Zeitschrift für
Ernährungswissenschaft Z Ernährungswiss 24:96–104 (1985)

The influence of two different essential amino acid/keto analogue preparations on the clinical status of patients with chronic renal failure

E. Meisinger and M. Strauch

Clinic of Nephrology, Klinikum Mannheim, University of Heidelberg, Mannheim (F.R.G.)

Summary

58 outpatients with a serum creatinine between 6–10 mg/dl received a low protein diet (LPD) with 30 g protein/day, supplemented with essential amino acids (EAA) or their keto analogues (KA). Group A (n = 19) was given an EAA/KA supplement according to the pattern proposed by Rose and group B (n = 39) received a preparation with an increased amount of KAs of branched chain amino acids (BCKA), as recommended by Walser. At the start of treatment with a LPD supplemented with either of the two supplements and after 6 months of treatment we assessed: plasma branched chain amino acids (BCAA), renal function, nutritional status, and bone metabolism. After six months of dietary treatment the results showed in group B in contrast to group A an improvement of nutritional status (body weight increased, urea decreased, and BCAA normalized). The same was true for bone metabolism (significantly lower phosphate levels, increased calcium values). In both groups progression of chronic renal failure slowed down, but the delay was more pronounced in group B. All results were statistically significant ($p < 0.01$).

Zusammenfassung

58 ambulante Patienten mit chronischer Niereninsuffizienz (Serumkreatinin 6–10 mg/dl) erhielten eine eiweißreduzierte Diät (30 g), substituiert mit essentiellen Aminosäuren (EAS) bzw. deren Ketoanalogen (KS). Gruppe A (n = 19) erhielt Substitutionspräparat A mit einer Zusammensetzung entsprechend dem Rose-Schema, Gruppe B (n = 39) erhielt das Substitutionspräparat B mit einer höheren Konzentration an verzweigtkettigen KS, entsprechend den Vorschlägen von Walser. Zu Beginn und nach Beendigung der Untersuchungsperiode von 6 Monaten wurden neben den Plasmakonzentrationen der verzweigtkettigen Aminosäuren Parameter der Nierenfunktion, des Ernährungsstatus und des Knochenstoffwechsels bestimmt. Die Ergebnisse zeigten, daß ein höherer Anteil an verzweigtkettigen EAS/KS (Gruppe B) in der Substitution eine Verbesserung ergab bezüglich des Ernährungsstatus. Es kam zu einem Anstieg des Körpergewichts, zu einem Abfall des Serumharnstoffs und zu einer Normalisierung der Plasma-Aminosäuren. Die Veränderungen bezüglich der renalen Osteopathie waren in Gruppe B deutlich geringer: Die Konzentrationen von Serumphosphat und alkalischer Phosphatase fielen ab, die Calciumwerte stiegen an. In beiden Gruppen ergab sich eine verlangsamte Progression der chronischen Niereninsuffizienz, die in Gruppe B deutlicher ausgeprägt war. Sämtliche hier genannten Ergebnisse waren statistisch signifikant ($p < 0{,}01$).

Key words: chronic renal failure, low protein diet, supplementation, branched chain amino acids

Introduction

Low protein diets (LPD) are increasingly being used to slow down the progression of chronic renal failure (CRF) (1–4). The lower the protein content of the diets the more important is the use of protein of high biological value or the supplementation of the diets with essential amino acids (EAA) or their keto analogues (KA). Up to now several supplements with different compositions have been used in uremic patients (5–7). Comparisons of the achieved effects on metabolism in uremia are scanty, mainly because there are only shortterm studies of less than two months duration per applied preparation. Studies with such short durations are of limited value, as amino acid and protein pools need time to be refilled.

The aim of the present study was to investigate the effect of two different essential amino acid/keto analogue (EAA/KA) preparations on biochemical parameters in patients with CRF after six months of application.

Methods

58 patients suffering from CRF (SCR 6–10 mg/dl) treated with LPD were divided into two groups. Group one (n = 19) received an EAA/KA supplement according to the pattern proposed by Rose (group A) and group two (n = 39) received a preparation with an increased amount of KAs of branched chain amino acids, as recommended by Walser (group B)*).

The components of the two supplements are listed in Table 1. At the start of the treatment with a LPD (30 g/day) supplemented with either of the two supplements (10 g/die 11.4 g/die) and after 6 months of treatment we assessed: plasma branched chain amino acids (valine, leucine and isoleucine), renal function: serum creatinine (SCR) (mg/dl), and urea (mg/dl), nutritional status: body weight (kg), total protein (g/l) and albumin (measured as % of total protein), and bone metabolism: calcium (mmol/l), phosphate (mmol/l) and alkaline phosphatase (mU/ml).

For the determination of plasma amino acid concentrations 4 parts of plasma from EDTA blood were deproteinized with 1 part of sulfosalicylic acid. Samples for

Table 1. Contents of the preparations used (mg/10 kg body weight).

	Group A	Group B
Keto-Isoleucine	0.144	0.234
Keto-Leucine	0.217	0.292
Keto-Valine	0.184	0.308
Keto-Methionine	0.127	0.175
Keto-Phenylalanine	0.146	0.158
L-Histidine	0.081	0.045
L-Lysine	0.225	0.075
L-Threonine	0.114	0.055
L-Tryptophane	0.050	0.028
L-Tyrosine	0.064	–
Calcium	0.107	0.155
Nitrogen	0.077	0.032

*) Ketoperlen® Pfrimmer

analysis were diluted with citrate buffer (pH 2) 1:2. The buffer contained norleucine for an internal standard. Amino acid determinations were carried out with the automatic analyzer LC 6000 (Biotronic, Munich) (8).

The differences between group A and B were evaluated by computing a t-statistic for unpaired observations (9). In the case of unequal variances an approximate t was calculated based on Satterthwaite's approximation (9). A paired comparisons t-test was computed to assess differences between the two observation points: start of treatment and 6 months afterwards (10). To reduce the effect of multiple testing only p values below 0.01 were considered as statistically significant. Average values are given as mean ± SD. Normal values for valine, leucine and isoleucine are presented as ± 2 SD.

Results

At the start of treatment the initial data of patients in group A (n = 19) and B (n = 39) demonstrated no statistically significant differences, whereas from a clinical point of view renal function, body weight and serum phosphate exhibited some degree of variation (Table 2). Six months after the start of dietary treatment patients of group B showed signifi-

Table 2. Initial patient data (n = 58)

Renal function

	SCR (mg/dl)	Urea (mg/dl)
Group A	6.3 ± 1.7	145 ± 35
Group B	7.6 ± 2.2	152 ± 26
p =	0.0254	0.3927

Nutritional status

	Albumin (rel. %)	Total protein (g/l)	Body weight (kg)
Group A	55.7 ± 4.8	6.5 ± 0.6	67.5 ± 9.9
Group B	54.6 ± 1.4	6.5 ± 0.5	60.2 ± 13.1
p =	0.5176	0.9092	0.0698

Bone metabolism

	Phosphate (mmol/l)	Calcium (mmol/l)	Alk. Phosphatase (mmol/l)
Group A	2.0 ± 0.4	2.1 ±0.2	242 ± 168
Group B	1.8 ± 0.4	2.2 ± 0.2	309 ± 127
p =	0.0322	0.06	0.1680

p = difference between groups

Table 3. Patient data after 6 months of treatment

Renal function

	SCR (mg/dl)	Urea (mg/dl)
Group A	7.8 ± 1.7	144 ± 40
Group B	7.8 ± 2.5	108 ± 31
p =	0.9158	0.0004

Nutritional status

	Albumin (rel. %)	Total protein (g/l)	Body weight (kg)
Group A	56.5 ± 9.6	6.7 ± 0.7	67.2 ± 10.1
Group B	57.3 ± 2.5	7.0 ± 0.7	62.3 ± 11.9
p =	0.8301	0.1905	0.2019

Bone metabolism

	Phosphate (mmol/l)	Calcium (mmol/l)	Alk. Phosphatase (mmol/l)
Group A	2.2 ± 0.5	2.17 ± 0.17	149 ± 99
Group B	1.4 ± 0.3	2.44 ± 0.11	168 ± 49
p =	0.0001	0.0001	0.5440

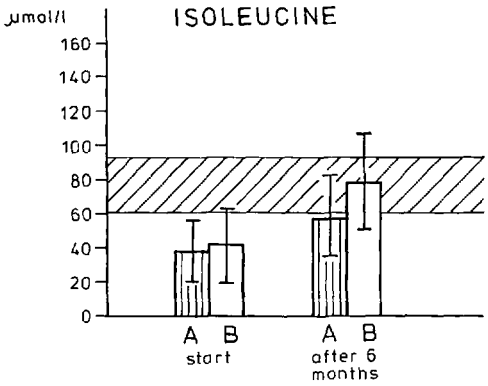
p = difference between groups

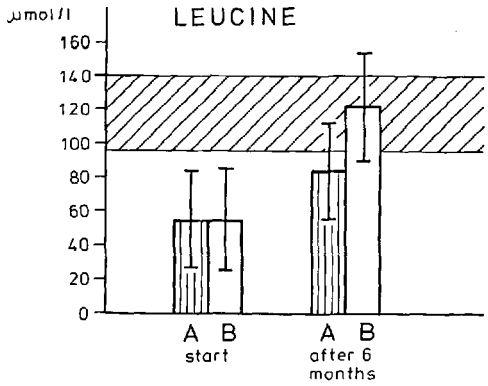
cantly lower urea and phosphate levels, the values for calcium increased (Table 3).

In group A renal function deteriorated as SCR increased, the plasma concentrations of valine, leucine and isoleucine improved, whereas all other parameters remained fairly stable. In group B renal function could be stabilized, urea went down "dramatically", the nutritional status improved, as did bone metabolism and the plasma concentrations of branched chain amino acids (BCAA).

Initially the BCAA were subnormal in all patients. With regard to the BCAA concentrations, at the start of treatment there was no significant difference between the two groups. Under both therapeutic regimens we observed an increase in the BCAA concentrations. But only in group B was a normalization noted (Fig. 1). These normal BCAA concentrations could be maintained up to the date when renal replacement therapy had to be installed.

In Table 4 differences between the data at the start of treatment and 6 months after are given once more accordingly for groups A and B. Negative values indicate that the second value was higher than the first and vice versa. p^+ specifies the level of significance for the difference between the


µmol/l
ISOLEUCINE
160
140
120
100
80
60
40
20
0
A B
start
A B
after 6
months


µmol/l
LEUCINE
160
140
120
100
80
60
40
20
0
A B
start
A B
after 6
months

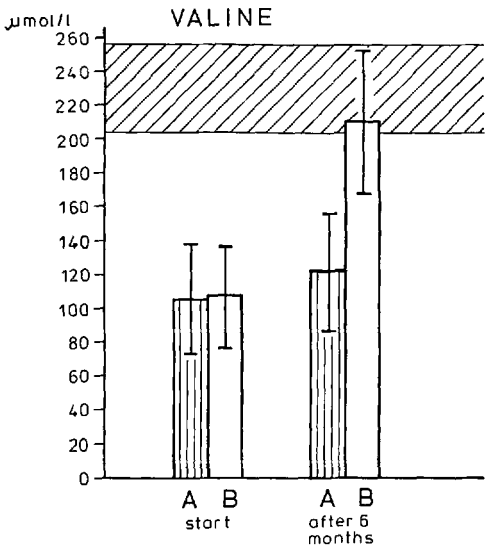

µmol/l
VALINE
260
240
220
200
180
160
140
120
100
80
60
40
20
0
A B
start
A B
after 6
months

Fig. I

Table 4. Change expressed as difference between the two values at start and 6 months after start of treatment

Renal function

	SCR		Urea	
	$\bar{x}$	p^+	$\bar{x}$	p^+
Group A	− 1.6	0.0031	1	0.8820
Group B	− 0.2	0.1558	44	0.0001
p =	0.0089		0.0001	

Nutritional status

	Albumin		Total protein		Body weight	
	$\bar{x}$	p^+	$\bar{x}$	p^+	$\bar{x}$	p^+
Group A	− 0.3	0.6563	0.2	0.0240	0.2	0.6507
Group B	− 2.2	0.0001	− 0.5	0.0001	− 2	0.0001
p =	0.0268		0.0724		0.0003	

Bone metabolism

	Phosphate		Calcium		Alk. Phosphatase	
	$\bar{x}$	p^+	$\bar{x}$	p^+	$\bar{x}$	p^+
Group A	− 0.4	0.0726	− 0.02	0.05999	54	0.0780
Group B	0.3	0.0001	− 0.17	0.0001	126	0.0001
p =	0.0027		0.0044		0.0158	

p^+ = difference within the group between start of treatment and 6 months after
p = difference between groups

two points, but within the same group, whereas p marks the level of significance of these differences between groups A and B.

Discussion

The results presented indicate an improvement of nutritional status in uremic patients treated by LPD supplemented with EAA/KA preparations.

Concerning SCR there was no statistically significant difference (p = 0.9158) between groups A and B after 6 months of treatment (Table 3). Due to the small number of patients and the unequal distribution of the underlying renal disease a definitive statement on the progression rate is difficult. Patients of group B showed a significantly lower serum urea concentration than patients in group A. This decrease in urea generation is probably caused by an improvement of uremic protein metabolism.

Other parameters of nutritional status such as body weight, total protein and albumin remained fairly similar in both groups. This fact indicates a stabilization of metabolism under LPD.

In uremia the serum calcium concentration is decreased, whereas PTH, PO_4 and alkaline phosphatase are increased, even in the early stages of the disease. Under LPD supplemented with EAA/KA we found less deranged values for PO_4 and AP. The values for calcium could be stabilized at a low normal level. PTH was not evaluated. The more normal values were reached with supplement B. The prevention of the usual derangements of bone metabolism is an important "side effect" of LPDs supplemented with KA. Possible mechanisms for the effect of KA supplements on bone metabolism are:

1. high calcium intake causes a higher absorption of calcium, which prevents the usual hypocalcemia. In turn this normalization of calcium reduces hyperparathyroidism resulting in a more or less normal bone turnover,
2. high calcium contents might inhibit absorption of phosphate by forming insoluble $Ca_3(PO_4)_2$ salts,
3. a possible direct effect of KAs on the PT suppressing the production of PTH is discussed by Fröhling (11).
4. increased uptake of calcium and phosphate by bone.

Usually the composition of preparations is according to the proposals of Rose. This pattern of AA is based on the theoretical background, which does not take into account the special requirements of uremic patients. This is true for supplement A. On the other hand, supplement B was composed by Walser, considering the special metabolic situation of uremic patients.

We analysed BCAA concentrations in our patients. The analysis was restricted to BCAA, as in uremic patients these AAS are the most valuable parameters for muscle metabolism. Despite subnormal initial values for the BCAA concentrations, improved levels were noted after 6 months of therapy with both preparations. In group B we even found normal values for these amino acids. The normalized BCAA values could be maintained until renal replacement therapy had to be installed. The improvement might be explained by the following hypothetic biochemical mechanisms:

1. the direct transamination of keto analogues and consecutive refill of AA pool. The rate of transamination of BCAA in uremic patients might be higher than the usual 20–40 % (12–14) as the plasma concentration of BCAA might be rate limiting for this conversion. This explains the high efficiency of the keto acid supplementation,
2. retention of AA in protein and reduced synthesis of urea,
3. regulatory effects for an increased protein synthesis caused by ketoleucine (15),
4. shifts between the intra- and extracellular pool.

The different results between groups A and B can be explained by the higher intake of keto analogues used in supplement B.

Our results contrast with the data presented by Kopple et al. (16), Rippich et al. (17), and Alvestrand (18). These authors detected an increase of valine, but not of leucine and isoleucine, whereas Ando et al. (19) found a plasma BCAA concentration comparable to ours. These varying results

are explained by the different degree of renal functional impairment and the duration of the underlying renal diseases analysed by the individual author. It is obvious that a patient with long-standing renal disease and a high degree of renal functional impairment will exhibit a depleted pool of BCAA compared to a patient with better renal function and a short duration of disease. Therefore we conclude that in future studies plasma concentrations of BCAA should be assessed according to the duration of the disease and the degree of renal impairment. As we analysed the plasma concentrations of patients who had a better renal function than patients in other studies, we suppose that the AA pool of our patients was less deranged.

In conclusion: the presented data demonstrate that a KA supplementation modified according to the considerations of Walser results in a slower rate of deterioration of renal function, an improved nutritional status of the uremia patients, and a lesser degree of renal osteodystrophy in patients with a serum creatinine between 6 and 10 mg/dl. Our results illustrate the importance of the composition of EAA/KA supplements. Furthermore this study underlines the importance of analysing plasma AA patterns of comparable stages of renal functional impairment and after a defined duration of the renal disease.

References

1. Alvestrand A, Ahlberg M, Bergström J (1983) Retardation of the progression of renal insufficiency in patients treated with low-protein diets. Kidney Int 24 Suppl 16:268–272
2. Gretz N, Korb E, Strauch M (1983) Low-protein diet supplemented by keto acids in chronic renal failure: A prospective controlled study. Kidney Int 24, Suppl 16:263–267
3. Maschio G et al (1983) Early dietary protein and phosphorus restriction is effective in delaying progression of chronic renal failure. Kidney Int 24, Suppl 16:273–277
4. Barsotti G et al (1983) Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure: a controlled trial. Kidney Int 24, Suppl 16:278–284
5. Alvestrand A, Ahlberg M, Bergström J, Fürst P (1983) Clinical results of long-term treatment with low protein diet and a new amino acid preparation in chronic uremic patients. Clin Nephrol 19:67–73
6. Walser M, Mitch WE, Abras E (1983) Supplements containing amino acids and keto acids in the treatment of chronic uremia. Kidney Int 24, Suppl 16:285–289
7. Broyer M et al (1983) Comparison of three low-nitrogen diets containing essential amino acids and their alpha analogues for severely uremic children. Kidney Int 24, Suppl 16:290–294
8. Stein WH, Moore S (1958) The free amino acids of human blood plasma. Analyt Chem 30:1190
9. Ray AA (1982) SAS User's Guide: Statistics
10. Ray AA (1982) SAS User's Guide: Basics
11. Fröhling, PT et al (1983) Influence of keto acids on serum parathyroid hormone levels in patients with chronic renal failure. Clin Nephrol 20:212–215
12. Walser M, Coulter AW, Dighe S, Crantz FR (1973) The effect of keto analogues of essential amino acids in severe chronic uremia. J clin Invest 52:678–690

13. Halliday D, Madigan M, Chalmers RA, Purkiss P, Ell S, Bergström J, Fürst P, Neuhäuser M, Richards P (1981) The degree of conversion of α-keto acids to valine and phenylalanine in health and uremia. Q JI Med 50:53–62
14. Epstein CM, Chawla RK, Wadsworth A, Rudman D (1980) Decarboxylation of α-ketoisovaleric acid after oral administration in man. Am J clin Nutr 33:1968–1974
15. Häussinger D, Gerok W (1984) Regulation of hepatic glutamate metabolism. Role of 2-oxoacids in glutamate release from isolated perfused rat liver. Eur J Biochem 143:491–497
16. Kopple JD, Flugel R, Jones MR (1981) Branched chain amino acids in chronic renal failure. In: Walser W (eds) Metabolism and clinical implications of branched chain amino and ketoacids: Developments in biochemistry, Vol 18:555–567 Elsevier/North Holland, New York, pp 555–567
17. Rippich T, Katz N, Schaeffer G, Schanz M, Schinle S, Südhoff A, Zimmerman W, Kluthe R (1976) Detoxification and amino acid metabolism in chronic uremia: A therapeutic approach using biochemically defined lipid diets. In: Heidland, Hennemann, Kult (eds) Würzburg Symp 1974, Renal insufficiency, Georg Thieme, Stuttgart, pp 174–180
18. Alvestrand A, Fürst P, Bergström J (1982) Plasma and muscle free amino acids in uremia: influence of nutrition with amino acids. Clin Nephrol 18:297–305
19. Ando A, Orita Y, Nakata K, Tsubakihara Y, Ueda N, Yanase M, Abe H (1979) Effect of low protein diet and surplus of essential amino acids on the serum concentration and the urinary excretion of methylguanidine and guanidinosuccinic acid in chronic renal failure. Nephron 24:161–169

Eingegangen 30. März 1985

Für die Verfasser:

Dr. E. Meisinger, Klinikum Mannheim, Klinik für Nephrologie d. Universität Heidelberg, 6800 Mannheim