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Ketoanalogues: Not Your Everyday Amino Acids

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THE USE OF ketoanalogues (KAs) with a very low-protein diet (VLPD) as a progressive approach to delay the progression of chronic kidney disease (CKD) has been appealing for decades (more than 40 years!), although cost-inhibitive, and in addition, KAs have not been readily available, at least in the United States, until recently. The updated Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in CKD, published in 2020, has increased a renewed focus on the use of KAs, also often referred to as ketoacid analogues, in the conservative management of the VLPD in delaying the progression of kidney disease to end-stage kidney disease. The guidelines state with regard to KAs as follows:

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)[1]

As noted, until recently, KAs were not readily available in the United States, and in addition, there has been confusion regarding amino acid supplements; thus, it is important to distinguish the difference between these products. We frequently assist our patients as they navigate through waves of information on products meant to impact their health from a variety of media outlets, and we, too, are often faced with the same dilemma in navigating through the social media platforms or e-commerce websites that our patients may be investigating to establish fact from fiction. What makes this more difficult is the speed with which products are marketed and often the lack of information relevant to ascertain the safety of products to our patients. Regarding KAs, there is limited information (and products); however, there are numerous videos on the internet on KAs and essential amino acids available. In addition, patients may be reviewing numerous products: is it an amino acid therapy, a ketoacid blend meant to support a ketogenic diet, or is it a ketoacid analogues. These are some of the factors to be aware of as our patients may be navigating this topic.

First and foremost, what is significant about KAs in the first place and what makes this useful as a viable approach with a VLPD? KAs 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 its 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 when needed. All the amino acids except for lysine, threonine, proline, and hydroxyproline undergo transamination. In addition, transaminases exist for histidine, serine, phenylalanine, and methionine although 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, transferred to acceptor ketoacids, and a ketoacid version of the original amino acid.[2] The reaction is highly specific and reversible with the direction of action dependent on availability of substrates. A VLPD-plus-KA reduces the generation of nitrogenous wastes!

Currently, KAs are available as tablets or powder, and the dosing is dependent on protein restriction and body weight, although 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). The appropriate dose of the KA preparation has not been thoroughly established[3] although data by Wu et al.[4] indicates a mean daily KA dose of 5.5 tablets with a LPD represented a therapeutic strategy in slowing the progression of CKD

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Intended Audience: patients with chronic kidney disease (CKD) and healthcare providers to patients with CKD

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Table 1. Ketoanalogues: Availability in the United States

Product Name	Manufacturer	Prescription Needed	Available	Product Description	Pricing	Website
Ketorena	Ketorena; Nephcentric LLC	No	Phone order, online	Vanilla-flavored powder in 90 dose canisters or coated tablets as 90 dose (270 tablets) per container	Powder/Tablets: $145.50 *30% off with free s/h with purchase of 2 or more	https://www.ketorena.com/
Albutrix-S5 Albutrix-S4 Albutrix-S3	Albutrix	No	Online	Pill form, available as 180 pills per bottle (1 month supply). Albutrix-S3 is formulated for patients with GFR >40; Albutrix-S4 is formulated for patients with GFR between 20-40; Albutrix-S5 is formulated for patients with a GFR <20	One-time purchase $199.00 or subscribe for auto-delivery saves 10%: $179.00; Tax and s/h are included either way. Microtrix MVI ships free with every order (30 day supply)	https://www.albutrix.com/pages/moving_science_forward
Ketosteril®	Fresenius Kabi	Depends on country-specific regulatory considerations; by prescription only in the United States	Multiple online pharmacies	Packs of 100 film-coated tablets	As low as $90.00 per pack of 100 tablets	https://www.fresenius-kabi.com/in/products/ketosteril

GFR, glomerular filtration rate; MVI, multivitamin; s/h, shipping and handling.

Table 2. Ketoanalogues: Characteristics

Product Name	Indications for Use (with a LPD or VLPD)	Dosing	Ingredients	Special Considerations
Ketorena	CKD 4-5; CKD 3 with progressive decline in GFR; nephrotic syndrome being considered for an LPD; post-transplant w/CKD 3-5 or w/proteinuria; people on dialysis w/ residual kidney function, or those w/advanced disease who wish to find an alternative to dialysis*	Powder (vanilla flavored): Typically 1 scoop 3 times per day (each scoop mixed with 3 ounces fluid: water or juice). Tablets: Typically 3 tablets 3 times per day. Each dose contains 2100 or 2.1 g of keto and amino acids; Site recommends the dose to be 0.1 g/kg BW/day	L-lysine acetate, alpha-ketoleucine, alpha-ketovaline, alpha-ketoisoleucine, alpha-ketophenylalanine, L-ornithine HCl, DL-alpha-hydroxymethionine, L-threonine, L-histidine, L-tyrosine, L-tryptophan; Other ingredients: maltodextrin, silica, sucralose, natural flavors. (b) Each dose provides 5.1 g protein. KAs are calcium-based and contain 76 mg calcium per 1000 mg/active ingredient.	Contains calcium. Choice of powder or tablet. Developed by a nephrologist with a medical team available to provide guidance. FDA classifies Ketorena as GRAS.
(Albutrix-S5, Albutrix-S4, Albutrix-S3) Albutrix-S5	Albutrix-S5 is formulated for patients with a GFR <20*	2 tablets 3 times per day with meals	KAs of leucine, valine, isoleucine, phenylalanine, methionine; amino acids: L-histidine, L-lysine monoacetate, L-threonine, L-tyrosine, L-tryptophan; Each tablet contains 76.5 mg calcium. Other ingredients: maltodextrin, kollidon Cl, microcrystalline cellulose, colloidal silicon dioxide, talc, starch, magnesium stearate, hypromellose, polyethylene glycol; 33 mg nitrogen per pill†	Claim on the website that Albutrix also acts as a phosphorus binder. Patent pending magnesium KA and magnesium/calcium blends. Although formulas are based on GFR levels, it is recommended to choose the KA based on serum magnesium levels. Developed by a patient and affiliated with Kidneyhood.org with additional products for sale. Noted kidneyhood.org is the Albutrix.com site

(*Continued*)

Table 2. Ketoanalogues: Characteristics (*Continued*)

Product Name	Indications for Use (with a LPD or VLPD)	Dosing	Ingredients	Special Considerations
Albutrix-S4	Albutrix-S4 is formulated for patients with GFR between 20-40*	2 tablets 3 times per day with meals	KAs of leucine, valine, isoleucine, phenylalanine, methionine; amino acids: L-histidine, L-lysine monoacetate, L-threonine, L-tyrosine, L-tryptophan; Each tablet contains 30 mg magnesium and 30 mg calcium. Other ingredients: acacia gum, kollidon Cl, microcrystalline cellulose, colloidal silicon dioxide, talc, starch, magnesium stearate, hypromellose, polyethylene glycol; 32 mg nitrogen per pill†	
Albutrix-S3	Albutrix-S3 is formulated for patients with GFR >40*	2 tablets 3 times per day with meals	KAs of leucine, valine, isoleucine, phenylalanine, methionine; amino acids: L-histidine, L-lysine monoacetate, L-threonine, L-tryptophan; Each tablet contains 60 mg magnesium. Other ingredients: acacia gum, kollidon Cl, microcrystalline cellulose, colloidal silicon dioxide, talc, starch, magnesium stearate, glycerol monoca prylocaprate, polyvinyl alcohol, polyethylene glycol; 31 mg nitrogen per pill†	

(*Continued*)

Table 2. Ketoanalogues: Characteristics (*Continued*)

Product Name	Indications for Use (with a LPD or VLPD)	Dosing	Ingredients	Special Considerations
Ketosteril®	Prevention and therapy of damages due to CKD until GFR is 15 mL/min, (stages 2-5 CKD) per package insert	4-8 tablets 3 times/day with meals (based on 70 kg adult)	L-lysine acetate 53 mg, L-threonine 23 mg, L-tryptophan 38 mg, L-histidine 30 mg, L-tyrosine. KAs of isoleucine 67 mg, leucine 101 mg, phenylalanine 86 mg, methionine 59 mg; Calcium based and provides 1.25 mmol/ 0.05 g; Other ingredients: corn starch, crospovidone, povidone, talc, silicon dioxide, magnesium stearate, macrogol polymethacrylate, glycerol triacetate	Prescription only in the United States. Nitrogen per tablet: 36 mg

CKD, chronic kidney disease; FDA, Food and Drug Administration; GFR, glomerular filtration rate; GRAS, generally recognized as safe; KAs, ketoanalogues; VLPD, very low-protein; LPD, low protein diet; BW, body weight.

*Medical foods are purchased OTC without a prescription, and while not covered by insurance, it may be a qualified tax deductible medical expense

†Amount of amino acids not provided.

and after a mean follow-up period of 1.57 years, a decreased risk of initiating dialysis by 46%. This study represents the largest cohort study of long-term KA supplementation in patients with advanced CKD with a total of 1,483 patients enrolled in Taiwan. In addition, Zhang et al.[5] demonstrates the contribution of a VLPD-plus-KA in conserving residual renal function in incremental twice weekly dialysis. Thus, this nutrition intervention has a role throughout the diagnosis, progression and as maintenance dialysis dose is adjusted according to residual function.

Oral essential amino acid supplements have been used to enhance the efficacy of a LPD in patients with CKD not on dialysis,[6] and there are a variety of products available although it is difficult to determine the efficacy and specificity to CKD. Several products are known to be available as powder, liquid, or chewable sticks and may contain fiber. It is important to note that although these products are amino acid supplements, they are not KAs and the accuracy of information may be scrutinized. In addition, amino acid preparations are those that are touted to prevent muscle damage, those that improve intense physical endurance and growth, and those promoted for the ketogenic diet or even liquid aminos such as aminos made from fermented soybeans or coconut, both often used in place of soy sauce.

Because KAs are considered a medical food, these products may be purchased without a prescription in the United States although it befits health care providers to become familiarized with these products and the dosing to be able to assist patients. It is important to note that some countries may recognize KAs as a nutritional supplement and as a type of medicine, thus available by prescription only. The barriers to the use of KAs are a lack of familiarity and education, both on the part of health care providers and patients, availability of the product, and cost, with cost being the single most obtrusive barrier to KAs becoming a consistent strategy of nutritional care in a population that strongly requires fastidious intervention. Table 1 provides information regarding availability of KAs within the United States and includes an overview of pricing at the time of this review. Table 2 provides additional product information on dosing, ingredients, and special considerations.

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