Ketoacid Analogues Supplementation in CKD

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Diet is a key component of care during chronic kidney disease (CKD). In order to reduce the risk of nutritional disorders in very-low protein diets (VLDP), supplementation by nitrogen-free ketoacid analogues (KAs) have been proposed.

Keywords: chronic kidney disease ; low protein diet ; ketoacid analogues ; intestinal microbiota ; dialysis

1. Introduction

End-stage kidney disease (ESKD) is a condition associated with a high mortality and poor quality of life combined with extremely high costs. Using interventions for delaying the need to start a kidney replacement treatment is, therefore, a major challenge. Experimentally, Brenner et al. [1] showed that high protein intake induced marked kidney hypertrophy, which is an increase in glomerular pressure and hyperfiltration that negatively impacts kidney function. Chronic kidney disease (CKD) is characterized by the accumulation of a number of organic solutes called uremic toxins. Many of these uremic toxins are produced by the degradation of dietary amino acids by intestinal microbiota and appears to accelerate CKD progression. Based on these observations, a reduction in protein intake can be expected to preserve renal function and reduce uremic toxicity. The main limitation of this diet is the risk of malnutrition and cachexia.

Different dietary protein regimens have been tested: low–protein diets (LPD, 0.6 g protein/kg/day) or very low–protein diets (VLPD: 0.3–0.4 g protein/kg/day) supplemented with essential amino acids (EAAs) or nitrogen-free ketoacid analogues (KAs). KAs are precursors of corresponding amino acids since they can undergo a transamination, e.g., a chemical reaction that transfers an amino group to a ketoacid to form a new amino acid (**Figure 1**). This pathway is responsible for the deamination of most amino acids. Through this conversion, KAs can be utilized in place of their respective EAAs without providing nitrogen products while re-using available nitrogen already in excess during CKD. If a diet does not provide enough EAAs or calories, then the nitrogen balance can become negative and could partly induce cachexia. Therefore, administration of KAs has been proposed to improve protein status while limiting the nitrogen burden on the body. VLDP + KAs are likely also efficient because the calcium content of KA preparation could allow a better correction of mineral metabolism impairment. Different compositions of KAs and EAAs have been tested, with most of them containing four KAs (of the EAA isoleucine, leucine, phenylalanine, and valine), one hydroxyacid (of the EAA methionine), and four amino acids considered essential in CKD (tryptophan, threonine, histidine, and tyrosine) (**Table 1**).

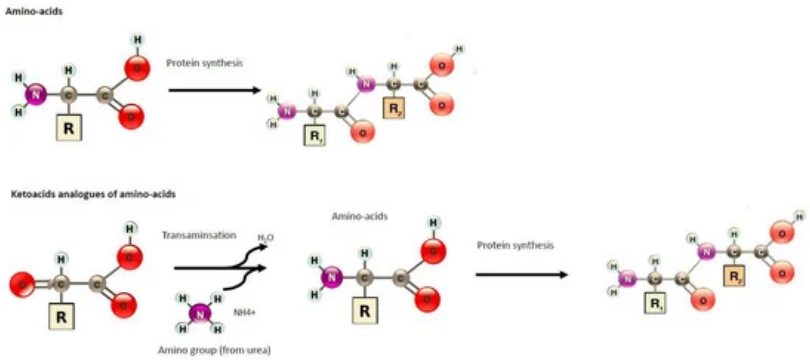

Figure 1. Amino-acid and transamination of ketoacid analogues of amino acids in order to synthesize protein.

Table 1. Ketoacid analogues composition.

Component Name	mg/pill
Ca-Keto-dl-isoleucine	67

Component Name	mg/pill
Ca-Ketoeucine	101
Ca-Ketophénylalanine	68
Ca-Ketovaline	86
Ca-Hydroxy-dl-methionine	59
l-Lysine monoacetate	105
l-Threonine	53
l-Tryptophan	23
l-Histidine	38
l-Tyrosine	30

2. Potential Benefit of Ketoacid Analogues

Do we have evidence in CKD of specific KAs actions on the reduction of kidney disease-associated comorbidity? New emerging studies suggest that restricted VLDP + KAs may improve renal function and nutritional status, while preventing hyperparathyroidism, insulin resistance, and accumulation of uremic retention solutes (URS), as summarized in **Figure 2**. The main concern about the interpretation of the literature is the fact that KAs are not given solely but in association with other EAAs and under LPD/VLPD condition. In particular, we do not know if a supplementation of KA alone without low protein diets has any benefit on metabolic disturbances related to CKD. Few studies [2][3][4][5][6] compared KAs supplementation with the same protein restriction and it is difficult to decipher if “KAs effects” are solely the consequence of a decrease of protein intake or if they act specifically. Another interrogation is the reproducibility of the diet composition in different groups. The composition of fibers, acid load, or sodium is difficult to assess and frequently not specified in dietary surveys, which can influence the results. In order to have a more detailed picture of the effects of KAs during CKD, the main experimental trials and RCTs have been summarized in **Table 2** and **Table 3**.

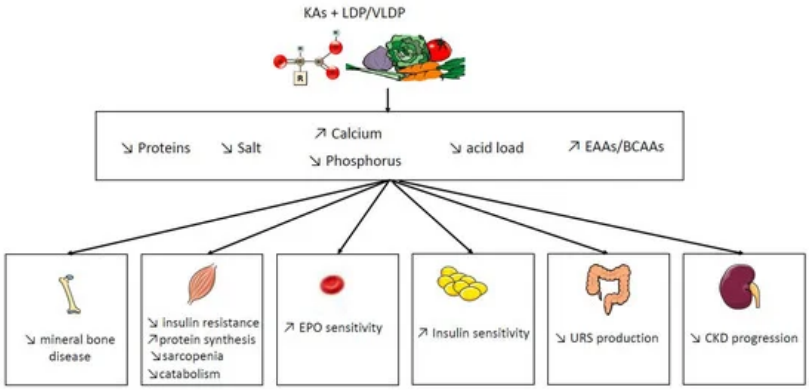

Figure 2. Proven and controversial mechanism of VLDP/LPD + KAs supplementation in CKD Abbreviations: URS: uremic retention solutes, EAAs: essential amino acids, BCAAs: branched-chain amino acids, LPD: low protein diet, VLDP: very low protein diet, GFR: glomerular filtration rate, and KAs: ketoacid analogues.

Table 2. Animal studies that examined the effects of VLPD/LPD supplemented with ketoacid analogues on various endpoints.

Study	Models	Diet Intervention	Follow-Up	Results (LPD vs. VLDP/LPD + KAs)
Wang et al., 2018 [7]	5/6 nephrectomy rats	NPD: 22% protein vs. LPD: 6% protein vs. LPD + KAs: 5% protein plus 1% KA	24 weeks	↓ muscle atrophy ↑ activities of mitochondrial electron transport chain complexes and mitochondrial respiration, ↓ muscle oxidative damage ↑body weight
Liu et al., 2018 [8]	KKAy mice, an early type 2 DN model	NPD: 22% protein vs. LPD: 6% protein vs. LPD + KAs: 5% protein plus 1% KA	12 weeks	↓ proteinuria ↓ mesangial proliferation and oxidative stress ↑ serum albumin and body weight No difference in creatinine and GFR
Zhang et al., 2016 [9]	3/4 nephrectomy rats	NPD: 18% protein vs. LPD: 6% protein vs. LPD + KAs: 5% protein plus 1% KA	12 weeks	↓ proteinuria ↓ intrarenal RAS activation. ↓ transforming growth factor-β1 in the mesangial cells
Zhang et al., 2015 [10]	5/6 nephrectomy rats	NPD: 11 g/kg/day protein vs. LPD: 3 g/kg/day protein vs. LPD + KAs: 3 g/kg/day protein which including 5% protein plus 1% KA	24 weeks	↑ body weight, gastrocnemius muscle mass ↓ autophagy marker in muscle No difference of inflammation markers

Study	Models	Diet Intervention	Follow-Up	Results (LPD vs. VLDP/LPD + KAs)
Wang et al., 2014 [11]	5/6 nephrectomy rats	NPD: 22% protein vs. LPD: 6% protein vs. LPD + KAs: 5% protein plus 1% KA	24 weeks	↑improved protein synthesis and increased related mediators such as phosphorylated Akt in the muscle ↓ protein degradation and proteasome activity in the muscle
Gao et al., 2010 [12]	5/6 Nephrectomy rats	NPD: 22% protein vs. LPD: 6% protein vs. LPD + KAs: 5% protein plus 1% KA	24 weeks	↓ proteinuria, glomerular sclerosis, and tubulointerstitial fibrosis ↑renal function ↑ body weight and albumin ↓ lipid and protein oxidative products
Gao et al., 2011 [13]	5/6 Nephrectomy rats	NPD: 22% protein vs. LPD: 6% protein vs. LPD + KAs: 5% protein plus 1% KA	6 months	↑ body weight and albumin ↑ Kruppel-like factor-15, a transcription factor shown to reduce fibrosis
Maniar et al., 1992 [14]	5/6 Nephrectomy rats	NPD: 16% casein vs. LPD + EAA: 6% casein + EAA vs. LPD + KAs: 6% casein + KA	3 months	No difference on body weight No difference on proteinuria vs. LDP + EAA but reduction vs. NPD ↓ creatinemia, proteinuria, glomerular sclerosis, and tubulointerstitial fibrosis vs. NPD but no difference vs. LPD + EAA ↑survival vs. NPD but no difference vs. LPD + EAA

Study	Models	Diet Intervention	Follow-Up	Results (LPD vs. VLDP/LPD + KAs)
Laouari et al., 1991 [15]	5/6 Nephrectomy rats	NPD: 12% casein vs. LPD + EAAs: 5% casein + EAA vs. LPD + KAs: 5% casein + KA		↓Appetite and growth No increase in BCAAs
Benjelloun et al., 1993 [16]	Rats with after a single 5 mg/kg intravenous injection of Adriamycin: a model of induces glomerular damage in glomerulonephritis.	NPD: 21% protein vs. LPD + KAs: 6% protein plus KA	15 days	↓ proteinuria ↓ glycosaminoglycan excretion and glomerular glycosaminoglycan contents
Barsotti et al; 1988 [17]	5/6 Nephrectomy rats	NPD: 20.5% protein vs. LPD + KAs: 3.3% protein plus 7.5% KA	3 months	↑survival ↑ GFR ↓ proteinuria and histological damage of kidney No difference in body weight and albuminuria
Meisinger et al., 1987 [18]	5/6 Nephrectomy rats	LPD: 8% protein vs. LPD + KAs: 8% protein plus KA	3 months	↓ proteinuria

NPD: normal protein diet. HPD: high protein diet. GFR: estimated Glomerular Filtration Rate. LPD: Low protein diet. KAs: ketoacid analogues. EAAs: essential amino acids. BCAAs: branched-chain amino acids; RAS: renin angiotensin system; NPD: normal protein diet.

Table 3. Main RCTs that examined the effects of LPD or VLDP/LPD supplemented with ketoacid analogues on various endpoints in non-dialysis patients with eDFG under 60 mL/min/1.73 m^2.

Study	Design of Study	Diet	Follow-Up	Results	Comments
Milovanova et al., 2018 [2]	RCT *n* = 42 in LPD + KA vs. LPD *n* = 37 Non-diabetic CKD 3B–4	LPD (0.6 g/kg of body weight/day, comprising 0.3 g of vegetable protein and 0.3 g of animal protein, phosphorus content ≤ 800 mg/day and calories: 34–35 kcal/kg/day) vs. LPD + KA: 0.6 g/kg of body weight/day	14 months	↑ eGFR (29.1 L/min/1.73 m^2 vs. 26.6) ↓SBP ↑BMI and muscle body mass NO change in albumin levels No change in lipids parameters ↓ phosphate, FGF23, and PTH levels ↑Klotho levels and phosphate binder uses ↑bicarbonates levels	Similar protein intake in both group Long follow up

Study	Design of Study	Diet	Follow-Up	Results	Comments
Di Iorio et al., 2018 [19]	RCT, crossover trial CKD stages 3B–4 Group A1: 3 months of FD, 6 months of VLPD + KA, 3 months of FD and 6 months of MD Group B: 3 months of FD, 6 months of MD, 3 months of FD and 6 months of VLPD + KA. *n* = 30 in each group	FD: proteins 1 g/kg body weight (bw)/day (animal proteins 50–70 g/day, vegetal proteins 15–20 g/day), energy 30–35 kcal/bw/day, calcium (Ca) 1.1–1.3 g/day, phosphorus (P) 1.2–1.5 g/day, sodium (Na) 6 g/day and potassium (K) 2–4 g/day. MD: proteins 0.7–0.8 g/kg bw/day (animal proteins 30–40 g/day, vegetal proteins 40–50 g/day), energy 30–35 kcal/bw/day, Ca 1.1–1.3 g/day, P 1.2–1.5 g/day, Na 2.5–3 g/day and K 2–4 g/day. VLPD + KA: proteins 0.3–0.5 g/kg bw/day (animal proteins 0 g/day, vegetal proteins 30–40 g/day), energy 30–35 kcal/bw/day, Ca 1.1–1.3 g/day, P 0.6–0.8 g/day, Na 6 g/day, K 2–4 g/day plus a mixture of KA	6 months	↓ SBP No change in creatinuria ↓proteinuria ↓ phosphate, FGF23, and PTH levels ↑bicarbonates levels ↑Hg levels ↓protein carbamylation	Sodium intake and phosphore intake was reduce in VLDP + KA group

Study	Design of Study	Diet	Follow-Up	Results	Comments
Garneata et al., 2016 [20]	RCT CKD stage 4–5, proteinuria < 1 g/24 h *n* = 207	LPD = 0.6 g protein/kg per day vs. VLPD + KA = vegetarian diet, 0.3 g protein/kg per day + KA	15 months	↓ RRT initiation or a >50% reduction in the initial GFR (13% in KA+LDP vs. 42% in LPD reached the primary composite efficacy point i.e., RRT initiation or a >50% reduction in the initial GFR) ↓CRP ↑bicarbonates levels ↓uric acid ↓ phosphate, FGF23 and PTH levels and phosphate binder uses No difference in proteinuria No difference of death and CV events No difference of albumin, BMI No change in lipids parameters	Long follow up Large effective Only 14% of patients screened was included

Study	Design of Study	Diet	Follow-Up	Results	Comments
Di Iorio et al., 2012 [21]	RCT, crossover trial eGFR < 55 and > 20 mL/min/1.73 m^2 Group A: VLDP + KA during the first week and LPD during the second week Group B: LPD during the first week and a VLPD + KA during the second week. *n* = 16 in each group	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	1 week	↓ phosphate (−12%), FGF23 (−33.5) No change on calcium a post hoc of this study, ↓ indoxyl sulfate [22] ↑bicarbonates levels	Short exposition
Di Iorio et al., 2009 [23]	RCT, crossover trial eGFR < 55 and > 20 mL/min Group A: VLDP + KA during 6 month and a LPD during 6 month Group B: LPD during 6 month and a VLDP + KA during 6 month. *n* = 16 in each group 32 patients	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	6 months	↓proteinuria and AGE	Open label Phosphor intake was different and lower in VLDP+ KA

Study	Design of Study	Diet	Follow-Up	Results	Comments
Menon et al., 2009 [24]	Post hoc study of MDRD study B CKD stage 4 nondiabetic *n* = 255	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	10.2 years	No delay progression to kidney failure ↑the risk of death.	Long follow up without intervention -Observance and protein intake was not monitored during the follow up
Teplan et al., 2008 [3]	RCT, double-blind placebo CKD stage 4 *n* = 111	LDP: 0.6 g protein/kg per day vs. LPD + KA: 0.6 g protein/kg per day + KA	36 months	↓ADMA ↓ BMI and visceral body fat in obese patients ↓proteinuria ↓ glycated hemoglobin ↓LDL-cholesterol	Mean BMI was > 30 kg/m^2 at the inclusion Long follow up No difference of protein intake Using a placebo
Mircescu et al., 2007 [25]	RCT eGFR <30 mL/min/1.73 m^2, nondiabetic *n* = 53	VLPD + KA =0.3 g/kg vegetable proteins + KA vs. LPD =0.6 g/kg/d)	48 weeks	↑bicarbonates levels ↑calcium levels and ↓ phosphate lower percentages of patients in group I required renal replacement therapy initiation (4% vs. 27%). No change of rate of eGFR and proteinuria No change in SBP	Open label
Gennari et al., 2006 [26]	Post hoc study of MDRD study RCT CKD stage 4–5 *n* = 255	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	2,2 years	No significant effect of diet on serum total CO2 was seen	

Study	Design of Study	Diet	Follow-Up	Results	Comments
Menon et al., 2005 [27]	Post oc study of MDRD study RCT CKD stage 4–5 *n* = 255	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	2.2 years	↓ homocysteinemia by 24% at 1 year	
Feiten et al., 2005 [28]	RCT *n* = 24 eGFR <25 mL/min	VLPD + KA = 0.3 g/kg vegetable proteins + KA vs. LPD = 0.6 g/kg/d	4 months	↑bicarbonates levels No change on calcium levels ↓ phosphate and PTH Decrease the progression of renal decline function of rate of eGFR No change in lipid parameters No change in nutritional status (BMI, albumin)	Open label Short time of follow up Significant reduction in dietary phosphorus (529 ± 109 to 373 ± 125 mg/day, $p < 0.05$)
Prakash et al., 2004 [29]	RCT, double-blind placebo eGFR:28 mL/min/1.73 m^2 *n* = 34	LPD = 0.6 g protein/kg per day + placebo vs. VLPD = 0.3 g protein/kg per day + KA	9 months	preserve mGFR (−2% in LDP + KA vs. −21% in LPD) No effect on proteinuria No effect of BMI and albumin	Measure of GFR with 99mTc-DTPA The placebo is problematic because protein intake was different between both groups.
Teplan et al., 2003 [4]	RCT eGFR: 22–36 mL/min/1.73 m^2 *n* = 186	LPD 0.6 g protein/kg per day + rhuEPO + KA vs. LPD: 0.6 g protein/kg per day + rhuEPO vs. LPD: 0.6 g protein/kg per day	3 years	Slower progression of CKD ↓proteinuria ↓LDL-cholesterol No change in SBP ↑albumin ↑ plasmatic leucine levels	Role of rhuEPO unclear Insulin clearance

Study	Design of Study	Diet	Follow-Up	Results	Comments
Di Iorio et al., 2003 [30]	RCT eGFR: < or =25 mL/min/1.73 m^2 *n* = 10 in each group	LPD = 0.6 g protein/kg per day vs. VLPD = 0.3 g protein/kg per day + KA	2 years	No difference on hemoglobin ↓ EPO dose ↓ phosphate and PTH No change in BMI and albumin No difference in the rate of RRT initiation (8 vs. 7) Slower rate of GFR decline (creatinine clearance) ↓SBP and 24 h NA excretion ↓LDL-cholesterol	Very few populations
Bernhard et al., 2001 [5]	RCT CKD stage 4–5 *n* = 6 in each group	LPD = 0.6 g protein/kg per day vs. LPD + KA = 0.6 g protein/kg per day + KA	3 months	No difference could be attributed to the ketoanalogs total body flux and leucine oxidation No difference on phosphorus, calcium levels No difference on BMI and albumin No difference in renal function and proteinuria No difference on bicarbonatemia	KA is metabolically safe Short follow-up Small effective
Malvy et al., 1999 [31]	RCT eGFR<20 mL/min/1.73 m^2 *n* = 50	LPD:LPD = 0.65 g protein/kg per day + Ca+ vs. VLPD + KA = 0.3 g protein/kg per day + KA	3 months or time to eGFR < 5 mL/min/1.73 m^2 or RRT	No difference on GFR progression ↑calcium levels ↓ phosphate and PTH No difference on lipid parameters	

Study	Design of Study	Diet	Follow-Up	Results	Comments
Kopple et al., 1997 [32]	Post hoc study of MDRD study RCT CKD stage 4–5 *n* = 255	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	2,2 years	No difference of death and first hospitalization ↑ albumin ↓ transferrin, body wt, percent body fat, arm muscle area, and urine creatinine excretion No correlation between nutritional parameters and death or hospitalization ↓ energy intake	
Levey et al., 1996 [33]	Post hoc study of MDRD study RCT CKD stage 4–5 *n* = 255	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	2.2 years	A 0.2 g/kg/d lower achieved total protein intake was associated with a 1.15 mL/min/yr slower mean decline in GFR (p = 0.011), which is equivalent to 29% of the mean GFR decline	Reanalyze of MDRD study by using correlations of protein intake with a rate of decline in GFR and time to renal failure
Klahr et al., 1994 Study 2 [34]	RCT CKD stage 4–5 *n* = 255	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	27 months	Marginally slower eGFR decline (−19% in LPD vs. 12% in VLDP + KA, p 0.067) No significant interactions between blood-pressure interventions and the rate of decline in eGFR No difference on albumin No difference in proteinuria	-Large RCT study -Good adherence of diet -Measured GFR with iothalamate

Study	Design of Study	Diet	Follow-Up	Results	Comments
Coggins et al. 1994 [35]	Feasibility phase of the MDRD Study eGFR: 8 to 56 mL/min/1.73 m^2 *n* = 96 25 participants were excluded	LPD = 0.6 g protein/kg per day vs. VLPD + KA = 0.3 g protein/kg per day + KA	6 months	No difference on lipid parameters	Pilot study
Lindenau et al. 1990 [36]	RCT eGFR<15 mL/min/1.73 m^2 *n* = 40	LPD = 0.6 g protein/kg per day + Ca+ vs. VLPD + KA = 0.4 g protein/kg per day + KA	12 months	Improvement in osteo-fibrotic as well as in osteo-malacic changes	A calcium supplementation was given in LPD diet as a control for KA
Jungers et al. 1987 [37]	RCT CKD stage 5 *n* = 19	LPD = 0.6 g protein/kg per day + Ca+ vs. VLPD + KA = 0.4 g protein/kg per day + KA	12 months	No difference on biochemical or morphometric sign of de-nutrition ↑mean renal survival duration until dialysis	Small and effective
Hecking et al., 1982 [6]	RCT Mean eGFR: 10.8 mL/min/1.73 m^2 *n* = 15	LPD = 0.6 g protein/kg per day + Ca+ vs. LPD + KA = 0.6 g protein/kg per day + KA or EAA or placebo	3 weeks per periods	↓ phosphate No difference on GFR and proteinuria No difference on lipids parameters No difference on albumin	Small and effective versus the placebo

FD: Free diet. P: phosphorus. MDRD: Modification of Diet in the Renal Disease Study. eGFR: estimated Glomerular Filtration Rate. RRT: renal replacement therapy. FGF23: Fibroblast Growth Factor 23. LPD: Low protein diet. VLDP: Very low protein diet. KA: Keto-analogues. RCT: randomized controlled trial. EAA: essential amino acids; PTH: parathyroid hormone.

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