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Effect of Malnutrition-Inflammation Complex Syndrome on EPO Hyporesponsiveness in Maintenance Hemodialysis Patients

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● **Background:** Elements of malnutrition-inflammation complex syndrome (MICS) may blunt the responsiveness of anemia of end-stage renal disease (ESRD) to recombinant human erythropoietin (EPO). **Methods:** The authors examined cross-sectional associations between the required dose of EPO within a 13-week interval as prescribed by practicing nephrologists who were blind to the study and several laboratory values known to be related to nutrition and/or inflammation, as well as the malnutrition-inflammation score (MIS), which is a fully quantitative assessment tool based on the subjective global assessment of nutrition. **Results:** A total of 339 maintenance hemodialysis (MHD) outpatients, including 181 men, who were aged 54.7 ± 14.5 years (mean $\pm$ SD), who had undergone dialysis for 36.3 ± 33.2 months, were selected randomly from 7 DaVita dialysis units in Los Angeles South/East Bay area. The average weekly dose of administered recombinant human EPO within a 13-week interval was 217 ± 187 U/kg. Patients were receiving intravenous iron supplementation (iron gluconate or dextran) averaging 39.5 ± 47.5 mg/wk. The MIS and serum concentrations of high-sensitivity C-reactive protein, interleukin 6 (IL-6), tumor necrosis factor- α , and lactate dehydrogenase had positive correlation with required EPO dose and EPO responsiveness index (EPO divided by hemoglobin), whereas serum total iron binding capacity (TIBC), prealbumin and total cholesterol, as well as blood lymphocyte count had statistically significant but negative correlations with indices of refractory anemia. Most correlations remained significant even after multivariate adjustment for case-mix and anemia factors and other relevant covariates. Similar associations were noticed across EPO per body weight tertiles via analysis of variance and after estimating odds ratio for higher versus lower tertile via logistic regression after same case-mix adjustment. **Conclusion:** The existence of elements of MICS as indicated by a high MIS and increased levels of proinflammatory cytokines such as IL-6 as well as decreased nutritional values such as low serum concentrations of total cholesterol, prealbumin, and TIBC correlates with EPO hyporesponsiveness in MHD patients. *Am J Kidney Dis* 42:761-773.

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INDEX WORDS: Recombinant human erythropoietin (EPO); inflammation; protein-energy malnutrition; cytokines; malnutrition-inflammation complex syndrome (MICS); malnutrition-inflammation score (MIS).

THE ANEMIA of end-stage renal disease (ESRD) is a multifactorial disorder that can be managed successfully by recombinant human erythropoietin (Epoetin or EPO) and iron supplementation.¹⁻³ However, the required doses of EPO and iron are quite variable in different maintenance dialysis patients or in the same patient at different periods of time.^{1,4,5} The factors contributing to the degree of refractory anemia or the so-called "EPO hyporesponsiveness" in dialysis patients are not well understood. It was believed that iron deficiency was the major predictor of EPO hyporesponsiveness.^{5,6} However, many dialysis patients, despite adequate iron supplementation, still require inappropriately higher doses of EPO.^{2,7-9} Refractory anemia appears to be more common in those dialysis patients who also suffer from protein-energy malnutrition (PEM) or inflammation.¹⁰⁻¹² Because inflammation and PEM have a high prevalence and are found to be closely related to each other in dialysis patients, together they are also referred to as malnutrition-inflammation complex syndrome (MICS).¹³⁻¹⁵ MICS also is re-

ported to correlate with poor outcome including decreased quality of life (QoL)¹⁶ and significantly greater rates of hospitalization and mortal-

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ity in maintenance hemodialysis (MHD) patients.^{13,16,17} Malnutrition and inflammation, independently or together as MICS, are felt to be the main etiology for the so-called reverse epidemiology of cardiovascular risk factors in dialysis patients as compared with the general population, in that a low, and not a high, body mass index or serum cholesterol concentration is associated with poor outcome in these individuals.¹⁵ However, the possible interactions between inflammatory and nutritional markers and their impact on refractory anemia and EPO hyporesponsiveness as possible modifiable risk factors of dialysis-associated morbidity and mortality are not well understood.

In the initial phase of the Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study, a National Institute of Diabetes, Digestive and Kidney Diseases–sponsored, 5-year prospective cohort, 385 MHD patients were examined. The association between the prescribed EPO dose and some markers of inflammation and nutrition was explored. This report reflects some of the results of the analysis of the baseline data from the above-mentioned ongoing prospective cohort study.

METHODS

Patients

The participating subjects in the NIED Study are from a pool of approximately 1,200 MHD outpatients in 8 DaVita, Inc, dialysis facilities in the South Bay Los Angeles area. Dialysis units, each treating 105 to 187 MHD patients at the time of the start of the study, are divided into 2 operational groups according to yearly quarters ([1] October–April group and [2] January–July group). Each operational group includes 4 dialysis units, of which approximately 180 consenting MHD patients are evaluated semiannually, including 30 to 60 MHD patients who are selected randomly at each dialysis facility (see NIED Study website at www.nephrology.rei.edu/NIED.htm for more details). Inclusion criteria were those outpatients who were undergoing MHD for at least 8 weeks, were 18 years or older, and who signed the written consent form. Patients with a life expectancy of less than 6 months, for example, because of a metastatic malignancy or terminal HIV disease, were excluded. In the initial phase of the NIED Study (October 2001 through March 2002), 385 patients signed the written consent form. However, 1 dialysis facility (in Norwalk, CA) with 30 participating subjects did not have complete records of the administered EPO and iron doses during the designated study period and hence was excluded from this analysis. Of the remaining 355 MHD patients from 7 dialysis facilities, 339 consenting patients underwent the blood tests and nutritional evaluations examined in this analysis, whereas 16 other patients were not

present in the dialysis units at the time of blood draws. The medical chart of each MHD patient was reviewed by a nephrologist, and data pertaining to underlying kidney disease, cardiovascular 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.^{18,19}

Erythropoietin, EPO Indices, and Iron

In all 7 dialysis facilities, precise documentation of the administered doses of recombinant human erythropoietin or epoetin (Epogen) (EPO) and iron was available. The total dose of EPO (U/wk) among all 339 MHD patients of this analysis was calculated over a 13-week interval, ie, from October 1 through December 31, 2001, for group 1 and from January 1 through March 31, 2002, for group 2. The average weekly EPO dose then was calculated by dividing the total 3-month dose by 13. For those patients who missed more than 1 week of dialysis treatment or who left the cohort before the end of the third month (because of death, transplant), the average EPO dose per week was calculated using the actual numbers of weeks they contributed to the cohort. EPO responsiveness (resistance) index was defined as the average weekly EPO dose divided by average blood hemoglobin as described by Gunnell et al⁶ to normalize the amount of required EPO for the degree of severity of anemia. Both average EPO dose and EPO responsiveness index also were divided by body weight (in kilograms) to obtain 2 additional variables to indicate the required EPO dose per kilogram of body weight. The route of EPO administration was considered intravenous (IV) or subcutaneous (SQ) based on the administration of more than 50% of EPO dose given within the study interval. All but 64 MHD patients (19%) received EPO intravenously.

Of all 339 MHD patients who were studied in this analysis, 217 patients received IV iron at least once within a 3-month period including 103 patients who received iron gluconate (Ferrlecit), 62.5 to 125 mg, and 14 patients (mostly those under the care of Kaiser Permanente of Southern California) who received iron dextran (Infed), 50 to 100 mg weekly to monthly. No patient received iron sucrose (Venofer) during this study period. Only 18 patients were on oral iron medications.

The decision as to how much EPO and/or iron was to be administered to each study patient was made blindly by at least 42 nephrologists who were in charge of dialysis treatment care of these 339 MHD patients. Most nephrologists were not aware of the periods in which this analysis was conducted. Almost all nephrologists treated the anemia of their MHD patients according to Kidney Disease and Dialysis Outcomes Quality Initiative (K/DOQI) guidelines,⁶ ie, to achieve a targeted hemoglobin of 11 to 12 g/dL (110 to 120 g/L) and/or a hematocrit of 33% to 36%. Furthermore, 8 nephrologists were asked randomly if they were aware of K/DOQI guidelines and whether they used these recommendations to prescribe EPO and iron to their patients. All interviewed nephrologists were fully aware of the guidelines, but 2 nephrologists argued that they might withhold iron administration with ferritin levels higher than 500 ng/mL (500 µg/L), whereas 1 nephrologist would continue iron administration with ferritin levels as high as 1,200

ng/mL (1,200 μ g/L). A separate subanalysis did not show any significant difference in EPO and iron administration pattern among nephrologists who provided care to the study patients. Only 7 patients did not receive any EPO during the 3 months of study observation, and the average hematocrit level on all these 7 patients was higher than 38%.

Malnutrition Inflammation Score

Using the 7 components of the conventional Subjective Global Assessment of Nutrition (SGA), a semiquantitative scale with 3 severity levels, and combining it with 3 new elements (body mass index, serum albumin, and total iron binding capacity [TIBC] to represent serum transferrin) in incremental fashion, the so-called Malnutrition-Inflammation Score (MIS) with 10 components has been created.¹⁷ Each MIS component has 4 levels of severity from 0 (normal) to 3 (very severe). The sum of all 10 MIS components ranges from 0 to 30 denoting the increasing degree of severity. In a recent prospective study on 83 MHD patients, the MIS was compared with the conventional SGA and its refinements, anthropometry, near infrared measured body fat percentage, laboratory measures including serum C-reactive protein (CRP), and 12-month prospective hospitalization and mortality rates.¹⁷ 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.

In this study, MHD patients were scored by 10 collaborating renal dietitians who were trained adequately for this purpose. To evaluate the degree of reproducibility, the MIS was reassessed randomly by a physician on a subset of 24 patients without reference to the first MIS evaluation. The correlation coefficient (r) between the two MIS assessments was 0.88 denoting a good degree of reproducibility.

Laboratory Evaluation

Blood samples were obtained in early October 2001 from group 1 and in early January 2002 from group 2 patients and coincided chronologically with the quarterly routine blood tests of DaVita facilities. The laboratory values, except for postdialysis serum urea nitrogen, which was used to calculate the urea reduction ratio (URR), were measured immediately before the initiation of dialysis treatment. The double-pool Kt/V was used to represent the weekly dialysis dose and the protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR) and was calculated to estimate the daily protein intake.²⁰ All routine laboratory measurements were performed by DaVita Laboratories (Deland, FL) using automated methods, and the average values of each laboratory test within the 13-week study period were calculated and used in this study.

Serum CRP and cytokines, including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), were obtained to indicate the presence of an inflammatory state. The high-sensitivity CRP was measured by a turbidometric immunoassay in which a serum sample is mixed with latex beads

coated with antihuman CRP antibodies forming an insoluble aggregate (WPCI, Osaka, Japan; mg/L; normal range, <3.0 mg/L).^{21,22} High-sensitivity IL-6 and TNF- α immunoassay kits based on a solid phase sandwich using recombinant human IL-6 and TNF- α were used to measure serum proinflammatory cytokines (R & D Systems, Minneapolis, MN; pg/mL; normal range, IL-6: <9.9 pg/mL, TNF- α : <4.7 pg/mL).²³⁻²⁵ CRP and cytokines were measured in the General Clinical Research Center Core Laboratories of Harbor-UCLA Medical Center. Serum prealbumin was analyzed by an antigen-antibody complex assay, and total plasma homocysteine concentrations were determined by high-performance liquid chromatography (HPLC) at Harbor-UCLA Clinical Laboratories.

Statistical Methods

Conventional Student's t test and analysis of variance (ANOVA) were used to detect significant differences among continuous variables between men and women and among EPO tertiles. Chi-square method was used for categorical variables including sex, race, ethnicity, diabetes, and route of EPO administration (IV v SQ). To determine the significance and strength of bivariate associations, we used Pearson's correlation coefficient r for analyses of associations between continuous variables. Multivariate regression analysis was performed to obtain partial (adjusted) correlations controlled for conventional case-mix features (sex, age, race, and presence of diabetes) and route of EPO administration, dialysis center, ZIP code, insurance status (fully Medicaid versus others), Kt/V (single pool), blood hematocrit, serum iron saturation ratio, administered IV iron dose, use of angiotensin pathway blocking medications, Charlson comorbidity score, and dialysis vintage. To calculate the odds ratios (ORs) and their 95% confidence interval (CI) levels for highest versus lowest EPO tertiles, we used logistic regression models after controlling for the above-mentioned demographic variables. Therefore, the association between variables was studied via separate multivariate models but with uniform adjustment in each model. Fiducial limits are given as mean $\pm$ SD. Charlson score and MIS were analyzed as continuous variables. Logarithmic conversion was carried out for nonnormally distributed variables such as inflammatory markers. A P value less than 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, version 7.0 (Stata Corporation, College Station, TX), and the results were verified using a second statistical software, Statistica for Windows, Release 6.0 (Statsoft, Inc, Tulsa, OK).

RESULTS

Table 1 shows some relevant descriptive data of study subjects. As noticeable in Table 1, the study population had a heavy Hispanic contribution of 47%, which is not an unusual ethnicity distribution in many Southern California dialysis facilities. Thirty-percent of patients were black, and more than half of them (55%) had diabetes. More than half (51%) of the study patients had a

Table 1. Descriptive Analysis of the Demographic and Laboratory Data of All 339 MHD Patients and a Comparison Between Men and Women

	All MHD Patients (n = 339)	Women (n = 158)	Men (n = 181)	P Value
Ethnicity (Hispanics %)	47	46	47	0.89
Race (black %)	30	34	28	0.24
Diabetes (%)	55	57	53	0.49
SQ EPO %	19	19	19	0.95
History of cardiac disease (%)	51	55	47	0.15
ACE inhibitor or ARB (%)	33	30	35	0.33
Age (y)	54.7 ± 14.5	56.7 ± 14.5	53 ± 14.3	0.02
Dialysis vintage (mo)	36.3 ± 33.2	35.4 ± 30.5	37.1 ± 35.5	0.64
Post-HD weight (kg)	72.5 ± 18.3	69.3 ± 17.48	75.4 ± 18.49	<0.01
BMI (kg/m ²)	26.7 ± 6.4	27.1 ± 6.1	26.3 ± 6.7	0.24
Kt/V (single-pool)	1.56 ± 0.28	1.66 ± 0.28	1.47 ± 0.25	<0.01
nPNA (nPCR) (g/kg/d)	1.05 ± 0.22	1.05 ± 0.21	1.05 ± 0.22	0.82
Blood hematocrit (%)	35.4 ± 3.1	35.6 ± 3	35.2 ± 3.1	0.18
Hemoglobin (g/dL)	11.9 ± 1	11.9 ± 1	11.9 ± 1	0.84
Peripheral lymphocyte count (%)	22.3 ± 8.2	21.4 ± 7.4	23.1 ± 8.9	0.06
Serum ferritin (ng/mL)	635 ± 461	646 ± 475	625 ± 450	0.67
Iron saturation ratio (%)	32 ± 11.5	31.8 ± 11.7	32.2 ± 11.4	0.78
TIBC (mg/dL)	199.7 ± 37.2	197.2 ± 34	202 ± 39.6	0.24
Albumin (g/dL)	3.86 ± 0.33	3.81 ± 0.30	3.91 ± 0.35	<0.01
Prealbumin (mg/dL)	28.7 ± 9.4	27.3 ± 8.1	29.9 ± 10.2	0.01
Total cholesterol (mg/dL)	144 ± 48.2	148.4 ± 48.1	140.2 ± 48.1	0.12
Total homocysteine (Mg/L)	24.6 ± 12.3	24.0 ± 10.2	25.2 ± 13.8	0.38
CRP (mg/L)	6.52 ± 8	5.95 ± 5.51	7.02 ± 9.65	0.22
IL-6 (pg/mL)	21.85 ± 57.82	24.74 ± 73.62	19.33 ± 39.2	0.39
TNF-α (pg/ml)	8.5 ± 6.46	9.25 ± 8	7.84 ± 4.66	0.05
LDH (u/dL)	165.8 ± 40.8	171.8 ± 41	160.6 ± 40	0.01
Aluminum (pg/dL)	18 ± 8	17.7 ± 7.3	18.2 ± 8.7	0.65
Intact PTH (mu/L)	357 ± 380	371 ± 378	346 ± 383	0.55
Charlson comorbidity score*	2.1 ± 1.5	2.1 ± 1.5	2 ± 1.6	0.69
MIS	6.26 ± 3.8	6.59 ± 3.42	5.97 ± 4.1	0.15
EPO dose (U/wk)	15,220 ± 13514	16,439 ± 15,016	14,155 ± 11,992	0.12
EPO dose per weight (U/kg/wk)	217 ± 187	244 ± 206	194 ± 165	0.01
EPO responsiveness index	1,329 ± 1,281	1,429 ± 1,427	1,242 ± 1,135	0.18
EPO responsiveness index per weight	3.28 ± 3.12	3.83 ± 3.49	2.8 ± 2.67	<0.01
Average IV iron dose (mg/wk)	39.5 ± 47.52	38.3 ± 47.1	40.5 ± 48	0.67

NOTE. P values are based on Student's *t*-test comparing men with women. To convert hemoglobin or albumin in g/dL to g/L, multiply by 10; ferritin in ng/mL to μg/L, multiply by 1; cholesterol in mg/dL to mmol/L, multiply by 0.02586; homocysteine is mg/L to μmol/L, multiply by 7.397. The modified Charlson comorbidity index used in this study does not include age and does not count for renal disease. P values smaller than 0.05 are bolded.

*Not adjusted for multiple comparisons.

history of cardiac disease. Almost one third of patients were on angiotensin-converting enzyme (ACE) inhibitors and/or angiotension-blocking agents that might play a role in EPO hyporesponsiveness.²⁶ There was no statistically significant difference between these features in men and women. Table 1 also shows descriptive analysis of continuous variables and compares them in men and women via Student's *t* test. Women

were slightly older than men and, as expected, had a lower postdialysis dry weight, but there was no difference between men and women in terms of body mass index (BMI). Kt/V was slightly higher in women. Men's serum albumin and prealbumin concentrations were 0.1 g/dL and 2.6 mg/dL higher than women's, respectively, but serum lactate dehydrogenase (LDH) concentration was higher in women. Adminis-

Table 2. Correlation Coefficients (r) Between Average EPO Dose, EPO Dose per Kilogram Weight, and EPO Responsiveness Index and Relevant Nutritional and Inflammatory Values

	EPO Dose (total per week)	EPO Dose per kg Weight	EPO Responsiveness Index
Age	-.07 (<i>P</i> = .19)	-.07 (<i>P</i> = .18)	-.06 (<i>P</i> = .26)
Dialysis vintage	+0.5 (<i>P</i> = .41)	+0.6 (<i>P</i> = .30)	+.04 (<i>P</i> = .49)
Kt/V (single pool)	-.08 (<i>P</i> = .12)	+.04 (<i>P</i> = .48)	.09 (<i>P</i> = .15)
Iron saturation ratio	-.16 (<i>P</i> = .003)	-.11 (<i>P</i> = .04)	-.14 (<i>P</i> = .01)
Administered IV iron dose	+.16 (<i>P</i> = .003)	+.15 (<i>P</i> = .007)	+.14 (<i>P</i> = .01)
Modified Charlson comorbidity score	+.09 (<i>P</i> = .09)	+.07 (<i>P</i> = .23)	+.10 (<i>P</i> = .07)
Blood hematocrit	-.27 (<i>P</i> < .001)	-.29 (<i>P</i> < .001)	-.35 (<i>P</i> < .001)
Blood lymphocyte percentage	-.18 (<i>P</i> = .001)/.17 (<i>P</i> < .002)	-.21 (<i>P</i> < .001)/.21 (<i>P</i> < .001)	-.18 (<i>P</i> = .001)/.17 (<i>P</i> = .002)
MIS	+.17 (<i>P</i> = .003)/.13 (<i>P</i> = .03)	+.24 (<i>P</i> < .001)/.23 (<i>P</i> < .001)	+.17 (<i>P</i> = .002)/.13 (<i>P</i> = .02)
nPNA (nPCR)	-.01 (<i>P</i> = .83)/.03 (<i>P</i> = .55)	+.03 (<i>P</i> = .55)/.06 (<i>P</i> = .30)	-.03 (<i>P</i> = .64)/.02 (<i>P</i> = .65)
Serum albumin	-.11 (<i>P</i> = .04)/.05 (<i>P</i> = .39)	-.13 (<i>P</i> = .01)/.11 (<i>P</i> = .07)	-.14 (<i>P</i> = .009)/.07 (<i>P</i> = .24)
Ferritin	+.05 (<i>P</i> = .38)/.04 (<i>P</i> = .45)	+.07 (<i>P</i> = .21)/.04 (<i>P</i> = .48)	+.07 (<i>P</i> = .17)/.06 (<i>P</i> = .28)
TIBC	-.15 (<i>P</i> = .006)/.15 (<i>P</i> = .006)	-.21 (<i>P</i> < .001)/.21 (<i>P</i> < .001)	-.17 (<i>P</i> = .002)/.15 (<i>P</i> = .006)
Total cholesterol	-.19 (<i>P</i> < .001)/.19 (<i>P</i> < .001)	-.20 (<i>P</i> < .001)/.22 (<i>P</i> < .001)	-.18 (<i>P</i> < .001)/.18 (<i>P</i> < .001)
Prealbumin	-.19 (<i>P</i> < .001)/.15 (<i>P</i> = .006)	-.22 (<i>P</i> < .001)/.20 (<i>P</i> < .001)	-.19 (<i>P</i> < .001)/.15 (<i>P</i> = .004)
CRP	+.21 (<i>P</i> < .001)/.18 (<i>P</i> < .001)	+.20 (<i>P</i> < .001)/.19 (<i>P</i> < .001)	+.20 (<i>P</i> < .001)/.17 (<i>P</i> < .001)
Log of CRP	+.22 (<i>P</i> < .001)/.18 (<i>P</i> < .001)	+.18 (<i>P</i> = .001)/.15 (<i>P</i> = .007)	+.22 (<i>P</i> < .001)/.17 (<i>P</i> = .001)
IL-6	+.19 (<i>P</i> = .001)/.14 (<i>P</i> = .007)	+.17 (<i>P</i> = .002)/.12 (<i>P</i> = .02)	+.18 (<i>P</i> = .001)/.14 (<i>P</i> < .005)
Log of IL-6	+.34 (<i>P</i> < .001)/.31 (<i>P</i> < .001)	+.32 (<i>P</i> < .001)/.30 (<i>P</i> < .001)	+.34 (<i>P</i> < .001)/.31 (<i>P</i> < .001)
TNF- α	+.16 (<i>P</i> = .003)/.18 (<i>P</i> = .001)	+.19 (<i>P</i> < .001)/.20 (<i>P</i> < .001)	+.15 (<i>P</i> = .007)/.18 (<i>P</i> = .002)
Log of TNF- α	+.17 (<i>P</i> = .001)/.18 (<i>P</i> = .001)	+.20 (<i>P</i> < .001)/.19 (<i>P</i> < .001)	+.16 (<i>P</i> = .002)/.18 (<i>P</i> = .001)
Aluminum	-.01 (<i>P</i> = .91)/.13 (<i>P</i> = .05)	+.06 (<i>P</i> = .35)/.02 (<i>P</i> = .70)	-.01 (<i>P</i> = .81)/.12 (<i>P</i> = .05)
Intact PTH	+.18 (<i>P</i> = .001)/.11 (<i>P</i> = .05)	+.15 (<i>P</i> = .007)/.09 (<i>P</i> = .12)	+.17 (<i>P</i> = .009)/.11 (<i>P</i> = .05)
LDH	+.27 (<i>P</i> < .001)/.19 (<i>P</i> < .001)	+.30 (<i>P</i> < .001)/.24 (<i>P</i> < .001)	+.28 (<i>P</i> < .001)/.20 (<i>P</i> < .001)

NOTE. In each cell, the first value is the unadjusted (bivariate) *r* with its Pearson *P* value in parentheses, and the second value is partial correlation based on multivariate regression analysis adjusted for case-mix (age, sex, race, diabetes), subcutaneous EPO administration, dialysis center, ZIP code, insurance status (fully Medicaid versus others), Kt/V (single pool), blood hematocrit level, serum iron saturation ratio, administered IV iron dose, use of angiotensin pathway blocking medications, Charlson comorbidity score, and dialysis vintage (partial correlation *P* values are in parentheses). Correlation coefficient values equal or greater than 0.20 are bolded. (*P* values are not adjusted for multiple comparisons.)

tered dose of EPO and EPO responsiveness index per kilogram of body weight were higher in women, probably because women weighed on average 6 kg less than men. There was no significant difference among other values between men and women.

Table 2 shows correlation coefficients (*r*) between average EPO dose, EPO dose per kilogram of weight, EPO responsiveness index, and relevant nutritional and inflammatory values. In each cell, the first value is the unadjusted (bivariate) *r* with its Pearson *P* value in parentheses, and the second value is partial correlation based on multivariate regression analysis adjusted for case-mix and other relevant covariates listed above. There was a weak but statistically significant correlation between EPO dose and serum iron saturation ratio (inversed correlation) and

administered IV iron dose (direct correlation), denoting that patients who required higher EPO doses had lower iron saturation ratios and also required more IV iron supplementation. As expected, anemic patients with lower hematocrit values required higher EPO doses. The percentage of peripheral blood lymphocyte, a known nutritional marker, was significantly higher in patients with EPO hyporesponsiveness, as indicated by inverse but statistically significant correlation between these 2 variables. The MIS was significantly higher in those who received higher EPO doses. Among other markers of nutrition, inflammation and iron stores, serum TIBC, prealbumin, and total cholesterol concentrations associated inversely with EPO dose indicating a diminished nutritional state among those who had EPO hyporesponsiveness. Similarly, inflam-

Fig 1. Bivariate correlations, in form of scatter diagrams, between administered EPO (per kilogram body weight per week, averaged over a 3-month period) and IL-6 to represent inflammation (A) and total serum cholesterol to represent nutritional state (B). To convert cholesterol in mg/dL to mmol/L, multiply by 0.02586.

matory markers including serum proinflammatory cytokines correlated positively with EPO dose and EPO index, suggesting the presence of refractory anemia among inflamed MHD patients. The strongest correlation was observed between serum IL-6 concentration (logarithmic scale) and EPO responsiveness index ($r = +0.34$; $P < 0.001$), which remained significant even after multivariate adjustment ($r = +0.31$; $P < 0.001$). Patients with a higher serum intact PTH

and especially higher LDH concentrations also tended to require higher EPO doses for treatment of their anemia to keep their hemoglobin and hematocrit levels within targeted range as recommended by K/DOQI guidelines.²⁶ Figure 1 shows scatter diagrams for serum IL-6 and total cholesterol concentrations plotted against administered EPO dose.

After dividing all 339 MHD patients into 3 equal groups (tertiles) of 113 patients according

Table 3. Demographic, Laboratory, and Other Pertinent Variables in 3 Tertiles of “EPO Dose Per Week per Kilogram Body Weight”

	First (Lowest) EPO/kg Tertile	Second (Middle) EPO/kg Tertile	Third (Highest) EPO/kg Tertile	P Value
Sex (men %)	63	54	43	0.01
Ethnicity (Hispanics %)	39	53	49	0.10
Race (blacks %)	26	29	36	0.21
Diabetes %	54	53	57	0.86
SQ EPO (%)	11	26	20	0.01
EPO dose (U/wk)	4,954 ± 3,331	13,209 ± 4,581	27,495 ± 16,020	<0.001
EPO dose per weight (U/kg/wk)	64 ± 36	178 ± 37	408 ± 202	<0.001
EPO respons index (EPO/Hb)	415 ± 286	1,117 ± 418	2,456 ± 1,590	<0.001
EPO respons./wt (EPO/Hb/kg)	0.88 ± 0.51	2.55 ± 0.84	6.41 ± 3.49	<0.001
MIS	5.8 ± 3.4	5.6 ± 3.8	7.5 ± 4.0	<0.001
Blood Hematocrit (%)	36.0 ± 2.7	35.6 ± 2.9	34.6 ± 3.4	0.001
periph. lymphocyte count (%)	23.8 ± 8.1	23.3 ± 8.7	19.7 ± 7.3	<0.001
Serum ferritin (ng/mL)	625 ± 378	600 ± 480	678 ± 515	0.43
Iron saturation ratio (%)	33.8 ± 10.9	32.5 ± 11.4	29.9 ± 11.9	0.03
TIBC (mg/dL)	205.4 ± 36.9	202.8 ± 36.3	191.1 ± 37.0	0.008
Albumin (g/dL)	3.88 ± 0.32	3.89 ± 0.32	3.81 ± 0.34	0.14
Prealbumin (mg/dL)	30.7 ± 9.8	28.8 ± 8.8	26.5 ± 9.1	0.003
Cholesterol (mg/dL)	152.3 ± 43.4	143.5 ± 51.7	135.9 ± 48.2	0.04
CRP (ng/mL)	6.26 ± 8.18	5.31 ± 4.92	8.00 ± 9.91	0.03 (0.04*)
IL-6 (ng/mL)	12.26 ± 19.09	23.64 ± 75.73	29.66 ± 61.92	0.07 (<0.001*)
TNF- α (ng/mL)	7.63 ± 6.78	8.77 ± 6.15	9.09 ± 6.41	0.20 (0.08*)
LDH (mg/dL)	153.6 ± 32.3	159.3 ± 31.5	184.6 ± 49.4	<0.001
Aluminum (ng/mL)	18.0 ± 8.0	16.9 ± 6.1	19.2 ± 9.8	0.17
Intact PTH (mcu/L)	337 ± 354	350 ± 345	385 ± 437	0.61
IV iron dose (mg/mo)	25.4 ± 31.2	45.7 ± 48.3	47.4 ± 56.6	<0.001
BMI (kg/m ²)	27.7 ± 7.6	27.0 ± 5.8	25.3 ± 5.5	0.01
Charlson comorbidity score	1.9 ± 1.5	2.0 ± 1.6	2.2 ± 1.5	0.31
Age (y)	55.2 ± 14.6	53.3 ± 14.2	55.6 ± 14.6	0.42
Dialysis vintage (mo)	36.6 ± 32.6	33.6 ± 32.6	38.7 ± 34.6	0.52

NOTE. To convert ferritin in ng/mL to μ g/L, multiply by 1; albumin in g/dL to g/L, multiply by 10; cholesterol in mg/dL to mmol/L, multiply by 0.02584. The listed *P* values are based on ANOVA.

*For inflammatory markers (CRP, IL-6, and TNF- α), additional *P* values based on logarithmic transformation of these markers have been listed in parentheses.

to ascending magnitude of administered EPO dose per kilogram of body weight, relevant variables were reexamined and compared with each other among EPO tertiles as shown in Table 3. Patients in the highest (third) EPO tertile had a higher proportion of women and received subcutaneous EPO more often than the other 2 tertiles. The MIS was almost the same in the lowest and middle tertiles (5.8 ± 3.4 and 5.6 ± 3.8 , respectively) but was significantly higher in the highest tertile (7.5 ± 4.0 ; $P < 0.001$). Blood hematocrit level and lymphocyte count were progressively lower across increasing EPO tertiles, and so were iron saturation ratio and most nutritional markers, ie, serum TIBC, prealbumin, and total cholesterol but not albumin concentration. Inflammatory markers showed a reversed trend and were

progressively higher across increasing EPO tertiles, with the exception of serum TNF- α , which did not achieve statistical significance despite a similar trend. Analogous association was observed with serum LDH level as well as required EPO dose. Figure 2 depicts bar diagrams of serum IL-6 and total cholesterol concentrations across EPO tertiles.

Table 4 shows logistic regression estimated ORs and 95% CIs for highest versus lowest EPO tertile adjusted for the same covariates as in Table 2. Hence, the OR values are representative of relative risks of EPO hyporesponsiveness in MHD patients. The magnitude and direction of changes for each variable to calculate OR are based on reported standard deviations (Table 1) and after being rounded to practical increments

Fig 2. Serum levels of IL-6 (A) and total cholesterol concentration (B) within the tertiles of administered EPO (per kilogram of body weight per week, averaged over a 3-month period). To convert cholesterol in mg/dL to mmol/L, multiply by 0.02586.

or decrements that appear to be relevant for clinical use. Associations and their directions were essentially similar to those seen in Tables 2 and 3. Each 5-unit increase in MIS increased the risk of EPO hypo-responsiveness by 64%. Similar associations also were observed between inflammatory markers and refractory anemia. Once again, most nutritional markers including serum concentrations of prealbumin, TIBC, and total

cholesterol as well as peripheral lymphocyte count had a negative association with EPO dose in that their decrease led to higher risk of EPO hypo-responsiveness.

DISCUSSION

In this study we found significant associations between markers of inflammation and PEM, together also known as MICS and indices of refrac-

Table 4. OR of EPO Hyporesponsiveness

	OR	95% CI	P value
MIS (for each 5 unit ↑)	1.64	1.02-2.65	0.04
Serum CRP (for each 10 mg/L ↑)	1.25	0.88-1.78	0.21
Log of CRP (for each 1 unit ↑)	1.44	0.75-2.81	0.27
IL-6 (for each 10 pg/mL ↑)	1.20	1.02-1.42	0.03
Log of IL-6 (for each 1 unit ↑)	4.45	1.94-10.20	<0.001
TNF- α (pg/mL)	1.66	1.03-2.69	0.04
Log of TNF- α (for each 1 unit ↑)	4.91	1.05-22.82	0.04
Albumin (for each 0.5 g/dL ↓)	1.12	0.65-1.94	0.67
Prealbumin (for each 10 mg/dL ↓)	1.65	1.13-2.42	0.01
TIBC (for each 50 mg/dL ↓)	2.15	1.30-3.56	0.003
Cholesterol (for each 50 mg/dL ↓)	2.22	1.49-3.30	<0.001
LDH (for each 50 mg/dL ↑)	3.06	1.75-5.38	<0.001
Ferritin (for each 500 ng/mL ↑)	1.42	0.95-2.13	0.09
Blood lymphocyte count (for each 10 % ↓)	2.74	1.56-4.82	<0.001

NOTE. OR and 95% CI for tertiles of "weekly administered EPO dose per body weight" comparing the odds of highest versus lowest EPO dose tertile, adjusted for case-mix (age, sex, race, DM), subcutaneous EPO administration, dialysis center, ZIP code, insurance status (fully Medicaid versus others), Kt/V (single pool), blood hematocrit, serum iron saturation ratio, administered IV iron dose, use of angiotensin pathway blocking medications, Charlson comorbidity score, and dialysis vintage by means of logistic regression analyses. The magnitude and direction of changes for each variable to calculate OR are based on considering the reported standard deviations (see Table 1) and after being rounded to practical increments or decrements for clinical use.

tory anemia including EPO hyporesponsiveness in a relatively large sample of MHD patients. Some degree of correlation was found also between serum LDH and indices of refractory anemia in these individuals. Most associations remained statistically significant even after rigorous multivariate adjustment.

The ESRD-associated anemia is one of the most salient features of over 250,000 dialysis patients in the United States and probably all throughout the world.^{1,2} Over the last several years, the amount of EPO and iron supplementation administered to dialysis patients has been increased considerably, and the trend is predicted to maintain its course.²⁷ However, to date, there is no uniform and reliable method to predict the required doses of EPO and iron in different dialysis patients or in the same patient at different periods based on the degree of sickness or other relevant clinical conditions.^{4,7}

An important finding of our study was the strong association between indices of refractory anemia in form of EPO hyporesponsiveness and high levels of inflammatory markers in 339 MHD patients. Several previous studies with smaller sample sizes had reported similar findings. Barany et al¹⁰ studied 30 MHD patients and showed that the weekly EPO dose in those patients with a

serum CRP level ≥ 20 mg/L was 80% higher than in patients with CRP less than 20 mg/L. Goicoechea et al²⁸ reported a significant direct correlation between IL-6 and TNF- α production and weekly EPO dose per kilogram of body weight in 34 MHD patients. Gunnell et al⁶ examined 92 MHD and 36 peritoneal dialysis patients and found that the acute-phase response in form of high-serum CRP, high ferritin, and low transferrin concentrations were predictors of EPO resistance. Sitter et al²⁹ found an association between dialysis-induced rise in serum IL-6 level and increasing required EPO dosage in 30 MHD patients. In our current study, the logarithm of serum IL-6 level had the strongest correlation with the required EPO dose, and the association remained statistically significant in different statistical analyses and after multivariate adjustments. Both serum CRP and TNF- α also showed a similar trend, and their associations with EPO dose remained significant in some but not all analyses we conducted in this study.

It has long been known that anemia is observed frequently in patients suffering from chronic inflammatory disorders even with a normal kidney function.³⁰ There is evidence that inflammation is much more common in dialysis patients than in the general population.¹⁴ The

serum levels of inflammatory markers in our MHD patients were higher than that reported in the general population, which was consistent with previous studies.¹⁴ A common underlying mechanism can be an increased prevalence of cytokine activation that is associated with reduced renal function, oxidative and carbonyl stress, or other proinflammatory conditions in dialysis patients such as frequent contact with dialysis membranes, vascular access grafts, catheters or dialysate, or PD fluid.^{14,31} It is not completely clear how inflammation is related to dialysis-associated refractory anemia. Several mechanisms for cytokine-induced anemia have been proposed, including impaired iron metabolism and suppression of bone marrow erythropoiesis and EPO production.^{12,32} Serum ferritin, a marker of iron store and also a positive acute phase reactant, has been shown to be paradoxically high in ESRD patients with refractory anemia.^{7,33} Increased ferritin production may prevent iron delivery to erythrocyte precursors.⁷ Moreover, the uptake of iron is lower than usual in inflammation.³² Patients with inflammatory diseases have inappropriately low levels of EPO in their blood.³⁴ IL-1 and TNF- α have been shown to inhibit EPO production in vitro.³⁵ Furthermore, increased release or activation of inflammatory cytokines, such as IL-6 or TNF- α , has been shown to have suppressive effect on erythropoiesis.³⁶ IL-6 and IL-1 have been found to antagonize EPO's ability to stimulate bone marrow proliferation in culture.³⁷ However, other studies did not find such effects or found paradoxical associations.³⁸ Finally, patients with inflammation may be more prone to gastrointestinal bleeding.^{12,32}

Another important finding in our study was the inverse association between such markers of nutritional state as serum prealbumin, TIBC and total cholesterol concentration, and blood lymphocyte count and required EPO dose. Such associations are less well described in the literature as compared with the association between EPO dose and inflammation. Improving nutritional state in dialysis patients may also improve anemia and lead to lower required EPO dose. A cross-sectional study on 59 MHD patients found that the required EPO dose was higher in the poorly nourished patients as per subjective global assessment of nutrition.¹¹ In a metaanalysis by

Huot et al,³⁹ L-carnitine administration that is used to improve nutritional state was associated with improved hemoglobin and a decreased EPO dose and EPO resistance in anemic dialysis patients. Moreover, anabolic steroids also have been used successfully to simultaneously improve both nutritional state and anemia in dialysis patients.⁴⁰ Insulinlike growth factor-1 (IGF-1) is reported to enhance bone marrow progenitor cell proliferation in uremic mice.⁴¹ Hence, ESRD anemia may represent both an EPO and a functional IGF-1 deficient state.⁴¹ Effects of nutrition on EPO responsiveness in nonuremic patients have also been reported. Brown et al⁴² showed that in premature infants with profound anemia who were treated with EPO, higher protein intake improved both erythropoietic response and protein utilization to achieve satisfactory growth.

PEM is a common phenomenon in dialysis patients and a well-established risk factor for poor outcome, including risk of cardiovascular disease and death, in these individuals.^{43,44} In this study, we found a negative correlation between blood lymphocyte count and EPO responsiveness in MHD patients. Peripheral lymphocyte count has long been debated as a nutritional marker both in the general population^{45,46} and in ESRD patients.^{47,48} Carvounis et al⁴⁹ showed a significant association between a low lymphocyte count and mortality rate in both peritoneal dialysis and MHD patients. Grzegorzewska and Leander^{47,48} showed that EPO could influence both total and subset lymphocyte counts in peritoneal dialysis patients.

We also found a negative association between total serum cholesterol concentration and the degree of EPO hyporesponsiveness in MHD patients. Serum cholesterol is a known nutritional marker and its low, rather than high, value is known to be paradoxically associated with poor outcome in dialysis patients, a phenomenon that has thus been called reverse epidemiology.^{15,50} Total serum cholesterol may also be a negative acute phase reactant,⁵¹ as are both serum prealbumin and TIBC concentrations.^{52,53} Hence, the association between these markers and refractory anemia may be yet another case for the effect of inflammation. However, the association between EPO response and serum albumin concentration, a very strong predictor of dialysis outcome, was poor to nonexistent in this study.

Gunnell et al⁶ found a significant association between serum albumin and required EPO dose. Serum albumin has a longer half-life than TIBC, prealbumin (20 days v 8 and 2 days, respectively),¹¹ and cytokines and does not show the same month-to-month fluctuations as inflammatory markers do.⁵⁴ Hence, its precision in predicting short-term changes in required EPO dose may be limited.

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 term malnutrition-inflammation complex syndrome (MICS) or malnutrition-inflammation atherosclerosis (MIA) has been suggested to denote the important contribution of both of these conditions to poor dialysis outcome.^{13,17,55} To that end, the MIS, an SGA-based scoring system that was reported to be a reliable measure of the degree of severity of MICS, was found to have a significant association with EPO hyporesponsiveness in this study.¹⁷ Some recent studies have indicated a close relationship between MICS and refractory anemia in ESRD patients.^{7,12,17}

We also found that serum LDH had a significant and direct association with the required EPO dose. Patients with liver disease or hemolysis may have a refractory anemia and also a chronic state of acute phase response similar to that seen in ESRD patients. In this study, only 2 patients were known to have hepatitis B antigenemia, and the prevalence of hepatitis C was not clear because its serology is not tested routinely in the studied dialysis facilities. Similar to MICS in dialysis patients, the compromised nutritional state of individuals with liver disease may also play a role, because Means et al⁵⁶ showed that TNF- α production in severe alcoholic liver disease is strongly correlated with caloric malnutrition and mortality.

Our current study should be qualified by its cross-sectional design and the possibility of selection bias at several levels. Moreover, practicing nephrologists might have had different approaches in managing anemia. During the initial recruitment in the study dialysis units (over 1,200 patients), it is possible that only those MHD

patients who were generally healthier or more health conscious agreed to participate. However, all consenting patients were studied no matter whether they did or did not complete the questionnaires or undergo MIS evaluation by dietitians. Even if a selection bias existed at the level of recruitment, it would generally lead to a bias toward the null, so that without this bias our reported associations would probably have been even stronger. In this study, serum B12 or folic acid concentrations were not measured and possible episodes of bleeding were not accounted for. Although B12 and folate deficiencies are relatively rare, gastrointestinal and other bleeding episodes may have happened. However, the EPO dose and blood levels of hemoglobin and hematocrit were averaged within a 13-week interval, attenuating the potential confounding effect of possible sporadic bleedings. Another possible limitation can be related to the relatively short period of required EPO dose, ie, only 13 weeks, and use of only 3 markers of inflammation. However, the proinflammatory cytokines measured in the current study have been used and validated in other studies to assess inflammation in dialysis patients.^{52,53} Inflammatory markers may fluctuate even month to month in dialysis patients.⁵⁴ Hence, a short cohort of up to 3 months would not be inappropriate for the goals of this analysis.

Our current study is the only one in which several novel markers of inflammation and nutrition including serum levels of proinflammatory markers have been used simultaneously to evaluate the response to EPO. This study brings us one step further toward a better understanding of the factors that are involved in the response to EPO and iron by using validated statistical and epidemiologic models. It also improves the predictability of the response and, hence, the efficacy of anemia management in dialysis patients. Longitudinal studies, currently in progress, are needed to explore the impact of EPO hyporesponsiveness on morbidity and mortality of dialysis patients to improve poor outcome based on a possibly modifiable role of factors related to refractory anemia. Our study may be a means to that end.

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