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Ketoanalogues Therapy for CKD Patients: History and Current Status

Review Article

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Introduction

Ketoanalogues therapy is a well-known nutritional therapy for delaying the start of dialysis in chronic kidney disease (CKD). The product is presented in packages containing 100 tablets and each tablet contains 630 mg of keto analogues of essential amino acids and essential amino acids. Ketoanalogues therapy is used to supplement low-protein diets. It allows nitrogen intake to be decreased and leads to a reduction in the accumulation of by-products of nitrogen metabolism. Thus, protein malnutrition can be avoided and a normal course of protein metabolism is guaranteed.

The principal goal of well-planned, protein-restricted dietary regimen in compliant patients is to decrease the accumulation of nitrogen waste products, hydrogen ions, phosphates and inorganic ions while maintaining an adequate nutritional state. This goal is achieved with Ketoanalogues therapy (Ketoanalogues + protein restricted diet). Ketoanalogues capture excessive nitrogen residues (of the urea) in patients with chronic renal insufficiency, neutralizing them in the process of transamination, thus breaking the vicious circle of the disease.

The use of Ketoanalogues therapy is based on the reversible transaminase reactions which take place in the humans, and this allows formation of relevant essential amino acids.These substances provide two benefits of Ketoanalogues therapy which decrease the amount of nitrogen to be eliminated by kidneys and help to stabilize kidney function: Nitrogen intake can be restricted and endogenous amino groups can be used thus ureagenesis is limited.

The use of calcium salts of keto acids also allows Ketoanalogues therapy to correct calcium and phosphate metabolism disturbances Keto analogues are different from amino acids and they counteract to certain metabolic alterations which are observed in CKD patients. The calcium salts of the keto acids foster the correction of hyperphosphatemia and of secondary hyperparathyroidism which are well known in chronic kidney disease.

The beneficial effect on the resistance to insulin, a factor which leads to increased cardiovascular morbidity and mortality, and the action on the cell sodium pumps appear to involve a decrease in the production of uremic toxins of dietary origin [115].

When used in accordance with the recommended dosage appropriate to the indication and in compliance with the known contraindications and precautions for use, Ketoanalogues therapy has very good efficacy/safety and benefit/risk ratios [115].

In Ketoanalogues therapy effects the metabolism of the CKD patient and leads to quality of life by decreasing uremic symptoms and improving metabolic disturbances associated with CKD.

Mode of Action

Ketoanalogue treatment allows for protein intake below the minimum daily requirement (0.6 g/kg/day). Furthermore, the combination of amino acids and ketoanalogues allows for a significant reduction in nitrogen intake. Although ketoanalogues of amino acids contain less nitrogen, they have the same effect on the nitrogen balance, according to experimental and clinical investigations [117]. The required quantities and balances of ketoanalogues in the formula were established in accordance with the demand for essential amino acids as per WHO 2007 standards, as opposed to other formulae that are based on previous criteria. Alpha-ketonic acids are simple carbon chains that lack an amino group. These analogs lack nitrogen and do not generate nitrogenous byproducts. They absorb amino groups and can be converted back into the matching amino acid in the organism. In the transaminase reaction that results in its synthesis, urea-generating amino acids such as glutamine and alanine serve as

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amino group donors. As a result, these amino acids are diverted from their original urea-generating pathway. This mechanism comprises amino group recycling, nitrogen conservation, and nitrogen trapping [115]. The transfer of the amino group to the ketoanalogues results in nitrogen savings and a direct suppression of ureagenesis. This behaviour was observed in numerous investigations. Inhibition of ureagenesis persists for 8 days after discontinuation of the ketoanalogues [115, 118].

Pharmacodynamic studies provide valuable information on the metabolic effects of therapy and serve as a solid foundation for the use of ketoanalogue-containing formulas. Ketogenic diets cure the majority of CKD metabolic abnormalities, such as phospho-calcic disorders, metabolic acidosis, and hypertriglyceridemia. Furthermore, the use of protein derived primarily from vegetables promotes increased nutritional diversity and patient compliance.The retention of nitrogenous byproducts is significant in uremic toxicity. Low-protein diets have been advocated for many years as a symptomatic treatment for uremic symptoms. Ketoanalogue treatment lowers dietary acid load and phosphate intake. At the same time, it avoids acidosis and hyperphosphatemia, both of which contribute to the development of metabolic and endocrine abnormalities in chronic kidney disease.

In vitro experiments have shown that ketoleucine and leucine can increase protein synthesis. These substances induce increased aggregation of polyribosomes. Ketoleucine stimulates the amino transferase activity (stimulating transfer of the amino group to alpha-ketonic acid) [119, 120].

According to some authors, ketoanalogues may hinder protein breakdown, and would therefore have an anti-catabolic effect. In addition, the decrease in urinary protein excretion contributes to the rise in serum albumin and the maintenance of various indices of nutritional status within the normal range which is usually observed in patients on ketodiet [121].

Presence of calcium in creates beneficial effects on calcium/phosphate metabolism and hyperparathyroidism. Ketoanalogues therapy has an undeniable hypophosphatemic effect, due to the anti-absorbent action on the phosphates as a result of the formation of insoluble calcium phosphate in the intestine [55].

Clinical Documentation

Numerous clinical trials have established the efficacy and acceptability of ketoanalogues treatment, with the majority of patients reporting a clear improvement in their overall health while their physical activity remained constant or improved [115].

Retardation of the progression of CKD

Numerous clinical investigations have consistently indicated that ketoanalogue treatment improves several features of CKD. Clinical investigations and meta-analyses have proven that combining a reduced protein diet with Ketoanalogues therapy considerably slows the course of renal failure and delays the start of dialysis. Teschan's re-analysis of the Modification of Diet in Renal Disease Study (MDRD) yielded the most remarkable results [16]. The pair-wise comparison revealed that the average loss of GFR in the amino/keto acid supplemented group was 53% slower than in the control group. Other smaller clinical studies have revealed similar findings. A recent meta-analysis published in the Cochrane Library, integrating 7 clinical studies, three of which used ketoacids, indicated that this protein diet reduced the risk of kidney mortality by around 40% when compared to a high or unrestricted protein intake [135]. Several clinical investigations have indicated that a low protein diet combined with ketoacid supplementation can postpone the onset of dialysis [42,69,135,116]. Walser and Hill demonstrated that patients with GFR < 10ml/min can be safely treated with a low protein diet and ketoacids for nearly a year without dialysis [8]. Similar findings were observed by Aparicio [13] and a re-analysis of the MDRD research [16]. A randomised, double-blind, placebo-controlled trial found that ketoanalogue therapy protects renal function and helps patients maintain their body mass index. Ketoanalogues were found to be both safe and effective in slowing the course of renal failure and maintaining nutritional status in CKD patients. GFR remained constant in the Ketoanalogues treatment group while decreasing considerably in the placebo group, indicating renal function protection. Serum total proteins dropped in the placebo group, and serum albumin trended downward, whereas both of these measures were unchanged in the Ketoanalogues treatment group [102].

A long-term, prospective, randomised study discovered that ketoanalogue medication has clear benefits for CKD patients. 186 patients were chosen at random and followed for three years, with updates every six months. The glomerular filtration rate decreased slightly from 26 to 23 mL/min in the ketoanalogues treatment group, but the decreases were substantially larger in the other two control groups. The authors discovered that this therapeutic technique significantly delays the progression of renal failure and reduces proteinuria [123].

CKD patients were given a protein-restricted diet supplemented with amino acids and ketoanalogues for two years. Urinary urea excretion dropped after 3 months and then marginally increased at 2 years. There was no significant difference in total fat mass or percentage fat mass. Lean body mass stabilised at 6 months, then rose dramatically between 6 and 24 months. The scientists found that a protein-restricted diet supplemented with keto mimics is nutritionally safe for the long term. [124, 125].

The nephroprotective function appears to be effective in both diabetic and nondiabetic nephropathies. The benefits of a low-protein diet combined with ketoanalogue therapy on metabolic abnormalities associated with chronic renal disease appear to have potential favourable effects on morbidity and mortality [115], as noted in numerous recent meta-analyses [69, 15].

In a study of 65 CKD patients followed for up to 5½ years, a protein-restricted diet combined with Ketoanalogues treatment resulted in a 65% reduction in progression [56]. Patients who follow the advised diet experience a significant slowdown of the progression of renal failure, as well as a large delay until end-stage renal failure. Several clinical trials have studied and proven that protein restriction and keto acid treatment prolong the course of CKD. [2-9, 11-16, 18-20, 22, 23, 25-28, 30, 35-37, 40, 42, 44, 45, 50, 54, 56, 58, 63, 64, 68, 69, 71-76, 78, 80-85, 95-97, 99, 101, 126, 127 128 129].

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Table 1: Characteristics of children and their mothers/caregivers (N=364).

Variable	Values	Frequency	Percent (%)
Sex	Male	173	47.5
	Female	191	52.5
Age of children (months)	24-36	143	39.3
	37-48	92	25.0
	49-59	130	35.7
Birth weight (Kg)	< 2.0	6	1.6
	2.0 – 3.0	164	45.1
	3.1 – 4.0	184	50.5
	>4.0	10	2.7
Immunization status	Immunized	355	97.5
	Not immunized	9	2.5
Suffered any illness	Yes	168	46.2
	No	196	53.8
Exclusively breastfed	Yes	360	98.9
	No	4	1.1
Mother/caregiver's age (years)	15 – 20	21	5.8
	21-30	164	45.1
	31-40	149	40.9
	≥41	30	8.2
Mother/caregiver's marital status	Married	213	58.5
	Single	133	36.5
	Separated/divorced	18	5
Mother/caregiver's education	No formal education	66	18.1
	Primary education	211	58.0
	Secondary education	78	21.4
	Tertiary education	9	2.5
Mother/caregiver's occupation	Unemployed	247	67.9
	Farmer	86	23.6
	Civil servant	7	1.9
	Business	22	6.0
	Student	2	0.6
Decision maker on use of money in the house	Husband	197	54.1
	Mother	144	39.6
	Grandmother	13	3.6
	Grandfather	10	2.7
Decision maker on food cooked	Husband	15	4.1
	Mother	339	93.1
	Grandmother	10	2.7

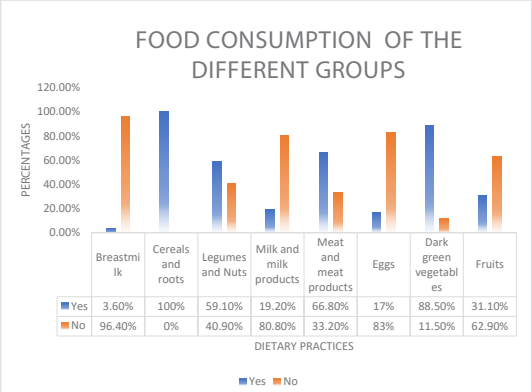

Figure 1: Food consumption from different food groups by the children.

Table 2: Dietary practices of children (N=364)

Variable	Frequency (N)	Percentage (%)
Number of meals eaten per day		
≤2	120	32.9
3 times	238	65.4
>3	6	1.6
Breakfast consumption		
Yes	213	58.5
No	151	41.5
Reason for skipping breakfast (N= 151)		
Food not available	142	39.1
Child does not like eating	6	1.6
Child goes to play	3	0.8
Mode of child feeding		
On demand	95	26.1
On request	269	73.9

Table 3: Dietary Diversity Score of children (N=364)

		Dietary Diversity Score		p-value
	Low DDS (< 5)	**Minimum DDS (≥5)**	**Total**	
Males	124 (71.1%)	49 (28.3%)	173 (100%)	0.453
Females	130 (68.1)	61 (31.9%)	191 (100%)	
Total	**254 (69.8%)**	**110 (30.2%)**	**364 (100%)**	

Beneficial effects on metabolic disturbances associated with CKD

The therapy also relieves uremic symptoms and improves metabolic disturbances associated with CKD giving a better quality of life. The following metabolic complications have been shown to be significantly improved by a Ketoanalogues therapy -supplemented low protein diet in predialysis CKD patients: correction of disturbances in the calcium and phosphate metabolism; secondary hyperparathyroidism and renal osteodystrophy; normalization of the carbohydrate metabolism including lowering of insulin; resistance and reduction in hyperinsulinemia; improvement of the disturbed serum lipid profile; improvement in endocrine disturbances. Information on the effect of Ketoanalogues therapy on these metabolic complications are given below.

It has been demonstrated that in patients with advanced CKD, a low protein diet supplemented with ketoanalogues can reduce the amount of Erythropoietin required to maintain target haemoglobin levels by approximately 35%. This effect appears to be linked to the correction of moderate hyperparathyroidism [103,104].

Majority of the clinical studies investigating the effects of keto acids on metabolic disorders associated with CKD are on Calcium / Phosphate metabolism distrubances namely renal osteodystrophia.

In one study, hyperparathyroidism was improved in more than 80% of patients [43]. Ketoanalogues treatment protects or improves bone deterioration caused by renal failure [32]. Ketoanalogues can

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Table 4: Anthropometric status of the participants based on sex.

Variables	Male		Female		Total		p-value
	F	%	F	%	F	%	
Weight for height							0.566
Not wasted (>-2SD)	154	89.0	170	89.0	324	89.0	
Wasted (<-2SD)	19	11.0	21	11.0	40	11.0	
Height for age							0.013*
Not stunted (>-2SD)	118	68.2	151	79.1	269	73.5	
Stunted (<-2SD)	55	31.8	40	20.9	95	26.5	
Weight for age							0.244
Not underweight (>-2SD)	144	83.2	165	86.4	309	85.0	
Underweight (<-2SD)	29	16.8	26	13.6	55	15.0	
BMI for age Z score							0.584
Normal (≥ -2 - ≤+2SD)	165	95.4	182	95.3	347	95.0	
Overweight/obesity (>+2SD)	8	4.6	9	4.7	17	5	
MUAC							0.280
Malnourished (<13.5cm)	34	19.7	32	16.8	66	12.1	
Not malnourished (>13.5cm)	139	80.3	159	83.2	298	87.9	

* Significant at p<0.05 using Fisher's test

Table 5: Anthropometric status of children based on age

Variables	Age(months)				
	24-36 (N=147)	37-8 (N=92)	49-59 (N=125)	Total	p-value
Weight for height					.020*
Not wasted (>-2SD)	122 (84)	86 (93.5)	116 (92.8)	324 (89.0)	
Wasted (<-2SD)	25 (16)	6 (6.5)	9 (7.2)	40 (11.0)	
Height for age					.031*
Not stunted (>-2SD)	97 (67.2)	71 (77.2)	101 (80.8)	269 (73.9)	
Stunted (<-2SD)	50 (32.8)	21 (22.8)	24 (19.2)	95 (26.5)	
Weight for age					.232
Not underweight (>-2SD)	118 (80.7)	81 (88.0)	110 (88.0)	309 (84.9)	
Underweight (<-2SD)	29 (19.3)	11 (12.0)	15 (12.0)	55 (15.0)	
BMI for age Z score					.098
Normal (≥ -2 - ≤+2SD)	141 (97.5)	85 (92.4)	121 (96.8)	347 (95.3)	
Overweight/ obesity (>+2SD)	6 (2.5)	7 (7.6)	4 (3.2)	17 (5)	

* Significant at p<.05 using Fisher's test

correct the majority of carbohydrate metabolism disorders seen in uremia, including improved tissue sensitivity to insulin [49, 122], even in uremic diabetic patients; reduced circulating insulin levels due to an increase in insulin metabolic clearance rate [21] and improved insulin inhibitory action on endogenous glucose production [17]. Meat, poultry, fish, and dairy products are the primary sources of protein and phosphorus. Reducing phosphorus consumption has been found to reduce the development of secondary hyperparathyroidism in CKD. Calcium salts of ketoacids act as phosphate binders, increasing the phosphorus-lowering effect of protein restriction [55].

Table 6: Relationship between dietary practices and nutritional status

	Low DDS		Minimum DDS		Total		p-value
	F	%	F	%	F	%	
Weight for height							0.406
Not wasted (>-2SD)	223	89.9	93	86.9	316	89	
Wasted (<-2SD)	25	10.1	14	13.1	39	11	
Height for age							0.224
Not stunted (>-2SD)	179	71.6	84	77.8	269	73.5	
Stunted (<-2SD)	71	28.4	24	22.2	95	26.5	
Weight for age							0.303
Not underweight (>-2SD)	211	83.7	95	88.0	306	85.0	
Underweight (<-2SD)	41	16.3	13	12.0	54	15.0	
BMI for age Z score							0.203
Normal (≥ -2 - ≤+2SD)	236	94.0	105	97.2	341	95.0	
Overweight/obesity (>+2SD)	15	6.0	3	2.8	18	5.0	
MUAC							0.917
Malnourished (<13.5cm)	31	12.2	97	88.2	44	12.1	
Not malnourished (>13.5cm)	223	87.8	13	11.1	320	87.9	

Table 7: Logistic regression analysis: Relationship between dietary practices and nutritional status

Categories	Outcome Variable	AOR	P-value	95% CI
Low DDS	WHZ	1.00		
Minimum DDS	WHZ	1.343	0.408	[0.669, 2.698]
Low DD	HAZ	1.00		
Minimum DDS	HAZ	0.720	0.225	[0.424, 1.224]
Low DD	WAZ	1.00		
Minimum DDS	WAZ	0.704	0.304	[0.361, 1.375]
Low DD	BAZ	1.00		
Minimum DDS	BAZ	0.450	0.214	[0.127, 1.586]
Low DD	MUAC	1.00		
Minimum DDS	MUAC	0.964	0.917	[0.484, 1.922]

The effect of ketoanalogue treatment on PTH levels is explored in individuals undergoing maintenance hemodialysis for up to ten years. Following treatment, there was a statistically significant decrease in PTH and inorganic phosphate levels. Early administration of ketoanalogues therapy may delay or even prevent the development of renal osteodystrophy due to a direct pharmacological effect of ketoanalogues [51,55,79,32]. The effects on phosphate and calcium metabolic indices are long-lasting. Beneficial effects on plasma phosphate and PTH concentrations were maintained in patients with advanced CKD using ketoanalogues treatment throughout a 2-year period [130].

In continuous ambulatory peritoneal dialysis, the quelating agents were replaced with ketoanalogues. After three months phosphate levels decreased significantly, serum calcium levels increased and parathormone levels decreased. All nutritional parameters increased

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at the end of the study. The authors concluded that calcium salts of ketoanalogues are effective alternative to aluminum containing phosphate binders [105, 43, 48].

Metabolic acidosis, which is common in CKD, is caused by poor hydrogen ion excretion, the majority of which is produced by the metabolism of sulfur-containing amino acids [120]. This acidosis has various negative implications, including impaired protein metabolism, glucose tolerance, and bone metabolism. Only a severe reduction or suppression of animal-derived protein can cure metabolic acidosis [115]. Lower bicarbonate levels were seen in patients treated with keto acids, indicating a beneficial effect against metabolic acidosis [32,65,90].

Abnormal glucose metabolism is seen in almost half of CKD patients. This is typically manifested as impaired glucose tolerance and hyperinsulinemia. Glucose tolerance was improved, with considerably lower insulin levels [49, 122, 21, and 131]. It has been demonstrated that a protein-restricted diet supplemented with keto analogues protects erytrocytes from lipoperoxidation in CKD patients, which improves some metabolic outcomes of uremic syndrome [22]. In 61 male CKD patients treated with ketoanalogues [132, 133], blood triglycerides decreased significantly while Apo A1 and the Apo-A1/Apo-B ratio increased significantly. These are crucial lipid metabolism indicators. Clinical studies have demonstrated that a Ketoanalogues therapy-supplemented low-protein diet lowers triglyceride level [115].

In two groups of patients with severe CKD, pH and bicarbonate levels were significantly higher in those treated with a protein-restricted diet supplemented with a combination of amino acids and ketoanalogues. The authors proposed that the vegetarian nature of the diet, which must be supplemented with ketoanalogues, was responsible for this impact in relation to its very low acidifying action [134].

The evolution of nutritional status after initiation of hemodialysis in patients previously treated by protein restricted diet supplemented with keto acids was assessed. Albumin, prealbumin and body mass index increased in all patients and lean body mass remained stable. The authors conclude that treatment was nutritionally safe. Protein restricted diet supplemented with essential amino acids or ketoacids has no detrimental effects on nutritional parameters. Also, the survival during dialysis was not negatively affected in patients who were previously treated with a supplemented protein restricted diet [27, 110.]

In CKD patients with Glomerular Filtration Rate (GFR) clearance less than 25 ml/min, a protein-restricted diet containing 0.3 g/kg/d of vegetable protein supplemented with ketoanalogues therapy resulted in a significant reduction in urinary albumin excretion and fractional renal albumin clearance, while serum albumin increased significantly [41]. It has been shown that protein restricted diet supplemented with ketoanalogues can maintain nutritional status of the patients. Investigators conclude that this therapy can constitute an efficient therapeutic alternative for CKD patients since it also reduces serum urea nitrogen and improves calcium and phosphate metabolism. These findings have been confirmed by a large number of studies covering hundreds of CKD patients [10, 17, 21, 26, 28-30, 32, 41, 43, 46-48, 51-53, 55, 57, 60, 65-67, 72, 77-79, 88, 89, 91, 94, 99, 100].

Conclusion

Protein-restricted diets supplemented with ketoanalogue therapy should be recommended to all CKD patients in conjunction with other nephroprotective measures such as blood pressure control and angiotensin converting enzyme inhibitor medications. It has been found to retard the progression CKD and various other beneficial effects discussed above.

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