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Dietary Protein Restriction and the Progression of Chronic Renal Disease: What Have All of the Results of the MDRD Study Shown?

ANDREW S. LEVEY, TOM GREENE, GERALD J. BECK, ARLENE W. CAGGIULA, JOHN W. KUSEK, LAWRENCE G. HUNSICKER, and SAULO KLAHR,
FOR THE MODIFICATION OF DIET IN RENAL DISEASE (MDRD) STUDY GROUP[a]
National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.

Abstract. The Modification of Diet in Renal Disease (MDRD) Study was the largest randomized clinical trial to test the hypothesis that protein restriction slows the progression of chronic renal disease. However, the primary results published in 1994 were not conclusive with regard to the efficacy of this intervention. Many physicians interpreted the failure of the MDRD Study to demonstrate a beneficial effect of protein restriction over a 2- to 3-yr period as proving that this therapy does not slow disease progression. The authors believe that this viewpoint is incorrect, and is the result of misinterpretation of inconclusive evidence as evidence in favor of the null hypothesis. Since then, numerous secondary analyses of the MDRD Study have been undertaken to clarify the effect of protein restriction on the rate of decline in GFR, urine protein excretion, and onset of end-stage renal disease. This review describes some of the principles of secondary analyses of randomized clinical trials, presents the results of these analyses from the MDRD Study, and compares them with results from other randomized clinical trials. Although these secondary results cannot be regarded as definitive, the authors conclude that the balance of evidence is more consistent with the hypothesis of a beneficial effect of protein restriction than with the contrary hypothesis of no beneficial effect. Until additional data become available, physicians must continue to make recommendations in the absence of conclusive results. The authors suggest that physicians incorporate the results of these secondary analyses into their interpretation of the findings of the MDRD Study.

The Modification of Diet in Renal Disease (MDRD) Study was a multicenter clinical trial designed to test the hypotheses that dietary protein restriction and strict BP control would delay the progression of chronic renal disease. The primary results reported in 1994 (1) revealed a significant beneficial effect of the low BP goal in patients with proteinuria. Subsequent publications described the relationship of baseline proteinuria to the beneficial effect on GFR decline (2), the beneficial effect of the low BP goal on urine protein excretion (2), the safety of the low BP goal (3), the lack of benefit in polycystic kidney disease (a subgroup with less proteinuria) (4), and a possibly greater beneficial effect in African-Americans (5).

However, the primary results were not conclusive regarding the efficacy of the low protein diet (1), *i.e.*, the results neither proved nor disproved the hypothesis of a beneficial effect. Although the primary analysis was inconclusive, numerous secondary analyses have been carried out using the MDRD Study database, several of which have implications for the efficacy of dietary protein restriction. The purpose of this review is to examine the results of these secondary analyses, compare them with other randomized trials, and assess the cumulative evidence regarding the efficacy of dietary protein restriction on the progression of chronic renal disease.

Throughout this review, it is important to recall that the methodology of randomized clinical trials requires that definitive conclusions must be based on the primary intent-to-treat comparisons of randomized groups specified before examination of the data (6). The interpretation of secondary analyses cited in this review is limited by one or both of the following. (*1*) Some comparisons of randomized groups are *post hoc*, or represent subgroup comparisons. Therefore, it is difficult to rule out the possibility that some of these findings may be chance results arising from the large number of separate statistical tests that were conducted. (*2*) Other analyses are correlational, *i.e.*, they relate the level of protein intake or changes in protein intake with one or more outcomes, rather than compare outcomes between randomized groups. As in all correlational analyses, unmeasured factors or patient selection may have biased the results. For these reasons, the secondary analyses from the MDRD Study cannot definitively establish or refute the dietary efficacy hypothesis. Nonetheless, these

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[a] Investigators and institutions participating in the MDRD Study are listed in reference 1.
Correspondence to Dr. Andrew S. Levey, Division of Nephrology, New England Medical Center, Box 391, 750 Washington Street, Boston, MA 02111. Phone: 617-636-5898; Fax: 617-636-8329; E-mail: Andrew.Levey@es.nemc.org
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analyses provide additional insight into the efficacy of dietary protein restriction.

Study Design and Diet Interventions

In Study A (moderate renal disease, GFR 25 to 55 ml/min per 1.73 m^2, mean [SD] serum creatinine 1.9 [0.5] mg/dl), patients were prescribed a usual or low protein diet, containing either 1.3 or 0.58 g/kg per d protein, respectively (Table 1). In Study B, (advanced renal disease, GFR 13 to 24 ml/min per 1.73 m^2, mean [SD] serum creatinine 3.4 [0.9] mg/dl), patients were prescribed one of two low protein diets: the same low protein diet as in Study A or a very low protein diet, containing 0.28 g/kg per d protein, supplemented with a mixture of ketoacids and amino acids. A usual protein diet was not used in Study B because of concern that patients with advanced renal disease might not be able to ingest a usual protein diet once GFR declined to very low levels. Thus, the comparison of randomized groups in Study B does not directly address the efficacy of a low protein diet in patients with advanced renal disease.

In both Studies A and B, patients in each diet group were also randomly assigned to either a usual or low BP goal, using a "two-by-two-factorial design" (7). The factorial design assumes that the dietary and BP interventions are independent (do not "interact"), *i.e.*, the diet intervention has the same effect in both BP groups, and the BP intervention has the same effect in the two diet groups. There was no significant interaction between diet and BP interventions in either study. Thus, for comparison of the diet groups, patients in both BP groups were combined.

Table 1. Assignment of patients to diet and blood pressure groups in Studies A and B[a]

Diet[b]	Mean Arterial Pressure[c]			
	Study A (n = 585)		Study B (n = 255)	
	Usual	Low	Usual	Low
Usual protein	145	149		
Low protein	140	151	62	67
Very low protein			61	65

[a] Patients in Study A had a GFR of 25 to 55 ml/min per 1.73 m^2 (mean [SD] serum creatinine 1.9 [0.5] mg/dl); patients in Study B had a GFR of 13 to 24 ml/min per 1.73 m^2 (mean [SD] serum creatinine 3.4 [0.9] mg/dl).

[b] 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; 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 ketoacid–amino acid mixture (0.28 g/kg per d) (Ross Laboratories, Columbus, OH).

[c] The usual mean arterial pressure was ≤107 mmHg for patients 18 to 60 yr old at entry (equivalent to 140/90 mmHg) or ≤113 mmHg for patients ≥61 yr old at entry (equivalent to 160/90 mmHg); low mean arterial pressure was ≤92 mmHg for patients 18 to 60 yr old at entry (equivalent to 125/75 mmHg) or ≤98 mmHg for patients ≥61 yr old at entry (equivalent to 145/75 mmHg). Reprinted with permission from *N Engl J Med* (1).

The primary analyses followed an "intention-to-treat" strategy, *i.e.*, patients in the different diet groups were compared regardless of actual protein intake. A clinically meaningful and statistically significant separation in achieved protein intake from food between the randomized groups was found over the follow-up period in both Studies A and B, although there was overlap (Figure 1) (8,9). Thus, the comparison of randomized groups should reflect the beneficial effects, if any, of the assigned diets. For secondary analyses, the association of the rate of disease progression with achieved protein intake was assessed by correlational analyses. Such analyses provide assessments of the biologic dose–response relationship between actual protein intake and progression. However, as described above, correlational analyses may be biased by uncontrolled confounding factors, and alone cannot establish cause and effect.

Patients with diverse renal diseases were included in the MDRD Study, excluding diabetic patients taking insulin and renal transplant recipients, assuming the effects of the intervention would be similar in all causes of renal disease. Unlike the BP intervention, which was more effective in patients with greater proteinuria, we found no significant differences in the effect of the dietary intervention among subgroups of patients defined by age, gender, renal diagnosis, baseline GFR, or proteinuria. However, the statistical power to detect differences in treatment efficacy among subgroups was lower than the power to detect differences between randomized groups. Therefore, meaningful differences in the efficacy of the diet interventions may not have been detected.

The primary outcome measure was the rate of decline in GFR. In planning the study, we assumed that the rate of decline would be relatively constant in individual patients and the mean decline would be about 6 ml/min per yr. We hypothesized that beneficial effects of the diet (and BP) intervention would result in a slowing in the mean GFR decline by at least 30% (7). Upon completion of the study, we found that the rate of GFR decline was not constant in Study A. During the first 4 mo of follow-up, patients assigned to the low protein diet (or the low BP goal) had a faster decline in GFR than during the subsequent months. Over a 3-yr interval, the average rate of GFR decline in Study A was 3.8 ml/min per yr. In Study B, the rate of GFR decline appeared constant; the overall mean decline was 4.0 ml/min per yr. These mean GFR declines were slower than expected, which had a major impact on the results and interpretation of the MDRD Study.

MDRD Study B (Advanced Renal Disease)

Comparison of Randomized Groups

Patients assigned to the very low protein diet had a 19% slower mean GFR decline (Table 2). This difference was of borderline statistical significance (P = 0.07). However, this trend was not evident in the incidence of the combined outcome of end-stage renal disease (ESRD) or death (relative risk 0.93; 95% confidence interval [CI], 0.65 to 1.33, P = 0.62)

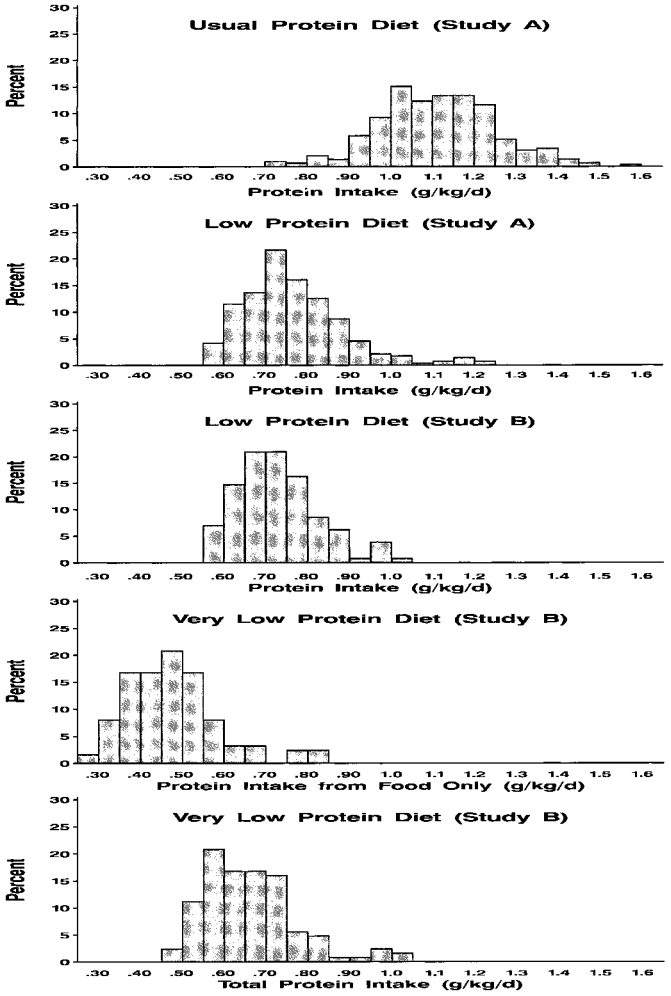

Figure 1. Distribution of protein intakes during follow-up in the MDRD Study. Panels show the distribution of mean protein intake during follow-up for patients assigned the usual, low, and very low protein diet groups. Mean protein intake is defined as the average of all values for protein intake, estimated from the urine urea nitrogen beginning at the second follow-up visit. Protein intakes are factored by standard body weight. (A) Study A, usual protein diet (prescribed protein intake 1.3 g/kg per d, achieved group mean protein intake 1.11 g/kg per d). (B) Study A, low protein diet (prescribed protein intake 0.58 g/kg per d; achieved group mean protein intake 0.77 g/kg per d). (C) Study B, low protein diet (prescribed protein intake 0.58 g/kg per d, achieved group mean protein intake 0.73 g/kg per d). (D) Study B, very low protein diet supplemented with ketoacids and amino acids (prescribed protein intake from food 0.28 g/kg per d, achieved group mean protein intake from food 0.48 g/kg per d). To estimate protein intake from food, the nitrogen contained in the ketoacid–amino acid mixture was subtracted from the urinary urea nitrogen. (E) Study B, very low protein diet supplemented with ketoacids and amino acids (prescribed protein intake from food and supplements 0.56 g/kg per d, achieved group mean total protein intake from food and supplements 0.66 g/kg per d). Reprinted with permission from *J Am Soc Nephrol* (8) and *Am J Kidney Dis* (9).

(Figure 2), where ESRD was defined as onset of uremic symptoms and referral for initiation of dialysis or transplantation. Thus, these results do not establish a beneficial effect of

Table 2. Rate of GFR decline (slope) in patients assigned to diet groups in Study B

Diet	Mean Slope (ml/min per yr)	
	Mean	SEM
Low protein	−4.4	0.3
Very low protein	−3.6	0.3
Very low–low protein	+0.9[a]	0.5

[a] The difference in mean GFR slopes between the low and very low protein diet groups was marginally significant ($P = 0.07$).

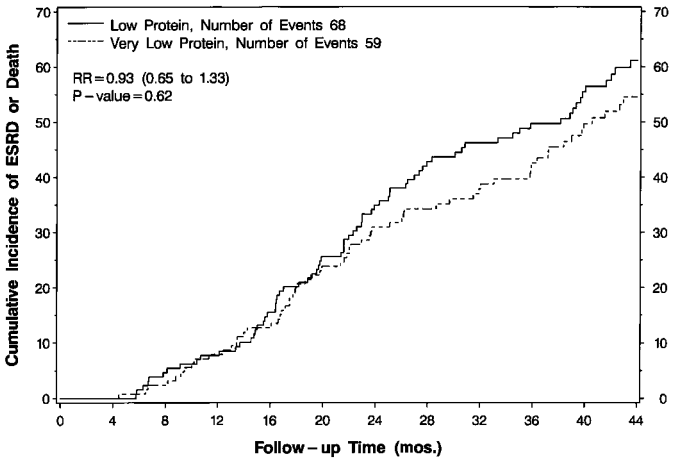

Figure 2. The occurrence of renal failure or death in patients in Study B. The graph compares the patients assigned to the low protein diet (solid line) with those assigned to the very low protein diet (dashed line) ($P = 0.62$). The numbers on the graph indicate the number of patients in each group being compared at each time point. The relative risk of renal failure or death was 0.93 (95% confidence interval [CI], 0.65 to 1.33) for the patients assigned to the very low protein diet, compared with those assigned to the low protein diet. Modified with permission from *N Engl J Med* (1).

the ketoacid–amino acid-supplemented very low protein diet compared to the low protein diet in patients with advanced renal disease. To evaluate the relationship of achieved dietary protein intake to these outcomes, we performed secondary analyses (9).

Effect of Achieved Protein Intake and the Ketoacid–Amino Acid Supplement in Study B

We first compared the prescribed and achieved intake of protein from food only and from food and amino acids in the supplement (defined as "total protein intake"). Patients assigned to the very low protein diet had a lower prescribed and achieved mean total protein intake than patients assigned to the low protein diet (Figure 1). We next correlated the rate of progression of renal disease with achieved total protein intake. For this analysis, we developed a regression model, using achieved total protein intake as the independent variable and rate of GFR decline as the dependent variable. Because these

analyses are correlational and not based on a direct comparison of randomized groups, we controlled for possible confounding variables related to the rate of GFR decline by adding them as covariates to the regression model. In addition, we added a term to the regression model to assess the effect of assignment to the ketoacid–amino acid-supplemented diet, independent of protein intake.

The results of the regression model are shown in Table 3 (top panel). After controlling for covariates, each 0.2 g/kg per d lower achieved total protein intake was associated with a 1.15 ml/min per /yr slower GFR decline (equivalent to 29% of the mean GFR decline). After adjusting for achieved total protein intake in addition to the baseline covariates, assignment to the ketoacid–amino acid-supplemented diet was not significantly related to GFR decline.

We then repeated the analysis, using the time to ESRD or death as the dependent variable (Table 3, bottom panel). These results corroborated the results of the first analysis. After controlling for covariates, each 0.2 g/kg per d lower achieved total protein intake was associated with a 0.51 relative risk of ESRD or death within a defined interval. Again, assignment to the ketoacid–amino acid-supplemented diet was not significantly related to GFR decline.

Although subject to the same limitations as all correlational analyses, these results suggest that a lower protein intake, but not the ketoacid—amino acid-supplemented diet *per se*, is associated with a slower progression of renal disease. The results also suggest that the trend toward a beneficial effect of the very low protein diet that we observed in the comparison of GFR declines between the randomized groups was due to a beneficial effect of the lower achieved total protein intake, rather than a beneficial effect of the supplement.

Table 3. Adjusted association of GFR slope and relative risk of renal failure or death with total protein intake and diet group in Study B[a]

Parameter	Estimate (CI)	*P* Value
GFR slope (ml/min per yr)		
protein intake (0.2 g/kg per d lower)	1.15 (0.27 to 2.03)	0.011
assignment to supplemented very low protein diet	−0.15 (−0.95 to 0.65)	0.71
Relative risk of renal failure or death		
protein intake (0.2 g/kg per d lower)	0.51 (0.34 to 0.76)	0.001
assignment to supplemented very low protein diet	1.03 (0.70 to 1.51)	0.87

[a] A 0.2 g/kg per d lower total protein intake was associated with a 1.15 ml/min per yr less steep mean GFR slope (29%) and a 51% relative risk of renal failure or death. Combining patients in both diet groups and controlling for baseline covariates associated with progression. Covariates included in both regression models included diagnosis of polycystic kidney disease, race, baseline levels of serum transferrin, high-density lipoprotein cholesterol, mean arterial pressure, and protein intake, as well as mean follow-up mean arterial pressure and its interaction with baseline proteinuria. Baseline GFR was also included in regression model for relative risk of renal failure or death.

Comparison to Other Studies in Nondiabetic Patients with Advanced Renal Disease

Although many studies have suggested a beneficial effect of a low protein diet in nondiabetic patients with advanced renal disease, only the studies of Ihle *et al.* (10) and Cockram *et al.* (11) were large, multicenter trials that used a parallel, randomized control design and assessed progression from clearance measurements. Ihle *et al.* (10) randomized 72 patients to a low protein diet (0.4 g/kg per d) or an unrestricted protein diet. They observed a large effect of the low protein diet (80% reduction in GFR decline), despite a small difference in achieved protein intake between the low protein and usual protein diet groups (0.69 *versus* 0.85 g/kg per d, respectively). MDRD Study B did not include a group of patients randomly assigned to a usual protein diet group; hence, the comparison of randomized groups in MDRD Study B cannot confirm or refute the findings of Ihle *et al.* (10). However, the correlational analyses from MDRD Study B are consistent with their findings of a beneficial effect of protein restriction.

Cockram *et al.* (11) randomized 141 patients to a low protein diet or a very low protein diet supplemented with the same ketoacid–amino acid mixture used in the MDRD Study. As in the MDRD Study, there was no significant beneficial effect of the ketoacid–amino acid-supplemented very low protein diet on the decline in renal function, as assessed from the mean of creatinine and urea clearance measurements.

In a single-center study, Walser *et al.* (12) compared the effect of a very low protein diet supplemented either by a ketoacid–amino acid mixture or a mixture of essential amino acids. The study by Walser *et al.* (12) differed in two important ways from MDRD Study B and the study by Cockram *et al.* (11). First, the composition of the ketoacid–amino acid supplement did not include tryptophan. Second, the effect of the supplements was assessed from short-term effects on GFR decline using a crossover design. This study suggested a beneficial effect of the ketoacid–amino acid supplement in comparison to the mixture of essential amino acids in slowing GFR decline. More recently, a re-analysis of the feasibility phase of the MDRD Study also suggested that the ketoacid–amino acid supplement used by Walser *et al.* (12) was more effective in slowing short-term GFR decline than was a mixture of essential amino acids (13,14).

Overall, the results of other studies, and the secondary correlational analyses of MDRD Study B, tend to support the hypothesis of a beneficial effect of a low protein diet in patients with advanced renal disease. A very low protein diet supplemented with a mixture of ketoacids and amino acids may also be beneficial, but differences in study design and in the composition of the supplements make it difficult to determine whether the very low protein diets are more beneficial than a low protein diet.

MDRD Study A (Moderate Renal Disease)

Comparison of the Randomized Groups

After 3 yr, the decline in GFR was only 1.2 ml/min (10%) less ($P = 0.3$) in the low protein diet group compared with the usual protein diet group (Figure 3). Thus, the intention-to-treat analysis did not demonstrate a beneficial effect of the low protein diet. However, the low protein diet had opposite short-term and long-term effects on the rate of GFR decline. Patients assigned to the low protein diet group had a 1.6 ml/min faster mean decline in GFR during the first 4 mo ($P = 0.004$), but a 1.1 ml/min per yr (28%) slower mean GFR decline thereafter ($P = 0.009$), compared to patients assigned to the usual protein diet group. The difference in long-term GFR declines was similar to the hypothesized beneficial effect of a 30% slower decline in GFR. However, the short-term effect of the low protein diet was opposite in direction to its hypothesized beneficial effect. Moreover, the magnitude of the short-term effect was sufficient to negate the long-term beneficial effect and obscure the interpretation of the clinical trial. These opposite short-term and long-term effects of dietary protein restriction on GFR are considered in more detail below.

Short-term reductions in GFR in humans following a lowering of protein intake are well known (15). Similar effects are observed in long-term studies of rodents with a variety of experimentally induced renal diseases treated with restriction of dietary protein (16). These studies show an initial decline in GFR, mediated by hemodynamic changes and leading to a reduction in single-nephron GFR (SNGFR). Subsequently, the progression of renal disease slows, as measured by the number of functional nephrons and by the level of GFR.

The opposite short-term and long-term effects of protein restriction on GFR decline have important implications for the interpretation of the MDRD Study, and for all studies of the progression of renal disease using the rate of decline in GFR as the outcome measure. In principle, if the long-term beneficial effect of the intervention is proportional to the underlying rate of GFR decline, but the intervention has an opposite short-term effect on GFR decline, then the final level of GFR attained in each diet group in a clinical trial would depend on the underlying rate of GFR decline and the duration of follow-up. During a short follow-up period, a detrimental effect would be observed, whereas after a long follow-up period, a beneficial effect would be observed. Among patients with more rapidly declining GFR, a beneficial effect would be observed in a shorter follow-up interval. In patients with more slowly declining GFR, a longer follow-up interval would be required to demonstrate a beneficial effect.

Alternatively, if there is no long-term beneficial effect of the intervention, then the apparent beneficial effects of the intervention on the long-term GFR decline may simply reflect attenuation of the initial hemodynamic effect on SNGFR (Figure 4) (17). In principle, if there is no benefit of the intervention, there would be no difference between the randomized groups, even with a longer duration of follow-up.

Because it is not possible to measure SNGFR or the number of nephrons in humans, the only way to distinguish between these two alternatives in a clinical trial is to plan for a follow-up of sufficient duration. Given the slow mean rate of GFR decline observed in the MDRD Study, we estimated that an additional 3 or more years of follow-up would have been required to detect a difference between the diet groups in the mean decline in GFR from baseline to the end of the MDRD Study. For these reasons, we judge the comparison of diet groups in MDRD Study A to be inconclusive. The GFR decline was too slow and the duration of follow-up too short to determine an effect of the dietary intervention on long-term GFR decline. Therefore, we performed secondary analyses to clarify the effects of the dietary intervention (8).

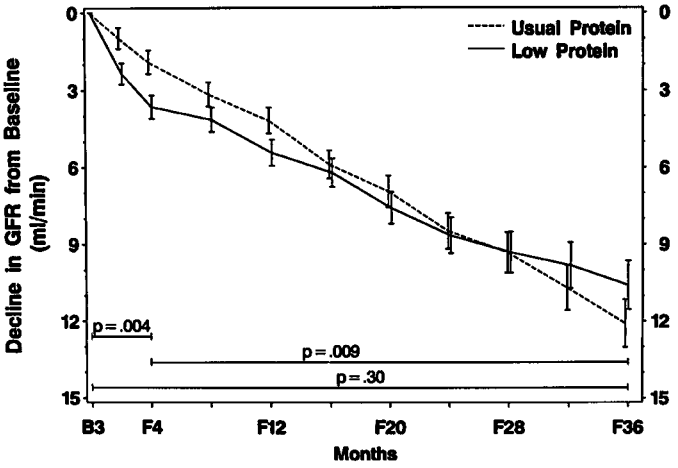

Figure 3. Estimated mean decline in the GFR from baseline in Study A. GFR declines are compared for patients in the usual and low protein diet groups in Study A. Estimated mean (±SEM) GFR declines from baseline (B) to selected follow-up times (F) are shown. To correct for any bias introduced by stopping 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 GFR. From baseline to 4 mo of follow-up, mean GFR decline was 1.6 ml/min faster in the low-protein diet group ($P = 0.004$). From 4 mo to the end of follow-up, mean GFR decline was 1.1 ml/min per year (28%) slower in the low protein diet group ($P = 0.009$). From baseline to 3 yr of follow-up, the projected mean decline in GFR was 1.2 ml/min (10%) less in the low protein diet group ($P = 0.30$). Adapted with permission from *N Engl J Med* (1) and reprinted with permission from *J Am Soc Nephrol* (8).

Effect of the Low Protein Diet on the Distribution of GFR Declines

We first compared the distribution of GFR declines in patients assigned to the usual and low protein diets in each follow-up time interval (Figure 5) (8). During the first 4 mo (top panel), the low protein diet group had a uniformly greater mean GFR decline, without a difference in variability of GFR declines (a shift of the distribution to the left, but without a change in spread). After 4 mo (middle panel), GFR declined more slowly in patients assigned to the low protein diet, and the variability of GFR slopes was significantly reduced (a shift of the left end of the distribution toward the center). The net effect of the low protein diet (bottom panel) was no significant difference in the mean GFR decline over 3 yr, but there was a

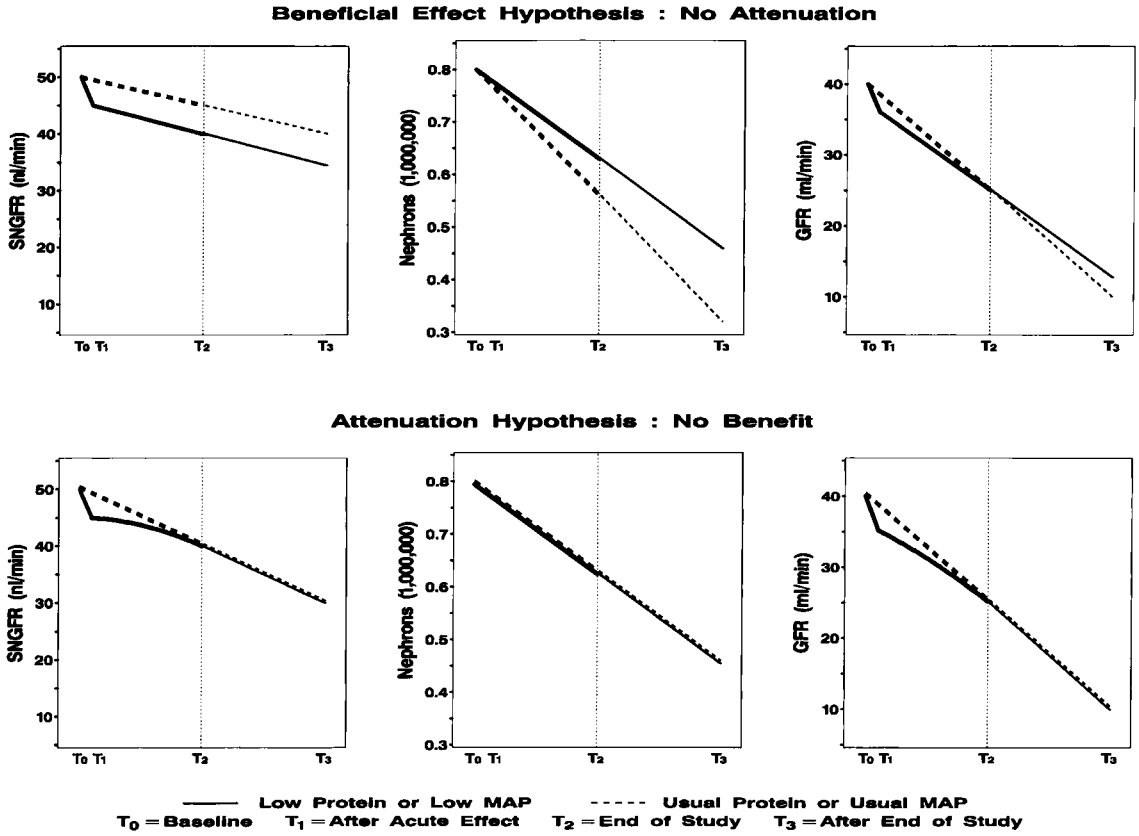

Figure 4. Alternative hypotheses to explain the two-slope GFR decline in MDRD Study A. Hypothetical examples of the effect of a low protein diet or low BP (mean arterial pressure [MAP]) goal on single-nephron GFR (SNGFR), number of nephrons, and GFR (the product of SNGFR and number of nephrons). T0 is baseline, T1 is after the short-term effect on SNGFR, T2 is the end of the study, and T3 is a future time after a longer follow-up interval. Solid line, low-protein diet or low MAP group; dashed line, usual protein diet or usual MAP group. In both the top and bottom panels, the low protein diet or low MAP initially reduces SNGFR. In the top panels, the low protein diet or low MAP slows the loss of nephrons (beneficial effect), and the difference in SNGFR persists over time (no attenuation). At the end of the study (T2), the initial reduction in SNGFR and the slower decline in the number of nephrons in the low protein diet or low MAP group result in a GFR decline equal to that which occurs in the usual protein diet or usual MAP group. After longer follow-up (T3), the slower decline in the number of nephrons dominates the initial reduction in SNGFR, so that the GFR decline is less than in the low protein diet or low MAP group. In the bottom panels, there is no beneficial effect on the loss of nephrons (no benefit), and the difference in SNGFR is attenuated over time (attenuation). At the end of the study (T2), the initial reduction in SNGFR and the subsequent attenuation of the initial effect in the low protein diet or low MAP group result in a GFR decline equal to that which occurs in the usual protein diet or usual MAP group. Because there is no difference in the decline in the number of nephrons, there is no difference between diet groups or between MAP groups after a longer follow-up interval (T3). In both the top and bottom panels, the effect of changes in SNGFR and the number of nephrons produce a nonlinear decline in GFR as observed in MDRD Study A. The pattern of GFR decline until T2 is nearly identical and cannot be distinguished statistically. With longer follow-up, the pattern of GFR decline could be distinguished. Revised and reprinted with permission from *J Am Soc Nephrol* (8).

significant reduction in variability of GFR slopes, compared with the usual protein diet group.

The distributions of GFR declines in different time intervals allow us, albeit indirectly, to examine the alternative hypotheses to explain the 2-slope GFR decline observed in Study A. The uniform increase in the GFR decline in the low protein diet group during the first 4 mo is consistent with an initial hemodynamic effect on SNGFR, which is not dependent on the underlying rate of GFR decline (a shift in distribution to the left, without a change in spread). In principle, if the slower GFR decline in the low protein diet group after the first 4 mo reflects attenuation of the initial hemodynamic effect, then the distribution of GFR declines should be similar to that observed in the usual protein diet group (no change in spread, but a shift in the distribution to the right). Thus, the observed reduction in variability in the distribution of GFR declines in the low protein diet group does not appear to be consistent with attenuation of an initial hemodynamic effect. Rather, it suggests a proportionately greater beneficial effect of the low protein diet in the subgroup of patients with more rapid GFR decline (a shift of the left end of the distribution to the center). In principle, over a relatively short period of follow-up, this shift in the distribution of GFR declines from the left to the center would reduce the incidence of ESRD. The comparison of randomized groups also suggests an apparent detrimental effect in patients with little or no GFR decline (a shift of the right end

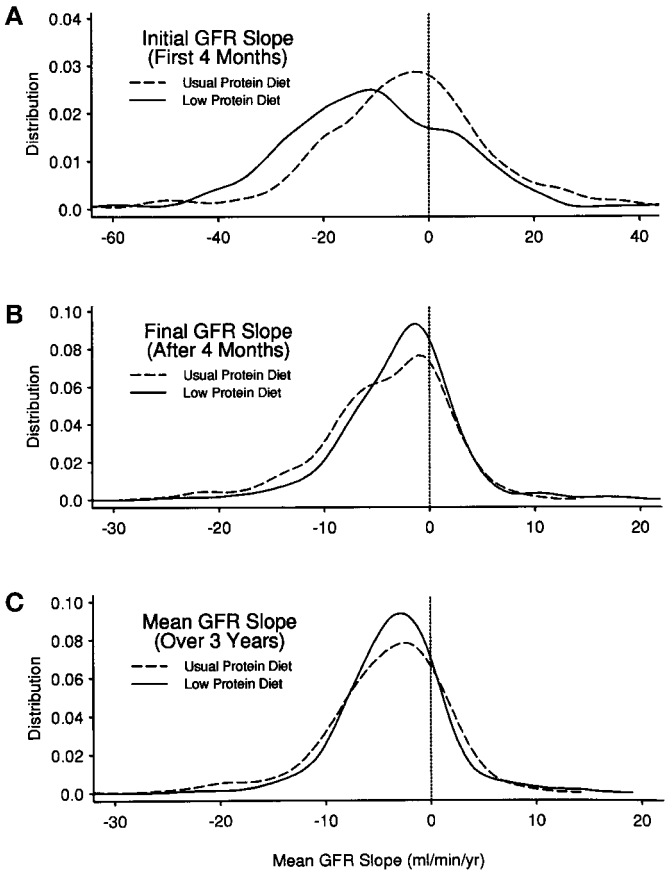

Figure 5. Distribution of GFR slopes in patients assigned to the usual *versus* low protein diets in Study A. Panel A compares the distribution of GFR slopes before the fourth month of follow-up. Panel B compares the GFR slopes after the fourth month of follow-up. Panel C compares the GFR slopes from baseline to 3 yr of follow-up. Only patients with at least 8 mo follow-up are included. Reprinted with permission from *J Am Soc Nephrol* (8).

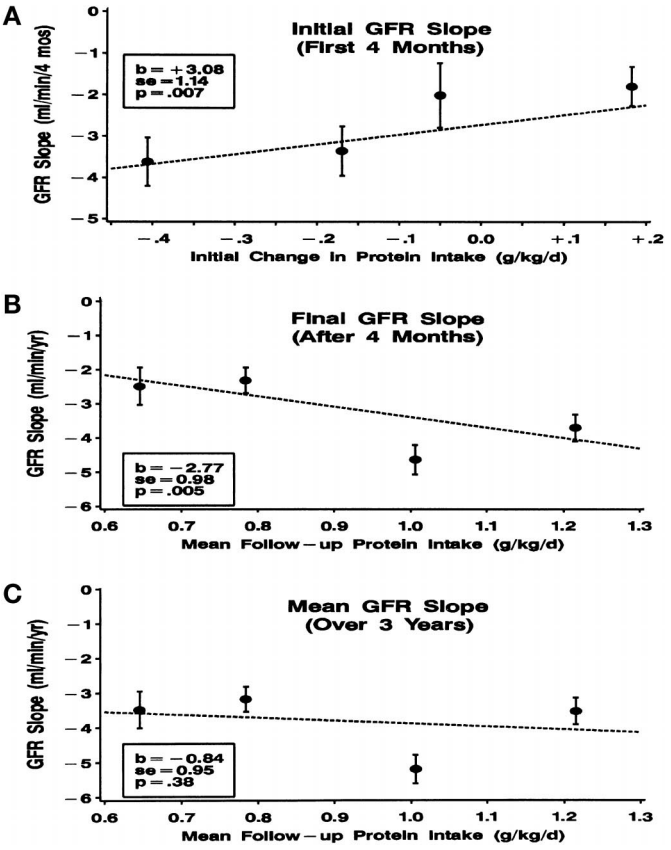

Figure 6. Relationship between protein intake and GFR decline for various intervals in Study A. The relationship is shown for baseline to 4 mo (A), from 4 mo to study end (B), and from baseline to 3 yr (C). The points represent means and SEM of GFR decline for patients with ranges of protein intake. During the initial 4 mo after randomization, patients were classified according to change in protein intake (a negative value indicates a reduction in protein intake): less than −0.25 g/kg per d ($n = 175$); −0.25 to −0.10 g/kg per d ($n = 89$); −0.10 to 0 g/kg per d ($n = 46$); and ≥0 g/kg per d ($n = 143$). After the first 4 mo and until the end of the study, and from baseline to 3 yr of follow-up, patients were classified according to mean protein intake during follow-up: <0.70 g/kg per d ($n = 84$); 0.70 to 0.90 g/kg per d ($n = 184$); 0.90 to 1.1 g/kg per d ($n = 149$); and ≥1.1 g/kg per d ($n = 160$). The dashed line represents the regression line for all patients. The slope (b), SEM, and P value for each regression line are given in the figure. Reprinted with permission from *J Am Soc Nephrol* (8).

of the distribution to the center). However, since the detrimental effect would occur in the subgroup of patients with the slowest GFR decline, a much longer duration of follow-up would be required for this shift in distribution of GFR from the right to the center to have a clinically significant impact on the progression of renal disease. Thus, these additional comparisons of randomized groups are consistent with a beneficial effect of protein restriction.

Effect of Achieved Protein Intake in Study A

Figure 6 shows the relationships of the decline in GFR to achieved protein intake during follow-up without adjustment for other covariates (8). For clarity, the GFR declines are presented for subgroups of patients with specified values of mean achieved protein intake. Changes in GFR and protein intake from baseline to 4 mo (top panel) were directly correlated. Additional analyses showed a similar relationship of short-term (4 mo) changes in protein intake to short-term changes in GFR whether protein intake was rising or falling, and independent of concurrent changes in BP, and changes in class of antihypertensive agents (17). These data strongly support the hypothesis that the short-term effects of dietary protein restriction of GFR decline are functional (presumably hemodynamic) rather than the results of structural renal damage.

After 4 mo (middle panel), there was an inverse correlation between the mean protein intake during follow-up and the long-term rate of GFR decline. However, the opposite directions of the short-term and long-term relationships of protein intake and GFR largely canceled each other, and the relationship was not significant for the mean decline in GFR over the full 3 yr of follow-up (bottom panel). Thus, the correlational analyses provide an ambiguous picture of the relationship between achieved protein intake and GFR decline in Study A, as does the comparison of randomized groups.

After adjusting for the relevant covariates, the inverse relationship between mean GFR decline after 4 mo and mean follow-up protein intake persists, but was no longer statistically significant ($P = 0.075$). The magnitude of the regression coefficient indicates that a 0.2 g/kg per d lower protein intake during follow-up was associated with a 0.32 ml/min per yr slower mean GFR decline, equivalent to only 9.6% of the mean GFR decline.

Comparison with Other Studies in Nondiabetic Patients with Moderate Renal Disease

Other studies have shown apparently conflicting results of protein restriction on the rate of decline in renal function. Analysis of the various measures of renal function during the MDRD Study suggests that the reasons for inconsistent results among other studies was due, in part, to differences in methods used to measure renal function (Figure 7) (18). For example, as in the studies by Maschio *et al.* (19), Mitch *et al.* (20), and Rosman *et al.* (21), the low protein diet in MDRD Study A had a beneficial effect on the decline in the reciprocal of the serum creatinine concentration (18). This effect was caused by a reduction in urinary creatinine excretion. As in the studies by Locatelli *et al.* (22) and Williams *et al.* (23), the low protein diet in the MDRD Study A had no benefit on the decline in creatinine clearance (18). Indeed, we found a significant detrimental effect on the decline in creatinine clearance, due to a reduction in creatinine secretion. Thus, the results of MDRD Study A are similar to those of other studies. The differences in conclusions among studies reflect the effects of diet on creatinine secretion and excretion. Another implication of these findings is that studies using different measures of renal function (GFR, creatinine clearance, and the reciprocal of serum creatinine) should not be combined in a meta-analysis to assess the rate of progression of renal disease (24).

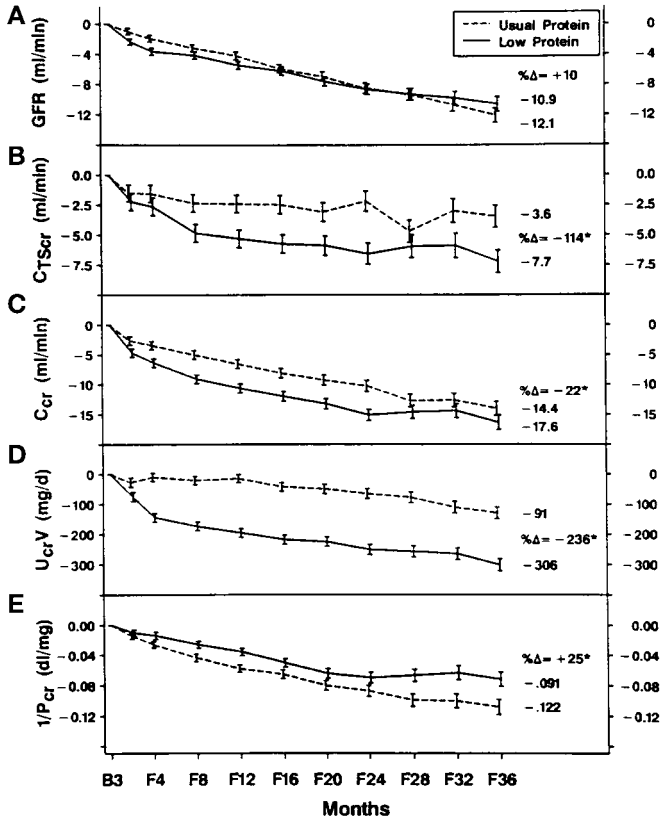

Figure 7. Effect of the low protein diet on rates of decline in various measures of renal functions in Study A. Dashed lines, usual protein diet; solid lines, low protein diet. (A) Effects on GFR. (B) Effects on creatinine secretion (C_{TScr}). (C) Effects on creatinine clearance (C_{Cr}). (D) Effects on creatinine excretion rate ($U_{Cr}V$). (E) Effects on reciprocal serum creatinine ($1/P_{Cr}$). Also shown are the estimated mean changes at 3 yr for each diet group. %Δ indicates the percentage difference in the estimated mean change between the low and usual protein diet groups. A positive value indicates a lesser decline in the low protein diet group. A negative value indicates a greater decline in the low protein diet group. *$P < 0.05$. Reprinted with permission from *J Am Soc Nephrol* (18).

Two studies have used meta-analyses to assess the effect of protein restriction on the risk of ESRD or death (25,26). Meta-analysis of randomized trials of protein restriction has both advantages and disadvantages. Because of the larger number of patients available for analysis compared to a single clinical trial, the "hard" clinical outcome of ESRD or death can be used as the primary outcome measure. This approach avoids the difficulties inherent in using comparatively "soft" surrogate outcomes based on the rate of decline in measures of renal function. These difficulties include the above-mentioned biases associated with generation and secretion of creatinine (18,27), and nonlinear rates of decline in GFR, as experienced in the MDRD Study. In addition, under some circumstances, the use of a time-to-event analysis may have greater statistical power than comparisons of the mean rate of decline in renal function (28). A potential disadvantage of using the onset of ESRD or death as the primary outcome is that the analysis may give more weight to patients with advanced renal disease or more rapidly declining GFR, because these patients would be more likely to develop ESRD during the relatively short follow-up times of the studies. Another potential disadvantage is that patients assigned to the low protein diet group may be diagnosed as having reached ESRD later than patients assigned to the usual protein diet group either because the low protein diet masks the symptoms of uremia, or because of investigator bias in these unmasked studies. In addition, there are the well-recognized disadvantages of meta-analysis resulting from the possibility of nonuniformity of studies and publication bias.

After initiation of the MDRD Study, but before its completion, Fouque *et al.* (25) reported the results of a meta-analysis of studies of dietary protein restriction in nondiabetic patients with chronic renal disease. They compared the risk of ESRD or death in 890 patients assigned to a low *versus* usual protein diet in six clinical trials. The relative risk for the low protein diet group was 0.54 (95% CI, 0.37 to 0.79). As discussed below, Pedrini *et al.* (26) recently updated and extended the meta-analysis of Fouque *et al.* (25) by adding the results from MDRD Study A.

During the trial, only 59 patients in MDRD Study A (10%) developed ESRD or died. Thus, the power to detect a difference between the randomized groups is low. Nonetheless, there

is a trend toward a lower incidence of ESRD or death in the low protein diet group (relative risk 0.65; 95% CI, 0.38 to 1.10, $P = 0.10$) (8). With 5 to 10 mo additional follow-up after discontinuation of the diet and BP interventions, the number of patients who developed ESRD or died increased to 68. The trend toward a beneficial effect of low protein diet persisted (relative risk 0.63; 95% CI, 0.38 to 1.02, $P = 0.056$), as shown in Figure 8 (29).

Pedrini *et al.* obtained data on 1413 patients in five published randomized clinical trials, including the MDRD Study, with a mean duration of follow-up greater than 1 yr. Two small studies included in the meta-analysis by Fouque *et al.* (25) were excluded from the analysis because one was not based on a comparison of randomized groups and the other was not a full-length publication. With the exception of the study of Ihle *et al.* (10), patients had moderate renal disease. Figure 9 shows the results from each study, as well as the pooled results (26). Overall, patients assigned to the low protein diet group had a relative risk of ESRD or death of 0.67 (95% CI, 0.50 to 0.89, $P = 0.007$). The relative risk of ESRD or death was similar to that observed in MDRD Study A. Because of the larger number of patients included in the meta-analysis, the result is statistically significant. These results provide strong evidence that dietary protein restriction delays the onset of ESRD. However, as mentioned above, there are limitations to the interpretation of this meta-analysis.

First, the reduced risk of ESRD or death in the low protein diet group observed in the meta-analysis probably reflects a beneficial effect principally in patients with lower initial GFR and faster GFR decline. The magnitude of the beneficial effect in patients with higher initial GFR or slower GFR decline may be different from the estimate derived from the meta-analysis.

Second, the reduced risk of ESRD might reflect delaying the initiation of dialysis due to amelioration of uremic symptoms rather than slowing the decline in renal function. This is suggested by data from MDRD Study B showing that patients with lower achieved protein intake during follow-up developed symptoms of uremia at slightly lower GFR than patients with higher protein intake (9). However, as shown earlier, correlational analyses from MDRD Study B also showed a slower GFR decline in patients with lower achieved protein intake during follow-up. This suggests that the lower risk of ESRD in patients in the low protein diet groups in the meta-analysis reflects both a slowing in the rate of decline in renal function and amelioration of uremic symptoms.

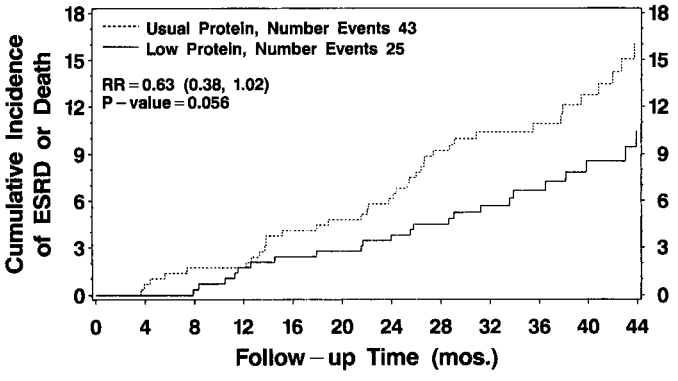

Figure 8. Occurrence of renal failure or death in patients in Study A including follow-up through 10 mo after study completion. Cumulative incidence of renal failure or death through completion of additional follow-up. Risk ratio is 0.63 (95% CI, 0.38 to 1.02; $P = 0.056$).

Effects of Dietary Protein Restriction in Patients with Polycystic Kidney Disease

A total of 200 patients (24%) in the MDRD Study had polycystic kidney disease (PKD), which represents the largest reported study of dietary interventions in this disease. Although we found no significant differences in treatment efficacy between patients with PKD *versus* other renal diseases, we reported the results separately in this subgroup (4).

In the 59 patients with PKD in Study B, as in the entire Study B group, there was a trend ($P = 0.06$) toward a less steep GFR decline in patients randomized to the very low protein diet group compared with the low protein diet group. Also, in correlational analyses, there was a trend ($P = 0.06$) toward a faster GFR decline in patients with higher achieved total protein intake. Therefore, the effects of protein restriction in advanced renal disease due to PKD appear similar to advanced renal diseases due to other causes.

However, in the 141 patients with PKD in Study A, the GFR decline after 4 mo was only 10% slower in the low protein diet group compared to the usual protein diet group. The 95% CI for the difference between randomized groups among patients with PKD was -0.8 to $+1.8$ ml/min per yr (equivalent to -15% to $+33\%$ of the mean GFR decline after 4 mo in usual protein diet group). The upper bound of the 95% CI for the benefit in PKD is barely greater than the 30% hypothesized beneficial effect of protein restriction. Although the formal statistical evaluation did not reveal differences in the efficacy of protein restriction among causes of renal disease, the MDRD Study provides little evidence of a beneficial effect of the low protein diet in moderate renal disease due to PKD.

Effects of Dietary Protein Restriction on Urine Protein Excretion

Recent studies have emphasized the potential beneficial effects of lowering urine protein excretion on the progression of chronic renal disease (30,31). In Study A, we observed a significant association between reduction in urine protein during the first 4 mo of follow-up and a slower subsequent GFR decline (2). An initial reduction in proteinuria of 1.0 g/d was associated with a 0.92 ± 0.31 ml/min per yr ($P = 0.003$) slower mean decrease in GFR after 4 mo. This correlational analysis included patients in all randomized groups and controlled for baseline covariates associated with GFR decline, as well as for changes between baseline and 4 mo in BP and protein intake. Comparison of randomized groups showed that the dietary protein restriction slowed the rate of rise of urine protein excretion during follow-up (Figure 10, left panel) (8). Similar effects were observed in a comparison of the BP group in Study A (Figure 10, right panel) (2).

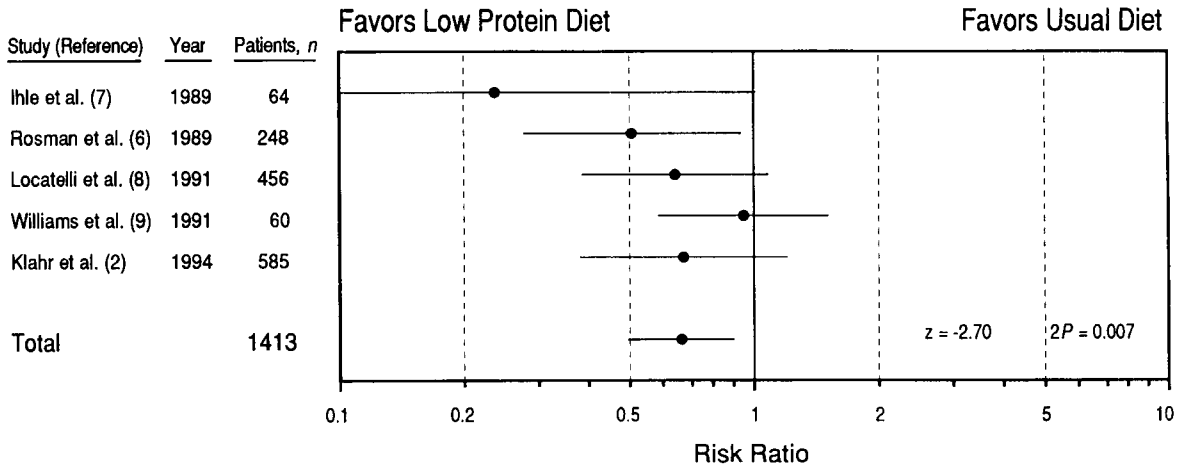

Figure 9. Meta-analysis of the effect of dietary protein restriction on progression of nondiabetic renal diseases. Data are presented as risk ratio with 95% CI on log scale. Risk ratio is 0.67 (95% CI, 0.50 to 0.89; $P = 0.007$). Reprinted with permission from *Ann Intern Med* (26).

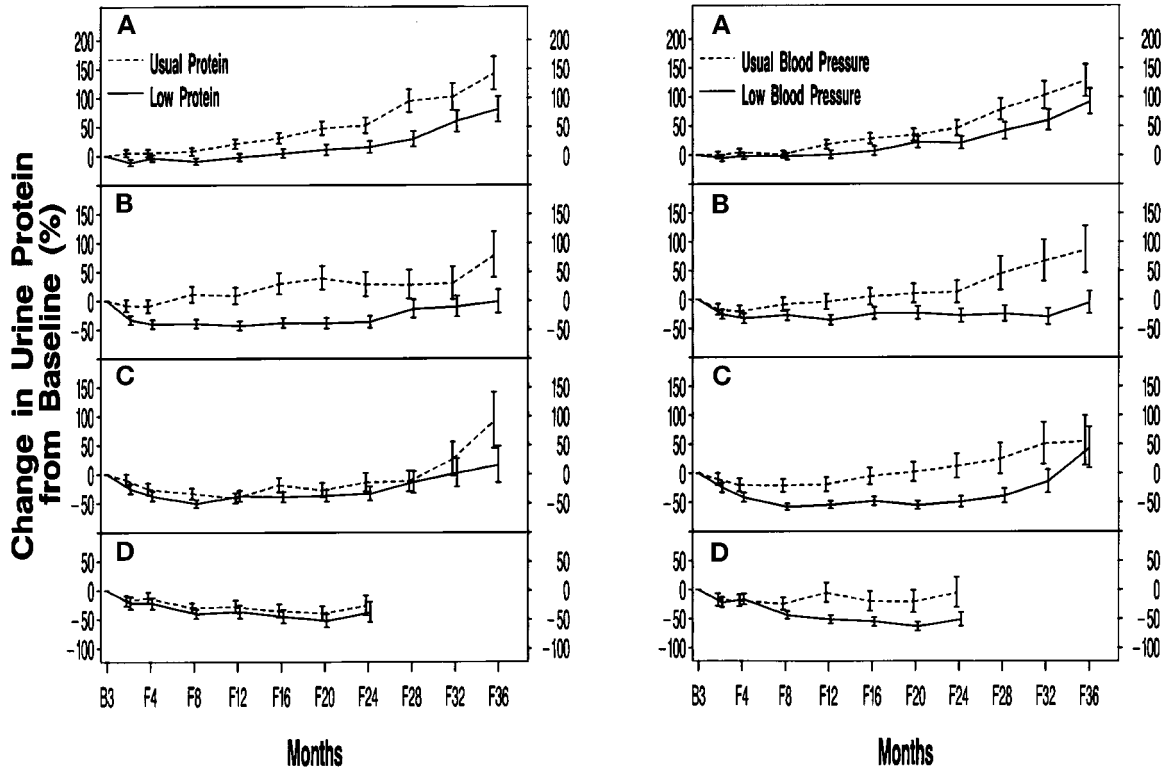

Figure 10. Effects of dietary protein restriction and strict BP control on urine protein excretion in MDRD Study A. Changes in urine protein from baseline by baseline urine protein excretion to selected follow-up times in Study A. Data are presented as mean and SEM. **Left Panel**: Dashed line, usual protein diet; solid line, low protein diet. **Right Panel**: Dashed line, usual BP goal; solid line, low BP goal. **Both Panels:** (A) 305 patients had baseline urine protein 0 to 0.25 g/d (mean 0.08 g/d). (B) 120 patients had baseline urine protein 0.25 to 1.0 g/d (mean 0.58 g/d). (C) 105 patients had baseline urine protein 1 to 3 g/d (mean 1.8 g/d). (D) 55 patients had baseline urine protein ≥3 g/d (mean 4.8 g/d). Modified with permission from *J Am Soc Nephrol* (8) and *Ann Intern Med* (2).

Clinical Significance

Thus far, we have reviewed evidence to evaluate whether there is a benefit of a low protein diet on the progression of renal disease. We next examined whether the potential benefits suggested by some of the secondary analyses of the MDRD Study and other studies are large enough to be of clinical importance. To address this issue, we focused on the "effect size"—the magnitude of differences in outcomes between randomized groups, and the magnitude of regression coefficients in correlational analyses. However, interpretation of the magnitude of a beneficial effect depends on several factors in addition to the measured effect size. Among these factors are

patient characteristics, including the distributions of the levels of renal function and the rates of disease progression, as well as study design, level of adherence achieved in the study, and method of analysis.

First, we consider the findings from the MDRD Study using GFR decline as the outcome measure. The comparison of randomized groups in MDRD Study A showed an approximately 28% reduction in the mean GFR decline after the initial 4 mo in the low protein diet group compared to the usual protein diet group. This effect size is comparable to the mean effect of the low BP goal in the MDRD Study, which reduced the mean rate of GFR decline after the initial 4 mo by approximately 29% compared to patients assigned the usual BP goal. In the subgroup of patients with urine protein excretion $\geq$1 g/d, where both the mean rate of GFR decline and the evidence for a beneficial effect of the low BP goal were greatest, the low BP goal reduced the mean rate of GFR decline by approximately 40%. It should be noted that the beneficial effect of the low BP goal in the MDRD Study was achieved with a separation in mean BP between the randomized groups of only approximately 5 mmHg. It is possible that a larger reduction in BP could be achieved in routine clinical practice and would lead to a larger beneficial effect of this intervention; however, it is doubtful that a larger reduction in protein intake could be achieved in routine clinical practice. Nonetheless, the observed 28% mean reduction in GFR decline associated with the low protein diet may be clinically significant. If the GFR decline after 4 mo remains constant thereafter, a patient with an initial GFR of 40 ml/min per 1.73 m^2 and a GFR decline of 4 ml/min per yr would reach ESRD (defined arbitrarily as a GFR of 10 ml/min per 1.73 m^2) in 7 ¼ yr. In the same patient, a 28% reduction in GFR decline to 2.9 ml/min per 1.73 m^2 would lengthen the interval until ESRD to 10 yr. Given the older age of many patients with chronic renal disease and the amelioration of uremic symptoms associated with lower protein intake, this delay would mean that some patients will not reach ESRD.

The correlational analyses suggest that a 0.2 g/kg per d lower protein intake is associated with an approximately 30% slower GFR decline in Study B ($P = 0.011$), but with only a 10% slower mean GFR decline after the initial 4 mo in Study A ($P = 0.075$). This is consistent with the interpretation that the effect of protein restriction was larger in Study B than in Study A. However, the possibility of different patterns of bias due to uncontrolled confounding factors in Studies A and B might also account for the difference in effect size.

Next, we consider analyses using ESRD or death as the outcomes. The correlational analysis in Study B showed that a 0.2 g/kg per d lower protein intake was associated with a 50% reduction in the risk of ESRD or death ($P = 0.001$). The comparison of randomized groups in Study A revealed a reduction in the risk of ESRD or death of 35 to 37%, although the result was not significant ($P = 0.10$ during regular follow-up and $P = 0.056$ during extended follow-up). The meta-analysis of randomized trials showed a 35% reduction in the proportion of patients who developed ESRD or died in the low-protein diet group ($P = 0.007$). In all likelihood, these effect sizes overstate the impact of the low protein diet on disease progression, since they may also be influenced by the tendency to initiate dialysis at a higher level of renal function in patients with a higher protein intake. In addition, comparisons of such event rates between studies can be influenced by many factors other than the actual effects on progression rates. Still, it is interesting to observe that the magnitudes of these effect sizes are similar to those of therapies that have been proven to slow the progression of renal disease, such as strict BP control and angiotensin-converting enzyme (ACE) inhibition. For example, the Collaborative Study Group found a 50% reduction in the risk of ESRD or death in a randomized trial of captopril in type 1 diabetes (32). Extended follow-up of patients in the Ramipril Efficacy in Nephropathy (REIN) Study documented a 46% reduction in the risk of ESRD or death in patients with nondiabetic renal disease and $>$3 g/d urine protein excretion (33,34). A recent meta-analysis of randomized trials of ACE inhibitors in nondiabetic renal disease, including patients with or without proteinuria, found a 30% reduction in the risk of ESRD (35).

Adherence to and Safety of Dietary Protein Restriction

The prescribed protein intake in the low protein and very low protein diets in the MDRD Study was approximately 0.6 g/kg per d. In the MDRD Study and in other clinical trials, a prescribed protein intake of 0.6 g/kg per d was associated with a mean achieved protein intake of about 0.70 to 0.75 g/kg per d, equivalent to approximately 45 to 60 g/d. This level of protein intake is substantially below the average protein intake in the United States of 90 to 100 g/d (36,37), but is similar to the Recommended Dietary Allowances (RDA) of the Food and Nutrition Board of 0.80 g/kg per d (38). The RDA is believed to provide a surfeit of protein for most healthy adult men and nonpregnant, nonlactating women. Protein intake of 0.6 g/kg per d, together with adequate energy intake, appears sufficient to maintain nitrogen balance in patients with chronic renal disease (39,40), and a number of studies have demonstrated the short-term safety of such dietary restrictions (41). Recent results from the MDRD Study reveal no clinically meaningful changes in weight, anthropometry, and serum proteins, lipids, and amino acids from dietary protein restriction (42). Studies by Walser *et al.* (43,44) also document the safety of dietary protein restriction of several years' duration. Our experience in the MDRD Study was that adherence to a low protein diet, although challenging, can be enhanced with regular follow-up with a skilled dietitian. However, physicians must be mindful of the detrimental effect of malnutrition at the onset of ESRD on subsequent survival (45). Frequent monitoring of protein and energy intake and nutritional status is necessary to assure the safety of patients following a low protein diet.

Lessons Learned

These analyses provide insights that may be useful in future investigations of therapies to slow the progression of renal disease. First, the finding of a significant interaction of the efficacy of the low BP goal and baseline urine protein in both

Studies A and B suggests that all renal diseases may not respond similarly to interventions. This indicates that one should exercise caution in including patients with heterogeneous causes of renal disease in the same study. We believe that future studies should focus more narrowly on types of patients or specific renal diseases that may be worsening through common mechanisms.

Second, the slow mean rate of GFR decline and the opposite effects of both the diet and BP interventions on the short-term and long-term GFR declines in Study A indicate serious methodologic issues that should be considered when designing future studies. It will be necessary to model the direction and magnitude of expected short-term effects when determining the sample size and duration of follow-up necessary to demonstrate a long-term effect. If the hypothesized beneficial effect of the intervention is greater for patients with faster GFR decline, as for the diet intervention in MDRD Study A, the length of follow-up required for a long-term effect to overcome an opposite initial short-term effect will be inversely related to the mean rate of GFR decline. In this situation, consideration should be given to using the amount of time until a specified decline in renal function is reached as the primary outcome. In populations with a large percentage of patients with little or no GFR decline, this type of time-to-event analysis can achieve greater statistical power than analyses of the mean slope, where the observed treatment effect is diluted by the absence of an effect in patients with little or no GFR decline (46).

When feasible, the above considerations suggest that interventions should be evaluated in subgroups of patients known to have relatively fast mean rates of GFR decline. High levels of baseline proteinuria and PKD were found to be strong predictors of subsequent mean GFR declines in the MDRD Study (47). However, it is often difficult to determine in advance which individual patients will progress more rapidly within a particular clinical subgroup. In the MDRD Study, the rate of decline in reciprocal serum creatinine before enrollment in the study was a poor predictor of the subsequent GFR decline. The requirements for sample size and duration of follow-up will be especially demanding for evaluation of interventions in populations with a slow mean GFR decline, especially if the initial short-term effect is in the opposite direction to the hypothesized long-term benefits.

Conclusion

In summary, we have examined evidence from the MDRD Study and other clinical trials of the effect of dietary protein to slow the progression of renal disease. For various reasons, this evidence is not fully conclusive. Some authors have interpreted the MDRD Study as showing that dietary protein does not slow disease progression. We believe that this view is incorrect, and is a result of misinterpretation of inconclusive evidence as evidence in favor of the null hypothesis. In fact, as described herein, the balance of evidence appears to be more consistent with the dietary efficacy hypothesis than with the contrary hypothesis of no beneficial effect. In addition, the evidence supports at least the possibility of substantial clinical benefit, and that such benefits are additive to the benefits of strict BP control using antihypertensive regimens containing ACE inhibitors and calcium channel blockers. The evidence also supports the safety of a low protein diet with appropriate counseling and monitoring.

It is difficult to make recommendations in the absence of conclusive results. Nonetheless, until additional data become available, physicians must continue to make decisions based on the current balance of evidence for and against the efficacy and safety of dietary protein restriction. These secondary analyses from the MDRD Study, in conjunction with the results of other randomized trials, provide some justification for recommending a low protein diet (prescribed protein intake of 0.6 g/kg per d) for patients with chronic renal disease. It is also difficult to compare the value of delaying the onset of ESRD to the difficulty in long-term adherence to a low protein diet. We believe that appropriate counseling by physicians and dietitians will enable patients to make this assessment.

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