Can Renal Replacement Be Deferred by a Supplemented Very Low Protein Diet?

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Abstract. Patients with chronic renal failure are commonly started on renal replacement therapy (RRT) as soon as (or, in some centers, before) the usual criteria for severity are met, *i.e.*, GFR <10 ml/min for nondiabetic patients and <15 ml/min for diabetic patients. To determine whether RRT can safely be deferred beyond this point, adults with all types of chronic renal failure who met these criteria on presentation (23 patients) or who reached these levels of severity during treatment (53 patients) were managed conservatively until RRT was judged necessary by their chosen dialysis or transplantation team, without input into this decision from the present authors. Patients were prescribed a very low protein diet (0.3 g/kg) plus supplemental essential amino acids and/or ketoacids and followed closely. The intervals between the time at which GFR became less than 10 ml/min (15 ml/min in diabetic patients) and the date at which renal replacement therapy was started were used as estimates of renal survival on nutritional therapy. Kaplan–Meier analysis showed median renal survival of 353 d. Acidosis and hypercholesterolemia were both predictive of shorter renal survival. Signs of malnutrition did not develop. Final GFR averaged 5.6 ± 1.9 ml/min. Two patients died; thus, annual mortality was only 2.5%. Hospitalizations totaled 19 in 93 patient-years of treatment, or 0.2 per year. Thus, these well motivated patients with GFR <10 ml/min (<15 ml/min in diabetic patients) were safely managed by diet and close follow-up for a median of nearly 1 yr without dialysis. It is concluded that further study of this approach is indicated.

In most dialysis centers, patients who first present with uremia severe enough to qualify for reimbursement of their medical costs under the end-stage renal disease program, according to guidelines set forth by the Health Care Financing Administration (1,2), are immediately started on renal replacement therapy (RRT). In fact, arguments for starting dialysis even earlier have been presented (3–6). The Medicare criteria for starting dialysis currently include a value for GFR less than 10 ml/min (less than 15 ml/min in diabetic patients), whether estimated as creatinine clearance or as the clearance of a marker substance that is freely filtered but neither reabsorbed nor secreted in the kidney (1,2) (as documented in the Discussion, GFR in end-stage renal failure averages about 25% less than creatinine clearance). In addition, the National Kidney Foundation has recently sponsored the establishment of guidelines for dialysis, known as the Dialysis Outcomes Quality Initiative (DOQI), which state: "Unless certain conditions are met, patients should be advised to initiate some form of dialysis when the weekly renal Kt/V_{urea} falls below 2.0. . . . The GFR . . . will be approximately 10.5 ml/min per 1.73 m². " (7).

These policies presuppose that the need for renal replacement is imminent when this level of renal function is reached.

However, the high morbidity and mortality of dialysis (8) make it worthwhile to examine alternative approaches. Unfortunately, there are as yet few studies of mortality and morbidity in predialysis patients. Obviously, in this population, comorbidities and severity of renal failure will both exert major influences on these parameters. Thus, any comparison of dialysis patients with predialysis patients, in these respects, is fraught with difficulty. This report is a first step in this direction.

We have been treating patients with chronic renal failure with a supplemented very low protein diet for some years. Most of these patients have gone on eventually to RRT. The decision to initiate RRT has always been made by the director of the patient's chosen dialysis unit (or transplant team), with no input from us. We have noted that the final GFR at which RRT has been initiated is usually less than 10 ml/min. We have also reported that these patients rarely exhibit hypoalbuminemia at the start of RRT, despite prolonged consumption of a severely protein-restricted diet (9). These findings contrast with a 25 to 50% incidence of hypoalbuminemia at the start of dialysis nationwide (10–14). Furthermore, survival during the first 2 yr of dialysis is not adversely affected; on the contrary, it is substantially better (in this unusually well motivated group of patients) than survival rates reported nationwide, after adjusting for age, race, gender, and diagnosis (15).

The present work was carried out to answer the following questions: (*1*) Can RRT be forestalled by conservative therapy of this type for more than a trivial interval? (*2*) Are measures of the uremic state well maintained during this interval? (*3*) Is nutrition maintained? and (*4*) Is the mortality rate and rate of

hospitalization of such subjects during conservative therapy low? As shown here, the answers to all four questions are affirmative.

Materials and Methods

Patients

Records were reviewed of all patients prescribed the dietary regimen described below since 1984. Many of these patients have been the subject of previous reports from this laboratory, generally describing their earlier courses (9,15–20). The present report is concerned only with the final stages of their predialysis course, beginning at the point at which they met the Medicare criteria for severity and ending at the point they entered RRT. A few patients treated during this same period were started on RRT before reaching the criteria for severity; these patients have been excluded. Patients over 18 yr of age were admitted to this program without restrictions as to diagnosis or severity of renal failure. Exclusions were the concomitant administration of steroids, immunosuppressive drugs, nonsteroidal anti-inflammatory agents more than once weekly, pregnant or planning to become pregnant, and inability to empty the bladder. However, no patients were excluded for these reasons. These patients were mostly self-referred and therefore are not representative of the renal failure population as a whole.

During this same period, seven patients declined to undertake dietary therapy; these subjects were also excluded. Thus, the cohort under study is compliance-confounded, but includes all patients who reached the criteria for severity defined below and who undertook to follow this dietary treatment. The effect of this exclusion on the outcome is uncertain. The renal diagnoses were as follows: chronic glomerulonephritis (including IgA nephropathy) ($n = 22$), diabetic nephropathy ($n = 16$), interstitial nephritis ($n = 11$), arteriolar nephrosclerosis ($n = 11$), polycystic kidney disease ($n = 9$), unknown ($n = 6$). Comorbidities were as follows: congestive heart failure ($n = 17$), coronary heart disease ($n = 7$), malignancy ($n = 2$). Informed consent was obtained. The protocols were approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Study Protocol

In each patient, GFR was measured before and during the study period at intervals varying from 1 to 3 mo as the urinary clearance of ^{99m}Tc-DTPA averaged over three collection periods (9,17,18). For each patient, the date was ascertained on which the GFR fell to consistently less than 10 ml/min (15 ml/min in diabetic patients). For several additional patients, this level was never reached and hence they are excluded from this analysis; for 23 (group 1), it was reached before their first visit; for the remaining 53 (group 2), it was reached only during the course of treatment. These 76 patients comprise the present study population.

All patients were prescribed a diet, described in detail elsewhere (9,16–18), containing 0.3 g/kg of ideal body weight (IBW) of protein, unrestricted as to quality, 7 to 9 mg/kg IBW of phosphorus, and 35 kcal/kg IBW. During the 14-yr course of these studies, six different registered dietitians were involved in this work. All became familiar with techniques for teaching patients a very low protein diet. Further details of the dietary regimen are given in the original publications (9,15–20). As noted in these publications, many patients received a nitrogen-free maltodextrin supplement and/or special low-protein foods. Caloric counts during treatment were performed only when undesirable weight loss occurred. All patients ingested either 10 g/d of essential amino acids, in the form of tablets of Aminess (distributed by

Nestlé Homelink), or 2.8 g per nearest 10 kg IBW of ketoacid mixture "EE," in the form of tablets of Cetolog. (Cetolog was produced by Clintec in France; it is not currently available), taken in divided doses with meals. Forty-seven of the 76 patients received the ketoacid supplement during part of their course. All patients received $CaCO_3$ and a multivitamin capsule.

Patients also received diuretics (7/8), beta-blockers (1/2), alpha-blockers (1/2), calcium channel blockers (2/5), $NaHCO_3$ (2/5), angiotensin-converting enzyme inhibitors (1/3), minoxidil, sodium polystyrene sulfonate, hydralazine, alpha-methyldopa, $FeSO_4$, colchicine, allopurinol, dihydroxycholecalciferol, and (in a few patients) transfusions (or later, erythropoietin) as indicated. Cardiac glycosides were used in only one patient. Use of nonsteroidal inflammatory agents or acetaminophen was limited; a few patients received salicyl salicylate for arthritic symptoms.

Seventeen patients received 200 mg/d ketoconazole plus 2.5 mg/d prednisone during part of their course, in an attempt to slow progression. As noted elsewhere (19), this regimen appears to slow progression in diabetic nephropathy, interstitial nephropathy, and chronic glomerular disease, but to accelerate progression in polycystic kidney disease.

When warranted by symptoms, the patients were referred to a dialysis unit or transplant team of their choice, usually near their home. RRT was begun whenever deemed indicated, using the same criteria as in nonstudy patients, by the director of the patient's chosen dialysis unit (or transplant team); it must be emphasized that the present authors played no role in these decisions, other than to refer the patients for consideration of RRT as soon as clinically indicated. The interval between referral and the start of RRT varied from a few weeks to 2 yr. Two patients received preemptive transplants; eight were started on peritoneal dialysis; the remaining 65 were started on hemodialysis. The interval between the date at which GFR became consistently <10 ml/min (<15 ml/min in diabetic patients) and the date on which RRT was started was taken as renal survival time.

At each visit, averaging eight per year, physical examination was performed, blood was obtained for routine hematologic and chemical analyses, a 24-h urine collection was obtained for measurement of protein and urea N, and GFR was measured. Dietary protein intake was estimated from 24-h urea N excretion according to Maroni *et al.* (21).

Results

The results of physiologic and chemical measurements are shown in Table 1, in which the findings are summarized separately for the 23 patients who presented with GFR <10 ml/min (<15 ml/min in diabetic patients) (group 1) and the 53 patients who presented and were started on nutritional therapy before GFR reached these values (group 2). In group 1, initial GFR averaged 7.4 ± 1.9 (SD) ml/min and initial serum creatinine concentration averaged 5.8 ± 1.4 (SD) mg/dl. Chemical values at entry are shown only for group 1. Last values for serum albumin and serum transferrin, in patients who progressed to RRT, are similar for both groups. Final GFR in all 76 patients averaged 5.6 ± 1.9 (SD) ml/min and did not differ significantly between diabetic patients and nondiabetic patients.

Mean arterial pressure averaged 108 ± 10 mmHg—higher than is now believed to be optimal. Mean hematocrit values were influenced by transfusions and by erythropoietin injections in a few patients. Significant weight loss did not occur.

Mean ± SD serum chemical values for all 76 patients,

Table 1. Parameters before, during, and at end of treatment

Parameter	At entry	During Treatment	Final
Group 1[a]			
weight (kg)	72.1 ± 13.9		69.1 ± 13.0
GFR (ml/min)	7.4 ± 1.9		4.5 ± 1.8
mean arterial pressure (mmHg)		109 ± 12	
hematocrit (%)		28.4 ± 4.7	
estimated protein intake (g/kg)		0.52 ± 0.15	
serum values			
creatinine (mg/dl)	5.8 ± 1.4		9.1 ± 2.2
urea N (mg/dl)	64 ± 16	62 ± 18	82 ± 26
calcium (mg/dl)	9.0 ± 0.8	9.0 ± 0.8	8.8 ± 0.9
phosphorus (mg/dl)	5.0 ± 0.9	4.9 ± 0.8	5.6 ± 1.4
CO_2 (mEq/L)	21 ± 4	22 ± 4	22 ± 5
albumin (g/dl)	4.1 ± 0.5	4.1 ± 0.4	4.1 ± 0.6
transferrin (mg/dl)	233 ± 38	221 ± 28	223 ± 46
cholesterol (mg/dl)	204 ± 32	190 ± 38	184 ± 39
triglycerides (mg/dl)	158 ± 74	165 ± 85	158 ± 74
renal survival (days) (median): 530			
Group 2[b]			
weight (kg)	69.6 ± 13.0		71.5 ± 14.2
GFR (ml/min)			6.2 ± 1.9
mean arterial pressure (mmHg)		108 ± 9	
hematocrit (%)		32.3 ± 4.6	
estimated protein intake (g/kg)		0.51 ± 0.13	
serum values			
creatinine (mg/dl)			8.3 ± 2.9
urea N (mg/dl)		60 ± 17	75 ± 26
calcium (mg/dl)		9.0 ± 0.5	9.0 ± 0.8
phosphorus (mg/dl)		4.8 ± 1.0	5.4 ± 1.4
CO_2 (mEq/L)		23 ± 3	23 ± 5
albumin (g/dl)		4.2 ± 0.4	4.1 ± 0.5
transferrin (mg/dl)		239 ± 48	239 ± 62
cholesterol (mg/dl)		201 ± 56	195 ± 59
renal survival (days) (median): 346			

[a] Patients presenting with GFR <10 ml/min (<15 ml/min in diabetic patients) (*n* = 23). Age: 57 ± 14. Gender: 8 women, 15 men.
[b] Patients presenting with GFR >10 ml/min (>15 ml/min in diabetic patients) who later reached <10 ml/min (<15 ml/min in diabetic patients) (*n* = 53). Age: 50 ± 14. Gender: 19 women, 34 men.

averaged for each patient for all 939 observations during treatment, were as follows: urea N 61 ± 18 mg/dl, CO_2 23 ± 3 mM, albumin 4.2 ± 0.4 g/dl, transferrin 232 ± 44 mg/dl. Serum CO_2 values during treatment showed only three patients with persistent acidosis, defined as average CO_2 during treatment of <20 mM. Average albumin values during treatment showed persistent hypoalbuminemia (<3.6 g/dl) in six, all of whom had presented with the nephrotic syndrome, which did not worsen (20). Final values for serum albumin were slightly lower: The mean change from average value during treatment to final value was −0.074 ± 0.081 (SD) g/dl (*P* = 0.022). However, two patients developed hypoalbuminemia just before RRT. Final values for serum albumin in 46 of these 76 patients were reported previously (9). Serum albumin at the start of

dialysis has been shown to predict outcome (22). Average serum transferrin values during treatment were consistently below normal (<200 mg/dl) in 16 patients; final transferrin values did not differ significantly from average values during treatment. Final values for serum transferrin in 46 of these patients were also reported previously (9).

Two patients died during treatment: one in an automobile accident and one of myocardial infarction. Four patients are still being treated.

Kaplan–Meier renal survival (23) is shown graphically in Figure 1. Median survival to RRT was 353 d, varying from less than 1 wk to 4 yr. When results from group 1 are analyzed separately, their renal survival is not significantly different from renal survival in group 2. Survival in patients who re-
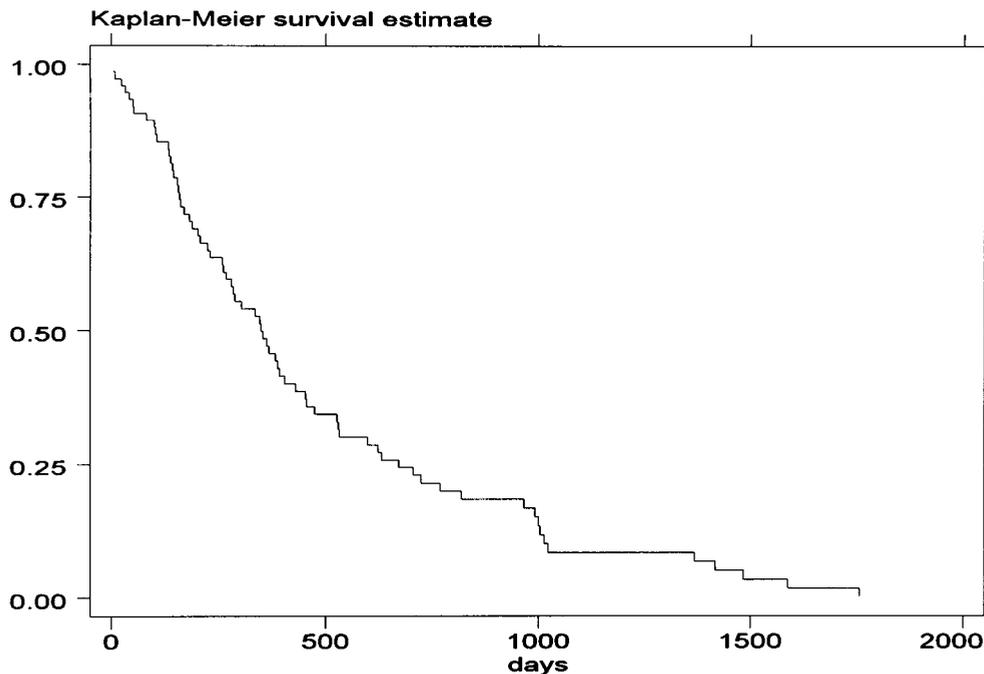
Kaplan-Meier survival estimate

Figure 1. Kaplan–Meier renal survival curve for 76 patients with chronic renal failure treated conservatively, determined as the interval between their meeting the Medicare criteria for starting renal replacement therapy (RRT) and the actual date of starting RRT. Median survival is 353 d.

ceived ketoconazole did not differ significantly from survival in those who did not. Survival in diabetic patients did not differ significantly from survival in nondiabetic patients.

There was no correlation between renal survival time and any of the other measured parameters considered singly, including average serum urea nitrogen, CO_2, albumin, transferrin, cholesterol, calcium, phosphorus, calcium $\times$ phosphorus, mean arterial pressure, or initial GFR, nor any significant effect of age, gender, or diagnosis. However, when stepwise multiple regression was performed using these variables, average serum CO_2 and average serum cholesterol both became significant predictors of survival: Acidosis and hypercholesterolemia were both predictive of shorter renal survival at the same significance level, $P = 0.022$. Together, these two variables accounted for 11.4% of the variation in renal survival time.

Compliance with the dietary protein prescription was only fair, as we have reported previously (9,16–18,20). Median protein intake (from food alone, after subtracting the N content of the supplements) was 0.48 g/kg, or 160% of that prescribed. This degree of compliance is similar to the compliance reported in other recent studies (24).

During the total of 93 patient-years of treatment, there were 19 hospitalizations, or an average of 0.2 per patient-year. Eleven of these occurred during the first year of treatment.

Discussion

The findings of this study clearly show that some patients can be safely managed by conservative therapy for substantial intervals after they have reached or passed the usual threshold for severity. Because all patients received the same diet prescription (0.3 g/kg of protein), it remains possible that the same

results could have been achieved by an unsupplemented low protein diet.

Another question unanswered by this study is what proportion of prospective dialysis patients is represented in the population included here. Clearly, it is a minority, as judged (for example) by their relatively low frequency of comorbidities. Thus, these patients are a self-selected group. However, it does not follow that the approach used here will be useful for only very unusual patients. In terms of diagnostic categories, age, presenting chemical values, and dietary compliance, this group of subjects was in fact quite typical.

This approach to treatment contrasts sharply with present trends in policies concerning the initiation of dialysis. Several recent studies have been interpreted as showing that the outcome of dialysis is improved if it is initiated earlier (4,6). Some workers (4) have even recommended initiating dialysis in any patient spontaneously consuming less than 0.85 g/kg of protein. For example, Ratcliffe *et al.* (25) compared two groups of patients: one that had been followed for an average of 4 yr before starting dialysis and another that was referred late and had lower residual renal function. Hospitalizations and major complications were much more frequent in those referred late. However, the conclusion of their study was that early referral to a nephrologist, not early dialysis, was important. Similarly, Jungers *et al.* (26) compared the outcome of 65 patients referred less than 1 mo before starting dialysis with the outcome of 153 patients previously followed for 6 mo or more; complications and hospital stays were far greater in the former group. Again, the inference is not that dialysis should be started earlier, but rather that referral to a nephrologist should take place earlier. Similar findings were reported by Khan *et al.* (27). Undoubtedly, early referral of our patients, as well as

frequent follow-up in the predialysis period, enhanced the creation of fistulae and helped to avoid the complications of central venous catheterization or grafts.

It should also be pointed out that the question is not whether mortality on dialysis is reduced, but whether overall mortality is reduced by any particular policy. In our highly selected patients, predialysis mortality was much lower than the 24% annual mortality on dialysis reported nationwide (8). In study B of the Modification of Diet in Renal Disease Study, annual mortality was again about 2.5% (28). In insulin-dependent diabetic patients with overt nephropathy followed for 10 yr, Rossing *et al.* (29) report predialysis mortality of 44%, or 4.4% per year, on average. There have been few other studies of predialysis mortality.

Tattersall *et al.* (5) recently reported that morbidity and mortality were significantly higher in patients who had lower renal function at the onset of dialysis. They inferred that dialysis should be initiated at higher levels of residual renal function than has been the practice in the past. The mean level of urea clearance at which dialysis commenced in these patients, when expressed as Kt/V, was 0.15 per day. In a patient of average age and size, this corresponds to an average urea clearance of approximately 4 ml/min, or a GFR of approximately 8 ml/min. Thus, these patients were started on dialysis at an average level of renal function close to the Medicare criterion. What is not taken into account in this study is the proportion of each group that were urgently placed on dialysis. It has been well established that urgent initiation of dialysis leads to a high incidence of complications and hospitalizations (25,27,30). None of our patients was urgently started on dialysis because all were referred to a dialysis or transplant unit as soon as symptoms warranted it. It is likely that patients in Tattersall *et al.*'s study (5) with the lowest clearances were urgently placed on dialysis; the authors give no information on predialysis care in these patients.

In the present study, the average level of renal function at which RRT commenced was lower (5.6 ± 1.9 ml/min in both diabetic patients and nondiabetic patients) than in Tattersall *et al.*'s study (5); it was also less than half of that recommended by DOQI (7). Yet mortality during the first 2 yr of dialysis, at least as judged from follow-up of 46 of these 76 patients, was far lower than the national average, after adjustment for age, gender, race, and renal diagnosis (15). Presumably, the explanation lies in the better nutritional state of our subjects, in whom hypoalbuminemia at the start of RRT was rare (9). However, the possible effects of selection bias in causing these differences are uncertain.

The nutritional effects of protein-restricted diets in the study Modification of Diet in Renal Disease have recently been summarized (24) as follows: "... patients assigned to the low protein or very-low protein diets lost about 2 kg and showed a decrease in other anthropometric parameters during the first 4 mo only, probably because of reduced energy intake. Serum albumin levels rose but transferrin levels fell (though not to subnormal values) in patients assigned to low protein or very-low protein diets. In summary, biochemical and anthropometric indices of nutritional status during follow-up were generally well within normal limits

in all four diet groups" (31). A progressive decline in creatinine excretion was observed in the low protein groups, and was probably related to reduced meat intake and/or by increasing degradation of creatinine (32). Loss of skeletal muscle mass could not have contributed in a major way to the reduction of urinary creatinine excretion, because arm muscle area remained the same or decreased only slightly. Importantly, the low protein regimens were not associated with higher rates of death, hospitalization, or any signs of malnutrition."

A level of residual renal function below a defined threshold is often used as a criterion for starting dialysis, as noted in the introductory remarks. Commonly, creatinine clearance is used, even though it is well known that creatinine clearance usually exceeds GFR. The relationship between these two measures in patients with GFR values ≤10 ml/min, according to 13 published reports (33–46), is depicted in Figure 2, including two studies (38,45) in patients on dialysis (many other publications do not report their data in sufficient detail to permit even approximate conversion of their graphical observations to numerical estimates). The ratio of creatinine clearance to simultaneously measured GFR in these 115 observations varies considerably; the mean is 1.34 ± 0.43 (SD). Thus, GFR, on average, is 25% less than creatinine clearance. Recent studies, summarized in a report by Walser (47), have shown that dosing with cimetidine before clearance determination virtually eliminates creatinine secretion, making the ratio of creatinine clearance to GFR indistinguishable from unity. As yet, this technique has apparently not been applied to patients with end-stage renal failure, but there is little reason to expect a different result. This technique could advantageously be applied as a criterion for starting dialysis, if a specific threshold level of renal function is believed to be critical (which we question).

Ketoconazole is readily available, but ketoacids are not, at least in the United States, at the present time. The importance of ketoconazole or of the ketoacid supplement in the results found in these patients is difficult to evaluate, because these treatments were not randomly assigned.

That protein restriction does not promote protein deficiency, but instead maintains protein nutrition, at first seems surprising. But the provision of essential amino acids as such prevents a shortage of these components from becoming rate-limiting for protein synthesis, without adding to the load of other dietary constituents found in high protein foods, such as non-essential amino acids, inorganic phosphate, phosphorylated amino acids, nucleotides, specific lipids, etc. This may be the explanation for the beneficial effect of a very low protein diet supplemented by essential amino acids that we have found in a preliminary study of nephrotic adults (20). Additional work will be required to identify the components of high protein foods that seem to aggravate protein deficiency.

The wide variation in renal survival time shown in Figure 1 is surprising. It is not a reflection of the severity of renal failure or the degree of uremia, as shown by the absence of a correlation between renal survival time and serum urea N concentration or GFR. Among the patients with the longest survival times, including 12 with survival times more than 2 yr, it is clear that the rate of decline of GFR was very low; in fact, it
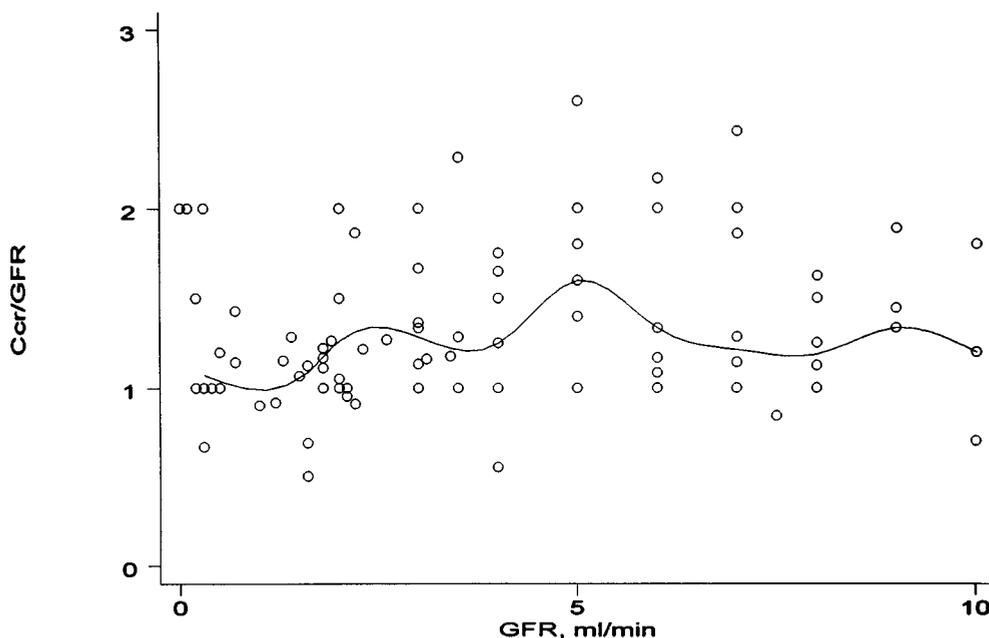
Figure 2. The ratio of creatinine clearance to measured GFR in severe renal failure (GFR <10 ml/min), according to 115 observations, approximately graphed from 13 published studies (32–45), including two (37,44) in patients on dialysis. Wide variation in the ratio is seen. The curve is a computer-generated cubic spline. The mean ratio, C_{Cr}/GFR, is 1.34 ± 0.43 (SD). Thus, GFR is, on average, 25% less than C_{Cr}.

averaged only 1.07 ± 0.32 (SD) ml/min per yr. The rate of progression in these same patients before they reached the end stage was uniformly greater. The explanation of this near-arrest of progression is not at hand. The only factors we could identify that were related to renal survival times were acidosis and hypercholesterolemia. Whether these biochemical abnormalities exerted their effects on survival time by altering rate of progression or by increasing symptoms at any level of renal function could not be determined in this small series.

Further study is necessary to determine the proportion of patients who could adhere to this dietary regimen, the short- and long-term safety in a more representative population, and the level of renal function at which uremic symptoms appear. Then a randomized trial would be desirable to determine efficacy, safety, and applicability in comparison with present policies concerning the initiation of dialysis.

Acknowledgments

References

1. End Stage Renal Disease Medical Evidence Report Medicare Entitlement and/or Patient Registration Form (HCFA 2728), Health Care Financing Administration, April 1, 1997
2. Wish JB, Webb RL, Levin AS, Port FK, Held PJ: Medical appropriateness of initiating chronic dialysis in the U.S.: Results of the revised medical evidence report pilot study [Abstract]. *J Am Soc Nephrol* 5: 345, 1994
3. Bonomini V, Vangelista A, Stefoni S: Early dialysis in renal substitutive programs. *Kidney Int* 13[Suppl 8]: S112–S116, 1978
4. Hakim RM, Lazarus JM: Initiation of dialysis. *J Am Soc Nephrol* 6: 1319–1328, 1995
5. Tattersall J, Greenwood RS, Farrington K: Urea kinetics and when to commence dialysis. *Am J Nephrol* 15: 283–289, 1995
6. Mehrotra R, Saran R, Moore HL, Prowant BF, Khanna R, Twardowski ZJ, Nolph KD: Toward targets for initiation of dialysis. *Perit Dial Int* 17: 497–508, 1997
7. National Kidney Foundation: NKF-DOQI clinical practice guidelines for peritoneal dialysis adequacy: I. Initiation of dialysis, Guideline 1. *Am J Kidney Dis* 30[Suppl 2]: S70–S73, 1997
8. U.S. Renal Data System: USRDS 1998 annual data report, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, April, 1998
9. Walser M: Does prolonged protein restriction preceding dialysis lead to protein malnutrition at the onset of dialysis? *Kidney Int* 44: 1139–1144, 1993
10. Goldwasser P, Mittman M, Antigani A, Burrell D, Michel M-A, Collier J, Avram MM: Predictors of mortality on hemodialysis. *J Am Soc Nephrol* 13: 1613–1622, 1993
11. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15: 458–482, 1990
12. Kaminski MV Jr, Lowrie EG, Rosenblatt SG, Haase T: Malnutrition is lethal, diagnosable and treatable in ESRD patients. *Transplant Proc* 23: 1810–1815, 1991
13. Churchill DN, Taylor DW, Cook RJ, Math M, LaPlante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H, McKenzie JK, Muirhead N, Parfrey PS, Posen GA, Slaughter D, Ulan RA, Werb R: Canadian hemodialysis morbidity study. *Am J Kidney Dis* 19: 214–234, 1992
14. Anonymous: Comorbid conditions and correlations with mortality risk among 3,399 incident hemodialysis patients. *Am J Kidney Dis* 20[Suppl 2]: 32–38, 1992

15. Coresh J, Walser M, Hill S: Survival on dialysis among chronic renal failure patients treated with a supplemented low protein diet before dialysis. *J Am Soc Nephrol* 6: 1379–1385, 1995

16. Walser M, LaFrance ND, Ward L, VanDuyn MA: Progression of chronic renal failure in patients given ketoacids following amino acids. *Kidney Int* 32: 123–128, 1987

17. Walser M, Hill S, Ward L: Progression of chronic renal failure on substituting a ketoacid supplement for an amino acid supplement. *J Am Soc Nephrol* 2: 1178–1185, 1992

18. Walser M, Hill S, Ward L, Magder L: A crossover comparison of progression of chronic renal failure: Ketoacids vs. amino acids. *Kidney Int* 43: 933–939, 1993

19. Walser M, Hill S: Effect of ketoconazole plus low-dose prednisone on progression of chronic renal failure. *Am J Kidney Dis* 29: 503–513, 1997.

20. Walser M, Hill S, Tomalis EA. Treatment of nephrotic adults with a supplemented, very low-protein diet. *Am J Kidney Dis* 28: 354–364, 1996

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

22. Struijk DG, Krediet RT, Koomen GCM, Boeschoten EW, Arisz L: The effect of serum albumin at the start of continuous ambulatory peritoneal dialysis on patient survival. *Perit Dial Int* 14: 121–126, 1994

23. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53: 457–481, 1958

24. Walser M, Mitch WE, Maroni BJ, Kopple JD: Should protein intake be restricted in pre-dialysis patients? *Kidney Int* 1999, in press

25. Ratcliffe PJ, Phillips RE, Oliver DO: Late referral for maintenance dialysis. *Br Med J* 288: 441–443, 1994

26. Jungers P, Zingraff J, Albouze G, Chauveau P, Page B, Hannedouche T, Man NK: Late referral to maintenance dialysis: Detrimental consequences. *Nephrol Dial Transplant* 8: 1089–1093, 1993

27. Khan IH, Catto GR, Edward N, MacLeod AM: Death during the first 90 days of dialysis: A case control study. *Am J Kidney Dis* 25: 276–280, 1995

28. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker LG, Kusek JW, for the Modification of Diet in Renal Disease Study Group: The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. *N Engl J Med* 330: 377–384, 1994

29. Rossing P, Hougaard P, Borch-Johnsen K, Parving HH: Predictors of mortality in insulin dependent diabetes: 10 year observational study. *Br Med J* 313: 779–784, 1996

30. Degoulet P, Legrain M, Reach I, Aime F, Devries C, Rojas P, Jacobs C: Mortality risk factors in patients treated by chronic hemodialysis: Report of the Diaphane collaborative study. *Nephron* 31: 103–110, 1982

31. Kopple JD, Levey AS, Greene T, Chumlea WC, Gassman JJ, Hollinger DL, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS: Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. *Kidney Int* 52: 778–791, 1997

32. Mitch WE, Collier VU, Walser M: Creatinine metabolism in chronic renal failure. *Clin Sci* 58: 327–335, 1980

33. Lubowitz H, Slatopolsky E, Shankel S, Rieselbach RE, Bricker NS: Glomerular filtration rate: Determination in patients with chronic renal disease. *JAMA* 199: 100–104, 1967

34. Lavender S, Hilton PJ, Jones NF: The measurement of glomerular filtration-rate in renal disease. *Lancet* 2: 1216–1219, 1969

35. Skov PE: Glomerular filtration rate in patients with severe and very severe renal insufficiency: Determined by simultaneous inulin, creatinine and ^{125}iothalamate clearance. *Acta Med Scand* 187: 419–428, 1970

36. Anderson CF, Jaecks DM, Ballon HS, De Palma JR, Cutler RE: Renal handling of creatinine in nephrotic and non-nephrotic patients. *Clin Sci* 38: 555–562, 1970

37. Heierli C, Tholen H, Bartels H: Estimation of the glomerular filtration rate from the serum creatinine [German translation]. *Dtsch Med Wochenschr* 97: 67–70, 1972

38. Milutinovic J, Cutler RE, Hoover P, Meigsen B, Scribner BH: Measurement of residual glomerular filtration rate in the patient receiving repetitive hemodialysis. *Kidney Int* 8: 185–190, 1975

39. Jagenburg R, Attman PO, Aurell M, Bucht H: Determination of glomerular filtration rate in advanced renal insufficiency. *Scand J Urol Nephrol* 12: 133–137, 1978

40. Brochner-Mortenson J, Freund LG: Reliability of routine clearance methods for assessment of glomerular filtration rate in advanced renal insufficiency. *Scand J Clin Lab Invest* 41: 91–97, 1981

41. Bauer JH, Brooks CS, Burch RN: Renal function studies in man with advanced renal insufficiency. *Am J Kidney Dis* 11: 30–35, 1982

42. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, Hunsicker LG, and the MDRD Study Group: Utility of radioisotopic filtration markers in chronic renal insufficiency: Simultaneous comparison of ^{125}I-iothalamate, ^{169}Yb-DTPA, ^{99m}Tc-DTPA, and inulin. *Am J Kidney Dis* 16: 224–235, 1990

43. Wharton WW III, Sondeen JL, McBiles M, Gradwohl SE, Wade CE, Ciceri DP, Lehmann HG, Stotler RE, Henderson TR, Whitaker WR, Lindberg JS: Measurement of glomerular filtration rate in ICU patients using ^{99m}Tc-DTPA and inulin. *Kidney Int* 42: 174–178, 1992

44. Pollock C, Gyory AZ, Hawkins T, Ross M, Ibels L: Comparison of simultaneous renal clearances of true endogenous creatinine and subcutaneously administered iothalamate in man. *Am J Nephrol* 15: 277–282, 1995

45. van Olden RW, Krediet RT, Struijk DG, Arisz L: Measurement of residual renal function in patients treated with continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 7: 745–750, 1996

46. Coresh J, Toto RD, Kirk KA, Whelton PK, Massry S, Jones C, Agodoa L, Van Lente F, and the AASK Pilot Study Investigators: Creatinine clearance as a measure of GFR in screenees for the African-American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *Am J Kidney Dis* 32: 32–42, 1998

47. Walser M: Assessing renal function from creatinine measurements in adults with chronic renal failure. *Am J Kidney Dis* 32: 23–31, 1998

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