Effect of a Very Low-Protein Diet on Outcomes: Long-term Follow-up of the Modification of Diet in Renal Disease (MDRD) Study

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Background: The long-term effect of a very low-protein diet on the progression of kidney disease is unknown. We examined the effect of a very low-protein diet on the development of kidney failure and death during long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study.

Study Design: Long-term follow-up of study B of the MDRD Study (1989-1993).

Setting & Participants: The MDRD Study examined the effects of dietary protein restriction and blood pressure control on progression of kidney disease. This analysis includes 255 trial participants with predominantly stage 4 nondiabetic chronic kidney disease.

Intervention: A low-protein diet (0.58 g/kg/d) versus a very low-protein diet (0.28 g/kg/d) supplemented with a mixture of essential keto acids and amino acids (0.28 g/kg/d).

Outcomes: Kidney failure (initiation of dialysis therapy or transplantation) and all-cause mortality until December 31, 2000.

Results: Kidney failure developed in 227 (89%) participants, 79 (30.9%) died, and 244 (95.7%) reached the composite outcome of either kidney failure or death. Median duration of follow-up until kidney failure, death, or administrative censoring was 3.2 years, and median time to death was 10.6 years. In the low-protein group, 117 (90.7%) participants developed kidney failure, 30 (23.3%) died, and 124 (96.1%) reached the composite outcome. In the very low-protein group, 110 (87.3%) participants developed kidney failure, 49 (38.9%) died, and 120 (95.2%) reached the composite outcome. After adjustment for a priori–specified covariates, hazard ratios were 0.83 (95% confidence interval, 0.62 to 1.12) for kidney failure, 1.92 (95% confidence interval, 1.15 to 3.20) for death, and 0.89 (95% confidence interval, 0.67 to 1.18) for the composite outcome in the very low-protein diet group compared with the low-protein diet group.

Limitations: Lack of dietary protein measurements during follow-up.

Conclusion: In long-term follow-up of the MDRD Study, assignment to a very low-protein diet did not delay progression to kidney failure, but appeared to increase the risk of death.

Am J Kidney Dis 53:208-217.

INDEX WORDS: Chronic kidney disease; low-protein diet; outcomes.

Editorial, p. 189

Although experimental data suggest a benefit of dietary protein restriction on slowing the progression of chronic kidney disease (CKD) in animal models,[1,2] clinical studies have shown conflicting results. Low-protein diets appear to slow the rate of decrease in kidney function in some studies,[3-6] whereas others have failed to show a benefit.[7-9] Very few of these studies were randomized controlled trials, most were short term, and many used outcomes based on creatinine levels, which are affected by level of dietary protein ingested as meat.[10]

The Modification of Diet in Renal Disease (MDRD) Study, the largest clinical trial to date to

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Received February 28, 2008. Accepted in revised form August 7, 2008. Originally published online as doi: 10.1053/j.ajkd.2008.08.009 on October 28, 2008.

Because an author of this manuscript is an editor for AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Paul Muntner, PhD, MHS, Mount Sinai School of Medicine) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Editorial Policies section of the AJKD website.

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0272-6386/09/5302-0005$36.00/0
doi:10.1053/j.ajkd.2008.08.009

examine the safety and efficacy of dietary protein restriction on the progression of kidney disease, was unable to show a conclusive benefit during the trial of low- or very low-protein diets in slowing the rate of measured glomerular filtration rate (GFR) decrease.[11] In long-term follow-up of patients randomly assigned to usual- versus low-protein diets, there was insufficient evidence supporting a benefit of the latter in retarding the progression to kidney failure.[12] There are limited data for long-term effects of very low-protein diets on clinical outcomes in patients with nondiabetic CKD; however, dietary protein restriction remains a therapeutic consideration in these patients.[10,13,14]

There are several precedents in the literature for interventions during a trial showing benefits or harm during long-term follow-up.[15-17] Therefore, we examined the effects of randomization to the low-protein diet versus the very low-protein diet supplemented with a mixture of essential keto acids and amino acids on the development of kidney failure or death during long-term follow-up of the MDRD Study randomized cohort.

METHODS

MDRD Study Randomized Controlled Trial

The MDRD Study was a randomized controlled trial conducted from 1989 to 1993 to study the effect of dietary protein restriction and strict blood pressure control on the progression of kidney disease. Details of this study have been published previously.[18,19] Eligibility criteria included age 18 to 70 years, serum creatinine concentration of 1.2 to 7.0 mg/dL in women and 1.4 to 7.0 mg/dL in men, and mean arterial pressure of 125 mm Hg or less. Exclusion criteria were insulin-requiring diabetes, class III or IV heart failure, urine protein excretion exceeding 10 g/d, kidney transplantation, or frequent hospitalizations. Participants with GFR of 25 to 55 mL/min/1.73 m^2 entered study A and participants with GFR of 13 to 24 mL/min/1.73 m^2 entered study B. The 255 participants in study B were randomly assigned to either a low-protein diet (0.58 g/kg/d) or a very low-protein diet (0.28 g/kg/d) supplemented with a mixture of keto acids and amino acids (0.28 g/kg/d; Table 1). Participants also were randomly assigned to either a low or usual blood pressure target. Participants in study A were randomly assigned to either a usual-protein diet (1.3 g/kg/d) or low-protein diet (0.58 g/kg/d), with approximately 65% of dietary protein of high biological value (from animal sources) and are not included in the analyses presented here. Long-term follow-up results of the dietary interventions in study A have been published previously.[12] GFR was measured by using iothalamate clearance. Decisions to initiate dialysis therapy were based on the clinical judgment of the primary nephrologists taking care of the patients. Iothalamate GFR values were not available to the primary physicians.

Table 1. Composition of the Keto Acid–Amino Acid Supplement Used in the Modification of Diet in Renal Disease Study

L-Tyrosine (μmol/kg/d)	271
L-Threonine (μmol/kg/d)	119
Calcium (μmol/kg/d)	17
D,L-Hydroxymethylthiobutyrate (μmol/kg/d)	34
L-Tryptophan (μmol/kg/d)	4
mL-Ornithine (μmol/kg/d)	491
L-Lysine (μmol/kg/d)	237
L-Histidine (μmol/kg/d)	68
Ketoisocaproate (μmol/kg/d)	305
Ketoisovalerate (μmol/kg/d)	254
R,S-Ketomethylvalerate (μmol/kg/d)	237

Note: Information provided by Ross Laboratories, Columbus, OH (David B. Cochram, personal communication, February 1996). The mixture combines mixed salts of basic amino acids (or calcium) with amino acid analogues. The table gives the constituents after hydrolysis of these salts. Dosages were administered to the nearest 10 kg of standard body weight.

Reproduced with permission from Levey et al.[22]

Ascertainment of Dietary Protein Intake

During the trial, protein and amino acid intake (Fig 1) was measured every 2 months from urea nitrogen excretion rate in 24-hour urine collections by using the formula of Maroni et al[20]:

$$\text{Protein intake (g/d)} = 6.25\,(\text{urine urea nitrogen excretion [g/d]} + 0.031\ \text{g/kg/d} \times \text{SBW [kg]})$$

where SBW is standard body weight computed from height and body frame.[21] Mean protein intake during the study was defined as the average of all measurements obtained after the first month of follow-up.[19,22] The median amount of prescribed keto acid–amino acid supplements used during the trial was estimated by using pill counts to be 92%.

No recommendations were made regarding dietary protein targets after completion of the trial. Protein intake was measured in a subgroup of participants 4 months after the end of the study (after close-out) and 5 months later (9 months after study end; phase 5). Thereafter, protein intake measurements are not available.

Outcome Ascertainment During Long-term Follow-up (1993-2000) of the MDRD Study

We assessed 3 outcomes: kidney failure (initiation of dialysis therapy or transplantation), all-cause mortality, and a composite outcome of kidney failure and all-cause mortality. We ascertained survival status from the National Death Index by using the participant's Social Security number,

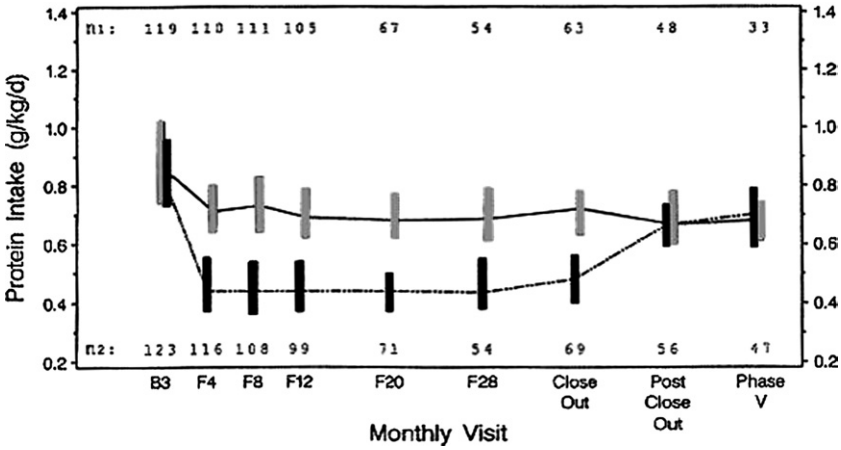

Figure 1. Dietary protein intake (excluding amino acid supplements) during and up to 9 months after the Modification of Diet in Renal Disease Study (1989-1993). Abbreviations: B3, baseline; F, months of follow-up; n1, participants with follow-up at any period in the low-protein diet group; n2, participants with follow-up at any period in the very low-protein diet group; Phase V, 9 months after completion of trial; post close-out, 4 months after the end of the study.

name, sex, and date of birth. The National Death Index is 93% accurate in identifying deaths with known social security numbers.[23] We obtained kidney failure outcomes, defined as initiation of dialysis therapy or transplantation, from the US Renal Data System by using the same identifying information. Death data from the National Death Index was confirmed by using data from the US Renal Data System. Participants were censored on December 31, 2000, if neither of these outcomes had occurred. The Institutional Review Boards of The Cleveland Clinic, Cleveland, OH, and Tufts Medical Center, Boston, MA, approved data collection procedures for the long-term follow-up study.

Statistical Analysis

Time-to-event analyses for the 3 outcomes were performed by using the Kaplan-Meier method to estimate cumulative incidence curves and log-rank tests stratified by clinical center. We compared the effect of randomized dietary protein group on risk of the 3 outcomes by using unadjusted and adjusted Cox regression models stratified by clinical center. The follow-up period included the duration of the trial (mean follow-up, 2.2 years) and long term follow-up until administrative censoring on December 31, 2000. Models for mortality outcome included deaths that occurred both before and after kidney failure and were censored at the end of follow-up. Models for kidney failure were censored at death or the end of follow-up, and models for the composite outcome were censored at the end of follow-up. All analyses were performed on an intention-to-treat basis, in which participants were analyzed according to diet group throughout the randomized trial and long-term follow-up.

To increase statistical power, we obtained hazard ratios (HRs) with adjustment for baseline factors. Covariates specified a priori in the adjusted models were blood pressure assignment, race, polycystic kidney disease as cause of kidney disease, log urine protein, serum transferrin concentration, high-density lipoprotein cholesterol level, and mean arterial pressure. We chose these factors based on their recognized associations with GFR decrease in the MDRD Study.[24] In addition, we adjusted for baseline age and GFR given their known relationship with death and kidney failure, respectively. Sex also was added for analyses for mortality.

We checked proportional hazards assumptions of the Cox regression models by testing the interaction of each baseline factor with duration of follow-up. As a result, we included interaction terms of follow-up time with baseline urine protein excretion and diagnosis of polycystic kidney disease in the multivariable model.

Using time-dependent Cox regression, we examined differences in HRs for the 3 outcomes for 2 periods: (1) during the trial period and posttrial follow-up period, and (2) before and after 6 years of follow-up, a cut-off point based on inspection of data in successive 2-year intervals. S-Plus 6.2 (Insightful Corp, Seattle, WA) and SPSS 14.0 (SPSS Inc, Chicago, IL) were used to perform statistical analyses.

Additional Analyses

We performed prespecified tests for interactions to determine whether effects of the dietary protein restriction on death differed between deaths occurring before or subsequent to kidney failure and whether effects for the 3 outcomes differed by blood pressure assignment (usual and low target).

The short-term exposure to the very low-protein diet may have deleterious effects during the long term and especially after the onset of kidney failure, in which case one would expect the majority of deaths to occur early, ie, a year or 2 after dialysis therapy initiation. Therefore, we also examined the effect of diet on the hazard for death subsequent to kidney failure by using 2 different times: (1) kidney failure that occurred during or after the trial, and (2) kidney failure that occurred within 4 years from the start of the trial versus after 4 years.

RESULTS

Baseline Characteristics of MDRD Study B Participants

The study cohort had an average age of 50.8 ± 12.8 (SD) years. The sample was predominantly white (85.9%), 59.2% were men, and 5.1% had a history of non–insulin-dependent diabetes. Mean

Table 2. Baseline and Follow-up Characteristics by Protein Diet

Factor	Low-Protein Diet (n = 129)	Very Low-Protein Diet (n = 126)	*P*
Baseline			
Age (y)	51.1 ± 12.8	50.5 ± 12.95	0.7
Men (%)	60.5	57.9	0.7
White (%)	82.9	88.9	0.1
Diabetes (%)	5.4	4.8	0.8
Kidney disease diagnosis (%)			
Polycystic kidney disease	22.5	23.8	
Glomerular disease	34.9	37.3	0.8
Other	42.6	38.9	
Median proteinuria (g/d)	0.7	0.7	0.9
GFR (mL/min/1.73 m^2)	18.7 ± 3.2	18.3 ± 3.5	0.3
Protein intake (g/kg/d)	0.9 ± 0.3	0.9 ± 0.3	0.9
Energy intake (kcal/kg/d)	25.0 ± 6.7	25.5 ± 6.5	0.5
Mean arterial blood pressure (mm Hg)	98.9 ± 10.2	97.6 ± 11.5	0.3
Systolic blood pressure (mm Hg)	132.5 ± 18.7	133.7 ± 16.4	0.6
Diastolic blood pressure (mm Hg)	80.2 ± 10.4	81.5 ± 10.1	0.3
Total cholesterol (mg/dL)	213.4 ± 43.2	213.1 ± 39.2	0.9
High-density lipoprotein cholesterol (mg/dL)	38.7 ± 13.5	39.0 ± 16.8	0.9
Albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.4	0.5
Transferrin (mg/dL)	262.0 ± 41.1	265.8 ± 47.3	0.5
Use of angiotensin-converting enzyme inhibitors (%)	37.2	34.1	0.2
Follow-up during trial			
Protein intake from food (g/kg/d)	0.73 ± 0.10	0.48 ± 0.11	<0.001
Protein intake from food and amino and keto acids (g/kg/d)	0.73 ± 0.10	0.66 ± 0.11	<0.001
Energy intake (kcal/kg/d)	21.9 ± 4.6	22.0 ± 4.7	0.8
Mean arterial pressure (mm Hg)	97.2 ± 8.0	96.1 ± 8.0	0.3
Systolic blood pressure (mm Hg)	132.9 ± 15.8	131.9 ± 14.9	0.6
Diastolic blood pressure (mm Hg)	79.3 ± 7.2	78.1 ± 7.7	0.2
Follow-up visits with angiotensin-converting enzyme–inhibitor use (%)	38.8 ± 1.9	32.5 ± 40.6	0.2

Note: Values expressed as mean ± SD or percent. Total and high-density lipoprotein cholesterol in mg/dL may be converted to mmol/L by multiplying by 0.02586; albumin in g/dL to g/L by multiplying by 10; transferrin in mg/dL to g/L by multiplying by 0.01.

baseline GFR was 18.5 ± 3.4 mL/min/1.73 m^2 (median, 18.6 mL/min/1.73 m^2), and proteinuria was 1.4 ± 1.7 g/d of protein (median, 0.7 g/d). These characteristics were balanced between the randomized groups (Table 2).

Nutritional Parameters During Follow-up

During the trial, mean separation in dietary protein intake, not including amino acids and keto acids, between the low- and very low-protein groups was 0.25 g/kg/d (Table 2; Fig 1). Selected nutritional parameters were measured in a subgroup of participants 9 months after study end (phase 5). There were no differences in protein intake, energy intake, serum albumin and creatinine levels, urinary creatinine excretion, and anthropometric measures between the low- and very low-protein diet groups (Table 3).

Effect of the Very Low-Protein Diet on Kidney Failure, the Composite Outcome, and Death

Median duration of follow-up until kidney failure, death, or administrative censoring was 3.2 years, and median time to death was 10.6 years. Of 255 participants, 227 (89.4%) developed kidney failure and 79 (30.9%) died of any cause, with 17 deaths occurring before kidney failure, and 244 (95.7%) reached the composite outcome. In the low-protein group, 117 (90.7%) participants developed kidney failure, 30 (23.3%, 16% due to cardiovascular disease) died, and 124 (96.1%) reached the composite outcome. In the very low-protein group, 110 (87.3%) participants developed kidney failure, 49 (38.9%, 21% due to cardiovascular disease) died, and 120 (95.2%) reached the composite outcome. Of patients who reached kidney failure during the trial, 12%

Table 3. Nutritional Parameters 9 Months After Completion of Trial

Factor	Low-Protein Diet		Very Low-Protein Diet		*P*
	No. of Patients	Value	No. of Patients	Value	
Protein intake from food (g/kg/d)	35	0.7 ± 0.2	50	0.7 ± 0.2	0.8
Energy intake (kcal/kg/d)	35	1,436 ± 332	50	1,562 ± 477	0.1
Urine creatinine (mg/d)	35	1,097.4 ± 308.5	50	1,086.7 ± 332.1	0.9
Transferrin (mg/dL)	35	256.3 ± 26.7	52	265.5 ± 44.3	0.2
Albumin (g/dL)	35	4.2 ± 0.4	52	4.2 ± 0.5	0.4
Body weight (kg)	35	75.2 ± 14.6	52	76.6 ± 16.1	0.7
Body mass index (kg/m^2)	35	25.8 ± 3.7	52	26.0 ± 4.1	0.8
Biceps skinfold thickness (mm)	31	7.2 ± 4.9	47	8.5 ± 5.8	0.3
Triceps skinfold thickness (mm)	30	15.8 ± 7.9	47	15.7 ± 6.4	0.9
Arm circumference (cm)	31	30.7 ± 4.0	47	31.0 ± 3.8	0.8
Subscapular skinfold (mm)	28	16.6 ± 7.6	44	16.3 ± 7.2	0.9

Note: Albumin in g/dL may be converted to g/L by multiplying by 10; transferrin in mg/dL to g/L by multiplying by 0.01.

underwent preemptive kidney transplantation in both diet groups.

Figure 2 shows numbers of events during and after the trial. Few participants died before kidney failure in either group, with no difference between groups; however, there were more deaths subsequent to kidney failure in the very low-protein group compared with the low-protein group.

Kaplan-Meier curves (Fig 3) by randomized groups did not show a difference in risk of kidney failure (log rank $P = 0.4$) or the composite outcome ($P = 0.5$; data not shown), but showed a greater probability of death in the very

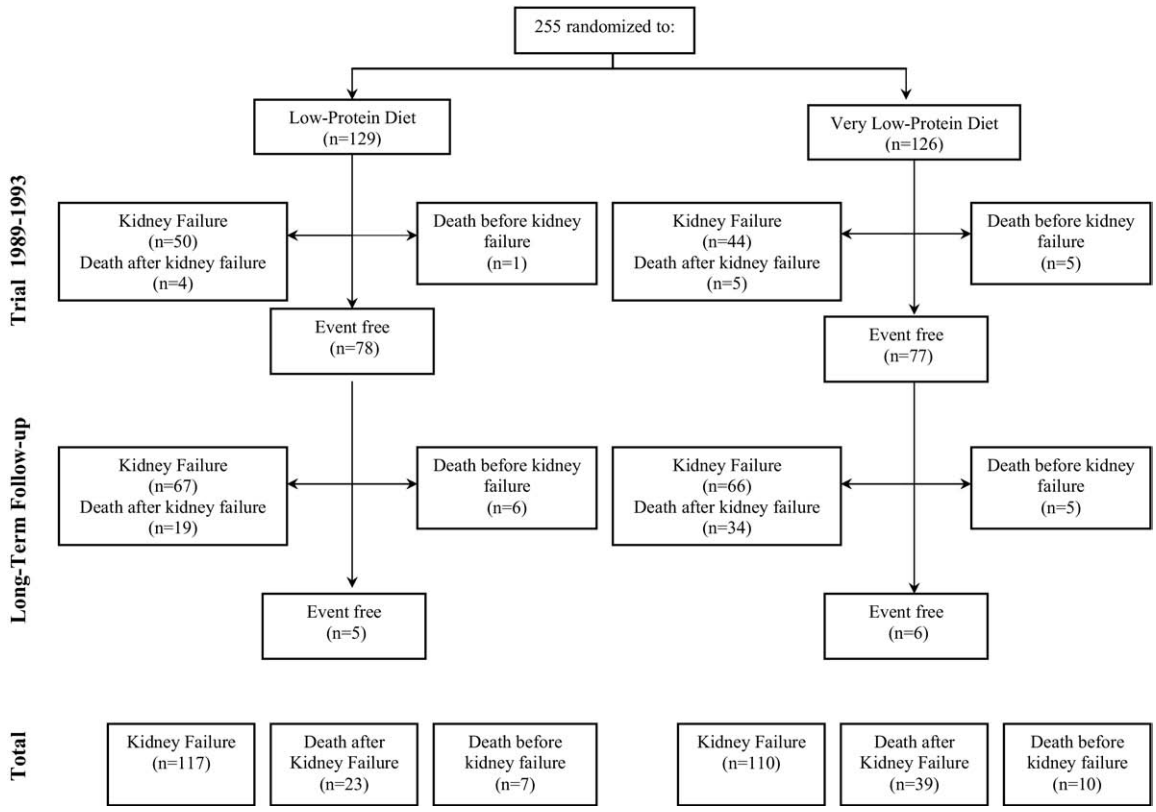

Figure 2. Patients at risk of kidney failure or death during the trial and long-term follow-up.

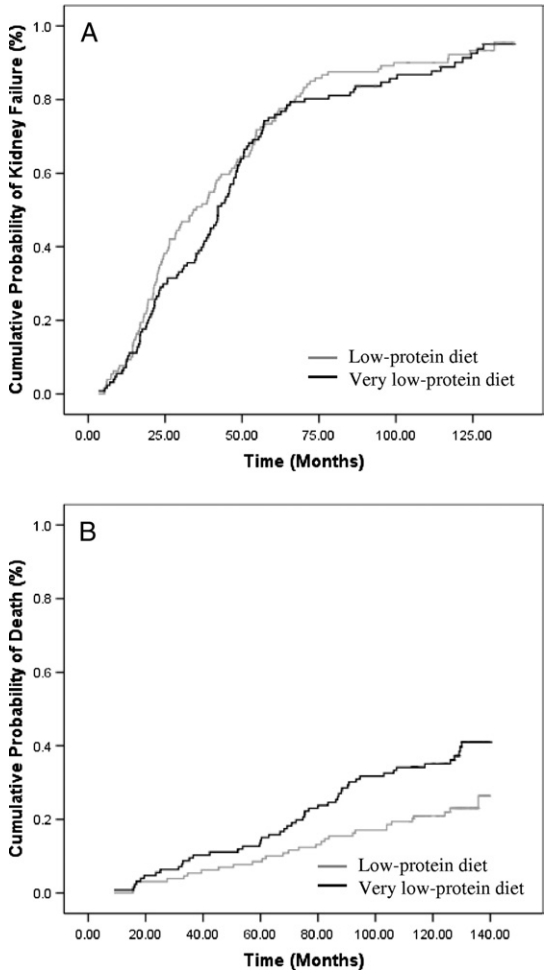

Figure 3. Kaplan-Meier survival curves for (A) kidney failure and (B) all-cause mortality. Low- and very low-protein intake refer to target protein intake of 0.58 and 0.28 g/kg/d, respectively. Note: the cumulative probabilities in the figure represent the conditional probabilities of having events and therefore are not identical to the percentage of the population who had events as reported in the text.

low-protein group ($P = 0.01$). In unadjusted analyses, randomized diet groups were not associated with kidney failure or the composite outcome; however, the very low-protein group had 82% greater risk of all-cause mortality (Table 4). Covariate adjustment did not appreciably alter the observed associations.

In time-dependent Cox models, there was no association between assignment to a very low-protein diet and risk of kidney failure or the composite outcome during or after the trial. However, the very low-protein diet was associated with increased risk of death after the trial. When follow-up time was categorized as less or greater than 6 years, the very low-protein diet was not associated with risk of kidney failure or the composite outcome at either time or with death at less than 6 years, but was associated with a greater than 2-fold increased risk of death after 6 years (P for interaction = 0.3).

Additional Analyses

There was no difference between diet groups in risk of death before kidney failure (HR, 1.12; 95% confidence interval, 0.42 to 2.94). However, the very low-protein diet was associated with a greater than 2-fold increased risk of death subsequent to kidney failure (HR, 2.43; 95% CI, 1.33 to 4.43). The interaction of protein group with deaths before or subsequent to kidney failure did not reach statistical significance ($P = 0.1$). There was no difference in risk of any of the outcomes by blood pressure assignment (data not shown).

The very low-protein diet was associated with increased risk of death after kidney failure occurring both during and after the trial and with risk of death after kidney failure occurring 4 years from the start of the trial and after 4 years (data not shown).

DISCUSSION

In the MDRD Study randomized cohort, assignment to a very low-protein diet with a mixture of essential keto acids and amino acids versus a low protein-diet during the trial was associated with a significantly greater risk of death during long-term follow-up, but had no effect on the development of kidney failure or a composite outcome of kidney failure and death. Although very low-protein diets generally are not recommended, we believe these findings are clinically relevant given the continued interest in the use of dietary protein restriction as an intervention to delay progression of kidney disease.[10,13,14]

There are limited data from randomized controlled trials examining the effect of very low-protein diet on the progression of advanced kidney disease and no data for long-term outcomes. Ihle et al[3] randomly assigned 64 patients with serum creatinine concentrations of 350 to 1,000 μmol/L (4 to 11.3 mg/dL) to a regular diet or 0.4 g of protein/kg of body weight per day with

Table 4. Effect of Very Low-Protein Versus Low-Protein Diet on Outcomes

	Hazard Ratio (95% Confidence Interval)		
	Kidney Failure	Deaths†	Kidney Failure and Deaths
Analysis*	No. of Events = 227	No. of Events = 79	No. of Events = 244
No covariate adjustment	0.90 (0.68-1.19)	1.82 (1.15-2.87)	0.92 (0.70-1.21)
Adjusted for baseline glomerular filtration rate	0.85 (0.64-1.13)	1.83 (1.16-2.89)	0.88 (0.67-1.16)
Adjusted for baseline covariates‡	0.83 (0.62-1.12)	1.92 (1.15-3.20)	0.89 (0.67-1.18)

*All analyses stratified by clinical center.

†Includes deaths before and after kidney failure.

‡Hazard ratios were adjusted for the following baseline variables: log urine protein, log urine protein × follow-up time interaction, polycystic kidney disease, polycystic kidney disease × follow-up time, African American race, transferrin level, high-density lipoprotein cholesterol level, mean arterial pressure, glomerular filtration rate, age, and blood pressure goal assignment. Sex was added for analyses for mortality.

an energy supplement to provide 35 to 40 kcal/kg/d. During 18 months of follow-up, the very low-protein diet was associated with lower rates of kidney failure and a slower decrease in kidney function measured by using chromium-51–labeled EDTA clearance. Pedrini et al[25] performed meta-analyses of randomized controlled trials of dietary protein restriction and found that a low-protein diet significantly reduced the risk of death or kidney failure in patients with nondiabetic kidney disease. In 1998, a meta-analysis by Kasiske et al[26] that included randomized and nonrandomized studies found a relatively small effect of dietary protein restriction on the rate of decrease in GFR. An updated meta-analysis of 7 randomized controlled trials with 1,494 patients with nondiabetic kidney disease found that protein restriction decreased the incidence of a composite outcome (death, dialysis therapy, or kidney transplantation during the trial; odds ratio, 0.61; 95% confidence interval, 0.46 to 0.83).[10] This analysis included patients at varying stages of CKD and studied low- and very low-protein diets, but did not analyze these diet groups separately. In a recent randomized controlled trial, a supplemented very low-protein diet (0.3 g/kg body weight per day supplemented with keto acids, amino acids, and vitamins) was effective in postponing dialysis therapy in elderly patients with stage 5 nondiabetic kidney disease.[13]

This analysis from the MDRD Study randomized cohort is the first to examine the long-term effects of a very low-protein diet on clinical outcomes in patients with advanced nondiabetic kidney disease. We found that assignment to a very low-protein diet significantly increased the risk of death during long-term follow-up, but did not affect the risk of kidney failure or a composite of kidney failure and death. The composite outcome reflects the kidney failure outcome for 2 reasons. First, there were many more kidney failure events than deaths, and second, the composite includes only deaths before kidney failure, and most of the deaths occurred after kidney failure. The increased risk of death is especially evident with longer follow-up and after kidney failure and may indicate a deleterious effect of the very low-protein diet on postdialysis death.

There are several potential explanations for the long-term findings. First, participants may have continued to adhere to a very low-protein diet beyond the duration of the trial and after the development of kidney failure, a circumstance in which the very-low protein diet may be harmful. Pollock et al[27] found that patients with reduced kidney function who were advised to restrict their protein intake were unable to increase their protein intake after the start of dialysis therapy despite dietary counseling. Because dialysis is a known catabolic event, the inability to increase their protein intake may have resulted in a negative nitrogen balance, a known risk factor for death.[28] Conversely, another observational study found that patients on very low-protein diets were able to increase their protein intake after the start of hemodialysis.[29] The phase 5 data from the MDRD Study do not support this first hypothesis because protein intake was similar in both study arms. However, it must be acknowledged that phase 5 represents a select and small subgroup of participants.

Second, short-term exposure to the very low-protein diet may have deleterious effects during the long term and especially at the onset of kidney failure and may potentiate the negative impact of malnutrition associated with dialysis and earlier stages of CKD.[28,30-33] The reduction in urine creatinine excretion seen with very low-protein diets may indicate a reduction in skeletal muscle mass.[34,35] Thus, although most studies investigating the effect of very low-protein diets on nutritional status report short-term changes in nutritional parameters with stabilization after 3 to 4 months, it is possible that there is a more sustained, but gradual, loss of muscle and/or somatic protein.[3,36-38] The safety of the dietary protein restriction during the MDRD Study was monitored by using several nutritional status indicators. During the trial, body weight, percentage of body fat, arm muscle area, serum transferrin level, and urine creatinine excretion decreased and serum albumin level increased in both the low- and very low-protein diet groups.[39] Percentage of body fat decreased more in the low-protein diet group, whereas urine creatinine excretion decreased to a greater extent in the very low-protein diet group. Mean energy intake decreased in both the low- and very low-protein diet groups. The mean change in these variables was small, and there was a more gradual, but continued, decrease after the first 4 months until the end of the trial. Two study B participants reached a stop point for malnutrition. However, the subgroup data available at phase 5 in the MDRD Study do not support this second hypothesis because nutritional parameters were similar between the diet groups. However, as noted, this represents a select subgroup of participants. In addition, if this hypothesis were true, one would expect the majority of deaths to occur early, ie, a year or 2 after dialysis therapy initiation. Our results indicate that the very low-protein diet is associated with increased risk of death after kidney failure both 4 years from the start of the trial and 4 years after completion of the trial.

Third, dietary protein restriction was accompanied by a concomitant decrease in mean energy intake in some studies, and this could potentially contribute to the development of protein calorie malnutrition.[40-42] However, although mean energy intake decreased in both diet groups in the MDRD Study, there was no difference in mean energy intake during the trial or at phase 5 between the diet groups.

Fourth, one could hypothesize a direct toxic effect of the keto acid–amino acid supplements. The original keto acid preparation used in the pilot and feasibility study had a relatively low tryptophan content, raising concerns that this might lead to decreased protein synthesis and therefore malnutrition. Hence, additional tryptophan was added to the keto acid–amino acid supplement used in the trial. After the trial began, human and animal studies described a potential nephrotoxic effect of a metabolite of tryptophan, indoxyl sulfate.[43-47] In addition, in a post hoc analysis from the pilot and feasibility phase of the MDRD Study in which the supplement had lower tryptophan content, there was a trend toward a slower rate of progression of kidney disease in patients on the keto acid–amino acid mixture than those supplemented with an amino acid mixture.[48] However, we are unable to directly test whether this mechanism may have a role in explaining our results.

Fifth, it must be acknowledged that the observed association of the very low-protein diet with increased death may be a spurious one.

The strengths of our study include random assignment to dietary protein groups, long-term follow-up, complete ascertainment of data by using clinical outcomes, and use of intention-to-treat principle in analyses. The primary limitation is lack of dietary protein and nutritional measurements and information for medical management and clinical course during long-term follow-up, leading to an inability to understand the exact mechanism underlying the increased risk of death seen in the very low protein-diet group. We also acknowledge that the study may have been underpowered to study the interactions tested. As presented in a previous publication from our group, the MDRD Study cohort has a lower competing risk of mortality compared with other populations with CKD.[49] The low risk of mortality may be attributable to the relatively young and healthy group of patients with predominantly nondiabetic CKD and low prevalence of cardiovascular disease at baseline represented by the MDRD cohort.

In summary, assignment to a very low-protein diet increased the risk of death in long-term follow-up of the MDRD Study, but had no im-

pact on delaying the progression to kidney failure and no relationship with a composite outcome of kidney failure and death. These results emphasize the importance of long-term follow-up when evaluating the impact of interventions designed to slow the progression of chronic diseases.

ACKNOWLEDGEMENTS

Some of these results were presented in abstract form at the 2004 American Society of Nephrology Meeting, St Louis, MO, October 24-November 1, 2004.

Support: This study was supported by grants K23 DK067303, K23 DK02904, K24 DK078204, and UO1 DK35073 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD). The NIDDKD had no role in the design, conduct, and analysis of this study or in the decision to submit the manuscript for publication. Drs Sarnak, Menon, Greene, and Wang had full access to the data.

Financial Disclosure: None.

REFERENCES

1. Hostetter TH, Meyer TW, Rennke HG, Brenner BM: Chronic effects of dietary protein in the rat with intact and reduced renal mass. Kidney Int 30:509-517, 1986

2. Salusky I, Kleinknecht C, Broyer M, Gubler MC: Prolonged renal survival and stunting, with protein-deficient diets in experimental uremia. Reversal of these effects by addition of essential amino acids. J Lab Clin Med 97:21-30, 1981

3. Ihle BU, Becker GJ, Whitworth JA, Charlwood RA, Kincaid-Smith PS: The effect of protein restriction on the progression of renal insufficiency. N Engl J Med 321:1773-1777, 1989

4. Mitch WE, Walser M, Steinman TI, et al: The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. N Engl J Med 311:623-629, 1984

5. Rosman JB, ter Wee PM, Meijer S, et al: Prospective randomised trial of early dietary protein restriction in chronic renal failure. Lancet 2:1291-1296, 1984

6. Walser M, Hill SB, Ward L, Magder L: A crossover comparison of progression of chronic renal failure: Ketoacids versus amino acids. Kidney Int 43:933-939, 1993

7. Locatelli F, Alberti D, Graziani G, et al: Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. Lancet 337:1299-1304, 1991

8. Rosman JB, Langer K, Brandl M, et al: Protein-restricted diets in chronic renal failure: A four year follow-up shows limited indications. Kidney Int Suppl 27:S96-S102, 1989

9. Williams PS, Stevens ME, Fass G, Irons L, Bone JM: Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure:A prospective, randomized, controlled trial. Q J Med 81:837-855, 1991

10. Fouque D, Wang P, Laville M, Boissel JP: Low protein diets delay end-stage renal disease in non diabetic adults with chronic renal failure. Cochrane Database Syst Rev CD001892, 2000

11. Klahr S, Levey AS, Beck GJ, et al: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 330:877-884, 1994

12. Levey AS, Greene T, Sarnak MJ, et al: Effect of dietary protein restriction on the progression of kidney disease: Long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. Am J Kidney Dis 48:879-888, 2006

13. Brunori G, Viola BF, Parrinello G, et al: Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: A prospective randomized multicenter controlled study. Am J Kidney Dis 49:569-580, 2007

14. Rabbat CG: Review: A low-protein diet delays end-stage renal disease or death in stage 3 to 5 chronic kidney disease. ACP J Club 145:64, 2006

15. Nathan DM, Cleary PA, Backlund JY, et al: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353:2643-2653, 2005

16. Rosborough TK, Bank CH, Cummings MK, Phillips PP, Pierach CA: MRFIT after 10.5 years. JAMA 264:1534-1535, 1990

17. Sarnak MJ, Greene T, Wang X, et al: The effect of a lower target blood pressure on the progression of kidney disease: Long-term follow-up of the Modification of Diet in Renal Disease Study. Ann Intern Med 142:342-351, 2005

18. Beck GJ, Berg RL, Coggins CH, et al: Design and statistical issues of the Modification of Diet in Renal Disease trial. The Modification of Diet in Renal Disease Study Group. Control Clin Trials 12:566-586, 1991

19. Klahr S: Role of dietary protein and blood pressure in the progression of renal disease. Kidney Int 49:1783-1786, 1996

20. Maroni BJ, Steinman TI, Mitch WE: A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 27:58-65, 1985

21. Metropolitan life Insurance Company: Metropolitan height and weight tables. Stat Bull 64:1-9, 1983

22. Levey AS, Adler S, Caggiula AW, et al: Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. Am J Kidney Dis 27:652-663, 1996

23. Curb JD, Ford CE, Pressel S, et al: Ascertainment of vital status through the National Death Index and the Social Security Administration. Am J Epidemiol 121:754-766, 1985

24. Hunsicker LG, Adler S, Caggiula A, et al: Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. Kidney Int 51:1908-1919, 1997

25. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: A meta-analysis. Ann Intern Med 124:627-632, 1996

26. Kasiske BL, Lakatua JD, Ma JZ, Louis TA: A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. Am J Kidney Dis 31:954-961, 1998

27. Pollock CA, Ibels LS, Zhu FY, et al: Protein intake in renal disease. J Am Soc Nephrol 8:777-783, 1997

28. Pollock CA, Ibels LS, Allen BJ, et al: Total body nitrogen as a prognostic marker in maintenance dialysis. J Am Soc Nephrol 6:82-88, 1995

29. Vendrely B, Chauveau P, Barthe N, et al: Nutrition in hemodialysis patients previously on a supplemented very low protein diet. Kidney Int 63:1491-1498, 2003

30. Avram MM, Mittman N, Bonomini L, Chattopadhyay J, Fein P: Markers for survival in dialysis: A seven-year prospective study. Am J Kidney Dis 26:209-219, 1995

31. Bergstrom J, Lindholm B: Malnutrition, cardiac disease, and mortality: An integrated point of view. Am J Kidney Dis 32:834-841, 1998

32. Kopple JD: Effect of nutrition on morbidity and mortality in maintenance dialysis patients. Am J Kidney Dis 24:1002-1009, 1994

33. Menon V, Greene T, Wang X, et al: C-Reactive protein and serum albumin as predictors of all-cause and cardiovascular mortality in patients with chronic kidney disease. Kidney Int 68:772-776, 2005

34. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S: Measurement of muscle mass in humans: Validity of the 24-hour urinary creatinine method. Am J Clin Nutr 37:478-494, 1983

35. Walser M: Creatinine excretion as a measure of protein nutrition in adults of varying age. JPEN J Parenter Enteral Nutr 11:S73-S78, 1987 (suppl 5)

36. Lucas PA, Meadows JH, Roberts DE, Coles GA: The risks and benefits of a low protein-essential amino acid-keto acid diet. Kidney Int 29:995-1003, 1986

37. Chauveau P, Barthe N, Rigalleau V, et al: Outcome of nutritional status and body composition of uremic patients on a very low-protein diet. Am J Kidney Dis 34:500-507, 1999

38. Chauveau P, Vendrely B, El Haggan W, et al: Body composition of patients on a very low-protein diet: A two-year survey with DEXA. J Ren Nutr 13:282-287, 2003

39. Kopple JD, Levey AS, Greene T, et al: Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. Kidney Int 52:778-791, 1997

40. Kopple JD, Monteon FJ, Shaib JK: Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. Kidney Int 29:734-742, 1986

41. Rigalleau V, Combe C, Blanchetier V, et al: Low protein diet in uremia: Effects on glucose metabolism and energy production rate. Kidney Int 51:1222-1227, 1997

42. Mehrotra R, Nolph KD: Treatment of advanced renal failure: Low-protein diets or timely initiation of dialysis? Kidney Int 58:1381-1388, 2000

43. Aoyama I, Niwa T: An oral adsorbent ameliorates renal overload of indoxyl sulfate and progression of renal failure in diabetic rats. Am J Kidney Dis 37:S7-S12, 2001 (suppl 2)

44. Kopple J: Nutritional Management of Renal Disease (ed 2) Baltimore, Lippincott Williams & Wilkins, 2003

45. Niwa T, Ise M: Indoxyl sulfate, a circulating uremic toxin, stimulates the progression of glomerular sclerosis. J Lab Clin Med 124:96-104, 1994

46. Niwa T, Tsukushi S, Ise M, et al: Indoxyl sulfate and progression of renal failure: Effects of a low-protein diet and oral sorbent on indoxyl sulfate production in uremic rats and undialyzed uremic patients. Miner Electrolyte Metab 23:179-184, 1997

47. Sanaka T, Sugino N, Teraoka S, Ota K: Therapeutic effects of oral sorbent in undialyzed uremia. Am J Kidney Dis 12:97-103, 1988

48. Teschan PE, Beck GJ, Dwyer JT, et al: Effect of a ketoacid-aminoacid-supplemented very low protein diet on the progression of advanced renal disease: A reanalysis of the MDRD feasibility study. Clin Nephrol 50:273-283, 1998

49. Menon V, Wang X, Sarnak MJ, et al: Long-term outcomes in nondiabetic chronic kidney disease. Kidney Int 73:1310-1315, 2008