Survival on Dialysis Among Chronic Renal Failure Patients Treated With a Supplemented Low-Protein Diet Before Dialysis[1]

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ABSTRACT

Concerns have been raised about the possibility of protein restriction resulting in malnutrition and poor subsequent survival on dialysis. However, no studies have examined patients treated with protein restriction to determine their subsequent survival on dialysis. This study prospectively monitored 67 patients with established chronic renal failure (mean initial serum creatinine of 4.3 mg/dL) who were treated with a very low-protein diet (0.3 g/kg per day) supplemented with either essential amino acids or a ketoacid-amino acid mixture and observed closely for clinical complications. Forty-four patients required dialysis. Once dialysis was started, dietary treatment was no longer prescribed. The cumulative mortality rate during the first 2 yr after starting dialysis was 7% (95% confidence interval, 0 to 16%). During this period, only two deaths occurred compared with 11.5 deaths expected on the basis of national mortality rates adjusted for age, sex, race, and cause of renal disease ($P = 0.002$). However, the protective effect was limited to the first 2 yr on dialysis. Thereafter, mortality rates increased, resulting in a total of 10 deaths during 96.4 person-years of follow-up, which was not significantly lower than the 14.9 deaths expected ($P = 0.25$). Extrapolation of sequential serum creatinine measurements made before dietary treatment suggests that the improved survival cannot be due to the early initiation of dialysis. Although the lack of an internal control group and data on dialysis lends uncertainty, the large difference in mortality rate between these patients and the nationwide experience indicates that protein restriction and close clinical monitoring predialysis does not worsen and may substantially improve survival during the first 2 yr on dialysis. These findings point out the importance of studying predialysis treatments as a means for lowering mortality on dialysis.

Key Words: *Chronic renal failure, ketoacids, amino acids, creatinine, hypoalbuminemia*

Patients with ESRD have benefitted greatly from the widespread availability of renal replacement therapy (RRT), consisting of dialysis and kidney transplantation. However, treated ESRD remains a serious condition associated with high rates of mortality and morbidity and substantial cost to individual patients and society (1). In recent years, efforts have been directed toward preventing ESRD by slowing the progression of chronic renal failure (CRF) toward the end stage and attempting to reduce mortality on RRT. Most studies have focused on one or the other of these strategies, with little emphasis on the effect of predialysis treatment on survival after the initiation of dialysis.

Protein restriction, with or without dietary supplementation, has been studied as a strategy for slowing the progression of severe CRF in numerous investigations. However, to date, there is no clear consensus on the efficacy of this treatment. The "Modification of Diet in Renal Disease" (MDRD) study (2) suggested, although inconclusively, that protein restriction and ketoacid supplementation slowed the rate of decline of GFR. Among patients with more severe CRF, those randomized to the supplemented very low-protein diet had a rate of decline in their GFR that was 19% (95% confidence interval, −2 to +41%) slower than that of patients randomized to a low-protein diet alone. In contrast, the incidence of ESRD or death was only reduced by a small amount (7%; 95% confidence interval, 35 to −33%) that was not statistically significant. Future analyses of this large study will be needed to further clarify this discrepancy. Smaller studies (3,4), including several from this clinical research center (5–7), have presented evidence for the slowing of the progression by protein restriction supplemented with ketoacid–amino acid mixtures different from the one used in the full-scale MDRD study. A recent meta-analysis (8) summarized the results of six randomized controlled trials of protein restriction in

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CRF. That analysis, combining the results of protein restriction with and without dietary supplementation, concluded that patients treated with dietary protein restriction were less likely to die or start dialysis during the course of follow-up.

Concerns have been raised about the possibility of malnutrition among patients treated with supplemented very low-protein diets (9). Serum albumin concentration provides a measure of nutritional status and has consistently been found to be the best predictor of mortality on dialysis (10–15). We have recently reported that hypoalbuminemia at the onset of dialysis can usually be prevented by nutritional treatment before dialysis with a supplemented, very low-protein diet (16). It might therefore be anticipated that implementing this dietary regimen before dialysis would reduce subsequent mortality on dialysis. The primary focus of this article is to test this hypothesis. The study also uses serum creatinine measurements to determine whether this regimen resulted in the postponement or hastening of the need for dialysis.

METHODS

Study Population

The records of all patients treated at our research facility since 1985 were reviewed. All patients who were prescribed a very low-protein diet (0.3 g/kg) plus a supplement of either essential amino acids or a ketoacid–amino acid mixture for at least 2 months and had at least four serum creatinine concentrations ([Cr]) of 1.3 mg/dL or higher in different weeks before starting treatment were included in this study. This resulted in 67 patients. The study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Treatment Regimen

Patients were seen once every 2 months, on average. At every visit, symptoms and physical signs were noted, routine hematologic and chemical measurements were performed, and a 24-hr urine sample for the measurement of protein, phosphate, and urea excretion was obtained. All patients received supplements of $CaCO_3$ and multivitamins. Complications of CRF were treated with antihypertensive drugs, diuretics, $NaHCO_3$, colchicine, allopurinol, sodium polystyrene sulfonate, and other drugs as indicated.

The dietary regimen, containing 0.3 g of protein per kilogram of ideal body weight, has been described in detail previously (5–7). Dietary counseling was provided whenever requested by the patient or by the study physician because of poor compliance or weight loss. In 57 of the 67 patients, the diet described below was started within a month of their first visit. In the other 10, the very low-protein diet was not begun until later, when it became clear (from sequential measurements of GFR) that renal disease progression was occurring. During this run-in period, the mean protein intake (0.84 ± 0.18 g/kg per day, as estimated from 24-h urinary urea nitrogen excretion) remained similar to the protein intake at the time of referral to this clinic. This run-in period in 10 patients lasted an average of 18 months.

Follow-Up Procedures

All patients were treated by one physician (M. Walser), with additional input in many cases from their local physician, until they were referred for RRT, dialysis, or transplantation. The mean duration of follow-up on the diet was 27 months (range, 2 to 72 months). The decision to initiate RRT was made by the director of the patient's chosen dialysis/transplantation unit, on the basis of the same criteria as used for patients not in this study; we played no role in this decision. Two patients received a kidney transplant before the initiation of dialysis. Four patients withdrew voluntarily, and two patients died during follow-up before needing RRT. One death was from a myocardial infarction, and the other was due to Goodpasture's syndrome. Vital status for all patients was determined by contacting them or their next of kin during April 1994.

Statistical Analysis

The survival of the study patients on dialysis was compared with the expected number of deaths by use of the usual methods for calculating standardized mortality rates (17) as described for use in renal disease (18). The expected number of deaths was calculated from the U.S. Renal Data System (USRDS) death rates for patients of the same age, sex, race, and presumed primary cause of renal disease (page D.3–4) (1). Rates from 1988 to 1990 were chosen because they represented the middle of the follow-up period, 1986 to 1994. Death rates were converted to probabilities of death. For each patient, the amount of follow-up time on dialysis was determined and the expected probability of death was calculated on the basis of the appropriate death rate and follow-up time. The expected number of deaths for each year after the start of dialysis was calculated as the sum of the probabilities of death for all patients during that year. The observed number of deaths was compared with the expected number of deaths by the use of a Poisson distribution, with the mean number of deaths equal to the expected deaths. These calculations were implemented in EXCEL 4.0 (Microsoft Corporation, Redmond, WA). Mortality rates were applied from the date of the initiation of dialysis therapy, rather than 3 months after the initiation of therapy, as is done in generating the USRDS rates (1). This method was used in order to avoid potential bias if deaths occurred during this time period. However, none of the findings reported are sensitive to this assumption, *i.e.*, the differences reported remain significant if the mortality rates are applied starting 3 months after the initiation of dialysis. All P values cited are two-tailed.

To examine the effect of the dietary treatment regimen on the time of the initiation of dialysis, pretreatment [Cr] data, obtained from chart review, were analyzed. All available [Cr] measures before treatment at this center were entered into a SAS database and verified. [Cr] values before the first documented abnormal [Cr] (≥1.3 mg/dL) were excluded because they predate the presence of known renal failure. In addition, [Cr] values were excluded if measured during an acute illness documented in the medical record and lasting less than 8 wk (N = 39 values). The remaining 842 [Cr] values (median of nine measures per patient) were used to calculate a linear regression of inverse serum [Cr] *versus* time for each patient. For each patient, a "breakpoint" analysis was conducted as described by Jones and Molitoris (19). When a significant breakpoint ($P < 0.05$ by F test) was found, only [Cr] measurements after that breakpoint were used. The projected date of RRT was estimated by extrapolating the line to the $[Cr]^{-1}$ value at which the patient started RRT, or a $[Cr]^{-1}$ value of 1/8.53 mg/dL for those patients who did not start RRT. The latter value was the mean [Cr] level at which patients were started on RRT.

For subjects who started dialysis, the observed and projected dates of dialysis were compared by use of the nonparametric sign test. In addition, a 95% confidence interval was constructed for each regression of $[Cr]^{-1}$ *versus* time and patients were classified as having either a significantly later or earlier date of dialysis than projected if their date of dialysis was outside the confidence interval for the projected date of dialysis. This confidence interval was estimated using the time where the 95% confidence interval of the regression intersected the [Cr] value at which dialysis was initiated. This confidence interval has several limitations, including the fact that the uncertainty in the final [Cr] value at which dialysis would be required is not taken into account. However, this procedure provides a useful tool for objectively deciding if dialysis was initiated significantly earlier or later than projected. The number of patients starting dialysis significantly later *versus* earlier than projected was compared by use of the sign test. Statistical analyses were done with the SAS computer package (SAS Institute Inc., Cary, NC) (20).

RESULTS

Table 1 describes the characteristics of all 67 patients who met the entry criteria as well as the 44 of them who started dialysis treatment. The patients who required dialysis were very similar to the other patients in gender, race, and diagnoses. Sixty percent of all patients were men, and all but two were white. The underlying renal disease diagnoses included all of the most common causes of ESRD, with some overrepresentation of patients with chronic glomerulonephritis and interstitial nephritis compared with the general U.S. population of patients with ESRD (25 *versus* 14% and 16 *versus* 3%, respectively) (1). At the start of dietary treatment, patients had a median age of 51 yr and relatively severe renal disease, as indicated by a median creatinine of 4.2 mg/dL. The median estimated protein intake during dietary treatment was 0.46 g/kg. This represents a 41% decrease from the protein intake immediately preceding the start of treatment but was higher than the dietary goal of 0.3 g/kg, indicating that on average compliance with the diet was fair. Among patients who started dialysis, the median albumin level was lower than among the other patients but remained stable with a median of 4.1 at both the beginning and the end of dietary treatment. As in our previous report (16), which included some of the patients in this study, there was, on average, a statistically significant but small weight loss (-0.08 ± 0.27 kg/month; $P = 0.024$);

TABLE 1. Patient characteristics immediately preceding, during, and at the end of dietary treatment

Characteristics	All Patients ($N = 67$)		Patients Started on Dialysis ($N = 44$)	
	N	%	*N*	%
Immediately Preceding Dietary Treatment				
Sex, male	40	60	28	64
Race, white	65	97	44	98
Diagnosis				
Chronic glomerulonephritis	17	25	12	27
Diabetes	15	22	9	20
Interstitial nephritis	11	16	7	16
Hypertension	12	18	8	18
Polycystic kidney disease	6	9	4	9
Other	6	9	4	9
	Median	(25th, 75th)	Median	(25th, 75th)
Age (yr)	51	(37, 65)	51	(37, 62)
Serum creatinine (mg/dL)	4.2	(3.1, 5.3)	4.3	(3.1, 5.4)
Body mass index (kg/m^2)	23	(22, 27)	24	(22, 26)
Serum albumin (mg/dL)	4.3[a]	(3.9, 4.6)	4.1[b]	(3.7, 4.4)
Protein intake (g/kg)[c]	0.78	(0.56, 0.89)	0.71	(0.65, 0.86)
During Dietary Treatment				
Protein intake (g/kg)[d]	0.46	(0.36, 0.56)	0.47	(0.36, 0.55)
At Referral for Dialysis (End of Dietary Treatment)				
Serum creatinine (mg/dL)			8.8	(7.3, 9.6)
Serum albumin (mg/dL)			4.1[e]	(3.7, 4.4)
Serum transferrin (mg/dL)			236	(222, 268)

[a] Six patients had hypoalbuminemia (<3.5 mg/dL).
[b] Four patients had hypoalbuminemia (<3.5 mg/dL).
[c] Based on urinary urea excretion available immediately before treatment for 56 of the 67 patients and 34 of the 44 patients starting dialysis.
[d] Based on the average of all available urinary urea excretion measurements (median, 9).
[e] Five patients had hypoalbuminemia (<3.5 mg/dL).

only two patients, one of whom was markedly obese and desired weight loss, lost 10 or more kilograms. Anthropometry was not performed.

Survival on Dialysis

Mortality follow-up was complete through April 15, 1994, on all patients. The mean time on dialysis was 2.1 (median, 1.7) yr. Figure 1 shows a Kaplan-Meier curve of the survival after the initiation of dialysis in this study population. The mortality rate during the first year was 3% (95% confidence interval, 0 to 8%) and cumulated over the first 2 yr was 7% (95% confidence interval, 0 to 16%). This pattern of lower mortality rates during the first 2 yr stands in marked contrast to the national pattern of equal or higher mortality rates in the first 2 yr on dialysis (1).

Figure 2 compares the observed cumulative number of deaths with the expected number using national rates after accounting for the age, sex, race, and cause of renal disease. As the figure indicates, the cumulative number of deaths was lower than expected throughout the follow-up period, but only significantly so during the first 3 yr of follow-up. During the 36.9 person-years of follow-up, in the first year, only one death occurred compared with 7.59 expected deaths ($P = 0.009$). The observed number of deaths continued to lag behind the expected number, with one additional death in the second year *versus* 3.97 deaths expected. From 3 yr after the start of dialysis onward, the observed number of deaths exceeded the expected number and this was significant for Years 4 and 5 combined (6 observed deaths *versus* 1.7 expected, $P = 0.01$). Overall, 10 deaths occurred during 96.4 person-years of follow-up compared with 14.9 expected deaths ($P = 0.25$). Therefore, treatment did not lower the total mortality but did substantially delay mortality by decreasing mortality in the first 2 yr after the initiation of dialysis.

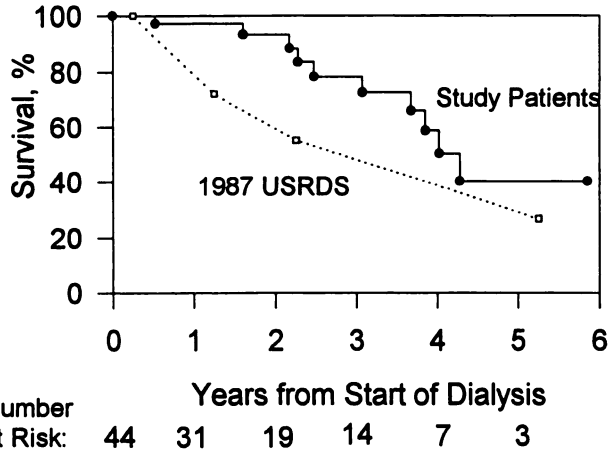

Figure 1. Survival after dialysis among study patients treated with a supplemented low-protein dietary regimen (solid line) and USRDS 1987 incident cohort (dashed lines; conservatively assumed to have no mortality during the first 91 days after dialysis when no national statistics are available).

Start of Renal Replacement Therapy

The possibility that the improved survival on dialysis was due to the early initiation of dialysis was examined. The mean creatinine at the initiation of dialysis was 8.53 mg/dL, comparable to the 9 mg/dL reported in a study of 1,760 patients starting ESRD therapy during October to December of 1993 in five states (21). Plasma creatinine among patients following a low-protein diet is likely to underrepresent the extent of renal damage because serum creatinine levels are lowered by dietary protein restriction. The timing of the initiation of dialysis among these patients was further examined by regressing $[Cr]^{-1}$ *versus* time in individual patients using creatinine data before the initiation of dietary treatment. Figure 3 shows data from two representative patients selected to illustrate the analysis. The projected RRT date is at the point where the regression line intersects the horizontal line indicating the final [Cr] value before the initiation of RRT. The curved lines show the 95% confidence interval around the regression lines. Panel A shows a patient (ID = 1) in whom RRT was initiated significantly later than expected. Panel B show a patient (ID = 32) who had a significant breakpoint. The straight dashed line indicates the initial slope, whereas the solid line indicates the slope after the breakpoint. The 95% confidence interval is calculated for the line after the breakpoint. This patient was also started on RRT significantly later than projected.

The $[Cr]^{-1}$ *versus* time regressions revealed the presence of a significant "breakpoint" before the initiation of dietary treatment in 13 of the 67 patients; 9 patients experienced a significant acceleration of their decline in $[Cr]^{-1}$ (Figure 3B provides an example), whereas 4 patients experienced a significant deceleration. As illustrated in Figure 3, the regression used to derive a projected date of dialysis included only [Cr] measurements made after the last significant breakpoint. Once breakpoints were taken into account, linear regression of $[Cr]^{-1}$ *versus* time gave a good fit to the data. The mean (SD) of the correlation coefficients of individual patients was 0.78 (0.24), and the root mean square errors and slopes had means (SD) of 0.034 (0.023) dL/mg and −0.084 (0.086) dL/mg per year, respectively.

Among the 44 patients started on dialysis, it was possible to examine directly whether dialysis was started before or after the projected time. The date of starting dialysis was later than projected in 29 patients (66%) and earlier than projected in 15 patients (34%) ($P = 0.05$, sign test). The median delay to the initiation of dialysis was 0.44 yr. Furthermore, 13 patients started dialysis significantly later than projected compared with 3 who started significantly earlier than projected ($P = 0.02$, sign test). A more stringent criterion for determining significant delay in

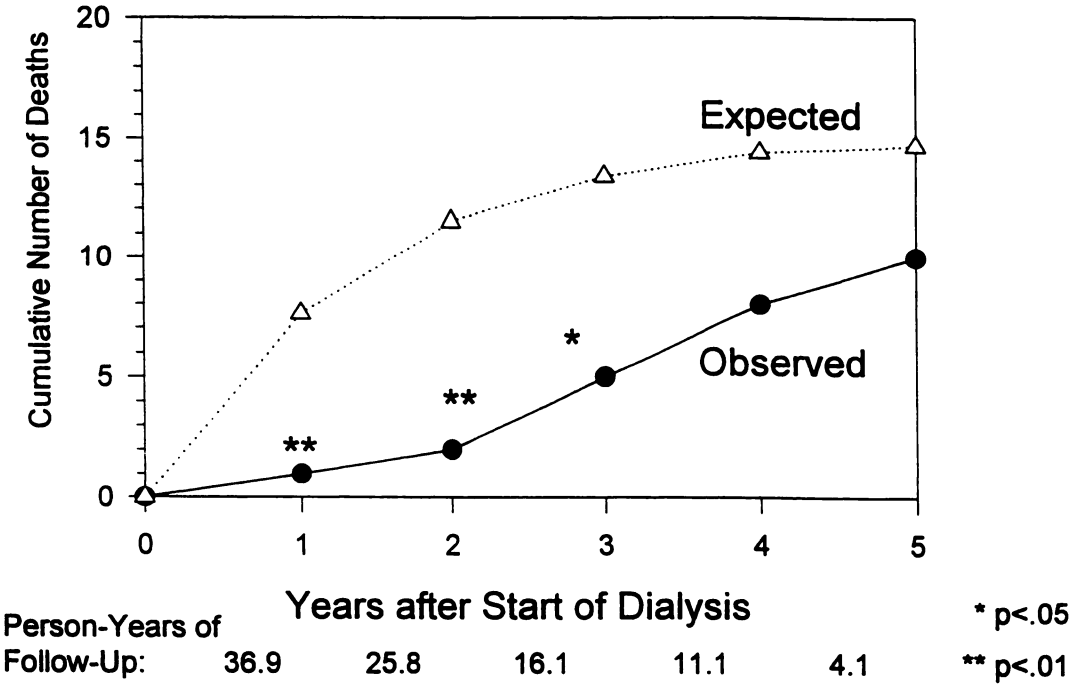

Figure 2. Cumulative observed and expected number of deaths after the initiation of dialysis among the 44 patients who started dialysis treatment. Expected death rates are adjusted for age, sex, and primary disease underlying CRF. $*P < 0.05$, $**P < 0.01$.

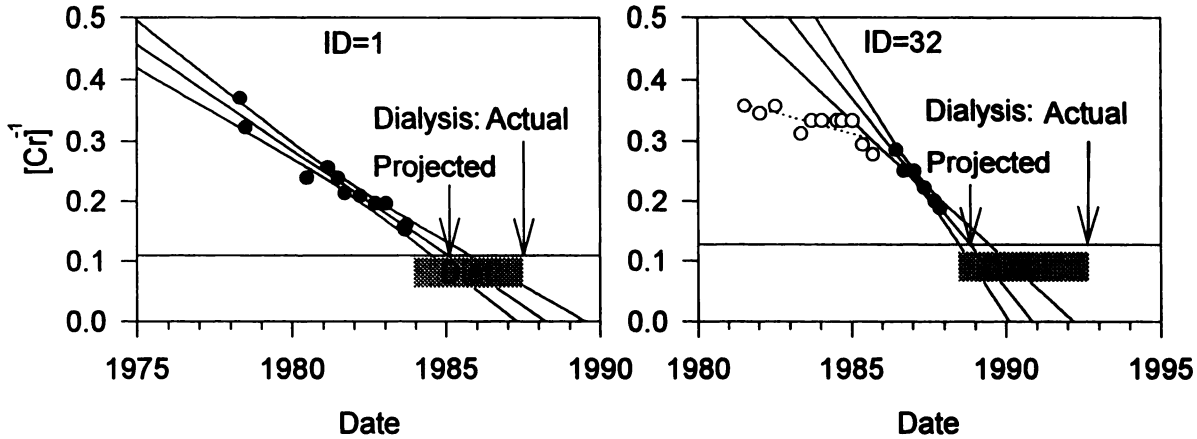

Figure 3. Examples of patient graphs of $(Cr)^{-1}$ *versus* calendar year. Solid line shows the least squares regression, and surrounding curves show its 95% confidence interval. All creatinine values are before the initiation of dietary therapy. Unfilled circles indicate creatinine values before the break point. Horizontal line shows the creatinine value at the start of dialysis, and vertical arrows show the projected and actual times of the initiation of dialysis. ID, patient identification number.

the time to dialysis, based on the 95% prediction intervals for individual points rather than the 95% confidence interval for the regression line, was used as well. This resulted in 10 patients classified as starting dialysis significantly later than anticipated compared with 2 patients starting significantly earlier than anticipated ($P = 0.03$). These results were obtained despite the fact that the group of patients who started dialysis is likely to contain all of the patients who fared poorly on the treatment while excluding all patients who did not require dialysis at the end of the study, a group that contains disproportionately more individuals who benefitted from treatment. An unbiased Kaplan-Meier survival analysis including all 67 patients, allowing for the censoring of patients who did not start dialysis, confirmed these results, indicating a delay in the median time to dialysis of approximately 1 yr (data not shown). Furthermore, the inclusion of the two individuals who were transplanted without the initiation of dialysis did not change any of the

results because one was transplanted earlier than expected and the other was transplanted later than expected (neither significantly so). Thus, regardless of the approach to analysis, treatment resulted in a significant delay in, rather than a hastening of, the initiation of dialysis.

DISCUSSION

A previous report from this laboratory (16) raised the possibility that mortality on dialysis would be lowered, rather than raised, by the prolonged administration of a supplemented low-protein dietary regimen predialysis, because rather than causing protein malnutrition, this regimen prevented it in most patients, and in some cases where malnutrition was initially present, it corrected it. We have confirmed this hypothesis by showing that mortality during the first 2 yr of dialysis was markedly reduced, by more than half. Because mortality on dialysis averages 25% per year in United States (1), a large reduction in mortality during the first 2 yr would translate to a substantial reduction in deaths nationwide. The utility of this predialysis dietary treatment of CRF in decreasing mortality on dialysis would be greatly amplified if it also postponed the need for dialysis. In our study population, the initiation of dialysis was significantly deferred in a substantial proportion of the patients treated.

The MDRD study has shown that compliance with the highly restrictive dietary regimen used in our patients can be obtained in most subjects (2). Essential amino acid preparations are commercially available and cost less than the food items that are omitted from the diet, such as meat, eggs, poultry, and fish. Thus, this regimen is practical. However, it does require close follow-up and dietary counseling. Indeed, close follow-up may be as important as the dietary regimen in accounting for the results observed. Bergström and associates (22) have demonstrated that the progression of CRF was retarded by blood pressure control and frequent follow-up, before they prescribed protein restriction. However, they could not rule out the possibility that their patients learned that protein restriction was the treatment to be tested and in fact restricted their protein intake during the blood pressure control phase.

Whether the amino acid supplement or the ketoacid–amino acid supplement was more effective in deferring dialysis or in reducing subsequent mortality on dialysis could not be determined, because these supplements were not randomly provided to most of these patients. However, in a subset of 16 patients (6), a randomized double crossover study indicated that a ketoacid–amino acid supplement led to a slower rate of progression than an amino acid supplement. Others (23) have reported similar findings, but clearly any comparisons of such pharmacologic supplementation must be viewed in the context of the exact formulation used.

The design of this study has several important limitations that suggest that these findings require confirmation by additional studies. The linear decline in reciprocal serum creatinine concentration, $[Cr]^{-1}$, with time, seen in most patients (24), provides a simple, if rather crude, estimate of the rate of progression, at least when diet is not changed (25). The "true" rate of progression, as measured by the rate of decline of GFR, correlates poorly with the $[Cr]^{-1}$ slope in individual patients, particularly when protein intake changes. However, the $[Cr]^{-1}$ slope can be used to differentiate between progressors and nonprogressors and to give (by extrapolation) a first approximation of the projected date when RRT may be necessary. Furthermore, by only using creatinine measurements before dietary treatment, we avoided including data when the dietary protein is changing markedly.

Gretz *et al.* (26) analyzed sequential [Cr] measurements in 110 adults with CRF and compared the actual date of RRT with a prediction based on linear regression. On the average, the actual date preceded the predicted date with difference of 11 ± 20 wk. This finding of the acceleration of renal disease as patients approach end stage is in contrast to the deferral of dialysis among patients in this study. "Breakpoint analysis," *i.e.*, the determination of which patients exhibit a significant change in the slope of their sequential $[Cr]^{-1}$ values, as implemented in this study, would increase the accuracy of the prediction of the projected date of RRT. Significant breakpoints were found in 19% (13 of 67) of the patients, somewhat less often than the 33 to 50% estimate by Shah and Levey (27). This suggests that it is important to incorporate such an analysis in attempting to project a date of the initiation of RRT. The availability of a relatively large number of creatinine measures (median, 9) over more than 2 yr before treatment (median, 3 yr) further enhanced the precision of the regressions. In summary, the regression of $[Cr]^{-1}$ *versus* time has distinct limitations but may be the most practical tool for objectively assessing renal disease progression in individual patients toward end stage over the long run.

The survival analysis in this study is limited by the lack of an internal control group and randomization to treatment. The calculation of expected mortality is based on national rates, which assumes the comparability of our patient population with the national ESRD patient population. This assumption is likely to be violated to some extent. Higher socioeconomic status, better access to health care, and compliance with medical interventions in this study population are likely to have played some role in contributing to their observed low mortality. Regarding socioeconomic status, a study of Michigan chronic dialysis patient survival showed that higher socioeconomic status as measured by average household income for the zip code of residence was associated with a 3% per $1,000 decrease in the relative risk of death among black patients, whereas the trend for white patients, who compose most of our study population, was negligible (28). This suggests that the socioeconomic status of

this study population is very unlikely to explain its high initial survival on dialysis. Given the large magnitude of the observed protective effect (83% protection, 2 deaths observed *versus* 11.5 expected), it is unlikely that patient selection alone would account for the whole observed effect. Furthermore, the data strongly refute claims of increased mortality once dialysis is initiated among patients treated with protein restriction. The timing of the protective effect, in the first two yr, and the consistency with higher albumin levels supports the credibility of the findings. A further strength of this study is the long period of observation (mean of 2 yr on treatment and an additional 2 yr on dialysis, as well as 5 yr of pretreatment creatinine data from medical records), which is difficult to achieve in larger studies.

After the initiation of dialysis, patients were treated at more than 10 dialysis facilities by many different nephrologists, thereby hindering the collection of data about the dose of dialysis received, serum albumin, or other important predictors of survival on dialysis (29). There is no reason to believe that these patients received different treatment than the national average. However, because no data were collected after the initiation of dialysis, it is possible that these patients received dialysis doses well above the national average, thus confounding the results. We also cannot confirm the possibility that the observed protection during the first years on dialysis is mediated by a continued low prevalence of hypoalbuminemia. Given the design of the study, it is impossible to dissect which element of the treatment regimen accounted for the protective effect. However, the data presented suggest that a supplemented low-protein diet plus close follow-up of patients with CRF may substantially reduce the early mortality on dialysis. Further studies of this finding are indicated.

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