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Ketoanalogue Review: New Update on an Old Therapy

AnnaMarie Rodriguez, RDN, LD, FAND

THE PREVALENCE AND incidence of chronic kidney disease (CKD) in the United States is problematic with an estimated thirty million people with CKD; the equivalence of 15% of the adult population.[1] Treatment of CKD is a multifactorial approach as is the nutritional management. While the nutritional components have historically sparked multiple debates and scrutiny, the discussion of protein influence on CKD has recently gained heightened interest. Reduction of protein intake has long been established to slow the progression of CKD. A systematic review and meta-analysis of controlled trials by Rhee et al[2] distinguishes that diets with a low protein intake <0.8 g/kg body weight/day were associated with lower rates of progression to end-stage kidney disease (ESKD) and all-cause death. In addition, very low protein intake, <0.4 g/kg body weight/day, illustrated the greatest preserved kidney function displayed by a 13% reduced risk of progression to ESKD in the very low protein intake versus the low protein intake groups.

The updated Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in CKD, published in 2020 has increased renewed focus on the use of ketoacids (KA), often referred to as ketoacid analogues or ketoanalogues, in the conservative management of the very low protein diet (VLPD) in delaying the progression of kidney disease to ESKD. The guidelines state with regards to KAs:

Protein Restriction, CKD Patients Not on Dialysis and Without Diabetes 3.0.1. *In adults with CKD 3-5 who are metabolically stable, we recommend, under close clinical supervision, protein restriction with or without keto acid analogs, to reduce risk for end-stage kidney disease (ESKD)/death (1A) and improve quality of life (QoL) (2C):*

- a low-protein diet providing 0.55–0.60 g dietary protein/kg body weight/day, or
- a very low-protein diet providing 0.28–0.43 g dietary protein/kg body weight/day with additional keto acid/amino acid analogs to meet protein requirements (0.55–0.60 g/kg body weight/day)[3]

It is an established fact that populations in Western countries consume an excess of the minimum daily protein requirement (1.35 g protein/kg/day) compared with daily needs estimated to be 0.8 g protein/kg/day. While protein metabolism is responsible for growth and development in children and for the maintenance of muscle mass in adults, protein intake in excess is a risk factor associated with an accumulation of by-products into the blood that will progressively impair kidney function for individuals at risk.[4] Excess protein intake is responsible for an increased workload on the kidneys and clinical research has long confirmed the impact of its deleterious role on the renal hyperfiltration response. In the situation of reduced nephrons, reducing protein intake reduces hyperfiltration, uremic toxins, and uremia and may delay the need for maintenance dialysis therapy.

Thus, a low protein diet (LPD) or VLPD in CKD 3-5 is highly strategic in preserving kidney function and quality of life. However, in the context of the guidelines, it is important to note these guidelines should be implemented in patients who are "metabolically stable," and this implies the absence of inflammation, infection, hospitalization within 2 weeks, consumptive diseases, absence of antibiotic or immunosuppressive medications, and absence of precipitous weight loss. Protein restriction may place individuals at risk for protein energy malnutrition (PEW). Although, provided there is adequate energy intake (>30 kcal/kg per day), then protein intake can safely be decreased to either a LPD around this (0.55–0.60 g/kg body weight/day) or a VLPD with the use of KA to maintain nitrogen balance. The guideline of a protein restriction with or without KA receives a "1A" rating which indicates a high quality of evidence and a strong recommendation.

The use of a LPD or VLPD with KA (Table 1) has many similarities in benefits and results as does the LPD when deciphering outcomes of interest in individuals with CKD 3-5. Research has shown a survival beneficial effect

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of protein restriction with the use of a LPD in adults with CKD 3-5 and studies report a mixed effect of use of a VLPD with KA.[5-8] Garneata et al[5] and Mircescu et al[6] indicate a significantly lower percentage of patients consuming the VLPD-plus-KA require kidney replacement therapy (KRT), and in addition, Garneata et al[5] indicates a delay in initiating KRT, while Mircescu et al[6] reports the percentage of patients requiring KRT in the VLPD-plus-KA group being 4% versus 27%. Levey et al[7] reports those following a VLPD did not have a significant effect on kidney failure and mortality risk. Likewise, Malvy et al[8] reported a protein restriction plus KA had no statistically significant effect on kidney survival. Conversely, data from randomized controlled trials support KRT and the use of a VLPD with KA supplementation in adults as beneficial in preserving kidney function by means of maintaining estimated glomerular filtration rate (GFR).[5-7,9] Interestingly, Mircescu et al[6] notes GFR did not change significantly in the VLPD with KA group but significantly decreased in the LPD group ($P < .05$). Similar findings are identified in the Modification of Diet in Renal Disease Study 2 indicating a trend for slower GFR decline with the VLPD in comparison with the LPD ($P = .07$).[8] Garneata et al[5] reported a lower GFR in the VLPD-plus-KA versus LPD group, and Prakash et al[9] indicated no GFR change in the KA group although the placebo group experienced a significant decrease ($P = .015$). The preservation of GFR is beneficial on kidney survival.

While there are mixed results regarding the effect of a LPD and serum phosphate levels,[3] there are promising data with the use of a VLPD supplemented with KAs. Multiple studies indicate decreased phosphorus with use of a VLPD-plus-KA.[6,8,10,12] Research by Feiten et al[10] demonstrated a reduction in phosphate levels in the VLPD-plus-KA ($P = .07$) group, whereas serum phosphate levels did not change in the VLPD group. Similar observations in phosphate reductions with the VLPD-plus-KA were seen by Li et al ($P < .001$)[11] and Mircescu et al ($P < .05$).[6] In addition, Feiten et al[10] note that serum parathyroid hormone did not change significantly in the VLPD-plus-KA group although did increase in the LPD group. It is worth noting there are limited data to review regarding the benefits of a LPD versus VLPD-plus-KA on electrolytes, and the study by Rosman et al[12] reports patients in the LPD group showed both decreased phosphorus levels and use of phosphate binders. It may be beneficial to further explore the effects of both a LPD and VLPD-plus-KA on the effects of electrolytes in the spectrum of CKD bone and mineral metabolism disorders to include phosphorus, FGF-23, calcium, and parathyroid hormone long term.

To be expected, a VLPD-plus-KA can improve serum lipid profiles and is supported by research although there are mixed reviews. While Feiten et al[10] and Malvy et al[8] report no effect of a VLPD-plus-KA on a serum lipid profile, Bellizzi et al[13] reports a decrease in both total cholesterol and triglyceride levels. In addition, Coggins et al[14] reports significant decreases in triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. The composition of carbohydrate sources, such as measure of fiber intake, makes an impact on lipid profiles, and this is not widely discussed in the selected research as the focus is rather on protein and protein intake. In addition, one study clearly indicates use of statins during the study duration, and this impacts the ability to identify if diet alone is beneficial.[5]

Dietary intake is often used as a measure of adherence. Multiple studies indicate a VLPD-plus-KA can be effectively achieved,[6,10,13,15-17] and in addition, Mircescu et al[6] identifies good adherence to the prescribed diets in both treatment arms receiving a LPD and VLPD-plus-KA. In a review of both protein and energy intake, Kopple et al[17] identifies that compared with a usual-protein group, dietary energy was significantly lower in those following a LPD ($P > .05$); however, there was no difference in dietary energy intake between the LPD and VLPD groups ($P > .05$), which may highlight the need for dietary education to promote appropriate caloric intake. However, research supports a VLPD with KA has potentially no significant impact on nutritional status. Multiple studies report no effect of a VLPD-plus-KA on serum albumin,[5,6,9,10,16,17] although the data on anthropometrics are inconclusive. Despite research by Kopple et al[17] indicating no significant differences in anthropometrics and Garneata et al[5] demonstrating no differences in body mass index, midarm muscle circumference, and triceps skinfold, the research by Malvy et al[8] reports a significant weight loss observed at the end of study in the VLPD group ($P < .01$). This observation heightens the necessity of nutrition intervention and dietary counseling to ensure energy needs are met.

Although a VLPD-plus-KA can be a tactical strategy in the nutritional management of CKD to delaying the progression to ESKD, a judicious approach must be taken with individuals with CKD and PEW. Correction of the underlying catabolic state is precedential as there are conflicting data regarding outcomes on anthropometric parameters with use of a VLPD-plus-KA. A VLPD-plus-KA is considered a long-term approach and thus it is critical to have routine anthropometric and biochemical monitoring in place owing to the adverse effects of PEW. As mentioned, a LPD or VLPD is implemented in a progressive manner taking into consideration an individual's overall nutritional status. An individual who is metabolically stable may benefit with a progressive transition from a plant dominant approach using a LPD of 0.6-0.8 g/kg body weight/day, with at least 50% plant-based sources[18] and transition to a LPD and ultimately to a VLPD-plus-KA. A realistic approach to transitioning a patient to a protein modified nutrition plan is to simply ease from one category to another based on patient readiness to change. As a point

of fact, the only protein-modified diets are either a VLPD or a plant-based diet. The LPD is in alignment with the Recommended Dietary Allowance as human needs are based on 0.8 g/kg body weight/day and this value has a large margin of safety; thus, protein needs may be lower for most people. The benefit of transitioning to a VLPD-plus-KA is not only reduced hyperfiltration and proteinuria but utilization of vegetable protein sources also reduced metabolic acidosis.[19]

Individuals with diabetes mellitus have the additional goal of maintaining glycemic control and there is conflicting evidence in the nondialyzed diabetic kidney disease population regarding the beneficial impact of a LPD. Thus, a more prudent approach of 0.8 g/kg body weight/day as illustrated by Ko et al[20] may be favorable based on the extensive review of existing guidelines and research surrounding this population. Of note, Barsotti et al[21] demonstrated results in patients with diabetes after the onset of CKD using both a vegetarian LPD-plus-KA and VLPD-plus-KA diet which led to a significant decrease in urinary protein loss in both groups ($P < .01$), while anthropometric indexes did not show significant changes. In addition, daily insulin requirements decreased significantly ($P < .01$) with evidence of improved fasting serum glucose in both groups ($P < .05$). Despite this small sample size of thirty-two patients, the results are worthy of review, noting the patients were followed up for 5.2 ± 3.8 years and creatinine clearance declined significantly ($P < .001$) in both populations. Thoughtful consideration to continue examination of this population is necessary with controlled research and larger population groups.

As initially stated, since the updated KDOQI Guidelines have been available, there has been a growing interest in the LPD and VLPD-plus-KA as a dietary intervention with CKD. However, the interest in KAs has been increasing before the publication of Guidelines. There is a broad deficiency of knowledge surrounding KAs and a hesitancy to their use. Historically, healthcare providers (HCPs) realize the strength of KAs with the use of a VLPD in effectively slowing the progression of CKD, though in addition to the lack of familiarity with how to implement the KAs is both the burden of cost and availability. Until recently, despite the use of KAs for more than 40 years, KAs have not been readily available in the United States and had been only available as tablets. Currently, KAs are available as tablets or powder, and the dosing is dependent on protein restriction and body weight, though is typically 4-8 tablets versus 2-3 scoops of powder per day which is mixed with water or juice (one scoop powder per three ounces fluid). Data by Wu et al[22] indicates a mean daily KA dose of 5.5 tablets with a LPD represented a therapeutic strategy in slowing the progression of CKD. After a mean follow-up period of 1.57 years, a decreased risk of initiating dialysis by 46% was seen. This study represents the largest cohort study of long-term KA supplementation in advanced patients with CKD with a total of 1,483 patients enrolled in Taiwan. In addition, Zhang et al[23] demonstrate the contribution of a VLPD-plus-KA in conserving residual kidney function in incremental twice weekly dialysis. Thus, this nutrition intervention has a role throughout the diagnosis, progression, and maintenance of CKD as dose is adjusted as per residual function.

A diet high in protein will result in an accumulation of multiple metabolic wastes and minerals, including excess phosphorus. A VLPD-plus-KA reduces the generation of these wastes. KAs are advantageous as they supplement additional amino acids without added nitrogen. Because KAs lack the amino group bound to the alpha carbon of an amino acid they can be converted to the respective amino acids without additional nitrogen. Transamination reactions combine reversible amination and deamination. Most amino acids, as they are degraded, will go through transamination involving a removal of the amino group bound to the alpha carbon and replacement by a hydroxy group. The KA formed by this transamination can be further degraded by oxidation. Likewise, transamination of KA to synthesize essential amino acids will occur if needed amounts are available, as needed. All the amino acids except for lysine, threonine, proline, and hydroxyproline undergo transamination. In addition, transaminases exist for histidine, serine, phenylalanine, and methionine though the major pathways do not involve transamination. To explain it simply, transamination is the process by which amino groups are removed from the amino acids and transferred to acceptor ketoacids and a ketoacid version of the original amino acid.[24] The reaction is highly specific and reversible with the direction of action dependent on availability of substrates (Figure 1).

Calcium salts of KAs also provide an alkalinizing effect, although this effect is minimal with KA supplementation.[26] The alkalinizing effects of KA salts are augmented by reduced acid generation from low-protein intake and from the vegetarian diets often concurrently prescribed.[24] Both the LPD and VLPD are higher in fruits and vegetables which are known to reduce dietary acid as evidenced in data by Goraya et al.[27,28] In these studies, patients with CKD 3 and 4, randomized to either sodium bicarbonate or a fruit and vegetable group, produced similar outcomes in preserving GFR. Because of the calcium content in KAs, calcium levels should be monitored though is not problematic. Because the VLPD is typically lower in phosphorus, the

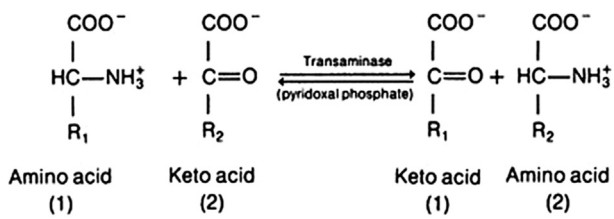

Figure 1. General reaction of transamination.[25]

Table 1. Renal Survival of LPD and VLPD-plus-KA

Publication	Publication date, authors	Design or method	Inclusion criteria	Intervention	Description of intervention	Identified outcomes on renal survival
ketoanalogue-Supplemented Vegetarian Very Low Protein Diet and CKD Progression[5]	(2016) Garneata, Stancu, Dragomir, Stefan & Mircescu	Prospective, single-center, open-label, randomized, controlled trial with a total duration of 18 mo	Nondiabetic adults with stable GFR<30 mL/min per 1.73 m^2, proteinuria <1 g/g urinary creatinine, n = 207	Safety and efficacy of ketoanalogue–supplemented vegetarian very low protein diet (KD) compared with conventional LPD.	Primary end point was KRT initiation or >50% reduction in initial eGFR.	28% of the cohort reached the primary composite efficacy end point (i.e., KRT initiation or a >50% reduction in the initial GFR). A significantly lower percentage of patients in the KD group reached the primary end point: 13% versus 42% in the LPD group ($P < .001$);
Effects of a Supplemented Hypoproteic Diet in Chronic Kidney Disease[6]	(2007) Mircescu, Garneata, Stancu & Capusa	Prospective, open-label, parallel, randomized, controlled trial.	Nondiabetic adults GFR <30 mL/min/1.73 m^2, proteinuria <1 g/g urinary creatinine	Group 1 (n = 27): SVLPD (0.3 g/kg/d of vegetable proteins and ketoanalogues, 1 capsule for every 5 kg of ideal body weight per day). Group 2 (n = 26) continued a conventional low mixed protein diet (0.6 g/kg/d).	Nitrogen waste products retention and calcium-phosphorus and acid-base disturbances were primary efficacy parameters, and "death" of the kidney or the patient and the GFR were secondary efficacy parameters.	Significantly lower percentages of patients in group I required KRT initiation (4% vs. 27%). After 48 weeks, GFR did not significantly change in patients receiving SVLPD (0.26 ± 0.08 mL/s vs. 0.31 ± 0.08 mL/s at baseline), but significantly decreased in controls (0.22 ± 0.09 mL/s vs. 0.30 ± 0.07 mL/s). No deaths in duration.
Effects of Severe Protein Restriction with ketoanalogues in Advanced Renal Failure[8]	(1999) Malvy, Maingourd, Pengloan, Bagros & Nivet	Prospective randomized study	50 uremic patients, GFR <20 mL/min/1.73 m^2; 25 in each group	Compare a severe protein restriction diet (0.30 g/kg/day) supplemented with ketoanalogues (Group A) to a moderate protein restriction diet (0.65 g/kg/day) (Group B)	Compare severe protein restriction diet supplemented with ketoanalogues to a moderate protein restriction diet to limit GFR decrease in advanced renal insufficiency stage.	There were no statistically significant differences between the two dietary regimens for the renal survival. Uremia decreased significantly in Group A (22.7 ± 5.2 to 18.5 ± 6.7 mmol/L) and increased in Group B (26.8 ± 9.0 to 34.9 ± 9.9 mmol/L).

(*Continued*)

Table 1. Renal Survival of LPD and VLPD-plus-KA (*Continued*)

Publication	Publication date, authors	Design or method	Inclusion criteria	Intervention	Description of intervention	Identified outcomes on renal survival
Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure[9]	(2004) Prakash, Pande, Sharma, Sharma, Shekhar & Kulkami	Prospective, randomized, double-blind, placebo-controlled trial	Inclusion: creatinine clearance between 20-50 mL/min. Exclusion: known end-stage kidney disease, severe cardiac disease, severe hepatic insufficiency, severe catabolic illness, known malabsorption, or polycystic kidney disease.	Randomized to either 0.6 g/kg/d protein plus placebo (n = 16) or 0.3 g/kg/d protein plus tablets of KAs (n = 18) for 9 months	To assess whether a ketodiet, a combination of ketoanalogues of essential amino acids (KAs) and a very low-protein diet, retards progression of chronic renal failure and maintains nutritional status.	GFR significantly decreased from 28.6 ± 17.6 to 22.5 ± 15.9 mL/min/1.73 m^2 in the placebo group ($P = .015$). Serum total proteins decreased significantly ($P = .038$) in the placebo group, and serum albumin showed a trend ($P = .061$) toward reduction, whereas both of these parameters were maintained in the ketodiet group.
Effects of dietary protein restriction on the progression of advanced renal disease in the modification of diet in renal disease study[7]	(1996) Levey, Adler, Caggiula, England, Greene, Hunsicker, Kusek, Rogers & Teschan	Randomized controlled trial	255 patients aged 18 to 70 y with baseline GFR 13-24 mL/min/1.73 m^2 who participated in MDRD Study B. Patients with diabetes requiring insulin were excluded.	A LPD (0.58 g/kg/d) or VLPD (0.28 g/kg/d) supplemented with keto acids-amino acids (0.28 g/kg/d); avg follow up was 2.2 y	Objective of these secondary analyses was to determine the relationship between achieved, in addition to prescribed, dietary protein intake and the progression of advanced renal disease.	After adjusting for total protein intake, no independent effect of prescription of the KA supplement to slow the GFR decline could be detected. If GFR decline is extrapolated until renal failure, a patient with 29% reduction in the rate of GFR decline would experience a 41% prolongation in the time to renal failure. Additional analyses confirmed a longer time to renal failure in patients with lower total protein intake. These secondary analyses of the MDRD Study suggest that a lower protein intake, not the KA, retards the progression of advanced renal disease

GFR, glomerular filtration rate; KA, ketoacid; KD, vegetarian very low protein diet; MDRD, Modification of Diet in Renal Disease; LPD, low-protein diet; KRT, kidney replacement therapy; SVLPD: severe hypoproteic diet supplemented with ketoanalogs; VLPD, very-low-protein diet.

calcium salts of the KAs may decrease serum phosphorus below an acceptable range. A knowledgeable dietitan nutritionist is necessary to provide appropriate monitoring and intervention.

Because KAs are considered a medical food, these products may be purchased without a prescription though it befits HCPs to become familiarized with these products to be able to assist patients. The barriers to use of KAs are a lack of familiarity and education, both on the part of HCPs and patients, availability of product, and cost. Of these, cost is the single most obtrusive barrier to KAs becoming a consistent strategy of nutritional care in a population that strongly requires fastidious intervention. The appropriate dose of the KA preparation has not been thoroughly established[26] thus a KA dose-response study would be particularly advantageous as the powder formulation offers a higher availability, accessibility and is slightly less cost inhibitive. The cost of a VLPD with KA, quality of life, and the potential number of years based on kidney survival may be far more beneficial than the cost of dialysis and it is up to the HCP to weigh these options with patients.

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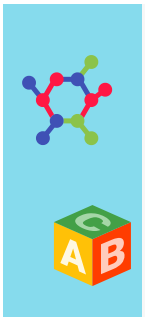
Ketoanalogues

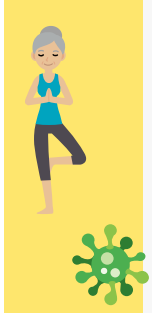
What are ketoanalogues?

Ketoanalogues (KAs) supplement the diet by adding amino acids without extra nitrogen, making a very low protein diet safe to follow. You might see these referred to as keto acids. This is a medical food - not a fad supplement.



What are Amino Acids?
Amino Acids are building blocks of protein and essential to health.

When foods are eaten with amino acids they are turned into proteins the body needs.



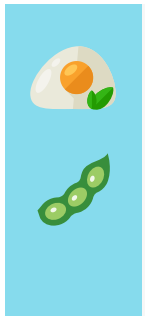
Why is Protein important?

The right amount of protein helps build and repair muscles and tissue in the body, and helps fight infection and illness.

Nutrition is important to help delay the progression of Chronic Kidney Disease (CKD)!

Decreasing protein in the diet is one step that can be taken to delay the progression of CKD.

Decreasing protein decreases nitrogen waste in the blood that the kidneys can no longer eliminate.



Decrease protein:

- **Low protein diet (LPD)**
- **Very low protein diet (VLPD) with ketoanalogues**

What is the difference?
What are ketoanalogues?
Why should they be used?

Ketoanalogues supplement the diet by providing amino acids without added nitrogen.

Like amino acids, these are the building blocks, but are missing pieces. The body will build with them when they need them.

A LPD can meet your body's needs and delay the progression of kidney disease.

A VLPD is highly recommended to delay the progression of kidney disease but will not meet daily protein needs.

Ketoanalogues (KAs) fill the gaps with a VLPD to help meet protein needs making a VLPD safe to follow!

This helps delay the progression of kidney disease and meets nutrition needs at the same time.

Ask your Physician or Renal Dietitian for more information about a LPD or VLPD and Ketoanalogues