Nephrologia Urologia: Open Access (NUO)

Research Article

Role of Ketoanalogues In Chronic Kidney Disease Stages 1-3

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Abstract

Low-protein diets (LPD) mitigate accumulation of nitrogenous wastes and metabolic disturbances, both of which are characteristic of advanced stages of CKD. This study was undertaken to evaluate i) effect of combined therapy of very low protein diet (vLPD) and ketoanalogues on renal function of patients in CKD stages 1-3, and ii) to study compliance to very low protein diet.

Material and Methods: This was a prospective randomized controlled study conducted on 40 predialysis patients divided into two groups: group1 ketoanalogues supplemented group on very low protein diet 0.4g/kg/d, and Group 2 was CKD patients who were not supplemented with ketoanalogues and were kept on low protein diet 0.6 g/kg /day. Biochemical parameters tested were serum creatinine, sodium, potassium, calcium, phosphorus, albumin, hemoglobin and fasting blood glucose.

Results: At base line, there was no significant difference between the parameters between the groups. At visit 2, the serum albumin level decreased from 3.8±0.90 g/dL to 3.09±0.38 g d/l in control group, while the levels were maintained in group 1 (4.11±0.43 at visit 1and 4.03±0. 52 at Visit 2). At visit 2 serum creatinine declined from 1.61±0.52 to 1.40±0.52 mg% in group 1. In group 2 serum creatinine increased from 2.20±0.29 to 2.47±0.33 mg%, GFR declined from 51.14±15.1 ml/minute to 37.8±10.0 and serum albumin declined to from 3.8±0.90 to 3.09±0.38 g/dL. There was significant difference between visit 1 and 2 in GFR in group 2. In group 1 GFR remained stable at 47.65±13.26 ml/minute and there was a significant difference in the GFRs of group1 and 2 at visit 2. There was significant difference (p = 0.023) in GFR of groups 1 (47.65±13.26 ml/minute) and 2 (37.8±10.0ml/minute) at visit 2.

Conclusion: In the intervention group GFR was maintained at 47.0 ml/min while in the control group the GFR decreased from 51.1±15.1ml/minute to 37.8±10.0 ml/minute. At the end of the study, the serum albumin level was higher in the intervention group compared to control group. Supplementation with ketoanalogues can prevent decline in renal function even without adherence to very low protein diet.

Keywords: *Very Low-Protein Diet, Chronic Kidney Disease, Ketoanalogues, Glomerular Filtration Rate*

Introduction

Low-protein diets (LPD) have been one of the cornerstones in the management of chronic kidney disease (CKD) for alleviating uremic symptoms and slowing the progression of renal dysfunction for more than five decades. Italian researchers have a longstanding tradition in implementing low protein diets in the treatment of CKD patients, with the principle objective of alleviating uremic symptoms, improving nutritional status and also a possibility of slowing down the progression of CKD or delaying the start of dialysis. Apart from mitigating the accumulation of nitrogenous wastes and metabolic disturbances, both of which are characteristic of advanced stages of CKD, such diets also reduce the quantities of sulfates, phosphates, potassium, and sodium ingested, thus leading to a more favorable metabolic profile and possibly improved disease progression [1] Ketoanalogues are essential amino acid tablets which contain all amino acids essential for uremic patients (50 mg /tablet; dose 5 mg/kg/g) prescribed as treatment of chronic kidney disease patients on conservative management therapy (CKD stage I, II, III). This medication allows reduction in the nitrogen supply and provides calcium. In combination with very low protein diet/ low protein diet, the medication helps in delaying progression of kidney disease in the predialysis period. Supplementation with ketoanalogues has been reported to reduce uremic symptoms, preserve residual renal function, slow down rate of progression of the disease, delay onset of dialysis and improve metabolic acidosis, reduce hyperphosphatemia, and hyper triglyceridemia complications due to renal insufficiency (like proteinuria, disturbances in calcium-phosphate, carbohydrate and lipid metabolism) [2].

Some studies recommend use of ketoanalogues in the conservative management of CKD [2,3]. MDRD study showed the benefits of dietary protein restriction and also more importantly an additional benefit by ketoanalogue supplementation in delaying progression of CKD [3]. Adding ketoanalogues, nitrogen-free analogues of essential amino acids, to very low-protein diets for patients with chronic kidney disease (CKD) may significantly delay dialysis initiation. But the extent of improvement and effect of ketoanalogue supplementation has not been clear. This study was undertaken to evaluate i) effect of combined therapy of very low protein diet (vLPD) and ketoanalogues on renal function of patients in CKD stages 1-3, and ii) to study compliance to very low protein diet.

Material and Methods

This was a prospective randomized controlled clinical study

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Received: April 12, 2018; **Accepted:** April 24, 2018; **Published:** April 27, 2018

which was conducted on 40 patients. The sample size was calculated using Students's t test to compare means of two groups at 0.05 % significance level and power of 85%. Based on these assumptions the minimum sample size derived using Student's T test was 19 ((10 patients in each group) and therefore we recruit 40 patients, 20 in each group.

Inclusion criteria was CKD patient with GFR <60 but >30 ml/ minute as calculated by Cockroft's formula [4] (males: 140-Age x Weight kg/ 72- Serum Creatinine mg/dl; for females product of the formula multiplied by 0.85). Exclusion Criteria was patients with cancer, systemic disease, obstructive uropathy and rapidly progressive glomerulonephritis. Patients were divided into 2 groups of 21 patients (15 males and 5 females) each. Group 1 was ketoanalogue group who were advised very low protein diet (vLPD) 0.4 gram /kg day protein along with 300 mg of ketoacids (1 tablet of Renhold manufactured by Pancea Biotech Ltd, contains 675 mg of ketoacids; recommended dose is 5 mg/kg/d)) in three divided doses and 35 kcal/kg/d of energy. Supplementation with ketoanalogues was done for 10 months. Group 2 was CKD patients who were not supplemented with ketoanalogues and were kept on low protein diet 0.6 g/kg /day and 35 kcal/kg /day energy [5]. Three days dietary recall was taken on visit 1 and 2 by a renal dietician but patient's dietary intake was not monitored between two visits.

The clinical trial was approved by ethics committee of the institute. Biochemical investigations included hemoglobin, serum creatinine, sodium, potassium, calcium, phosphorus, albumin and random blood glucose done at baseline (visit 1) and at 10 months (Visit 2). Glomerular filtration rate (GFR) was calculated using Cock-Croft–Gault equation mentioned above. Demographic profile of the patients is given in the Table 1. The final sample size was 40 as 1 patient dropped out from ketoanalogue group because of generalized weakness soon after ingesting medicine perhaps due to drop in blood pressure and one 1 dropped out from control group due to non-compliance to investigations. Nutritional status was assessed using subjective global assessment (SGA) score [6]. Compliance to drug intake was monitored by counting empty (used) tablet strips returned by the patient. Disease profile, dietary intake, biochemical profile and anthropometric profile of the patients are given in Tables 1-3.

Table 1: Disease Profile of the Patients.

Disease (s)	Group 1 N=20 (Ketoanalogue)	Group 2 N=20 (Control)
CKD	5	10
CKD, Hypertension	6	6
CKD, Diabetes mellitus	2	1
CKD, Diabetic kidney disease	1	-
CKD, Hypertension, Diabetic kidney disease	5	-
CKD Hypertension, Diabetes mellitus	-	3
CKD Hypertension, Rheumatoid arthritis.	1	-

Table 2: Dietary Intake of The Patients at Visit 1 and 2.

Parameter	Group1(Ketoanalogue)	Group 2 (Control)
Dietary Energy kilocalories/d	1104.59±212.29	991.21±258.49
Dietary Energy kilocal/kg/d	19.48±6.84	16.15±5.85
Dietary Protein gram/d	35.11±7.80	30.72±6.76
Dietary Protein gram/kg/d	0.62±0.24	0.50±0.16
Carbohydrate gram/d	186.45±40.31	171.09±54.75
Fat gram/d	26.03±12.59	18.91±13.46
Dietary Sodium mg/d	222.94±102.26	200.95±174.84
Dietary Potassium mg/d	1187.86±338.27	1123.76±430.73
Dietary Calcium mg/d	443.25±271.33	446.18±248.67
Dietary phosphorus mg/d	999.50±238.42	836.41±238.17
Dietary Iron mg/d	17.53±22.06	11.00±3.29

Table 3: Biochemical Profile of The Patients at Visit 1 and 2.

Parameter	Group 1 (Ketoanalogue)		Group 2 (Control)	
	Visit 1	Visit 2	Visit 1	Visit 2
Age years	52.26±13.17	No change	46.86±13.64	No change
Weight kg	61.53±13.49	No change	61.95±10.85	No change
Hemoglobin g%	12.19±1.95	14.20±1.00	12.35±1.48	12.50±1.00
Serum Creatinine	1.61±0.52	1.40±0.52	2.20±0.29	2.47±0.33
GFR ml/min 0.023*	47.79±13.2	47.65±13.26*	51.14±15.1	37.8±10.0*
Blood Sugar Fasting	117.77±33.2	92.00±31.1	139.71±90.2	120.00
Serum Albumin	4.11±0.43	4.03 ±0. 52	3.8±0.90	3.09±0.38*
Serum Sodium	137.5±3.39	140.3±2.52	138.9±4.12	138.00
Serum Potassium	4.43±0.63	4.35±0.62	4.43±0.63	4.35±0.62
Serum Calcium g/dL	8.55±1.98	9.87±1.04	8.62±2.05	8.55±0.78
Serum Phosphorus mg/ dL 0.018	3.67±0.86*	3.88±0.88	3.54±0.89	4.00±0.28
SBP mmHG	130.35±15.06	136.6±25.17	127.44±15.5	116.50±9.19
DBP mmHG	81.29±7.55	81.33±10.26	82.78±8.95	74.00±5.66

SBP: Systolic blood pressure; DBP: Diastolic blood pressure *Significance (2-tailed)

Results

Table 3 shows that at visit 1, serum creatinine was 1.61±0.52 mg% in group1 and 2.20±0.29 mg% in group 2, hemoglobin was 12.19±1.95 mg% in group 1 and 12.35±1.48 mg% in group 2, serum albumin was 4.11±0.43 g/dL in group 1 and 3.8±0.90 g/dL in group 2, serum calcium was 8.55±1.98 mg/dL in group 1 and 8.62±2.05 mg/dL in group 2, serum phosphorus was 3.67±0.86 mg/dL in group 1 and 3.54±0.89 mg/dL in group 2, serum sodium was 137.5±3.39 mg/dL in group 1 and 138.9±4.12 mg/dL in group 2, serum potassium was 4.43±0.63 mg/dL in group 1 and 4.43±0.63 in group 2, GFR was 47.79±13.2 ml/minute in group 1 and 51.14±15.1 ml/minute in group 2 and SBP was 130.35±15.06 mmHG and 127.44±15.5 mmHG and DBP 81.29±7.55 mmHG and 82.78±8.95 mmHG. There was no significant difference between the parameters between the groups at base line. After 10 months, at visit 2, the serum albumin level decreased from 3.8±0.90 g/dL to 3.09±0.38 g d/l in control group, while the levels were maintained in group 1 (4.11±0.43 at visit 1and 4.03 ±0. 52 at Visit 2). At visit 2 hemoglobin increased to 14.20±1.00 mg%, serum calcium increased to 9.87±1.04 mg dL and serum sodium increased to 140.3±2.52, serum creatinine declined to 1.40±0.52 mg% in group 1. In group 2 except for serum creatinine which increased to 2.47±0.33 mg%, GFR declined from 51.14±15.1 ml/minute to 37.8±10.0 and serum albumin declined to from 3.8±0.90 to 3.09±0.38 g/dL all other parameters were unchanged. There was significant difference in serum albumin level (p =0.000) between visit 1and 2 in group 2. There was significant difference between visit 1 and 2 in GFR in group 2. In group 1 GFR remained stable at 47.65±13.26 ml/minute and there was a significant difference in the GFRs of group1 and 2 at visit 2. There was significant difference (p = 0.023) in GFR of groups 1 (47.65±13.26 ml/minute) and 2 (37.8±10.0ml/minute) at visit 2.

Systolic blood pressure at visit 1 in ketoanalogue group was 130.35±15.06 mm HG and in control group was 127.44±15.56 mm HG. Systolic blood pressure at visit 2 in ketoanalogue group was 136.67±25.17 and in control group was 116.50±9.19 mmHG. The energy intake was 19.48±6.84 kcal/kg/d and 16.15±5.85 kcal/kg/d in group 1 and 2 respectively which is significantly low compared to recommended dietary allowance for CKD patients. The protein intake was 0.62±0.24 g/kg/d and 0.50±0.16 g/kg/d in groups 1 and 2 respectively.

Discussion

Once chronic kidney disease sets in, vicious cycle of malnutrition, inflammation, infection, anemia, fluid imbalance, hormonal imbalance and other associated disorders begins which affects quality of life and survival. As kidney disease progresses, the capacity to respond to

changes in nutrients and water intake becomes less flexible. Solute and water excretion per nephron increases, but the fewer number of functional nephrons leads to a more restricted range of solute or water excretion. In the remnant glomeruli hyperfiltration appears with subsequent histological lesions and decreased glomerular filtration [8]. When diet exceeds daily protein requirement, the excess protein is degraded to urea and other nitrogenous wastes and these products accumulate. Because the severity of uremic syndrome is proportional to the accumulation of these waste products and ions, therefore, dietary intake needs to be adjusted. A lot of data have been published on beneficial effect of ketoanalogues [9-20] in combination with very low protein diet /low protein diet in CKD stages 1,2,3. In chronic kidney disease studies have suggested that dietary protein restriction can prevent functional deterioration in humans, due to reduction in glomerular capillary pressure and filtration [9-14]. Moderate dietary protein restriction is an effective way of delaying functional renal deterioration [15]. An improvement in clinical and nutritional status in patients with a low protein diet supplemented by ketoanalogues [16-20] is also well established.

Despite obvious benefits of protein restriction, concern has been raised in patients on very low dietary protein (very-low-protein diets; VLPDs), which could lead to deterioration in the nutritional status of CKD patients [3]. In present study, even though protein intake was normal 0.62±0.24 g/kg/d instead of 0.4 g/kg/d as advised to group 1, the GFR remained stable at 47.7 ml/min over 10 months in intervention group. It is possible that the extra 0.2g/kg/d of protein that the intervention group took was utilized for providing energy as energy intake was 50% less than recommended because of which GFR remained stable. Also, the serum albumin level was well preserved 4.11±0.43 g/dL at visit 1 and 4.03±0.52 g/dL at 10 months. Hence, this study shows that even without very low protein diet (vLPD), ketoanalogue supplementation even with standard low protein diet can preserve renal function. The nutritional status was preserved as per the SGA scores. In our cohort, at baseline, the GFR was higher in group 2 (controls 51.14±15.1 ml/minute) compared to group 1 (ketoanalogue 47.79±13.2 ml/minute). However, the GFR declined in group 2 (control) from 51.14 ml/min at baseline to 37.8 ml/minute over a period of 10 months which was significant. The serum calcium, phosphorus, sodium and potassium remained unaffected with ketoanalogue supplementation. The fasting blood glucose was better controlled in supplemented group (117.77±33.2 mg% at visit 1 and 92.00±31.1 mg% at visit 2) at 10 months compared to controls (139.71±90.2mg % at visit 1 and 120.00mg % visit 2).

In another study [3] conducted on 132 adult patients with Stage 3 to Stage 5 (predialysis) initiated on a protein restricted ketoanalogue supplemented diet, the serum creatinine decreased from 3.52±00 mg/dl to 3.30±1.63 mg/dl(p>0.05) in the standard low protein diet of 0.6g/kg/d (SLPD) group and a decrease from 3.74±00 mg/dl to 3.55±1.67 mg/dl(p>0.05) in the SVLPD (very low protein diet) group though the difference was not statistically significant. The eGFR showed improvement from 26.76±00 ml/min to 30.75±17.31 ml/min (p<0.05) at end of six months in the SLPD group and an increase from 23.62±00 ml/min to 26.35±10.58 ml/min(p>0.05) in the SVLPD group. Serum albumin increased from 3.85±00 gm/dl to 4.00±0.56 gm/dl (p<0.05) in the SLPD group and an increase from 4.03±00 gm/dl to 4.07±0.47 gm/dl in the SVLPD group indicating an improvement in nutrition in SVLPD group (p>0.05). The ketoanalogue treated patients showed significant improvement in their renal function, metabolic status and other nutritional parameters over a period of 6 months.

Studies so far advocate right dosage of the ketoanalogue supplements in addition to ensuring strict compliance of dietary restrictions [3]. A sixty-three (63) patient-months of therapy on nine patients who were on a protein-restricted diet with severe chronic renal failure (mean glomerular filtration rate 4.8 ml/min; mean serum creatinine 11.3 mg/dl) were treated with a diet containing 33 kcal/kg and 22.5 g/day of mixed quality protein [21]. Patients were supplemented by a combination of amino acids and mixed salts formed between basic amino acids and keto-analogues of essential amino acids. The supplement was designed to minimize or reverse the amino acid abnormalities of chronic renal failure rather than to meet the normal requirements for the essential amino acids. Results showed that specially designed supplement can improve or maintain protein nutrition in patients with severe chronic renal failure who would otherwise require dialysis. In this study energy intake of patients in both the groups was below what was recommended (35kcal/kg/d) for CKD patients. The most important point to remember while prescribing vLPD supplemented with ketoanalogues is to ensure optimal intake of energy in order to preserve nutritional status. Blood pressure was controlled in both the groups. A rise in hemoglobin from 12.19±1.95 mg% to14.20±1.00 mg% was observed in group 1 as also observed in another study3 while hemoglobin remained stable in group 2 (12.35±1.48 at visit 1 and 12.50±1.00 at visit 2).

Limitations of the study

Patients were counseled to adhere to 0.4 g/kg/d of protein intake or 0.6 g/kg/d of protein intake only once at the start of the study. Patient's dietary intake was not monitored between two visits. It was only after completion of the visit one that data showed that patients in group 1 had not changed their dietary intake as per protocol.

Conclusion

Reduction in progression of renal insufficiency through reduction of proteinuria, a better control of blood pressure values and correction of metabolic acidosis is the main attraction of vLPD administered with ketoanalogues. The major goal of implementing low-protein diet in CKD patients should be improvement of patient adherence to VLPD, a crucial factor in determining the role of ketoanalogues. In this study GFR was preserved at 47.0 ml/min in the intervention group while in the control the GFR decreased from 51.1±15.1ml/minute to 37.8±10.0 ml/minute in 10 months. At the end of the study, the serum albumin level was higher in the intervention group compared to control group. Supplementation with ketoanalogues can prevent decline in renal function even without adherence to very low protein diet. Care should be taken to ensure recommended intake of energy.

References

1. Chang JH, Kim DK, Park JT, Kang EW, et al. (2009) Influence of ketoanalogs supplementation on the progression in chronic kidney disease patients who had training on low-protein diet. *Nephrology (Carlton)* 14: 750-757.

2. Saulo Klahr, Andrew S Levey, Gerald J Beck (1994) for the Modification of Diet in Renal Disease Study Group* The Effects of Dietary Protein Restriction and Blood-Pressure Control on the Progression of Chronic Renal Disease. *N Engl J Med*.

3. Subhramanyam SV, Lakshmi V, Nayak KS (2014) Treatment of chronic kidney disease patients with ketoanalogue-supplemented low-protein diet and ketoanalogue-supplemented very-low-protein diet. *Hong Kong Journal of Nephrology* 16: 34-41.

4. Klahr S, Levey AS, Beck GJ (1994) The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 330: 877.

5. KDOQI Clinical Practice Guidelines in chronic renal failure. 2000, Vol 35, No 6 Suppl 2 page S116-117.

6. Ikizler TA, Kalantar-Zadeh K, Secker D (2004) Subjective Global Assessment in chronic Kidney Disease: A Review: *J Renal Nutr* 14: 194-200.

7. Brenner BM, Meyer TW, Hostetter TH (1982) Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 307: 652-659.

8. Barsotti G, Morelli E, Giannoni A, Guinucci A, Lupetti S, et al. (1983) Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure: a controlled trial. *Kidney Int* 24: S278-S284.

9. Gretz N, Korb E, Strauch M (1983) Low protein diet supplemented by keto acids in chronic renal failure. A prospective controlled study. *Kidney Int* 24: S263-S267.

10. Ihles BU, Becker GJ, Whitworth JA, Charlwood RA, Kincaid- Smith PS, et al. (1989) The effect of protein restriction on the progression of renal insufficiency. *N Engl J Med* 321: 1773-1777.

11. Mitch WE, Walser M (1976) The effect of nutritional therapy on progression of chronic renal failure: quantitative assessment. *Clin Res* 24: 407.

12. Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, et al. (1991) Prospective, randomised, multicentre trial of effect of protein on progression of chronic renal insufficiency. *Lancet* 337:1299-1304.

13. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson MR, et al. (1991) Effect of restricting dietary protein on the progression of renal failure in patients with insulin dependent diabetes mellitus. *N Engl J Med* 34: 78-84.

14. Rosman JB, Ter Wee PM, Meijer S, Piers-Becht TPM, Sluiter WJ, et al. (1984) Prospective randomised trial of early dietary protein restriction in chronic renal failure. *Lancet* 2: 1291-1296.

15. Barsotti G, Guiducci A, Ciardella F, Giovanetti S (1981) Effects on renal function of a low nitrogen diet supplemented with essential aminoacids and ketoanalogues and of hemodialysis and free protein supply in patients with chronic renal failure. *Nephron* 27: 113-117.

16. Kopple JD, Swendseid ME (1977) Amino acid and keto acid diets for therapy in renal failure. *Nephron* 18: 1-12. [crossref]

17. Meisinger E, Strauch M (1987) Controlled trial of two ketoacids supplements on renal function, nutritional status and bone metabolism in uremic patients. *Kidney Int* 32: 5170-5173.

18. Mitch WE, Walser M, Steinman TI, Hill S, Zeger S, et al. (1984) The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *N Engl J Med* 311: 623-629. [crossref]

19. Walser M (1978) Keto acid therapy in chronic renal failure. *Nephron* 21: 57-74. [crossref]

20. Walser M, Mitch WE, Abras E (1983) Supplements containing amino acido and keto acids in the treatment of chronic uremia. *Kidney Int* 24: S285-S289.

21. Mitch WE, Collier VU, Walser M: Treatment of chronic renal failure with branched chain ketoacids plus the other essential amino acids or their nitrogen free analogues, in Metabolism and Clinical Implications of Branched Chain Amino and Ketoacids, edited by Walser M, Williamson JR, New York, Elsevier/North-Holland, 1981, p. 587