Relationship between nutritional status and the glomerular filtration rate: Results from the MDRD Study

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Background. The relationship between the protein-energy nutritional status and renal function was assessed in 1785 clinically stable patients with moderate to advanced chronic renal failure who were evaluated during the baseline phase of the Modification of Diet in Renal Disease Study. Their mean ± SD glomerular filtration rate (GFR) was 39.8 ± 21.1 mL/min/1.73 m^2.

Methods. The GFR was determined by ^{121}I-iothalamate clearance and was correlated with dietary and nutritional parameters estimated from diet records, biochemistry measurements, and anthropometry.

Results. The following parameters correlated directly with the GFR in both men and women: dietary protein intake estimated from the urea nitrogen appearance, dietary protein and energy intake estimated from dietary diaries, serum albumin, transferrin, percentage body fat, skinfold thickness, and urine creatinine excretion. Serum total cholesterol, actual and relative body weights, body mass index, and arm muscle area also correlated with the GFR in men. The relationships generally persisted after statistically controlling for reported efforts to restrict diets. Compared with patients with GFR > 37 mL/min/1.73 m^2, the means of several nutritional parameters were significantly lower for GFR between 21 and 37 mL/min/1.73 m^2, and lower still for GFRs under 21 mL/min/1.73 m^2. In multivariable regression analyses, the association of GFR with several of the anthropometric and biochemical nutritional parameters was either attenuated or eliminated completely after controlling for protein and energy intakes, which were themselves strongly associated with many of the nutritional parameters. On the other hand, few patients showed evidence for actual protein-energy malnutrition.

Conclusions. These cross-sectional findings suggest that in patients with chronic renal disease, dietary protein and energy intakes and serum and anthropometric measures of protein-energy nutritional status progressively decline as the GFR decreases. The reduced protein and energy intakes, as GFR falls,

may contribute to the decline in many of the nutritional measures.

Many studies report that there is a high prevalence of protein-energy malnutrition (PEM) in patients undergoing maintenance hemodialysis or chronic peritoneal dialysis [1–4]. This high prevalence of malnutrition is a source of concern because parameters of nutritional status are among the most powerful predictors of morbidity and mortality [3–8]. The nutritional status of patients commencing maintenance dialysis is also a powerful predictor of their protein-energy nutritional status one to two years later (abstract; Salusky et al, *Kidney Int* 23:159, 1983) and also of their clinical course on dialysis therapy [4, 9]. In addition, a number of reports indicate that there is already a high incidence of PEM in patients who are beginning maintenance dialysis treatment (abstract; Salusky et al, ibid) [4, 9]. These considerations suggest that PEM begins before patients with chronic kidney disease develop end-stage renal failure. We attempted to investigate this possibility by examining the nutritional status of patients who were participating in the Modification of Diet in Renal Disease (MDRD) Study. The analysis was carried out on 1785 patients who were evaluated during their baseline visits for this study.

METHODS

The MDRD Study was a randomized, prospective clinical trial of the effects of dietary protein and phosphorus restriction and of two different levels of blood pressure control on the rate of progression of renal failure in patients with chronic renal disease. This study was carried out in 15 clinical centers throughout the United States. Details of the hypotheses, experimental design characteristics of the patients, and results of the trial have been published elsewhere [10–19]. A total of 840 patients was randomized to the different diet and blood

pressure groups. However, 1785 individuals were evaluated in the baseline period of this trial prior to randomization and provided measurements of glomerular filtration rate (GFR) based on ^{125}I-iothalamate clearance. The present report describes a cross-sectional study, during the baseline period, of the relationship between the nutritional status and GFR in this larger group of 1785 patients.

The methods for measuring nutritional status are described in detail elsewhere [17, 18]. The dietitians who participated in this study were trained in the calculation of nutrient intake using the University of Pittsburgh Nutrient Database and in anthropometry, as indicated in the next paragraph [17–19]. All dietitians were tested and certified for uniformity and accuracy in their techniques before they were allowed to collect data from the patients. Dietary protein intake was estimated from the urea nitrogen appearance (UNA) as follows [19, 20]: protein intake (g/day) = 6.25 [UUN (g/day) + 0.31 (g/kg/day) × SBW (kg)], where UUN is the urine urea nitrogen and SBW is the standard body weight for normal individuals of the same height, age range, gender, and frame size, as determined from the NHANES I and II data [21]. The dietary protein intake was also assessed from dietary diaries, as was the dietary energy intake [17–19]. With the exception of anthropometry, all measurements described in this article were obtained within the first two weeks of enrollment in baseline.

The following anthropometric measurements were made at the second month of baseline [19]: Weight was measured using a calibrated clinical scale with the patient wearing street clothes without shoes. Height was determined with a stadiometer, also without the patient wearing shoes. Skeletal frame size was assessed by measuring the bicondylar width of the elbow of the dominant arm with Holtain Vernier Calipers (Holtain Ltd., Crymych, UK). Midarm muscle circumference was measured using a metal tape; skinfold thickness at the biceps, triceps, and subscapular locations was measured with Holtain calipers (Holtain Ltd.). The percentage of standard body weight was calculated as the patient's weight × 100/standard body weight. Body mass index (BMI) was calculated as [body weight (kg)]/[height(m)]^2. Arm muscle area (AMA) was calculated from the following equation [22]: AMA (cm^2) = [MAC − π × triceps skinfold thickness (cm)]^2/4, where the arm circumference (MAC) and the triceps skinfold thickness were measured at the midarm. The AMA measurements reported in this article were adjusted to delete bone mass using the following equations: for men, AMA = AMA (unadjusted) − 1900; for women, AMA = AMA (unadjusted) − 1550 [22]. The percentage of body fat was estimated from the patient's body weight and height and the biceps, triceps, and subscapular skinfold thicknesses using the equations of Durnin and Womersley [23].

Serum albumin concentrations were measured by dye binding using the bromcresol green technique and an Astra 8 analyzer (Beckman Instruments, Brea, CA, USA). Serum transferrin levels were analyzed by immunonephelometry using specific antibodies and calibrators and an Array nephelometer (Beckman Instruments). Serum total cholesterol was measured using a standard enzymatic method, and urine creatinine was determined using a Jaffe alkaline picrate method. The GFR was determined by the renal clearance of ^{125}I-iothalamate as previously described [15, 16]. All chemical measurements in serum and urine were performed in the MDRD Study Central Biochemistry Laboratory. Measurements of ^{125}I-iothalamate radioactivity and calculation of the renal clearance of this compound were carried out in the MDRD Study GFR Laboratory. These two laboratories, as well as the Data Coordinating Center, where the data were collated and the statistical analyses were performed, were located at the Cleveland Clinic Foundation (Cleveland, OH, USA).

The following are the normal or healthy range of values for some of the measurements: serum albumin, 4.0 to 5.0 g/dL; serum transferrin, 250 to 300 mg/dL; percentage of standard body weight, 90 to 110%; and a BMI of 19 to 25 kg/m^2.

Data analyses

Statistical analyses were conducted in men and women separately because it was considered likely that many of the biological relationships of various nutritional parameters with the GFR would be different in men and women. To maximize the precision of the results, all available data for the 1785 patients with baseline GFRs were used for each analysis. Thus, different sample sizes were used for analyses of different variables with different numbers of missing observations. To assess the robustness of our results, we repeated all analyses, including only the 988 patients for whom we had complete data for all variables. The results in this subset of patients were similar to those obtained using all available data. Sample sizes for the different variables considered in this article are presented in Table 1. Two-sided P values are provided to assess the level of statistical significance for hypothesis tests and are noted as significant if $P < 0.05$, without adjustment for multiple comparisons. Thus, in instances in which the null hypothesis is true, approximately 5% of the hypothesis tests are reported as significant with $P < 0.05$, and 1% are reported as significant with $P < 0.01$. Variability is reported as standard deviation unless otherwise stated.

In all analyses, the GFR was standardized to body surface area (BSA) by multiplying the measured values by 1.73/BSA, where BSA was computed using the patient's measured height and weight [24]. Protein and energy intakes were factored by standard weight.

Table 1. Summary of nutritional status and other variables at entry to baseline by GFR group

| | GFR < 21 | | GFR 21–37 | | GFR > 37 | | All |
	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Men							
Age *years*	51.3 ± 13.2	204	51.2 ± 13.6	355	51.0 ± 12.4	540	51.2 ± 12.9
Serum creatinine *mg/dL*	4.35 ± 1.14[b]	201	2.61 ± 0.62[b]	331	1.59 ± 0.34	533	2.43 ± 1.22
Protein intake from UNA *g/kg/day*	0.88 ± 0.19[b]	192	0.97 ± 0.22[b]	321	1.06 ± 0.30	506	1.00 ± 0.25
Protein intake from diaries/interviews *g/kg/day*	0.90 ± 0.27[b]	157	1.05 ± 0.34[b]	310	1.13 ± 0.35	337	1.05 ± 0.34
Energy from diaries/interviews *kcal/kg/day*	26.4 ± 6.90[b]	157	29.2 ± 10.0[a]	309	31.0 ± 9.30	337	29.4 ± 9.31
Serum albumin *g/dL*	3.99 ± 0.40[b]	201	4.03 ± 0.38[b]	331	4.10 ± 0.39	533	4.06 ± 0.39
Serum transferrin *mg/dL*	255 ± 42.5[b]	201	270 ± 48.3[b]	331	280 ± 45.9	533	272 ± 46.9
Serum total cholesterol *mg/dL*	204 ± 47.4[b]	201	217 ± 49.9	330	216 ± 48.4	532	214 ± 48.9
Body weight *kg*	82.4 ± 13.2[b]	204	84.9 ± 15.6[a]	334	87.4 ± 14.4	539	85.7 ± 14.7
Percent standard body weight %	106 ± 13.9[b]	204	109 ± 15.4[a]	334	112 ± 15.1	539	110 ± 15.1
Body mass index *kg/m²*	26.4 ± 3.71[b]	202	27.4 ± 4.33[a]	334	28.1 ± 4.11	533	27.6 ± 4.15
Percent body fat %	24.9 ± 5.39[b]	134	27.1 ± 5.97	251	27.7 ± 5.89	264	26.9 ± 5.91
Arm muscle area *cm²*	42.3 ± 11.6[b]	138	44.2 ± 13.1[b]	269	48.1 ± 11.3	288	45.5 ± 12.3
Biceps skinfold *mm*	5.69 ± 2.56[b]	138	6.90 ± 4.16	271	7.48 ± 4.07	292	6.90 ± 3.91
Triceps skinfold *mm*	12.4 ± 5.12[b]	138	14.3 ± 6.48	268	14.2 ± 5.76	288	13.9 ± 5.97
Subscapular skinfold *mm*	16.2 ± 5.87[b]	134	18.0 ± 6.36[a]	253	20.1 ± 6.74	267	18.8 ± 6.57
Sum of skinfolds *mm*	34.1 ± 11.5[b]	134	39.2 ± 13.8	250	40.8 ± 13.8	264	38.8 ± 13.6
Urine creatinine *mg/kg/day*	17.5 ± 3.46[b]	192	18.6 ± 3.85[b]	320	20.2 ± 4.24	505	19.2 ± 4.12
Women							
Age *years*	50.8 ± 12.6[a]	146	50.3 ± 12.7[a]	231	47.7 ± 12.5	329	49.2 ± 12.6
Serum creatinine *mg/dL*	3.57 ± 1.07[b]	145	2.04 ± 0.50[b]	227	1.25 ± 0.30	326	1.99 ± 1.07
Protein intake from UNA *g/kg/day*	0.90 ± 0.21[b]	140	0.93 ± 0.20[b]	216	1.03 ± 0.24	312	0.97 ± 0.23
Protein intake from diaries/interviews *g/kg/day*	0.84 ± 0.28[b]	108	0.97 ± 0.31	210	0.99 ± 0.30	203	0.95 ± 0.30
Energy from diaries/interviews *kcal/kg/day*	24.6 ± 8.58[b]	108	27.9 ± 8.58	210	27.7 ± 8.84	201	27.2 ± 8.76
Serum albumin *g/dL*	3.88 ± 0.36[b]	145	3.96 ± 0.34[b]	227	4.06 ± 0.32	326	3.99 ± 0.34
Serum transferrin *mg/dL*	261 ± 46.0[b]	145	276 ± 45.3[b]	227	287 ± 46.2	326	278 ± 46.9
Serum total cholesterol *mg/dL*	225 ± 48.9	145	228 ± 54.2	227	222 ± 46.9	322	225 ± 49.8
Body weight *kg*	68.2 ± 14.7	146	70.8 ± 15.6	231	70.9 ± 15.1	325	70.3 ± 15.2
Percent standard body weight %	109 ± 19.3	146	113 ± 19.8	231	112 ± 18.6	325	112 ± 19.2
Body mass index *kg/m²*	26.0 ± 5.27	145	26.8 ± 5.55	231	26.8 ± 5.36	325	26.6 ± 5.41
Percent body fat %	32.5 ± 6.23[b]	91	34.5 ± 6.35	171	35.5 ± 5.69	152	34.4 ± 6.17
Arm muscle area *cm²*	28.1 ± 15.9	94	29.1 ± 13.1	180	29.6 ± 12.6	161	29.0 ± 13.6
Biceps skinfold *mm*	9.69 ± 5.34[b]	96	11.6 ± 6.74	190	12.3 ± 6.43	167	11.5 ± 6.41
Triceps skinfold *mm*	19.7 ± 7.81[b]	94	22.0 ± 7.14	178	23.4 ± 7.05	159	22.0 ± 7.37
Subscapular skinfold *mm*	16.7 ± 7.46[b]	93	18.8 ± 7.99	177	19.8 ± 7.61	156	18.7 ± 7.80
Sum of skinfolds *mm*	45.1 ± 17.4[b]	92	50.9 ± 18.2	169	53.7 ± 17.5	149	50.6 ± 18.0
Urine creatinine *mg/kg/day*	15.3 ± 3.14[b]	140	15.2 ± 3.16[b]	216	16.5 ± 3.48	308	15.8 ± 3.36

[a] $P < 0.05$ as compared to GFR > 37 group
[b] $P < 0.01$ as compared to GFR > 37 group

Initial descriptive analyses

For initial descriptive analyses, we divided the patients into three groups defined by GFR < 21 mL/min/1.73 m², GFR between 21 and 37 mL/min/1.73 m², and GFR > 37 mL/min/1.73 m². The boundary points of 21 and 37 mL/min/1.73 m² were selected arbitrarily but were intended to divide the sample into subgroups with severe, moderately severe, and moderate renal insufficiency while maintaining a sufficient sample size in each subgroup to retain adequate precision.

Two-sample *t*-tests were used to compare the mean levels of the nutritional variables between males and females and between the group with GFR > 37 mL/min/1.73 m² and the subgroups of patients with severe (GFR < 21 mL/min/1.73 m²) or moderately severe (GFR between 21 and 37 mL/min/1.73 m²) renal insufficiency. Analysis of covariance was used to compare the mean values of the nutritional variables between those patients attempting to follow protein- or energy-restricted diets and those not attempting diet restriction after controlling for GFR, age, and race. Analysis of covariance was also used to describe the association of the nutritional variables with race (black vs. non-black) after controlling for GFR, age, and reported diet restriction.

Relationship of glomerular filtration rate with nutritional parameters

We expected that the strength of the relationships of the nutritional parameters with GFR would often differ between the lower and higher levels of GFR. Therefore, to account for relationships that may not be linear, nonparametric regression with cubic smoothing splines [25] was used in our formal statistical analyses that modeled the mean of each nutritional parameter as a function of baseline GFR while controlling for age, race, and the use of protein- or energy-restricted diets. Cubic spline

regressions do not require the specification of arbitrary boundary points between GFR subgroups as in Table 1, and relate the nutritional parameters to GFR without imposing any assumptions as to the shape of the relationships, except that they are "smooth," without abrupt changes for small increments of the GFR. Smoothness parameters were selected to allow five degrees of freedom for the relationship of each nutritional parameter with GFR.

The overall relationship of GFR with each nutritional parameter was tested by comparing the mean value of the nutritional parameter under the cubic spline model at a low value of GFR (taken to be 12 mL/min/1.73 m²) to the mean value at a relatively high GFR of 55 mL/min/1.73 m². The lower GFR value of 12 mL/min/1.73 m² was selected as the smallest GFR where the sample size permitted accurate estimation of the means of the nutritional parameters. We determined whether the strength of the relationship between the nutritional parameters and the GFR increased at lower GFR values by comparing the slope of the relationship at a GFR of 12 mL/min/1.73 m² to the slope at a GFR of 55 mL/min/1.73 m². Standard errors for these analyses were computed using the bootstrap method, with 800 independent bootstrap samples for each analysis [26]. Similar cubic spline models were used in logistic regression analyses to relate the baseline GFR to the fraction of patients for whom nutritional parameters fell within specified "unsafe" ranges, again controlling for age, race, and the use of protein or energy-restricted diets.

Joint relationship of nutritional status parameters with glomerular filtration rate and protein and energy intakes

We used multiple regression analyses to investigate the independent contributions of GFR, protein intake, and energy intake to the nutritional parameters while controlling for age. However, because of measurement error and large fluctuations in dietary intake over time, it is well known that regression coefficients of dietary intake variables may be severely biased [27, 28]. To control for this bias, the within-patient variability of the protein intake and energy intake measurements were estimated by comparing the initial baseline measurements used in the cross-sectional analyses with repeat measurements that were taken at the end of the baseline period (about 3 months after the initial measurement) in 738 patients. Based on these results, an errors-in-variables technique described by Fuller was used to reduce the bias in the regression coefficients relating the nutritional status variables to the dietary intake variables and GFR [29]. To account for nonlinear relationships of GFR with some parameters, the effect of GFR was evaluated using a linear spline model with separate

slopes for GFR < 21, GFR between 21 and 37, and GFR > 37 mL/min/1.73 m².

RESULTS

Descriptive analyses

Characteristics of the patients are shown separately by gender and level of GFR in Table 1. In all patients combined, the mean age was 50.4 ± 12.8 years (range, 19 to 71). Sixty percent of the individuals were male. Eighty percent were white, 13% black, 5% Hispanic, 1% Asian, and 1% other. In subsequent analyses, the 13% of blacks are compared with the remaining 87% of patients, who are referred to as non-black. Six percent of all patients had non–insulin-dependent diabetes mellitus. The causes of renal disease recorded at the initial baseline assessment were glomerular diseases in 32%, polycystic kidney disease in 22%, tubulointerstitial diseases in 7%, and other or unknown diseases in 39%. The GFR averaged 39.8 ± 21.1 mL/min/1.73 m² (10th and 90th percentiles, 15.5 and 67.3, respectively). The dietary protein intake of all patients, determined from the UNA or the dietary records, averaged 0.99 ± 0.24 g/kg/day and 1.01 ± 0.33 g/kg/day, respectively. Protein intake exceeded 0.75 g/kg/day for 84% of patients when estimated from the UNA and for 79% of patients when estimated from diet records. The energy intake from all patients combined, determined from dietary diaries, averaged 28.5 ± 9.2 kcal/kg/day. In the men and women taken together, serum albumin was less than 3.8 g/dL in 19.4%. Serum transferrin was less than 250 mg/dL in 30.1%. Serum total cholesterol was below 160 mg/dL and above 200 mg/dL in 9.0 and 60.6%, respectively, and standard body weight was below 90% and above 110% in 10.2 and 45.9%, respectively.

Table 1 considers three ranges of GFR: less than 21 mL/min/1.73 m² (350 patients), 21 to 37 mL/min/1.73 m² (566 patients), and greater than 37 mL/min/1.73 m² (869 patients). In men, all 16 of the dietary and other nutritional status factors listed had significantly lower values for patients with GFR < 21 mL/min/1.73 m² than for patients with GFR > 37 mL/min/1.73 m². With the exception of serum total cholesterol, percentage body fat, and three of the skinfold indices, in the men, the remaining 11 dietary and nutritional factors also exhibited significant decreases at the GFR range between 21 and 37 mL/min/1.73 m² as compared with the GFR > 37 group.

In women, the means of the following 11 factors were significantly lower in the GFR < 21 group than in the GFR > 37 group: protein intake determined from UNA and from diet diaries, dietary energy intake, serum albumin and transferrin, percentage body fat, the biceps, triceps, and subscapular skinfolds, the sum of the three skinfolds, and urine creatinine excretion. With the exception of dietary energy intake, the other 10 of these same

Table 2. Dietary protein and energy intake according to the GFR in patients describing no dietary restrictions or restrictions in protein or energy intake

	Group 1, GFR < 21 mL/min/1.73 m²						Group 2, GFR 21–37 mL/min/1.73 m²						Group 3, GFR > 37 mL/min/1.73 m²					
	No restricts (137, 109)[a]		Protein restrict (186, 147)		Energy restrict (31, 24)		No restricts (329, 320)		Protein restrict (169, 164)		Energy restrict (63, 59)		No restricts (595, 383)		Protein restrict (147, 107)		Energy restrict (100, 66)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dietary protein intake *g/kg/day*																		
from UNA	0.909[b]	0.20	0.860[b]	0.19	0.984	0.25	0.960[b]	0.21	0.912[b]	0.21	1.03	0.23	1.05	0.26	1.01	0.24	1.09	0.25
from diaries	0.967[b]	0.29	0.810[b]	0.24	0.893	0.21	1.07[c]	0.34	0.915[c]	0.27	0.932	0.32	1.10	0.35	0.993	0.31	1.04	0.30
Dietary energy intake	26.6[b]	8.1	25.1[b]	7.2	27.3	8.9	29.6[c]	10	27.1	7.9	25.6	8.3	30.3	9.3	28.4	8.9	28.5	9.4

[a] First number in parentheses indicates sample size for protein intake determined from urea nitrogen appearance and second number indicates sample size for protein and energy intake determined from diaries/interviews

[b] Differs ($P < 0.01$) from dietary intake of patients with the same type of protein or energy restriction or lack of dietary restriction who have a GFR > 37 ml/min/1.73 m²

[c] Differs ($P < 0.01$) from dietary intake of patients with the same type of protein or energy restriction or lack of dietary restriction who have a GFR < 21 ml/min/1.73 m²

factors also had lower mean values in the GFR 21 to 37 group than in the GFR > 37 group, although several of the differences were not statistically significant. In women, the mean serum total cholesterol, total body weight, percentage standard weight, BMI, and AMA were not significantly associated with the GFR level.

Diet restriction

Of the 1785 patients for whom data are available, 528 individuals reported that they had attempted or had been advised to follow a low-protein diet, and 203 patients indicated that they had attempted or been advised to reduce their energy intake. Some of these patients attempted to follow both protein and energy restriction, and therefore, a total of 657 individuals attempted to follow protein- and/or energy-restricted diets. Fifty-six percent, 32%, and 17% of the patients with a GFR (mL/min/1.73 m²) of less than 21, between 21 and 37, and above 37, respectively, indicated that they had attempted to restrict their dietary protein intake. Nine percent, 12%, and 12% of patients with a GFR (mL/min/1.73 m²) of below 21, between 21 and 37, and above 37, respectively, had attempted to reduce their dietary energy intake.

Compared with patients not attempting to follow protein-restricted diets, after controlling for GFR, age, and race, patients attempting to follow protein-restricted diets had significantly lower protein intakes from diet records (mean ± SEM of difference, −0.138 ± 0.026, $P < 0.001$, and −0.128 ± 0.029 g/kg/day, $P < 0.001$, in men and women, respectively). The association of dietary protein restriction with protein intakes determined from the UNA was weaker in men and women (−0.066 ± 0.017, $P < 0.001$, and −0.043 ± 0.019 g/kg/day, $P = 0.03$, respectively). Men and women indicating attempts at protein-restricted diets had lower serum transferrin (−9.20 ± 3.32, $P = 0.006$, and −7.97 ± 3.85 mg/dL, $P = 0.04$), total body weight (−4.20 ± 1.04, $P < 0.001$, and

−2.89 ± 1.24 kg, $P = 0.02$), standard weight (−3.71 ± 1.06, $P < 0.001$, and −3.83 ± 1.45%, $P = 0.01$), BMI (−1.11 ± 0.29, $P < 0.001$, and −1.13 ± 0.44 kg/m²; $P = 0.01$), and AMA (−2.38 ± 1.04, $P = 0.02$, and −3.17 ± 1.41 cm², $P = 0.02$), respectively. Patients attempting to follow protein-restricted diets also tended to have higher urine creatinine excretion (+0.38 ± 0.28, $P = 0.17$, and +0.63 ± 0.26 mg/kg/day, $P = 0.02$) and a lower sum of skinfolds (−2.73 ± 1.15, $P = 0.02$, and −2.13 ± 1.93 mm, $P = 0.27$). Patients attempting to follow energy-restricted diets had significantly higher levels of several anthropometric parameters, including total body weight (7.86 ± 1.50 and 9.34 ± 1.56 kg), percentage standard weight (8.95 ± 1.52 and 11.72 ± 1.97%), and BMI (2.49 ± 0.42 and 3.35 ± 0.55 kg/m²) in both men and women ($P < 0.001$ for each comparison). The dietary energy intake of patients attempting dietary energy restriction, as determined from dietary diaries, in comparison with patients not attempting to follow protein- or energy-restricted diets, was slightly greater in group 1 (GFR < 21 mL/min/1.73 m²) and lower in group 2 (GFR 21 to 37 mL/min/1.73 m²) and group 3 (GFR > 37 mL/min/1.73 m²; Table 2).

Racial differences

Compared with non-blacks, after controlling for age, GFR, and the use of restricted diets, blacks had lower protein intake, as determined from UNA (−0.106 ± 0.023, $P < 0.001$, and −0.085 ± 0.025 g/kg/day, $P < 0.001$) but not from diet records (−0.034 ± 0.040, $P = 0.39$, and 0.005 ± 0.040 g/kg/day, $P = 0.89$) for men and women, respectively. Blacks also differed from non-blacks on most of the other nutritional status parameters. In particular, both male and female blacks had higher urine creatinine excretion (1.07 ± 0.37, $P = 0.004$, and 0.69 ± 0.35 mg/kg/day, $P = 0.05$) and BMI (0.88 ± 0.38, $P = 0.02$, and 2.83 ± 0.57 kg/m²; $P < 0.001$), and lower serum transferrin

$(-13.9 \pm 4.33, P = 0.001$, and -17.7 ± 5.06 mg/dL, $P < 0.001$) than did male and female non-blacks. Black males had higher serum total cholesterol (9.95 ± 4.66 mg/dL, $P = 0.033$) and reported a lower energy intake (-3.70 ± 0.92 kcal/kg/day, $P < 0.001$) than non-black males.

Relationships of nutritional parameters with the glomerular filtration rate

Figure 1 shows the nonparametric regression curves relating the mean values of the dietary intake parameters to GFR after controlling for age and race. These analyses were done separately for each gender and for patients attempting or not attempting to follow restricted diets. As shown in Figure 1 C and D, the strength of the relationship between GFR and protein intake from the diet records (assessed as the difference in the mean protein intake between a GFR of 55 mL/min/1.73 m² and a GFR of 12 mL/min/1.73 m²) was stronger for men attempting to follow restricted diets than for men not attempting to follow restricted diets ($P = 0.001$). The relationship between GFR and energy intake from diet records was also stronger in men attempting to follow restricted diets than for men not attempting to follow restricted diets ($P = 0.04$). However, when protein intake was estimated from UNA, there was no indication of a difference between the effect of GFR in the subgroups attempting or not attempting to follow dietary restriction ($P = 0.23$ in men, and $P = 0.33$ in women).

Aside from protein and energy intake from the diet records, the strength of the association of GFR with each of the remaining nutritional parameters did not differ significantly between those attempting or not attempting to follow restricted diets ($P > 0.05$ for each parameter in both men and women). Accordingly, Figures 2 and 3 present the relationships of GFR with the anthropometric and biochemical nutritional parameters for all males and females regardless of diet restriction. However, as described in the Methods section, protein- and energy-restricted diets were included in the regression models used to obtain the plots to control for the association of diet restriction with the mean levels of the nutritional parameters.

The results of these analyses controlling for age and restricted diets are generally consistent with the unadjusted analyses presented in Table 1. In men, lower values of GFR were associated with lower mean levels of all dietary parameters and nutritional measures. This association was statistically significant for all parameters except for serum total cholesterol ($P = 0.052$) and the protein and energy intakes estimated from the diet records in the subgroup not attempting restricted diets ($P = 0.052$ and $P = 0.082$, respectively). In women, a lower GFR was associated with lower mean levels of protein intake from UNA, serum albumin, serum transferrin, and urine creatinine excretion. Protein and energy in-

takes estimated from diet records were also significantly associated with GFR in the subgroup of women attempting protein- or energy-restricted diets. The mean percentage of body fat also tended to decline at lower GFR values, but not significantly ($P = 0.057$). In women, serum total cholesterol, total body weight, percentage standard weight, BMI, AMA, and the sum of the skinfolds were not significantly associated with the GFR level ($P > 0.11$ for each analysis).

Tables 1 and 2 and Figures 1 to 3 examine the relationship between GFR and the mean levels of the nutritional status parameters, but do not address the association of GFR with the percentage of patients with abnormal levels of these parameters. The four panels of Figure 4 provide nonparametric regression curves describing the association of GFR with the fraction of patients having abnormal nutritional measures, particularly those with serum albumin < 3.8 g/dL, serum transferrin < 250 mg/dL, serum total cholesterol < 160 mg/dL, or percentage standard weight $< 90\%$ after controlling for age and use of protein- or energy-restricted diets. It is apparent that a lower GFR is significantly associated with a greater fraction of patients with abnormally low serum albumin and transferrin concentrations in both men and women and abnormally low serum total cholesterol values in men (Fig. 4 A–C). The GFR was not significantly related to the fraction of patients with percentage standard weight $< 90\%$ in women (Fig. 4D) or to the fraction of patients with percentage standard weight $> 110\%$ or with serum total cholesterol > 200 mg/dL (data not shown).

Joint association of nutritional measures with the glomerular filtration rate and protein and energy intakes

The preceding analyses show that a lower GFR is associated both with lower levels of dietary protein and energy intake and with parameters of nutritional status, suggesting nutritional deterioration. It is possible that the lower measures of nutritional status are a consequence of the reduced protein and energy intake at lower GFRs; alternatively, the lower GFR may be associated with lower values of the nutritional parameters independently of dietary intake. To address this issue, we jointly related the parameters of nutritional status to GFR, protein intake calculated from UNA, and dietary energy intake separately in men and women after controlling for age and race. Protein intake was calculated from UNA based on the assumption that in these patients the UNA gives a more accurate estimate of dietary protein intake than do dietary diaries. As described in the **Methods** section, it was necessary to control for the within-patient variances of the protein and energy intake measurements, which were estimated from the changes in these measurements between two baseline measurements. The within-patient variance of the protein intake measure-

ments was 55% of the total variance of the initial baseline protein intake for males and 67% of the variance of the initial baseline protein intake for females. The within-patient variances of energy intake were 46 and 41% of the variances of the initial measurement in males and females, respectively.

The results, shown in Table 3, indicate that after adjusting for protein and energy intakes and taking into account the within-patient variability in these intakes, the strength of the association of GFR with most of the nutritional parameters is substantially reduced from the previous analyses, which did not adjust for protein and energy intakes. As indicated in Table 3, only the percentage of body fat and serum transferrin had significant, positive relationships with GFR in men, and only serum transferrin and serum albumin had significant, positive relationships with GFR in women. By contrast, Table 3 indicates strong positive associations of protein and energy intake with many of the nutritional status variables after controlling for GFR.

The estimated relationships between GFR and several of the nutritional parameters are in the negative direction in Table 3. The negative trends may be due in part to the standardization of GFR by BSA, which is calculated using measured body weight. The presence of weight in the denominator for GFR may suppress the association of GFR with anthropometric measurements, which either directly involve weight or are highly correlated with weight.

Pair-wise correlations

In Table 4, a correlation matrix is shown for data from the 988 patients in whom values were obtained for each nutritional parameter. Many nutritional parameters were positively or negatively correlated with each other. Because with large sample sizes statistically significant correlations can be observed with variables that have very low levels of correlation, this discussion focuses on those variables that co-vary with each other with correlation coefficients of 0.35 or greater. It is noteworthy that the two methods of assessing dietary protein intake were rather poorly correlated with each other ($r = 0.316$). Dietary energy intake was directly and rather strongly correlated with protein intake when dietary protein was calculated from dietary records ($r = 0.680$), but

not when it was determined from the UNA ($r = 0.216$). As might be predicted, actual body weight, percentage standard body weight, and the BMI were each rather strongly correlated with the other two variables ($r = 0.714$ to 0.941). The percentage body fat also correlated well with percentage standard body weight ($r = 0.597$) and BMI ($r = 0.522$), but not with the actual body weight ($r = 0.189$). AMA correlated well with the actual body weight ($r = 0.770$), relative body weight ($r = 0.522$), and BMI ($r = 0.655$). Urine creatinine correlated most strongly and also negatively with the percentage of body fat ($r = -0.545$). Biceps, triceps, and subscapular skinfold thicknesses also correlated strongly with each other ($r = 0.511$ to 0.761) and, in general, with the body mass measures (actual body weight, percentage standard body weight, BMI, and body fat). On the other hand, the visceral proteins, serum albumin and transferrin, and serum total cholesterol correlated weakly with each other and with all of the anthropometric parameters and urine creatinine. Protein and energy intake correlated weakly with serum albumin, transferrin, and total cholesterol and only slightly better with anthropometric measures and urine creatinine.

DISCUSSION

The results of this cross-sectional study indicate that in a large sample size of clinically stable patients with chronic renal insufficiency, many parameters of protein-energy nutritional status correlate directly with the GFR. This relationship was observed over a wide GFR range (10th to 90th GFR percentiles, 15.5 and 67.3 mL/min/ 1.73 m^2). This was found for dietary protein intake—especially when assessed by the UNA rather than dietary records, dietary energy intake, serum albumin, serum transferrin, body fat, and urine creatinine excretion, and in males also for serum total cholesterol, actual and standard body weights, AMA, and the sum of the biceps, triceps, and subscapular skin folds (Figs. 1 to 3). The relationships between the nutritional parameters and the GFR often varied according to the GFR range. In general, it was observed that the lower the GFR, the lower were the values for the nutritional parameters. Indeed, the percentage of individuals with abnormally low serum albumin, transferrin, and total cholesterol increased as

Fig. 1. **Mean levels of protein and energy intake as a function of glomerular filtration rate (GFR).** The estimated mean levels with 95% confidence limits of protein and energy intakes are shown as a function of baseline GFR (solid line, males; dashed line, females) controlling for age and race. The *P* values refer to the overall relationship of GFR with the respective dietary intake variables, based on the difference in the means of dietary variables between GFR = 55 and GFR = 12 mL/min/1. 73 m^3. In men attempting to follow a restricted diet, the slope of the relationship of protein intake estimated from diet records was steeper when GFR = 12 than when GFR = 55 mL/min/1. 73 m^3 ($P < 0. 001$). (*A*) Males, $N = $ 352 ($P < 0.001$); females, $N = 274$ ($P < 0.001$). (*B*) Males, $N = 667$ ($P < 0.001$); females, $N = 394$ ($P < 0.001$). (*C*) Males, $N = 291$ ($P < 0.001$); females, $N = 220$ ($P = 0.008$). (*D*) Males, $N = 513$ ($P = 0.052$); females, $N = 301$ ($P = 0.42$). (*E*) Males, $N = 290$ ($P < 0.001$); females, $N = 220$ ($P = 0.004$). (*F*) Males, $N = 513$ ($P = 0.084$); females, $N = 299$ ($P = 0.26$).

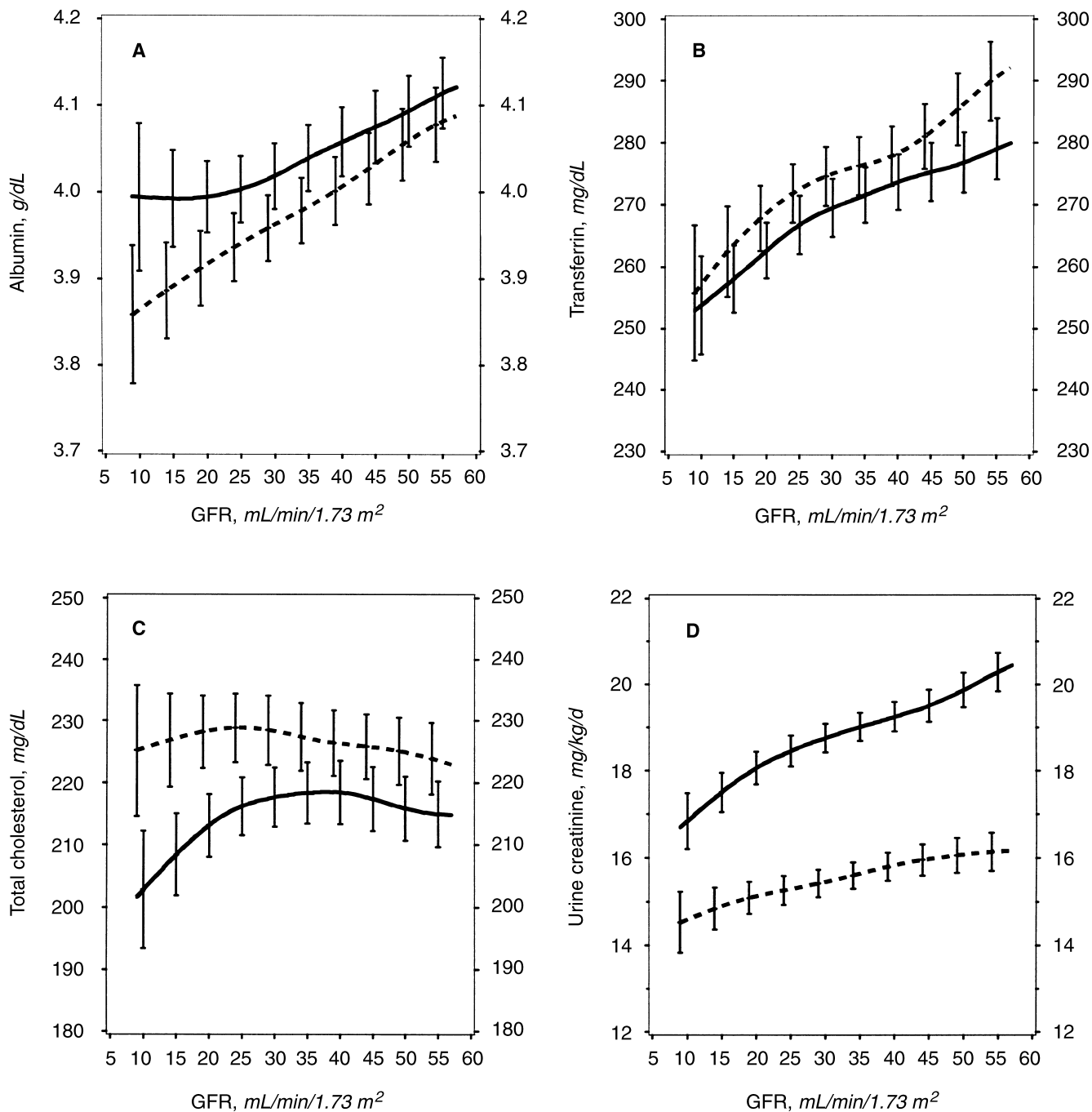On restricted diet

Not on restricted diet
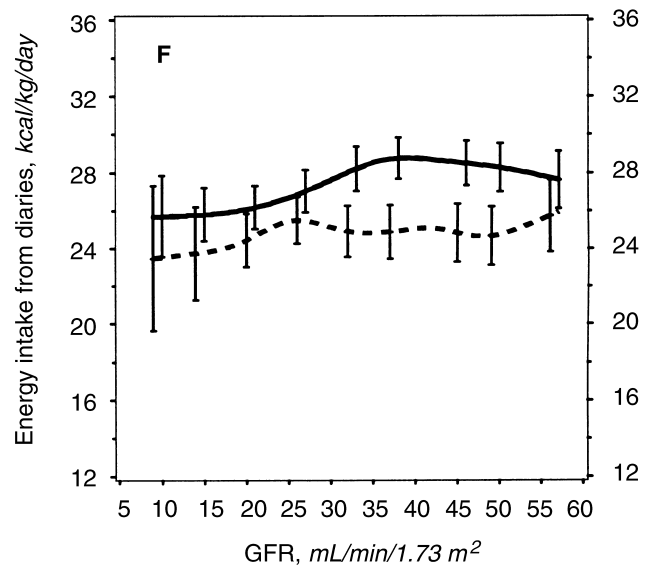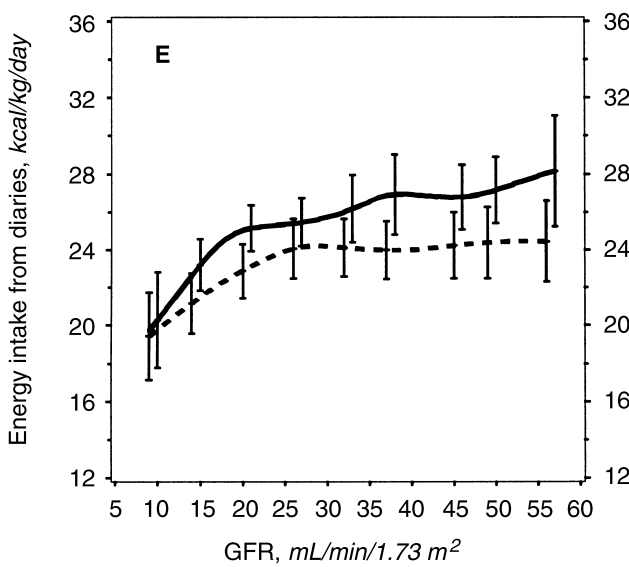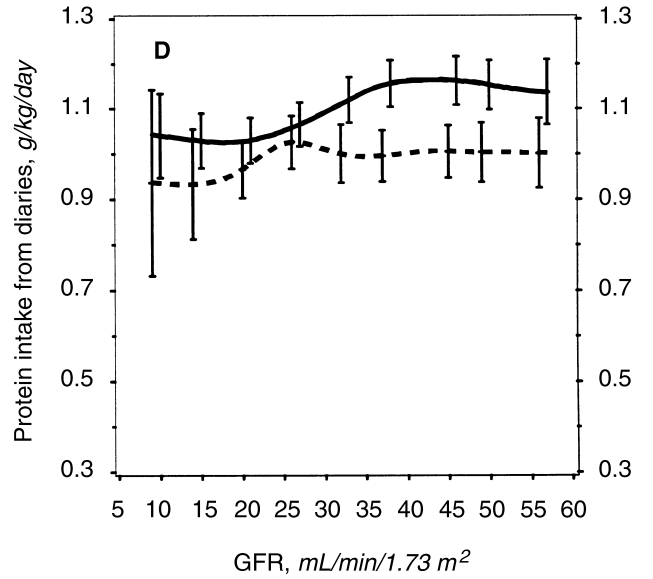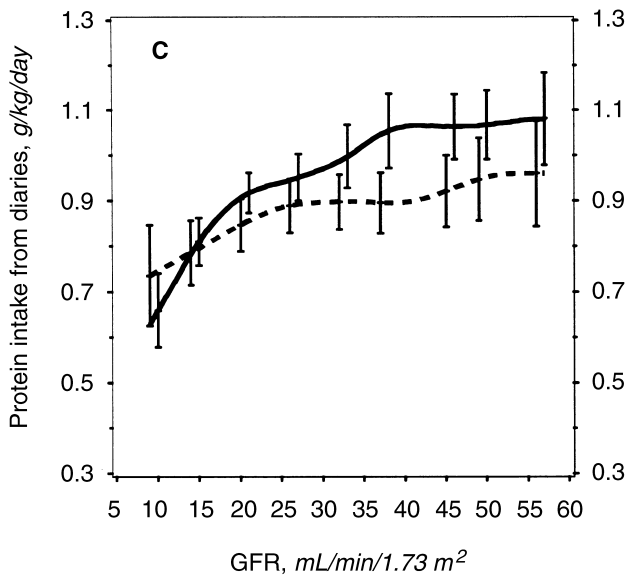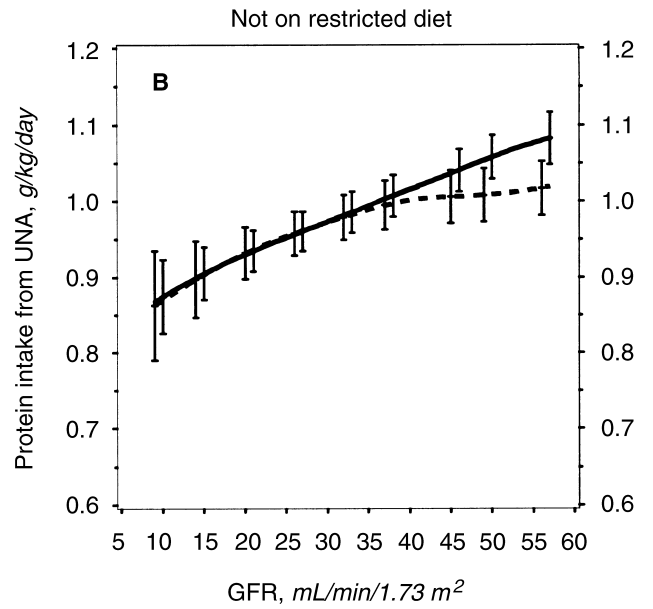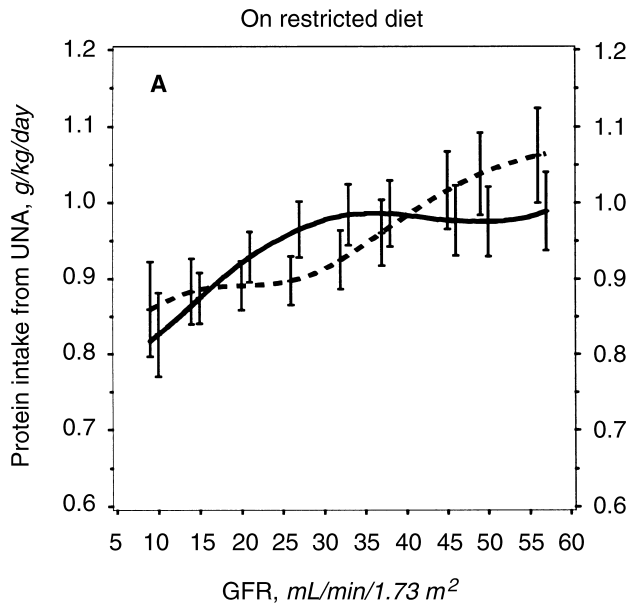
Fig. 2 . Mean levels of biochemical measures of nutritional status as a function of GFR. The estimated mean levels with 95% confidence limits of biochemical nutritional markers are shown as a function of GFR (males, solid line; females, dashed line) controlling for age, race and use of protein and energy restricted diets. In men, the slope of the relationship was greater at GFR = 12 than GFR = 55 mL/min/1.73 m^2 for serum total cholesterol (P = 0.014). Figure 1 legend has further details. (A) Males, N = 1065 (P = 0.004); females, N = 698 (P < 0.001). (B) Males, N = 1065 (P < 0.001); females, N = 698 (P < 0.001). (C) Males, N = 1063 (P = 0.052); females, N = 694 (P = 0.63). (D) Males, N = 1017 (P < 0.001); females, N = 664 (P < 0.001).

Fig. 3. Mean levels of anthropometric measures of nutritional status as a function of GFR. The estimated mean levels with 95% confidence limits of anthropometric measures of nutritional status are shown as a function of GFR (males, solid line; females, dashed line) controlling for age, race and use of protein and energy restricted diets. In men, the slope of the relationship was greater at GFR = 12 than GFR = 55 mL/min/1.73 m^2 for total body weight (P = 0.008), percent standard weight (P = 0.002), percent body fat (P = 0.004), body mass index (P = 0.002), and the sum of skinfolds (P = 0.003). Figure 1 legend has further details. (A) Males, N = 1077 (P = 0.009); females, N = 702 (P = 0.61). (B) Males, N = 1077 (P < 0.001); females, N = 702 (P = 0.62). (C) Males, N = 649 (P < 0.001); females, N = 414 (P = 0.057). (D) Males, N = 1069 (P = 0.002); females, N = 701 (P = 0.67). (E) Males, N = 695 (P < 0.001); females, N = 435 (P = 0.26). (D) Males, N = 648 (P < 0.001); females, N = 410 (P = 0.11).
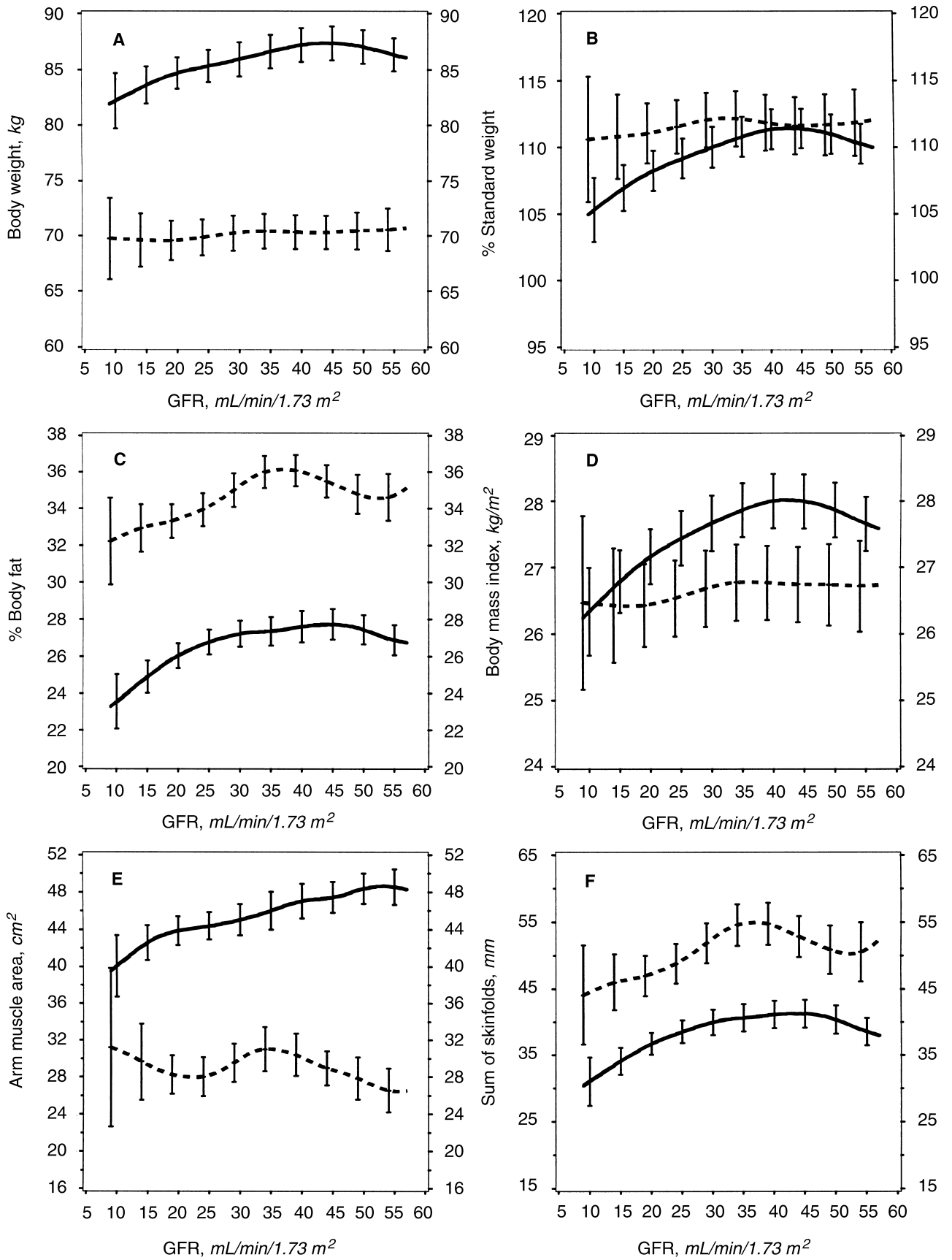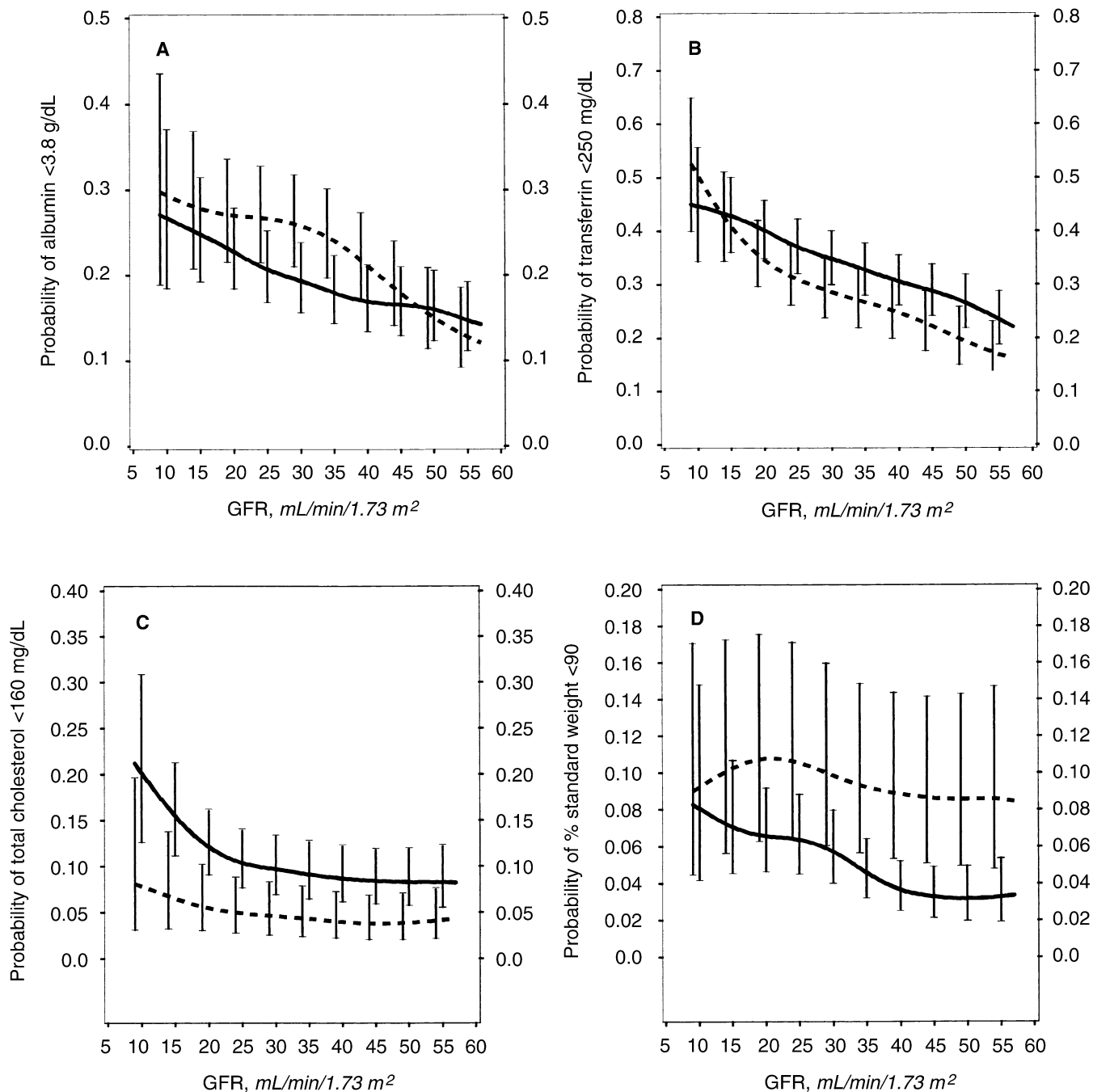
Fig. 4. Probability of "unsafe" levels of nutritional status parameters as a function of GFR. The estimated probabilities with 95% confidence limits [brackets] that serum albumin, serum transferrin, serum total cholesterol, and percent standard weight fall in designated unsafe ranges as a function of GFR (males, solid line; females, dashed line) controlling for age, race and use of protein and energy restricted diets. The *P* values are for the overall relationship of GFR with the probability that the nutritional parameters fall in the designated unsafe ranges, based on the difference in these probabilities between GFR = 55 and GFR = 12 mL/min/1. 73 m². (*A*) Males, *N* = 1065 (*P* = 0.007); females, *N* = 698 (*P* = 0.002). (*B*) Males, *N* = 1065 (*P* < 0.001); females, *N* = 698 (*P* < 0.001). (*C*) Males, *N* = 1063 (*P* = 0.006); females, *N* = 694 (*P* = 0.24). (*D*) Males, *N* = 1077 (*P* = 0.036); females, *N* = 702 (*P* = 0.72).

the GFR fell (Fig. 4). These findings are even more noteworthy because patients with many inflammatory or catabolic diseases (for example, chronic infection, AIDS, active cancer other than basal cell carcinoma, and severe lung, liver, or heart failure), insulin-dependent diabetes

mellitus, nephrotic syndrome, or frank malnutrition were excluded from the study [10, 13, 14, 19]. Thus, these findings were observed in what was probably a healthier subset of individuals with chronic renal insufficiency.

It should be emphasized that the mean values for the

Table 3. Multiple regression analyses relating nutritional status variables to GFR, protein intake and energy intake

	Males						Females					
	GFR[a] 12–55 mL/min/1.73 m²		Protein intake[b] per 0.2 g/kg/day		Energy intake[c] per 5 kcal/kg/day		GFR[a] 12–55 mL/min/1.73 m²		Protein[b] per 0.2 g/kg/day		Energy intake[c] per 5 kcal/kg/day	
Nutritional status outcome	Est. effect	SE	Est. effect	SE	Est. effect	SE	Est. effect	SE	Est. effect	SE	Est. effect	SE
% Standard weight	−5.86	2.65	+6.33[e]	1.12	+4.57[e]	0.58	−9.63	3.90	+12.19[e]	2.77	+5.41[e]	0.90
Weight *kg*	−0.77	2.62	+3.32[e]	1.10	+3.87[e]	0.58	−5.42	2.94	+5.81[e]	2.01	+3.62[e]	0.69
Body mass index	−1.12	0.74	+1.66[e]	0.31	+1.27[e]	0.16	−1.96	1.08	+2.93[e]	0.76	+1.23[e]	0.25
% Body fat	+2.09[d]	1.05	+0.82	0.45	+0.75[e]	0.25	−0.35	1.35	+2.59[e]	0.98	+1.08[e]	0.37
Urine creatinine *mg/kg/day*	−0.96	0.78	+3.66	0.37	−0.23	0.18	−0.17	0.94	+3.44[e]	0.77	−0.63[d]	0.27
Total cholesterol *mg/dL*	+1.18	9.46	+12.23[e]	4.00	+1.86	2.27	+23.27	12.09	+13.90	9.18	−5.33	3.60
Transferrin *mg/dL*	38.25[e]	8.97	−1.08	3.76	+2.22	2.16	+28.65	11.36	+11.71	8.58	−0.87	3.35
Albumin *g/dL*	0.07	0.07	+0.04	0.03	−0.03	0.02	+0.23[e]	0.08	+0.03	0.06	−0.01	0.03
Arm muscle area *cm²*	−0.10	2.55	+3.65[e]	1.07	+4.27[e]	0.63	−3.81	3.16	+6.53[e]	2.47	+1.42	0.92
Sum of skinfolds *mm*	+3.80	2.77	+2.18	1.17	+2.36[e]	0.67	−3.03	4.62	+9.97[e]	3.57	+4.12[e]	1.32

[a] GFR adjusted to BSA calculated using measured body weight; estimated effects (Est. effect) provide the mean difference of the nutritional variables between GFR = 55 and GFR = 12 mL/min/1.73 m², controlling for protein intake, energy intake, race and age; SE is standard error of estimated effect

[b] Protein intake from UNA factored by standard weight; estimated effects provide mean differences in nutritional variables per 0.2 g/kg/day in protein intake, controlling for GFR, energy intake, race and age

[c] Energy intake from diet records factored by standard weight, estimated effects provide mean differences in nutritional variables per 5 kcal/kg/day in energy intake, controlling for GFR, protein intake, race and age

[d] $P < 0.05$

[e] $P < 0.01$

nutritional parameters did not indicate that the patients, as a group, had protein-energy malnutrition (PEM) (discussed in the **Methods** section). However, the trend for most of the parameters was for a worsening of nutritional status as the GFR declined. Moreover, the mean dietary energy intake of the individuals was below both the recommended daily energy intakes of normal adults, as determined from the Food and Nutrition Board, National Academy of Sciences [30] and the currently recommended dietary energy requirements for nondialyzed chronic renal failure patients and maintenance hemodialysis and peritoneal dialysis patients (Table 1) [31–33]. These abnormally low dietary energy intakes were observed even for patients at the upper range of the GFR levels for this study (that is, above 50 mL/min/1.73 m²; Fig. 1). Many patients had one or more nutritional parameters that were below the lower limit of normal. On the other hand, the mean BMI in both men and women can be classified in the overweight category (Table 1) [34], although the BMI and the percentage of standard body weight also declined as the GFR decreased.

Some patients indicated that they were attempting to follow protein-restricted diets. Patients indicating restricted diets had lower mean values of several of the dietary and other nutritional parameters. However, the following considerations suggest that the reduction in protein and energy intakes and the decrease in other nutritional parameters as a function of decreasing GFR cannot be primarily accounted for by conscious attempts to follow such restricted diets. First, with the exception of dietary protein and energy intakes calculated from diaries, the reductions in the nutrient intake and nutritional parameters as GFR varied from 55 to 12 mL/min/

1.73 m² did not differ significantly between the 1128 patients who were not attempting to ingest protein- or energy-restricted diets and those patients who were attempting to follow restricted diets. In fact, each statistically significant relationship shown in Figures 2 to 4 remains statistically significant if the analysis was restricted to the subgroup attempting protein restriction. Second, while the relationship of GFR with protein intake calculated from dietary diaries was significantly stronger in the subgroup of men indicating restricted diets, this difference was not observed when the protein intake was estimated by the UNA (Fig. 1). There is no compelling evidence that patients who report attempting to restrict protein or energy intake actually succeed in this endeavor unless they undergo intensive and recurrent dietary counseling. Indeed, this is a reason why, for the population at large, there has been such a widespread proliferation of weight-reduction clinics, fat-reduction diets, and appetite-suppressant medicines. It is the authors' impression that prior to the onset of the experimental phase of the MDRD Study, few, if any, patients received such intensive dietary counseling.

The different nutritional parameters exhibited varying patterns of association with GFR over the ranges of GFR observed in this study. Some variables had approximately linear relationships with GFR, such that their rate of decline as a function of GFR was similar at all levels of GFR. Other nutritional variables did not correlate with the GFR. For several nutritional parameters, the rate of decline as a function of GFR was greater at lower than at higher GFRs. This was especially so in men, in whom the rate of decline was significantly greater at lower GFRs for dietary protein intake (patients at-

Table 4. Correlation matrix among nutrition variables ($N = 988$)

	Protein intake/ UNA	Protein intake/ diaries	Energy intake/ diaries	Albumin	Transferrin	Total cholesterol	Body weight	Standard body weight	Body fat	Urine creatinine	Body mass index	Arm muscle area	Biceps	Triceps	Sub-scapular
Protein intake g/kg/day by UNA	1.000	+0.316[a]	+0.216[a]	+0.075	+0.087[a]	+0.109[a]	+0.185[a]	+0.290[a]	+0.121[a]	+0.382[a]	+0.275[a]	+0.214[a]	+0.128[a]	+0.102[a]	+0.180[a]
by Diaries		1.000	+0.680[a]	+0.021	+0.053	+0.034	+0.099[a]	+0.062	-0.113[a]	+0.243[a]	+0.074	+0.176[a]	-0.057	-0.088[a]	+0.060
Dietary energy intake kcal/kg/day			1.000	+0.024	+0.044	-0.005	+0.287[a]	+0.327[a]	+0.013	+0.143[a]	+0.300[a]	+0.290[a]	+0.080	+0.073	+0.192[a]
Albumin g/dL				1.000	+0.286[a]	-0.057	+0.018	-0.070	-0.076	+0.136[a]	-0.060	+0.039	-0.035	-0.071	+0.012
Transferrin mg/dL					1.000	+0.119[a]	+0.032	+0.099[a]	+0.170[a]	-0.033	+0.094[a]	+0.035	+0.125[a]	+0.112[a]	+0.155[a]
Total cholesterol mg/dL						1.000	-0.017	+0.115[a]	+0.209[a]	-0.063	+0.102[a]	+0.022	+0.141[a]	+0.152[a]	+0.138[a]
Body weight kg							1.000	+0.714[a]	+0.189[a]	-0.037	+0.812[a]	+0.770[a]	+0.241[a]	+0.127[a]	+0.533[a]
Standard body weight %								1.000	+0.597[a]	-0.309[a]	+0.941[a]	+0.522[a]	+0.576[a]	+0.525[a]	+0.665[a]
Body fat %									1.000	-0.545[a]	+0.520[a]	-0.060	+0.777[a]	+0.855[a]	+0.675[a]
Urine creatinine mg/kg/day										1.000	-0.247[a]	+0.176[a]	-0.415[a]	-0.460[a]	-0.243[a]
Body mass index kg/m²											1.000	+0.655[a]	+0.512[a]	+0.431[a]	+0.679[a]
Mid-arm muscle area cm²												1.000	+0.044	-0.183[a]	+0.335[a]
Biceps skinfold mm													1.000	+0.761[a]	+0.511[a]
Triceps skinfold mm														1.000	+0.519[a]
Subscapular skinfold mm															1.000

Entries are the Pearson correlation coefficients (r values).
[a] $P < 0.01$

tempting a restricted diet only), serum cholesterol, body weight, percentage standard weight, percentage body fat, BMI, and the sum of the three skinfolds.

This association of low GFRs with lower levels of nutritional parameters is potentially of substantial clinical importance. PEM is a common complication of patients undergoing maintenance hemodialysis or chronic peritoneal dialysis [2–8]. Measures of PEM are powerful predictors of the morbidity and mortality of maintenance dialysis patients [3–8]. This has perhaps been shown most strongly for the serum albumin concentration, but also for other parameters, including both serum chemistries and weight-for-height ratios [3–8]. Several studies indicate that PEM is very prevalent in patients commencing chronic dialysis therapy (abstract; Salusky et al, *Kidney Int* 23:159, 1983) [4, 9]. Moreover, some reports indicate that the nutritional status of patients at the commencement of maintenance dialysis therapy is a strong predictor of their nutritional status one or two years later (abstract; Salusky et al, ibid) [4, 9]. Although clinical studies have not yet tested the thesis that prevention or correction of PEM in this patient population will improve outcome, this would seem to be a likely possibility. Thus, it would seem important to prevent the decline in nutritional parameters in patients, such as those in the present study, who have mild to moderate renal failure.

In this regard, it may be relevant that these patients displayed a reduction in dietary energy and protein intake. Decreased protein and energy intakes are probably among the most common causes of PEM in nondialyzed chronic renal failure and maintenance dialysis patients [35, 36]. Nondialyzed chronic renal failure patients prescribed low-protein diets providing about 0.60 g protein/ kg/day of primarily high biological value protein and high energy intakes generally maintain neutral or positive nitrogen balance [19, 37–40]. However, without dietary training, such individuals may ingest too little total protein or high biologic value protein and/or eat too few calories [35]. It is pertinent that although in the present study there was a decline in protein intake as the GFR fell, the protein intake remained, on average, above 0.75 g/kg/day at the lowest levels of GFR (Fig. 1 A, B). This amount of protein should be sufficient to maintain nitrogen balance not only in patients with chronic renal failure, but also in almost all healthy, nonpregnant, nonlactating adults [19, 30, 37–40]. Even though 0.75 g protein/ kg/day is the mean value for the dietary protein intake, of the patients in the present study, only a small proportion of individuals were ingesting less than 0.60 g protein/ kg/day.

In contrast, the average dietary energy intake in the entire population was low, 28.5 ± 9.16 kcal/kg/day, and it was even lower in the patients with the more reduced levels of GFR (Fig. 1C). These data are consistent with the hypothesis that low energy intakes are a major con-

tributor to PEM in patients with chronic renal failure. As a corollary, maintenance of higher energy intakes in these individuals may prevent a decline in their nutritional status. Data from the present study, of course, do not prove this thesis. However, this interpretation is consistent with two short-term studies in which an increase in dietary energy intake improved parameters of protein-energy nutritional status in clinically stable nondialyzed chronic renal failure [40] and maintenance hemodialysis patients [41]. In each of these latter studies, the dietary protein intake was kept constant as the dietary energy intake was varied.

We found that the strength of the relationships of many of the nutritional parameters with GFR was markedly reduced in multiple regression analyses after controlling for protein and energy intakes, particularly when errors-in-variables regression was used to account for measurement error and longitudinal fluctuations in the dietary intakes. A notable exception to this pattern was seen in serum transferrin, which remained strongly associated with GFR after an adjustment for protein and energy intake in both men and women. After the same adjustments, serum albumin also remained significantly associated with GFR in women and with the percentage of body fat in men. The attenuation of the strength of the association of GFR with other nutritional parameters after adjustment for protein and energy intake is consistent with the hypothesis that the reductions seen in these parameters at lower GFR levels are mediated by the lower dietary intakes also seen at the lower GFR values. However, because the analyses are cross-sectional, a cause and effect relationship cannot be proved. Thus, it is also possible that low GFR is associated both with lower dietary intakes and lower values of nutritional parameters, without a direct causal link between the dietary intakes and the nutritional variables.

Because the patients in this cross-sectional study were potential entrants to a clinical trial, the distribution of patient characteristics in this patient sample can be expected to differ from that of the general population with chronic renal disease. In particular, the proportion of blacks (13%) is probably lower and the proportion of patients with polycystic kidney disease (22%) higher than in the general chronic renal disease population. However, whereas the mean levels of some nutritional parameters differed between blacks and non-blacks, none of the slopes of the relationships between the nutritional parameters and GFR differed significantly between blacks and non-blacks or between the renal diagnosis categories of polycystic kidney disease, glomerular diseases, and other renal diseases (data not shown). The adjustment of the analyses in Figures 1 to 4 and Table 3 for race controls for effects of race on the mean levels of the nutritional parameters and the results of these analyses were not substantially altered by also control-

ling for renal diagnosis (data not shown). Thus, it is unlikely that our results were substantially biased by the under-representation of blacks or the over-representation of polycystic kidney disease.

Some caution should be used in interpreting the errors-in-variables regression analyses (Table 3) because the estimates of the within-patient variances in protein and energy intake were based on the changes in these parameters over the three-month baseline period. Some patients received dietary counseling during the baseline period, and some patients may have been motivated to change their diet spontaneously because of their awareness of the MDRD Study goals; this may have increased the variability between the initial and final baseline measurements beyond the naturally occurring longitudinal variation. In this case, the regressions may have overadjusted for the effects of the variation in the protein and energy intake measurements.

It is important to interpret the results presented in this article in the context of the methods used to adjust GFR, protein intake, and energy intake for body size. The GFR was factored by BSA, in which the calculation depends primarily on actual body weight. The presence of body weight in the BSA term in the denominator of GFR may have suppressed the correlations observed between GFR and those anthropometric measurements, which are highly correlated with weight. In fact, we found that the relationships of GFR with most of the nutritional variables are substantially stronger if standard weight is used rather than actual body weight in the calculation of BSA (data not shown). Also, the relationships of protein and energy intake with the anthropometric parameters are stronger when the dietary intakes are factored by standard weight (as done here) than when the intakes are factored by actual weight.

It is of interest that within clusters of nutritional parameters, statistically significant correlations were often observed (Table 4). Thus, parameters of body mass (actual and standard body weights, BMI, AMA, percentage body fat, and skinfold thicknesses) were often correlated with each other. In contrast, none of these parameters were well correlated with the serum visceral proteins, albumin or transferrin. These findings suggest that the factors influencing these parameters of body mass may be different from the factors affecting serum albumin and transferrin. There may be several reasons why urinary creatinine excretion might not co-vary more closely with those parameters that are affected by muscle mass (that is, actual and relative body weights, BMI, AMA). First, because the urinary creatinine excretion is expressed per kg body weight per day, this should factor out the effect of body mass on urine creatinine excretion. Also, independent of the individual's muscle mass, recent intake of skeletal muscle (that is, most meats) and the level of

renal function will each affect urinary creatinine excretion [42].

Serum albumin and transferrin also did not correlate closely with each other. Since both proteins are influenced by both nutritional intake and inflammatory processes [43–45], the cause for the poor correlation is unclear. This lack of a close correlation between different parameters of protein-energy nutritional status has been described previously in studies of the nutritional status of patients with advanced renal failure who were undergoing maintenance dialysis therapy [1, 46].

It is striking that the two methods of assessing dietary protein intake, UNA and three-day dietary records, were poorly correlated with each other. This discrepancy may have several causes. First, the data for the UNA were collected during the first month of the baseline phase, whereas the dietary diaries were obtained two weeks later. Second, although both techniques are considered to be accurate when performed correctly [20, 47, 48], each method has its own sources of error [47, 49–51]. Notwithstanding, the poor correlation between these two parameters the relationships between each parameter and the GFR was usually similar (Fig. 1 and Table 2). On the other hand, there was a good correlation between the dietary protein and energy intakes, as determined from the dietary records (Table 4).

The serum creatinine levels of the patients in this study were rather low, averaging 2.4 ± 1.2 and 2.0 ± 1.1 mg/dL in the men and women, respectively. A large number of patients with these serum creatinine levels may be managed by physicians who perceive the patients to be clinically stable and not in need of nutritional intervention. Moreover, patients with this range of serum creatinine concentrations are often treated by physicians who are not nephrologists. However, the results of the present study indicate that these patients, and particularly those with a GFR of 21 mL/min/1.73 m² or lower, frequently show evidence for nutritional deterioration. Thus, if nutritional management to prevent or treat PEM is considered to be beneficial in these patients, it would be necessary to develop strategies to educate both nephrologists and nonnephrologist physicians with regard to the rationale and methods for the nutritional management of these patients.

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