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Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study

MODIFICATION OF DIET IN RENAL DISEASE STUDY GROUP, prepared by JOEL D. KOPPLE, ANDREW S. LEVEY, TOM GREENE, W. CAMERON CHUMLEA, JENNIFER J. GASSMAN, DONNA L. HOLLINGER, BRADLEY J. MARONI, DONNA MERRILL, LAURA K. SCHERCH, GERALD SCHULMAN, SHIN-RU WANG, and GAIL S. ZIMMER

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Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. The safety of dietary protein and phosphorous restriction was evaluated in the Modification of Diet in Renal Disease (MDRD) Study. In Study A, 585 patients with a glomerular filtration rate (GFR) of 25 to 55 ml/min/1.73 m^2 were randomly assigned to a usual-protein diet (1.3 g/kg/day) or a low-protein diet (0.58 g/kg/day). In Study B, 255 patients with a GFR of 13 to 24 ml/min/1.73 m^2 were randomly assigned to the low-protein diet or a very-low-protein diet (0.28 g/kg/day), supplemented with a ketoacid-amino acid mixture (0.28 g/kg/day). The low-protein and very-low-protein diets were also low in phosphorus. Mean duration of follow-up was 2.2 years in both studies. Protein and energy intakes were lower in the low-protein and very-low-protein diet groups than in the usual-protein group. Two patients in Study B reached a "stop point" for malnutrition. There was no difference between randomized groups in the rates of death, first hospitalizations, or other "stop points" in either study. Mean values for various indices of nutritional status remained within the normal range during follow-up in each diet group. However, there were small but significant changes from baseline in some nutritional indices, and differences between the randomized groups in some of these changes. In the low-protein and very-low-protein diet groups, serum albumin rose, while serum transferrin, body wt, percent body fat, arm muscle area and urine creatinine excretion declined. Combining patients in both diet groups in each study, a lower achieved protein intake (from food and supplement) was not correlated with a higher rate of death, hospitalization or stop points, or with a progressive decline in any of the indices of nutritional status after controlling for baseline nutritional status and follow-up energy intake. These analyses suggest that the low-protein and very-low-protein diets used in the MDRD Study are safe for periods of two to three years. Nonetheless, both protein and energy intake declined and there were small but significant declines in various indices of nutritional status. These declines are of concern because of the adverse effect of protein caloric malnutrition in patients with end-stage renal disease. Physicians who prescribe low-protein diets must carefully monitor patients' protein and energy intake and nutritional status.

Dietary protein restriction has long been advocated to ameliorate the symptoms of renal failure and to slow the progression of chronic renal disease. However, the safety of low-protein diets and their long-term effects on nutritional status have not been adequately evaluated. This evaluation is especially important because of the well-recognized adverse effects of malnutrition in patients beginning dialysis for end-stage renal disease.

The Modification of Diet in Renal Disease (MDRD) Study was the largest clinical trial to examine whether the prescription of low protein and low phosphorus diets would retard the rate of progression of renal disease and whether such therapy was safe for long term use [1]. During the course of the study, patients with moderate to advanced renal disease from various causes were randomly assigned and trained to follow specific diets, and their renal function, dietary intake and nutritional status were monitored periodically. The primary and secondary analyses of the efficacy of dietary protein restriction have been reported elsewhere [1–3], as have two meta-analyses [4, 5]. Although not definitive, these analyses provide some support for the hypothesis that protein restriction slows the progression of renal disease.

This manuscript examines the effects of both prescribed and achieved protein intake on nutritional status during the course of the MDRD Study. Specifically, we compared the randomized groups for various outcomes related to nutritional status. In addition, we correlated the achieved dietary protein intake with these parameters. These results demonstrate the safety of dietary protein restriction over two to three years in patients with moderate to advanced renal disease.

METHODS

The MDRD Study was a multicenter, randomized clinical trial of the effects of restriction of dietary protein and phosphorus and strict blood pressure control on the progression of chronic renal disease of various causes. The design, recruitment and baseline characteristics of the patients, effects of the diet and blood pressure interventions, and dietary adherence have been described previously [1, 6–12].

Study design

The study was approved by the review boards at all participating institutions, and informed consent was obtained from all patients.

Baseline period. Patients were eligible to enter the baseline period if they were 18 to 70 years of age, had chronic renal disease

Key words: dietary protein, MDRD Study, chronic renal failure, malnutrition, anthropometry, serum albumin.

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with a serum creatinine of 1.4 to 7.0 mg/dl (men) or 1.2 to 7.0 mg/dl (women). Patients with diabetes mellitus requiring insulin or a previous renal transplant were excluded. A total of 2507 patients were screened, and 1785 individuals entered the baseline period for assessment of glomerular filtration rate (GFR), dietary intake, nutritional status and blood pressure. Patients with a GFR $\geq$ 25 ml/min/1.73 m^2 were assigned a dietary protein intake > 1.0 g/kg/day. Patients with a GFR $\leq$ 24 ml/min/1.73 m^2 were assigned a dietary protein intake $\geq$ 0.6 g/kg/day. All patients were required to satisfy the following criteria regarding their nutritional status in order to be eligible for randomization: relative body wt 80% to 160%, defined as body wt/standard body wt $\times$100%, as determined from the National Health and Nutrition Evaluation Survey (NHANES) I and II data [13]; serum albumin of 3.0 g/dl or greater; and urine protein less than 10 g/day. After three months, GFR, protein intake and blood pressure were re-assessed. A total of 585 patients with a GFR of 25 to 55 ml/min/1.73 m^2 and protein intake $\geq$ 0.9 g/kg/day entered Study A, and 255 patients with a GFR of 13 to 24 ml/min/1.73 m^2 entered Study B.

Follow-up period. Patients in Study A were randomly assigned to a usual (1.3 g/kg/day) or a low protein diet (0.58 g/kg/day). Patients in Study B were randomly assigned to the same low protein diet as in Study A or a very low protein diet (0.28 g/kg/day) supplemented with a mixture of ketoacids and amino acids (0.28 g/kg/day). The mean duration of the follow-up period was 2.2 years (range, 0 to 44 months). The nutrition intervention program, "Protein Wise," was designed by the clinical center dietitians with the Nutrition Coordinating Center (NCC) at the University of Pittsburgh and has been described in detail previously [14]. The program was based primarily on behavioral principles and techniques and was similar across all diet groups, although the content was tailored to support the specific goals of each diet group. The major goal was to support long-term adherence by developing self-management skills (the ability to select foods and prepare meals which meet study goals) and increase feelings of self-efficacy. The NCC trained the dietitians, developed the intervention materials and *Manual of Operations* (available upon request from the NCC), coordinated daily phone contact to individual clinical center dietitians and conference calls which focussed on identifying and solving adherence problems for individual patients. The NCC also supplied the clinical centers with a wide variety of special food products, including low-protein foods and high-calorie, low-protein supplements. Protein intake was assessed monthly from urine urea nitrogen (UUN) excretion. Nutritional status was assessed from measurements of serum levels of albumin and transferrin, body weight, percent body fat (computed from the thickness of biceps, triceps and subscapular skinfolds), arm muscle area, and urine creatinine. Safety of the diet interventions was assessed by examining the frequency of action items and stop points, hospitalizations and deaths. Details of the dietary intervention, methods for follow-up measurements, and definitions of action items and stop points are reported in the **Appendix** and elsewhere [13–22].

Statistical methods

Hypothesis tests were regarded as statistically significant if $P \leq 0.05$ (two sided). No adjustment was made for multiple comparisons.

Comparisons of randomized groups. Within each diet group in Study A and Study B during the baseline and follow-up periods, the values for nutritional intake, anthropometry and biochemical indices of nutritional status, with few exceptions, were not different between patients randomized to the usual and low blood pressure goals. Consequently, comparisons of the diet groups are presented for all patients regardless of blood pressure assignment. Because normal values for nutritional status variables differ between men and women [6], results are shown for each gender. Changes in nutritional status parameters during follow-up were expressed as the change from the final baseline measurement (B2 or B3). To account for different lengths of follow-up, plots of the pattern of change are based on a statistical model in which the estimated mean change to later follow-up times takes into account early measurements from patients with shorter follow-up [23]. As shown in these plots, some variables changed gradually after randomization, but others changed abruptly within the first four months and gradually thereafter. Therefore, we computed the mean follow-up value for each nutritional status variable in an individual as the mean of all values from the fourth month (F4) until the end of the follow-up period. Similarly, we defined mean follow-up protein intake in an individual as the average of all measurements of protein intake beginning with the F4 visit. In Study A, the median number of monthly UUN measurements used in calculating mean follow-up protein intake was 21, with at least six measurements available for 552 of 585 (94%) patients. In Study B, the median number was 20, with at least six measurements available for 230 of 255 (90%) patients. Baseline and follow-up characteristics and changes during follow-up were compared between the diet groups using *t*-tests, analysis of variance, or chi-square tests, as appropriate. The effect of the diet interventions on urine creatinine was also analyzed using a two-slope model with a breakpoint at F4, in which the decline in urine creatinine in each patient was assumed to have one slope from B3 to F4 and possibly a different slope from F4 to the end of follow-up [1].

Correlation of safety measures and nutritional status with protein intake. For correlational analyses, we combined patients in both diet groups in each study (Study A and Study B) and related safety measures and nutritional status to achieved mean follow-up protein intake estimated from UUN. To maximize the number of patients included in these analyses, mean follow-up protein intake for an individual was computed beginning with the second follow-up visit (F2).

For descriptive purposes, measures of safety (rates of death, hospitalization and reaching a stop point) are presented for subgroups of patients defined by quartiles of mean follow-up protein intake. Only the first hospitalization was used in the analyses to avoid giving too much weight to patients with multiple hospitalizations. For statistical tests, time-dependent Cox regression analyses [24] were used to relate each safety measure to the mean follow-up protein intake (only including measurements prior to the occurrence of the outcomes).

The average rates of change in nutritional status variables beginning with the F4 visit were estimated for each patient by regressing the nutritional status measurements beginning with F4 against time. Regression coefficients and Pearson correlation coefficients were computed for the relationships between the rates of changes in these variables and mean follow-up protein intake.

Table 1. Characteristics at the end of baseline for the randomized patients by study and diet group

	Study A		Study B	
	Usual protein diet	Low protein diet	Low protein diet	Very low protein diet
Number of men/women	186/108	171/120	78/51	73/53
Age *years*	52.5 ± 12.2	51.8 ± 12.1	51.1 ± 12.8	50.5 ± 12.9
GFR *ml/min/1.73 m²*	37.9 ± 8.78	39.3 ± 8.97	18.7 ± 3.21	18.3 ± 3.55
Urine urea nitrogen *g/day*	10.8 ± 2.46	10.5 ± 2.67	7.52 ± 2.17	7.63 ± 2.41
Serum urea nitrogen *mg/dl*	32.3 ± 9.34	31.3 ± 10.3	46.0 ± 12.7	46.3 ± 12.5
Serum creatinine *mg/dl*	1.98 ± 0.52	1.89 ± 0.52	3.46 ± 0.85	3.39 ± 0.91
Hematocrit %	40.1 ± 4.85	39.5 ± 4.59	35.8 ± 5.06	36.1 ± 5.14

Data are given as mean ± standard deviation. Study A, GFR 25 to 55 ml/min/1.73 m²; Study B, GFR 13 to 24 ml/min/173 m².

These analyses included only patients with ≥ one year of follow-up (553 patients in Study A and 219 patients in Study B). Because these were correlational analyses and were not based on a direct comparison of randomly assigned groups, these analyses were repeated after controlling for possible confounding variables related to nutritional status. Covariates in the analysis included mean follow-up energy intake and the following baseline variables: age, gender, body wt, desire to lose weight, percent body fat, serum concentrations of albumin, transferrin and total cholesterol, and urine creatinine excretion per kg body wt. For these analyses, the Pearson partial correlation coefficient is reported.

RESULTS

Comparisons of randomized groups

Baseline characteristics. The most common causes of renal disease were polycystic kidney disease (25% of all patients) and glomerular diseases (24%). Patients' gender, age, and selected measures of renal function are shown in Table 1. By definition, patients in Study B had more advanced renal disease than in Study A, but within each study, the forgoing characteristics were similar between diet groups.

Mean baseline protein and energy intakes and biochemical and anthropometric parameters are shown in Table 2. The nutrient intake calculated from the dietary diaries and interviews and from urine urea excretion are reported in more detail elsewhere [11, 12]. In comparison with patients in Study A, both men and women in Study B had significantly lower mean values for the following parameters: protein and energy intake, serum transferrin, body wt, percent body fat, arm muscle area and urine creatinine excretion. Mean serum albumin concentrations did not differ between Studies A and B. Within each study, however, there were few differences between the two diet groups for either men or women. In Study A men, body wt was slightly lower in the low-protein diet group as compared to the usual-protein diet group. In Study B women, arm muscle area was lower in the very-low-protein diet group as compared to the low-protein diet group.

Follow-up characteristics. Table 3 shows the mean follow-up values of the nutritional status variables. As reported elsewhere [1–3, 11], there were large significant differences in dietary protein intake (from food only) between the usual and the low-protein diet groups in Study A and between the low and the very-low-protein diet groups in Study B. In addition, there was a small, but significant difference in total protein intake (from food and amino acids in the supplement) between the low-protein and the very-low-protein diet groups in Study B. In all diet groups, men and women had similar protein intake (and total protein intake) per kg body wt during follow-up.

Also as reported elsewhere [11], there was a significant difference in energy intake during the follow-up between the usual and low-protein diet groups in Study A, but not between the low-protein and very-low-protein diet groups in Study B (Table 3). In all diet groups, women had lower energy intake per kg body wt than men in all diet groups.

Biochemical and anthropometric indices of nutritional status during follow-up were generally well within normal limits in all four diet groups. Thus, mean serum albumin and transferrin levels were normal. Relative body wt averaged above 100% in each group, and the arm muscle area and percent body fat were also within normal ranges. However, many of these variables differed significantly between the diet groups in both Study A and Study B. The men in the low-protein diet group in Study A had lower mean serum transferrin, body wt, relative body wt, percent body fat, arm muscle area and urine creatinine excretion compared to men in the usual-protein diet group. Similarly, women in the low-protein diet group in Study A had lower serum transferrin and urine creatinine excretion compared to women in the usual-protein diet group. Both men and women in the very-low-protein diet group in Study B had lower urine creatinine excretion than patients in the low-protein diet group.

Changes from baseline to follow-up. Figures 1 to 6 show changes in biochemical and anthropometric indices of nutritional status during baseline and follow-up. The data for men and women in each diet group are combined in these Figures because the direction of the changes did not differ by gender.

In Study A, these variables did not change significantly from baseline to follow-up in the usual-protein diet group. However, in the low-protein diet group, serum albumin rose significantly, while serum transferrin, body wt, relative body wt, arm muscle area and urine creatinine excretion declined significantly. The decline in serum transferrin, body wt, arm muscle area and urine creatinine was significantly greater in the low-protein diet group compared with the usual-protein diet group.

In Study B, the low-protein diet group had a significant rise in serum albumin, but significant declines in serum transferrin, body wt, percent body fat, arm muscle area and urine creatinine excretion. Similar findings were observed in patients in the very-low-protein diet group, except for percent body fat. The only significant differences between the diet groups were that percent body fat declined more in the low-protein diet group and urine creatinine excretion declined more in the very-low-protein diet group.

Importantly, with the exception of the decrease in urine creatinine excretion, the above described changes in nutritional status from baseline to follow-up were usually of minor absolute magnitude. The temporal pattern of changes in these variables is also of interest. The decline in serum transferrin and weight in the low-protein and very-low-protein diet groups occurred abruptly after randomization and appeared to stabilize after about the

Table 2. Parameters of nutritional status at the end of baseline by gender, study and diet group[a]

	Study A		Study B	
	Usual protein diet	Low protein diet	Low protein diet	Very low protein diet
Men				
Number of subjects	163–186	143–171	69–78	71–73
Protein intake from UUN *g/kg/day*	1.12 ± 0.18	1.12 ± 0.19	0.84 ± 0.20	0.87 ± 0.18
Energy intake *kcal/kg/day*	27.6 ± 7.01	27.6 ± 7.27	25.3 ± 7.04	25.9 ± 7.48
Albumin *g/dl*	4.05 ± 0.35	4.04 ± 0.36	4.05 ± 0.36	4.08 ± 0.33
Transferrin *mg/dl*	272 ± 44.5	270 ± 40.1	257 ± 40.4	266 ± 48.3
Body weight *kg*	89.0 ± 14.9	85.4 ± 13.5[b]	80.8 ± 11.5	81.9 ± 11.16
Relative body weight %	113 ± 14.9	110 ± 13.5	104 ± 11.7	106 ± 12.5
Biceps skinfold *mm*	7.74 ± 4.55	6.90 ± 3.71	5.88 ± 2.85	6.01 ± 2.69
Triceps skinfold *mm*	14.9 ± 6.39	13.7 ± 6.05	13.1 ± 5.97	12.8 ± 5.09
Subscapular skinfold *mm*	20.7 ± 7.08	19.4 ± 6.65	17.1 ± 5.63	16.5 ± 5.04
Percent body fat %	28.3 ± 5.87	27.0 ± 6.51	25.9 ± 5.46	25.3 ± 5.20
Arm muscle area cm^2	48.6 ± 13.7	46.8 ± 11.9	41.5 ± 9.64	43.2 ± 11.2
Urine creatinine *mg/day*	1743 ± 325	1700 ± 320	1421 ± 318	1465 ± 367
Women				
Number of subjects	93–108	107–120	48–51	43–53
Protein intake from UUN *g/kg/day*	1.13 ± 0.17	1.12 ± 0.22	0.89 ± 0.15	0.87 ± 0.21
Energy intake *kcal/kg/day*	26.4 ± 6.64	26.9 ± 7.40	24.1 ± 5.83	23.3 ± 5.81
Albumin *g/dl*	4.01 ± 0.33	3.97 ± 0.32	3.86 ± 0.36	3.91 ± 0.37
Transferrin *mg/dl*	288 ± 47.8	288 ± 49.1	270 ± 41.2	266 ± 46.3
Body weight *kg*	71.8 ± 15.0	70.5 ± 14.3	67.6 ± 12.4	66.1 ± 15.7
Relative body weight %	114 ± 18.2	113 ± 17.1	109 ± 15.8	108 ± 22.1
Biceps skinfold *mm*	11.9 ± 5.77	11.6 ± 6.34	9.47 ± 4.81	10.5 ± 7.42
Triceps skinfold *mm*	23.0 ± 7.01	22.5 ± 7.05	20.4 ± 6.67	19.4 ± 7.56
Subscapular skinfold *mm*	19.7 ± 7.61	19.5 ± 7.57	18.2 ± 7.89	16.1 ± 8.00
Percent body fat %	35.8 ± 5.64	35.0 ± 5.94	33.2 ± 6.53	32.0 ± 6.84
Arm muscle area cm^2	30.0 ± 13.7	29.1 ± 11.7	29.3 ± 10.6	23.6 ± 10.4[c]
Urine creatinine *mg/day*	1153 ± 271	1120 ± 218	1021 ± 181	980 ± 202

[a] Data are given as mean ± standard deviation. Study A, GFR 25 to 55 ml/min/1.73 m^2; Study B, GFR 13 to 24 ml/min/173 m^2
[b] $P \leq 0.05$ between diet groups
[c] $P \leq 0.01$ between diet groups

fourth month of follow-up. Changes in other parameters occurred more gradually.

Urine creatinine excretion declined approximately 15% to 20% from baseline. Inspection of Figure 6 reveals an abrupt decline in some diet groups during the first four months (B3 to F4), and a gradual decline thereafter in all four diet groups. Therefore, we performed additional analyses comparing the decline in urine creatinine between randomized groups both during and after the first four months. In Study A, the decline was significantly faster in the low-protein diet group as compared to the usual-protein diet group both during ($P < 0.001$) and after ($P = 0.013$) the first four months of follow-up. In Study B, the decline in the very-low protein diet group as compared to the low-protein diet group was significantly faster during the first four months of follow-up ($P < 0.001$), but significantly slower thereafter ($P < 0.001$).

Safety measures. The rate of deaths, hospitalizations and stop points during follow-up are shown in Table 4. In both studies, the rates of such events were low, and there were no significant differences between diet groups in either study.

Only deaths that occurred prior to reaching a stop point are shown in Table 4. In Study A, there were two deaths in the low-protein diet group, both due to cardiovascular disease, compared to nine deaths in the usual-protein diet group, five due to cardiovascular disease, two to cancer, one to respiratory disease, and one to trauma. Four other patients died after reaching a stop point, three patients in the low-protein diet group (cardiovascular disease in two patients and cancer in one patient) and one patient in the usual-protein diet group (renal failure). After extensive review, the External Monitoring Committee concluded that neither the higher number of deaths in the usual protein diet group, nor the causes of death, was related to the Study diets.

In Study B, there were four deaths in the very-low-protein diet group and two deaths in the low-protein diet group. Causes of death in the very-low-protein diet group were cardiovascular disease in two patients and trauma in two patients, and cardiovascular disease in both patients in the low-protein diet group. In addition, 10 patients died after reaching a stop point. These included six patients in the very-low-protein diet group (two patients each with cardiovascular disease, cancer, or infection) and four patients in the low-protein diet group (three patients with cardiovascular disease and one patient with cerebrovascular disease).

In Study A, 84 patients reached a stop point (14%), mostly due to rapidly declining GFR (60 patients, 10%) or renal failure (12 patients, 2%). No patients in Study A reached a stop point due to malnutrition. Twelve patients (2%) reached stop points due to serious medical conditions. These included six patients in the low-protein diet group (one patient who became pregnant, two patients who developed a stroke, and one patient each who developed acute renal failure, diabetes requiring insulin, or cancer), and six patients in the usual-protein diet group (three patients who developed diabetes requiring insulin and one patient

Table 3. Parameters of nutritional status during follow-up by gender, study and diet group[a]

	Study A		Study B	
	Usual protein diet	Low protein diet	Low protein diet	Very low protein diet
Men				
Number of subjects[b]	179–183	165–170	74–77	69–71
Protein intake from UUN *g/kg/day*[c]	1.11 ± 0.14	0.77 ± 0.13[g]	0.72 ± 0.11	0.48 ± 0.11[g]
Total protein intake from UUN *g/kg/day*[d]	1.11 ± 0.14	0.77 ± 0.13[g]	0.72 ± 0.11	0.66 ± 0.11[g]
Energy intake *kcal/kg/day*	26.7 ± 5.44	23.1 ± 5.72[g]	22.5 ± 4.83	22.7 ± 4.92
Albumin *g/dl*	4.09 ± 0.34	4.12 ± 0.31	4.14 ± 0.32	4.11 ± 0.35
Transferrin *mg/dl*	271 ± 42.3	258 ± 35.0[g]	250 ± 36.6	258 ± 44.1
Body weight *kg*	88.5 ± 14.6	83.2 ± 12.8[g]	79.6 ± 11.5	79.3 ± 10.9
Relative body weight %	112 ± 14.4	107 ± 12.9[g]	102 ± 11.9	103 ± 11.2
Biceps skinfold *mm*	7.65 ± 3.67	6.49 ± 3.11[g]	5.96 ± 3.60	6.33 ± 3.03
Triceps skinfold *mm*	14.9 ± 6.26	13.4 ± 5.44[e]	12.6 ± 5.87	12.7 ± 4.77
Subscapular skinfold *mm*	21.2 ± 7.38	19.0 ± 6.37[f]	16.8 ± 6.01	16.6 ± 4.93
Percent body fat %	28.6 ± 6.04	27.1 ± 5.89[e]	25.7 ± 5.73	25.9 ± 5.16
Arm muscle area cm^2	48.3 ± 12.4	45.2 ± 11.5[e]	40.2 ± 9.64	39.7 ± 8.59
Urine creatinine *mg/day*	16.98 ± 316	1470 ± 261[g]	1307 ± 261	1185 ± 244[f]
Women				
Number of subjects[b]	98–105	107–115	49–51	49–52
Protein intake from UUN *g/kg/day*[c]	1.09 ± 0.14	0.76 ± 0.11[g]	0.73 ± 0.09	0.47 ± 0.11[g]
Total protein intake from UUN *g/kg/day*[d]	1.09 ± 0.14	0.76 ± 0.11[g]	0.73 ± 0.09	0.65 ± 0.11[g]
Energy intake *kcal/kg/day*	24.7 ± 5.31	21.9 ± 6.26[g]	20.6 ± 3.78	21.1 ± 4.74
Albumin *g/dl*	4.02 ± 0.25	4.02 ± 0.26	4.03 ± 0.35	4.01 ± 0.34
Transferrin *mg/dl*	288 ± 45.6	262 ± 39.3[g]	253 ± 34.9	252 ± 42.9
Body weight *kg*	72.2 ± 14.9	69.3 ± 13.7	65.9 ± 11.9	65.0 ± 14.3
Relative body weight %	114 ± 18.1	111 ± 16.7	106 ± 14.4	106 ± 20.2
Biceps skinfold *mm*	13.1 ± 6.15	11.8 ± 6.42	9.43 ± 5.58	9.88 ± 5.65
Triceps skinfold *mm*	23.7 ± 7.32	22.2 ± 6.70	19.3 ± 5.87	19.9 ± 7.74
Subscapular skinfold *mm*	20.5 ± 7.74	19.3 ± 6.66	16.8 ± 6.53	16.5 ± 7.07
Percent body fat %	36.7 ± 6.02	35.4 ± 5.69	32.6 ± 6.22	33.0 ± 6.24
Arm muscle area cm^2	30.7 ± 13.7	28.9 ± 11.9	29.8 ± 10.9	27.0 ± 14.3
Urine creatinine *mg/day*	1108 ± 231	970 ± 173[g]	912 ± 153	789 ± 165[g]

[a] Data are given as mean ± standard deviation; Study A, GFR 25–55 ml/min/1.73 m^2; Study B, GFR 13–24 ml/min/173 m^2

[b] Analyses are restricted to data obtained after the first four months of follow-up (F4); mean follow-up of patients included in the analysis was 2.5 years in Study A and 2.2 years in Study B

[c] Protein intake from food only (all diet groups)

[d] Total protein intake from food and amino acids in the ketoacid-amino acid supplement (very-low-protein diet group only)

[e] $P \leq 0.05$ between diet groups

[f] $P \leq 0.01$ between diet groups

[g] $P \leq 0.001$ between diet group

each with cardiomyopathy, cancer, or severe liver disease). In Study B, 103 patients (40%) reached stop points, including 94 patients (37%) due to renal failure. Two patients (0.8%, one from each diet group) reached a stop point because of malnutrition related to weight loss. Seven patients (2.7%) reached stop points due to serious medical conditions. These included four patients in the very-low-protein diet group (one patient who became pregnant and one patient each who developed diabetes requiring insulin, severe arthritis, or cancer) and three patients in the low-protein diet group (one each with cancer, emphysema, or ischemic bowel disease).

A large number of patients reached action items requiring dietary modification. In Study A, significantly more patients in the low-protein diet group than in the usual-protein diet group reached action items for weight loss (29% vs. 18%), declining serum transferrin (9.3% vs. 4.1%) and low serum magnesium (16% vs. 7.5%). Fewer patients in the low-protein diet than in the usual-protein diet group reached action items for weight gain (25% vs. 40%), high serum phosphorus (12% vs. 26%), high serum potassium (10% vs. 17%), and low serum bicarbonate (7.2% vs. 20%). There were no significant differences between the number of patients in the low-protein and usual-protein diet groups reaching action items for declining serum albumin (8% vs. 11%) or low serum albumin (3% vs. 3%). In Study B, fewer patients in the very-low-protein diet group than in the low-protein diet group had action items for high serum LDL cholesterol (31% vs. 48%). There were no significant differences between the very-low-protein and low-protein diet groups in the number of patients reaching action items for weight loss (40% vs. 30%), declining serum albumin (10% vs. 5%), low serum albumin (3% vs. 2%) or declining serum transferrin (10% vs. 12%).

Correlations of safety measures and nutritional status with achieved protein intake

For these analyses, patients in both diet groups were combined in each study. Safety measures and nutritional status variables were correlated with follow-up achieved protein intake in Study A and with achieved total protein intake in Study B.

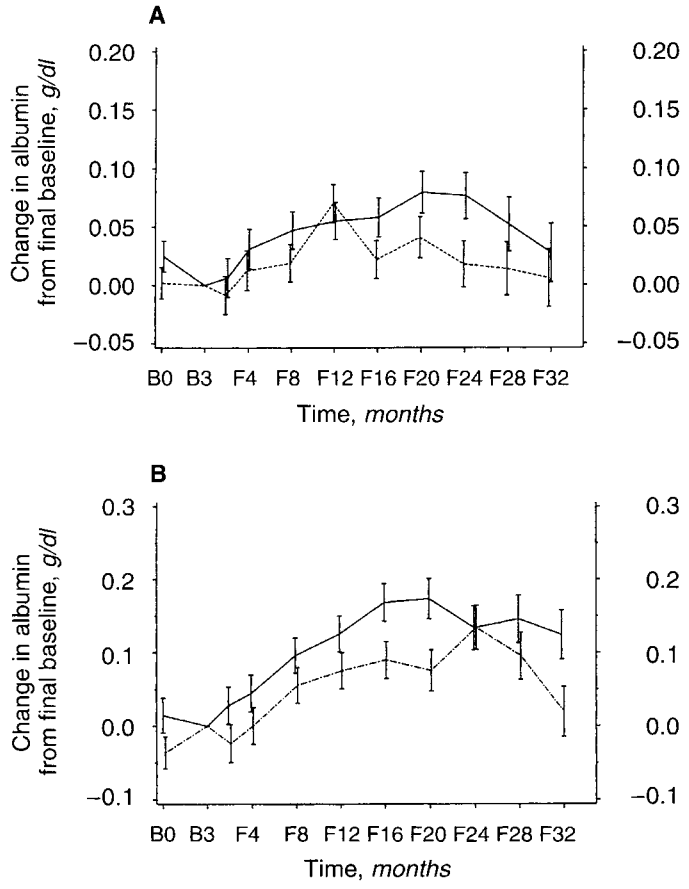

Fig. 1. Estimated mean changes in serum albumin concentrations (g/dl) during follow-up. In this and subsequent figures, the values shown are calculated as the mean of the differences between the data at the end of baseline (the second or third visit, B2 or B3) and values during follow-up visits (F) for each individual patient. Data from men and women are combined. Lines indicate the mean change from baseline at each time point. Brackets indicate ± 1 standard error. Statistical tests compare mean changes from baseline to the mean value during follow-up (beginning at F4) in each diet group and between diet groups (see text). (*A*) In Study A, serum albumin increased from baseline in the low-protein diet group ($P < 0.001$, dashed lines), but not in the usual-protein diet group (solid line). However, the change in serum albumin was not significantly different between the diet groups. (*B*) In Study B, serum albumin increased from baseline in both the very-low-protein (dashed lines) and low-protein (solid line) diet groups ($P < 0.001$), but the change was not significantly different between diet groups.

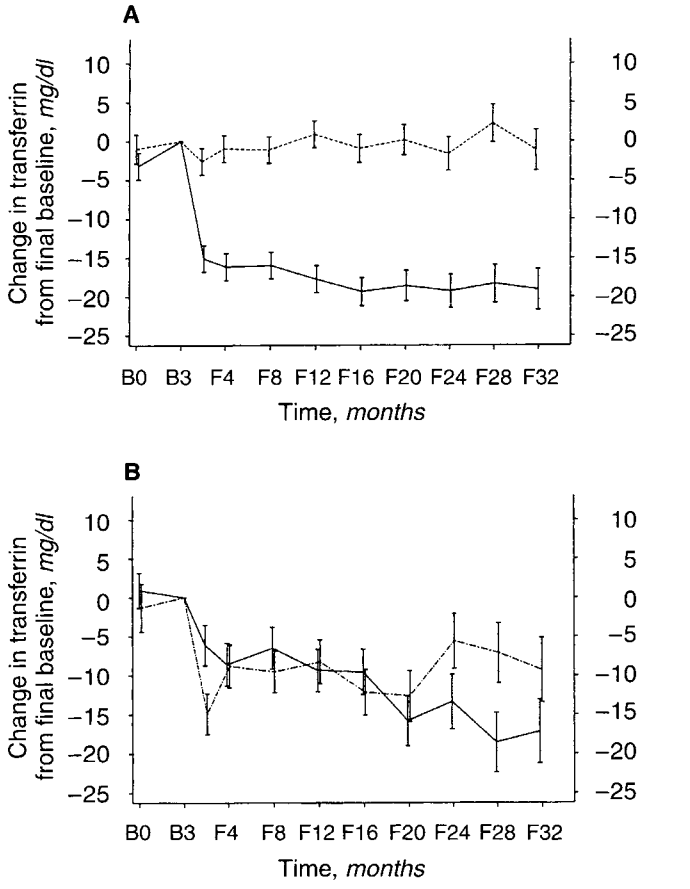

Fig. 2. Estimated mean changes in serum transferrin levels (mg/dl) during follow-up. (*A*) In Study A, serum transferrin declined from baseline in the low-protein (solid line) diet group ($P < 0.001$), but not in the usual-protein diet group (dashed lines). The change in serum transferrin was greater ($P < 0.001$) in the low-protein diet group. (*B*) In Study B, serum transferrin declined from baseline ($P < 0.001$) in both the very-low-protein (dashed lines) and the low-protein diet groups (solid line), but the change was not significantly different between diet groups.

Safety measures. Patients in each study were grouped into quartiles according to achieved protein intake, and the rates of death, hospitalizations and stop points were compared among quartiles (Table 5). Mean follow-up protein intake was not associated with these outcomes in either Study A or Study B.

Changes in nutritional status variables from the fourth month to the end of follow-up. As discussed earlier, some anthropometric and biochemical indices of nutritional status changed gradually during follow-up, while others showed abrupt changes within the first four months and only gradual changes thereafter. To determine whether these gradual changes were associated with protein intake, we related mean follow-up protein intake with changes in these variables from the fourth month to the end of follow-up.

Table 6 shows the results of the univariate and multivariate analyses. After controlling for a number of baseline factors and for follow-up energy intake, the correlations and regression coefficients (data not shown) were all weak and non-significant. This indicates that changes in nutritional status variables from four months to the end of follow-up were not associated with the mean level of protein intake during follow-up. Additional analyses (data not shown) revealed a significant univariate correlation between the rates of decline in urine creatinine and GFR after the fourth month of follow-up in Study B ($r = 0.30$, $P < 0.001$), but not in Study A ($r = -0.002$, $P = 0.97$).

DISCUSSION

Protein-calorie malnutrition is a well described important risk factor for morbidity and mortality in maintenance hemodialysis and peritoneal dialysis patients [25–28]. Many studies have demonstrated a high prevalence of protein-calorie malnutrition in dialysis patients [29–33]. Moreover, the prevalence of protein-calorie malnutrition in patients beginning dialysis treatment is similar to that of patients who have undergone maintenance dialysis for months or years [25, 30–32]. This suggests that

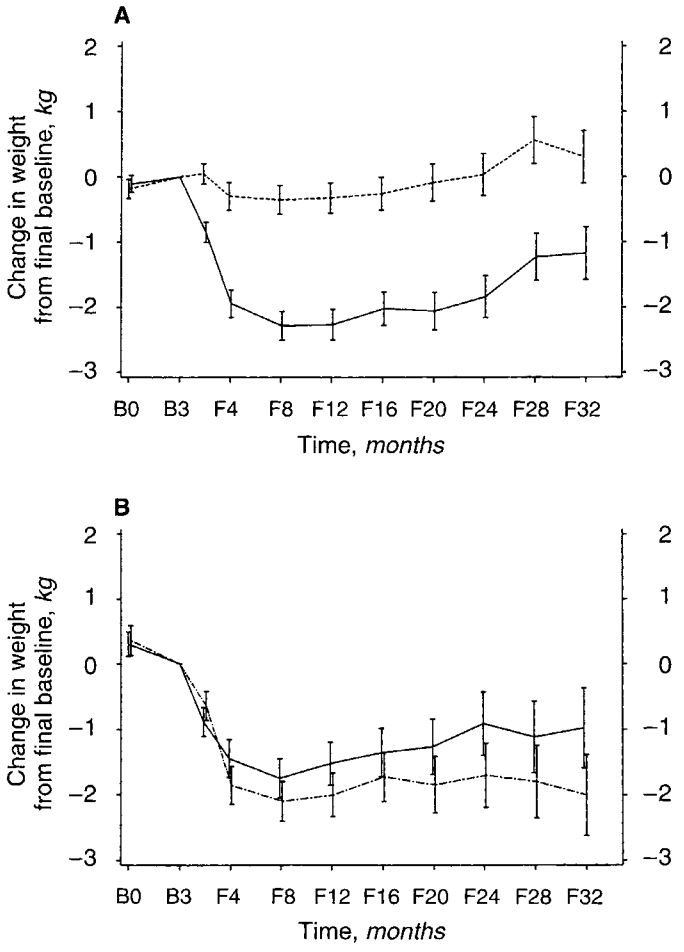

Fig. 3. Estimated mean changes in body weight (kg) during follow-up. (*A*) In Study A, weight declined from baseline in the low-protein diet group (solid line; *P* 0.001), but not in the usual-protein diet group (dashed line). The change in weight was greater (*P* 0.001) in the low-protein diet group. (*B*) In Study B, weight declined from baseline in both the very-low-protein (dashed lines) and low-protein (solid line) diet groups, but the change was not significantly different between diet groups.

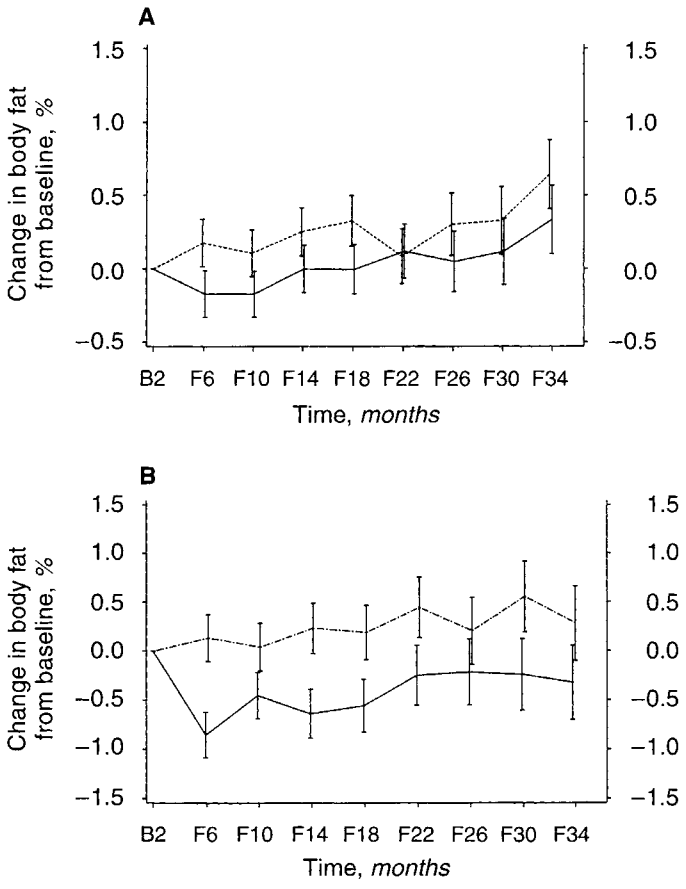

Fig. 4. Estimated mean changes in percent body fat (%) during follow-up. (*A*) In Study A, the percent of body fat did not change significantly from baseline in either diet group (dashed line, usual-protein; solid line, low-protein) and the change was not significantly different between diet groups. (*B*) In Study B, the percent of body fat declined from baseline in the low-protein group (solid line; $P = 0.008$) but not in the very-low-protein group (dashed lines). The decline was significantly greater in the low-protein diet group ($P = 0.02$).

protein-calorie malnutrition in chronic renal disease often becomes established before the onset of renal failure. Thus, it is essential that clinical recommendations for the use of low protein diets to slow the progression of chronic renal disease be accompanied by demonstration of their safety.

The MDRD Study was the largest clinical trial thus far to examine the safety of dietary protein restriction. In Study A, prescribed and mean achieved protein intake were 1.3 and 1.11 g/kg/day, respectively, in the usual-protein diet group, and 0.58 and 0.77 g/kg/day, respectively, in the low-protein diet group [3]. In Study B, prescribed and mean achieved protein intake (from food and supplement) were 0.58 and 0.73 g/kg/day, respectively, in the low-protein diet group, and 0.56 and 0.66 g/kg/day, respectively, in the very-low-protein diet group [2]. Prescribed energy intake was similar in all diet groups, requiring deliberate efforts to avoid weight loss concomitant with protein restriction. The results presented here indicate that nutritional status was in general well maintained in each diet group in both studies for periods of two to three years (Table 3). Serum albumin and transferrin values remained within normal limits. The relative body wts averaged above 100% (that is, the mean body wts remained above the median weights of normal Americans of the same age, gender, height and frame size). Body fat and arm muscle area during the course of study also were not low [13]. Only two patients, both in Study B, reached a stop point for malnutrition. In correlational analyses, there was no apparent association between lower protein intakes and higher rates of death, hospitalization, or other stop points.

On the other hand, there were changes over time and differences between the randomized groups in the mean values of many nutritional indices (Figs. 1 to 6). This suggests that the nutritional status of some patients in the low-protein and very-low-protein diet groups may have deteriorated, even though the mean values did not become abnormal during the course of the study. However, with the exception of urine creatinine, the mean change in these variables was small, and the follow-up values remained relatively stable at the lower levels. In Study A, there were significant declines from baseline to follow-up in serum transferrin, body wt, arm muscle area and urine creatinine in the

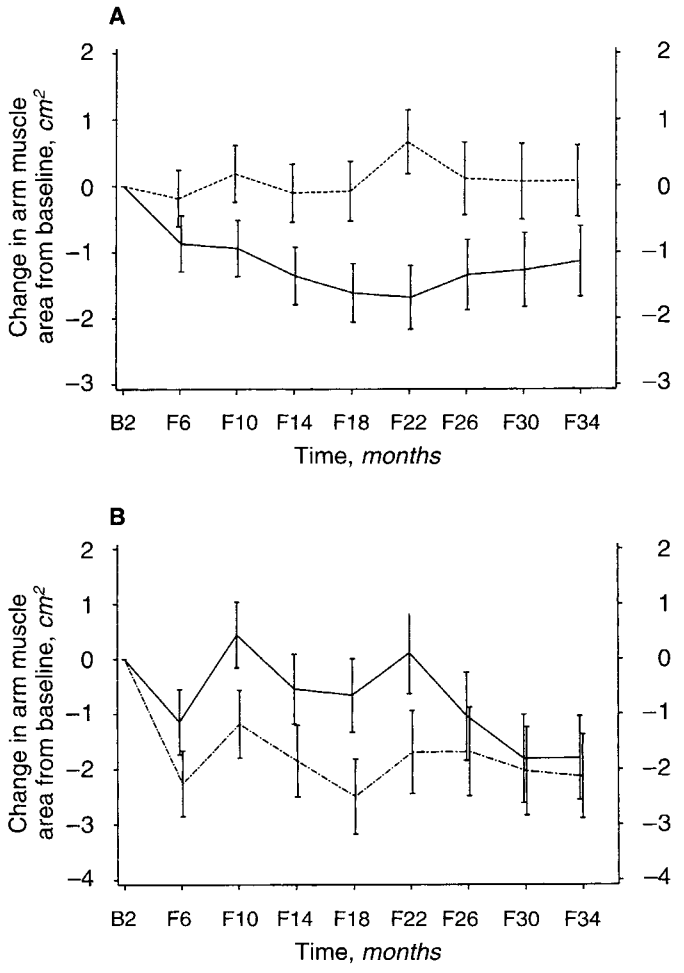

Fig. 5. Estimated mean changes in arm muscle area (cm^2) during follow up. (*A*) In Study A, arm muscle area declined from baseline in the low-protein diet group ($P < 0.001$; solid line) but not in the usual-protein diet group (dashed line). The decline in arm muscle area was greater in the low-protein group ($P = 0.009$). (*B*) In Study B, arm muscle area declined from baseline in the very-low-protein diet group ($P < 0.001$), but not in the low-protein diet group. Nonetheless, the decline was not significantly different between the diet groups.

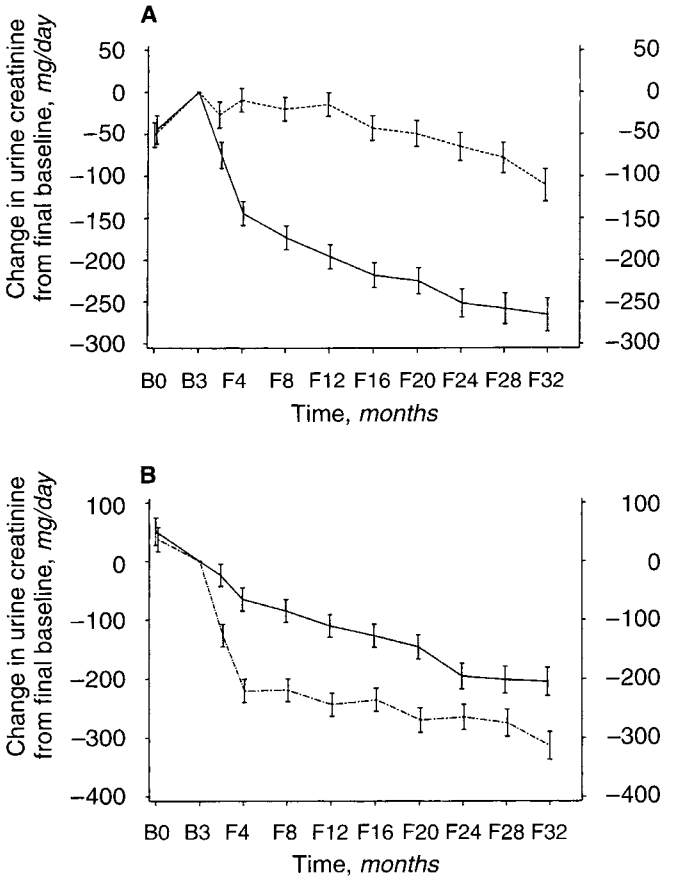

Fig. 6. Estimated mean changes in urine creatinine excretion (mg/day) during follow-up. Symbols in A are: (dashed lines) usual-protein; (solid lines) low-protein. Symbols in B are: (dashed lines) low-protein; (solid lines) very-low-protein. First, the mean value during follow-up (from F4) was compared to the baseline (B3) value in each diet group (as for Figs. 1–5). (*A*) In Study A, urine creatinine excretion declined from baseline in the low-protein diet group ($P < 0.001$) but not significantly in the usual-protein diet group. The decline in urine creatinine excretion was greater ($P < 0.001$) in the low-protein diet group. (*B*) In Study B, urine creatinine excretion declined from baseline in both the very-low-protein and the low-protein diet groups ($P < 0.001$). The decline was greater ($P < 0.001$) in the very-low-protein diet group. Second, the change from B3 to F4 and from F4 to the end of follow-up was computed for each diet group (two-slope method [1]). In Study A, the decline in the low-protein diet group was greated compared to the usual-protein diet group both before ($P < 0.001$) and after ($P = 0.013$). In Study B, the decline in the very-low-protein diet group as compared to the low-protein diet group was faster before ($P < 0.001$) and slower after ($P < 0.001$) four months.

low-protein diet group, but not in the usual-protein diet group. Interestingly, there was a concomitant significant increase in mean serum albumin concentration in the low-protein diet group but not in the usual-protein diet group. In Study B, there were significant declines from baseline to follow-up in serum transferrin, body wt, and urine creatinine in both diet groups. During the first four months, the decline in urine creatinine was significantly greater in the very-low-protein diet group as compared to the low-protein diet group, whereas after four months, urine creatinine declined more slowly in the very-low-protein diet group than in the low-protein diet group. In addition, there was a significant decline in arm muscle area in the very-low protein diet group and in percent body fat in the low-protein diet group. Interestingly, there was also a concomitant significant increase from baseline in serum albumin in both the very-low-protein and low-protein diet groups.

For some indices, notably, mean serum transferrin, body wt and urine creatinine, there was an abrupt decline within the first four months after prescription of the low-protein and very-low-protein diets, followed by a stabilization or more gradual decline thereafter. Thus, we reasoned that if dietary protein restriction had a marked adverse effect on nutritional status, we would observe a correlation between the rate of change in these parameters from four months to the end of follow-up and the long-term average value of achieved protein intake during the same interval. The correlational analyses presented in Table 6 do not reveal significant relationships with any of the variables examined. Overall, this suggests that reductions in long-term protein intake over a wide

Table 4. Rates of deaths, hospitalizations and stop points by study and diet groups[a]

Study A				Study B			
Diet group	Event	*N*	Per patient-year of follow-up	Diet group	Event	*N*	Per patient-year of follow-up
Usual-protein diet	Deaths	9	1.3%	Low-protein diet	Deaths	1	0.3%
(*N* = 294)	First hosp.	66	11.1%	(*N* = 129)	First hosp.	32	12.7%
	Stop points	46	6.7%		Stop points	55	19.0%
Low-protein diet	Deaths	2	0.3%	Very-low-protein diet	Deaths	4	1.4%
(*N* = 291)	First Hosp.	63	10.3%	(*N* = 126)	First hosp.	28	11.6%
	Stop points	38	5.5%		Stop points	48	17.3%

[a] Study A, GFR 25–55 ml/min/1.73 m^2; Study B, GFR 13–24 ml/min/173 m^2

Table 5. Rates of deaths, first hospitalizations and stop points by study and quartiles of achieved protein intake[a]

Study A				Study B			
Achieved protein intake[b]	Event	*N*	Per patient-year of follow-up	Achieved protein intake[b]	Event	*N*	Per patient-year of follow-up
<0.74	Deaths	1	0.3%	<0.61	Deaths	0	0.0%
	First hosp.	31	9.9%		First hosp.	15	11.5%
	Stop points	20	5.7%		Stop points	26	17.5%
	Total patients	145			Total patients	64	
0.75–0.93	Deaths	1	0.3%	0.62–0.67	Deaths	1	0.7%
	First hosp.	31	10.8%		First hosp.	13	10.3%
	Stop points	19	5.9%		Stop points	22	14.9%
	Total patients	144			Total patients	63	
0.94–1.12	Deaths	5	1.5%	0.68–0.75	Deaths	1	0.7%
	First hosp.	35	12.3%		First hosp.	19	16.0%
	Stop points	26	7.9%		Stop points	23	16.0%
	Total patients	144			Total patients	64	
≥1.13	Deaths	3	0.9%	≥0.76	Deaths	3	2.4%
	First hosp.	32	10.5%		First hosp.	13	11.2%
	Stop points	18	5.1%		Stop points	31	24.5%
	Total patients	145			Total patients	63	

[a] Study A, GFR 25–55 ml/min/1.73 m^2; Study B, GFR 13–24 ml/min/173 m^2

[b] Protein intake for patients in the usual-protein and low-protein diet groups, total protein intake for patients in the very-low-protein diet group. Protein intake and total protein intake are defined as the mean of all values beginning at the second month of follow-up (F2)

Table 6. Correlations between mean follow-up protein intake and rates of change in nutritional status variables during follow-up[a]

	Study A				Study B			
			Partial[b]				Partial[b]	
Nutritional status variable	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Energy intake *kcal/kg/day*	−0.064	0.14	—	—	+0.022	0.75	—	—
Body weight *kg*	+0.073	0.09	+0.067	0.17	+0.017	0.80	+0.045	0.55
Percent body fat %	+0.069	0.12	+0.005	0.91	−0.010	0.89	+0.055	0.47
Albumin *g/dl*	−0.061	0.15	−0.066	0.17	+0.034	0.61	−0.016	0.83
Transferrin *mg/dl*	+0.084	0.05	+0.075	0.13	−0.095	0.16	−0.041	0.59
Urine creatinine *mg/kg/day*	+0.079	0.07	+0.073	0.14	−0.207	0.002	−0.140	0.06

[a] Protein intake for patients in the usual-protein and low-protein diet groups, total protein intake for patients in the very-low-protein diet group. Protein intake and total protein intake are defined as the mean of all values beginning at the second month of follow-up (F2). Nutritional status variables are computed for all values beginning at the fourth month of follow-up (F4).

[b] Partial correlation, controlling for baseline (B3) measurement for age, gender, body weight, desire to lose weight, percent body fat, albumin, transferrin, urine creatinine per kg body weight, total cholesterol and mean follow-up calorie intake. Analysis restricted to patients with ≥ 1 year of follow-up. Interpretation: A positive sign indicates patients with higher protein intake had higher (less negative) slopes of rate of change in nutritional status variables during follow-up.

range for two to three years were not associated with a progressive decline in nutritional status.

Nonetheless, the change in urine creatinine is striking and deserves further comment. Urine creatinine is derived largely from the degradation of creatine in skeletal muscle originating from synthesis of creatine in the liver or from ingestion of creatine in meat. A smaller proportion of urine creatinine is derived from ingestion of creatinine in meat. Normally, steady-state urine creatinine excretion is nearly equal to creatinine generation, with little extra-renal elimination. In principle, the decrease in urine

creatinine excretion that we observed may have several causes. These include reduction in skeletal muscle mass [34, 35], reduction in creatine synthesis due to decreased protein intake [35, 36], reduction in creatine degradation, decreased intake of meat [35–37], and increased extra-renal elimination of creatinine, which has been observed in chronic renal insufficiency due to degradation of creatinine by intestinal bacteria [38, 39]. The reduction in urine creatinine in the first four months after prescription of a low-protein or very-low-protein diet (Fig. 6) is consistent with a reduction in creatine and creatinine intake. However, this effect would not be expected to lead to a continuing decline in creatinine excretion over two to three years. The continued gradual fall in urine creatinine throughout the follow-up period occurred in all four diet groups and was not related to the level of achieved protein intake. Possibly it indicates a reduction in muscle mass, as suggested by the reduction in arm muscle area in some diet groups. Alternatively, it could be due to a reduction in muscle creatine degradation rate or an increase in extra-renal creatinine elimination, neither of which were measured in this study.

Results from the MDRD Study [40], as well as from Ikizler et al [41], show that the magnitude of urine creatinine excretion is lower in patients with lower levels of renal function. Further, we found that the rate of decline in creatinine excretion after four months of follow-up correlated with the GFR decline in Study B. This suggests that the gradual rate of decline in creatinine excretion observed in both diet groups in Study B is related, in part, to declining renal function. Nonetheless, the significantly faster decline in the low-protein diet group (Fig. 6) suggests a relationship to this diet, although not to the quantity of achieved dietary protein intake. Interestingly, other studies of very-low-protein diets supplemented with a mixture of essential amino acids or ketoacids and amino acids also demonstrated reduced creatinine excretion [42, 43]. Long-term follow-up of these studies demonstrated no long-term adverse clinical effects of these diets, including no increase in morbidity or mortality after beginning maintenance dialysis [44, 45]. Additional studies will be necessary to determine whether the faster decline in creatinine excretion in patients following a low-protein or very-low-protein diet is an indication of malnutrition.

The importance of the small changes in nutritional indices other than urine creatinine is also not clear. A decrease in skinfold thickness is considered to reflect a fall in body fat mass [33]. It is noteworthy that the reductions in mean percent body fat that we observed underestimate the actual decrease in body fat because the mean body wt also decreased. A reduction in arm muscle area is thought to reflect a loss of muscle protein or somatic protein mass [33]. Decreases in serum albumin and transferrin are considered to reflect a decrease in visceral protein mass [33], which refers to proteins synthesized by the liver and other viscera. The decrease in serum transferrin in the face of rising serum albumin in the low-protein and very-low-protein diet groups is somewhat puzzling. Serum transferrin has a shorter half-life, about eight to nine days, in contrast to serum albumin which has a half-life of about 18 to 20 days [46]. However, during the course of a 2.2 years study, this small difference in half-lives should not be influential. Serum albumin and transferrin are also influenced by non-nutritional factors [46] that may have exerted different effects on the serum concentrations. Serum albumin was measured by a dye binding method that may overestimate albumin levels in individuals with chronic renal failure [46]. However, the decrease in GFR during the study did not seem to be of sufficient magnitude to account for a change in the dye binding to albumin. Possibly, the decrease in serum transferrin may reflect a specific response to declining renal function.

The causes for protein-calorie malnutrition in patients with renal failure have been reviewed elsewhere [29, 47]. A major cause of malnutrition is considered to be reduced nutrient intake. Hence, it is pertinent that the groups of patients that displayed the greatest mean decline in nutritional parameters were the low- and very-low protein diet groups. On the other hand, low-protein diets and very-low-protein diets have been shown in previous metabolic balance studies to maintain nitrogen balance [48–52].

Possibly the conclusions of these metabolic balance studies are not applicable to patients with chronic renal disease in the MDRD Study for the following reasons. First, short-term studies of 15 to 40 days duration may not indicate the quantities of dietary protein necessary to maintain long-term protein balance. Second, the patients who underwent nitrogen balance studies with these low- or very-low-protein diets had more advanced renal disease than most of the participants in the MDRD Study. Possibly, patients with more advanced renal disease might tolerate these diets better, because they may already have experienced some degree of protein wasting. Third, the dietary energy intake in the balance studies was higher than the mean achieved energy intake in the MDRD Study, especially in the low-protein and very-low-protein diet groups. Fourth, the range of achieved protein intake observed in the MDRD Study included some patients with lower protein intakes than in the balance studies.

However, it is likely that protein intake was sufficient in most patients for the following reasons. The mean achieved protein intakes (from food and supplement) in the low-protein and very-low-protein diet groups during follow-up (from 0.66 to 0.77 g/kg/day [2, 3]) were well above the level (about 0.6 g/kg/day) that has been shown to maintain nitrogen balance in previous metabolic balance studies [48–52]. Moreover, the mean achieved intakes in these diet groups were not much lower than the Recommended Dietary Allowances of the Food and Nutrition Board [53]. This allowance, about 0.80 g of miscellaneous biological value protein/kg/day for nonpregnant, nonlactating normal adults, is believed to provide a surfeit of protein for most normal men and women [53]. Finally, the correlational analyses that we performed, controlling for baseline nutritional status and follow-up energy intake, do not reveal a relationship between lower protein intake and long-term deterioration in nutritional status across a broad range of intakes.

The metabolic and endocrine disorders associated with renal failure *per se* may have contributed to the decline in nutritional indices. The baseline GFR of most patients in the MDRD Study was above the level that would traditionally be considered to cause severe metabolic abnormalities (Table 1). However, the rate of GFR decline was variable and some patients in both Studies A and B developed renal failure. Moreover, we have reported preliminary data suggesting that alterations in dietary intake and indices of nutritional status are observed beginning at GFR values from 30 to 50 ml/min/1.73 m^2 [54]. Thus, declining renal function seems likely to be responsible, at least in part, for some of the observed changes in nutritional status.

Another possible cause for the decline in nutritional indices in these patients is low energy intake. Mean energy intake was below normal at baseline and declined further in all four diet groups

(Tables 2 and 3), due in part to the desire of many study participants (about 65% in Study A and 50% in Study B) to lose weight. However, weight loss was most pronounced in the low-protein and very-low-protein diet groups. In these latter groups, the mean energy intake fell by 3.1 to 4.3 kcal/kg/day to mean values ranging from 20.7 to 23.3 kcal/kg/day during follow-up (Table 3). In contrast, in the usual-protein diet group, mean energy intakes in men and women during follow-up averaged 26.7 and 24.8 kcal/kg/day, respectively (Table 3). For comparison, the Recommended Dietary Allowances by the Food and Nutrition Board for energy intake in normal men and women undergoing light physical activity is approximately 35 kcal/kg/day for adults 60 years old or younger and 30 kcal/kg/day for individuals 61 years of age or older [53]. Studies of nondialyzed patients with chronic renal failure suggest that their energy expenditure and energy requirements are not different from normal [51, 55]. Thus, the low dietary energy intakes of the patients in the MDRD Study at baseline and during follow-up can be considered to be maladaptive and probably inadequate for their nutritional needs. The nutritional hazards of low energy intake may be enhanced in individuals ingesting low protein diets, because the ability to maintain nitrogen balance may be strongly dependent on the magnitude of dietary energy intake [51].

The finding that energy intake was lower with the low-protein and very-low-protein diet groups, as compared to the usual-protein diet group, suggests that the quantity of dietary protein or phosphorus prescribed may have influenced the patients' energy intakes. Indeed, the patients assigned to these latter two diets described more difficulty in attaining the prescribed energy intake than did the patients assigned to the usual protein diet. This probably reflects the reduced food choices available with these latter diets. In fact, many of the MDRD Study dietitians indicated that they had more difficulty in providing the prescribed energy intake with their meal plans for patients in the low-protein and very-low-protein diet groups, as compared to the usual-protein diet group. These findings underscore the necessity for intensive dietary counseling and monitoring of nutritional status during initiation and follow-up of dietary protein restriction.

In summary, nutritional status was generally well-maintained over the two to three years follow-up in the MDRD Study. We found no definite evidence of malnutrition in patients in any of the diet groups. Neither the comparisons of randomized groups nor correlational analyses showed an association of higher rate of death, hospitalization, or the frequency of predetermined stop points with lower protein intake. On average, most anthropometric and biochemical indices of nutritional status remained within the normal range. However, there were some changes from baseline to follow-up in a variety of nutritional variables and differences in these changes between the randomized groups. In the low-protein and very-low-protein diet groups, mean serum albumin remained constant or rose slightly during follow-up. Mean serum transferrin, weight, percent body fat, and arm muscle area declined, but the decrease was mild and not progressive. Mean urine creatinine excretion declined soon after prescription of the low-protein and very-low-protein diets, probably due to reduced meat intake. In addition, urine creatinine continued to decline thereafter in all diet groups. The achieved level of protein intake was not related to the rate of decline in any of these nutritional variables.

Secondary analyses from the MDRD Study [2, 3] and two meta-analyses of randomized trials [4, 5] provide some support for the hypothesis that protein and phosphorous restriction slows the progression of renal disease. Overall, the analyses presented here show that the dietary intervention program used in the MDRD Study is safe for a period of two to three years. However, the small but significant decline in various indices of nutritional status is of concern because of the simultaneous reduction in protein and energy intake in the low-protein and very-low-protein diet groups, and because of the high incidence and adverse effect of protein-calorie malnutrition in patients with end-stage renal disease. We suggest that physicians who prescribe low-protein diets must carefully and frequently monitor patients' protein and energy intake and nutritional status. The involvement of a skilled dietitian is essential to assist patients in simultaneously adhering to the protein restriction and maintaining sufficient energy intake.

ACKNOWLEDGMENTS

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APPENDIX

Dietary intervention

Research dietians trained the patients to prepare and follow their prescribed diets, monitored patients' nutrient intakes and provided dietary counseling and performed anthropometric measurements. Dietitians were trained by the MDRD Study Nutritional Coordinating Center in the education, monitoring and counseling of patients with regard to their dietary intake and in anthropometry. Each dietitian was required to be certified and that he or she had obtained a standard of accuracy and reproducibility in the asessment of the patients' nutrient intake and the performance of anthropometry before he or she was allowed to train patients or collect data for the study. The methods employed by the Nutrition Coordinating Center for these procedures are described elsewhere [14–17].

The protein and phosphorus content of the three prescribed diets was as follows: usual-protein diet, 1.30 g protein per kg body wt per day (target range 0.975 to 1.625) and 16 to 20 mg phosphorus per kg per day; low-protein diet, 0.575 g protein per kg per day (target range 0.402 to 0.748) and 5 to 10 mg phosphorus per kg per day; very-low-protein diet, 0.28 g protein per kg per day (target range 0.224 to 0.420), 0.28 g/kg/day of a ketoacid-amino acid mixture (Ross Laboratories, Columbus, OH, USA) and 4 to 9 mg phosphorus per kg per day. The biological value of the other two protein diets was not specified. All dietary prescriptions and estimates of dietary intake are expressed according to the patients' standard body weight. Standard body weight refers to the median value for weights of normal Americans of the same age, range, height, gender and skeletal frame size as the patient, as determined from the NHANES I and II data [13]. The composition of the ketoacid-amino acid mixture (μmol/kg/day) was as follows: (L)-tyrosine 271, (L)-threonine 119, calcium 17, (D,L)-hydroxymethylthiobutyrate 34, (L)-tryptophan 4, and a mixture of basic amino acid salts containing the following components, (L)-ornithine 491, (L)-lysine 237, (L) histidine 68, ketoisocaproate 305, ketoisovalerate 254, and (R,S) ketomethylvalerate 237. In each diet group dietary protein was increased by 1 gram of high biological value protein for each gram of urinary protein excreted per day up to a total of 8 g per day of protein.

The dietary prescriptions did not differ for nutrients other than protein, phosphorus and the ketoacid supplement. Patients were prescribed at

least 30 kcal/kg standard body weight/day unless they were overweight (greater than 115% of standard body weight), gaining unwanted weight or fearful of gaining weight. Patients who were underweight or losing weight were often prescribed higher calories. Patients who were overweight, particularly those with hypertension, hyperlipidemia or non-insulin-dependent diabetes mellitus, were prescribed a weight reduction diet with an energy intake between 25 and 30 kcal/kg/day.

The daily intake of other nutrients were as follows: calcium 1300 to 1700 mg (including supplements of calcium carbonate tablets), magnesium 300 to 350 mg, sodium 1200 mg or greater, potassium 50 to 150 mg, iron 10 mg or greater for men and 18 mg or greater for women, zinc 15 to 20 mg/day (including zinc supplements, see below) and vitamin A about 5,000 IU.

Patients were prescribed one multivitamin/mineral tablet each day that provided the following nutrients per day: thiamine 1.5 mg, riboflavin 1.7 mg, niacinamide 20 mg, pyridoxine hydrochloride 10 mg (8.12 mg of free pyridoxine), panthothenic acid 10 mg, vitamin B12 6 μg, biotin 300 μg, ascorbic acid 60 mg, folic acid 1 mg, cholecalciferol 5 μg, vitamin E 6 mg, and zinc 8 mg.

Measurements

Dietary protein intake was estimated at monthly intervals from the urine urea excretion according to the following formula [17]. Protein intake (g/day) = 6.25 [UUN (g/day) + 0.31 (g/kg/day) × SBW (kg)], where UUN is urea nitrogen and SBW is standard body weight. In Study B, this value included protein intake from food as well as amino acids in the ketoacid-amino acid supplement, and for convenience is termed "total protein intake" [2]. Dietary nutrient intake was also calculated at three-month intervals from dietary diaries and interviews. Each clinical center dietitian calculated the patient's nutrient intake using the University of Pittsburgh Nutrient Database [14]. Compliance to intake of the ketoacid-amino acid mixture was estimated by pill count and by measuring plasma alloisoleucine concentrations.

Weight (wearing street clothes without shoes) was obtained monthly. Height, measured with a wall-mounted stadiometer, and skeletal frame size, assessed by measuring the biocondylar width of the elbow of the dominant arm using a Biocondylar Vernier calipers, were assessed at the second month of baseline (B2) and then annually. Mid arm circumference (MAC) and skinfold thickness in the triceps, biceps and subscapular areas were measured at B2 and six month intervals thereafter. A metal tape was used for measuring MAC, and a Holtain calipers (Holtain Ltd., Crymych, UK) was used for measuring skinfold thickness. The percent relative body weight was calculated as the patient's weight × 100/SBW. The percent of body fat was estimated from body weight and height and the biceps, triceps and subscapular skinfold thicknesses using the equations of Durnin and Wormersley [18]. Arm muscle area (AMA) was calculated at the mid arm from the MAC and the triceps skinfold thickness according to the following equation [19]: AMA (cm^2) = [MAC − π × triceps skinfold thickness (cm)]^2/4. AMA measurements presented in this paper were corrected to delete bone mass using the following equations: AMA (men) = AMA − 1900; AMA (women) = AMA − 1550.

Serum albumin and transferrin were measured at monthly intervals. Albumin concrentrations were determined by dye-binding using bromcresol green reagents and an Astra 8 analyzer obtained from Beckman Instruments (Brea, CA, USA). Transferrin concentrations were determined by immunonephrolometry using reagents including specific antibody and calibrators, and an Array nephelometer obtained from Beckman Instruments. Urine was collected over a 24 hour period for measurement of urea, creatinine and protein at monthly intervals. GFR was measured by the renal clearance of ^{125}I-iothalamate as previously described [21, 22]. These measurements were performed in the MDRD Study Central Biochemistry Laboratory and GFR Laboratory at the Cleveland Clinic Foundation. Normal values for some of the nutritional parameters are as follows: serum albumin 4.0 to 5.0 g/dl, serum transferin 250 to 300 mg/dl and relative body weight 90% to 110%.

Action items and stop points

An action item was defined as the occurrence of a condition requiring modification of diet, vitamin prescription or frequency of measurement. Action items were defined in the protocol and reported as they occurred. Action items specifically related to serum protein levels or weight and the responses to these action items included the following: (*1*) Weight loss, defined as an undesired weight loss of greater than 2.5 kg below the patient's weight at the end of the second month of the baseline period (B2) or of 5% of standard body weight, whichever was less, or a loss of weight to less than 80% of standard weight. The response was to increase the dietary energy intake. (*2*) Weight gain, defined as a gain in weight greater than 5% of the patient's B2 weight (in the absence of edema). (*3*) Overweight diabetic, defined as weight greater than 115% of standard weight in a diabetic patient (in the absence of edema). For the latter two action items, the response was to reduce the energy intake. (*4*) Declining serum albumin, defined by a decrease in serum albumin by more than 0.5 g/dl from the B3 value to a value between 3.0 and 3.9 g/dl. (*5*) Low serum albumin, defined as a decrease serum albumin to below 3.0 g/dl. For the latter two action items, the response was to first increase the energy prescription; if this was unsuccessful in raising serum albumin, then the dietary protein intake was increased. For patients in any diet group whose protein intake was below the target range, the patient was urged to raise protein intake to target levels for patients whose dietary protein intake was above the target range, there was no recommended change in protein intake in response to the declining serum albumin. For patients whose dietary protein intake was at the target range, the response was to increase protein intake to 0.70 g/kg/day for patients prescribed the low-protein diet (50% of the increase in protein was of high biological value protein) and to 0.40 g/kg/day for patients prescribed the very-low-protein diet for patient prescribed the usual-protein diet whose dietary protein intake was within the target range, no increase in protein intake was recommended for a decreasing serum albumin. (*6*) Declining serum transferrin was defined as a decrease by more than 50 mg/dl below the B3 level to a value below 200 mg/dl. The response was the same as for a declining serum albumin level.

In addition, there were numerous other action items requiring specific dietary modifications, including alterations in serum concentrations of phosphorus, calcium, potassium, bicarbonate, magnesium, iron, total cholesterol, LDL cholesterol, and triglycerides. As reported elsewhere, there were other action items related to compliance with the prescribed dietary protein or ketoacid-amino acid supplements [11] or the blood pressure intervention [10].

A stop point was a defined adverse event after which the investigator was no longer obligated to treat the patient with his study diet or blood pressure goal. Stop points specifically related to nutritional status included the following: (*1*) low serum albumin, defined as persistent serum albumin less than 3.0 g/dl for more than four consecutive months. (*2*) Weight loss, defined as persistent body weight less than 75% of standard for three months after dietary intervention for a weight loss action item. (*3*) Very high serum phosphorus, defined as fasting serum phosphorus greater than 6.0 mg/dl on four consecutive monthly measurements after a high serum phosphorus action item. In addition, there were other stop points for onset of renal failure, rapid decline in GFR (Study A only), and serious intercurrent medical conditions.

Information on hospitalization was obtained routinely during study visits or if a study visit was missed. Patient deaths were reported using a special form. Information about cause of death was sought from several sources, including family members, hospital records, and a copy of the death certificate. Cause of death was classified by the clinical center principal investigators.

In addition to these activities, a subcommittee of the External Monitoring Committee met at regular intervals during the follow-up period to review detailed statistical summaries of these events. Profiles of dietary and nutritional status variables were also prepared for individual patients selected because of either undesired weight loss or changes in biochemical or anthropometric indices of nutritional status that were not sufficient to trigger a stop point. The subcommittee found no serious problems related to the safety of either diet intervention in either study.

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