Kidney International, Vol. 43 (1993), pp. 933–939

A crossover comparison of progression of chronic renal failure: Ketoacids versus amino acids

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A crossover comparison of progression of chronic renal failure: Ketoacids versus amino acids. Rates of progression of chronic renal failure were compared in patients receiving alternately an amino acid supplement (AA) and a ketoacid supplement (KA) to a very low protein (0.3 g/kg), low phosphorus (7 to 9 mg/kg) diet. The first supplement was randomly chosen. Bias due to carryover effects was minimized by delaying the regression analysis until one month after starting or changing supplements. In order to minimize possible bias caused by initiating the two supplements at differing levels of severity, a multiple crossover design was used (ABA, BAB, ABAB, or BABA) with at least four GFR's in each treatment period (except for three GFR's in one instance). Sixteen patients completed the protocol; five dropped out. Average starting GFR's were nearly identical for the two supplements (15.4 and 15.9 ml/min). For each patient, mean progression on KA was compared with mean progression on AA. Thirteen out of 16 patients progressed more slowly on KA than AA. On the average, progression on KA was significantly slower (95% confidence limits = −0.36 to 0.09 ml/min/month) than on AA (−0.91 to −0.41 ml/min/month; $P = 0.024$). There was no significant difference in estimated protein intake, phosphate excretion, or mean arterial pressure between KA and AA periods. Serum triglyceride concentration was significantly lower on KA ($P = 0.0026$). 17-hydroxycorticosteroid excretion was also lower ($P = 0.031$). We conclude that KA slow progression, relative to AA, independently of protein or phosphorus intake, in patients on this regimen.

The possibility that a low protein diet supplemented by ketoacids might slow the progression of chronic renal failure was first suggested by anecdotal accounts of the clinical course of renal failure in the first patients treated in this way [1]. Several other studies have appeared, using sequential observations of creatinine clearance or reciprocal serum creatinine as measures of progression, that support this possibility [2–11]. However, creatinine measurements have subsequently been found to be unreliable guides to the rate of change of isotopically measured glomerular filtration rate (GFR) [12–14]. Furthermore, these trials, with one exception [7], have either employed a crossover design, in which the low protein, ketoacid regimen is administered following a control period on a different regimen—either protein restriction alone or more severe protein restriction plus a supplement of essential amino acids [5, 6, 8]—or a non-randomized comparison of two groups [2–4, 9–11]. Uncertainty exists in the former studies, as to how GFR would have progressed downward if the change in therapy had not been instituted, and in the latter, as to whether the two groups were comparable.

Whether a very low protein diet with amino acid supplements is effective in slowing progression also remains uncertain. Initially, several studies appeared, in which creatinine measurements were employed to assess progression, concluding that low protein diets supplemented by essential amino acids slow progression relative to a free diet [15, 16]. When radioisotopically measured GFR was used, however, no change in progression on initiating amino acid supplements could be found in one of these same centers [17].

We compared progression in a small number of patients switched from an essential amino acid supplement to a ketoacid supplement [8]. Isotope GFR was employed only after the change of supplements. In five cases with less advanced renal failure, progression on ketoacids measured in this way virtually ceased. Later, we demonstrated significantly slower progression (on the average) by sequential isotope GFR determination in 12 patients switched from amino acids to ketoacids [18].

These results suggest a pharmacological effect of the ketoacid supplement to slow progression, apart from whatever benefit is obtained by protein or nitrogen restriction. However, in the crossover studies, ketoacids were always given last.

The traditional approach to this problem is a prospective randomized comparison of two or more groups of patients. At least two such studies of ketoacid supplementation, using a low-protein diet in the control group, are currently in progress [19, 20]. Owing to the wide variability between patients in rates of progression, large numbers of subjects must generally be entered in such trials, at considerable expense, in order to obtain enough statistical power.

Crossover studies are more economical. However, crossover designs in a progressive disorder suffer not only from the common problem of carryover effects from one treatment to another, but also from the fact that patients may not be at the same stage of severity when each treatment is initiated.

We have attempted to circumvent this problem by performing multiple crossovers (two or three) in each subject. This minimizes any possible differences caused by starting the two

Received for publication June 29, 1992
and in revised form November 9, 1992
Accepted for publication November 9, 1992

Table 1. Patients randomized

Pt. no.	Gender	Race	Age	Diagnoses[a]	Pre-study GFR, *ml/min*	Months of study	No. of study GFR's	Sequence of treatments completed[b]
14	M	W	37	1	20.3	16	18	AKAK
17	M	W	39	2,3	24.1	13	12	KAK
24	M	W	67	3,9	10.5	15	13	AKA
25	M	B	61	4,5	16.3	21	19	AKAK
26	M	W	73	3,5	19.4	23	17	AKAK
33	M	W	32	4	23.5	13	16	AK[c]
36	M	W	35	3,4	24.9	17	13	KAK
38	F	W	33	4	14.8	16	14	AKA
39	F	W	47	3,5	13.4	29	29	AKA
42	M	B	57	1,3,5	15.0	18	16	KAK
43	M	W	60	4	16.5	5	4	K[c]
44	M	W	31	1	9.6	4	5	A[c]
45	F	W	62	5	12.5	23	20	KAKA
46	F	W	79	3,4	25.2	21	17	KAKA
47	M	W	34	6	15.3	19	19	AKAK
51	M	W	55	3,6	23.3	24	19	KAKA
53	M	W	36	1	28.9	17	15	AKA
54	F	W	65	3,5	10.3	10	11	A[c]
56	M	W	51	5,7	18.3	17	16	AKAK
57	F	W	62	2	10.2	14	13	AKA
60	F	W	72	8	23.9	4	5	K[c]

[a] Numbers represent: 1, diabetes; 2, polycystic kidney disease; 3, gout; 4, chronic glomerulonephritis; 5, arteriolar nephrosclerosis; 6, interstitial nephritis; 7, analgesic nephropathy; 8, fibrillary nephritis; 9, arteriosclerosis.
[b] A, amino acids; K, ketoacids
[c] Dropped out

supplements at differing levels of severity and provides more power to distinguish between a nonlinear trend in GFR progression and the effects of a treatment switch. Bias due to possible carryover effects was reduced or eliminated by estimating progression rates, following a change in treatment, only after a month had elapsed. The results indicate a significant effect of ketoacid supplements in slowing progression, compared with amino acid supplements to the same low protein diet.

Methods

The following protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Twenty-one patients were selected for study (Table 1). None of these patients participated in previous studies from this laboratory [8, 18]. Criteria for inclusion and exclusion are given in Table 2. After informed consent was obtained, patients were randomized, using a table of random numbers, by a third party not involved in the study, to receive as their initial dietary supplement either a mixture of essential amino acids (AA) or a mixture of ketoacids and amino acids (KA).

Composition of these mixtures was previously reported [8]. KA was obtained as "CSW20/4" from Sylatec/Clintec Technologies, Tours, France, and supplied as coated tablets. AA was compounded by the Johns Hopkins Hospital Pharmacy and supplied as gelatin capsules. Dosage of AA was 10 g daily in divided doses with meals, providing 1.1 g N per day. Dosage of KA was 2.8 g per nearest 10 kg of ideal body weight, in divided doses with meals, providing 0.28 g N/10 kg. The reason for varying the dosage of KA but not AA with body weight was that no pharmacological effects of AA have ever been reported; they serve only to correct for the otherwise inadequate intake of essential amino acids from the diet. On the other hand, KA have been reported to exert a number of effects beyond serving as precursors to essential amino acids [21]. Consequently we felt it was appropriate to vary dosage with body weight. Ideal

Table 2. Patient inclusion and exclusion criteria

Inclusion criterion

Chronic renal failure, as defined by a subnormal glomerular filtration rate (GFR) in the absence of acute renal failure.

Exclusion criteria

1. Age less than 18 or over 75 years.
2. Pregnant or planning to become pregnant.
3. Compliance doubtful owing to drug abuse, alcohol abuse, psychiatric illness, poor understanding of study, limited motivation, transient residence, or unsuitable home environment.
4. Impaired nutrition, as evidenced by body weight less than 85% or more than 150% of standard weight, serum albumin less than 3.5 g/dl or serum transferrin less than 180 mg/dl.
5. Proteinuria greater than 10 g/day.
6. Presence of urinary tract obstruction, vesicoureteral reflux grade III or worse, branched or staghorn calculi, kidney transplant, or cystinuria.
7. Chronic serious medical condition such as malignancy, severe heart failure, collagen vascular disease, or any other condition leading to frequent hospitalization or severe disability.
8. Immunosuppressive drugs, gold, penicillamine, frequent doses of salicylates or non-steroidal anti-inflammatory drugs, or any investigational new drug.
9. Inability to empty the bladder.

body weight was employed rather than actual body weight because metabolically active body cell mass is more closely related to ideal body weight.

Following randomization, patients were instructed by one of us (L.W.) on the diet. Caloric prescription was derived from three-day diet diaries, a 24-hour diet recall and an estimate of basal energy expenditure adjusted for activity. Average caloric intake was 35 kcal per kg of actual body weight, except that in cases where weight loss was desirable, total intake was reduced by 500 to 1000 calories per day. Mixed quality protein was prescribed at 0.3 g/kg ideal body weight. Phosphorus was prescribed at 7 to 9 mg per kg ideal body weight. All patients received a low protein exchange list, sample menus and a cookbook containing patient-developed low protein recipes. To meet caloric needs it was necessary to include extra fats, simple sugars, and low protein specialty products. However, the intake of fat did not exceed 30% of the total caloric intake. Simple sugars as soft drinks and candy provided additional calories. The acceptance of low protein specialty products varied among patients. Average dietary potassium was 65 mEq/day, except when hyperkalemia occurred; in these instances potassium intake was decreased slightly, and a potassium-binding resin (sodium polystyrene sulfonate) was prescribed. All patients consumed a vitamin-mineral preparation (Theragran M), one tablet per day. A total of 1000 mg of supplemental elemental calcium was prescribed as $CaCO_3$. Follow-up was provided by phone or at clinic visits whenever requested by the physician, patient, or dietician.

Compliance with the dietary protein prescription was assessed from measurements of 24-hour urinary urea N at each visit. When this value exceeded its target (**Results**), patients were referred for additional dietary counseling and exhorted as to the importance of compliance with the diet. When both urinary phosphate excretion and plasma phosphate were relatively high, dietary counseling regarding possible dietary sources of phosphorus was provided. Compliance with the supplements prescribed was informally assessed by questioning the patients; pill counts were not conducted.

By random assignment, 13 patients received AA first and 8 patients received KA first (Table 1). Patients were seen monthly, on the average, although the interval between visits varied from three to six weeks. This was because patients progressing rapidly, such as #14, were seen slightly more frequently, whereas one patient (#26) missed several appointments.

At each visit patients brought in a 24-hour urine collection and arrived fasting, or in a few cases (mostly diabetics), after a light breakfast.

Body weight was measured without shoes. Blood pressure was measured in the sitting posture, except where there was a question of postural hypotension, in which case blood pressure was also measured in the supine posture. Anti-hypertensive drugs (including angiotensin-converting enzyme inhibitors, employed in the last two periods in patient #38 and all three periods in patient #53), diuretics, allopurinol, colchicine and $NaHCO_3$ were prescribed as indicated.

GFR was measured at each visit. GFR values were not corrected for body size except for screening purposes. Following an oral water load of 10 to 15 ml/kg, 100 μCi ^{99m}Tc-labeled diethylenetriamine-pentaacetic acid was injected intravenously. Beginning 60 minutes later, three timed urine collections with blood samples at the beginning and end of each period were obtained. Studies in which urine flow was judged inadequate, based on criteria reported elsewhere [22, 23], were repeated. Two patients had one GFR each rejected on this basis.

At each visit, blood samples for routine chemical and hematological determinations were performed in the Johns Hopkins Hospital Chemistry and Hematology Laboratories, using automated methods. Twenty-four-hour urine was analyzed for protein, phosphate, and urea N by the Chemistry Laboratory. Excreted/filtered phosphate was calculated as 24-hour urinary phosphate/(plasma phosphate, mg/l $\times$ GFR, l/day).

After four GFR's, least squares linear regression slope of GFR on time in months was calculated. If the slope was positive, crossover was deferred and GFR measurements were continued at monthly intervals until the slope became negative or until two years elapsed. This deferral permitted patients to continue receiving therapy that appeared to be effective. As soon as a negative slope was estimated (based on at least four GFR's), the supplement was switched. Calculation of the new slope after a change of supplement began with the first GFR after switching, that is, one month later. This process was repeated until at least three periods of $\geq$4 GFR's each were completed. As noted below, five patients failed to complete this protocol. If the second treatment was associated with slower progression, patients were switched back to it for four more GFR's in a fourth period of observation.

The effects of treatment on GFR progression, chemical measures, and blood pressure were calculated separately for each patient by taking the difference between the patient's average value during KA and the average value during AA periods. As noted, the GFR progression outcomes were calculated using least squares regression. These patient-specific estimates were then analyzed by standard methods (t-test, Wilcoxon signed rank test) [24].

Pooled mean square error about the regression lines of GFR versus time was 2.05 (ml/min/month)^2.

In a second approach to the analysis, a linear random effects model was postulated [25] and restricted maximum likelihood estimates were found using an "EM" algorithm [26].

Results

Drop-outs

Patient #33, randomized to AA, progressed at -0.501 ml/min/month. After switching to KA, he did not progress for two months, then his GFR suddenly fell 60%. This was confirmed on two repeat determinations. No cause could be found. He declined to continue the study and obtained a renal transplant. The effect of including his results is considered in the Discussion. Patient #43, a 60-year-old man with biopsy-proven glomerulonephritis, randomized to KA, developed Goodpasture's syndrome and died. Patient #44, a 31-year-old insulin-dependent diabetic with a pre-treatment GFR of 9.6 ml/min, was randomized to amino acids. His GFR fell at 1 ml/min/month and he was started on dialysis four months later. Patient #54, a 65-year-old woman with gout and hypertension, had an initial GFR of 10.3 ml/min. Randomized to AA, she at first exhibited no progression but then went downhill. Dialysis was begun. Patient #60, a 72-year-old woman with biopsy-proven fibrillary

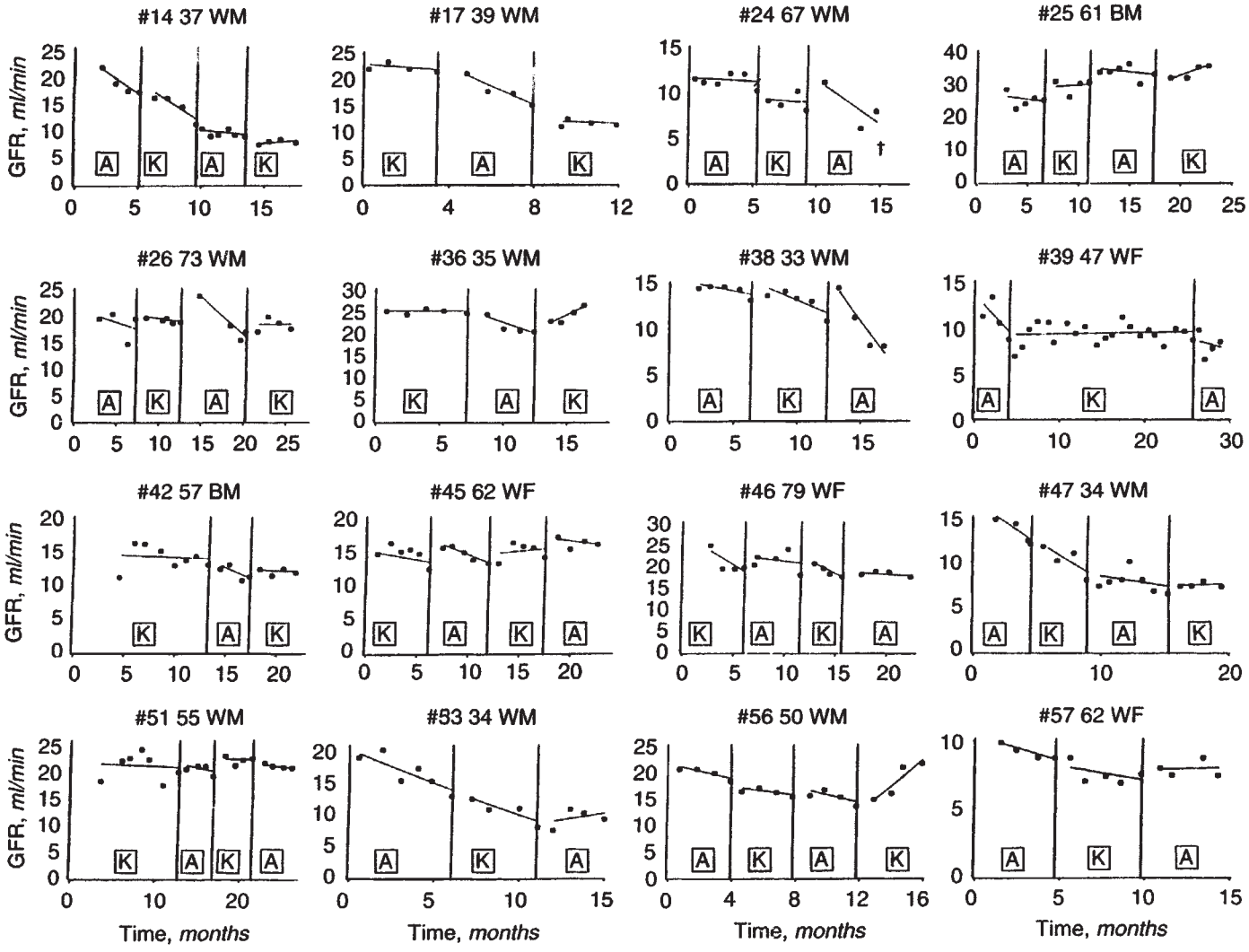

Fig. 1. *Sequential GFR values in 16 patients alternately given supplements of amino acids (A) or ketoacids (K).* Linear regression lines are shown.

nephritis, was withdrawn by her daughter after five GFR's on KA, the last value being 17.8 ml/min.

All three periods of patient #24 are included in the analysis even though a fourth GFR was not obtained in his third treatment period, owing to his death from myocardial infarction; no apparent change in his clinical condition preceded this fatal event.

Comparison of randomized groups

There were no major differences between the ten patients completing the protocol who were randomized to receive AA first and the six randomized to receive KA first with respect to gender, age, or initial GFR.

Postponements

As noted in the **Methods** section, crossovers were postponed whenever the estimated rate of change of GFR was positive rather than negative (ignoring statistical significance), for a maximum of two years. This occurred in eight periods on KA supplements and in seven periods on AA supplements. As shown in Figure 1, patient #39 remained on KA for two years without progression.

Side effects

No side effects of either supplement were observed.

Nutritional parameters

One patient (#46) was hypoalbuminemic throughout the study (3.1 to 3.3 g/dl), but her serum transferrin concentration was normal (248 to 263 mg/dl). One patient (#47) exhibited a slightly subnormal transferrin (175 to 187 mg/dl) but a normal albumin concentration (4.5 to 4.8 g/dl). Hypercholesteremia and hypertriglyceridemia were both common, as was anemia. Body weight (not shown) did not change.

None of these parameters differed significantly between the two supplements (Table 3) except serum triglyceride concentration, which was 31 mg/dl lower ($P = 0.0026$) on KA than on AA. The high level of significance of this relatively small (15%) change is a reflection of the statistical power of this repeated crossover design.

Table 3. Mean values ± SD during each supplement

	Supplement		
	AA	KA	*P*
GFR, *ml/min*	15.8 ± 5.6	15.6 ± 6.8	NS
Progression, *ml/min/month*	−0.67 ± 0.42	−0.15 ± 0.62	0.024
Blood pressure, *mm Hg*			
Systolic	146 ± 12	146 ± 13	NS
Diastolic	86 ± 7	86 ± 7	NS
Mean	105 ± 6	107 ± 7	NS
Hematocrit, *%*	34 ± 3	33 ± 4	NS
Serum			
Urea N, *mg/dl*	41 ± 16	43 ± 16	NS
Creatinine, *mg/dl*	4.0 ± 1.5	4.0 ± 1.7	NS
Albumin, *g%*	4.4 ± 0.4	4.4 ± 0.5	NS
Transferrin, *mg/dl*	252 ± 41	254 ± 50	NS
Uric acid, *mg/dl*	8.5 ± 1.8	8.4 ± 1.0	NS
Calcium, *mg/dl*	9.0 ± 0.5	9.0 ± 0.4	NS
Phosphate, *mg/dl*	4.0 ± 0.7	4.1 ± 0.9	NS
Ca × P, mg^2/dl^2	36 ± 7	37 ± 9	NS
Cholesterol, *mg/dl*	214 ± 60	206 ± 55	NS
LDL cholesterol, *mg/dl*	127 ± 52	126 ± 51	NS
HDL cholesterol, *mg/dl*	38 ± 14	38 ± 15	NS
Triglycerides, *mg/dl*	242 ± 119	209 ± 83	0.0021
24-Hr urine			
Urea N, *g/day*	5.0 ± 1.3	5.2 ± 1.2	NS
Protein, *g/day*	1.8 ± 1.6	1.7 ± 1.4	NS
Phosphate, *mg/day*	403 ± 119	380 ± 128	NS
Excreted/filtered *P*	0.49 ± 0.18	0.47 ± 0.19	NS
17-hydroxycorticosteroids, *mg/day*	4.2 ± 1.8	3.4 ± 0.9	0.031

Table 4. Average rates of progression in each patient and changes, KA–AA, *ml/min/month*

Patient no.	Slope on KA	Slope on AA	Change in slope
14	−0.679	−0.912	0.232
17	−0.201	−1.796	1.595
24	−0.083	−0.532	0.449
25	0.650	−0.387	1.038
26	−0.109	−1.000	0.891
36	0.754	−1.031	1.785
38	−0.578	−1.088	0.510
39	0.027	−0.634	0.662
42	−0.054	−0.644	0.590
45	−0.152	−0.373	0.222
46	−1.375	−0.217	−1.158
47	−0.441	−0.600	0.160
51	−0.078	−0.297	0.220
53	−0.910	−0.292	−0.618
56	1.092	−0.769	1.860
57	−0.225	0.015	−0.240

Table 5. Estimated expected progression rates, ml/min/mo, based on the random effects model

Parameter	Estimate	95% Confidence limits
Rate of progression on KA	−0.14	−0.36, 0.09
Rate of progression on AA	−0.66	−0.91, −0.41
Difference, KA-AA	0.52	0.21, 0.84
Change in GFR during first month after switching from KA to AA	0.12	−0.82, 1.08
Change in GFR during first month after switching from AA to KA	0.13	−0.77, 1.02

Compliance

Target values for urinary urea N were calculated as dietary protein prescription × 0.16 plus supplement N content minus 31 mg N/kg (for N excretion in forms other than urea [27]) minus urinary protein × 0.16. The difference between measured urinary urea N and target urinary urea N ÷ 0.16 represents dietary protein ingested in excess of prescribed. Actual dietary protein estimated in this way averaged 0.45 g/kg, instead of 0.3 g/kg as prescribed. Thus dietary compliance was relatively poor. However, protein intake before starting dietary therapy, estimated in 16 of these patients from 24-hour urinary urea N, was considerably higher (mean ± SD = 0.82 ± 0.20 g/kg).

No patients admitted to failing to consume the supplements, except during intercurrent illnesses, such as upper respiratory infections.

Blood pressure

Mean arterial pressure averaged 107 mm Hg during KA supplementation and 105 mm Hg during AA supplementation (Table 3). These values do not differ significantly, nor do values for mean systolic or diastolic pressure.

Renal function

GFR, serum urea N, and serum creatinine did not differ between AA and KA (Table 3).

Progression

The rate of change of GFR during KA averaged −0.15 ml/min/month, while the rate of change of GFR during AA averaged −0.67 ml/min/month (Table 4). The estimate of the difference in progression rates is therefore 0.52 ± 0.18 (SEM) ml/min/month ($P = 0.024$ by t-test). Using Wilcoxon's signed rank test [24], $P < 0.05$.

Mean period-to-period differences in progression rates, KA-AA, were all of the same sign but failed to achieve statistical significance individually: period 1 to period 2, 0.29 ± 0.15 ml/min/month, $P = 0.07$; period 2 to period 3, 0.38 ± 0.27 ml/min/month, $P = 0.18$; period 3 to period 4, 0.79 ± 0.47 ml/min/month, $P = 0.14$. Mean difference between slopes on the same treatment (period 1 vs. period 3 or period 2 vs. period 4) were not significant. These differences presumably reflect the error of measurement. No relationship between rate of progression and clinical condition was apparent.

We also modelled GFR progression over time using a linear random effects regression model which allowed four distinct rates of progression: (1) treatment AA, (2) treatment KA, (3) first month on AA after switching from KA, (4) first month on KA after switching from AA. All terms were modeled as random effects (Table 5). Consistent with the first analysis, the expected progression rate during AA periods was estimated as −0.66 ml/min/month (95% confidence interval −0.91, −0.42). The expected progression rate during KA was estimated as −0.14 ml/min/mo (95% confidence interval −0.36, 0.09). The expected difference in progression rates was 0.52 ml/min/month (95% confidence interval 0.21, 0.84).

Very similar results were obtained when a quadratic term of

follow-up time squared was added to the regression model to allow for the possibility of individual secular trends.

Discussion

In summary, we found that when 16 patients were alternately provided with KA or AA supplements for three or four treatment periods, 13 of them exhibited slower progression on KA supplements and three exhibited slower progression on AA supplements. This difference is statistically significant. One further patient (#33) had observations during two treatment periods, but he failed to complete the three period protocol. Even if this patient is included, so that 13 out of 17 progress more slowly on KA, this result remains significant ($P < 0.05$) by the sign test [24].

In the 16 subjects who completed the protocol, mean progression rate on KA is only 22% of that on AA. This difference, if projected to a final GFR of 6 ml/min (a typical value for the initiation of dialysis), would predict postponement of the need for dialysis for many years. Since the patients were only followed for a few months on each supplement, extrapolation to time of dialysis from these data is hazardous. However, the protocol was designed so that each patient would end by receiving the supplement that was associated with a slower rate of progression. Long-term follow-up on the final supplement has been carried out in seven of these patients (#25, #36, #42, #47, #51, #53 and #56), two on AA and five on KA, for an average of 14 months following the completion of the present protocol. Most recent GFR's in these seven patients are, on the average, 97 ± 17% (SD) of last GFR's during the protocol, shown in Figure 1. Thus it appears that long-term arrest of progression predicted by these repeated crossover results is borne out.

It is difficult to conceive an effect of ketoacid or amino acid supplements on chronic renal failure that could persist more than a month after withdrawing the supplement. Hence our method of analyzing the data should eliminate bias due to carryover effects.

The patients who progressed more slowly on AA (#46, #53, and #57) do not differ in any obvious way from the others. Thus it is not possible from these limited observations to predict which patients will respond more favorably to one supplement or the other. Nevertheless, the results suggest that use of the ketoacid-supplemented regimen in all patients would increase the average time to dialysis by many years. However, only a long-term randomized study without crossovers can establish this point.

These results do not shed any light on the efficacy of AA supplements, in comparison with an unsupplemented diet, on the progression of renal failure.

There is a highly significant correlation ($r = -0.674$, $P = 0.004$) between the treatment effect of KA, as shown in Table 4, and the progression rate on AA. Thus more rapidly progressing subjects exhibit a larger treatment effect of KA. This is important from the practical point of view as well as from the point of view of study design and statistical analysis. Perhaps a model which postulates that KA effects a percentage change in rate of progression is to be preferred over assumption of an absolute change. However, regression towards the mean could be a factor in producing this correlation.

An important inference from this study is that statistically significant results can be obtained concerning effects of any agent on progression with relatively small numbers of patients (providing the effect is sufficiently large). This conclusion contradicts the view that hundreds of patients must be studied, at enormous cost, in order to assess the effect of any experimental variable on rate of progression. Multicenter trials now in progress [19, 20] are based on this latter view, even though one of them [19] includes a crossover design ("Study C"). While non-crossover studies are more universally accepted, it is clear that progress in this field will be far more rapid if crossover studies can be viewed as providing statistically valid information.

The mechanism by which ketoacids slowed progression is not apparent from these data. Estimated protein intake, blood pressure, and severity of renal insufficiency did not differ significantly between the two supplements. 17-Hydroxyglucocorticoid excretion, which we previously found to be correlated with progression rate and to be reduced by KA supplements [28], was measured in 208 of the 270 samples of the present study. It fell 19% ($P = 0.031$) on KA. Serum triglyceride concentration was significantly lower on KA supplements. This could be a factor in the change in progression, since hyperlipidemia has been identified as an important contributor to progression in patients [29]. However, there was no correlation between period-to-period change in triglyceridemia and change in progression.

Salahudeen, Clark and Nath [30] have suggested that ketoacids may lessen renal injury by an antioxidant mechanism. We have recently observed that continuous intravenous infusion of 2-ketoisocaproate in septic rats significantly reduces plasma and whole blood ratios of oxidized/total glutathione (Yonekura, Matsusue, and Walser, unpublished observations). In addition, we found that plasma nitrate elevation in these animals is markedly attenuated, suggesting that 2-ketoisocaproate may also suppress the induction by sepsis of nitric oxide production. The roles of oxygen free radicals and of nitric oxide in progression of chronic renal failure remain to be clarified.

Our patients were probably more motivated and compliant than average. Hence, it remains to be determined whether nutritional therapy of this type, even if efficacious, would be acceptable to the general population of patients with chronic renal failure.

Acknowledgments

Supported by a Research Grant (DK-32008) and a Clinical Center Grant (RR-00722) from the National Institutes of Health, and by the Leonard Kapiloff Foundation. We are indebted to Helen Drew for performing the GFR's and to Dr. Scott Zeger for statistical advice.

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