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Total Iron-Binding Capacity–Estimated Transferrin Correlates With the Nutritional Subjective Global Assessment in Hemodialysis Patients

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• **We examined the value of transferrin concentrations in estimating nutritional status as determined by the subjective global assessment (SGA) score. Fifty-nine hemodialysis patients (37 men and 22 women, aged 59 ± 16 years, dialyzed for 3.6 ± 3.9 years) were selected by predetermined criteria. All received erythropoietin (EPO) and oral iron therapy. SGA evaluation was conducted twice by both a dietitian and a physician. Serum iron, total iron-binding capacity (TIBC; which is linearly correlated with transferrin), transferrin saturation ratio, ferritin, albumin, total protein, and cholesterol were measured. Twenty-seven (46%) patients were well nourished (group A), 20 (34%) were moderately nourished (group B), and 12 (20%) were poorly nourished (group C) according to the SGA. TIBC values were 276 ± 47 mg/dL, 217 ± 54 mg/dL, and 176 ± 41 mg/dL, respectively ($P < 0.00001$), and thus directly correlated with the state of nutrition. The relationship between TIBC and nutritional status was independent of age and number of years on hemodialysis. Serum ferritin values were 104 ± 93 ng/mL, 161 ± 154 ng/mL, and 363 ± 305 ng/mL, respectively ($P < 0.0003$), and thus inversely correlated with the state of nutrition. Transferrin saturation ratios were slightly higher in the severely malnourished patients. The number of years on dialysis were a determinant of nutritional status. These values were 2.4 ± 2.4 years for group A, 3.9 ± 4.0 years for group B, and 5.7 ± 3.9 years for group C ($P < 0.05$). The average age of the poorly nourished patients was 10 years older than the well-nourished patients. Serum iron values were lower but transferrin saturation ratios were higher in the severely malnourished patients. The required EPO doses were higher in the poorly nourished patients. We suggest that transferrin values are superior to other laboratory tests in assessing nutrition and will supplement SGA criteria. Serum ferritin may be useful as a predictor of illness. Older patients who have been on dialysis longer warrant special concern. Malnutrition may be an indicator of EPO resistance in dialysis patients. Finally, since a decreased TIBC level in poorly nourished patients may erroneously increase the transferrin saturation ratio, our findings may have implications in making the diagnosis and treatment of anemia and iron deficiency in malnourished dialysis patients.**

INDEX WORDS: Dialysis patients; nutrition; iron; total iron-binding capacity; transferrin; ferritin; subjective global assessment; EPO.

MALNUTRITION in hemodialysis patients is common and may affect as much as one third of the dialysis population.[1-4] Protein malnutrition is a major risk factor for morbidity and mortality in dialysis patients.[4-7] There are several objective methods for assessing the nutritional status; however, all have shortcomings that hamper their systematic clinical application.[8,9] Anthropometric methods, which are unquestionably valuable, have inherent limitations and are impractical for many renal units.[10] A number of recent reports have advocated the use of the subjective global assessment (SGA) in renal patients.[1,3,10] The SGA is a practical, inexpensive method that relies on clinical judgment accrued from grading scales calculated from a brief history and physical examination.[3,8] The test has been verified and can be readily applied by clinicians, dietitians, or other personnel.[3] Laboratory criteria also are very important tools that are frequently used to assess nutrition in dialysis patients.[6,11,12] Commonly used parameters include the serum concentrations of albumin,[5] total protein,[6] transferrin,[12,13] and prealbumin.[14] Other parameters, including iron homeostasis, efficacy of renal replacement therapy, and general risk factor assessment, also

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provide indirect assistance.[5] Our goal was to compare the nutritional status of hemodialysis patients using the SGA scoring system as the reference standard with inexpensive laboratory parameters, as well as with dialysis-related clinical features. We tested the hypothesis that transferrin, as estimated by the total iron-binding capacity (TIBC), is superior to albumin or total protein measurements.

MATERIALS AND METHODS

Patients

Our university-affiliated dialysis program currently serves 210 patients. We used a computer-assisted method to select those patients who had never changed their modality of treatment (ie, to peritoneal dialysis or transplantation), who had received no blood transfusions in the past 4 weeks, who had required no hospitalizations in the month before the study, who had no signs of infections or disease activity (collagen vascular disease), and who agreed to participate. Seventy patients were enrolled into the study; we then excluded 11 patients from the analysis because they had received intravenous iron in the month before the study, which we felt might influence the results. Thus, data from 59 patients were analyzed. Our institutional review committee approved the protocol, and written informed consent was obtained from all participants.

The patients' ages ranged from 25 to 84 years (mean, 58.9 ± 16.5 years). They had received hemodialysis from 4 months to 21 years (mean, 3.58 ± 3.89 years). All received erythropoietin (EPO), 1,000 to 10,000 units (mean, 4,627 ± 2,384 units) three times a week, as well as oral iron supplementation (ferrous sulfate) for at least 2 months before the study. The dose ranged from 325 mg once a day to three times daily. The ''dry'' body weight was the average edema-free weight immediately at the end of the hemodialysis sessions.

The SGA

The SGA was originally developed to assess nutritional status in hospitalized patients postoperatively,[15] but it also has been applied to nutritionally deprived patients in other clinical settings, including hemodialysis.[2,3,15] The assessment is based on the history and physical examination as described by Detsky et al.[16] The history consists of five criteria and focuses on weight loss in the preceding 6 months, gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea), dietary food intake, functional capacity, and comorbidities. Each of these features are scored separately in terms of A, normal or well nourished; B, partially abnormal or moderately malnourished; or C, extremely abnormal or severely malnourished. The physical examination includes three items that focus on loss of subcutaneous fat over the triceps and mid-axillary line of the lateral chest wall, muscle wasting in the deltoids and quadriceps, and the presence of ankle edema and/or ascites. These features are classified as 0, normal; 1, mild; 2, moderate; and 3, severe. The data are weighted, and the patients are then classified in terms of three major SGA scores: A, well nourished, B, mild to moderate malnutrition; or C, severe malnutrition. Details on the SGA and its assessment are given in the Appendix to this article at the AJKD website (www.ajkdjournal.org).

We performed the SGA at two different sessions; a physician and a renal nutritionist (dietitian) performed the test independently. To minimize variability in the SGA, the physicians underwent a 2-hour training session conducted by a dietitian instructor. The training was done according to the SGA Training Packet (Baxter Healthcare Corp, Renal Division, in collaboration with K.N. Jeejeebhoy, Toronto, Canada). This packet includes videotapes, monographs, and rating forms. We modified the SGA slightly so that patients were primarily assessed by four criteria from the medical history: weight change, especially over the previous month; food intake, particularly over the previous 4 weeks; gastrointestinal symptoms, such as loss of appetite, anorexia, vomiting, and diarrhea; and functional capacity of the patient. We concentrated on three criteria from physical examination: subcutaneous fat mass, particularly in the triceps area and chest; muscle wasting, especially in the quadriceps and shoulder area; and lower extremity edema at putatively ''dry weight'' levels and/or ascites. Each patient was assessed by the two examiners separately within 48 hours. Differences in SGA assessment results were noticed on eight patients or less than 15% of our study population (interrater reliability of 0.85) and were resolved by a combined assessment consensus of the two observers.

Laboratory Evaluation

The following laboratory parameters were measured on all patients immediately before the dialysis session: serum TIBC to estimate transferrin, serum iron, transferrin saturation ratio (iron saturation ratio), serum ferritin, hemoglobin, serum creatinine, blood urea nitrogen (BUN), serum albumin, total protein, and total cholesterol. Postdialysis BUN values were measured as well to calculate the urea reduction ratio (URR). Red blood cell indices and hemoglobin, as well as the TIBC and serum iron value (colorimetric method), were obtained by automated methods. The hematocrit was measured by centrifugation. The serum ferritin value was measured by an immunoradiometric assay with polyclonal reagents. The measurements of transferrin correlate closely with indirect transferrin concentrations determined from measurements of TIBC, with a correlation coefficient of 0.96.[17-19] Thus, the TIBC levels can be reliably used to calculate transferrin concentrations. We calculated serum transferrin on the basis of TIBC according to the following formula, as described elsewhere[19]:

$$\text{Serum transferrin (mg/dL)} \times 1.25 = \text{TIBC (mg/dL)}$$

The transferrin saturation index (iron saturation ration) was calculated according to the following formula[19]:

$$\text{Saturation (\%)} = \text{serum iron/TIBC}$$

The calculation of the URR correlates closely with Kt/V in hemodialysis patients.[5] Thus, URR was used as the indicator of the hemodialysis efficacy as shown below:

$$\text{URR (\%)} = (\text{predialysis BUN} - \text{postdialysis BUN})/\text{predialysis BUN}$$

Statistics

Analysis of variance (F test) was used for group mean comparisons. In each category with significant mean value differences, post hoc analysis for multiple comparisons was performed. The modified least-significant difference test of Bonferroni was used to determine which pair members of a set of comparisons were significantly different. We used the randomized complete block design for multiple population means comparison to analyze whether the relationship between TIBC and nutrition was independent of patient age and number of years on hemodialysis. We further used Wilks' lambda (discriminant) analysis to determine the predictive values of the variables on nutritional status and to evaluate the degree of dependence or independence of TIBC from other characteristics. Small values of lambda indicated differences in group means (U statistic). Chi-square analysis was used for nonparametric variables to evaluate the interference of characteristics. To assess the strength of associations between variables, we used Pearson's correlation r and the Spearman's rank correlation coefficient (nonparametric testing with Spearman's ρ) for selected analysis. Descriptive statistics and analyses were conducted with the help of statistical software (Statistics for Windows, Release 4.0; Statsoft, Inc, Tulsa, OK). Fiducial limits are given as mean values ± SD. $P < 0.05$ was considered significant.

RESULTS

Demographic information and laboratory data are given in Table 1. Twenty-seven (46%) patients were well nourished (group A), 20 (34%) were moderately malnourished (group B), and 12 (20%) were poorly nourished (group C). Gender had no significant bearing on the SGA in the total population; women represented 37% of all patients. However, there was a significant difference in gender distribution of the three different SGA groups. Among the well-nourished patients, 27% were women; this value increased to 35% in the moderately malnourished patients and in the poorly nourished patients, 67% were women ($P < 0.05$, chi-square analysis). The patient diagnoses included diabetes, hypertensive nephrosclerosis, glomerulonephritis, polycystic disease, vascular renal disease, and interstitial nephritis. No single diagnosis was associated with SGA score.

The serum TIBC levels were significantly different in the three SGA groups. Group A had 276.0 ± 47.7 mg/dL, group B had 217.4 ± 53.6 mg/dL, and group C had 176.1 ± 41.4 mg/dL. The post hoc analysis for A + B, A + C, and B + C pairs were all significant. Thus, transferrin as assessed by TIBC correlated directly with the state of nutrition: the lower the value, the poorer the patient's nutrition. These data are graphically displayed in Fig 1. The individual TIBC values in terms of SGA groups A, B, and C are shown (top), as well as bars with fiducial limits (bottom).

Duration of dialysis had a bearing on nutri-

Table 1. Patients, Age, Number of Years on Hemodialysis, rhEPO Dose, and All Laboratory Data (mean ± SD) in Terms of SGA Categories

		SGA Assessed Nutritional Categories			ANOVA	
	All Patients	Group A	Group B	Group C	F	*P*
No. of patients	59	27	20	12		
Women (%)	37	27	35	67		
Age (yr)	58.9 ± 16.5	53.1 ± 16.8	58.2 ± 18.0	63.7 ± 11.3	1.827	0.17
Dialysis (yr)	3.6 ± 3.9	2.4 ± 2.3	3.9 ± 4.0	5.7 ± 3.9	3.17	0.05*
rhEPO (100 U)	46.3 ± 23.8	39.6 ± 20.8	50.5 ± 26.0	55.41 ± 24.30	2.10	0.13
TIBC (mg/dL)	236 ± 62	276 ± 48	217 ± 54	176 ± 41	19.68	0.00001†
Ferritin (ng/mL)	176 ± 198	104 ± 93	161 ± 154	363 ± 305	9.27	0.0003‡
Albumin (g/dL)	3.8 ± 0.4	3.9 ± 0.3	3.8 ± 0.4	3.4 ± 0.3	7.76	0.01‡
Total protein (g/dL)	7.0 ± 0.8	7.0 ± 0.8	7.0 ± 0.6	6.9 ± 1.3	0.01	0.99
Hemoglobin (g/dL)	10.3 ± 1.1	10.5 ± 1.0	10.2 ± 0.9	9.9 ± 1.6	1.38	0.26
Iron (mg/dL)	40.5 ± 16.0	45.8 ± 15.7	37.0 ± 12.6	34.7 ± 19.0	2.95	0.06
Transferrin saturation (%)	17.7 ± 6.9	17.0 ± 6.7	17.2 ± 4.8	20.3 ± 10.3	1.08	0.35
Cholesterol (mg/dL)	170 ± 62	172 ± 40	175 ± 93	158 ± 38	0.30	0.74
Creatinine (mg/dL)	10.8 ± 3.2	10.8 ± 3.2	11.3 ± 2.9	9.7 ± 3.8	0.90	0.41
URR (%)	60.7 ± 10.2	59.6 ± 11.4	59.7 ± 9.7	64.8 ± 7.7	1.19	0.31

*Only significant for A + C (post hoc analysis of Bonferroni).
†Significant ($P < 0.05$) for all three combinations A + B, B + C, and A + C.
‡Only significantly for A + C and B + C.

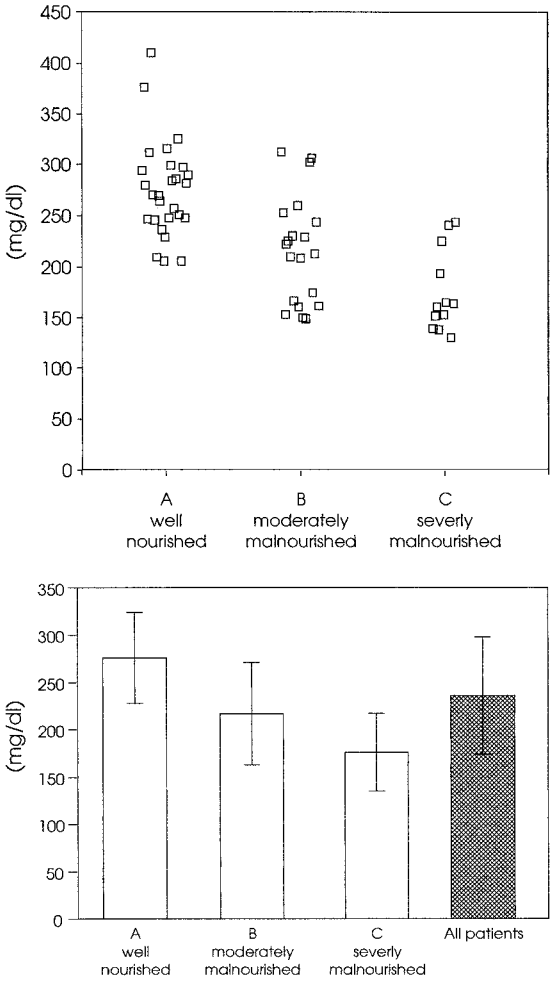

Fig 1. (Top panel) All individual TIBC (transferrin) values are given in terms of SGA groups A, B, or C. (Bottom panel) A bar graph (mean ± SD) shows the inverse correlation between TIBC and nutritional status ($P < 0.00001$).

tional status. The values for SGA groups A, B, and C were 2.4 ± 2.4 years, 3.9 ± 4.0 years, and 5.7 ± 3.9 years, respectively ($P = 0.048$). Post hoc analysis for A + B, A + C, and B + C pairs were $P = 0.19$, $P = 0.016$, and $P = 0.20$, respectively, denoting a significant difference between group C (poor nutrition status) and group A (well nourished). Thus, patients who were dialyzed for a longer period of time tended to have poorer nutritional status. Moreover, the risk of malnutrition may be somewhat greater in older patients as our severely malnourished patients (group C) were on average 10 years older than the well-nourished patients (group A). For the three SGA groups, the mean ± SD ages were 53.1 ± 16.8 years in group A, 58.2 ± 18.0 years in group B, and 63.7 ± 11.3 years in group C. However, no significant group differences were found ($P = 0.17$), which may be attributed to the patients' age range.

Serum albumin levels in three SGA groups showed no difference between group A (3.9 ± 0.3 g/dL) and group B (3.8 ± 0.4 g/dL). In group C (3.4 ± 0.3 g/dL), the albumin concentrations were lower ($P = 0.001$). Post hoc analysis for A + B, A + C, and B + C pairs revealed $P = 0.45$, $P = 0.00028$, and $P = 0.0033$, respectively, confirming the significant difference of albumin values in group C (poor nutrition status) compared with either group A or B. However, the difference between mean albumin values in the two latter groups (A and B) was not significant. This finding suggests that albumin is only a predictor of severe malnutrition; however, mild to moderate degrees of malnutrition can be easily missed if one were to rely exclusively on albumin concentration in nutritional assessment. Total protein and serum cholesterol values were no better than serum albumin concentration in predicting nutritional status.

Serum ferritin concentrations were also examined for group differences. The mean ± SD values were 104 ± 93 ng/mL in group A, 161 ± 154 ng/mL in group B, and 363 ± 305 ng/mL in group C ($P = 0.0003$). The post hoc analysis for A + B, A + C, and B + C pairs revealed $P = 0.27$, $P = 0.000074$, and $P = 0.0024$, respectively. The higher ferritin values in group C (poor nutrition status) were significantly greater compared with the lower ferritin levels in the two other groups. Nonparametric testing with Spearman's rank-order ρ revealed $\rho = 0.39$ ($P < 0.01$), indicating an inverse relationship between ferritin levels and nutritional status. Lower ranking of nutritional status was correlated with higher ferritin levels. The mean values for URR in three SGA groups were not significantly different, indicating similar degrees of dialysis efficacy for all patients despite different degrees of malnutrition. Although slightly lower in group C or severely malnourished patients, predialysis serum creatinine concentrations did not show any significant differences in the three SGA groups. Likewise, there were no differences among the three groups with regard to hemoglo-

bin, hematocrit, mean corpuscular volume, or other erythrocyte indices.

The serum iron concentrations were different in the three SGA groups. They were highest in the well-nourished patients and lowest in the severely malnourished patients ($P = 0.06$). Moreover, Patients with higher degrees of malnutrition were generally receiving increased doses of recombinant human EPO (rhEPO) compared with the better-nourished patients ($P = 0.13$). The group differences for serum iron concentrations and doses of rhEPO were not significant. Transferrin saturation (iron saturation) ratios were slightly higher in group C (severely malnourished patients), with a mean ± SD value of 20.3% ± 10.3%, compared with those in groups A and B, which were 17.7% ± 6.9% and 17% ± 6.7%, respectively. Although statistically not significant, this upward trend of group differences was the opposite of the above-mentioned downward trend for serum iron in the three SGA groups, namely, against the general expectation that patients with decreased serum iron concentrations should have decreased transferrin saturation ratios as well.

We used Wilks' lambda (discriminant) analysis to determine predictors of nutritional status and to address the degree of independence of TIBC from age and dialysis treatment time as classifiers of nutritional status. Variable selection indicated that TIBC had an F value of 19.3 ($P < 0.00001$). The TIBC as a variable had an adjusted $r^2 = 0.41$. The variable of hemodialysis duration had an F value of 1.8 ($P = 0.17$, $r^2 = 0.06$). Age was not a significant predictor, with an F value of 1.1 ($P = 0.32$, $r^2 = 0.04$). The overall Wilks' lambda was 0.58. These results indicate that the TIBC is a predictor of nutritional status independent of number of years on dialysis or the patient's age. Similar results were obtained when the effect of rhEPO dose was analyzed, demonstrating that the strong correlation of TIBC with malnutrition was independent of the rhEPO dose as well. Albumin was then entered into the equation and the Wilks' lambda was 0.48. Compared with TIBC, albumin was not as strong a predictor of classification ($F = 9.4$, $P < 0.0003$, $r^2 = 0.25$).

To further evaluate the effect of age and number of dialysis treatment years on the relationship between serum TIBC and malnutrition, we divided the patients into seven different age groups by 10-year increments, as shown in Table 2. This approach (randomized complete block design for multiple population means comparison) was performed to eliminate the effect of age variable. The total mean values for the three SGA groups were 270 ± 26 mg/dL for group A, 209 ± 37 mg/dL for group B, and 178 ± 43 mg/dL for group C (group difference, $P < 0.001$). In a similar procedure outlined in Table 3, we categorized patients into four different groups according to the number of years dialyzed (<1 year, 1 to 3 years, 3 to 5 years, and >5 years). In that way, the effect of the dialysis treatment time as an interfering variable was eliminated. The total mean TIBC values for groups A, B, and C (276 ± 3 mg/dL, 219 ± 24 mg/dL, and 172 ± 25 mg/dL, respectively) were still significantly different ($P = 0.00016$). Therefore, the TIBC mean values in different SGA groups were almost the same in spite of the three different approaches (Tables 1, 2, and 3). This finding emphasizes a strongly independent relationship between serum TIBC levels and the severity of malnutrition, namely, independence from the variables age and number of dialysis treatment years.

Table 4 shows all the pertinent correlation coefficients. Semiquantitative SGA scoring revealed a very significant, direct correlation with

Table 2. Mean Values for Serum TIBC Concentrations (mg/dL) at Three Different SGA Levels by Age in 10-Year Increments

Age Groups	SGA Assessed Nutritional Categories			Mean Values
	A	B	C	
<30 yr	303 ± 71 (3)	196 ± 49 (2)	—	249
30-39 yr	291 ± 21 (4)	153 ± 0 (1)	—	222
40-49 yr	230 ± 30 (2)	213 ± 74 (4)	246 ± 0 (1)	230
50-59 yr	285 ± 59 (9)	175 ± 31 (3)	166 ± 28 (3)	209
69-69 yr	273 ± 60 (3)	233 ± 73 (3)	159 ± 7 (3)	222
70-79 yr	258 ± 19 (5)	242 ± 42 (4)	190 ± 52 (4)	230
>80 yr	248 ± 0 (1)	254 ± 9 (3)	130 ± 0 (1)	211
Total (mg/dL)	270 ± 26	209 ± 37	178 ± 43	

NOTE. The total mean values were significantly different ($P = 0.0011$) and independent of age. For A + B, A + C, and B + C, the results were $P = 0.0053$, $P = 0.00041$, and $P = 0.15$, respectively. Numbers in parentheses indicate number of patients.

Table 3. Mean ± SD Values for Serum TIBC Concentrations (mg/dL) at Three Different SGA Levels Distributed in Four Different Groups According to the Number of Dialysis Treatment Years

No. of Years on Dialysis	SGA Assess Nutritional Categories			Mean Values
	A	B	C	
<1 yr	275 ± 55 (10)	235 ± 105 (2)	165 ± 0 (1)	225
1-3 yr	274 ± 46 (6)	216 ± 41 (7)	143 ± 8 (3)	211
3-5 yr	277 ± 27 (6)	186 ± 40 (5)	204 ± 54 (4)	222
>5 yr	280 ± 66 (5)	239 ± 61 (6)	176 ± 34 (4)	232
Total (mg/dL)	276 ± 3	219 ± 24	172 ± 25	

NOTE. The total mean values of three SGA groups were significantly different ($P = 0.00016$), independent of the dialysis treatment time. For A + B, A + C, and B + C pairs, the results were $P = 0.0031$, $P = 0.000045$, and $P = 0.0092$, respectively.

serum TIBC ($r = +0.64$). SGA also was directly correlated with serum albumin ($r = +0.43$), serum iron ($r = 0.+29$), and rhEPO dose ($r = +0.26$), but was inversely correlated with serum ferritin ($r = -0.43$). Serum TIBC correlated directly with serum iron ($r = +0.39$) and inversely with serum ferritin ($r = -0.61$) and rhEPO dose ($r = -0.38$). However, serum TIBC was not correlated with serum albumin, total protein, cholesterol, creatinine, or hemoglobin concentrations. The serum ferritin concentration correlated directly with rhEPO dose ($r = +0.36$) and the transferrin saturation ratio ($r = +0.30$), and indirectly with hemoglobin ($r = -0.28$). Neither serum TIBC nor serum ferritin revealed any correlation with the patients' age, gender, or number of years of dialysis treatment. The serum albumin concentrations were not correlated with any of the above-mentioned laboratory parameters, but were partially correlated with patient age and gender, denoting slightly lower albumin concentrations in female or elderly patients.

DISCUSSION

Protein and calorie malnutrition is common in hemodialysis patients[4,6,20] and is linked to increased morbidity and mortality.[5,21,22] Nutritional status receives inadequate attention in many dialysis centers.[1,3,23] Thus, simple methods of nutritional assessment could have a favorable impact on patient management. Several indices of malnutrition are available, ranging from the well-known anthropometric measurements,[24] such as skinfold thickness and mid-arm muscle circumference, to skin testing for anergy and other indices of immune deficiency.[25,26] However, the sensitivity of these methods in detecting early malnutrition, their practicability, and their

Table 4. Pearson Rank Correlation Coefficients

	TIBC	Ferritin	Albumin	Transferrin Saturation Ratio	Iron	rhEPO Dose
TIBC	+1					
Ferritin	−0.61*	+1				
Albumin	+0.09	−0.25	+1			
Transferrin saturation	−0.26z	+0.30z	−0.11	+1		
Iron	+0.39*	−0.19	+0.02	+0.76*	+1	
rhEPO dose	−0.38*	+0.36*	−0.01	+0.06	−0.19	+1
Hemglobin	+0.11	−0.28†	+0.18	+0.16	+0.25	−0.23
Hematocrit	+0.06	+0.26z	+0.14	+0.11	+0.16	−0.21
Total protein	+0.0	−0.32†	−0.02	−0.05	−0.02	+0.01
Mean corpuscular volume	−0.09	+0.11	−0.03	+0.27	+0.21	+0.23
Cholesterol	−0.01	+0.05	+0.09	−0.02	+0.01	−0.11
URR	+0.05	−0.03	−0.17	−0.10	−0.05	−0.04
Creatinine	−0.03	−0.02	+0.21	−0.10	−0.11	−0.03
Patient age (yr)	−0.14	+0.02	−0.30†	+0.09	−0.01	+0.16
No. of years on diaglysis	−0.09	−0.15	+0.08	+0.02	+0.01	+0.24
Patient gender‡	+0.15	−0.01	+0.27†	−0.08	+0.03	+0.01
SGA group§	+0.64*	−0.47*	+0.43*	−0.17	+0.29†	+0.26†

*Highly significant ($P < 0.001$).
†Significant ($0.05 < P < 0.01$).
‡Gender: female, 1; male, 2.
§SGA group: A, 3; B, 2; C, 1.

applicability to hemodialysis patients have not been convincing.[9,10] More elaborate methods, such as impedance testing, total body nitrogen determinations, and total body potassium estimates, may give reliable results; however, the techniques are costly and their use is confined to a few major research centers.[3,6]

The SGA was designed to circumvent many of these problems.[3,16] The test relies on a simple history and physical examination, which can be performed by a physician, dietitian, or a trained nurse.[27] The method correlates closely with more objective measures.[16,27] Moreover, the SGA has been validated prospectively in both uremic and nonuremic populations.[1,2,23,27] Results of studies by Baker et al,[28] Detsky et al,[29] and Jeejeebhoy et al[30,31] suggest that the SGA not only predicts nutritional status, but also serves to predict complications in terms of measuring ''sickness'' rather than solely nutrition. The SGA also has been successfully used to assess lung transplant patients[32] and liver transplant candidates.[33] We used a slightly modified SGA as our reference standard. The time involved ranged from 12 to 25 minutes. Differences in interpretation occurred only in eight cases (15% of all patients) and were quickly resolved by consensus.

The important findings in our study were that parameters of iron metabolism proved to be strong predictors of SGA nutritional classification. TIBC to reflect transferrin was strongly directly correlated with the nutritional state, while serum ferritin values were inversely correlated. Interestingly, neither total protein values, cholesterol concentrations, nor an indicator of dialysis urea transfer were helpful in this regard. Serum albumin concentration was not as helpful as TIBC and showed only minimal decrease exclusively in the patients with the poorest nutritional status (SGA group C); however, no significant difference was noticed between the well-nourished patients (group A) and those with mild to moderate malnutrition (group B). The TIBC is regularly obtained as part of iron studies needed for rhEPO and iron administration.[12,13,19] However, the TIBC fluctuation with rhEPO, iron administration, and the effect of malnutrition has not yet been well studied.[2,4,21] Although malnourished patients in our study were found to be older, to have been receiving dialysis for a longer period of time, and to have been receiving higher doses of rhEPO, our multiple analyses demonstrated that the highly significant relationship between nutrition and TIBC was independent of age, dialysis treatment time, and the rhEPO dose.

Transferrin, which has been used previously to assess nutrition,[34-36] is a 90-kd globulin that binds and transports iron in the plasma.[13] The liver is the primary synthesis site. Serum levels are similar for men and women, and decrease only slightly with age. Low values are found in many disease states, including infection, malignancy, hepatocellular disease, and nephrotic syndrome.[12] Increased serum transferrin values occur in iron deficiency, pregnancy, and other high estrogen and progesterone states, including administration of oral contraceptives.[19] Although the calculated transferrin concentration from the TIBC is considered to be unreliable in some reports,[6] there is adequate evidence that such is not the case.[18,19] Transferrin measurements correlate closely ($r = +0.96$) with TIBC.[17,18] Thus, the less-expensive TIBC levels can be used to calculate transferrin concentrations. We used TIBC, the readily available laboratory parameter, to calculate the transferrin level according to a formula described elsewhere.[17,19] A decreased serum TIBC value due to factors unrelated to iron status can affect the calculated saturation ratio. This situation can result in a saturation ratio that is higher than expected.[37]

In an earlier study, we[19] compared bone marrow iron stores with transferrin saturation ratio and serum ferritin in the diagnosis of iron deficiency in patients with renal insufficiency. We found that serum transferrin values can be sharply reduced in chronic illness. The results of our current study also show that a decrease in serum iron concentration, which is partially parallel to the decreased transferrin levels, is in accord with the SGA score. However, the transferrin saturation ratio was increased across the groups, from 17.0% in group A to 20.3% in group C. Thus, our data suggest that by lowering the serum transferrin level, malnutrition may interfere with the reliability of the iron saturation ratio as a diagnostic tool for iron deficiency in dialysis patients. On the basis of these findings, we recently suggested a new algorithm for iron deficiency diagnosis in the end-stage renal disease patients, in which we again recommended not using the transferrin saturation ratio as a

diagnostic tool of iron deficiency if serum TIBC is less than 200 mg/dL.[37] Nevertheless, our study indicates that serum TIBC (transferrin) is a good prognostic parameter in assessing the nutritional status independent of patient age or number of years on hemodialysis. Furthermore, the transferrin value seems to be relatively independent of iron status or other hemoglobin-related factors in this group of patients.

Serum ferritin correlated inversely with the state of nutrition in our study. Madore et al[38] examined more than 21,000 uremic patients and found that serum ferritin was inversely correlated with serum iron and hemoglobin. Ferritin is an acute phase reactant; thus, the serum concentrations may increase for reasons independent of malnutrition or iron metabolism.[19] In our study, patients receiving higher doses of rhEPO had lower serum TIBC values ($r = -0.38$) but higher serum ferritin concentrations ($r = +0.36$). Furthermore, the correlation coefficient between TIBC and serum ferritin was quite high ($r = -0.61$). TIBC was low in malnourished patients, whereas ferritin was high in the same group of patients. This striking reversal, accompanied by the finding that EPO dose was also inversely correlated with TIBC and directly correlated with serum ferritin, suggests that malnutrition, reflected by low serum TIBC and high ferritin values, is an indicator of resistance to rhEPO in dialysis patients. Likewise, a high TIBC level reflecting the nutritional adequacy may indicate rhEPO receptivity.

Serum albumin and prealbumin generally have been considered good laboratory parameters of nutrition in dialysis patients.[4,7,14,20,21] Owen et al[5] presented the most convincing link between albumin concentrations and mortality. However, albumin is a late index of malnutrition,[6] perhaps in part because of its relatively long half-life (20 days) and the large capacity of the liver to synthesize albumin. Thus, a decrease in albumin concentration may follow the onset of malnutrition by several months. Jones et al[39] reported that serum albumin was not a useful index in assessing the nutritional status of continuous ambulatory peritoneal dialysis patients, which is consistent with our findings in hemodialysis patients. A possible explanation for the relative insensitivity of albumin in predicting nutrition has been provided by Kaysen et al.[40] These investigators found that high concentrations of acute-phase reactants had a greater impact on serum albumin than did dietary protein intake. This finding coincides with the observation that C-reactive protein predicts the rhEPO resistance mentioned earlier and with the observation that the acute-phase reactant ferritin correlated inversely with the state of nutrition.

Lowrie[41] recently proposed a conceptual model to explain persistent anemia, malnourishment, and mortality among dialysis patients. He refers to *provocateurs* (namely, underlying disease, adjustments to uremia, and the dialysis procedure itself) *responses*, such as mediators of inflammation, and *effects*, such as the malnutrition of chronic illness. Proinflammatory cytokines downregulate the hepatic production of transferrin, as well as albumin and prealbumin, but stimulate the hepatic production of apoferritin, a number of scavenger proteins, and other acute-phase reactants.[42,43] Recently, Barany et al[44] reported that a high C-reactive protein is a strong predictor of resistance to rhEPO in hemodialysis patients. Our data suggest the presence of a proinflammatory, chronic ''acute-phase reactant'' process. Furthermore, the process is strongly associated with malnutrition, as estimated by the SGA. The patients in group C in our study had been dialysis patients for the longest period and generally had multiple clinical problems, making them the ''sickest'' patients. Jeejeebhoy et al[30] pointed out that SGA predicts the index of ''sickness'' as well. Thus, a high serum ferritin in the face of a low transferrin saturation ratio should be considered an index of high risk as well as an indicator of rhEPO resistance in uremic patients.

Our nutritional assessments in our own dialysis program gave us the rather sobering finding that at least half of our dialysis patients were suboptimally nourished and 20% severely so. Nutritional status provides access to a potentially reversible state of affairs, with a direct impact on survival.[5,6] Our observations emphasize the value of the SGA (12 to 20 minutes of effort) and straightforward laboratory testing. Although we did not find the serum albumin concentration, creatinine, or cholesterol values to be helpful, we observed that TIBC (to reflect transferrin) and serum ferritin values were predictors. On the

basis of our findings, we have altered our approach to nutritional assessment.

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