such as those being developed in the NIH-funded PROMIS study (13). However, these findings still demonstrate profound differences in the fatigue experienced by people on dialysis and the general populations. Third, these findings represent only two assessments of the individual, one at baseline and one at 1 yr on dialysis. Dialysis patients experience considerable diurnal and day-to-day variations in fatigue that are probably not captured by the questionnaire. Further work might consider using ecological momentary assessment to incorporate repeated real-time measurement of symptoms to assess subjective fatigue repeatedly and reliably (52). Fourth, we did not have information whether the study participants carried a clinical diagnosis of depression. Thus, we were not able to elicit any direct association of depression with vitality. Lastly, the longitudinal analyses of change in vitality score included only those who responded to the CHEQ at 1 yr, potentially leading to informative censoring; however, the data presented addresses the clinically relevant question of what correlates with worsening fatigue among dialysis survivors.

In summary, this report demonstrates that fatigue is an important problem for patients beginning maintenance dialysis. The presence of fatigue may be an indicator of an underlying inflammatory burden and also help predict patients at increased risk of dying. Even more importantly, dialysis patients desire the energy to carry out a normal life, and the profound fatigue associated with kidney failure and dialysis treatment interferes with rehabilitation and diminishes quality of life. Our findings provide a promising starting point for addressing the correlates of fatigue, such as obesity and inflammation. A better understanding of the interactions between factors such as dialysis modality, sleep, depression, and cytokine production may help clinicians develop interventions to improve survival and quality of life among dialysis patients.

Acknowledgments

We thank the patients, clinical and laboratory staff, and physicians who participated in the CHOICE Study at Dialysis Clinic, Inc, St. Raphael's Hospital, and New Haven CAPD. CHOICE was supported by R01-HS-08365 (AHRQ) from June 1995 to May 2000, R01-HL-62985 (NHLBI) from September 2000 to June 2006, and R01-DK-07024 (NIDDK) from September 2000 to June 2007. Other grants supporting this research are K24-DK-02643 (NIDDK; Powe); K23-DK-66006 and R01-DK-77785 (Unruh); and K07-CA-118576 (Steel).

Disclosures

None.

References

1. Garcia SF, Cella D, Clauser SB, Flynn KE, Lad T, Lai JS, Reeve BB, Smith AW, Stone AA, Weinfurt K: Standardizing patient-reported outcomes assessment in cancer clinical trials: A patient-reported outcomes measurement information system initiative. *J Clin Oncol* 25: 5106–5112, 2007
2. Lee KA, Hicks G, Nino-Murcia G: Validity and reliability of a scale to assess fatigue. *Psychiatry Res* 36: 291–298, 1991
3. Chang WK, Hung KY, Huang JW, Wu KD, Tsai TJ: Chronic fatigue in long-term peritoneal dialysis patients. *Am J Nephrol* 21: 479–485, 2001
4. Laupacis A, Muirhead N, Keown P, Wong C: A disease-specific questionnaire for assessing quality of life in patients on hemodialysis. *Nephron* 60: 302–306, 1992
5. Murtagh FE, Addington-Hall J, Higginson IJ: The prevalence of symptoms in end-stage renal disease: A systematic review. *Adv Chronic Kidney Dis* 14: 82–99, 2007
6. Parfrey PS, Vavasour HM, Henry S, Bullock M, Gault MH: Clinical features and severity of nonspecific symptoms in dialysis patients. *Nephron* 50: 121–128, 1988
7. Ramkumar N, Beddhu S, Eggers P, Pappas LM, Cheung AK: Patient preferences for in-center intense hemodialysis. *Hemodial Int* 9: 281–295, 2005
8. Weisbord SD, Fried LF, Arnold RM, Fine MJ, Levenson DJ, Peterson RA, Switzer GE: Prevalence, severity, and importance of physical and emotional symptoms in chronic hemodialysis patients. *J Am Soc Nephrol* 16: 2487–2494, 2005
9. Jhamb M, Weisbord SD, Steel JL, Unruh M: Fatigue in patients receiving maintenance dialysis: A review of definitions, measures, and contributing factors. *Am J Kidney Dis* 52: 353–365, 2008
10. Jager A, Sleijfer S, van der Rijt CC: The pathogenesis of cancer related fatigue: Could increased activity of pro-inflammatory cytokines be the common denominator? *Eur J Cancer* 44: 175–181, 2008
11. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE: The association between fatigue and inflammatory marker levels in cancer patients: A quantitative review. *Brain Behav Immun* 21: 413–427, 2007
12. Wu AW, Fink NE, Cagney KA, Bass EB, Rubin HR, Meyer KB, Sadler JH, Powe NR: Developing a health-related quality-of-life measure for end-stage renal disease: The CHOICE Health Experience Questionnaire. *Am J Kidney Dis* 37: 11–21, 2001
13. Lai JS, Chen WH: Fatigue Archival Analysis Report. Available at: www.nihpromis.org. Accessed May 3, 2008
14. Athienites NV, Miskulin DC, Fernandez G, Bunnapradist S, Simon G, Landa M, Schmid CH, Greenfield S, Levey AS, Meyer KB: Comorbidity assessment in hemodialysis and peritoneal dialysis using the index of coexistent disease. *Semin Dial* 13: 320–326, 2000
15. Ware JE: *SF-36 Health Survey Manual and Interpretation Guide,* Boston, The Health Institute, New England Medical Center, 1993
16. Unruh ML, Buysse DJ, Dew MA, Evans IV, Wu AW, Fink NE, Powe NR, Meyer KB: Sleep quality and its correlates in the first year of dialysis. *Clin J Am Soc Nephrol* 1: 802–810, 2006
17. Corwin EJ, Klein LC, Rickelman K: Predictors of fatigue in healthy young adults: Moderating effects of cigarette smoking and gender. *Biol Res Nurs* 3: 222–233, 2002
18. Liu HE: Fatigue and associated factors in hemodialysis patients in Taiwan. *Res Nurs Health* 29: 40–50, 2006
19. Unruh M, Miskulin D, Yan G, Hays RD, Benz R, Kusek JW, Meyer KB: Racial differences in health-related quality of life among hemodialysis patients. *Kidney Int* 65: 1482–1491, 2004
20. Chikotas N, Gunderman A, Oman T: Uremic syndrome and end-stage renal disease: Physical manifestations and beyond. *J Am Acad Nurse Pract* 18: 195–202, 2006
21. Jones M, Ibels L, Schenkel B, Zagari M: Impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis. *Kidney Int,* 65: 757–767, 2004
22. McCann K, Boore JR: Fatigue in persons with renal failure who require maintenance haemodialysis. *J Adv Nurs* 32: 1132–1142, 2000
23. Ossareh S, Roozbeh J, Krishnan M, Liakopoulos V, Bargman JM, Oreopoulos DG: Fatigue in chronic peritoneal dialysis patients. *Int Urol Nephrol* 35: 535–541, 2003
24. Kimmel PL, Cukor D, Cohen SD, Peterson RA: Depression in end-stage renal disease patients: A critical review. *Adv Chronic Kidney Dis* 14: 328–334, 2007
25. Unruh ML, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB: Restless legs symptoms among incident dialysis patients: Association with lower quality of life and shorter survival. *Am J Kidney Dis* 43: 900–909, 2004
26. Yngman-Uhlin P, Edell-Gustafsson U: Self-reported subjective sleep quality and fatigue in patients with peritoneal dialysis treatment at home. *Int J Nurs Pract* 12: 143–152, 2006
27. Balakrishnan VS, Guo D, Rao M, Jaber BL, Tighiouart H, Freeman RL, Huang C, King AJ, Pereira BJ: Cytokine gene polymorphisms in hemodialysis patients: Association with comorbidity, functionality, and serum albumin. *Kidney Int* 65: 1449–1460, 2004
28. Buchwald D, Wener MH, Pearlman T, Kith P: Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. *J Rheumatol* 24: 372–376, 1997
29. Kurzrock R: The role of cytokines in cancer-related fatigue. *Cancer* 92: 1684–1688, 2001
30. R: A Language and Environment for Statistical Computing. Available at: www.r-project.org. Accessed September 3, 2008
31. Wu AW, Fink NE, Marsh-Manzi JV, Meyer KB, Finkelstein FO, Chapman MM, Powe NR: Changes in quality of life during hemodialysis and peritoneal dialysis treatment: Generic and disease specific measures. *J Am Soc Nephrol* 15: 743–753, 2004

32. Ware JE, Kosinski M, Keller SK: *SF-36 Physical and Mental Health Summary Scales: A User's Manual*, Boston, The Health Institute, New England Medical Center, 1994
33. Localio AR, Berlin JA, Ten Have TR, Kimmel SE: Adjustments for center in multicenter studies: An overview. *Ann Intern Med* 135: 112–123, 2001
34. Grambsch P, Louis TA, Bostick RM, Grandits GA, Fosdick L, Darif M, Potter JD: Statistical analysis of proliferative index data in clinical trials. *Stat Med* 13: 1619–1634, 1994
35. The USRDS Dialysis Morbidity and Mortality Study: Wave 2. United States Renal Data System. *Am J Kidney Dis* 30: S67–S85, 1997
36. DeOreo PB: Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. *Am J Kidney Dis* 30: 204–212, 1997
37. Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK: Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 64: 339–349, 2003
38. Morsch CM, Goncalves LF, Barros E: Health-related quality of life among haemodialysis patients–relationship with clinical indicators, morbidity and mortality. *J Clin Nurs* 15: 498–504, 2006
39. Depner TA: Uremic toxicity: Urea and beyond. *Semin Dial* 14: 246–251, 2001
40. Depner T, Himmelfarb J: Uremic retention solutes: The free and the bound. *J Am Soc Nephrol* 18: 675–676, 2007
41. Vgontzas AN, Bixler EO, Chrousos GP: Obesity-related sleepiness and fatigue: The role of the stress system and cytokines. *Ann N Y Acad Sci* 1083: 329–344, 2006
42. Wee CC, Davis RB, Hamel MB: Comparing the SF-12 and SF-36 health status questionnaires in patients with and without obesity. *Health Qual Life Outcomes* 6: 11, 2008
43. Katz DA, McHorney CA, Atkinson RL: Impact of obesity on health-related quality of life in patients with chronic illness. *J Gen Intern Med*, 15: 789–796, 2000
44. Johansen KL, Kutner NG, Young B, Chertow GM: Association of body size with health status in patients beginning dialysis. *Am J Clin Nutr* 83: 543–549, 2006
45. Alexander JW, Goodman HR, Gersin K, Cardi M, Austin J, Goel S, Safdar S, Huang S, Woodle ES: Gastric bypass in morbidly obese patients with chronic renal failure and kidney transplant. *Transplantation* 78: 469–474, 2004
46. Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Rhys Williams G, Guralnik JM, Ferrucci L: Inflammatory markers and physical performance in older persons: The InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 59: 242–248, 2004
47. Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S: Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. *Brain Behav Immun* 19: 555–563, 2005
48. Kamimura MA, Draibe SA, Dalboni MA, Cendoroglo M, Avesani CM, Manfredi SR, Canziani ME, Cuppari L: Serum and cellular interleukin-6 in haemodialysis patients: Relationship with energy expenditure. *Nephrol Dial Transplant* 22: 839–844, 2007
49. Kimmel PL, Phillips TM, Simmens SJ, Peterson RA, Weihs KL, Alleyne S, Cruz I, Yanovski JA, Veis JH: Immunologic function and survival in hemodialysis patients. *Kidney Int* 54: 236–244, 1998
50. Adams SM, Miller KE, Zylstra RG: Pharmacologic management of adult depression. *Am Fam Physician* 77: 785–792, 2008
51. Kutner NG, Zhang R, Brogan D: Race, gender, and incident dialysis patients' reported health status and quality of life. *J Am Soc Nephrol* 16: 1440–1448, 2005
52. Hacker ED, Ferrans CE: Ecological momentary assessment of fatigue in patients receiving intensive cancer therapy. *J Pain Symptom Manage* 33: 267–275, 2007