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Is There a Role for Ketoacid Supplements in the Management of CKD?

Anuja P. Shah, MD,¹ Kamyar Kalantar-Zadeh, MD, PhD,² and Joel D. Kopple, MD^{1,3}

Ketoacid (KA) analogues of essential amino acids (EAAs) provide several potential advantages for people with advanced chronic kidney disease (CKD). Because KAs lack the amino group bound to the α carbon of an amino acid, they can be converted to their respective amino acids without providing additional nitrogen. It has been well established that a diet with 0.3 to 0.4 g of protein per kilogram per day that is supplemented with KAs and EAAs reduces the generation of potentially toxic metabolic products, as well as the burden of potassium, phosphorus, and possibly sodium, while still providing calcium. These KA/EAA-supplemented very-low-protein diets (VLPDs) can maintain good nutrition, but the appropriate dose of the KA/EAA supplement has not been established. Thus, a KA/EAA dose-response study for good nutrition clearly is needed. Similarly, the composition of the KA/EAA supplement needs to be reexamined; for example, some KA/EAA preparations contain neither the EAA phenylalanine nor its analogue. Indications concerning when to inaugurate a KA/EAA-supplemented VLPD therapy also are unclear. Evidence strongly suggests that these diets can delay the need for maintenance dialysis therapy, but whether they slow the loss of glomerular filtration rate in patients with CKD is less clear, particularly in this era of more vigorous blood pressure control and use of angiotensin/aldosterone blockade. Some clinicians prescribe KA/EAA supplements for patients with CKD or treated with maintenance dialysis, but with diets that have much higher protein levels than the VLPDs in which these supplements have been studied. More research is needed to examine the effectiveness of KA/EAA supplements with higher protein intakes.

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INDEX WORDS: Renal nutrition; very-low-protein diets; ketoacid/essential amino acid supplement; protein intake; urea; nitrogenous waste product; chronic kidney disease (CKD); disease progression; dialysis; renal replacement therapy (RRT); end-stage renal disease (ESRD).

Management of patients with chronic kidney disease (CKD) requires attention to their altered metabolism and nutritional status, as well as their nutritional needs. Low-protein diets (LPDs) have been recommended for patients with CKD to reduce the accumulation of various toxins (including products of protein and amino acid metabolism), slow the rate of disease progression, and maintain or improve nutritional status.¹ Current clinical practice guidelines for CKD recommend LPDs for non-dialysis-dependent patients with CKD stages 3 to 5.²⁻⁷ However, the quantity and character of the recommended LPDs vary substantially. Ketoacids (KAs) have been used for more than 40 years to supplement LPDs for patients with CKD.⁸⁻¹¹ Many investigators recommend supplemented very-low-protein diets (VLPDs) for these individuals. Such diets are composed of protein of any quality at very low levels (\sim 20-28 g/d [\sim 0.3-0.4 g of protein per kilogram of body weight]) supplemented with a mixture of essential amino acids (EAAs) and KA or hydroxyacid (HA) analogues of 5 other EAAs (at \sim 0.1-0.28 g/kg/d).¹ This perspective reviews the evidence for the use of supplements containing KA and HA analogues and EAAs for the treatment of patients with CKD and evaluates the clinical experience with these supplements, focusing heavily on randomized prospective controlled trials of these preparations. We also

suggest the most likely beneficial uses and potential limitations of these supplements for patients with CKD and propose potentially fruitful areas for future research.

BIOCHEMISTRY OF KA AND HA ANALOGUES

For most EAAs, the first step in degradation is transamination, which involves removal of the amino group (NH_2) bound to the α carbon and its replacement by a keto or hydroxy group.^{12,13} The KA formed by transamination can be degraded further by oxidation (see biochemical schema in Fig 1). Conversely, KA or HA analogues of the EAAs, except for lysine or threonine, can be transaminated to form the respective EAA.¹³ Thus, when a person consumes KA or HA

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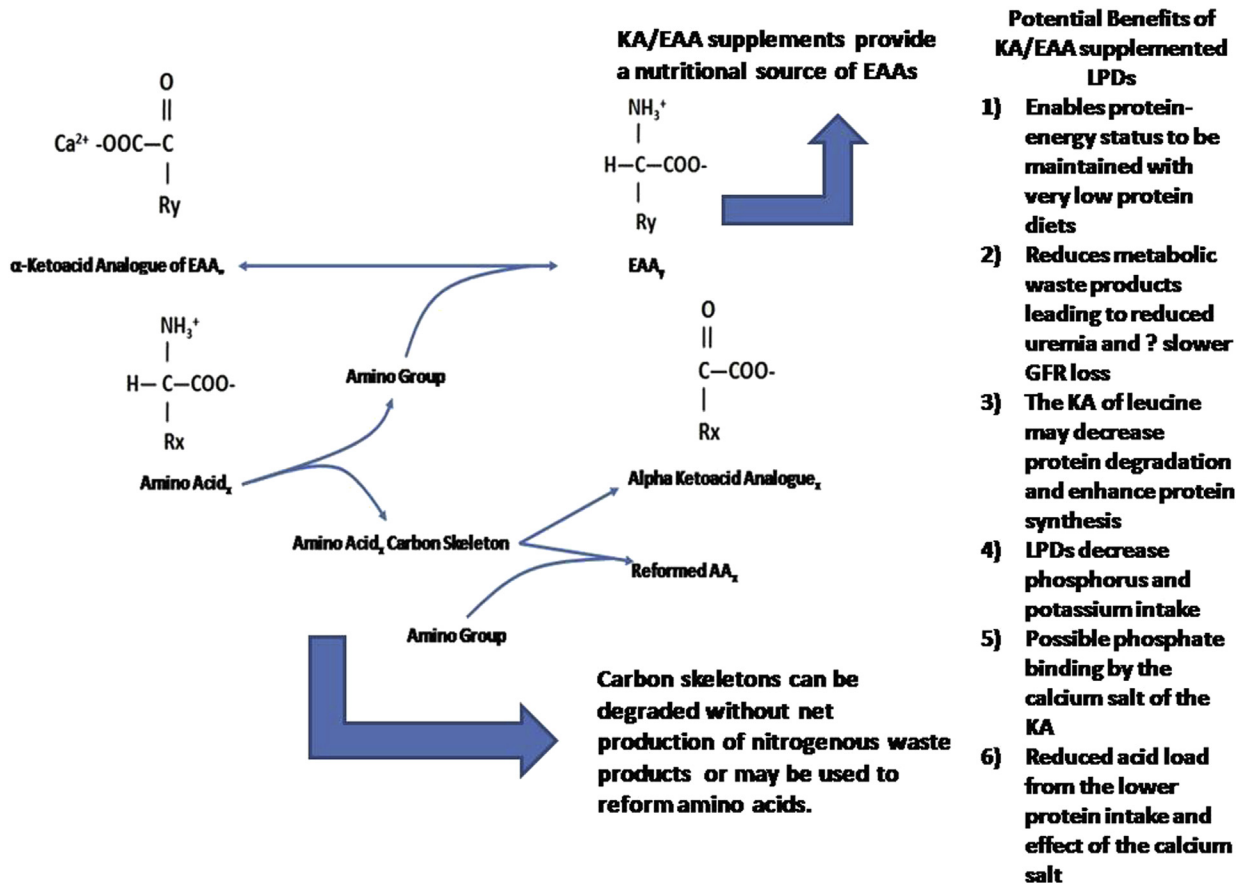


Figure 1. Reversible transamination of a ketoacid (KA) analogue of an amino acid (AA) and an AA. The R denotes the side chain of the AA, and the subscripts (x) and (y) refer to different AAs or KAs. Transamination is catalyzed by aminotransferase enzymes (ie, transaminases). During this process, there 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.

analogues of EAAs, some will be transaminated, increasing the respective EAA. Transamination of most KA and HA analogues of EAAs would be expected to be concentration dependent, and EAA concentrations increase after the administration of their respective KAs.¹⁴⁻¹⁶ This process uses circulating amino groups, thus preventing their incorporation into urea or other potentially toxic nitrogenous waste products. Transamination of KA or HA analogues to synthesize the respective EAA would occur in abundance only if significant amounts of the KA or HA analogue were available. Conversely, with a surfeit of the EAA, the enzyme kinetics of mass action would appear to favor degradation of the KA or HA rather than formation of new EAAs.^{17,18}

COMPOSITION OF KA/EAA SUPPLEMENTS

Although different mixtures of KA and HA analogues and EAAs (referred to hereafter as KA/EAA supplements) have been used, most supplements

contain 4 KA analogues (of the EAAs valine, leucine, isoleucine, and phenylalanine), the HA analogue of methionine, and 4 EAAs (tryptophan, histidine, threonine, and lysine). The α carbon of threonine and lysine cannot be reversibly transaminated and therefore KA or HA analogues of these 2 EAAs are not used.¹³ Because synthesis rates of tyrosine from its sole metabolic precursor, phenylalanine, are impaired in advanced CKD,¹⁹ KA supplements also may contain tyrosine. A urea cycle amino acid such as ornithine also may be added. KA and HA analogues constitute rather strong acids, so KAs are given as salts (generally calcium salts). Table 1 shows typical KA/EAA supplement contents; Table 2 lists potential benefits and risks reported with KA/EAA supplements.

NUTRITIONAL VALUE OF KA ANALOGUES

Initially, it was thought that substantial quantities of urea are hydrolyzed in patients with kidney failure and the amino groups released from urea could

Table 1. Reported Content of Typical Ketoacid/Hydroxyacid/Essential Amino Supplement Preparations

Component No.	Preparation 1		Preparation 2		Preparation 3	
	Component Name	mg/pill	Component Name	mg/pill	Component Name	mg/pill
1	Ca (RS)-3-methyl-2-oxovaleric acid (ketoisoleucine)	67	Ketoisoleucine	76	Ca ketoisoleucine	67
2	Ca 4-methyl-2-oxovaleric acid (ketoleucine)	101	Ketoleucine	97	Ca ketoleucine	101
3	Ca 2-oxo-3-phenylpropionic acid (ketophenylalanine) ^a	68	—	—	Ca phenylpyruvate	68
4	Ca 3-methyl-2-oxobutyric acid (ketovaline)	86	Ketovaline	68	Ca ketovaline	86
5	Ca (RS)-2-hydroxy-4-methylthio-butyric acid (hydroxymethionine)	59	Hydroxymethionine	26	Ca hydroxymethionine	59
6	L-Lysine acetate	105	L-Lysine	129	L-Lysine acetate	105
7	L-Threonine	53	L-Threonine	75	L-Threonine	53
8	L-Tryptophan	23	—	—	—	—
9	L-Histidine	38	L-Histidine	26	L-Histidine	38
10	L-Tyrosine ^b	30	L-Tyrosine ^b	152	L-Tyrosine ^b	30
11	—	—	L-Ornithine ^c	118	—	—
12	Ca	50	Ca	3.4	—	—

Abbreviations: Ca, calcium; RS, racemic mixture of both R and S stereoisomers.

^aPhenylalanine or its ketoacid analogue is not present in all supplement preparations.

^bSemi-essential amino acid.

^cUrea cycle amino acid.

aminate KA analogues, thereby forming new EAAs, as well as nonessential amino acids.²⁰⁻²² Subsequent evidence has indicated that only small amounts of urea can be reused for amino acid synthesis. Hence, reduction in net urea generation (ie, urea appearance) with LPDs or EAA- or KA/EAA-supplemented VLPDs is due more to decreased amino acid degradation and reduced urea synthesis than to reuse of amino groups released from hydrolyzed urea.²³⁻²⁵ The use of KA analogues to form EAAs has been shown particularly well in studies in which KA analogues were used as supplements to VLPDs or amino acid diets for patients with CKD, and neutral or positive nitrogen balance was maintained.^{24,26-30}

The anticatabolic or anabolic actions of KA/EAA supplements are still incompletely understood. KA/EAA supplements commonly contain substantial amounts of 4-methyl-2-oxovaleric acid, the KA analogue of leucine (ketoleucine),³¹ which may suppress protein degradation.³² In contrast, leucine may increase protein synthesis in muscle; hence, both leucine and ketoleucine and possibly also KA/EAA supplements may promote net protein anabolism and suppress urea formation.^{29,33-36} The mechanisms for these possible anabolic effects are not clear, but in a rat model of CKD, when animals are fed KA/EAA-supplemented VLPDs, they show evidence of suppression of apoptotic and ubiquitin pathways in muscle, with increased protein synthesis and inhibited protein degradation.³⁷

EFFECTS OF A SUPPLEMENTED VLPD ON PROGRESSION OF CKD AND NEED FOR RENAL REPLACEMENT THERAPY

The most important reported benefits of the supplemented VLPDs include retarding both the progression of CKD and the initiation of renal replacement therapy. A 1975 report by Walser²⁶ demonstrating that KA/EAA-supplemented VLPDs appear to slow the progression of CKD motivated many investigators to carry out clinical trials concerning this phenomenon.^{8,29,31,38-42} Walser's²⁶ observation was confirmed by some of these trials, and the National Institutes of Health therefore funded the Modification of Diet in Renal Disease (MDRD) Study. This study is the largest randomized prospective trial to date designed to assess whether LPDs and low-phosphorus diets could retard CKD progression. In Study B of this trial, 255 patients with a measured glomerular filtration rate (GFR) of 13 to 24 mL/min/1.73 m² were assigned randomly to an LPD (0.58 g/kg/d) or VLPD (0.3 g/kg/d) supplemented with 0.28 g/kg/d of KA/EAA.⁴³ The trial findings suggested a slower rate of GFR loss with the supplemented VLPD compared to the LPD; however, this difference was not statistically significant ($P = 0.067$).

Several factors may have inadvertently prejudiced the MDRD Study results against finding a difference in GFR loss between these 2 diets. First, the 2.2-year

Table 2. Potential Benefits and Risks Reported for KA/EAA-Supplemented Low- or Very-Low-Protein Diets

Benefit/Risk	Supporting Evidence
Decreases uremic toxins	Shown in multiple studies; reducing protein intake decreases azotemia and waste products of protein metabolism ^{39,66}
Prevents protein-energy wasting	In randomized studies, these diets have been shown to maintain nutritional status; body weight may decrease but this may be due to inadequate energy intake, which usually is preventable. Treatment with KA/EAA SVLPDs requires careful attention to nutrient intake to ensure adequacy ^{48,66,68}
Slows rate of GFR loss	The MDRD Study (the largest randomized trial to date) did not demonstrate a clear benefit; other smaller trials show mixed data with regard to slowing progression ^{43,48,49}
Delays the need for RRT	Meta-analyses of randomized trials consistently indicate a significant delay in the start of maintenance dialysis in patients receiving LPDs and particularly KA/EAA SVLPDs ^{63,65}
Reduces proteinuria	Common finding with LPDs. SVLPDs have not been studied extensively in combination with RAAS inhibition and may add a modest additional reduction ^{53,54}
Improves altered mineral metabolism	Many studies show a decrease in urine phosphorus and serum PTH levels, which may be due to the lower phosphorus intake, increased calcium intake, and decreased bioavailability of phosphate in the vegetarian diets often prescribed in SVLPDs ^{50,99,100}
Prevents or decreases metabolic acidemia	Lower protein diets provide a lower acid load. Vegetarian diets also have been shown to have an alkalinizing effect. ^{80,100} Calcium salts of KAs or hydroxyacid provide additional alkali
Improves quality of life	Has not been extensively studied in non-dialysis-dependent CKD
Increases insulin sensitivity	Small metabolic studies describe this finding ⁸⁸
Improves BP control	Only been shown in 1 randomized trial ⁷⁰ ; other studies do not report a consistently lower BP for SVLPDs
Improves lipid profile	Data are inconsistent across multiple randomized trials. Clinical effects of these changes also are incompletely understood
Improves sensitivity to ESAs	Not been extensively studied, but has been described in 1 randomized prospective trial ⁷⁰
Has a potential economic benefit	KA/EAA SVLPDs appear to often delay the need for maintenance dialysis; also may delay dialysis treatment until creation/maturation of dialysis access grafts, thereby avoiding the need for temporary vascular access catheters or peritoneal dialysis catheters. The safe delay of dialysis treatment with SVLPDs may avoid hospital admissions related to urgent need for a dialysis access and the cost of in-hospital dialysis treatment. KA/EAA SVLPDs are costly and often require intensive physician management of patients to ensure adherence to the diets and adequate nutrient intake ⁶⁴
Increased risk for death	Described in a retrospective analysis of MDRD Study patients in which patients were maintained on the interventional diet for an average of only 2.2 years of the 10-year follow-up period. Three nonrandomized clinical studies have not confirmed an increased mortality rate with KA/EAA SVLPDs ⁵⁹
Difficulty with adherence and tolerance	Adherence to KA/EAA SVLPDs reported to be difficult for many CKD patients. Hypercalcemia occasionally has been reported ^{92,98}

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; ESAs, erythropoiesis-stimulating agents; GFR, glomerular filtration rate; KA/EAA, ketoacid/essential amino acid; LPDs, low-protein diets; MDRD, Modification of Diet in Renal Disease; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RRT, renal replacement therapy; SVLPDs, supplemented very-low-protein diets.

Based on Aparicio et al⁶⁹ and Teplan.¹⁰¹

mean follow-up may have been inadequate to fully assess the effects of these diets on GFR loss.⁴⁴ Second, ~23% (59 of 255) of the MDRD Study B patients had polycystic kidney disease,⁴⁵ which is a genetic nonglomerular disease that may be particularly resistant to dietary therapy. Third, to reduce the possibility of inadequate tryptophan intake, tryptophan content of the KA/EAA supplement was increased.⁴⁶ The tryptophan metabolite indoxyl sulfate appears to be nephrotoxic and may increase the rate of CKD progression.⁴⁷ The MDRD feasibility study, in which additional tryptophan was not added, showed that GFR loss in the KA-treated group was significantly slower than in the EAA-supplemented

VLPD group ($P < 0.01$), though not compared to the 0.6-g/kg/d diet group ($P = 0.15$).

Since the MDRD Study, smaller randomized clinical trials of KA/EAA-supplemented LPDs or VLPDs usually have reported various benefits, often including slowing of the rate of GFR loss (Table 3).^{39,42,48-52} Teplan et al,^{53,54} in randomized studies that prescribed LPDs providing protein of 0.6 g/kg/d with or without KA/EAA supplements, showed lower 24-hour urine protein excretion and slower decline in estimated GFR (eGFR) in the KA/EAA-supplemented groups. Mircescu et al⁵⁰ conducted a randomized prospective trial in 53 patients with eGFRs < 30 mL/min/1.73 m² and demonstrated that

at 48 weeks, just 4% of patients in the supplemented VLPD group required renal replacement therapy compared to 27% of the LPD patients (moreover, eGFR decreased significantly in only the LPD group). Prakash et al⁴⁹ randomly assigned 34 patients to diets providing 35 kcal/kg/d and either very low protein (0.3 g/kg/d) supplemented with KA/EAA tablets or low protein (0.6 g/kg/d) plus placebo. GFR, as measured by technetium diethylenetriaminepentaacetic acid, did not change significantly in the supplemented VLPD patients (28.1 and 27.6 mL/min/1.73 m² at baseline and study end, respectively), but decreased significantly in the LPD group (from 28.6 to 22.5 mL/min/1.73 m² [$P < 0.02$]). However, Malvy et al,⁴⁸ following up 50 patients as their eGFRs declined from <20 to <5 mL/min/1.73 m² (or until they required renal replacement therapy), found no difference in rates of loss of eGFR in those randomly assigned to the supplemented VLPD versus the LPD.

Several meta-analyses have indicated that LPDs and supplemented VLPDs can significantly delay the start of maintenance dialysis therapy.⁵⁵⁻⁵⁷ In contrast, one meta-analysis that examined the effect of LPDs and supplemented VLPDs on the rate of GFR decline determined that reduction in GFR loss with these diets averaged only 0.53 mL/min/1.73 m² per year ($P < 0.05$).⁵⁸ Many studies in these meta-analyses examined LPDs (~ 0.6 g/kg/d) without KA/EAA supplements, which may have attenuated the results. This modest effect on progression also may reflect poor dietary adherence in many of these studies. No study has tested the effect of LPDs or supplemented VLPDs on progression only in patients who were demonstrated to adhere to their dietary prescription. Such a study would be very difficult, if not impossible, to conduct because patients who adhere strongly to dietary prescriptions probably are more likely to follow other medical recommendations and health-enhancing lifestyles. However, the effect of LPDs and KA/EAA-supplemented VLPDs on delaying the need for renal replacement therapy is much better established; this effect probably is due to reduced generation of toxic metabolites with these diets, as well as possible slowing of GFR loss. No meta-analysis has compared the degree of delay in postponing renal replacement therapy for patients consuming LPDs versus supplemented VLPDs. However, despite the small difference between LPDs and supplemented VLPDs in providing nitrogen and protein, some studies have reported that supplemented VLPDs more effectively delay loss of GFR and onset of renal replacement therapy (Table 3).

Interestingly, Menon et al⁵⁹ analyzed the 10-year outcomes of MDRD Study patients and found an increased hazard ratio for death (1.92; 95% confidence interval, 1.15-3.20) in the KA/EAA-supplemented

VLPD patients compared with those randomly assigned to the LPD (0.58 g/kg/d). The strength of this analysis is that comparisons were made in patients who were randomly assigned to their dietary therapy; the limitation is that patients were lost to follow-up for a mean of 7.8 years after the study ended, during which time they almost certainly had no access to the KA/EAA supplements. Three other studies have described the same or greater survival after starting maintenance hemodialysis therapy among patients prescribed KA/EAA-supplemented VLPDs compared with those who were not.⁶⁰⁻⁶² However, in each of these studies, patients were not randomly assigned and comparisons were made to historical controls. These latter reports are difficult to interpret because patients who agree to consume KA/EAA-supplemented VLPDs may be more highly motivated to pursue all aspects of better medical care.

Brunori et al⁶³ investigated delaying dialysis therapy with supplemented VLPDs using another strategy: they randomly assigned elderly patients with stage 5 CKD to either this diet or dialysis treatment. The diet group displayed a median 10.7-month delay in starting dialysis therapy without an increase in mortality and without a decrease in body mass index or serum albumin level. Moreover, the hazard ratio for hospitalization was increased in the dialysis group ($P < 0.01$), with 41% of hospitalizations related to dialysis access. In another study, emergent access creation decreased with a supplemented VLPD, suggesting that this morbidity and cost could be avoided or temporarily delayed with dietary therapy.^{64,65} One-year survival was 83.7% in the dialysis group and 87.3% in the diet group, though this did not represent a statistically significant difference ($P = 0.06$). Taken together, these observations suggest that supplemented VLPDs may be useful for delaying the need for dialysis therapy in patients with stage 5 CKD.

OTHER POTENTIAL CLINICAL BENEFITS OF KA-SUPPLEMENTED DIETS

Protein-Energy Status

Metabolic balance studies indicate that KA/EAA-supplemented VLPDs maintain nitrogen balance and serum protein levels. These studies generally provided KA/EAA supplementation of ~ 0.28 g/kg/d with protein at a level of ~ 0.30 g/kg/d.^{9,42,66,71} The MDRD Study maintained good nutrition with similar KA/EAA supplementation.^{67,68} Currently, KA/EAA levels of ~ 100 to 126 mg/kg/d often are prescribed^{61,69}; this reduces the cost of treatment and should facilitate patient acceptance. It is not clear whether most patients with CKD receiving KA/EAA supplementation at 100 to 126 mg/kg/d will maintain protein balance with a protein intake of only

Table 3. Randomized Trials Using KA/EAA Supplementation

Study	Description	Prescribed Diets	Daily KA/EAA Dose	F/U Period	Protein-Energy Status	Effect on Need for RRT	Effect on Kidney	Mineral Metabolism	Lipid Changes	Other Differences	Comments
Bernhard ⁸⁶ (2001)	12 pts w/ nonprogressive kidney disease, mean eGFR 30 mL/min/1.73 m ²	LPD vs SLPD	0.153 g/kg/d (not inc Ca [3.8 mg/100 g])	3 mo	No diff in serum albumin, bicarbonate, & protein between groups; no change in BMI	NR	NR	NR	NR	No metabolic benefit when Leu turnover measured	All pts given Ca carbonate & sodium bicarbonate
Prakash ⁴⁹ (2004)	34 pts w/ CL _{cr} >20-<50 mL/min	LPD vs SVLPD	0.0917 g/kg/d (0.100 g/kg/d inc Ca)	9 mo	On LPD & SVLPD, no change in serum albumin or BMI; on LPD, midarm circumference declined (<i>P</i> = 0.048)	NR	mGFR by ^{99m} Tc-DTPA declined in only LPD group (<i>P</i> = 0.015)	NR	NR	On LPD & SVLPD, no diff in Hb	3-d food diaries to assess adherence; 24-h urine for urea not collected; placebo used in place of supplement in LPD group
Di Iorio ⁹⁹ (2012)	32 pts w/ mCL _{cr} >20-<55 mL/min	LPD vs SVLPD	0.121 g/kg/d (inc Ca)	Randomized crossover w/ 1-wk periods	No diff in serum albumin	NR	No diff in eCL _{cr}	FGF-23 (<i>P</i> < 0.001) & urinary P (<i>P</i> < 0.008) declined after change to SVLPD	NR		Very short F/U
Teplan ⁵⁴ (2001)	105 pts w/ endogenous CL _{cr} 22-36 mL/min/1.73 m ² , Hb < 11.5 g/dL	SLPD + rHuEPO vs LPD + rHuEPO vs LPD	0.0917 g/kg/d (0.100 g/kg/d inc Ca)	≤36 mo	On SLPD + rHuEPO, slightly higher serum albumin (<i>P</i> < 0.02) & slight comparative increase in BMI (<i>P</i> < 0.05); also, serum & urine urea declined & lower than other groups (<i>P</i> < 0.05)	NR	On SLPD + rHuEPO, slower decline in mGFR by inulin clearance, & lower proteinuria	NR	On SLPD + rHuEPO, lower TG & higher LDL than either other group (<i>P</i> < 0.01)		Did not use a VLPD; pts seen every 4 wk

(Continued)

Table 3 (Cont'd). Randomized Trials Using KA/EAA Supplementation

Study	Description	Prescribed Diets	Daily KA/EAA Dose	F/U Period	Protein-Energy Status	Effect on Need for RRT	Effect on Kidney	Mineral Metabolism	Lipid Changes	Other Differences	Comments
Teplan ⁵³ (2003)	186 pts w/ mCL _{cr} 22-36 mL/min	SLPD + rHuEPO vs LPD + rHuEPO vs LPD	0.0917 g/kg/d (0.100 g/kg/d inc Ca)	36 mo	On SLPD + rHuEPO, serum urea declined ($P < 0.025$) & higher increase in Leu & serum albumin ($P < 0.01$) vs other groups	NR	On SLPD + rHuEPO, proteinuria declined ($P < 0.01$) & smaller decline in inulin clearance ($P < 0.01$)	NR	On SLPD + rHuEPO, decline in chol ($P < 0.05$), LDL ($P < 0.05$), & TG ($P < 0.01$) vs other groups	No diff in BP	
Teplan ⁵² (2001)	38 pts w/ CL _{cr} 20-36 mL/min	LPD vs SLPD	0.917 g/kg/d (0.1 g/kg/d inc Ca)	12 mo	On SLPD, serum albumin increased ($P < 0.01$) & urea declined more ($P < 0.025$)	NR	On SLPD, proteinuria declined ($P < 0.01$); on LPD, greater eGFR decline ($P < 0.01$)	NR	On SLPD, greater decline in chol & LDL ($P < 0.02$)	In SLPD group, serum level of free radicals declined	
Mircescu ⁵⁰ (2007)	53 pts w/ eGFR < 30 mL/min/1.73 m ²	LPD vs SVLPD (vegetable protein)	0.116 g/kg/d KA/EAA (0.126 g/kg/d inc Ca)	48 wk	Decline in serum urea only on SVLPD; no change in serum albumin in either group	4% vs 27% of pts needed RRT on SVLPD vs LPD	On SVLPD, eGFR stable; on LPD, eGFR declined; no change in proteinuria in either group	Serum bicarbonate & Ca increased, P declined only on SVLPD	No change in chol in either group	No change in BP in either group	Open label; used eGFR
Di Iorio ⁷⁰ (2003)	20 pts w/ CL _{cr} < 25 mL/min/1.73 m ²	LPD vs SVLPD (vegetable protein); achieved protein intake: 0.79 vs 0.5 g/kg/d	0.121 g/kg/d (inc Ca)	24 mo or until CL _{cr} < 7 mL/min/1.73 m ² or needed RRT	Albumin & body weight stable in both groups	On LPD, 7/10 pts started RRT by 24 mo; on SVLPD, 8/10 pts made it to 24 mo w/o RRT	On SVLPD, slower decline in 24-h urine mCL _{cr}	On SVLPD, iPTH declined ($P < 0.001$) & urinary P, SUN, & UUN lower at 18 mo ($P < 0.05$); also, serum P declined ($P < 0.001$), but no diff vs LPD at 18 mo	On SVLPD, TG & chol declined ($P < 0.01$) & lower than LPD group at 18 mo ($P < 0.05$)	MAP declined only on SVLPD ($P < 0.01$)	On SVLPD, ESA needed to achieve Hb target declined until 18 mo ($P < 0.05$)

(Continued)

Table 3 (Cont'd). Randomized Trials Using KA/EAA Supplementation

Study	Description	Prescribed Diets	Daily KA/EAA Dose	F/U Period	Protein-Energy Status	Effect on Need for RRT	Effect on Kidney	Mineral Metabolism	Lipid Changes	Other Differences	Comments
Feiten ⁷² (2005)	24 pts w/ eCL _{cr} < 25 mL/min/1.73 m ²	LPD vs SVLPD (vegetable protein)	KA/EAA of 0.116 g/kg/d (0.126 g/kg/d inc Ca)	4 mo	No change in BMI; on SVLPD, serum urea declined; no diff in serum albumin change between groups	Not assessed	On LPD, eCL _{cr} declined from 17.8 to 16.1; on SVLPD, no change	iPTH increased only on LPD (P = 0.01); urinary P declined on SVLPD (P = 0.001); bicarbonate declined on SVLPD vs LPD (P = 0.03)	No diff in chol or TG in either group		Short-term study; low numbers
Menon ⁵⁹ (2009) ^a	255 pts w/ mGFR 13-24 mL/min/1.73 m ²	LPD (0.58 g/kg/d protein) vs SVLPD (0.28 g/kg/d protein)	KA/EAA of 0.204 g/kg/d (0.28 g/kg/d inc Ca)	10 y; mean of 7.8 y after MDRD Study ended	No diff in serum albumin, energy intake, or anthropometric measures during F/U	No diff in risk of kidney failure	GFR not measured after end of MDRD Study	NR	NR	On SVLPD, higher risk of death; no diff in MAP	Diet of pts during last 7.8 y of F/U unknown
Klahr ⁴³ (1994) ^b	255 pts w/ mGFR 13-24 mL/min/1.73 m ²	LPD (0.58 g/kg/d protein) vs SVLPD (0.28 g/kg/d protein)	KA/EAA of 0.204 g/kg/d (0.28 g/kg/d inc Ca)	Mean of 27 mo	Serum albumin increased in both groups & did not differ between groups	No diff in rate of death or dialysis	On SVLPD, marginally slower GFR decline (P = 0.067)	Urinary P declined in both groups but no statistically significant diff in levels ¹⁰²	NR		Very good adherence to diet; iothalamate mGFRs
Malvy ⁴⁸ (1999)	50 pts w/ eGFR < 19 mL/min/1.73 m ²	LPD (0.65 g/kg/d protein) vs SVLPD	0.17 g/kg/d (inc Ca)	≥3 mo; time to eGFR 5 mL/min/1.73 m ² or need for RRT	On SVLPD, LBM, fat mass declined (P < 0.01), as did weight (P < .02); no changes in albumin; on SVLPD, urea lower at 3 mo (P < 0.001)	No diff in start of HD or time to lower eGFR	No diff in renal survival	On SVLPD, higher mean Ca, & lower mean P, ALP, & iPTH at study end (all P < 0.05)	No change in TG or chol in either group	Ca 1-4 g/d added to both diets depending on serum Ca levels	Dietician recall to assess adherence; initial P values not identical between groups; diff in P change NR

(Continued)

Table 3 (Cont'd). Randomized Trials Using KA/EAA Supplementation

Study	Description	Prescribed Diets	Daily KA/EAA Dose	F/U Period	Protein-Energy Status	Effect on Need for RRT	Effect on Kidney	Mineral Metabolism	Lipid Changes	Other Differences	Comments
Lindenau ⁴⁰ (1990)	40 pts w/ CL_{cr} < 15 mL/min	18 pts on LPD w/ 750 mg Ca supplementation vs 22 pts on SVLPD (0.4 g/kg protein)	NR	12 mo	NR	NR	NR	On SVLPD, serum P declined ($P < 0.05$) & improved markers of bone breakdown in bone biopsies	NR		Adherence NR; Ca supplementation given in LPD group
Brunori ⁶³ (2007)	56 elderly CKD5 pts; eGFR 5-7 mL/min/1.73 m ²	SVLPD (vegan) vs dialysis w/o protein restriction	0.121 g/kg/d (inc Ca)	26.5 mo median F/U	No diff in serum albumin & BMI after SVLPD from randomization to before dialysis	No increased mortality, w/ median 10.7-mo dialysis delay	No change in proteinuria	NR	Chol declined w/ SVLPD from randomization to before dialysis ($P = 0.04$)	More hospitalizations in dialysis group	Unblinded study; bicarbonate & P binders given as needed
Jiang ⁹⁶ (2009)	60 PD pts	LPD (0.6-0.8 g/kg/d protein) vs SLPD (0.6-0.8 g/kg/d protein) vs 1-1.2 g/kg/d protein	0.12 g/kg/d (NR if inc Ca)	12 mo	No change in nutritional status; BMI, LBM, serum albumin went up in all 3 groups	Not assessed	On SLPD, eGFR stable	iPTH lower in SLPD group vs high protein group at 1 y ($P < 0.05$)	NR		Used eGFR; degree of adherence assessed

Note: Studies are arranged by GFR range of participants.

Abbreviations and definitions: ^{99m}Tc-DTPA, 99m-technetium diethylenetriaminepentaacetic acid plasma sample method; ALP, alkaline phosphatase; BMI, body mass index; BP, blood pressure; Ca, calcium; CDK5, chronic kidney disease stage 5; chol, total cholesterol; diff, difference; EAA, essential amino acid; eCL_{cr} , estimated creatinine clearance; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; F/U, follow-up; Hb, hemoglobin; HD, hemodialysis; inc, including; iPTH, intact parathyroid hormone; KA, ketoacid; LBM, lean body mass; LDL, low-density lipoprotein; Leu, leucine; LPD, low-protein diet with protein of 0.6 g/kg/d unless otherwise stated; MAP, mean arterial pressure; mCL_{cr} , measured creatinine clearance; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; NR, not reported; P, phosphorus or phosphate; PD, peritoneal dialysis; pts, patients; rHuEPO, recombinant human erythropoietin; RRT, renal replacement therapy; SUN, serum urea nitrogen; SVLPD, KA/EAA-supplemented diet with protein of 0.3 g/kg/d unless otherwise stated; TG, triglycerides; UUN, urine urea nitrogen; VLPD, very-low-protein diet; w/, with; w/o, without.

^aReports are derived from the same clinical trial (MDRD Study).

0.30 g/kg/d. To the authors' knowledge, there are no dose-response studies that have demonstrated nutritional adequacy of these lower KA/EAA intakes. Although many randomized prospective trials indicate nutritional adequacy with KA/EAA supplementation at 100 to 126 mg/kg/d, this may be due to many outpatients with CKD ingesting protein levels closer to 0.4 or even >0.5 g/kg/d.^{67,70,71}

The MDRD Study indicated that both the supplemented VLPD and the LPD were associated with decreased body weight, which may reflect inadequate attention to patients' energy intake; urine creatinine excretion also decreased.⁶⁸ However, serum albumin levels, which at the onset of study averaged 4.05 g/dL and 4.08 g/dL in the LPD and supplemented VLPD groups, respectively, increased during its course.⁶⁸ Prakash et al⁴⁹ found no change in body mass index or serum albumin levels in patients randomly assigned to a supplemented VLPD or a LPD plus placebo and followed up for 9 months; midarm circumference decreased in only the latter group. Feiten et al randomly assigned 24 patients with creatinine clearances < 25 mL/min to either an LPD or a supplemented VLPD with follow-up for 4 months.⁷² They demonstrated stable nutritional status with no change in body mass index with both diets. Malvy et al⁴⁸ found a slight decrease in lean body mass and fat mass in patients with CKD randomly assigned to a supplemented VLPD versus an LPD ($P < 0.02$), but serum albumin levels remained stable. Mircescu et al⁵⁰ reported that nutritional status was well maintained in patients with CKD receiving a supplemented VLPD and initiation of maintenance dialysis treatment was delayed.^{60,61} Although many of these randomized studies are relatively small with variable follow-up times (as indicated in Table 3), there is a consistent trend in the lack of adverse nutritional effects and potential nutritional benefits with KA/EAA-supplemented LPDs or VLPDs.

Uremic Toxicity

Consistent with the aforementioned findings, both metabolic balance studies and clinical trials have demonstrated repeatedly that KA/EAA-supplemented VLPDs that provide ~0.3 to 0.4 g/d of protein of miscellaneous biological value generate lesser amounts of metabolic products of nitrogen metabolism.^{8,39,48,50} The reduced generation of potentially toxic nitrogenous products protects against uremic toxicity in patients with advanced CKD.^{39,43,66,73} KA/EAA supplements provide amino acid or protein equivalents without additional sodium, potassium, or phosphorus intake, which also is advantageous for patients with CKD. In addition, the low-protein foods in supplemented VLPDs usually are low in these minerals.⁷⁴ Studies in 5/6-nephrectomized rats

suggest that the renal hyperfiltration that accompanies CKD may be attenuated with KA/EAA supplements,⁷⁵ an effect also seen with protein restriction,⁷⁶ but not in KA-supplemented high-protein diets.⁷⁷ Further, recent studies using this rat model show that a supplemented LPD, compared to a normal-protein diet, leads to increased expression of the antifibrotic transcription factor KLF15 without a decrease in serum albumin level.^{78,79} These studies suggest a possible mechanism for attenuating the progression of kidney disease with dietary therapy.

Calcium salts of the KAs can provide needed calcium to otherwise low-calcium diets for patients with CKD. Calcium salts of KAs also provide an alkalinizing effect, although this effect is minimal with KA/EAA supplements of only 100 mg/kg/d. The alkalinizing effects of KA salts are augmented by reduced acid generation from low-protein intake and from the vegetarian diets often concurrently prescribed.⁸⁰ Even slight increases in arterial pH to normal or high-normal can improve protein balance and slow progression of CKD.^{81,82} Thus, alkalinizing properties of KA/EAA and reduced acid generation from VLPDs may contribute to both anabolism and slowing of progressive CKD.

Bone-Mineral Metabolism

Some studies suggest that KA/EAA-supplemented VLPDs may improve abnormal bone and bone mineral metabolism in CKD. Several observational studies and randomized prospective trials describe increased serum calcium and decreased serum phosphorus levels with these diets.^{8,31,83-85} Feiten et al⁷² reported decreased urine and serum phosphorus levels in patients with CKD who consumed a KA/EAA-supplemented VLPD compared to an LPD, potentially reflecting the low phosphorus content of the KA/EAA-supplemented VLPD. In addition, the calcium-KA salts from the KA/EAA supplements both increase dietary calcium (eg, ~600-700 mg/d of calcium for a 70-kg person) and may bind to phosphate, thereby decreasing intestinal phosphorus absorption and augmenting the effects of the low dietary phosphorus intake. In some studies, serum parathyroid hormone (PTH) levels also have been reported to decrease with supplemented VLPDs.^{48,85} Lindenau et al⁴⁰ described improvements in bone histology and serum phosphorus levels with KA/EAA-supplemented VLPDs independent of the effects of calcium intake in their study of 18 patients with CKD randomly assigned to either a KA/EAA-supplemented VLPD or a calcium-supplemented LPD. Bernhard et al⁸⁶ observed no difference in serum phosphorus, calcium, bicarbonate, or intact PTH levels with a KA/EAA-supplemented LPD versus a more standard LPD; however, both groups

received calcium carbonate and sodium bicarbonate supplements, which could have masked changes due to the KA/EAA supplement.

Other Potential Benefits

In randomized studies of KA/EAA-supplemented LPDs or VLPDs, Teplan et al⁵²⁻⁵⁴ and Di Iorio et al⁷⁰ demonstrated improved lipid profiles in KA/EAA-treated patients; this has been observed in many nonrandomized trials. Di Iorio et al⁷⁰ observed increased responsiveness to erythropoietin in patients with CKD prescribed a KA/EAA-supplemented VLPD, which was attributed to reduced serum PTH levels with this diet. The low phosphorus and higher calcium content of this diet presumably decreased serum PTH levels. In 38 patients with CKD with creatinine clearances between 20 and 36 mL/min followed up for 12 months, Teplan et al⁵⁴ observed lower serum concentrations of free radicals in those treated with a KA/EAA-supplemented diet with a low protein level (~ 0.6 g/kg/d) compared with those receiving an LPD alone. Heidland et al⁴¹ observed improved insulin sensitivity in patients with CKD after they were changed from EAA- to KA/EAA-supplemented VLPDs. Rigalleau et al^{87,88} also described increased insulin sensitivity, confirmed by insulin clamp studies, after patients with CKD changed from an unrestricted protein diet to KA/EAA-supplemented VLPDs.

KA/EAA- VERSUS EAA-SUPPLEMENTED VLPDS

In the late 1970s, there were reports of patients with CKD treated with VLPDs supplemented with the 9 EAAs rather than KA/EAs.^{89,90} Although this is no longer a common treatment, some of the same benefits described with KA/EAA-supplemented VLPDs were reported with the EAA-supplemented VLPDs,⁹¹ including positive nitrogen balance, reduced generation of nitrogenous waste, decreased potassium and phosphorus intake, slowing of CKD progression, and more normal plasma and muscle intracellular amino acid concentrations.⁹⁰ The few studies that directly compared KA/EAA- and EAA-supplemented VLPDs usually evaluated small numbers of patients and suggested either no differences or possibly modest advantages to the KA/EAA-supplemented VLPD in terms of lower serum urea, phosphorus, and possibly triglyceride levels.^{8,28,41,92,93} Two randomized studies indicated slower GFR loss with the KA/EAA- versus EAA-supplemented VLPD.^{46,94}

KA/EAA SUPPLEMENTS FOR HIGHER PROTEIN DIETS

The optimal and maximal amounts of dietary protein that can be ingested with KA/EAA supplements are not well defined. Although protein levels of ~ 0.3

to 0.4 g/kg/d were prescribed in most initial studies,^{43,70,95} some authorities prescribed protein levels of ~ 0.6 g/kg/d for non-dialysis-dependent patients with CKD.^{53,69} The extent to which the greater EAA load from the higher protein intake will move the equilibrium equation (Fig 1) toward more degradation of the ingested KAs or HAs is not known.

Jiang et al⁹⁶ described more positive nitrogen balance in patients receiving maintenance peritoneal dialysis when a KA/EAA supplement was added to a diet with a protein level of 0.8 g/kg/d. However, these balance studies were conducted in outpatients, and fecal nitrogen was estimated. Jiang et al⁹⁶ also studied 60 patients receiving peritoneal dialysis who were prescribed a diet with a protein level of 0.8 g/kg/d with or without KA/EAA supplements or a high-protein (1.2 g/kg/d) diet for 12 months. Residual kidney function remained stable in the KA/EAA-treated group, and as was observed for non-dialysis-dependent patients with CKD, intact PTH concentration was lowest in the supplemented group.⁹⁶ Zakar⁹⁷ described improved subjective global assessment scores in malnourished patients receiving both PD and a KA-supplemented high-protein diet. Rats fed a high-protein diet demonstrated no histologic evidence of renoprotection when their casein-based diet was supplemented with KAs.⁷⁷ The possible usefulness of KA/EAA supplements with higher protein intakes is intriguing; however, further studies are necessary to confirm these findings and to demonstrate that similarly effective results cannot be obtained with protein supplements or simply from foods with higher protein content.

POTENTIAL LIMITATIONS OF KA/EAA-SUPPLEMENTED DIETS

There are occasional reports of nausea or vomiting with ingestion of KA/EAA supplements, which in some cases may be due to uremia rather than the supplements themselves.³⁹ Occasionally, hypercalcemia is reported, presumably due to intake of calcium salts of the KA analogues or the decrease in serum phosphorus levels.^{92,98} There are no reports of metabolic intolerance to the ketoacid component of KA salts. However, many patients have difficulty accepting and adhering to the KA/EAA-supplemented VLPDs. Also, the amount of labor required by health care workers to prescribe and monitor adherence to these diets and the costs of the KA/EAA supplements can be high.

WHY IS A KA/EAA-SUPPLEMENTED VLPD NOT GENERALLY PRESCRIBED FOR CKD STAGES 3 TO 5?

To our knowledge, there are no systematic studies examining why KA/EAA supplements are not used

more commonly for patients with CKD and why use of such supplements varies widely among and within countries. The following comments are based on medical publications, conversations with nephrologists and other health care workers, and our experiences with these supplements.

One possible factor is that the most prominent study of KA/EAA-supplemented VLPDs, the MDRD Study, failed to clearly show that this dietary intervention slows CKD progression, although at the time it was thought that this was the diet's most important benefit. In addition, some of the hemodynamic changes engendered by VLPDs also occur with improved blood pressure control and use of angiotensin/aldosterone blockade. Moreover, adherence to and satisfaction with dietary modification can be difficult for patients. Furthermore, there is an unfounded concern that supplemented VLPDs may cause protein-energy malnutrition.

In many parts of the world, maintenance dialysis is readily available and, from the perspective of the physician, may be less time consuming and potentially more lucrative than dietary therapy. KA/EAA supplements may not be inexpensive, but they are less expensive than maintenance dialysis therapy. KA/EAA-supplemented VLPDs appear to be used more widely in developing countries where patients with CKD may not have free access to dialysis treatments.

It is our perception that in this modern era of CKD treatment, the most beneficial effect of KA/EAA-supplemented VLPDs may be the reduced burden of uremic toxins. It is unfortunate that the large-scale clinical trials of KA/EAA in the United States were designed to test the effectiveness of these supplements at reducing progression of CKD rather than decreasing uremic toxicity, whereas the latter benefit probably would have been easier to demonstrate.

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