Original Article

Rationale of α-Ketoanalogue Supplemented with Low Protein Diet for the Treatment of Chronic Kidney Disease

Arun Sharma[1], Sitaram Khadka[1*], Kapil Amgain[2], Smriti Acharya[1], Prem Prasad Panta[2]
[1]Shree Birendra Hospital, Nepalese Army Institute of Health Sciences, Kathmandu, Nepal
[2]Karnali Academy of Health Sciences, Jumla, Nepal
Corresponding Author: Dr. Sitaram Khadka; Email: sitaramkhadka5693@gmail.com,

ABSTRACT
Background: Chronic kidney disease (CKD) has challenged the healthcare system for years. Use of α-ketoanalogue (KA) supplemented with a low protein diet (LPD) may improve renal function. In this study, we aim to find out the effectiveness of KA supplemented with LPD for the therapy of CKD.
Methods: A quantitative cross-sectional study was conducted at Shree Birendra Hospital with 25 control and 25 treatment groups. The control group was treated with LPD (0.8 g/kg/day), while the treatment group was treated with KA (3 tablets/day for 4 weeks followed by 6 tablets/day for the next 16 weeks) along with LPD. The baseline parameters were measured on day 0, then subsequently at week 4, week 12, and lastly at the end of week 16. Results were then compared with the control group for analysis.
Results: The serum level of creatinine showed a progressive decline in the treatment group (2.03±0.39 to 1.68±0.51) in comparison to the control group (2.03±0.36 to 2.54±0.69). However, there was a progressive decline in the level of blood urea (99.07±11.87 to 72.11±26.90) up to 12th week of treatment, and a slight increment was observed in the 16th week of treatment (72.11±26.90 to 86.06±27.90) but the level was below the baseline value (99.07). Similarly, the blood level of sodium and potassium was slightly affected by the increase in sodium and decrease in potassium level from the baseline in the treatment group. The level of serum albumin was increased in the treatment group as compared to the control group. The systolic blood pressure was increased in both the treatment and control group whereas the diastolic blood pressure was decreased in the treatment group rather than the control group.
Conclusion: KA supplemented with LPD shows a significant improvement in renal function of CKD III patients that delays the time for dialysis or transplant. However, further substantial multi-institutional randomized studies are necessary to generalize the findings.
Keywords: Protein-Restricted Diet, Creatinine, Sodium, Potassium, Serum Albumin, Chronic Renal Insufficiency

Access this article Online	Article Info.
Quick Response (QR) Code	**How to cite this article in Vancouver Style?**
	Sharma A, Khadka S, Amgain K, Acharya S, Panta PP. Rationale of α-Ketoanalogue Supplemented with Low Protein Diet for the Treatment of Chronic Kidney Disease: Rationale of α-Ketoanalogue. Journal of Karnali Academy of Health Sciences. 2020; 3(3)
	Received: 21 September 2020 **Accepted**: 29 December 2020 **Published Online**: 30 December 2020
	Source of Support: Self **Conflict of Interest**: None

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem that may eventually lead to end-stage renal disease (ESRD) if not controlled properly.[1] The number of ESRD cases is rapidly growing nowadays.[2] The goal of CKD therapy is to prevent or slow further damage to the kidneys, and dietary intervention plays a pivotal role.[3]

α-ketoanalogue (KA) with dietary protein restriction is one of the major treatment strategies for CKD.[4-7] Clinical improvement with better renal function, serum albumin levels, and blood pressure (BP) have been documented under such therapy.[8-10]

A low protein diet (LPD) may accompany the risk of protein energy malnutrition (PEM).[11-13] KA are nitrogen-free analogs of essential amino acids with therapeutic value. The components of KA such as leucine as well as ketoleucine help synthesis of muscle protein by overturning protein catabolism.[3, 14] Therefore, complementing the LPD with KA are an essential approach to avoid PEM.[15]

Such a strategy may also defer the need for dialysis or transplant.[16,17] Though the government has facilitated dialysis service, frequent hospital visits; invasive procedures; and a limited number of beds cause poor patient compliance that ultimately decreases the quality of life of patients. As this being a per oral therapy, better patient compliance can be achieved that ensures rationalization of therapeutic outcome.

To the best of our knowledge, it is the first of its kind study in Nepal. This study is conducted with the objective to assess the renal function of patients by application of KA supplemented with LPD and hence to delay the time for dialysis in CKD stage III patients.

MATERIALS AND METHODS

A quantitative cross sectional study was conducted at Shree Birendra Hospital during the period of May 2020 to August 2020. Shree Birendra Hospital is a tertiary care level teaching hospital located in Kathmandu, Nepal. It is the only referral center for the Nepali army and their dependents. A total enumerating sample was utilized to select a sample of 50 patients from the nephrology clinic of the medical out-patient department (MOPD) and divided into two groups; 25 control and 25 treatment groups. The patients of either sex, age more than 30 years with CKD III under regular follow up and those who were willing to take part in the study were included in the study. The patients of age below 30 and above 90 years, with other serious comorbidities requiring ICU and/or ventilator, and those who were not willing to take part in the study were excluded from this study. Written and verbal consent from all patients and ethical approval from IRC of NAIHS was taken for the conduct of the study.

The patients of the control group were treated with LPD (0.8 g/kg/day), while the test patients were treated with KA (3 tablets/day for 4 weeks followed by 6 tablets/day for the next 16 weeks) along with LPD (0.8 g/kg/day). The intervention period lasted for 16 weeks. The baseline renal function tests (RFT), serum albumin level, and BP were measured at day 0, then subsequently at week 4, week 12, and lastly at the end of 16 weeks. Results were compared with the control group for analysis after 16 weeks.

The data were collected in a pre-formed performa after taking written and verbal consent from the patients. Hence collected data were entered into excel and transferred

into SPSS version 16 for the statistical analysis. Before conducting the inferential statistics, the normality of each variable was tested using the Shapiro Wilk test. The variables did not support the normality (P<.05). A non-parametric Wilcoxon sign rank test was applied to show the significant change of the variables in the different time periods. The values of the different variables taken at different time periods were compared with the baseline data of treatment and control respectively. A P-value of less than .05 was considered as a significant change.

RESULTS

In total, 50 patients were enrolled in the study. Out of them, 25 were from the control group and the rest were from the treatment group. There were 13 (52%) males in the treatment group and 17 (68%) in the control group. A total of 10 (40%) and 12 (48%) patients in the test and the control group were in the 40-59 age group (Table 1).

Table 1: Socio-demographic variables

Variables	Group		Total
	Treatment	Control	
Sex			
Male	13(52%)	17(68%)	30(60%)
Female	12(48%)	8(32%)	20(40%)
Age			
Below 40	3(12%)	4(16%)	7(14%)
40-59	10(40%)	12(48%)	22(4%)
60 and above	12(48%)	9(36%)	21(42%)
Total	25	25	50
Mean	58.8(16.9)	54.2(15.3)	56.5(16.1)

The most common comorbid condition in the present study was hypertension (HTN) being 44.7% in the treatment group and 45.5% in the control group. Similarly, coronary artery disease (CAD), glomerulonephritis (GN), immunoglobulin A nephropathy (IgA-N), chronic obstructive pulmonary disease (COPD), and systemic lupus erythematosus (SLE) were the least common comorbid conditions in the treatment group (2.1%). Correspondingly, nephrotic syndrome (NS), obstructive uropathy (OU), SLE, focal segmental glomerulosclerosis (FSGS), acute coronary syndrome (ACS), and dilated cardiomyopathy (DCM) were the least common in comorbid conditions the control group (2.3%) (Table 2).

Table 3 showed the comparison of the progress of RFT, serum albumin level, and BP in both the treatment and control groups.

Table 2: Comorbidities in both the treatment and control groups

Comorbidities	Treatment			Comorbidities	Control		
	Responses		Cases (%)		Responses		Cases (%)
HTN	21	44.70%	87.5	HTN	20	45.50%	80
DM	11	23.40%	45.8	DM	8	18.20%	32
CVD	2	4.30%	8.3	CVD	3	6.80%	12
COPD	1	2.10%	4.2	COPD	3	6.80%	12
SLE	1	2.10%	4.2	NS	1	2.30%	4
IgA-N	1	2.10%	4.2	OU	1	2.30%	4

GN	1	2.10%	4.2	SLE	1	2.30%	4
CCF	2	4.30%	8.3	RA	2	4.50%	8
FSGS	2	4.30%	8.3	FSGS	1	2.30%	4
ACS	2	4.30%	8.3	ACS	1	2.30%	4
ADPKD	2	4.30%	8.3	DCM	1	2.30%	4
CAD	1	2.10%	4.2	ADPKD	2	4.50%	8
	47	100.00%	195.8		44	100.00%	176

Abbreviations:- ACS: Acute coronary syndrome; ADPKD: Autosomal dominant polycystic kidney disease; CAD: Coronary artery disease; CCF: Congestive cardiac failure; DCM: Dilated cardiomyopathy; COPD: Chronic obstructive pulmonary disease; CVD: Cerebrovascular disease; DM: Diabetes mellitus; FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; IgA-N: Immunoglobulin A nephropathy; NS: Nephrotic syndrome; OU: Obstructive uropathy; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus

Table 3: Parameters of renal function test, serum albumin level, and blood pressure

Parameter	**Treatment**		**Control**	
	Mean	SD	Mean	SD
Renal function test (RFT)				
Creatinine I	2.03	0.39	2.03	0.36
Creatinine II	1.97	0.37	2.10	0.37
Creatinine III	1.85	0.41	2.25	0.48
Creatinine IV	1.68	0.51	2.54	0.69
Urea I	99.07	11.87	78.70	20.26
Urea II	84.33	14.59	85.96	13.64
Urea III	72.11	26.90	98.97	18.30
Urea IV	86.06	27.90	114.51	36.74
Sodium I	135.36	5.13	136.48	4.67
Sodium II	136.28	4.52	135.44	4.82
Sodium III	137.68	4.73	136.32	4.36
Sodium IV	138.48	5.38	136.40	4.11
Potassium I	4.31	0.53	4.02	0.61
Potassium II	4.28	0.49	5.07	6.27
Potassium III	4.14	0.58	3.76	0.94
Potassium IV	4.15	0.60	4.15	0.55
Serum albumin				
Albumin I	2.90	0.70	3.12	0.56
Albumin II	2.90	0.60	3.12	0.60
Albumin III	2.99	0.62	3.06	0.64
Albumin IV	3.02	0.63	2.95	0.61
Blood pressure (BP)				
Systolic BP I	133.20	11.45	129.60	10.98
Systolic BP II	132.40	8.79	133.20	12.15
Systolic BP III	135.60	11.58	138.40	13.75
Systolic BP IV	136.00	11.90	141.20	15.09
Diastolic BP I	83.60	7.00	80.40	7.90
Diastolic BP II	81.20	6.66	83.20	7.48
Diastolic BP III	82.80	7.92	86.40	5.69
Diastolic BP IV	81.20	7.26	83.60	4.90

I = Baseline, II = Week 4, III = Week 12, IV = Week 16

The level of creatinine in the blood showed a progressive decline in the treatment group in comparison to the control group of the patients (Figure 1). However, there was a progressive decline in the level of blood urea in the first 4 and 12 weeks of treatment, a

slight increment was seen in the week 16 but the level was below the baseline value (Figure 2). Similarly, the blood level of sodium (Figure 3) and potassium (Figure 4) were slightly affected by the increase in sodium and decrease in potassium level from the baseline in the treatment group. The level of serum albumin was increased in the treatment group as compared to the control group. The systolic blood pressure (SBP) was increased in both the treatment and control group whereas the diastolic blood pressure (DBP) was decreased in the treatment group rather than the control group (Figure 5 and 6).

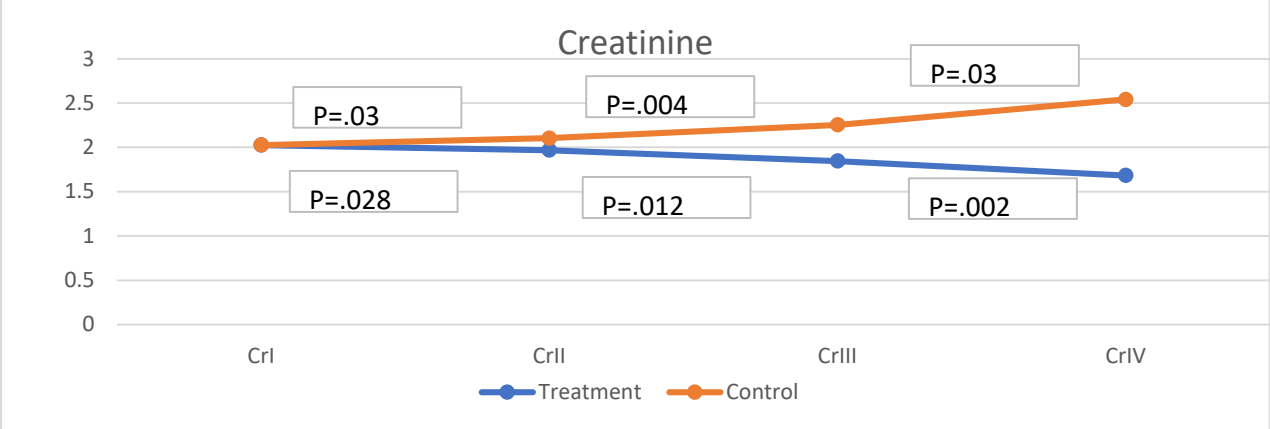

Figure 1: Trend of creatinine in the control and the treatment group

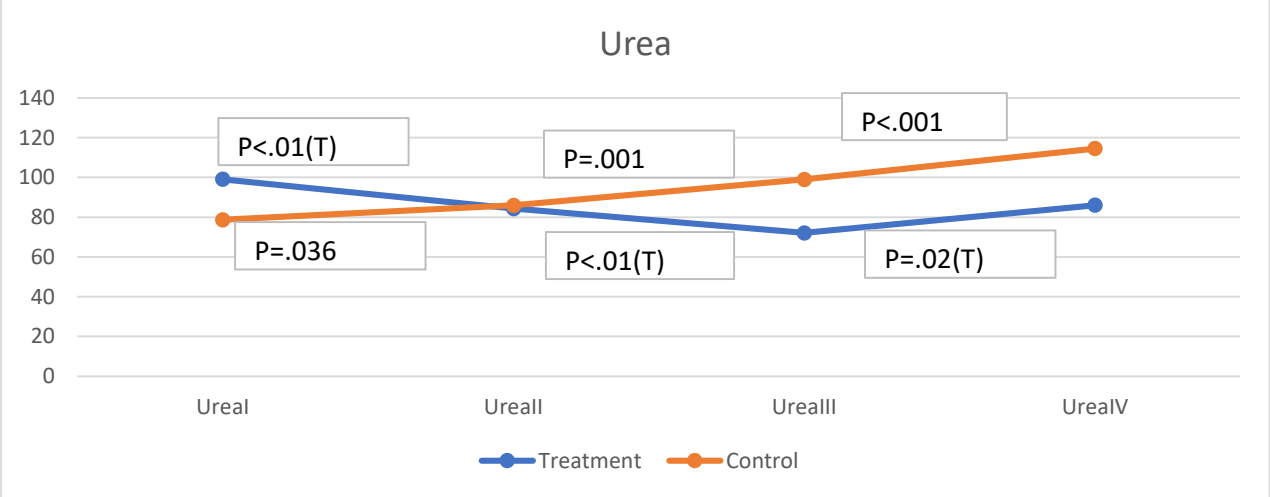

Figure 2: Trend of urea in the control and the treatment group

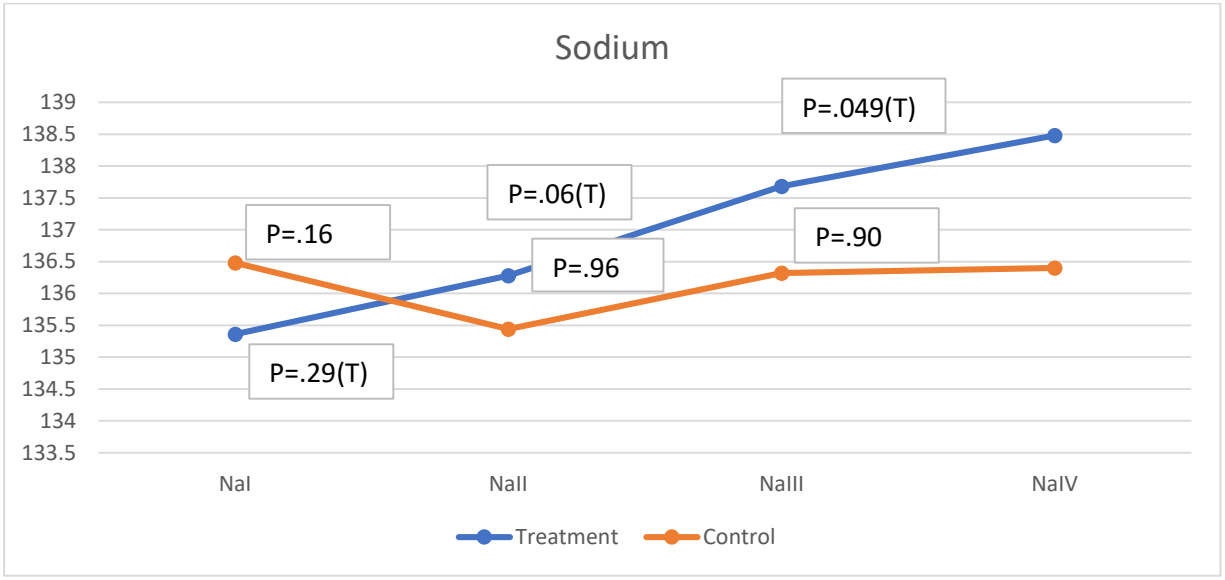

Figure 3: Trend of sodium in the control and the treatment group

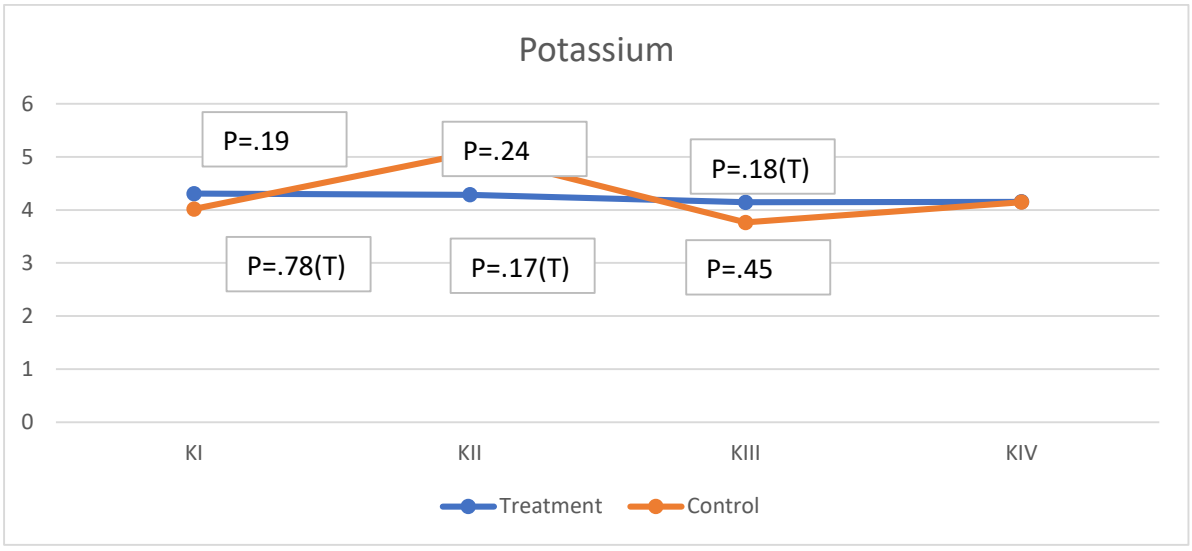

Figure 4: Trend of potassium in the control and the treatment group

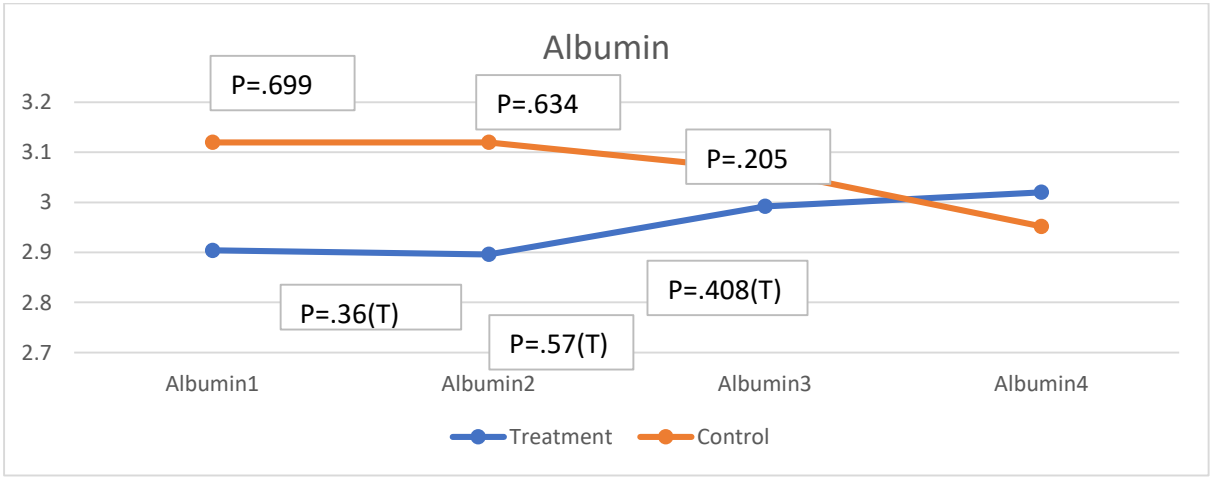

Figure 5: Trend of albumin in the control and the treatment group

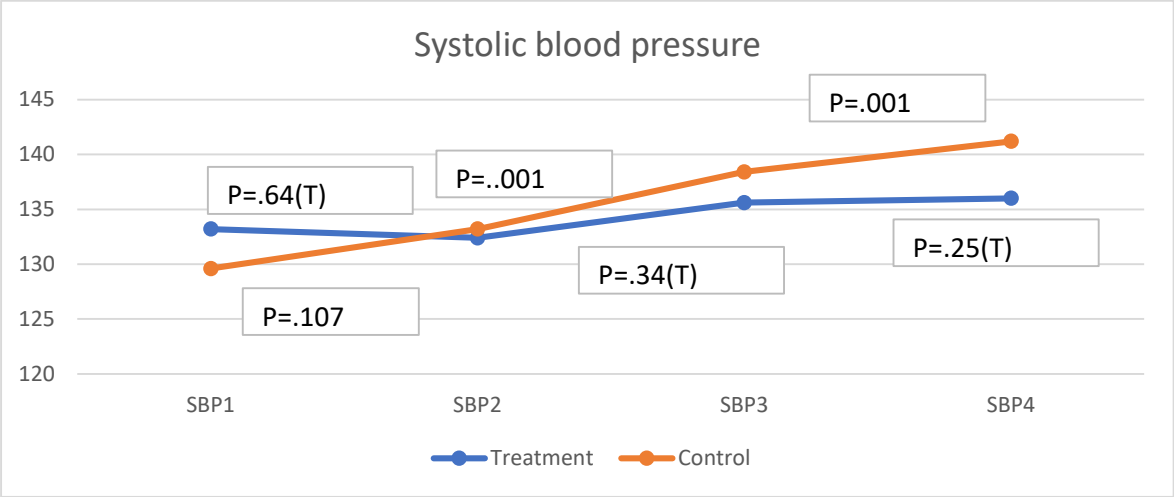

Figure 6: Trend of systolic blood pressure (SBP) in the control and the treatment group

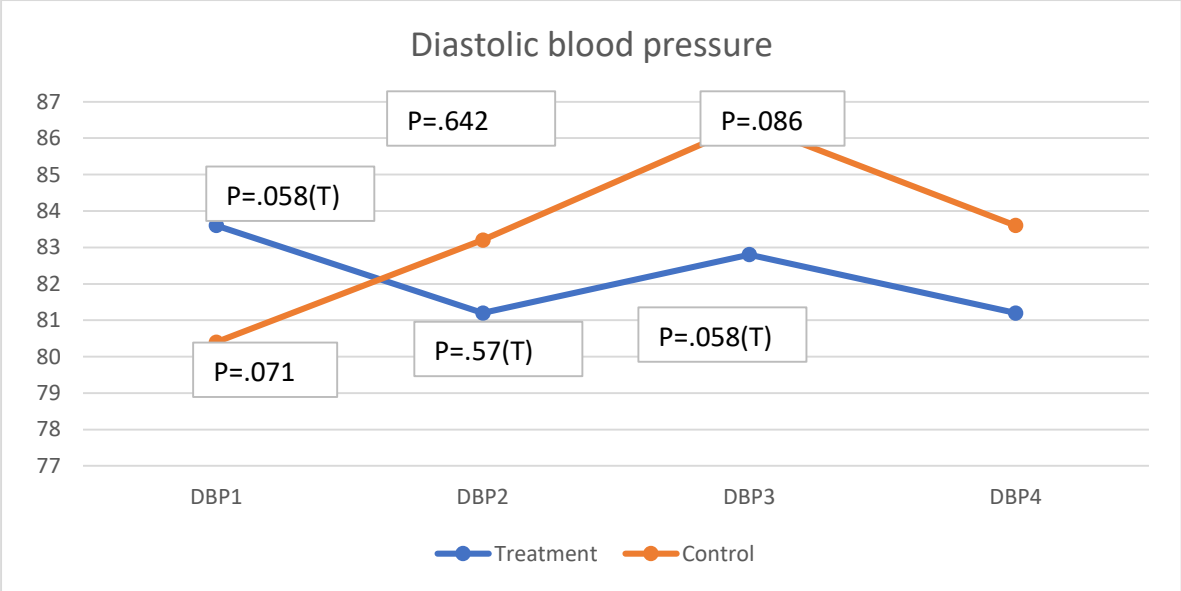

Figure 7: Trend of diastolic blood pressure (DBP) in the control and the treatment group

DISCUSSION

The present study demonstrates the improvement in RFT, albumin level, and BP of patients in the treatment group under KA supplemented with LPD as compared to the control group under LPD alone.

These findings correlate with the findings of similar studies conducted worldwide. A retrospective study conducted by Chang JH et al in a hospital setting in Korea demonstrated delayed progression in CKD with a better renal profile in patients under KA with LPD.[9] Similar findings were reported by a cohort study conducted at Taiwan National Health Insurance where KA supplementation had substantially reduced the risk of long-term dialysis or developing complex outcomes on an appropriate dose.[16] A long-term prospective randomized study designed by Teplan et al suggested similar results where

the co-administration of erythropoietin along with LPD and KA were proved as an effective alternative to manage CKD that delayed the progression of renal failure maintaining a renal profile in adequate level.[18] KA supplemented with LPD was shown to reduce proteinuria in CKD patients.[19,20] Correspondingly, a recently published meta-analysis conducted by Chewcharat et al which included 17 RCTs in 1459 participants also reported effectiveness in maintaining a renal profile of CKD patients diminishing proteinuria.[21] Another meta-analysis conducted by Li et al which included 11 RCTs concluded that KA with LPD had a significant role in managing CKD.[1] Similarly, another meta-analysis including 7 RCTs by Jiang et al also indicated the significant prevention of the deterioration of renal function and hence delay in the progression of CKD under such therapy.[10]

The level of serum creatinine showed a progressive decline in the treatment group in this study. However the value of blood urea and potassium remained lower as compared to that of baseline, there was a progressive decline from baseline to 12 weeks with a slight increase in level after 12 weeks till 16 weeks. Similarly, the value of the sodium level was slightly higher in the treatment group as compared to the control group. The slight increment in the value could be due to comorbidities, age, and the other medications patients were taking.

The increasing level of albumin in the treatment group as compared to the control group could be attributed to the use of KA to maintain PEM caused by LPD. This finding is similar to the results of Teplan et al [18] but contrasts the results of Chang et al[9] where the albumin level was constant. The higher level of albumin in the baseline to 12 weeks in the control group than in the treatment group is due to the pre-sample bias with higher albumin in the control group.

Though the SBP, as well as DBP, were improved in the treatment group compared to the control group, a slight increment in the value of SBP from baseline was observed in the treatment group. The finding coincides with the findings of Chewcharat et al[21] and Jiang et al[10] where a reduction in BP was observed. The slight increment in SBP from baseline value could be attributed to the comorbidities, age, and other medications patients were taking.

In a study conducted by You et al from Taiwan, a Markov model demonstrated cost-effectiveness in participants upon the timely start of KA due to higher quality-adjusted life-years (QALYs) with lower cost in comparison to the watchful-waiting group.[22] The findings of our study can also be further used for pharmacoeconomic, QALY, and compliance evaluation. An animal study conducted by Gao et al showed KA complemented with LPD better than LPD alone in protecting remnant kidneys from advanced injury.[7]

In an observational study, malnourished advanced CKD patients treated with a KA supplement had increased body weight, body mass index, serum albumin levels, and appetite scores.[14] Moreover, irrespective of drug class, for each 30% decrease in albuminuria the risk of ESRD reduced by 23.7%, and could further result in reducing the cardiovascular risks.[23] In geriatrics, there has been chances of linkage between dialysis, increased mortality risk, and healthcare cost in comparison to the conventional approach.[24] Likewise, a prospective randomized multicenter controlled study conducted in Italy by Brunori et al showed that dietary protein

restriction and KA supplementation could delay the start of dialysis in geriatrics with CKD for about a year without increasing the hospitalization or mortality risk.[25] Such findings were further supported by the results of our study.

Our study did not validate the significance of increasing doses of KA in improving renal function and BP as compared to a normal dose in CKD III patients. The findings can be correlated with a prospective, open-labeled, group-comparison design by Chen et al which showed the effectiveness of low dose KA (Ketosteril one tablet/10 kg/day) combined with LPD as compared to a standard dose (Ketosteril one tablet/5 kg/day) to manage the renal function in patients with CKD.[26]

Moderately restricted LPDs can be adjusted and be personalized to the patients' favorites, while very low protein diet (VLPDs) normally necessitate proficient, compliant patients.[27] We used LPD for the study which exhibited a significant outcome. A study conducted by Walser et al indicated that the need for renal transplantation may be delayed beyond one year by a VLPD in 0.3g/kg/day in progressive CKD patients.[28] The finding was supported by the study by Jiang et al.[10] But a study by Li et al[1] gave contradictory findings which concluded that a VLPD may not bring extra benefit to patients along with KA to manage CKD.

Limitation: The study had been conducted in a single tertiary care hospital with a limited number of patients (n = 50) in the limited time frame (16 weeks). The effects of different medications, comorbidities, age, and sex were not assessed that might have an impact on CKD management under such therapy. This study might not reflect the scenario of the general population as a whole.

CONCLUSION

Renal profile in CKD can be maintained by the use of KA supplemented with LPD. A significant decrease in serum creatinine, potassium, urea, and BP along with an increase in serum albumin level suggests the effectiveness of KA therapy in CKD patients. The application of KA along with LPD delays the time for dialysis in CKD III patients improving renal function at a significant level. From this study, we recommend the use of KA supplemented with LPD for the therapy of CKD-III with appropriate clinical assessment. However, to generalize the findings, the results from further substantial multi-institutional randomized studies are required.

Acknowledgment: We would like to acknowledge all the staffs of nephrology department of Shree Birendra Hospital for their continuous support in completion of this study.

REFERENCES

1. Li A, Lee HY, Lin YC. The effect of ketoanalogues on chronic kidney disease deterioration: A meta-analysis. Nutrients. 2019;11(5):957. https://doi.org/10.3390/nu11050957 [Google Scholar] [PubMed]
2. Prasad N, Jha V. Hemodialysis in Asia. Kidney Dis (Basel, Switzerland). 2015 Dec;1(3):165–77. https://doi.org/10.1159/000441816 [Google Scholar] [PubMed]
3. Mitch WE. Dietary protein restriction in

chronic renal failure: nutritional efficacy, compliance, and progression of renal insufficiency. J Am Soc Nephrol. 1991;2(4):823–31. https://doi.org/10.1038/ki.1991.217 [Google Scholar] [PubMed]

4. King AJ, Levey AS. Dietary protein and renal function. J Am Soc Nephrol. 1993;3(11):1723–37. [Google Scholar] [PubMed]
5. Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low–protein diet and CKD progression. J Am Soc Nephrol. 2016;27(7):2164–76. https://doi.org/10.1681/ASN.2015040369 [Google Scholar] [PubMed]
6. Fouque D, Wang P, Laville M, Boissel JP. Low protein diets delay end-stage renal disease in non-diabetic adults with chronic renal failure. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2000 Dec;15(12):1986–92. https://doi.org/10.1093/ndt/15.12.1986 [Google Scholar] [PubMed]
7. Gao X, Wu J, Dong Z, Hua C, Hu H, Mei C. A low-protein diet supplemented with ketoacids plays a more protective role against oxidative stress of rat kidney tissue with 5/6 nephrectomy than a low-protein diet alone. Br J Nutr. 2010 Feb;103(4):608–16. https://doi.org/10.1017/S0007114509992108 [Google Scholar] [PubMed]
8. Oh SE, Lee YK, Kim JK, Lee DH, Kim SJ, Kim SG, et al. Effects of Keto Acids on Serum Albumin Level in Hemodialysis Patients with Hypoalbuminemia. Korean J Nephrol. 2010;29(1):82. [Google Scholar]
9. Chang J, Kim D, Park J, Kang E, Yoo T, Kim B, et al. Influence of ketoanalogs supplementation on the progression in chronic kidney disease patients who had training on low-protein diet. Nephrology. 2009;14(8):750–7. https://doi.org/10.1111/j.1440-1797.2009.01115.x [Google Scholar] [PubMed]
10. Jiang Z, Zhang X, Yang L, Li Z, Qin W. Effect of restricted protein diet supplemented with keto analogues in chronic kidney disease: a systematic review and meta-analysis. Int Urol Nephrol. 2016 Mar;48(3):409–18. https://doi.org/10.1007/s11255-015-1170-2 [Google Scholar] [PubMed]
11. Cupisti A, D'Alessandro C, Fumagalli G, Vigo V, Meola M, Cianchi C, et al. Nutrition and physical activity in CKD patients. Kidney Blood Press Res. 2014;39(2–3):107–13. https://doi.org/10.1159/000355784 [Google Scholar] [PubMed]
12. Walser M, Hill SB, Ward L, Magder L. A crossover comparison of progression of chronic renal failure: Ketoacids versus amino acids. Kidney Int. 1993;43(4):933–9. https://doi.org/10.1038/ki.1993.131 [Google Scholar] [PubMed]
13. Walser M, Mitch WE, Maroni BJ, Kopple JD. Should protein intake be restricted in predialysis patients? Kidney Int. 1999;55(3):771–7.https://doi.org/10.1046/j.1523-1755.1999.055003771.x [Google Scholar] [PubMed]
14. Aparicio M, Bellizzi V, Chauveau P, Cupisti A, Ecder T, Fouque D, et al. Protein-Restricted Diets Plus Keto/Amino Acids - A Valid Therapeutic Approach for Chronic Kidney Disease Patients. J Ren Nutr. 2012;22(2, Supplement):S1–21. https://doi.org/10.1053/j.jrn.2011.09.005 [Google Scholar] [PubMed]
15. Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr. 2013 Jun;97(6):1163–77. https://doi.org/10.3945/ajcn.112.036418

[Google Scholar] [PubMed]

16. Wu CH, Yang YW, Hung SC, Kuo KL, Wu KD, Wu, et al. National Taiwan University Study Group on Acute Renal Failure (NSARF. Ketoanalogues supplementation decreases dialysis and mortality risk in patients with anemic advanced chronic kidney disease. PLoS One. 2017;12(5). https://doi.org/10.1371/journal.pone.0176847 [Google Scholar] [PubMed]
17. Zemchenkov A, Konakova IN. Efficacy of the Essential Amino Acids and Keto-Analogues on the CKD progression rate in real practice in Russia - city nephrology registry data for outpatient clinic. BMC Nephrol. 2016 Jul;17(1):62. https://doi.org/10.1186/s12882-016-0281-z [Google Scholar] [PubMed]
18. Teplan V, Schück O, Knotek A, Hajný J, Horácková M, Skibová J, et al. Effects of low-protein diet supplemented with ketoacids and erythropoietin in chronic renal failure: a long-term metabolic study. Ann Transplant. 2001;6(1):47–53. [Google Scholar] [PubMed]
19. Bellizzi V, Di Iorio BR, De Nicola L, Minutolo R, Zamboli P, Trucillo P, et al. Very low protein diet supplemented with ketoanalogs improves blood pressure control in chronic kidney disease. Kidney Int. 2007;71(3):245–51.https://doi.org/10.1038/sj.ki.5001955 [Google Scholar] [PubMed]
20. Chauveau P, Combe C, Rigalleau V, Vendrely B, Aparicio M. Restricted Protein Diet Is Associated With Decrease in Proteinuria: Consequences on the Progression of Renal Failure. J Ren Nutr. 2007;17(4):250–7. https://doi.org/10.1053/j.jrn.2007.02.007 [Google Scholar] [PubMed]
21. Chewcharat A, Takkavatakarn K, Wongrattanagorn S, Panrong K, Kittiskulnam P, Eiam-Ong S, et al. The Effects of Restricted Protein Diet Supplemented With Ketoanalogue on Renal Function, Blood Pressure, Nutritional Status, and Chronic Kidney Disease-Mineral and Bone Disorder in Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis. J Ren Nutr. 2020;30(3):189–99. https://doi.org/10.1053/j.jrn.2019.07.005 [Google Scholar] [PubMed]
22. You JHS, Ming W-K, Lin W-A, Tarn Y-H. Early supplemented low-protein diet restriction for chronic kidney disease patients in Taiwan - A cost-effectiveness analysis. Clin Nephrol. 2015 Oct;84(4):189—196. https://doi.org/10.5414/CN108560 [Google Scholar] [PubMed]
23. de Zeeuw D, Remuzzi G, Parving H-H, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004 Aug;110(8):921–7. https://doi.org/10.1161/01.CIR.0000139860.33974.28 [Google Scholar] [PubMed]
24. Shih C-J, Chen Y-T, Ou S-M, Yang W-C, Kuo S-C, Tarng D-C. The impact of dialysis therapy on older patients with advanced chronic kidney disease: a nationwide population-based study. BMC Med. 2014 Oct;12:169. https://doi.org/10.1186/s12916-014-0169-3 [Google Scholar] [PubMed]
25. Brunori G, Viola BF, Parrinello G, De Biase V, Como G, Franco V, et al. Efficacy and Safety of a Very-Low-Protein Diet When Postponing Dialysis in the Elderly: A Prospective Randomized Multicenter Controlled Study. Am J Kidney Dis. 2007;49(5):569–80. https://doi.org/10.1053/j.ajkd.2007.02.278 [Google Scholar] [PubMed]
26. Chen J-B, Cheng B-C, Kao T-W. A COMPARISON OF PROGRESSION OF CHRONIC RENAL FAILURE: LOW DOSE VS STANDARD DOSE KETOACIDS. Kidney Res Clin Pract. 2012;31(2):A24.

https://doi.org/10.1016/j.krcp.2012.04.357 [Google Scholar]

27. Piccoli GB, Vigotti FN, Leone F, Capizzi I, Daidola G, Cabiddu G, et al. Low-protein diets in CKD: how can we achieve them? A narrative, pragmatic review. Clin Kidney J. 2014;8(1):61–70. https://doi.org/10.1093/ckj/sfu125 [Google Scholar] [PubMed]
28. Walser M, Hill S. Can renal replacement be deferred by a supplemented very low protein diet? J Am Soc Nephrol. 1999 Jan;10(1):110–6. [Google Scholar] [PubMed]