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THE EFFECTS OF DIETARY PROTEIN RESTRICTION AND BLOOD-PRESSURE CONTROL ON THE PROGRESSION OF CHRONIC RENAL DISEASE

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Abstract *Background.* Restricting protein intake and controlling hypertension delay the progression of renal disease in animals. We tested these interventions in 840 patients with various chronic renal diseases.

Methods. In study 1, 585 patients with glomerular filtration rates of 25 to 55 ml per minute per 1.73 m^2 of body-surface area were randomly assigned to a usual-protein diet or a low-protein diet (1.3 or 0.58 g of protein per kilogram of body weight per day) and to a usual- or a low-blood-pressure group (mean arterial pressure, 107 or 92 mm Hg). In study 2, 255 patients with glomerular filtration rates of 13 to 24 ml per minute per 1.73 m^2 were randomly assigned to the low-protein diet (0.58 g per kilogram per day) or a very-low-protein diet (0.28 g per kilogram per day) with a keto acid–amino acid supplement, and a usual- or a low-blood-pressure group (same values as those in study 1). An 18-to-45-month follow-up was planned, with monthly evaluations of the patients.

Results. The mean follow-up was 2.2 years. In study 1, the projected mean decline in the glomerular filtration rate at three years did not differ significantly between the diet groups or between the blood-pressure groups. As compared with the usual-protein group and the usual-blood-pressure group, the low-protein group and the low-blood-pressure group had a more rapid decline in the glomerular filtration rate during the first four months after randomization and a slower decline thereafter. In study 2, the very-low-protein group had a marginally slower decline in the glomerular filtration rate than did the low-protein group ($P = 0.07$). There was no delay in the time to the occurrence of end-stage renal disease or death. In both studies, patients in the low-blood-pressure group who had more pronounced proteinuria at base line had a significantly slower rate of decline in the glomerular filtration rate.

Conclusions. Among patients with moderate renal insufficiency, the slower decline in renal function that started four months after the introduction of a low-protein diet suggests a small benefit of this dietary intervention. Among patients with more severe renal insufficiency, a very-low-protein diet, as compared with a low-protein diet, did not significantly slow the progression of renal disease. (N Engl J Med 1994;330:877-84.)

PROTEIN restriction and control of blood pressure delay the progression of renal disease in laboratory animals.[1-3] Most studies in humans[4-10] have suggested that a restriction of dietary protein is beneficial, especially in patients with advanced renal disease,[4,10] but some of these studies were inconclusive because of deficiencies in their design or because changes in renal function were assessed only by measurements of serum creatinine, which may be affected by diet. Furthermore, few previous studies of renal disease have examined the effect on renal function of a reduction in blood pressure to a level below that currently recommended for the prevention and treatment of cardiovascular disease.[11]

We describe the results of the intention-to-treat analyses of the Modification of Diet in Renal Disease (MDRD) Study, which included two randomized, multicenter trials involving a total of 840 patients with various chronic renal diseases. The study tested the hypotheses that two interventions — a reduction in dietary protein and phosphorus intake and the maintenance of blood pressure at a level below that usually recommended[11] — retard the progression of renal disease and that these interventions are safe and acceptable to patients for long-term use.[12-14]

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*The institutions and investigators participating in the study group are listed in the Appendix.

METHODS

The organization, design, and methods of the MDRD Study have been reported in detail previously.[12-22] The study was approved by the institutional review committee at each participating center, and all patients gave written informed consent.

Recruitment, Screening, and Base-Line Period

The recruitment procedures have been described elsewhere.[21] The following enrollment criteria were used: an age of 18 to 70 years, a serum creatinine concentration of 1.2 to 7.0 mg per deciliter

(106 to 619 μmol per liter) in women and 1.4 to 7.0 mg per deciliter (124 to 619 μmol per liter) in men or a creatinine clearance of less than 70 ml per minute per 1.73 m^2 of body-surface area, and a mean arterial pressure (calculated as two thirds of the diastolic plus one third of the systolic blood pressure) of 125 mm Hg or less. Normotensive patients were included in the study, and evidence of a progressive decline in the glomerular filtration rate was not required for enrollment. Patients were excluded for the following reasons: pregnancy, a body weight under 80 percent or over 160 percent of standard body weight,[23] diabetes mellitus requiring insulin therapy, urinary protein excretion exceeding 10 g per day, a history of renal transplantation or chronic medical conditions, or doubts about compliance.[13] Patients were eligible for study 1 or 2 on the basis of their glomerular filtration rate. In each study, we assessed the effects of two dietary and two blood-pressure interventions. The planned duration of follow-up was 18 to 45 months.

During a three-month base-line period, patients were deemed eligible for study 1 if their glomerular filtration rate was 25 to 55 ml per minute per 1.73 m^2, their dietary protein intake was ≥0.9 g per kilogram of body weight per day, and their mean arterial pressure was ≤125 mm Hg. Patients were eligible for study 2 if their glomerular filtration rate was 13 to 24 ml per minute per 1.73 m^2 and their mean arterial pressure was ≤125 mm Hg, irrespective of protein intake. Blood pressure, creatinine clearance, and urinary protein excretion were measured initially and then every month during the base-line period (a total of four measurements). During this period, patients were instructed about the study procedures, dietary protein intake, and control of blood pressure.

Randomization and Intervention

For randomization, patients were stratified according to the clinical center and the average base-line blood pressure (in both studies) and according to the rate of change in the serum creatinine concentration during the screening period (in study 1 only).[13] After randomization, the patients were instructed to modify their intake of protein and phosphorus to achieve the goals of the diet to which they had been assigned. Dietary sodium intake was not restricted.

We used pharmacologic and nonpharmacologic therapies to achieve the desired blood-pressure values in the usual- and low-pressure groups. The recommended antihypertensive regimen was an angiotensin-converting–enzyme inhibitor with or without a diuretic agent; a calcium-channel blocker and other medications were added as needed. Hyperphosphatemia was treated with calcium carbonate as needed.

Follow-up Procedures and Measurements

Protein intake was assessed monthly on the basis of 24-hour urinary excretion of urea nitrogen.[24] Nitrogen in the prescribed keto acid–amino acid supplement was subtracted from urinary urea nitrogen. The intake of protein, calories, and other nutrients was assessed every two months on the basis of three-day dietary records. Blood pressure was measured monthly, and when necessary, adjustments in therapy were made monthly or more often. The glomerular filtration rate was measured at two months, at four months, and every four months thereafter on the basis of the renal clearance of [^{125}I]iothalamate (Isotex Diagnostics, Friendswood, Tex.).[17] Anthropometric measurements were obtained every four months.[16,23]

Definition and Ascertainment of End Points

The rate of change in the glomerular filtration rate (the slope) was the primary outcome measure. Slopes were calculated on the basis of the final base-line glomerular filtration rate and all follow-up rates without adjustment for the body-surface area. Slopes were not calculated for 11 patients for whom we lacked measurements after the base-line period.

Conditions requiring withdrawal from the study (stopping points) included malnutrition (weight loss to a level below 75 percent of standard body weight or a serum albumin concentration under 3.0 g per deciliter despite corrective measures), a rapid decline in the glomerular filtration rate in study 1 only (to a value <50 percent of the base-line rate, if that value was ≤40 ml per minute per 1.73 m^2, or to a value of ≤20 ml per minute per 1.73 m^2, if the base-line rate was >40 ml per minute per 1.73 m^2), end-stage renal disease requiring dialysis or transplantation, and the development of other serious medical conditions.

Statistical Analysis

Using an intention-to-treat approach, we related follow-up measurements of the patients' glomerular filtration rates to the prescribed interventions. Although the protocol called for testing the effects of diet and blood pressure on the decline in the glomerular filtration rate with the use of a single-slope linear model, the possibility of a nonlinear decline was also considered.[13] In study 1, patients assigned to either the low-protein diet or the low-blood-pressure group had a faster initial decline in the glomerular filtration rate (from base line to four months) and a slower subsequent decline than those assigned to the usual-protein diet or the usual-blood-pressure group. Therefore, the primary analysis used a two-slope spline model in which each patient was assumed to have an initial slope from base line to four months and a different slope subsequently. The mean initial and subsequent slopes were estimated for each group by the method of maximum likelihood in a mixed-effects model,[25] with the stratification factors used at randomization included as covariates. The effects of the dietary and blood-pressure interventions were tested on the initial and subsequent slopes and on the mean projected change in the glomerular filtration rate from base line to three years.

In study 2, a single-slope linear model was used. Because of the large number of stopping points due to end-stage renal disease, however, we obtained maximum-likelihood estimates of the intercept and slope using an informative censoring model,[26] which took into account the time to the occurrence of end-stage renal disease or death.

In both studies, the interaction between the diet and blood-pressure interventions was tested for significance before the effects of individual interventions were evaluated. To assess the uniformity of the effects of diet and blood pressure, we compared their effects in subgroups defined initially by age, sex, renal diagnosis, base-line glomerular filtration rate, and urinary protein excretion. Subsequently, other base-line factors were also examined, including race, the presence or absence of hypertension, blood pressure, protein intake, the serum cholesterol concentration, and the rate of change in the serum creatinine concentration during screening.

Time-to-event analyses were conducted with the use of the Kaplan–Meier method to estimate cumulative-incidence curves[27] and with stratified log-rank tests to compare the diet and blood-pressure groups. The data from these analyses were censored at the date of the final follow-up visit in study 1 and on June 15, 1993, approximately five months after the final follow-up visit, in study 2. When testing for the effect of one intervention, we stratified the analysis according to the other intervention and the randomization strata. All statistical analyses were performed with two-tailed tests.

Results

Recruitment and Follow-up

A total of 840 patients were enrolled in the study and randomly assigned to the various diet and blood-pressure interventions (Table 1). The mean follow-up was 2.2 years (range, 0 to 3.7). Eleven of the 585 patients in study 1 (1.9 percent) and 3 of the 255 in study 2 (1.2 percent) were lost to follow-up.

Base-Line Characteristics

The clinical characteristics of the patients in each diet and blood-pressure group are shown in Table 2.[22] Sixty percent of the patients were men, 85 percent were white, and the average age was 52 years. The most common renal diagnoses were glomerular diseases (25 percent) and polycystic kidney disease

(24 percent); 3 percent of the patients had non-insulin-dependent diabetes.

Adherence

Differences in protein intake between the diet groups were achieved by the fourth month of follow-up and remained relatively constant throughout the follow-up period (Fig. 1). On the basis of pill counts, the median amount of prescribed keto acid–amino acid supplements taken was 92 percent.

The difference in mean blood pressure between the usual-pressure and the low-pressure groups during the follow-up period was 4.7 mm Hg ($P<0.001$) in studies 1 and 2 (Fig. 1). Antihypertensive (including diuretic) drugs were taken for more than half the follow-up period by 80 percent and 90 percent of the patients in the usual- and low-pressure groups, respectively, in study 1 and by 85 and 98 percent in study 2. In study 1, angiotensin-converting–enzyme inhibitors were taken alone or in combination for more than half the follow-up period by 34 and 54 percent of the patients in the usual- and low-pressure groups, respectively, and by 44 percent of those in each diet group. In study 2, angiotensin-converting–enzyme inhibitors were used by 27 and 43 percent of the patients in the usual- and low-pressure groups, respectively, and by 39 and 32 percent of the patients in the low- and very-low-protein groups, respectively.

Table 2. Clinical Characteristics of the Study Population at the Time of Randomization.*

Variable	Usual Protein		Low Protein		Overall
	Usual Pressure	Low Pressure	Usual Pressure	Low Pressure	
			mean ±SD		
Study 1 (n = 585)					
Glomerular filtration rate (ml/min/1.73 m²)	37.6±9.0	38.2±8.6	38.9±8.8	39.7±9.1	38.6±8.9
Creatinine clearance (ml/min/1.73 m²)	49.2±12.6	49.2±11.6	51.3±14.4	51.9±13.7	50.4±13.1
Serum creatinine (mg/dl)†	2.0±0.5	2.0±0.5	1.9±0.5	1.9±0.5	1.9±0.5
Systolic pressure (mm Hg)	132±17	131±19	131±19	132±16	131±18
Diastolic pressure (mm Hg)	80±10	81±10	81±10	82±10	81±10
Mean arterial pressure (mm Hg)	97±10	98±11	98±11	98±10	98±11
Protein (g/kg/day)‡	1.12±0.18	1.12±0.18	1.13±0.21	1.11±0.20	1.12±0.19
Phosphorus (mg/kg/day)	17.5±5.4	17.7±4.8	17.9±5.4	17.9±4.9	17.8±5.1
Total calories (kcal/kg/day)	27.6±7.0	26.8±6.8	27.0±7.8	27.6±6.9	27.2±7.1
	Low Protein		Very Low Protein		Overall
	Usual Pressure	Low Pressure	Usual Pressure	Low Pressure	
Study 2 (n = 255)					
Glomerular filtration rate (ml/min/1.73 m²)	18.7±3.1	18.8±3.3	18.3±3.7	18.4±3.5	18.5±3.4
Creatinine clearance (ml/min/1.73 m²)	24.3±5.2	24.2±7.2	25.3±8.3	24.6±7.3	24.6±7.1
Serum creatinine (mg/dl)†	3.5±0.9	3.4±0.8	3.2±0.9	3.5±0.9	3.4±0.9
Systolic pressure (mm Hg)	131±17	134±20	135±16	132±17	133±18
Diastolic pressure (mm Hg)	80±11	80±10	81±11	82±9	81±10
Mean arterial pressure (mm Hg)	97±12	98±11	99±11	99±10	98±11
Protein (g/kg/day)‡	0.89±0.19	0.83±0.16	0.89±0.20	0.86±0.19	0.87±0.19
Phosphorus (mg/kg/day)	14.4±4.3	14.4±4.3	14.1±5.1	13.6±4.3	14.1±4.5
Total calories (kcal/kg/day)	24.8±6.9	24.9±6.3	24.6±6.6	25.0±7.2	24.9±6.7

*Usual pressure and low pressure refer to usual and low mean arterial pressure, respectively.

†To convert serum creatinine values to micromoles per liter, multiply by 88.4.

‡Protein was calculated on the basis of urinary excretion of urea nitrogen.

Table 1. Assignment of Patients to Diet and Blood-Pressure Groups in Studies 1 and 2.*

Diet†	Study 1 (N = 585)		Study 2 (N = 255)	
	Mean Arterial Pressure‡			
	usual	low	usual	low
	no. of patients			
Usual protein	145	149	—	—
Low protein	140	151	62	67
Very low protein	—	—	61	65

*Patients in study 1 had a glomerular filtration rate of 25 to 55 ml per minute per 1.73 m²; patients in study 2 had a rate of 13 to 24 ml per minute per 1.73 m².

†The usual-protein diet consisted of 1.3 g of protein and 16 to 20 mg of phosphorus per kilogram (standard body weight) per day, the low-protein diet consisted of 0.58 g of protein (≥0.35 g of protein high in essential amino acids) and 5 to 10 mg of phosphorus per kilogram per day, and the very-low-protein diet consisted of 0.28 g of protein and 4 to 9 mg of phosphorus per kilogram per day, supplemented by a keto acid–amino acid mixture (0.28 g per kilogram per day) (Ross Laboratories, Columbus, Ohio).

‡Mean arterial pressure is defined in the Methods section. The usual mean arterial pressure was ≤107 mm Hg for patients 18 to 60 years old at entry (equivalent to 140/90 mm Hg) or ≤113 mm Hg for patients ≥61 years old at entry (equivalent to 160/90 mm Hg); low mean arterial pressure was ≤92 mm Hg for patients 18 to 60 years old at entry (equivalent to 125/75 mm Hg) or ≤98 mm Hg for patients ≥61 years old at entry (equivalent to 145/75 mm Hg).

Renal Function

There were no significant interactions between the dietary or blood-pressure interventions and the rate of decline in the glomerular filtration rate in either study 1 or study 2; that is, the effects of the dietary interventions were similar in the two blood-pressure groups, and the effects of the blood-pressure interventions were similar in the two diet groups. Thus, the effects of the dietary interventions were tested by comparing all patients in the two diet groups (including those in both blood-pressure groups; right column, Tables 3 and 4), and the effects of the blood-pressure interventions were tested by comparing all patients in the two blood-pressure groups (including those in both diet groups; bottom row, Tables 3 and 4).

Study 1

The effects of diet and blood pressure on the initial and subsequent rates of decline in the glomerular filtration rate and on the projected change in the glomerular filtration rate from base line to three years, according to the two-slope model, are shown in Figure 2 and Table 3. During the first four months, both the low-protein and the low-blood-pressure interventions were associated with significantly steeper rates of de-

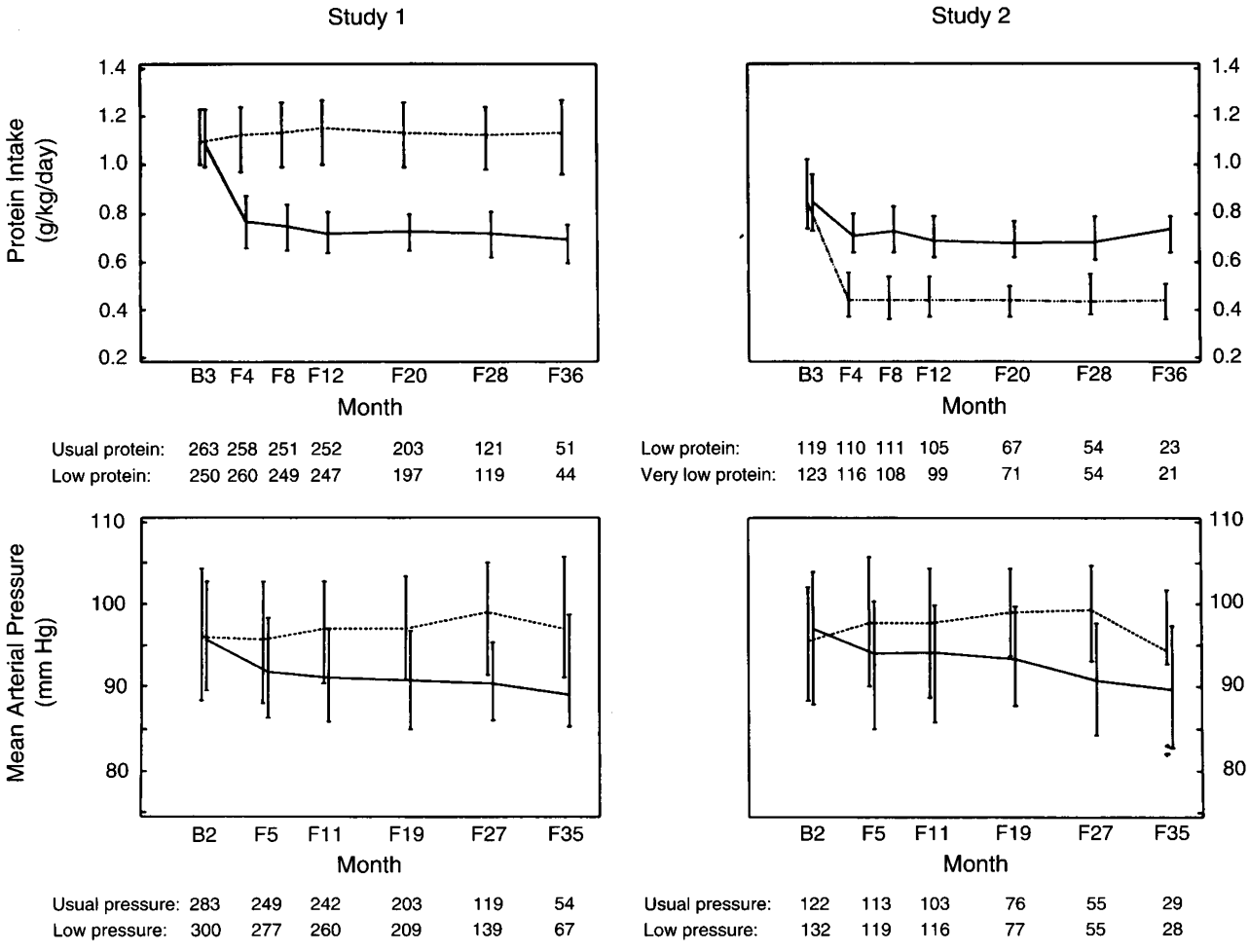

Figure 1. Estimated Protein Intake and Mean Arterial Pressure in Patients with Renal Disease Enrolled in Studies 1 and 2.

Protein intake was estimated from urinary excretion of urea nitrogen. The two diets in study 2 were designed to provide the same amount of nitrogen, but the nitrogen contained in the keto acid–amino acid mixture was subtracted from the urinary urea nitrogen in the very-low-protein group. The median values at each base-line (B) and follow-up (F) visit are given for the patients on the usual-protein diet (dashed line), the low-protein diet (solid line), and the very-low-protein diet (dashed-and-dotted line) and for those with usual blood pressure (dashed line) and low blood pressure (solid line). The bars show the 25th and 75th percentiles. The numbers of patients with estimated protein intake and blood-pressure measurements at each visit are shown below the panels. Urea nitrogen values are shown at selected times; mean arterial pressure is shown at selected visits when the glomerular filtration rate was not measured.

cline in the glomerular filtration rate than were the usual-protein and usual-blood-pressure interventions ($P = 0.004$ and $P = 0.01$, respectively). The mean decline in the glomerular filtration rate during the first four months was 2.6 ml per minute per 1.73 m^2 in all groups combined. The change in the glomerular filtration rate during this interval correlated with the changes in dietary protein intake and blood pressure (data not shown). Subsequently, the rate of decline in the glomerular filtration rate was 28 percent less in the low-protein group than in the usual-protein group ($P = 0.009$) and 29 percent less in the low-pressure group than in the usual-pressure group ($P = 0.006$). The average rate of decline after four months was 3.3 ml per minute per year in all groups combined.

The projected decline in the glomerular filtration rate at three years did not differ significantly between the diet groups or the blood-pressure groups and averaged 11.5 ml per minute for all groups combined (Table 3). The mean decline was 1.2 ml per minute less (95 percent confidence interval, −1.1 to 3.6) in the low-protein group ($P = 0.30$) and 1.6 ml per minute less (95 percent confidence interval, −0.8 to 3.9) in the low-pressure group ($P = 0.18$).

The effect of the dietary interventions was not related to age, sex, renal diagnosis, base-line glomerular filtration rate, or urinary protein excretion. However, there was a significant influence of the prescribed blood pressure and the degree of proteinuria during the base-line period (considered on the log scale) on the rate of decline in the glomerular filtration rate beginning at four months ($P = 0.006$) and on the projected decline in the rate from base line to three years ($P = 0.02$). Among the 578 patients in study 1 with follow-up measurements of the glomerular filtration rate, the benefit of low blood pressure was greatest in the 54 patients with urinary protein excretion that exceeded 3 g per day at base line, the benefit was

Table 3. Mean Rate of Decline in the Glomerular Filtration Rate in Study 1, According to Diet and Blood-Pressure Group.*

Study Period and Diet	Decline in Glomerular Filtration Rate		
	Usual Pressure	Low Pressure	Both
	milliliters per minute per 4 months		
Base line to 4 months			
Usual protein	1.2 (0.1–2.3)	2.4 (1.4–3.5)	1.8 (1.1–2.6)
Low protein	2.6 (1.5–3.7)	4.3 (3.2–5.3)	3.4 (2.7–4.2)
Both	1.9 (1.1–2.7)	3.4 (2.6–4.1)	2.6 (2.1–3.2)
	milliliters per minute per year		
4 Months to end			
Usual protein	4.5 (3.7–5.3)	3.3 (2.5–4.1)	3.9 (3.3–4.4)
Low protein	3.3 (2.5–4.2)	2.3 (1.5–3.0)	2.8 (2.2–3.4)
Both	3.9 (3.3–4.5)	2.8 (2.2–3.3)	3.3 (2.9–3.7)
	milliliters per minute per 3 years		
Base line to 3 years			
Usual protein	13.1 (10.8–15.4)	11.2 (8.8–13.5)	12.1 (10.5–13.8)
Low protein	11.5 (9.1–13.9)	10.3 (8.0–12.6)	10.9 (9.2–12.5)
Both	12.3 (10.6–14.0)	10.7 (9.1–12.4)	11.5 (10.3–12.7)

*The means were estimated with the maximum-likelihood method for the two-slope model (with separate slopes from the final base-line visit to the fourth month of follow-up and from the fourth month of follow-up to the end of follow-up) and for the projected decline in the glomerular filtration rate from base line to three years. There were no significant interactions between the diet and blood-pressure interventions. There were significant effects of dietary and blood-pressure interventions from the final base-line visit to the fourth month of follow-up ($P = 0.004$ and $P = 0.010$, respectively) and from the fourth month to the end of follow-up ($P = 0.009$ and $P = 0.006$, respectively). The estimated decline in the glomerular filtration rate over three years did not differ significantly between the diet groups or between the blood-pressure groups. Values in parentheses indicate 95 percent confidence intervals.

moderate in the 104 patients with urinary protein excretion of 1 to 3 g per day, and there was no benefit in the 420 patients with urinary protein excretion under 1 g per day (Fig. 3).

The 53 black patients had a more rapid projected mean decline in the glomerular filtration rate (19 ml per minute over three years) than the 525 other patients (11 ml per minute over three years, $P = 0.02$). The projected decline in the glomerular filtration rate in the black patients assigned to the low-blood-pressure group was approximately half that in the black patients in the usual-blood-pressure group (14 vs. 25 ml per minute over three years, $P = 0.11$). The patients with polycystic kidney disease had a faster projected decline in the glomerular filtration rate than the patients with other renal diseases (17 vs. 10 ml per minute over three years, $P<0.001$). However, there was no benefit of prescribed low blood pressure in the patients with polycystic kidney disease.

Study 2

The average rate of decline in the glomerular filtration rate did not differ significantly between the two diet groups or between the two blood-pressure groups. When the linear (one-slope) model was used, the overall mean rate of decline in the glomerular filtration rate was 4.0 ml per minute per year (Table 4). The mean rate of decline was 0.8 ml per minute per year less (95 percent confidence interval, −0.1 to 1.8) in the patients on the very-low-protein diet than in those on the low-protein diet ($P = 0.07$) and 0.5 ml per minute per year less (95 percent confidence interval, −0.4 to 1.4) in the patients with low blood pressure than in those with usual blood pressure ($P = 0.28$), representing decrements in the glomerular filtration rate of 19 percent and 12 percent, respectively. There were no significant interactions between base-line demographic characteristics and diet interventions, but there was a significant interaction between base-line urinary protein excretion and the blood-pressure interventions ($P = 0.01$) (Fig. 3).

Adverse Events

There were no significant differences in the number or causes of deaths or stopping points between the diet and blood-pressure groups in either study. There were 30 deaths: 15 in study 1 (3 percent) and 15 in study 2 (6 percent). Cardiovascular diseases and cancer accounted for 18 and 5 deaths, respectively. Most stopping points in study 1 were due to a rapidly declining glomerular filtration rate (60 patients, 10 percent) or end-stage renal disease (12 patients, 2 percent). In study 2, end-stage renal disease developed in 94 patients (37 percent). The time to the occurrence of a rapid decline in the glomerular filtration rate (a stopping point in study 1 only) or end-stage renal disease or death (stopping points in studies 1 and 2) did not differ significantly between the diet groups or the blood-pressure groups. The cumulative percentage of patients in study 2 who had end-stage renal disease or died is shown in Figure 4.

There were small but significant differences between the diet groups in changes in weight and serum concentrations of albumin, transferrin, and cholesterol (data not shown). Two patients (one from each diet group in study 2) reached a stopping point because of malnutrition related to weight loss. In 10 patients (2 percent) in study 1 and 7 patients (3 percent) in study 2, the blood pressure had to be raised because of persistent symptoms of hypotension. No patient reached a stopping point because of complications of hypotension.

Discussion

Two previous studies have examined the effects of a low-protein diet in nondiabetic patients with glomerular filtration rates in the range specified for study 1.[5,28] In one study, only serum creatinine concentrations were reported,[5] and in the other, the difference in protein intake between the two diet groups was small, and

Table 4. Mean Rate of Decline in the Glomerular Filtration Rate from Base Line to the End of the Study in Study 2.*

Diet	Decline in Glomerular Filtration Rate		
	Usual Pressure	Low Pressure	Both
	milliliters per minute per year (95% confidence interval)		
Low protein	4.9 (3.8–5.9)	3.9 (3.2–4.7)	4.4 (3.7–5.1)
Very low protein	3.6 (2.8–4.4)	3.5 (2.6–4.5)	3.6 (2.9–4.2)
Both	4.2 (3.6–4.9)	3.7 (3.1–4.3)	4.0 (3.5–4.4)

*The mean rates of decline in the glomerular filtration rate, which were estimated according to the single-slope informative censoring model, did not differ significantly between the diet groups ($P = 0.07$) or between the blood-pressure groups ($P = 0.28$).

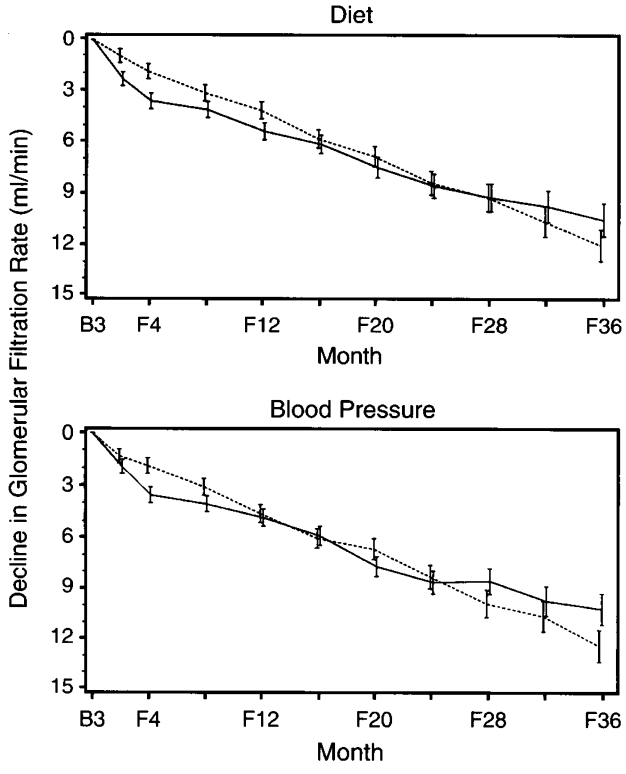

Figure 2. Estimated Mean (± SE) Decline in the Glomerular Filtration Rate from Base Line (B) to Selected Follow-up Times (F) in Study 1.

The upper panel compares the patients assigned to the usual-protein diet (dashed line) with those assigned to the low-protein diet (solid line). The lower panel compares the patients assigned to the usual-blood-pressure group (dashed line) with those assigned to the low-blood-pressure group (solid line). To correct for any bias introduced by stopping points, the mean declines were estimated by the maximum-likelihood method with a two-slope model for the covariance matrix of the serial measurements of the glomerular filtration rate.

there was no beneficial effect.[28] Study 1 overcomes these limitations. However, the interpretation of the results is complicated by the fact that the rate of decline in the glomerular filtration rate was slower than expected and not constant.

The glomerular filtration rate has been measured serially in nondiabetic patients in a few previous studies. We found that the rate declined more rapidly in patients with a higher degree of proteinuria, in those with polycystic kidney disease, and in blacks. However, the majority of patients had other conditions and a slower mean decline in the glomerular filtration rate. Given the slow overall rate of decline in our study, a longer follow-up might have detected

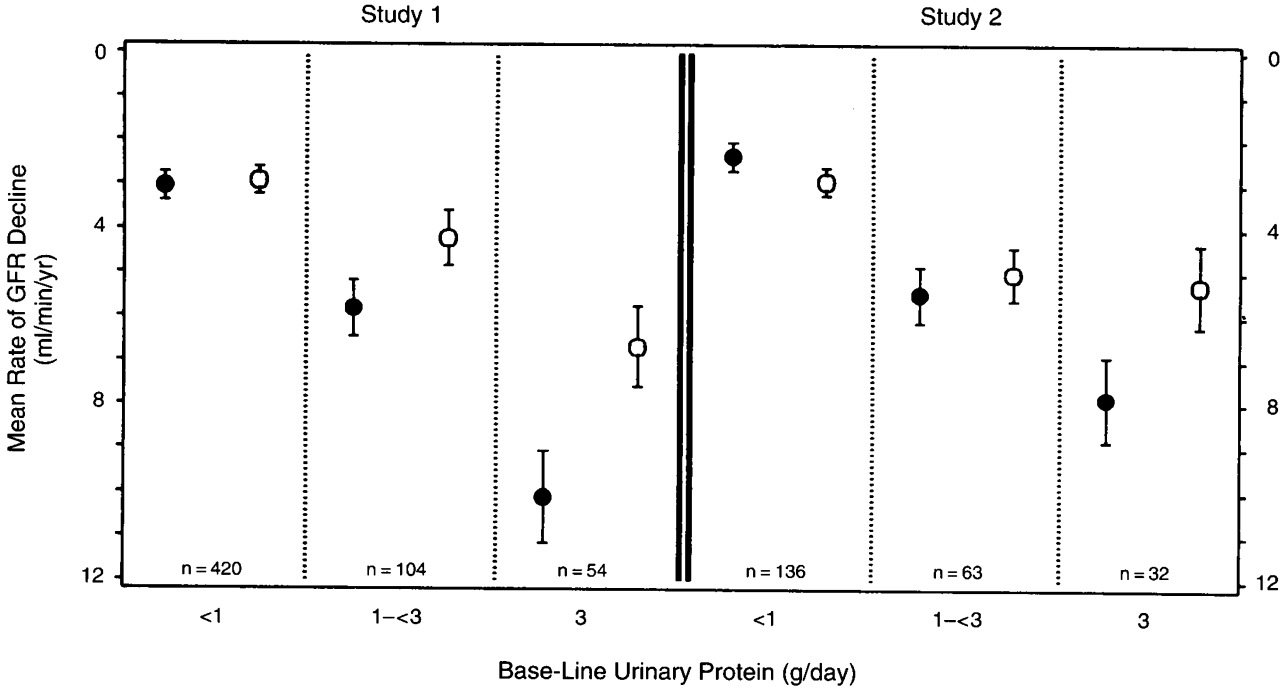

Figure 3. Decline in the Glomerular Filtration Rate (GFR) According to Base-Line Urinary Protein Excretion and Blood-Pressure Group in Studies 1 and 2.

The projected mean (± SE) rate of decline per year in the glomerular filtration rate from base line to three years, based on the two-slope model, is shown for study 1. The mean rate of decline in the glomerular filtration rate per year, estimated from the single-slope informative censoring model, is shown for study 2. The solid and open circles designate the patients with usual and low blood pressure, respectively. The number at the bottom of each panel indicates the total number of patients with follow-up glomerular filtration rate measurements in the two blood-pressure groups combined. A higher level of base-line urinary protein excretion was associated with a more rapid mean decline in the glomerular filtration rate and a larger difference in the mean rate of decline in the glomerular filtration rate between the two blood-pressure groups.

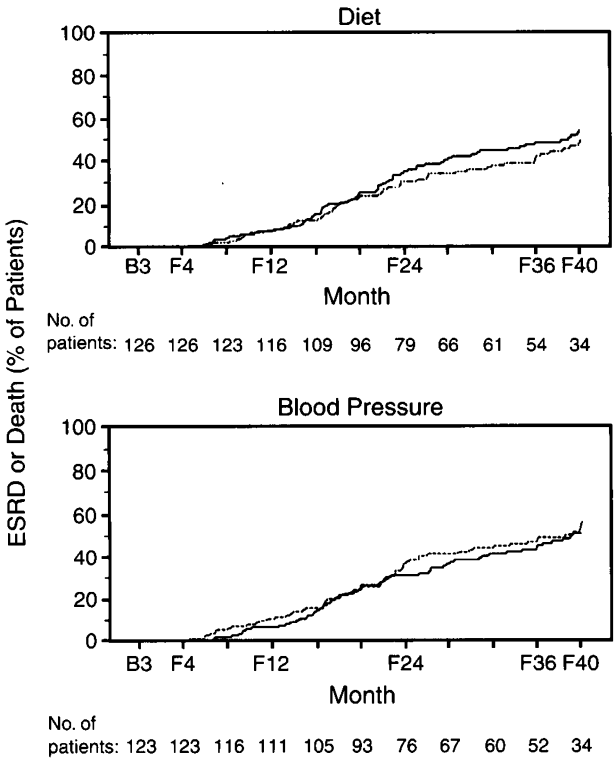

Figure 4. The Occurrence of End-Stage Renal Disease (ESRD) or Death in Patients in Study 2.

The upper panel compares the patients assigned to the low-protein diet (solid line) with those assigned to the very-low-protein diet (dashed-and-dotted line) (P = 0.62). The lower panel compares the patients in the usual-blood-pressure group (dashed line) and those in the low-blood-pressure group (solid line) (P = 0.33). The numbers below each panel indicate the total number of patients in the two groups being compared at each base-line (B) or follow-up (F) visit. The relative risk of ESRD or death was 0.93 (95 percent confidence interval, 0.65 to 1.33) for the patients assigned to the very-low-protein diet, as compared with those assigned to the low-protein diet and 0.85 (95 percent confidence interval, 0.60 to 1.22) for the patients in the low-blood-pressure group, as compared with those in the usual-blood-pressure group.

a difference in the glomerular filtration rate between the treatment groups at a later date.

The reason for the differential effect of the low-protein diet on the initial and subsequent rates of decline in the glomerular filtration rate in study 1 is not known. Similar effects have not been reported previously in humans and were not observed in our feasibility study.[14] The steeper initial decline probably reflects a hemodynamic response to the reduction in protein intake and blood pressure rather than a progression of renal disease,[29] because the initial decline correlated with the lower protein intake and lower blood pressure. The less steep subsequent slopes associated with the low-protein diet in study 1 are consistent with a small beneficial effect of this intervention on the progression of renal disease.

For patients with glomerular filtration rates in the range of the values specified for study 2 (13 to 24 ml per minute per 1.73 m^2), most[4-7,10] but not all[28] previous studies have suggested that a low-protein diet is beneficial. Since we did not include a group of patients on a usual-protein diet, we cannot confirm or refute this conclusion. There was a nonsignificant trend toward a slower decline in the glomerular filtration rate in the patients on the very-low-protein diet, which is consistent with a moderate effect of very low protein intake or of the keto acid–amino acid mixture.[10] Nonetheless, there was no significant difference between the diet groups in the time to the occurrence of end-stage renal disease or death.

Few studies have examined the effect of lower-than-usual blood pressure on the progression of renal disease. Like the low-protein diet, low blood pressure had different effects on the initial and subsequent rates of decline in the glomerular filtration rate in study 1. In both studies, patients with a higher degree of proteinuria had a more rapid decline in the glomerular filtration rate, and a significant benefit of low blood pressure was apparent at three years (Fig. 3). The greater benefit of low blood pressure in the patients whose urinary protein exceeded 1 g per day suggests that the mechanism of progression is specific to the disease and that different diseases may respond differently to the same treatment.

In summary, the dietary and blood-pressure interventions we prescribed were well tolerated. No significant benefit of these interventions was demonstrated at the end of follow-up in either study group, when patients with diverse renal diseases were considered together. However, certain findings may affect the treatment of some patients with chronic renal disease. These include a benefit of low blood pressure in patients with urinary protein excretion exceeding 1 g per day, a trend toward a greater benefit of low blood pressure in blacks with moderate renal insufficiency (study 1), and a more rapid mean decline in the glomerular filtration rate in patients with polycystic kidney disease. Because renal diseases can vary in their rate of progression and their response to treatments, future studies should be performed in patients with specific renal diseases and more rapid decline in the glomerular filtration rate.

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Appendix

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References

1. Klahr S, Buerkert J, Purkerson ML. Role of dietary factors in the progression of chronic renal disease. Kidney Int 1983;24:579-87.
2. Brenner BM. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int 1983;23:647-55.
3. Keane WF, Anderson S, Aurell M, de Zeeuw D, Narins RG, Povar G. Angiotensin converting enzyme inhibitors and progressive renal insufficiency: current experience and future directions. Ann Intern Med 1989;111:503-16.
4. Mitch WE, Walser M, Steinman TI, Hill S, Zeger S, Tungsanga K. The effect of a keto acid–amino acid supplement to a restricted diet on the progression of chronic renal failure. N Engl J Med 1984;311:623-9.
5. Rosman JB, ter Wee PM, Meijer S, Piers-Becht TPM, Sluiter WJ, Donker AJM. Prospective randomised trial of early dietary protein restriction in chronic renal failure. Lancet 1984;2:1291-6.
6. Hunsicker LG. Studies of therapy of progressive renal failure in humans. Semin Nephrol 1989;9:380-94.
7. 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 1989;321:1773-7.
8. Levey AS, Gassman JJ, Hall PM, Walker WG. Assessing the progression of renal disease in clinical studies: effects of duration of follow-up and regression to the mean: Modification of Diet in Renal Disease (MDRD) Study Group. J Am Soc Nephrol 1991;1:1087-94.
9. Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M, Zech PY. Controlled low protein diets in chronic renal insufficiency: meta-analysis. BMJ 1992;304:216-20.
10. Walser M, Hill SB, Ward L, Magder L. A crossover comparison of progression of chronic renal failure: ketoacids versus amino acids. Kidney Int 1993;43:933-9.
11. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154-83.
12. Klahr S. The Modification of Diet in Renal Disease study. N Engl J Med 1989;320:864-6.
13. 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. Controlled Clin Trials 1991;12:566-86.
14. The Modification of Diet in Renal Disease Study: design, methods, and results from the feasibility study. Am J Kidney Dis 1992;20:18-33.
15. Levey AS, Berg RL, Gassman JJ, Hall PM, Walker WG. Creatinine filtration, secretion and excretion during progressive renal disease: Modification of Diet in Renal Disease (MDRD) Study Group. Kidney Int Suppl 1989;27:S-73–S-80.
16. Kopple JD, Berg R, Houser H, Steinman TI, Teschan P. Nutritional status of patients with different levels of chronic renal insufficiency: Modification of Diet in Renal Disease (MDRD) Study Group. Kidney Int Suppl 1989;27:S-184–S-194.
17. Perrone RD, Steinman TI, Beck GJ, et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of ^{125}I-iothalamate, ^{169}Yb-DTPA, ^{99m}Tc-DTPA, and inulin. Am J Kidney Dis 1990;16:224-35.
18. Kusek J, Caggiula A, Williams G, Klahr S. Modification of Diet in Renal Disease Study. In: Albertazzi A, Cappelli P, Del Rosso G, Di Paolo B, Evangelista M, Palmieri PF, eds. Nutritional and pharmacological strategies in chronic renal failure. Vol. 81 of Contributions in nephrology. Basel, Switzerland: S. Karger, 1991:50-60.
19. Levey AS, Greene T, Schluchter MD, et al. GFR measurements in clinical trials. J Am Soc Nephrol 1993;4:1159-71.
20. Yamamoto ME, Averbach FM, Caggiula AW, Jones FL, Gillis BP, Modification of Diet in Renal Disease Study. The production of quality dietary data: a collaborative effort of the Modification of Diet in Renal Disease Study. J Renal Nutr 1992;2:117-25.
21. Kusek JW, Coyne T, deVelasco A, et al. Recruitment experience in the full-scale phase of the Modification of Diet in Renal Disease Study. Controlled Clin Trials 1993;14:538-57.
22. Greene T, Bourgoignie JJ, Habwe V, et al. Baseline characteristics in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol 1993;3:1819-34.
23. Frisancho AR. Anthropometric standards for the assessment of growth and nutritional status. Ann Arbor: University of Michigan Press, 1990.
24. Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 1985;27:58-65.
25. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963-74.
26. Schluchter MD. Methods for the analysis of informatively censored longitudinal data. Stat Med 1992;11:1861-70.
27. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
28. Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A. Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency: Northern Italian Cooperative Study Group. Lancet 1991;337:1299-304.
29. King AJ, Levey AS. Dietary protein and renal function. J Am Soc Nephrol 1993;3:1723-37.