Complex Cases and Supplements: Essential Amino Acids, Ketoacid and Hydroxyacid Analogues

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Potential Conflicts of Interest: Nephroceuticals
Shire Pharmaceuticals

In Potential Benefits of Low Protein Diets for Nondialyzed CKD Patients

1. Maintain good nutritional status
2. Slow progression of CKD - retard rate of GFR loss
3. Reduce generation of uremic toxins
   - i. Decrease potentially toxic metabolites of protein
   - ii. Reduce intake of other compounds found in protein-containing foods (e.g., creatine,)
   - iii. Decrease excess intake of potentially toxic cations and anions: e.g., sodium, potassium, phosphorus, certain trace elements e.g., lead

Effect of Dietary Protein Restriction on Generation of a Potential Uremic Toxin: Guanidinosuccinic Acid

Table II. Urinary GSA in normal subjects and chronically uremic patients ingesting different quantities of dietary protein

Normal			Chronically uremic			
No.	Dietary protein (gm/day)	Urinary GSA (mg/day)	No.	Dietary protein (gm/day)	Urinary GSA (mg/day)	p*
3	21.1 ± 1.2†	4.4 ± 0.058‡	4	21.0 ± 0.8	12.8 ± 1.9§	<0.001
3	43.4 ± 1.6	4.5 ± 1.7‡	10	42.3 ± 3.0	22.6 ± 6.2§	<0.001
3	62.6 ± 1.4	13.8 ± 2.0	6	59.0 ± 3.2	41.4 ± 6.7	<0.001

*Urinary GSA in normal vs. chronically uremic subjects.
†Mean ± standard deviation.
‡Significantly less than in normal subjects ingesting 63 gm/day of protein, $p < 0.01$.
§Significantly less than in the chronically uremic patients ingesting 59 gm/day of protein, $p < 0.001$.
‖Significantly less than in the chronically uremic patients ingesting 42 gm/day of protein, $p < 0.02$.

Kopple et al J Lab Clin Med 1977;90:303-311

Essentially Two Types of Protein Restricted Diets for Chronic Kidney Disease (CKD) Patients

1. Low Protein Diet (LPD): 0.60 - 0.80 g protein/kg/day; 50% high biological value protein. 0.60 g protein/kg/day for advanced CKD patients (GFR about ≤ 20 ml/min/1.73m2).

2. Supplemented Very Low Protein Diet (SVLPD): 0.3-0.4 g protein/kg/day plus ~7-15 g/day of the 9 essential amino acids (EAA) or a mixture of 4 EAA plus ketoacid or hydroxyacid analogues of the other 5 EAA.

Low Protein Diet (LPD): 0.60 - 0.80 g protein/kg/day; 50% High Biological Value Protein.

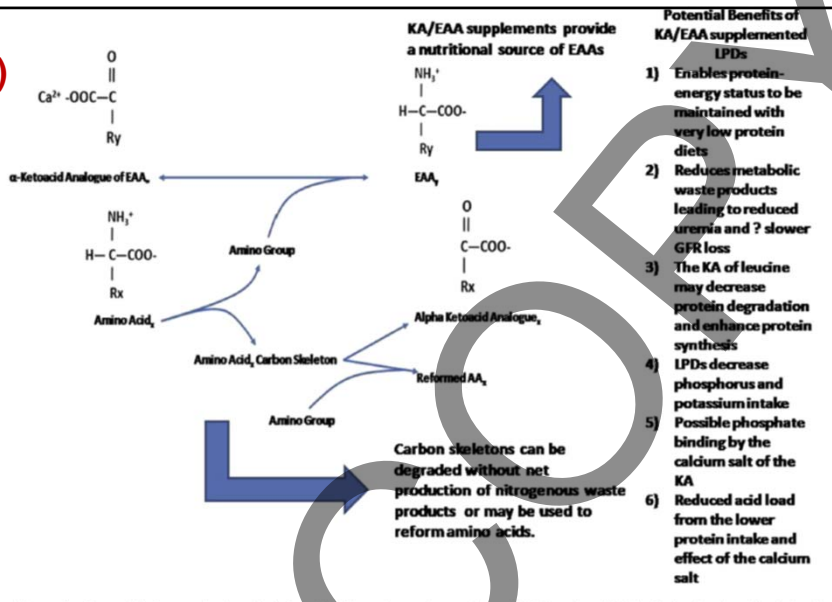
Actually 0.60 g protein/kg/day is nutritionally adequate for almost all clinically stable CKD patients and generates less toxicity. But this intake, compared to 0.70 or 0.80 g protein/kg/day:

1. Is harder for many CKD patients to adhere to.
2. Is somewhat harder to attain dietary energy needs.
3. Is most strongly indicated at low GFRs (e.g., ≤ ~15 ml/min) when sufficient accumulation of uremic toxins is most likely to cause uremic toxicity.

The Essential Amino Acid (EAA) or Ketoacid (KA) Supplemented Very Low Protein Diet (SVLPD)

Traditionally the SVLPD provides 0.3-0.4 g protein/kg/day plus ~7-15 g/day of the 9 EAA or a mixture of 4 EAA plus ketoacid (KA) or hydroxyacid analogues of the other 5 EAA. Often 1-2 nonessential amino acids are added.

What is a Ketoacid (KA) or Hydroxyacid (HA)? What does it do?



Shah et al. Am J Kidney Dis 65:659-673, 2015

Figure 1. Reversible transamination of a ketoacid (KA) analogue of an amino acid (AA) and an AA. The R denotes the side chain of the AA, and the subscripts (x) and (y) refer to different AAs or KAs. Transamination is catalyzed by aminotransferase enzymes (ie, transaminases). During this process, there is a substitution of the amino group with either a keto group (forming a KA) or a hydroxyl group (yielding a hydroxyacid).[12] The α amino group of the essential AA (EAA) is commonly transferred to α ketoglutarate or oxaloacetate to generate the AAs glutamate or aspartate, respectively. Glutamate, a major recipient of these amino groups, can be oxidatively deaminated to generate NH_3 and regenerate α ketoglutarate. The KA formed by transamination can be degraded by oxidation. KA or hydroxyacid analogues of the EAAs, except lysine or threonine, can be transaminated to form their respective EAA. Abbreviations: GFR, glomerular filtration rate; LPD, low-protein diet.

KA/EAA SVLPD (Supplemented Very Low Protein Diet) (1)

The EAA SVLPD is very uncommonly used today. The KA/EAA which traditionally provided about 0.30-0.40 g/kg/d of miscellaneous protein, often vegetarian protein, and about 0.28 g/kg/d of 4KA,1HA,4EAA is nutritionally adequate for almost all clinically stable CKD patients and generates less toxicity. This intake, compared to 0.60 or more g protein/kg/d:

1. **Also maintains good nutritional status**
2. **Probably slows the loss of GFR in CKD more effectively**
3. **Because roughly one-half of the protein source is pure KA, HA and EAA, there is less sodium, potassium and phosphorus in the diet.**

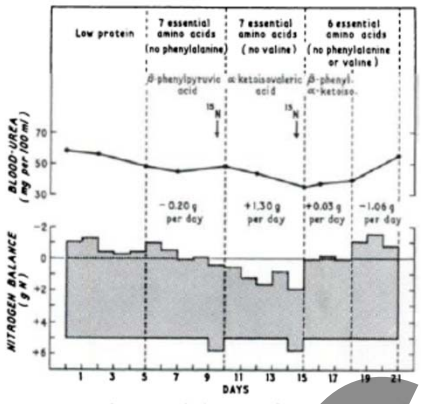


FIG. 4. Nitrogen balance of a 47-year-old woman with chronic renal failure during sequential replacement of phenylalanine, valine, and both phenylalanine and valine with their α-keto acid analogs. (Reprinted by courtesy of *Lancet* (77).)

From Richards, P. Am J Clinical Nutrition 1972;25:615-625

KA/EAA SVLPD (Supplemented Very Low Protein Diet) (2)

The ketoacid (KA) and hydroxyacid (HA) analogues of EAA are strong acids. Thus, to prevent acidemia in the patient, the KA and HA are given as the calcium salt.

This not only gives added calcium to the patient but also provides an alkaline load, which, in itself, may slow the rate of progression of CKD.

KA/EAA SVLPD (Supplemented Very Low Protein Diet) (3)

Currently CKD patients are often prescribed only one tablet providing ~667 mg of KA/HA/EAA per 5 kg BW/day.

This is much less than originally developed or studied, and it is not clear that it has the same nutritional and metabolic benefits as the original preparation.

Potential Benefits of Ketoacid/EAA Supplemented Low Protein Diets

- Decreases uremic toxins.
- Reduces proteinuria.
- Prevents malnutrition.
- Improves calcium–phosphate metabolism/ hyperparathyroidism.
- Improves insulin sensitivity.
- Improves lipid profile.
- Contributes to a better blood pressure control.
- Will delay the time until dialysis is required to treat uremic symptoms.
- May slow progression of CKD.
- Improves quality of life.

Ketoacid/Hydroxyacid/Essential Amino Acid Supplemented Very Low Protein Diets (SVLPDS) in CKD Patients

Effect of These Diets on Progression of CKD

MDRD Study: KA/EAA (Very Low Protein)Diet vs 0.60 g pro/kg/d (Low Protein)Diet

Table 4. Mean Rate of Decline in the Glomerular Filtration Rate from Base Line to the End of the Study in Study 2.*

DIET	DECLINE IN GLOMERULAR FILTRATION RATE		
	USUAL PRESSURE	LOW PRESSURE	BOTH
	milliliters per minute per year (95% confidence interval)		
Low protein	4.9 (3.8–5.9)	3.9 (3.2–4.7)	4.4 (3.7–5.1)
Very low protein	3.6 (2.8–4.4)	3.5 (2.6–4.5)	3.6 (2.9–4.2)
Both	4.2 (3.6–4.9)	3.7 (3.1–4.3)	4.0 (3.5–4.4)

*The mean rates of decline in the glomerular filtration rate, which were estimated according to the single-slope informative censoring model, did not differ significantly between the diet groups (P = 0.07) or between the blood-pressure groups (P = 0.28).

Klahr et al NEJM 1994;330:877-884

Effect of KA/EAA Diet (KD) vs 0.60 g Protein/Kg/D Diet (LPD) on eGFR and Proteinuria in CKD Patients

	KD (104 Patients)	LPD (103 Patients)	
Renal function			
eGFR (ml/min)			
Baseline	18.0 (15.5 to 20.1)	17.9 (14.3 to 19.3)	0.68
End of study	15.1 (13.2 to 17.4)	10.8 (9.0 to 12.2)	<0.01
Proteinuria (g/d)[a]			
Baseline	0.88 (0.79 to 0.96)	0.88 (0.82 to 0.96)	0.73
End of study	0.78 (0.67 to 0.85)	0.67 (0.57 to 0.81)	0.06

Garneata et al. JASN 2016;27:2164-2176

The effect of a ketoacid essential amino acid diet (KD) vs an 0.60 g protein/kg/day diet (LPD) on developing the composite end point. The composite endpoint was either the initiation of renal replacement therapy or a greater than 50% reduction in the initital estimated glomerular filtration rate (eGFR).

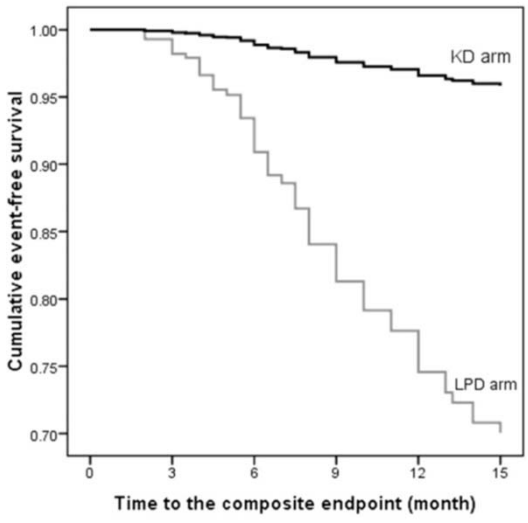


Figure 2. Adjusted event–free survival rates of patients assigned to the KD or the LPD. The probability to reach the end-point was even lower in KD group when adjusted for the other significant predictors of outcome in a Cox proportional hazard model.

Garneata et al. JASN 2016;27:2164-2176

Effect of KA/HA/EAA Supplemented Very Low Protein Diet on Mineral Bone Disease

Phosphorus Estimation Equation ← Protein Intake
(assuming minimal additives)

Dietary phosphorus (milligrams) = 78 + 11.8*(protein intake [grams])

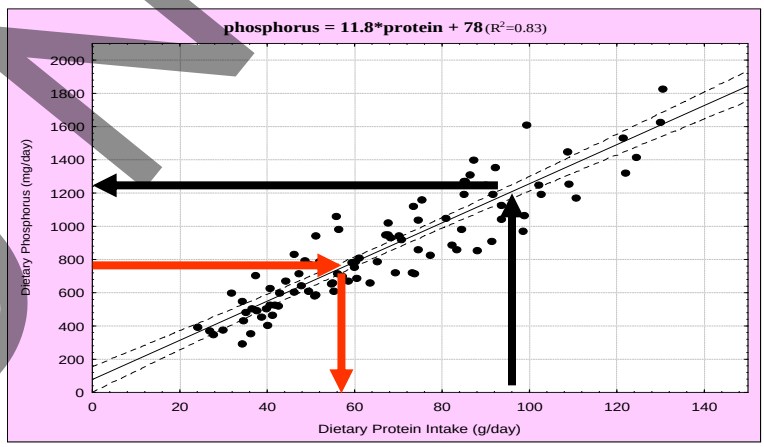


Table 3 | Renal function and cardio-renal risk parameters at baseline and after 6 months in patients at VLPD, LPD, and FD

	VLPD		LPD		FD	
	Baseline	6 months	Baseline	6 months	Baseline	6 months
Body weight, kg	67.5±10.2	67.1±11.0	67.8±13.6	68.0±13.9	65.1±7.3	65.6±7.3
GFR, ml/min/1.73 m^2	17.1±5.5	17.8±6.6	18.2±6.0	17.7±7.0	17.6±5.3	16.1±5.8
Urea, mg/dl	146±39	48±19[a,b]	146±48	145±44	160±37	165±34
Albumin, g/dl	3.9±0.4	3.9±0.4	4.0±0.3	4.0±0.4	3.9±0.4	4.0±0.3
Hemoglobin, g/dl	11.6±0.8	11.5±0.8	11.6±1.2	11.6±0.9	11.5±1.2	11.3±1.0
TC, mg/dl	223±36	169±26[a,b]	216±38	206±36	214±39	217±36
TG, mg/dl	170±40	140±28[a,b]	176±63	167±37	170±38	217±36
CaxP, mg^2/dl^2	41±10	31±8[b,c]	38±6	40±5	38±5	39±5
PTH, pg/ml	175±115	109±73[a,d]	168±114	170±108	190±72	189±82
UK, mEq/day	52±17	51±17	48±13	48±14	48±14	49±15
Proteinuria, g/day	1.34±1.2	0.87±0.8[a]	1.43±1.55	1.29±1.4	0.79±0.9	0.86±0.7

CaxP, calcium-phosphorus product; FD, free diet; GFR, 24-h measured creatinine clearance; LPD, low protein diet; PTH, parathyroid hormone; TC, total cholesterol; TG, triglycerides; UK, urinary potassium excretion; VLPD, very low protein diet.

Bellizi et al. Kidney Int 2007;71:245-251

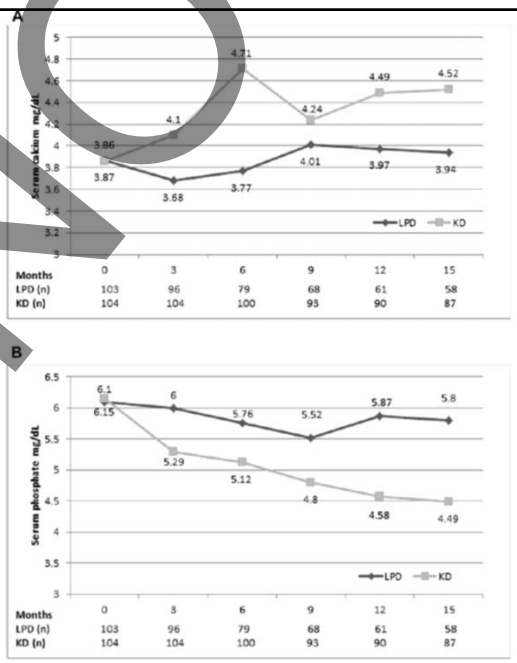
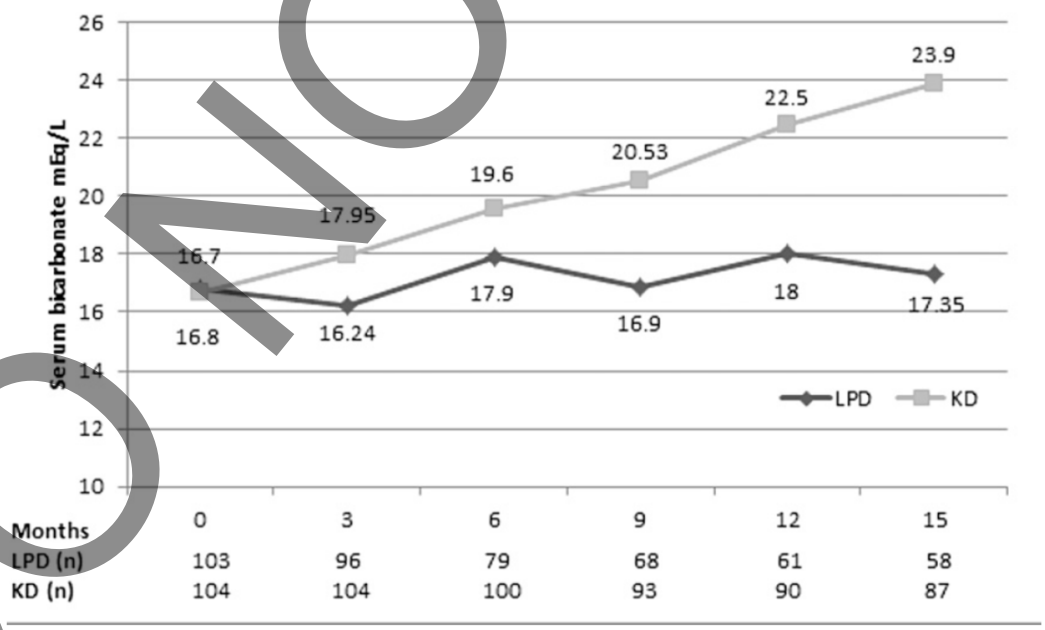


Figure 6. (A) Serum calcium (milligrams per deciliter) and (B) serum phosphates (milligrams per deciliter) during the study. Serum calcium increased and serum phosphates decreased only in KD arm; opposite variations were seen in the LPD group.

Garneata et al. JASN 2016;27:2164-2176

Effect of KA/HA/EAA Supplemented Very Low Protein Diet on Acid Base Status

i. Could alkalization by KA and HA salts account for the particularly effective slowing of GFR loss by this diet?



Garneata et al. JASN 2016;27:2164-2176

Using KA/HA/EAA SVLPDs to Safely Delay Onset of Chronic Dialysis

Using KA/HA/EAA SVLPDs to Safely Delay onset of Chronic Dialysis

1. Non-diabetic CKD patients >70 y/o with GFR (mean of creatinine and urea clearances) of 5-7 (Mean=6) mL/min/1.73m2.
2. Randomized to MHD or CPD (n=56) or KA/EAA supplemented VLPDs (n=56).
3. Median delay in starting chronic dialysis with SVLPDs: 10.7months
4. Eventually, 71% of SVLPD Patients started chronic dialysis 6-20 months later because of fluid overload or hyperkalemia.

Brunori et al. AJKD 2007; 49: 569-580

Per Protocol Analysis: Brunori et al. AJKD 2007; 49: 569-580

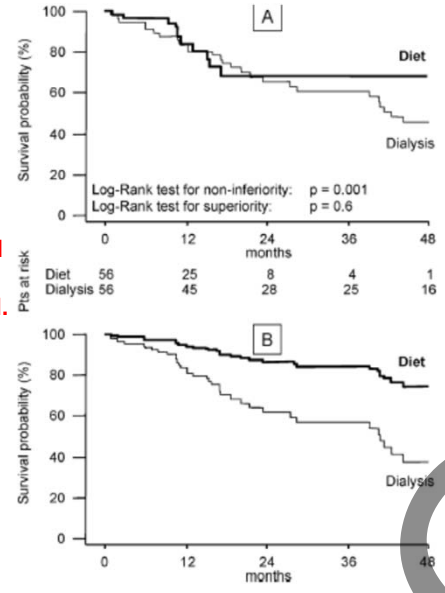


Figure 3. Survival curves as PP analysis: (A) observed survival according to Kaplan and Meier, (B) predicted survival by Cox model after adjustment for unbalance.

21 CKD Patients Fed a Ketoacid/Essential Amino Acid Supplemented Very Low Protein Diet for 30 Days While an AV-Fistula was Created or Matured or PD Was Initiated

Table 3. Biochemistry characteristics of 21 patients with CKD with VLPD supplemented with ketoacids in 30 days

	Tstart (n = 21)	T15 (n = 21)	T30 (n = 21)	p
Serum creatinine (mg/dl)	5.1 ± 1.4	4.8 ± 1.4	4.7 ± 1.8	0.114
Creatinine clearance (ml/min/1.73 m^2)	12.1 ± 3.9	12.0 ± 3.5	12.0 ± 3.6	0.991
Serum urea (mg/dl)[1]	175.3 ± 48.3	123.4 ± 31.9	109.0 ± 25.8	< 0.001
Albumin (g/dl)	3.9 ± 0.4	3.9 ± 0.3	3.9 ± 0.3	0.855
Hemoglobin (g/dl)	10.4 ± 1.6	10.5 ± 1.6	10.3 ± 1.6	0.265
Hematocrit (%)	31.5 ± 4.8	31.7 ± 4.7	31.7 ± 5.0	0.913
Glucose (mg/dl)	105.6 ± 27.4	96.2 ± 21.0	105.5 ± 28.0	0.134
Bicarbonate (mmol/l)	22.0 ± 3.7	23.4 ± 4.9	23.2 ± 3.3	0.365
Total calcium (mg/dl)[2]	8.2 ± 0.7	8.7 ± 0.9	8.5 ± 0.6	0.004
Phosphorus (mg/dl)[3]	4.7 ± 0.6	4.2 ± 0.8	3.9 ± 1.0	0.007
Total cholesterol (mg/dl)	192.4 ± 56.9	186.0 ± 48.4	183.9 ± 41.4	0.603
Triglycerides (mg/dl)	141.2 ± 57.7	152.2 ± 58.3	165.4 ± 76.6	0.065

Values given as x ± SD. [1]p < 0.001 T15 vs. T0; p = 0.043 T30 vs. T15; [2]p = 0.011 T15 vs. T0; [3]p = 0.008 T15 vs. T0.

Duenhas et al. Clin Nephrology 2013;78:387-393

IMPROVED ADJUSTED SURVIVAL (P=0.002) FOR FIRST TWO YEARS OF CHRONIC DIALYSIS IN 44 PATIENTS TREATED PREDIALYSIS WITH A KA/EAA SUPPLEMENTED VERY LOW PROTEIN DIET

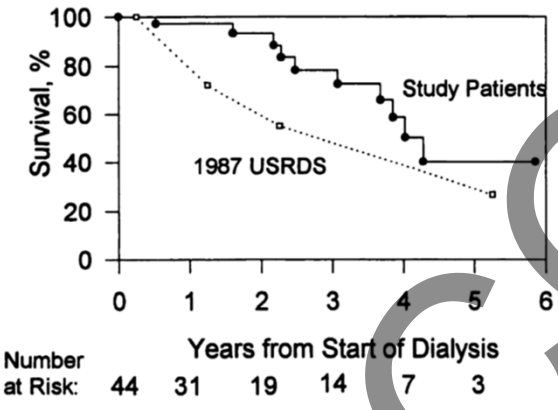


Figure 1. Survival after dialysis among study patients treated with a supplemented low-protein dietary regimen (solid line) and USRDS 1987 incident cohort (dashed lines; conservatively assumed to have no mortality during the first 91 days after dialysis when no national statistics are available).

Coresh et al. JASN 1995;6:1379-1385

(Mortality Adjusted for Age, Sex, Race, Cause of Renal Disease)

Conclusions

The Ketoacid/Hydroxyacid/Essential Amino Acid (KA/EAA) Supplemented Very Low Protein Diet (SVLPD):

1. Probably slows progression of kidney disease in some CKD patients.
2. The effectiveness of this slowing in CKD patients treated with inhibitors of the RAS system and receiving urinary alkalizing treatment is unclear.
3. The diet is nutritionally adequate at least when patients ingest at least 0.30 g protein/kg/day and 0.28 g KA/EAA/kg/day
4. This treatment does reduce accumulation of toxic chemicals and therefore will enable many advanced patients to safely delay starting renal replacement therapy.

END