Dietary Protein Restriction, Blood Pressure Control, and the Progression of Polycystic Kidney Disease[1,2]

Modification of Diet in Renal Disease Study Group[3,4] (prepared by Saulo Klahr, Julia A. Breyer, Gerald J. Beck, Vincent W. Dennis, Judith A. Hartman, David Roth, Theodore I. Steinman, Shin-Ru Wang, and Monica E. Yamamoto)

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ABSTRACT

In the Modification of Diet in Renal Disease Study, a follow-up (mean, 2.2 yr) of 200 study participants with autosomal dominant polycystic kidney disease (ADPKD) was conducted to determine the effect of lowering protein intake and blood pressure on the rate of decline in GFR. The rate of decline was faster in participants with ADPKD than in persons with other diagnoses, reflecting, in part, faster disease progression in the ADPKD group. Baseline characteristics that predicted a faster rate of decline in GFR in persons with ADPKD were greater serum creatinine (independent of GFR), greater urinary protein excretion, higher mean arterial pressure (MAP), and younger age. In patients with initial GFR values between 25 and 55 mL/min per 1.73 m^2, neither assignment to a low-protein diet group nor assignment to a low blood pressure group significantly reduced the rate of decline of GFR in ADPKD participants. Similarly, the decline in GFR was not related to achieved protein intake or MAP. In participants with GFR values between 13 and 24 mL/min per 1.73 m^2, assignment to the low MAP group led to a somewhat more rapid decline in GFR. However, the more rapid decline in GFR did not appear to be due to a detrimental effect of low blood pressure or the antihypertensive agents used to reach the low blood pressure goal. Lower protein intake, but not prescription of the keto acid-amino acid supplement, was marginally associated with a slower progression of renal disease.

Key Words: *Keto acid–amino acid supplement, glomerular disease; GFR, clinical trials*

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Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic diseases, occurring in 1:500 to 1:1,000 live births ((1)). ADPKD is characterized by multiple bilateral renal cysts and is the primary diagnosis in 10 to 12% of patients with ESRD requiring renal replacement therapy in the United States ((2)). The gene responsible for most cases of ADPKD is located in the short arm of chromosome 16 ((3)). Despite this common genetic expression, patients with ADPKD have widely differing rates of decline in renal function. Patients with ADPKD rarely develop ESRD before 30 yr of age, and half of the patients with ADPKD do not have ESRD at age 58 ((4,5)). This suggests that factors other than gene inheritance may affect the rate of decline of renal function ((6,7)). The prospective identification of such factors would allow better counseling of patients with ADPKD and may also suggest new interventions for altering the progression of renal insufficiency in patients with ADPKD.

The Modification of Diet in Renal Disease (MDRD) was a multicenter, randomized clinical trial designed to determine whether lowering dietary protein/phosphorus intake and/or reducing blood pressure would slow the rate of progression of chronic renal diseases of diverse cause ((8)). Two hundred of the 840 participants enrolled in this study had ADPKD. This large number of ADPKD study participants allowed us not only to assess the effects of the study interventions in such patients but also to examine other demographic and clinical factors in the progression of their renal disease.

METHODS

Two hundred patients with ADPKD were enrolled in the MDRD study. The diagnosis of ADPKD was based on family histories and radiographic imaging studies obtained at the 15 clinical centers. The design of the MDRD trial has been described previously ((8,9)). Briefly, between January 1989 and March 1991, patients with suspected renal insufficiency were screened at 15 clinical centers for entry into the MDRD study ((10)). Of the 2,507 individuals screened, 1,795 satisfied the selection criteria and underwent monthly baseline evaluation for a period of 3 months ((9)); these baseline monthly visits were denoted as B0, B1, B2, and B3. During the baseline period, participants had their GFR determined by the clearance of iothalamate (B0, B3), their protein intake estimated by 24-h urine urea nitrogen excretion (B0, B1, B2, B3) and by 3-day food records (B0, B3), and their blood analyzed for hematologic and serum chemical characteristics (B0, B3).

During baseline, study participants were given dietary protein goals on the basis of their GFR at the first baseline

visit (B0). Participants with a GFR in the Study A range (*i.e.*, 25 to 55 mL/min per 1.73 m^2) were prescribed protein intakes between 0.9 and 1.3 g/kg per day. For participants with a GFR ≤24 mL/min per 1.73 m^2, the protein prescription was consistent with the participant's usual intake, as long as this exceeded 0.6 g/kg per day; otherwise, it was set at 0.6 g/kg per day. Antihypertensive regimens were adjusted to achieve a usual mean arterial pressure (MAP) treatment goal.

After the baseline period, 585 individuals with GFR values of 25 to 55 mL/min per 1.73 m^2 were assigned to Study A, and 255 participants with GFR values of 13 to 24 mL/min per 1.73 m^2 were assigned to Study B. Individuals assigned to Study A or Study B were randomly allocated to one of two prescribed levels of dietary protein and phosphorus intake and one of two prescribed levels of blood pressure control (usual or low). Study A participants were randomized to either a usual protein and phosphorus diet (1.30 and 16 to 20 mg/kg per day, respectively) or to a low-protein and low-phosphorus diet (0.58 and 5 to 10 mg/kg per day, respectively). Individuals in Study B were randomized to either the low-protein diet or to a very low-protein and low-phosphorus diet (0.28 g/kg per day of protein and 4 to 9 mg/kg per day of phosphorus) supplemented with a mixture of keto acids and essential amino acids (Ross Laboratories, Columbus, OH). The "usual" MAP goal was ≤107 mm Hg for participants 60 yr old or younger and ≤113 mm Hg for participants older than 60 yr; the low MAP goal was ≤92 mm Hg for participants 60 yr old or younger and ≤98 mm Hg for participants older than 60 yr. Randomization was stratified according to clinical center and by diet and average MAP during the baseline period (both Study A and B) and rate of change in serum creatinine during the screening period (Study A only) ([9]). The participants were not stratified on the basis of their renal diagnosis. The ADPKD patients were assigned to study groups as shown in Table 1.

After randomization, patients were instructed to modify their dietary protein and phosphorus intake to achieve their assigned diet goal. Pharmacologic and nonpharmacologic therapies were used to achieve the target blood pressure values. The recommended antihypertensive regimen was an inhibitor of angiotensin-converting enzyme (ACE) with or without a diuretic, the addition of a calcium channel blocker, and the addition of other medications.

During follow-up, GFR was measured by the clearance of iothalamate at 2 and 4 months after randomization and every 4 months thereafter, and protein intake was estimated monthly by 24-h urinary/urea nitrogen. Nitrogen contained in the keto acid–amino acid supplement was subtracted from urea nitrogen excretion. Blood was analyzed for hematologic and serum chemical characteristics every 2 months. Blood pressure was measured monthly with a random zero sphygmomanometer. Diet counseling and a limited physical examination were also done monthly. Conditions requiring withdrawal from the study (stop points) included malnutrition, rapid decline in GFR (Study A only, to <50% of baseline if initial GFR ≤40 mL/min per 1.73 m^2 or to a value of ≤20 mL/min per 1.73 m^2 if initial GFR >40 mL/min per 1.73 m^2), ESRD requiring dialysis or transplantation, and serious intercurrent medical conditions.

TABLE 1. Distribution of patients with polycystic kidney disease between diet and blood pressure treatment groups

Protein Diet[b]	Study A (GFR, 25 to 55 mL/min per 1.73 m^2) (N = 141)		Study B (GFR, 13 to 24 mL/min per 1.73 m^2) (N = 59)	
	Usual MAP[a]	Low MAP[a]	Usual MAP	Low MAP
Usual Protein Diet	35	39		
Low-Protein Diet	33	34	15	14
Very Low-Protein Diet			11	19

[a] MAP goal: Usual MAP, ≤107 mm Hg for 18 to 60 yr old at entry (equivalent to 140/90 mm Hg); ≤113 mm Hg for ≥61 yr old at entry (equivalent to 160/90 mm Hg); Low MAP, ≤92 mm Hg for 18 to 60 yr old at entry (equivalent to 125/75 mm Hg); ≤98 mm Hg for ≥61 yr old at entry (equivalent to 145/75 mm Hg).

[b] Protein diet: Usual Protein Diet: protein, 1.3 g/kg per day; phosphorus, 16 to 20 mg/kg per day; Low-Protein Diet: protein, 0.58 g/kg per day (≥0.35 g/kg per day as high biologic value); phosphorus, 5 to 10 mg/kg per day; Very Low-Protein Diet: protein, 0.28 g/kg per day; phosphorus, 4 to 9 mg/kg per day, supplemented with a keto acid–amino acid mixture, 0.28 g/kg per day (Ross Laboratories).

Statistics: Baseline Characteristics and Comparison of Groups by Diagnosis

For comparative purposes, in this study, the randomized participants were divided into subgroups by renal disease diagnoses. These subgroups were: (*1*) ADPKD (N = 141 in Study A, N = 59 in Study B); (*2*) glomerular disease including diabetic nephropathy and hereditary nephritis (N = 169 in Study A, N = 87 in Study B); and (3) other or unknown, which includes all participants with neither ADPKD nor glomerular disease (N = 275 in Study A, N = 109 in Study B). Participants with at least 1 yr of GFR follow-up were classified as progressors if their rate of decline in GFR was >0 and as nonprogressors if their rate of decline in GFR was ≥0. Baseline and other characteristics of these subgroups were compared with unpaired t tests for symmetrically distributed continuous variables, Wilcoxon rank sums tests for highly skewed variables, and χ^2 tests for categorical variables. Analysis of covariance was used to compare hematocrit levels adjusted for GFR at baseline among the renal diagnosis subgroups.

Renal Function Assessment

In Study A, the decline in GFR during follow-up was compared between the diet or blood pressure groups by use of a two-slope model in which each patient was assumed to have a rate of decline (slope) in GFR during the initial 4 months of follow-up and a different slope thereafter. A mixed-effect model was used ([11]). In Study B, the decline in GFR between groups was compared by use of an informative censoring model with lognormally distributed times to renal failure stop points or death. There were no significant interactions between the dietary or blood pressure interventions and the renal function outcomes. Therefore, for the intention-to-treat analyses, the effects of the dietary interventions were assessed by comparing all patients in the two diet groups (including those in both blood pressure groups). Similarly, the effects of the blood pressure intervention were assessed by comparing all patients in the two blood pressure groups (including both diet groups). For correlational analyses, the mixed effects model was used to relate rates of GFR decline to renal diagnoses and other baseline characteristics. In Study B, a one-slope model was used because the mean

decline in GFR was found to be linear in all treatment groups throughout follow-up. In Study B, because of the large number of variables examined, an unweighted regression of GFR slopes for patients with ≥8 months of follow-up was used rather than the informative censoring model. This approach seemed valid because the unweighted regressions in patients with ≥8 months of follow-up gave similar results to the informative censoring model in the intention-to-treat analyses. These methods were also used to conduct multiple regressions relating GFR decline to mean follow-up levels of achieved MAP and estimated protein intake after controlling for baseline MAP and estimated protein intake as well as four other baseline variables found to be jointly significant predictors of GFR decline in the entire study group (unpublished observations). These variables were: log(baseline urine protein), black race, serum levels of transferrin, and high-density lipoprotein (HDL) cholesterol.

RESULTS

Characteristics of Patients with ADPKD at Entry into Baseline

The demographic characteristics of randomized participants are shown in Table 2. Most participants with ADPKD (90%) were white, as was true for the MDRD trial as a whole (85%) ((9)). Slightly more than half were male. The distribution of ages at entry of ADPKD patients into both Studies A and B showed a peak in the age range of 40 to 49 yr for Study A and 50 to 59 yr for Study B with a subsequent decline in both studies. This is in contrast to the age profile for all MDRD study participants and the subgroups of participants with glomerular disease, or other renal diseases, in which there was a steady increase in the percentage of participants in the older age groups (including ≥60).

At randomization, mean GFR (iothalamate clearance) was 37.8 and 17.4 mL/min per 1.73 m^2 in patients with ADPKD in Studies A and B, respectively (Table 3). The mean creatinine clearance values were 48.0 mL/min per 1.73 m^2 (Study A) and 22.0 mL/min per 1.73 m^2 (Study B). The mean difference between creatinine clearance and GFR (the clearance of creatinine due to tubular secretion) was smaller in ADPKD patients (10.0 mL/min per 1.73 m^2, Study A; 4.5 mL/min per 1.73 m^2, Study B) than in patients with glomerular disease ($P < 0.001$) (12.9 mL/min per 1.73 m^2, Study A; 7.9 mL/min per 1.73 m^2, Study B) or other renal diagnoses ($P < 0.05$) (12.0 mL/min per 1.73 m^2, Study A; 5.9 mL/min per 1.73 m^2, Study B). The mean urinary protein excretion was also lower ($P < 0.05$) in the ADPKD group (0.29 g/day, Study A; 0.46 g/day, Study B) than in the glomerular disease group (2.13 g/day, Study A; 2.60 g/day, Study B) or the other renal disease group (0.53 g/day, Study A; 1.04 g/day, Study B). The mean serum cholesterol was lower in ADPKD participants in Study A (207 mg/dL) compared with non-ADPKD participants in Study A (222 mg/dL) ($P < 0.001$). Over 90% of the ADPKD participants were hypertensive at entry into the study (Table 3).

The relationship between hematocrit (Hct) and GFR levels was examined at baseline. As in the entire MDRD study group, lower GFR values correlated with lower Hct (Figure 1). No significant differences in Hct levels at any given level of GFR were observed between ADPKD participants and participants with glomerular disease or other renal diseases.

TABLE 2. Demographic characteristics of patients with polycystic kidney disease

Demographic Characteristic	Study A		Study B	
	N	%	*N*	%
Race				
White	127	90	53	90
Black	8	6	3	5
Hispanic	4	3	2	3
Other	2	1	1	2
Gender (Male)	79	56	34	58
Age (yr)				
20–29	4	3	0	0
30–39	23	16	9	15
40–49	57	40	20	34
50–59	39	28	22	37
≥60	18	13	8	14

Adherence to Dietary and Blood Pressure Goals

Differences in protein intake between the two diet groups in both Studies A and B were achieved by the fourth month of the follow-up period and remained approximately constant throughout follow-up (Figure 2). The median percentage of the prescribed keto acid–amino acid supplements taken by those following the very low protein diet, based on pill counts, was 95%. The difference in MAP between the usual and low blood pressure groups during the follow-up period was 6.3 mm Hg in Study A ($P < 0.0001$) and 3.9 mm Hg in Study B ($P = 0.01$). However, substantial overlap between the distributions of MAP remained throughout follow-up (Figure 2). The percentage of ADPKD participants prescribed ACE inhibitors, alone or in combination, for more than half of the follow-up period was 49 and 74% in the usual and low blood pressure groups in Study A and 42% in both the usual and low blood pressure groups in Study B. Twenty-four patients in Study A (17%) and 25 patients in Study B (42%) reached a renal function stop point at or before the close-out visit. In Study A, 11 patients in the usual blood pressure group and 13 in the low blood pressure group reached a stop point. In Study B, 9 patients in the usual blood pressure group and 16 in the low blood pressure group reached a stop point. In Study A, 14 patients in the usual protein diet reached stop point *versus* 10 patients in the low-protein diet group. In Study B, 14 patients reached a stop point (low-protein diet) *versus* 11 patients in the very low-protein diet group.

TABLE 3. Clinical characteristics of patients with polycystic kidney disease at randomization

Clinical Characteristic	Study A		Study B	
	N	Mean ± SD	*N*	Mean ± SD
GFR (mL/min per 1.73 m^2)	141	37.8 ± 9.0	59	17.4 ± 3.2
Creatinine (mg/dL)	140	2.0 ± 0.5	59	3.7 ± 0.9
Creatinine Clearance (mL/min per 1.73 m^2)	119	48.0 ± 13.6	57	22.0 ± 5.5
Mean Baseline Urinary Protein Excretion (g/day)	141	0.29 ± 0.53	59	0.46 ± 0.75
MAP (mm Hg)	141	99 ± 10	59	99 ± 8
Total Cholesterol (mg/dL)	139	207 ± 41	59	210 ± 37
Number and % Hypertensive	127	90.1%	54	91.5%

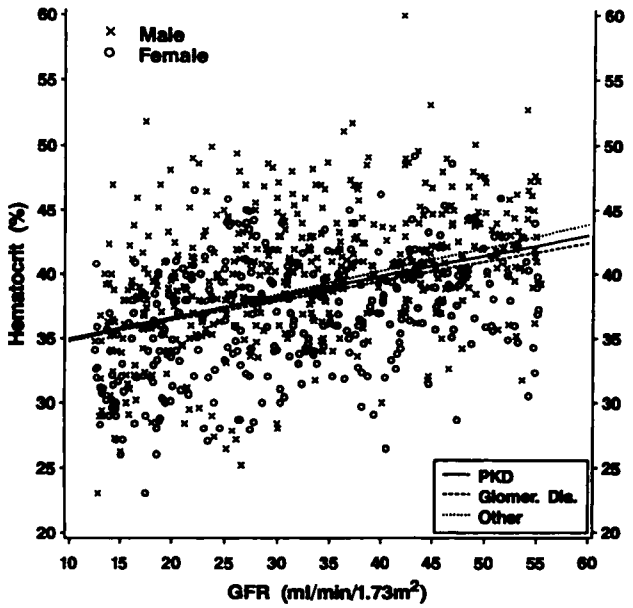

Figure 1. Hct values in males (X) and females (O) at different levels of GFR in patients with ADPKD (PKD; solid line), glomerular disease (Glomer. Dis.; dashed line), or other renal diseases (short- and long-dashed line). No significant differences in Hct levels were observed at any level of GFR among the three groups of patients (ADPKD, glomerular disease, other renal diseases).

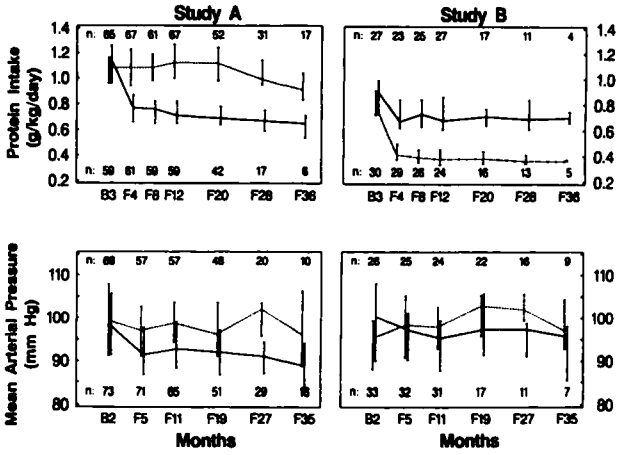

Figure 2. Estimated protein intake and MAP in patients with adult polycystic kidney disease enrolled in Studies A and B. Protein intake was estimated from urinary excretion of urea nitrogen. The two diets in Study B were designed to provide the same amount of nitrogen, but the nitrogen contained in the keto acid–amino acid supplement was subtracted in the very low-protein group. The mean values at each baseline (B) and follow-up (F) visit are given for patients on the usual protein diet (dashed line), the low-protein diet (solid line), and the very low-protein diet (dashed and dotted lines) and for those with usual blood pressure (dashed line) and low blood pressure (solid line). The bars show the 25th and 75th percentile of protein intake and MAP at each visit. The number (n) of patients with estimated protein intake and blood pressure measurements are shown within the panels. B3, baseline visit at 3 months after entry into the study; F4, F5, *etc.*, follow-up visit 4 months after randomization, 5 months after randomization, *etc.*

Assessment of Renal Function

Comparison of Renal Diagnostic Groups. ADPKD participants in Study A had a greater mean decline in GFR than did non-ADPKD participants. In Study A, the projected mean rate of decline in GFR averaging all four treatment groups was 5.9 mL/min per year for the ADPKD participants (Table 4) *versus* 3.1 mL/min per year for non-ADPKD participants ($P < 0.001$). In Study B, the mean rate of decline of GFR was 4.4 mL/min per year for ADPKD patients (Table 5), compared with 3.5 mL/min per year for non-ADPKD participants ($P < 0.05$).

Although the mean rate of decline in GFR was greater for ADPKD than for non-ADPKD participants, the variability in the rate of GFR decline was smaller in ADPKD participants. In Study A, the standard deviation in GFR slope after 4 months of follow-up was 3.1 mL/min per year for ADPKD participants as compared with 4.3 mL/min per year for non-ADPKD participants. Consistent with this smaller variability, in both Studies A and B, the proportion of ADPKD participants classified as "nonprogressors" (GFR slope <0 with at least 1 yr of follow-up GFR measurements) was substantially smaller than for participants with either

TABLE 4. Mean (SE) rates of GFR decline[a] by diet and blood pressure groups of patients with ADPKD in Study A

Group	Baseline to F4 (mL/min per 4 months)		
	Usual MAP	Low MAP	Both MAP Groups
A			
Usual Protein Diet	1.8 (0.8)	4.5 (0.8)	3.2 (0.6)
Low-Protein Diet	3.8 (0.9)	4.6 (0.8)	4.2 (0.6)
Both Diet Groups	2.8 (0.6)	4.6 (0.6)	3.7 (0.4)
B	F4 to End (ml/min/yr)		
	Usual MAP	Low MAP	Both MAP Groups
Usual Protein Diet	5.3 (0.7)	5.7 (0.6)	5.5 (0.5)
Low-Protein Diet	5.4 (0.7)	4.5 (0.7)	5.0 (0.5)
Both Diet Groups	5.4 (0.5)	5.1 (0.5)	5.2 (0.3)
C	Baseline to 3 Years (ml/min/yr)		
	Usual MAP	Low MAP	Both MAP Groups
Usual Protein Diet	5.3 (0.6)	6.6 (0.6)	5.9 (0.4)
Low-Protein Diet	6.1 (0.7)	5.5 (0.6)	5.8 (0.5)
Both Diet Groups	5.7 (0.5)	6.0 (0.5)	5.9 (0.3)

[a] Means were estimated by use of the maximum likelihood method for the two-slope model, with separate slopes from the baseline visit to the fourth month of follow-up (F4) (initial slope) and from F4 to the end of follow-up (final slope). Mean GFR slopes from baseline to 3 yr were computed as time-weighted averages of the initial and final slopes. There were no significant interactions of diet and MAP effects. There were no significant diet or MAP effects, except for a significant (P = 0.03) MAP effect from baseline to F4.

TABLE 5. Mean (SE) rates of GFR decline[a] in diet and blood pressure groups of patients with ADPKD in Study B

Group	Baseline to End (mL/min per yr)		
	Usual MAP	Low MAP	Both MAP Groups
Low-Protein Diet	4.3 (0.5)	5.5 (0.5)	4.9 (0.4)
Very Low-Protein Diet	3.5 (0.5)	4.4 (0.5)	4.0 (0.3)
Both Diet Groups	3.9 (0.3)	4.9 (0.3)	4.4 (0.2)

[a] Means were estimated by use of the single-slope informative censoring model. The effect of diet was not significant (P = 0.06), and the effect of MAP was significant (P = 0.03), but in the opposite direction of the hypothesis.

glomerular or other renal diseases (Table 6). In Study A, among patients with at least 1 yr of follow-up GFR measurements, seven patients with ADPKD (5.1%) had a positive GFR slope; four of these nonprogressors were females (57%). The percentage of nonprogressors was substantially higher in the glomerular disease group (17%) and the other renal disease group (28%). All Study B participants with ADPKD had a decline in GFR during follow-up, as compared with patients with glomerular disease, 13% of whom showed no decrease, and patients with other renal diseases, 19% of whom were nonprogressors.

TABLE 6. Percent nonprogressors[a] by renal diagnosis

Renal Diagnosis	Study A		Study B	
	N[b]	% Nonprogressors	N[b]	% Nonprogressors
Polycystic	137	5	55	0
Glomerular	157	17	67	13
Other or Unknown	259	28	97	19

[a] GFR slope ≥0. GFR slopes were computed by ordinary least squares regression.
[b] Number of participants with at least 1 yr of follow-up GFR measurements.

Intent-to-Treat Analysis. Similar to the effect observed in the entire Study A group ((11)), ADPKD participants in Study A who were randomized to the low blood pressure goal had a significantly faster mean rate of decline in GFR (4.6 mL/min per 4 months) in the first 4 months after randomization (initial slope) than did participants assigned to the usual blood pressure goal (2.8 mL/min per 4 months) (Table 4A and Figure 3). Also, as in the entire Study A group, the initial mean decline in GFR was greater in ADPKD participants randomized to the low-protein diet (4.2 mL/min per 4 months) *versus* the usual protein diet (3.2 mL/min per 4 months), although this difference did not reach statistical significance (Figure 4). In Study A, the mean GFR slope from 4 months to the end of follow-up (final slope) did not differ significantly between the two ADPKD diet groups (low protein, −5.0 mL/min per year; usual protein, −5.5 mL/min per year) (Table 4B) or the two blood pressure

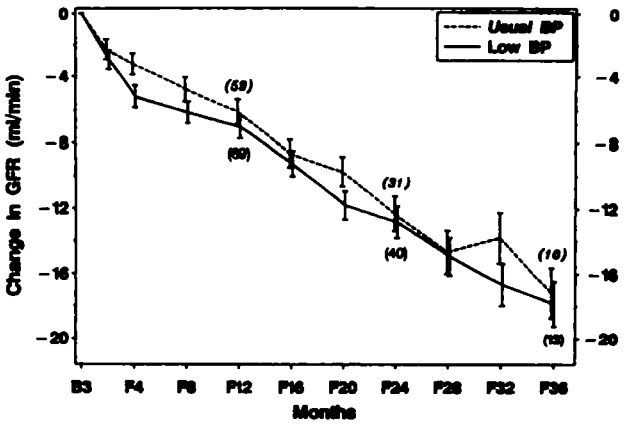

Figure 3. Mean changes in GFR *versus* time in patients randomized to a usual (dashed line) or a low blood pressure (solid line) group. There was a greater decline in GFR from baseline to follow-up visit at 4 months (F4) in patients with ADPKD randomized to the low blood pressure group (solid line).

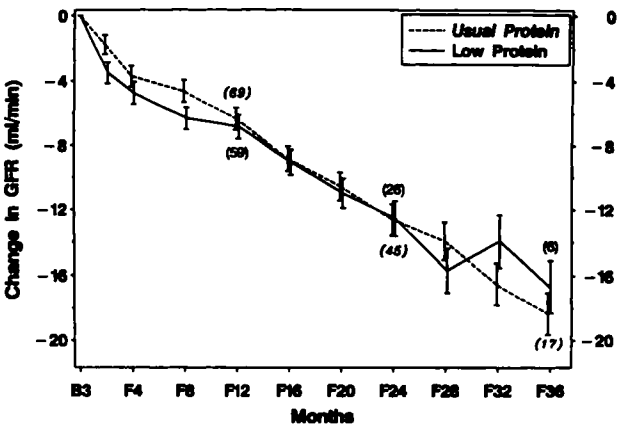

Figure 4. Mean changes in GFR *versus* time in patients randomized to a usual protein intake (dashed line) or patients randomized to a low-protein intake (solid line). There was a greater decline in GFR from baseline to follow-up visit at 4 months (F4) in patients with ADPKD randomized to the low-protein group (solid line).

groups (usual blood pressure, −5.4 mL/min per year; low blood pressure, −5.1 mL/min per year). The projected mean GFR slope over the 3 yr of follow-up also did not differ significantly between either the two dietary groups or between the two MAP groups of patients with ADPKD (Table 4C; Figures 3 and 4).

The 95% confidence interval for the difference in mean final slopes (after 4 months) between blood pressure groups of patients with ADPKD was −1.0 to +1.6 mL/min per year. This indicates that any beneficial effect of blood pressure control on mean final GFR slope in the group with the low MAP goal is unlikely to have exceeded 1.6 mL/min per year, or about 30% of the mean final slope in the usual MAP group. By contrast, the low blood pressure intervention significantly reduced the steepness of the mean final GFR slope in non-ADPKD patients ($P = 0.002$) and in the entire Study A group ((10)). The trend toward a stronger effect of the low MAP intervention in non-ADPKD patients is consistent with the reported beneficial effect of the low MAP intervention in participants with greater baseline proteinuria ((10)), who generally had diagnoses other than ADPKD. The 95% confidence interval for the difference in mean final GFR slopes between ADPKD patients assigned to the low- or usual protein diet groups was −0.8 to +1.8 mL/min per year, indicating that any undetected beneficial effect of the low-protein diet on mean GFR slope is unlikely to have exceeded 1.8 mL/min per year, or about 33% of the mean final slope in the usual protein diet group. The effect of the diet intervention on the final GFR slope did not differ significantly between ADPKD and non-ADPKD participants ($P = 0.56$).

In Study B, the mean rate of decline in GFR among ADPKD participants was significantly faster ($P = 0.03$) in the low MAP group (4.9 mL/min per year) than in the usual MAP group (3.9 mL/min per year) (Table 5). This finding must be interpreted cautiously because it may be a chance result occurring in one of numerous secondary analyses. As in the entire Study B group ((10)), there was a trend ($P = 0.06$) toward a less steep mean rate of GFR decline among persons randomized to the very low-protein diet group (4.0 mL/min per year) than among those randomized to the low-protein diet group (4.9 mL/min per year). However, the proportion of patients reaching renal failure or death was similar in the low-protein diet group (20 of 29; 69%) and the very low-protein (18 of 30; 60%) diet group. As in the entire Study B group, time to renal failure or death did not differ significantly between the diet groups after controlling for baseline GFR and the randomization stratification factors.

Correlational Analyses. Table 7 summarizes the association by the use of univariate analysis between various baseline factors and GFR decline during follow-up for ADPKD participants. The estimates of GFR slope were standardized to show the change in slope associated with a 1 SD increase in continuous variables and the difference in mean GFR slope between the two levels of dichotomous variables. A negative estimate means that higher values of the baseline variable were associated with a faster decline in GFR, whereas a positive estimate means that higher values of the baseline were associated with a slower GFR decline.

TABLE 7. Baseline predictors of decline in GFR

Baseline Variable[a]	Study A Effect on Projected Mean GFR Slope Over 3 yr (mL/min per month)		Study B Effect on Overall Slope (mL/min per month)	
	Estimate	*P* Value[b]	Estimate	*P* Value
Age	+0.087	**0.004**	+0.37	0.09
Preexisting Hypertension[c]	−0.035	0.70		
GFR ≥ Median[c]	−0.091	0.07	−0.006	0.89
Smoker[c]	−0.087	0.18	−0.013	0.83
1/(Serum Creatinine)	+0.078	**0.007**	+0.029	0.17
Log (Urine Protein)	−0.105	**0.006**	−0.026	0.25
Serum Albumin	−0.026	0.40	−0.041	0.06
HDL Cholesterol	+0.092	**0.001**	+0.024	0.39
Low-Density Lipoprotein Cholesterol	+0.028	0.32	+0.048	**0.04**
Estimated Protein Intake	−0.000	0.99	−0.006	0.79
MAP	−0.087	**0.001**	−0.022	0.33
Hct	−0.040	0.12	−0.049	**0.04**
Serum Transferrin	+0.022	0.42	−0.019	0.41
Hemoglobin	−0.041	0.11	−0.045	0.05
Uric Acid	+0.019	0.46	−0.020	0.39

[a] Nondichotomous baseline variables scaled to have an SD of 1.
[b] Boldface type indicates significance.
[c] Dichotomous variable.

In Study A, a higher age, HDL cholesterol, and reciprocal of serum creatinine (*i.e.*, lower serum creatinine) were associated with a slower decline in GFR in ADPKD participants. Greater levels of proteinuria and MAP were associated with a steeper decline in GFR. In addition, the mean rate of GFR decline was more rapid in males with ADPKD than in females (Figure 5). This more rapid decline in GFR was independent of the diet or MAP groups to which the male ADPKD participants were assigned. In Study B, only a higher low-density lipoprotein cholesterol was associated with a slower GFR decline, although the power for detection of this association was less. In a multivariate analysis including the entire MDRD study population (unpublished observations), higher baseline urine protein, black race, higher MAP, and lower serum levels of HDL cholesterol and serum transferrin were independently predictive of the subsequent GFR decline.

As shown in Figure 2, there was substantial interpatient variability in achieved levels of MAP and dietary protein intake during follow-up. We therefore examined the association of GFR decline with achieved MAP and protein intake, controlling for the relevant baseline factors specified in the Correlational Analysis. GFR slope was not significantly related to mean follow-up MAP in Study A [b = −0.06 (mL/min per year)/(mm Hg), $P = 0.26$] or in Study B [b = −0.05 (mL/min per year)/(mm Hg), $P = 0.21$]. The association of GFR slope with mean follow-up protein intake was also nonsignificant in Study A [b = +0.1 (mL/min per year)/(g/kg per day), $P = 0.94$]. However, consistent with the trend of a less steep GFR slope in the very low-protein group, higher mean follow-up protein intake was marginally associated with a more rapid decline in GFR in Study B [b = −3.1 (mL/min per year)/(g/kg per day), $P = 0.06$].

The significantly more rapid decline in GFR in the low *versus* usual MAP group in Study B, without a relationship between the level of blood pressure and the rate of decline of GFR, raises the possibility that increased use of ACE inhibitors or some other class of antihypertensives adversely affected renal function among ADPKD participants with advanced renal insufficiency. To evaluate this possibility, GFR slope was regressed on the proportion of follow-up visits at which each of the following drug classes was prescribed: ACE inhibitors, beta blockers, calcium channel blockers, diuretics, and other antihypertensives. This analysis controlled for (achieved) mean follow-up MAP and mean follow-up estimated protein intake, as well as for the baseline factors specified in the Correlational Analysis. Neither the use of ACE inhibitors nor the use of any other class of antihypertensives was significantly associated with GFR slope in ADPKD participants in either Study A or Study B. However, because the blood pressure intervention in the MDRD study was not designed to distinguish the effects of specific antihypertensives, these results are not conclusive.

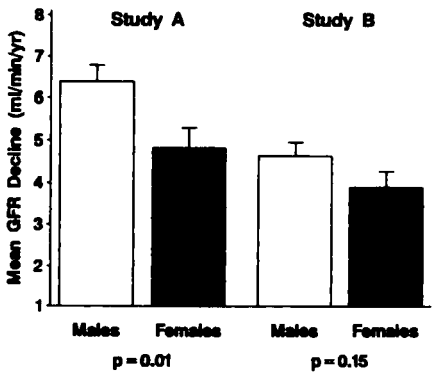

Figure 5. Mean rates of GFR decline in male and female patients with adult polycystic kidney disease in Studies A and B. In Study A, males had a significantly greater ($P = 0.01$) decline in GFR than did females. There were no significant differences in the rate of GFR decline between males and females in Study B ($P = 0.15$).

DISCUSSION

Adult polycystic kidney disease affects more than half a million people in the United States, and approximately 5 million persons worldwide are at risk for the disease ([12]). Despite this high incidence, major gaps in our understanding of the natural history of this disease remain. Dalgaard's classic monograph has long served as a major source of information about ADPKD ([13]). Although Dalgaard reported on a large number of patients, the study was retrospective, with one-third of the patients diagnosed at autopsy. More recent studies of patients with ADPKD have been limited by relatively small numbers of patients, by the retrospective nature of the review, or by insensitive measures of renal function ([14–19]). The inclusion of 200 participants with ADPKD in the MDRD study has provided a unique opportunity to characterize a large population of patients with ADPKD, carefully describe their rate of decline in GFR, examine potential predictors of the rate of decline in GFR, and document the efficacy of dietary and blood pressure interventions.

The racial and gender distribution of the ADPKD participants in this study was similar to that described in previous studies ([14,19,20]). ADPKD is inherited in an autosomal dominant fashion, and hence, approximately equal numbers of affected males and females would be anticipated. The slightly higher percentage of males in the MDRD study may reflect phenotypic variability, because some authors but not all have reported that females may be older at the time of the initial diagnosis of ADPKD and have preserved renal function later in life ([4,13,15,21,22]). Using iothalamate clearances as a measure of GFR, we confirmed that females have a slower rate of decline in GFR ([23]) in early renal insufficiency (GFR, 25 to 55 mL/min per 1.73 m^2). However, once GFR fell below 25 mL/min per 1.73 m^2, the rate of decline in

GFR was equivalent in males and females. This is consistent with the report by Gretz *et al.* ((22)) that GFR declined more slowly in females when serum creatinine levels were less than 3 mg/dL but declined equally in males and females when serum creatinine levels were higher than 3 mg/dL.

The distribution of ADPKD participants by age in the MDRD study parallels the age distribution of patients at first diagnosis of ADPKD: most were in the 40- to 60-yr age group ((15)). This was in contrast to the age distribution of MDRD participants in other disease categories, which indicated an increased or unchanged incidence of disease with increasing age. Although all patients with ADPKD have the gene putatively associated with it, the age of onset of renal insufficiency varies widely, from 3 to 80 yr. Indeed, in two recent series, only 50% of subjects had died or reached ESRD by age 59 or 73 ((4,5)). In another series, participants who survived to their 60th birthday with normal renal function, as measured by serum creatinine, were unlikely to develop significant renal insufficiency before death ((14)). Thus, in the MDRD study, the age distribution of the ADPKD participants at the time of enrollment and the fact that older age predicted a slower progression of renal disease during the follow-up period may have a common explanation. Patients with ADPKD who are going to have significant renal functional impairment tend to present in the age range of 40 to 60 yr and have a more rapid decline in GFR than older patients. Older patients with ADPKD who are relatively asymptomatic and have well-preserved renal function may have a very good prognosis ((16)).

In the MDRD study, the GFR of ADPKD participants in Study A decreased at a mean rate of 5.8 mL/min per year, whereas the GFR of non-ADPKD participants decreased only 3.1 mL/min per year. Similarly, in Study B, the GFR of the ADPKD participants decreased a mean of 4.3 mL/min per year, whereas the GFR of other participants decreased 3.5 mL/min per year. The greater mean rate of decline of renal function in ADPKD participants may largely reflect the fact that they were a more homogenous group of participants, most of whom sustained a decline in renal function. The slightly more rapid mean rate of decline of GFR among ADPKD participants in Study A than in Study B may reflect: a true decrease in the rate of decline once a patient's GFR falls below a certain level; the selection of participants for Study A and Study B with different rates of decline in GFR; or a possible effect of the lower protein diets in Study B *versus* Study A. The rate of decline of renal function among ADPKD patients in previous studies has varied from 1.1 to 7 mL/min per year ((14,24)). Previous studies were largely retrospective, examined renal function by less sensitive measures such as serum creatinine and creatinine clearance, and also included patients who did not have a documented baseline decrease in renal function. The inclusion of asymptomatic participants and a subset of participants whose renal function may have remained virtually stable would contribute greatly to the variable rates of decline in renal function previously reported.

In addition, the rate of decline in GFR was less variable among ADPKD participants in the MDRD study than among non-ADPKD participants, and a smaller proportion of nonprogressors (*i.e.*, participants with GFR slope ≤ 0) was observed among the ADPKD participants than among participants with glomerular disease or among those with other renal diagnoses. Thus, the mean rate of decline in GFR was greater in patients with ADPKD than in patients with other renal diagnoses and the rate of loss of renal function was also less variable (*i.e.*, more uniform) in patients with ADPKD.

Certain clinical characteristics of patients with ADPKD may predict the progression of their renal disease ((20,21)). Worse renal function at a given age has been associated with the PKD1 gene, younger age at diagnosis, increased left ventricular mass, hepatic cysts in women, three or more pregnancies, gross hematuria, urinary tract infections in men, and renal size expressed as renal volume. Clinical findings not associated with worse renal function include mitral valve prolapse, intracranial aneurysms, absence of pregnancies, hepatic cysts in men, and urinary tract infections in women ((20)). However, the design of the MDRD study did not allow for analysis of these potentially predictive factors.

Other findings of the MDRD study do help to characterize ADPKD more fully. As in previous reports, among the MDRD participants with ADPKD, male gender and increasing MAP or proteinuria were associated with a more rapid progression of renal disease ((6,20)). In a study by Murphy *et al.* ((25)), heavy proteinuria in two patients with ADPKD was associated with focal sclerosing glomerulonephritis and immunoglobulin A nephropathy. Higher HDL cholesterol levels in ADPKD participants in the MDRD study were strongly associated with a less steep decline in GFR. Higher Hct levels were not significantly associated with a steeper decline in renal function. Also, in contrast to previous reports, ADPKD participants in the MDRD study did not have higher Hct for any given level of renal function compared with participants with renal insufficiency of other causes ((21)). This may reflect the more accurate measurements of renal function in this study. The use of ACE inhibitors or the inclusion of patients with different rates of decline in renal function did not appear to account for the absence of higher Hct levels among the patients with ADPKD in this study.

Prior data on the efficacy of a low-protein diet in ADPKD patients are scarce. A positive effect of a low-protein diet on the rate of progression of chronic renal failure has been reported in five different studies that had a total of 115 patients enrolled ((6,26–29)). There was no significant effect of a low-protein diet in two studies with a total of 81 patients ((30,31)). Each of these studies had one or more limitations, such as

small sample size, lack of a randomized design, and imprecise measures of renal function. The study with the largest sample size (74 patients) demonstrated no effect of a low-protein diet ((32)). Our data do not support a beneficial effect of a low-protein diet on the rate of GFR decline in ADPKD patients with moderate renal insufficiency (25 to 55 mL/min per 1.73 m^2).

Study B (GFR, 13 to 24 mL/min per 1.73 m^2) was not designed to evaluate the effect of a usual protein diet. Only the effects of a low- or very low-protein diet were compared. Interestingly, as in the entire MDRD study, participants with ADPKD randomized to the very low-protein diet supplemented with keto acids demonstrated a nonstatistically significant trend toward a slower rate of decline in GFR. When patients in both diet groups are combined, there is a trend toward a slower GFR decline and a longer interval until renal failure among patients who complied with either diet. However, after controlling for actual protein intake, there is a trend toward a beneficial effect of assignment to the very low-protein diet group. This suggests a benefit of the low-protein diet but not the keto acid–amino acid supplement.

There are no prospective studies of blood pressure control in ADPKD patients with multiple years of follow-up. Over 90% of the ADPKD participants in this study were hypertensive at baseline. Widely varying rates of hypertension have been reported previously in ADPKD (13 to 81%), but this variability may have been the result of the differing degrees of renal insufficiency in the populations studied ((13,16,17,32–40)). However, even in the absence of a significant decline in GFR (>75 mL/min per 1.73 m^2), up to 59% of ADPKD patients have blood pressures >150/90 mm Hg ((40)). The high incidence of hypertension (>90%) in the ADPKD participants in the MDRD study may reflect their decreased renal function (GFR ≤55 mL/min per 1.73 m^2) and/or the greater accuracy of blood pressures repeatedly measured by random zero sphygmomanometers.

Although higher baseline MAP values predicted a steeper decline in follow-up GFR in patients with ADPKD (Table 7) in Study A, assignment to the lower blood pressure group did not significantly slow the rate of GFR decline in Study A and was actually associated with a faster mean decline in GFR in Study B (GFR, 13 to 24 mL/min per 1.73 m^2). The faster decline in the low blood pressure group in Study B must be interpreted cautiously because actually achieved MAP during follow-up was not significantly correlated with the rate of GFR decline and the direction of the correlation that was observed was negative, indicating slightly steeper GFR slopes at higher MAP levels. However, these findings are consistent with those of a retrospective study in 26 patients with ADPKD in which the association between blood pressure and the rate of progression of renal disease was expressed as a polynomial regression. In this model, the lowest and highest values of MAP were associated with faster rates of progression than were intermediate blood pressures ((7)).

The hypertension associated with ADPKD is believed to be due to cyst enlargement causing renal ischemia and release of renin ((41,42)). ADPKD patients with hypertension have more stimulated renin-angiotensin-aldosterone systems than do patients with essential hypertension, and this may contribute to increased cardiac preload and, thus, to the development of hypertension ((43,44)). ACE inhibitors may therefore be of particular benefit in patients with ADPKD. In two short-term studies, ACE inhibitors given to ADPKD patients with GFR values within the normal range were associated with increased RPF, decreased MAP, decreased renal vascular resistance, decreased filtration fraction, and unchanged GFR ((45,46)). On the other hand, eight episodes of acute renal failure in five patients with ADPKD, massive renal involvement, and chronic renal insufficiency have been described ((47)). In all cases, ACE inhibitor therapy was considered as the most likely cause. Nearly three-fourths of the ADPKD participants in the MDRD study assigned to the low MAP goal were prescribed ACE inhibitors alone or in combination for over 50% of follow-up visits. This was in contrast to other antihypertensive agents such as beta blockers, calcium channel blockers, and diuretics, which were prescribed for over 50% of follow-up visits in only 30 to 40% of the ADPKD participants assigned to the low MAP goal. Also, only 40 to 50% of MDRD participants with glomerular or other renal diseases who were assigned to the low MAP goal were prescribed ACE inhibitors (data not shown). This preponderance of ACE inhibitor use may be because of its presumed effectiveness in ADPKD patients. Correlational analyses of MDRD participants showed no significant association between the use of ACE inhibitors and the rate of decline in renal function after controlling for achieved blood pressure. However, because the participants were not randomized to receive or not receive ACE inhibitors, no firm conclusions can be made about their effectiveness in slowing the rate of decline of renal function.

It should be pointed out that this study of patients with ADPKD in the MDRD has several shortcomings. The interventions—protein restriction and blood pressure control—were introduced at a late stage of the natural history of the renal disease. In both Studies A and B, control of blood pressure was achieved but the differences in blood pressure levels between the usual blood pressure group and the low blood pressure group were small and may have precluded the uncovering of an effect of hypertension on the progression of renal disease. Certainly, careful and adequate control of blood pressure should be prescribed in patients with ADPKD. It is also possible that a longer period of follow-up would have uncovered an effect of blood pressure on the progression of renal disease in patients with ADPKD in the MDRD study.

In summary, the mean rate of decline in GFR was

greater in patients with ADPKD than in patients with other renal diagnoses. Also, the rate of loss of renal function was less variable (*i.e.*, more uniform) in patients with ADPKD. Neither the low-protein diet nor the lower than usual blood pressure goal was effective in slowing the progression of renal disease in patients with GFR of 25 to 55 mL/min per 1.73 m^2. In patients with GFR of 13 to 24 mL/min per 1.73 m^2, there was a suggestion of a beneficial effect of adherence to a low-protein diet. There was a suggestion of a harmful effect of a lower than usual blood pressure goal in patients with advanced renal failure; however, this result is not robust because the faster GFR decline in the low blood pressure group was not related to the achieved blood pressure or to the antihypertensive regimen used.

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