

Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients¹⁻⁴

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ABSTRACT

Background: Malnutrition-inflammation complex syndrome, an outcome predictor in maintenance hemodialysis (MHD) patients, may be related to anorexia.

Objectives: We examined whether subjectively reported appetite is associated with adverse conditions and increased morbidity and mortality in MHD patients.

Design: A cohort of 331 MHD outpatients was asked to rate their recent appetite status on a scale from 1 to 4 (very good, good, fair, and poor appetite, respectively). Anemia indexes and nutritional and inflammatory markers—including serum concentrations of C-reactive protein, tumor necrosis factor α , and interleukin 6—were measured. The malnutrition-inflammation score was used to evaluate the malnutrition-inflammation complex syndrome, and the SF36 questionnaire was used to assess quality of life (QoL). Mortality and hospitalization were followed prospectively for up to 12 mo.

Results: Patients were aged 54.5 ± 14.4 y. Diminished appetite (fair to poor) was reported by 124 patients (38%). Hemoglobin, protein intake, and QoL scores were progressively lower, whereas markers of inflammation, malnutrition-inflammation scores, and the required erythropoietin dose were higher across the worsening categories of appetite. The adjusted odds ratios of diminished versus normal appetite for increased serum tumor necrosis factor α and C-reactive protein concentrations were significant. Significant associations between a poor appetite and an increased rate of hospitalization and mortality were observed. The hazard ratio of death for diminished appetite was 4.74 (95% CI: 1.85, 12.16; $P = 0.001$).

Conclusion: Diminished appetite (anorexia) is associated with higher concentrations of proinflammatory cytokines and higher levels of erythropoietin hyporesponsiveness and poor clinical outcome, including a 4-fold increase in mortality, greater hospitalization rates, and a poor QoL in MHD patients. Appetite status may yield significant insight into the clinical status of dialysis patients. *Am J Clin Nutr* 2004;80:299–307.

KEY WORDS Dialysis, anorexia, inflammation, protein-energy malnutrition, outcome, appetite

INTRODUCTION

Patients undergoing maintenance hemodialysis (MHD) have a high prevalence of protein-energy malnutrition (PEM) and inflammation (1–3). Because these 2 conditions often occur concomitantly in MHD patients, they have been referred to together as the malnutrition-inflammation complex syndrome (MICS) (2–5), or malnutrition-inflammation atherosclerosis (1, 6)—to

underscore the atherosclerotic complications of this entity. MICS is also reported to correlate with poor outcome, including a decreased quality of life (QoL) (7–10), refractory anemia (11–13), and significantly greater rates of hospitalization and mortality in MHD patients (3, 14–16). Indeed, MICS may be the major cause of the paradoxical exposure-outcome association, also known as reverse epidemiology of cardiovascular disease risk factors in maintenance dialysis patients (17).

Appetite, a subjective desire to ingest food, is diminished in many dialysis patients (18, 19). However, it is not clear whether and to what extent a reduced appetite, also known as anorexia, is related to the elements of MICS, especially inflammation, in these persons. Anorexia may indeed be a key component in the development and maintenance of PEM, inflammation, and MICS in these patients. An abnormally low appetite per se may be a risk factor in dialysis patients for such unfavorable outcomes as erythropoietin hyporesponsiveness, poor QoL, and increased mortality and hospitalization.

To examine the above hypotheses, we assessed appetite by using a simple questionnaire and examined the associations between self-reported appetite and the indicator of MICS and measures of clinical outcome both cross-sectionally and longitudinally in a group of MHD patients. This assessment was made during the first year of the Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study, a 5-y prospective, observational

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cohort study sponsored by the National Institute of Diabetes, Digestive and Kidney Diseases targeting up to 1000 MHD patients.

SUBJECTS AND METHODS

Subjects

Subjects participating in the NIED Study originated from a pool of \approx 1200 MHD outpatients in 8 DaVita, Inc, dialysis facilities in the South Bay Los Angeles area. [See the NIED Study website at www.nephrology.rei.edu/NIED.htm and a previous publication (13) for more details]. To be eligible for inclusion in the study, subjects had to be outpatients who had been undergoing MHD for \geq 8 wk, had to be aged \geq 18 y, and had to have signed a consent form. Patients with an anticipated life expectancy of $<$ 6 mo (eg, because of a metastatic malignancy or terminal HIV disease) were excluded. In the initial phase of the NIED Study (October 2001–March 2002), 385 patients from 8 dialysis units signed the written consent form. Subsequently, blood samples were obtained from 367 of these patients; 18 patients were not present in the dialysis units at the time of blood drawing. The medical chart of each MHD patient was thoroughly reviewed by a nephrologist (KKZ), and data pertaining to underlying kidney disease, cardiovascular disease history, and other comorbid conditions were extracted. A modified version of the Charlson comorbidity index, ie, without the age and kidney disease components, was used to assess the severity of comorbidity (20, 21).

Appetite assessment

The first 3 questions of the Hemodialysis (HEMO) Study Appetite questionnaire (7, 22, 23) were used to assess the appetite of the MHD patients. The multiple-choice answers for the first question (“During the past week, how would you rate your appetite?”) were as follows: 1) very good, 2) good, 3) fair, 4) poor, or 5) very poor. The second and third questions asked whether there had been a change in appetite and, if so, whether the appetite had decreased or increased.

All 367 patients who provided blood samples were asked to answer these 3 appetite-related questions and to complete other questionnaires concerning food intake and QoL. These questionnaires were completed either at the time of or within 4 wk of blood sample collection. Most of the patients answered the appetite questions independently while undergoing MHD treatment. Those who required assistance (34 patients) because of visual impairment, illiteracy, or other handicaps were assisted by study personnel. Twenty-one patients who had provided blood samples did not answer the appetite-related questions because they transferred out of their original dialysis units, withdrew from chronic dialysis treatment, died, received a transplant, were hospitalized for $>$ 4 wk, or refused to cooperate. Fifteen other patients chose \geq 2 options as answers to the appetite questions or did not answer the questions legibly or unequivocally; these subjects did not agree to revise their answers or were not available for this purpose. Hence, 331 MHD patients provided analyzable answers to the appetite questions.

SF36 quality of life scoring system

The SF36, a short-form QoL scoring system with 36 items and 8 independent scales, is a well-documented, self-administered

questionnaire that has been widely used and validated in MHD patients (8, 9). The 8 scales of the SF36 are summarized in 2 dimensions: physical health and mental health. We recently used a more user-friendly format of the SF36 without modifying the content of the original questions or their answers (8). All but 7 patients who answered the appetite questions were also able to complete the SF36 questionnaire independently within 8–25 min while undergoing MHD treatment.

Malnutrition-inflammation score

The so-called malnutrition-inflammation score (MIS), which has 10 components, was created (3) by combining the 7 components of the conventional Subjective Global Assessment (SGA) of Nutrition (24)—a semiquantitative scale with 3 severity levels—with 3 new elements [body mass index, serum albumin, and total-iron-binding capacity (TIBC) to represent serum transferrin] in incremental fashion. Each MIS component has 4 levels of severity from 0 (normal) to 3 (very severe). In a recent prospective study, the MIS was found to be a comprehensive scoring system with significant associations with prospective hospitalization and mortality as well as measures of nutrition, inflammation, and anemia in MHD patients and was superior to conventional SGA and to individual laboratory values as a predictor of dialysis outcome and an indicator of MICS (3).

Anthropometric evaluation

Body weight assessment and anthropometric measurements were performed while the patients were undergoing hemodialysis treatment or within 5–20 min after termination of the treatment. Biceps skinfold and triceps skinfold thicknesses were measured with a conventional skinfold caliper according to standard techniques, as described elsewhere (3, 25, 26). Midarm circumference was measured with a plastic tape. Midarm muscle circumference was calculated by using the following formula (3, 8): midarm circumference – $(3.1416 \times \text{triceps skinfold thickness})$. Height was obtained from the patient’s chart.

Near infrared interactance

To evaluate the percentage of body fat and lean body mass, near infrared (NIR) interactance (27, 28) was performed at the same time as the anthropometric measurements. A commercial NIR interactance sensor (portable model 6100; Futrex, Gaithersburg, MD) was used. NIR measurements were performed by placing a Futrex sensor on the nonaccess upper arm for several seconds, after the required data (date of birth, sex, weight, and height) from each patient were entered. NIR measurements of body fat have been shown to correlate significantly with SGA and other nutritional measures in MHD patients (27, 28).

Erythropoietin and iron dose and the erythropoietin index

In all but one dialysis facility (with 30 subjects), precise documentation of the administered doses of recombinant human erythropoietin (EpoGen; Amogen, Thousand Oaks, CA) and intravenous iron was available. The average dose of erythropoietin (units/wk) for the remaining 301 MHD patients was calculated over a 13-wk interval. For those patients who missed more than 1 wk of hemodialysis treatment or left the cohort, the average erythropoietin dose was calculated for those weeks that they were part of the cohort. The erythropoietin responsiveness (resistance)

index was defined as the average weekly erythropoietin dose divided by the average blood hemoglobin value, as described by Gunnell et al (29). Of the 301 MHD patients with documented erythropoietin doses, 197 patients received 62.5–125 mg iron gluconate (Ferrlecit; Watson Inc, Morristown, NJ) and 15 patients received 50–100 mg iron dextran (Infed; Watson Inc) weekly to monthly. The remaining patients did not receive any intravenous iron during the 13-wk follow-up period.

Laboratory evaluation

Blood samples were obtained and coincided chronologically with the quarterly blood tests of DaVita facilities. The double-pool Kt/V was used to represent the weekly dialysis dose and the normalized protein equivalent of total nitrogen appearance (nPNA), also known as the normalized protein catabolic rate (nPCR), was calculated to estimate the daily protein intake (30). All routine laboratory measurements were performed by DaVita Laboratories (Deland, FL) with the use of automated methods, and the average values for each laboratory test within the 13-wk study period were calculated and used for data analyses in this study.

Serum C-reactive protein (CRP) and cytokines, including interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α) were measured as indexes of the degree of inflammation. The high-sensitivity CRP was measured with a turbidimetric immunoassay in which a serum sample is mixed with latex beads coated with anti-human CRP antibodies to form an insoluble aggregate (normal range: <3.0 mg/L; WPCI, Osaka, Japan) (31, 32). High sensitivity IL-6 and TNF- α immunoassay kits based on a solid-phase sandwich enzyme-linked immunoassay with the use of recombinant human IL-6 (normal range: <9.9 pg/mL; R&D Systems, Minneapolis) and TNF- α (normal range: <4.7 pg/mL; R&D Systems) were used to measure serum proinflammatory cytokines (33–35). CRP and cytokines were measured in the General Clinical Research Center Core Laboratories of Harbor-UCLA (University of California, Los Angeles) Medical Center. Serum prealbumin and total cholesterol concentrations were measured via automated methods in the Harbor-UCLA Clinical Laboratory.

Hospitalization

The hospitalization data were studied by assessing the for hospitalization and its total duration in days as defined by the US Renal Data System report (36). Hospitalization data during the 12-mo period after the completion of the above measurements were obtained on all 331 MHD patients. Hospitalization was defined as any hospital admission that included at least one overnight stay in the hospital (8). The admission day was counted as one full hospitalization day, but the discharge day was not. Therefore, the minimum duration of hospitalization per admission was 1 d. No exclusion criterion was used. Hence, hospital admissions for a variety of disorders were counted. However, because the vast majority of hospitalizations for dialysis access did not require overnight admission, essentially only those access-related hospitalizations that were associated with other comorbid conditions, such as infection or cardiovascular events, were included. For those patients who were in a hospital at the end of the 1-y cohort, all hospitalization days during this last admission were counted. For those patients who died or left the

cohort during the prospective follow-up period, the hospitalization rates during the survival time were standardized by using the factor 12/survival time (in mo) (8). *Annual hospitalization days* was defined as the sum of all hospitalization days of a given patient during the 12-mo prospective cohort as defined above. *Annual hospitalization frequency* was the total number of hospital admissions during the same period irrespective of the length of each admission.

Moreover, the number of days at risk from the start of the study until the first hospitalization event for each patient per year was assessed. Accordingly, the risk time for each individual was defined as the number of days from study entry until the date of the first hospitalization, a censoring event, or a study anniversary. A patient's risk period was truncated 3 d before a kidney transplant to avoid attributing the transplant-related hospitalization to the observed days to event. This approach has been used by the US Renal Data System for calculating the standardized hospitalization ratio (37).

Statistical methods

Logarithmic conversion was carried out for nonnormally distributed variables such as inflammatory markers. A conventional Student's *t* test or analysis of variance (ANOVA) with adjustment for multiple comparisons according to Bonferroni was used to detect significant differences among continuous variables in ≥ 2 groups. A chi-square test was used for nonparametric variables such as sex, race, ethnicity, and diabetes. We used Pearson's correlation coefficients (*r*) for analyses of associations between continuous variables, and we used Spearman's correlation coefficients for ordinal variables such as appetite score. Multivariate regression analyses were performed to obtain partial (adjusted) correlations controlled for case-mix features (sex, age, race, and diabetes) and dialysis center, operational group, dialysis vintage (months of MHD treatment), history of cardiovascular disease, and medical insurance status (full Medicaid versus other). To calculate the odds ratios (ORs) of diminished appetite after appetite status was dichotomized, we used logistic regression models after controlling for the abovementioned confounding variables. Poisson regression analyses were used to calculate hospitalization rate ratios (RR) for different appetite groups. To calculate the relative risks of first hospitalization or death, we obtained hazard ratios (HRs) by using Cox proportional hazard models after controlling for the abovementioned covariates. Plots of $\log [-\log (\text{survival rate})]$ against $\log (\text{survival time})$ were performed to establish the validity of the proportionality assumption. Kaplan-Meier analyses were used to assess the statistically significant differences in surviving proportions. Fiducial limits are given as means \pm SDs. RRs and relative risks include 95% CIs. A *P* value < 0.05 or a 95% CI that did not span 1.0 was considered to be statistically significant. Descriptive and multivariate statistics were carried out with the statistical software STATA 7.0 (Stata Corporation, College Station, TX).

RESULTS

Self-reported appetite scores for the 331 MHD patients according to their subjective level of appetite intensity and whether any recent change has occurred are shown in **Table 1**. None of the patients reported a "very poor" appetite. After the reported appetite was dichotomized into 2 major categories, 207 of the 331

TABLE 1

Self-reported appetite status of 331 maintenance hemodialysis patients based on responses to an appetite questionnaire

Appetite status	Normal appetite (<i>n</i> = 207, 62%)		Diminished appetite (<i>n</i> = 124, 38%)		
	Very good (<i>n</i> = 83, 25%)	Good (<i>n</i> = 124, 37%)	Fair (<i>n</i> = 101, 31%)	Poor (<i>n</i> = 23, 7%)	Very poor (<i>n</i> = 0, 0%)
	<i>n</i>		<i>n</i>		
No change (<i>n</i> = 265, 80%)	73	115	67	10	0
Improved (<i>n</i> = 22, 7%)	7	6	8	1	0
Worsened (<i>n</i> = 44, 13%)	3	3	26	12	0

MHD patients (62%) had a “normal” (very good to good) appetite, whereas 124 patients (38%) had a “diminished” (fair to poor) appetite. Two hundred sixty-five MHD patients (80%) reported no recent change in appetite, 22 (7%) reported a recent improvement in appetite, and 66 (13%) reported a recent decrease in their appetite.

Demographic and laboratory data for all 331 MHD patients combined and self-reported ratings of appetite intensity are shown in **Table 2**; the ANOVA *P* values are shown as well. The study population consisted of 51% men and was heavily dominated by Hispanics (47%). More than 50% of the patients (56%) had diabetes mellitus and nearly the same proportion had a history of cardiovascular disease. The average annual mortality rate was 7.6%, but it was as high as 30.4% in the poor appetite group. A similar trend was also observed for hospitalization indexes. The average age of the patients was 54.5 y, and the average duration of dialysis was 36 mo. The patients’ average Kt/V (double-pool;38) was 1.33. There was no statistically significant difference between the 4 appetite groups with regard to demographic characteristics or dialysis vintage or dose. Protein intake, as reflected by the 3-mo average nPNA values, was progressively and significantly lower as appetite categories worsened, which indicated that the self-reported appetite was a somewhat reliable reflection of food intake. A similar trend was also found for blood hemoglobin, ie, patients with a diminished appetite had a slightly lower hemoglobin concentration, although the mean hemoglobin value for each group was within the recommended range (11–12 g/dL) according to K/DOQI (Kidney-Dialysis Outcome Quality Initiative) guidelines (39). Most laboratory values reflecting nutritional or iron status—including TIBC (to reflect transferrin), albumin, and prealbumin—showed a somewhat similar trend, which indicated a worsening nutritional state across the worsening appetite categories; however, the ANOVA *P* values were not statistically significant for any of these measures. Serum lactate dehydrogenase rose progressively with worsening appetite (*P* = 0.01).

Serum concentrations of the inflammatory markers measured, including the proinflammatory cytokines CRP, IL-6, and TNF- α , increased significantly with diminishing appetite. The values for all 3 inflammatory markers in all 4 appetite categories were approximately twice the upper limit for the general population. Because excessively high serum concentrations of inflammatory markers were observed in the various appetite categories, these values were analyzed after a logarithmic transformation. The mean administered dose of erythropoietin was significantly greater in the MHD patients with a poor appetite, who required an average of 23 982 units/wk, almost 10 000 units/wk higher than any other group. The erythropoietin responsiveness index (ie, the

ratio of the administered erythropoietin dose divided by the hemoglobin concentration) showed a similar statistically significant relation and trend. No significant differences in midarm muscle circumference or NIR-measured body fat were observed between appetite categories, nor were there any trends across declining appetite categories. The Charlson comorbidity index score was significantly higher in those patients who described themselves as having a poor appetite. The MIS was progressively greater across worsening appetite groups, which indicated a higher degree of severity of the MICS among persons with a diminished appetite. The SF36 QoL score and its mental and physical dimensions showed a similar but reversed statistically significant association, which indicated a worsening mental and physical status and total QoL in MHD patients with anorexia.

Unadjusted bivariate Pearson correlation coefficients and multivariate-adjusted partial correlation coefficients (after control for confounders) between diminishing appetite (as a continuous variable with 1 of the 4 integer numbers between 1 and 4, corresponding to a very good to poor appetite) and pertinent variables were examined. Most variables with statistically significant differences in different appetite groups, as per ANOVA (Table 2), also showed significant correlations with declining appetite on the basis of both Pearson’s and Spearman’s rank correlations as well as multivariate-adjusted partial correlations (data not shown). The MIS had the strongest multivariate-adjusted correlations with declining appetite (*r* = 0.30, *P* < 0.001). The SF36 QoL scores had moderately strong but inverse correlations with declining appetite (*r* = 0.26–0.29, *P* < 0.001).

Logistic-regression estimated ORs and 95% CIs for diminished versus normal appetite, after dichotomization of the self-reported appetite categories into 2 main groups (*see* above and Tables 1 and 3) and adjustment for confounders, are shown in Table 3. The OR values represent the relative risk of diminished appetite (anorexia). To calculate the estimated OR for each variable, we selected magnitudes and directions of changes based on reported SDs (Table 2) that were rounded to practical increments or decrements relevant for clinical use. Of the nutritional markers, each 50-mg/dL decrease in serum TIBC increased the risk of diminished appetite by 57%. In contrast, the ORs for serum albumin were not significant. Inflammatory markers appeared to have a stronger bearing on diminished appetite, because each 1-unit increase in logarithm of serum CRP was associated with a 49% increased risk of anorexia (OR = 1.49, *P* = 0.001), and each 1-unit increase in logarithm of serum TNF- α was associated with an 88% increase in the risk of anorexia (OR = 1.88, *P* = 0.01). In addition to the predictive value of the SF36 QoL score in

TABLE 2Demographic characteristics and laboratory values and outcomes in 331 maintenance hemodialysis patients¹

Variable	Very good appetite (n = 83)	Good appetite (n = 124)	Fair appetite (n = 101)	Poor appetite (n = 234)	P ²
Sex (% male)	49.4	57.3	43.6	60.9	0.16
Ethnicity (% Hispanic)	42.2	45.2	55.4	34.8	0.16
Race (% black)	31.3	28.2	25.7	43.5	0.4
Diabetes (%)	46.3	57.7	58.4	69.6	0.16
Cardiovascular disease (%)	48.8	55.3	46.5	60.9	0.4
Mortality (%) ³	4.8	2.4	10.9	30.4	<0.001
Hospitalization frequency (admissions/y) ³	1.73 ± 2.88 ⁴	1.39 ± 2.41	1.77 ± 2.88	5.44 ± 8.72	<0.001
Duration of hospitalization (d) ³	8.2 ± 20.5	10.5 ± 26.4	10.6 ± 28.8	45.9 ± 82.3	<0.001
Age (y)	53.4 ± 13.6	56.0 ± 14.7	53.0 ± 15.2	57.8 ± 10.7	0.3
Dialysis vintage (mo)	39.1 ± 38.1	33.8 ± 35.2	37.7 ± 31.0	27.6 ± 22.6	0.4
Kt/V, double pool	1.36 ± 0.26	1.32 ± 0.26	1.35 ± 0.23	1.25 ± 0.25	0.2
nPNA (g · kg ⁻¹ · d ⁻¹)	1.091 ± 0.210	1.055 ± 0.233	1.026 ± 0.210	0.950 ± 0.234	0.04
Blood hemoglobin (g/dL)	12.1 ± 0.7	12.1 ± 1.0	11.8 ± 1.0	11.4 ± 1.5	0.002
Serum concentrations					
Ferritin (ng/mL)	624 ± 400	632 ± 464	634 ± 438	894 ± 555	0.07
TIBC (mg/dL)	205.2 ± 29.6	201.2 ± 43.1	193.4 ± 37.3	188.8 ± 40.8	0.09
Albumin (g/dL)	3.91 ± 0.32	3.83 ± 0.30	3.84 ± 0.34	3.72 ± 0.41	0.08
Prealbumin (mg/dL)	30.0 ± 9.7	27.6 ± 9.1	28.3 ± 8.7	25.3 ± 8.0	0.11
Cholesterol (mg/dL)	143.3 ± 45.2	144.8 ± 44.3	144.1 ± 49.9	138.7 ± 49.0	0.9
Phosphorus (mg/dL)	5.9 ± 1.3	5.6 ± 1.4	6.1 ± 1.7	5.6 ± 1.6	0.12
LDH (U/dL)	161 ± 32	160 ± 42	165 ± 41	191 ± 58	0.01
C-reactive protein (μg/mL) ⁵	5.4 ± 5.5	5.0 ± 4.4	7.4 ± 8.8	9.6 ± 7.4	0.005 ⁶
TNF-α (pg/mL) ⁷	7.5 ± 4.1	7.3 ± 4.8	9.5 ± 8.6	10.0 ± 7.3	0.01 ⁶
IL-6 (pg/mL) ⁸	13.5 ± 23.3	24.2 ± 80.3	22.8 ± 48.2	29.6 ± 40.3	0.004 ⁶
EPO dose (units/wk)	13 699 ± 11 618	11 967 ± 8479	14 446 ± 12 045	23 983 ± 22 451	<0.001
EPO responsiveness index	1164 ± 1062	1019 ± 769	1270 ± 1,136	2240 ± 2257	<0.001
BMI (kg/m ²)	27.3 ± 6.1	26.5 ± 6.6	25.8 ± 5.9	28.2 ± 6.4	0.3
Midarm muscle circumference (cm)	29.0 ± 5.0	29.1 ± 4.3	28.4 ± 5.6	29.1 ± 4.5	0.7
NIR-measured body fat (%)	26.7 ± 9.8	26.8 ± 11.7	26.5 ± 10.4	27.7 ± 10.3	0.9
Charlson comorbidity index	1.8 ± 1.6	2.1 ± 1.5	2.0 ± 1.4	2.9 ± 1.5	0.02
Malnutrition-inflammation score	5.0 ± 3.3	6.1 ± 3.8	7.3 ± 3.9	8.5 ± 3.8	<0.001
SF36 physical health score	56.1 ± 20.6	51.7 ± 22.5	43.0 ± 20.9	34.0 ± 20.3	<0.001
SF36 mental health score	63.4 ± 18.6	58.3 ± 19.3	50.4 ± 19.7	43.9 ± 21.5	<0.001
SF36 Total score	60.4 ± 19.5	56.4 ± 21.0	47.6 ± 21.0	40.0 ± 21.4	<0.001

¹ Kt/V, dialysis dose; nPNA, normalized protein nitrogen appearance (also known as normalized protein catabolic rate, or nPCR); TIBC, total-iron-binding capacity; LDH, lactate dehydrogenase; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; EPO, erythropoietin; NIR, near infrared; SF36, short-form (36-item) questionnaire used to assess quality of life.

² Frequency data (sex, ethnicity, race, diabetes, cardiovascular disease, and mortality) were compared by using chi-square test; data for continuous data were compared by ANOVA.

³ Data were collected over 12 mo.

⁴ $\bar{x} \pm$ SD (all such values).

⁵ Normal range: < 3.0 mg/L.

⁶ Obtained after logarithmic conversion of the values for inflammatory markers.

⁷ Normal range: < 4.7 pg/mL (31–35).

⁸ Normal range: < 9.9 pg/mL.

estimating the risk of anorexia, the MIS too had a strong association with this risk; for each 5-unit increase in MIS, the relative risk of anorexia increased by 2.36 ($P < 0.001$).

During the 12-mo follow-up period, 169 MHD patients were hospitalized at least once, 25 died, 8 underwent renal transplantation, and 33 transferred to other dialysis facilities outside the cohort. The calculated annual prospective hospitalization RRs by Poisson regression analyses in an unadjusted model and a 2-multivariate-adjusted models are shown in **Table 4**. Both hospitalization frequency and total days of hospitalization were higher across worsening appetite categories. Anorexia was associated with a 43% increased RR of hospitalization frequency and nearly a 2-fold increase in the RR of annual hospitalization days in extended multivariate models. The HRs derived by using Cox proportional hazard regression analyses for the same bivariate and multivariate models described above are presented in

Table 5. Mortality HRs nearly doubled across each of the 4 worsening appetite categories. There was also a 20–25% increase in the HRs of first hospital admission across the categories. After the appetite categories were dichotomized, anorexia was associated with an increase (≈ 4.5 –5 times) in mortality risk. Risk of first hospital admission was 41–48% higher for anorexic patients. Kaplan-Meier diagrams for the cumulative proportion of surviving patients in different appetite groups, consistent with the above-mentioned results from Cox proportional hazard models, are illustrated in **Figures 1 and 2**.

DISCUSSION

In this study, we found that the response of the 331 MHD patients to a simple question about appetite was significantly associated with several measures of inflammatory and nutritional status. Poor

TABLE 3

Odds ratios (ORs) and 95% CIs for diminished appetite (anorexia) after dichotomization of self-reported appetite categories into 2 main groups: normal appetite (very good and good) and diminished appetite (fair and poor)¹

Variable (magnitude and direction of change)	OR (95% CI)	P
nPNA (for each 0.2 g · kg ⁻¹ · d ⁻¹ ↓)	1.30 (1.04, 1.63)	0.02
Hematocrit (for each 3% ↓)	1.40 (1.10, 1.79)	0.007
Hemoglobin (for each 1.0 g/dL ↓)	1.43 (1.11, 1.84)	0.005
Serum ferritin (for each 500 ng/mL ↑)	1.12 (0.86, 1.47)	0.38
TIBC (for each 50 mg/dL ↓)	1.57 (1.12, 2.21)	0.009
Albumin (for each 0.3 g/dL ↓)	1.07 (0.86, 1.35)	0.53
LDH (for each 50 mcu/dL ↑)	1.12 (0.82, 1.53)	0.46
Log of CRP (for each 1 unit ↑)	1.49 (1.17, 1.90)	0.001
Log of IL-6 (for each 1 unit ↑)	1.22 (0.97, 1.54)	0.09
Log of TNF-α (for each 1 unit ↑)	1.88 (1.16, 3.02)	0.01
EPO dose (for each 10 000 units/wk ↑)	1.23 (0.99, 1.53)	0.06
EPO responsiveness index (for each 1000 unit EPO/Hb ↑)	1.29 (1.02, 1.63)	0.03
Charlson score (for each 1 unit ↑)	0.90 (0.70, 1.17)	0.44
Malnutrition-inflammation score (for each 5 unit ↑)	2.36 (1.61, 3.48)	<0.001
SF36 physical health score (for each 10 unit ↓)	1.29 (1.14, 1.45)	<0.001
SF36 mental health score (for each 10 unit ↓)	1.32 (1.16, 1.50)	<0.001
SF36 total score (for each 10 unit ↓)	1.30 (1.15, 1.46)	<0.001

¹ The ORs were adjusted for age, sex, race, diabetes, dialysis center, dialysis vintage, cardiovascular disease, and insurance status (full Medicaid or other) by means of logistic regression analyses. The magnitude and direction of change for each variable to calculate OR are based on reported SDs (*see* Table 2) and after being rounded to practical increments or decrements for clinical use. nPNA, normalized protein nitrogen appearance (also known as normalized protein catabolic rate, or nPCR); TIBC, total-iron-binding capacity; LDH, lactate dehydrogenase; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis α; EPO, erythropoietin; SF36, short-form (36-item) questionnaire used to assess quality of life.

appetite was associated with evidence for both low protein intake and inflammation. Serum concentrations of 3 exclusively inflammatory markers, including CRP and 2 proinflammatory cytokines (IL-6 and TNF-α), were higher in anorexic MHD patients. Some degree of association was also found between selected markers of nutrition, such as nPNA and TIBC, and anorexia. Moreover, a poor appetite correlated with an increased erythropoietin dose requirement and hence a higher risk of refractory anemia. However, markers of body composition such as BMI, percentage body fat, and upper arm skinfold thicknesses, and muscle circumference did not correlate with appetite intensity. The MHD patients with a poor appetite also reported a lower subjective QoL. Moreover, prospective hospitalization measures and mortality were significantly higher in anorectic patients.

Appetite is described as an instinctive physical desire, especially one for food or drink (40). Hence, a normal appetite is essential to maintain adequate food intake and to avoid undernourishment. A diminished appetite, also known as anorexia, which is one of the early signs of uremia progression in chronic kidney disease, has been reported in patients with end-stage renal disease undergoing maintenance dialysis and has been implicated as one of the main underlying etiologies of PEM and hypoalbuminemia (19, 41). However, very few studies have used a systematic assessment of appetite or examined its associations in such an extensive and comparative fashion with markers of nutrition, inflammation, anemia, and outcome measures in MHD patients. The HEMO Study investigators recently reported the

TABLE 4

Twelve-month prospective hospitalization rate ratios (RRs) and 95% CIs (in parentheses) across the 4 consecutively worsening self-reported appetite categories and for diminished appetite after dichotomization of self-reported appetite categories into 2 main groups [normal appetite (very good and good) versus diminished appetite (fair and poor)] by means of Poisson regression analysis models¹

	Unadjusted RR	Adjusted RR for case mix (demographic data, comorbidity, and dialysis vintage) ²	Adjusted RR for case mix and serum albumin, BMI, nPNA, and cardiovascular disease history
Hospitalization RR across 4 worsening appetite categories			
Hospitalization frequency	1.26 (1.16, 1.36)	1.21 (1.12, 1.31)	1.20 (1.10, 1.30)
Duration of hospitalization	1.67 (1.61, 1.73)	1.63 (1.57, 1.69)	1.65 (1.59, 1.71)
Hospitalization RR for diminished versus normal appetite (dichotomized)			
Hospitalization frequency	1.36 (1.18, 1.57)	1.40 (1.21, 1.62)	1.43 (1.23, 1.66)
Duration of hospitalization	1.79 (1.69, 1.91)	1.85 (1.74, 1.97)	1.95 (1.83, 2.08)

¹ P < 0.001 for all values. nPNA, normalized protein nitrogen appearance (also known as normalized protein catabolic rate, or nPCR).

² Demographic data include age, sex, race (black versus other), ethnicity (Hispanic versus other), insurance status (full Medicaid versus other), diabetes, dialysis center, and study group (January–July versus October–April). Comorbidity reflects the modified Charlson comorbidity index (*see* text).

Table 5

Hazard ratios (HRs) of death and first hospital admission and 95% CIs (in parentheses) across the 4 consecutively worsening self-reported appetite categories and for diminished appetite after dichotomization of self-reported appetite categories into 2 main groups [normal appetite (very good and good) versus diminished appetite (fair and poor)] by means of Cox proportional hazard regression analysis models¹

	Unadjusted RR	Adjusted RR for case mix (demographic data, comorbidity, and dialysis vintage) ²	Adjusted RR for case mix and serum albumin, BMI, nPNA, and cardiovascular disease history
HR across 4 worsening appetite categories			
Mortality	2.32 (1.47, 3.66)	2.07 (1.34, 3.20)	1.96 (1.25, 3.07)
<i>P</i>	<0.001	0.001	0.003
First hospital admission	1.25 (1.05, 1.48)	1.20 (1.01, 1.43)	1.22 (1.02, 1.46)
<i>P</i>	0.01	0.04	0.03
HR for diminished versus normal appetite (dichotomized)			
Mortality	4.47 (1.88, 10.71)	4.93 (2.01, 12.08)	4.74 (1.85, 12.16)
<i>P</i>	0.001	<0.001	0.001
First hospital admission	1.42 (1.05, 1.92)	1.41 (1.04, 1.91)	1.48 (1.08, 2.03)
<i>P</i>	0.02	0.03	0.02

¹ nPNA, normalized protein nitrogen appearance (also known as normalized protein catabolic rate, or nPCR).

² Demographic data include age, sex, race (black versus other), ethnicity (Hispanic versus other), insurance status (full Medicaid versus other), diabetes, dialysis center, and study group (January–July versus October–April). Comorbidity reflects the modified Charlson comorbidity index (*see* text).

appetite status in their cohort, which showed a distribution similar to that seen in our study (23).

An important finding of this study was the strong and consistent association between poor appetite and high levels of inflammatory markers. Maintenance dialysis patients are reported to have a higher prevalence of inflammation than the general population (42). The repetitive or ongoing episodes of occult or overt inflammation have occasionally been referred to as the chronic acute phase response (24, 43, 44). Serum CRP is the most frequently measured inflammatory marker and is associated with an increased risk of cardiovascular disease and mortality in both the general population (31) and in maintenance dialysis patients (45, 46). Of the proinflammatory cytokines, IL-6 is reported to have a central role in the pathophysiology of adverse effects of inflammation and is a predictor of poor outcome and increased mortality in patients with renal disease (33, 47). TNF- α , also known as cachectin, is believed to induce anorexia (48). Both IL-6 and TNF- α may mediate the onset of anorexia with infection or inflammation (49, 50). Although IL-6 and TNF- α have overlapping effects on food intake, the mechanisms of action are not identical. McCarthy (50) showed that the injection of TNF- α

reduced food intake in starved rats, but it did not affect gastric emptying; however, the injection of IL-6 reduced both food intake and gastric emptying.

Another important finding was the significant associations between self-reported appetite and measures of clinical outcome in MHD patients. PEM is a common phenomenon in dialysis patients and is a well-established risk factor for poor QoL and increased morbidity and mortality in these persons (51–54). According to some hypotheses, cardiac diseases—such as heart failure—may engender reduced appetite or anorexia and, if sufficiently severe, may independently induce muscle wasting, which is also known as cardiac cachexia (51). We found that the mortality risk in anorexic patients was 4–5 times that in those with a normal appetite. This finding may have major clinical implications because it implies that a patient’s subjective answer to a simple question about appetite has a high magnitude of predicting clinical outcome in MHD patients.

In our current study, we found no independent association between underlying cardiovascular disease or comorbid conditions and diminished appetite in MHD patients. Moreover, the

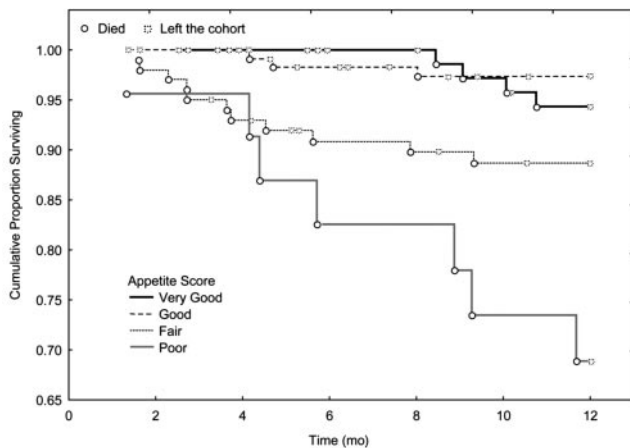


FIGURE 1. Kaplan-Meier diagram reflecting the cumulative proportion of surviving patients in each of the 4 appetite categories.

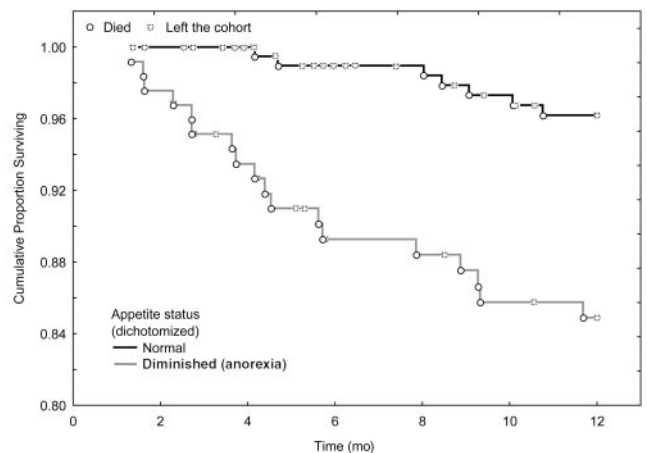


FIGURE 2. Kaplan-Meier diagram reflecting the cumulative proportion of surviving patients in 2 dichotomized appetite categories: normal appetite (very good to good) and diminished appetite or anorexia (fair to poor).

correlations between nutritional markers, including diminished appetite and body-composition measures such as NIR-measured percentage body fat or midarm muscle circumference were very weak and mostly insignificant. This may be due to the fact that such so-called nutritional markers reflect long-term effects of nutrition, whereas instantaneous appetite changes may not last long enough to have any effect on body composition. In contrast, both appetite and inflammatory state have short-term fluctuations (55), which may explain the significant association between these 2 entities in our study. One of the exceptional nutritional markers was nPNA (30), which was lower in those MHD patients with a diminished appetite. nPNA is a reflection of the amount of protein intake, which represents total food intake. Therefore, our abovementioned finding can indeed be considered proof of the reliability of appetite status reported by the MHD patients in the current study. We recently showed that a low nPNA, even in the setting of adequate to high dialysis doses, was a strong predictor of hospitalization and mortality in MHD patients (30). Therefore, a diminished appetite, by reducing food intake, may be a main cause of PEM and its consequent poor outcome and high mortality in dialysis patients.

The results of our study are evidence for the central role of appetite as a link between inflammation and PEM and their relation to poor clinical outcome. It has been postulated that inflammation is the common link between PEM and poor dialysis outcome (6). Increased release or activation of inflammatory cytokines, such as IL-6 or TNF- α , may simultaneously suppress appetite, may cause muscle proteolysis and hypoalbuminemia, and may be involved in the processes that lead to atherosclerosis (35, 56, 57). Hence, a diminished appetite, determined by patients' answer to a simple question, is indeed a marker of inflammation.


Because both PEM and inflammation are strongly associated with each other and can change many nutritional measures in the same direction, and because the relative contributions of measures of these 2 conditions to each other and to outcomes in dialysis patients are not yet well defined, the terms MICS or malnutrition-inflammation atherosclerosis have been suggested to denote the important contribution of both of these conditions to dialysis outcome (2, 3, 5, 6). To that end, MIS was found to have a prominent correlation with reported appetite intensity in the current study (3), although this may have been due to some degree of mathematical collinearity because MIS includes components related to appetite (3).

Another important finding in our study was the association between poor appetite and anemia as well as an increased requirement for erythropoietin administration, even after adjustment for hemoglobin concentration, the so-called erythropoietin responsiveness index. Some recent studies have indicated a close relation between inflammation and malnutrition, or MICS, and refractory anemia in patients with end-stage renal disease (3, 11, 13, 58). Thus, our findings may have major clinical implications in the management of anemia in dialysis patients, because appetite assessment can be conveniently used to predict the degree of erythropoietin responsiveness in these patients.

The positive association between appetite and QoL was not unexpected. Intuitively, a good appetite is an important component of a satisfactory QoL (9, 59). Markers of inflammation and PEM, independently or together as MICS, are significant predictors of QoL in dialysis patients. Moreover, we have reported a strong correlation between the QoL SF36 score and other pertinent clinical outcomes, such as mortality and hospitalization in MHD patients

(8). Both appetite and QoL can be affected by the same underlying factors that can lead to poor outcome in dialysis patients.

Our current study should be qualified by the possibility of selection bias. During the initial recruitment in 8 dialysis units (with >1200 patients), it is possible that only those MHD patients who were generally healthier or more health conscious agreed to participate (385 patients). This is evident from the fact that the annual mortality rate was 15% in these 8 dialysis units in the same period of time, 10% in the 367 recruited MHD patients for the NIED Study, and only 7% in the 331 patients in the current study. However, a selection bias with such a direction would generally lead to a bias toward the null, so that without this selection bias our positive results would probably have been even much stronger and the associations more prominent.

Appetite status is a key indicator of general health and of QoL and is a main contributor to nutritional status and clinical outcome. It may be the missing link between inflammation and PEM and contributes to the development of the reverse epidemiology phenomenon (5, 17). The findings of our current study are yet another step toward a better understanding of the mechanisms underlying the PEM- and inflammation-associated poor outcome in patients with end-stage renal disease. Our observed associations between a diminished appetite and poor QoL and increased mortality and hospitalization may have clinical implications in MHD patients. More studies are required to verify the predictive value of the subjective assessment of appetite in the clinical management of dialysis patients. 

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KK-Z and JDK helped design and conduct the study and analyze the data. GB helped design and conduct the study. CJM helped conduct the study. MHH helped design the study and analyze the data. No conflicts of interest were declared by any of the authors.

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