ORIGINAL ARTICLE

Do Alpha-Ketoanalogues Slow Down Disease Progression in Non-Dialysis Dependent Chronic Kidney Disease?

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ABSTRACT

Objective: To observe the effectiveness of keto-analogues in slowing down the disease progression in non-dialysis dependent CKD patients.

Study Design: Quasi-experimental study.

Place and Duration of Study: The study was carried out at Nephrology Department of Combined Military Hospital (CMH), Peshawar, Pakistan from August 2022 to February 2023.

Methods: Data was collected on 290 kidney disease improving global outcomes (KDIGO) stage 3 and 4 CKD patients through non-probability consecutive sampling technique. The cohort was divided into group A (Low protein diet) and B (ketodiet). Group A received low protein diet in addition to standard chronic disease treatment while Group B was labelled as keto-diet group which received ketoanalogues in addition to low protein diet and standard chronic kidney disease treatment. Baseline and six months eGFR was calculated and compared for both groups. SPSS version 23.00 was used for data analysis. The *P* value ≤ 0.05 was considered significant.

Results: 286 patients aged 51.84±18.127 were selected for our study. 188(65.73%) were males while females were 98 (34.26%). There were 142 (50.34%) and 144(50.34%) patients in group A and B respectively. Duration of CKD in group A and B was 6.45±2.55 and 6.49±1.75 years respectively. The means difference of eGFR in group A (low protein diet) at baseline and after six months was 3.64±1.09mL/ min/ 1.73m2 while that of group B was 1.48±0.41 mL/ min/ 1.73m2 (*P*-value <0.000).

Conclusion: Ketoanalogues is an emerging therapy which slows down disease progression in non-dialysis dependent CKD patients. Although its use is recommended by some clinicians in CKD stage 3 and 4 non-dialysis dependent but still controversial.

Keywords: *Chronic Kidney Disease, Estimated Glomerular Filtration Rate, Protein Restricted Diet, Supplements.*

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Introduction

Chronic kidney disease is an emerging ailment throughout the globe which if not timely managed may end up in end stage renal disease.[1] Almost every system of CKD patients is affected resulting in serious comorbidities.[2] CKD is the foremost cause of mortality and morbidity globally.[3] Therefore, timely screening, diagnosis and management of CKD is important to slow down the deterioration in renal function and complications.[4]

CKD management is multi-dimensional ranging from dietary regulation to renal replacement therapy as the morbid kidneys are unable to excrete different products formed as a result of different metabolic reactions in healthy people.[5,6]

Dietary control and modification is the key element

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of CKD management.[1] Over the past years, the use of low protein diet have been associated with slowing down the drop in glomerular filtration rate in CKD patients. However, this increase the risk of protein energy malnutrition in such patients. Therefore, the provision of certain protein elements is essential in CKD patients.[6]

Studies have revealed that keto-analogues have been associated with prevention of protein malnutrition and slows down the progression of disease in non-dialysis dependent CKD patients.[7] the Bellizi study revealed that mortality was 8% in ketoanalogues group as compared to 10% in the control group.[8] Various meta-analysis and randomized control trial has proved that keto-diet significantly reduce the decline of glomerular filtration rate in advanced CKD patients.[1]

Some latest trials have shown that ketodiet not only slows down the progression of CKD but also prevent malnutrition, Bone mineral disorders, insulin resistance and nitrogenous base containing products retention. It also improves blood pressure, vascular calcification and serum bicarbonate levels.[8]

We conducted this study to observe the effectiveness of keto-analogues in slowing down the disease progression in non-dialysis dependent CKD patients.

Methods

This quasi-experimental study was carried out at the Nephrology Department of Combined Military Hospital (CMH), Peshawar, Pakistan from 1st august 2022 to 28th February 2023. Sample size was decided by using WHO calculator keeping the confidence interval 95% and anticipated percentage frequency of 5% in a population based on study conducted by Wang YC, Juan SH, Chou CL, Hsieh TC, Wu JL, Fang TC.[9] subsequently, we collected the data from about 286 patients through non-probability consecutive sampling technique. Approval was granted by the hospital ethics review committee held on August 17, 2021 vide reference number: 52. CKD staging and diagnosis was done on the basis of National Quality Foundation/Kidney Disease Out-come Quality Initiative 2002.[10] After taking informed consent, KDIGO stage 3 and 4 non-dialysis needy CKD patients were counted in our study. Non-complaint patients and those who had undergone renal replacement therapy of any kind were excluded. The patients were allocated into groups A and group B. Group A was labelled as low protein diet group which received low protein diet in addition to standard chronic disease treatment while Group B was labelled as ketodiet group which received ketoanalogues in addition to low protein diet and standard chronic kidney disease management. Fasting venous blood samples were taken for the measurement of urea, creatinine and electrolytes along with urinary creatinine levels and eGFR was measured by using the formula eGFR (mL/min) = [(140-age) × Wt/(0.814 × S.Cr in μmol/L)] × (0.85 if female).[10] The participants were regularly followed up on monthly basis and progression of CKD was compared in both groups by relating variation in initial eGFR and 06 months afterwards in each group.

SPSS version 23.00 was used for data analysis. Mean ± SD was calculated for continuous variables while frequency and percentage were considered in case of categorical variables. Independent sample t test was used for the comparison of eGFR both baseline and after six months of specific treatment given to group A and B. The *P*-value of ≤0.05 was set as cut-off for statistically significant results.

Results

286 patients were included aged 51.84±18.127. 188 (65.73%) were males while females were 98 (34.26%). Patients were segregated into two groups i.e. Group A (low protein diet and standard CKD treatment) and B (alpha keto-analogues along with low protein diet and standard CKD treatment). Table 1 shows, there were 142 (50.34%) and 144 (50.34%) patients in group A and B correspondingly. The most prevalent comorbidity in our cohort was hypertension followed by diabetes mellitus and ischemic heart disease. Duration of CKD in group A and B was 6.45±2.55 and 6.49±1.75 respectively.

As shown in Table 2, 146 (51.04%) patients of our cohort were suffering from CKD KDIGO stage 3 while 140 (48.95%) patients were in KDIGO stage 4. Table 3 shows that the means difference of eGFR in group A (low protein die) at baseline and after six months was 3.64±1.09mL/ min/ 1.73m2 while that of group B was 1.48±0.41 mL/ min/ 1.73m2 (*P*-value<0.000). This result was statistically significant.

Table 1: Baseline characteristics

Parameter		n (%)
Age (years)		51.84±18.127
Gender	Male	188 (65.73%)
	Female	98 (34.26%)
Duration of chronic kidney Disease		6.91± 2.20
Group	A (low protein diet)	6.45±2.55
	B (keto-diet)	6.49±1.75
Co-morbidities	Hypertension	150 (52.4%)
	Diabetes mellitus	106 (37.6%)
	Ischemic heart disease	98 (34.26%)
Number of patients in each group	Group A	142 (50.34%)
	Group B	144 (50.34%)

Table 2: Number of patients in KDIGO CKD stage

KDIGO CKD stage	Group	Number of patients
Stage 3	A	74 (25.87%)
	B	72 (25.17%)
Stage 4	A	68 (23.77%)
	B	72 (25.17%)

Table 3: Difference in eGFR of both groups at baseline and post-intervention after six months follow-up

Parameter	Group A (low protein diet group)	Group B (keto-diet group)	*P*-value
Difference in eGFR of group A and B (Means ± SD)	3.64±1.09 (mL/ min/ 1.73m2)	1.48±0.41 (mL/ min/ 1.73m2)	0.000

Discussion

Chronic kidney disease is affecting people globally at an alarming rate. Study of Jager et al. have revealed prevalence of CKD 843.6 million worldwide.[11] Dietary assessment and modification in CKD patients is a key element of disease management. Use of keto-analogues in CKD progression is controversial as many studies have reported its role in slowing GFR decline while some studies have shown no beneficial effect.[4] Therefore, we carried out this study in a tertiary care hospital located in Peshawar Pakistan to evaluate the role of alpha-ketoanalogues in slowing down the decline in renal function in non-dialysis needy individuals.

Our study revealed that alpha keto-analogues plays a statistically significant role in the slowing down the disease progression in non-dialysis dependent CKD patients. The mean GFR decline in keto-diet group was low as compared to that of the group which was administered low protein diet in addition to standard CKD management (*P* value < 0.000). This result is consistent with the study of Saba Umer et al. carried out a tertiary care hospital of Pakistan which have proved the efficacy of ketoanalogues in management of CKD.[10] Study of Lee TW et al. have demonstrated the effectiveness of keto-analogues in non-dialysis dependent CKD patients.[12]

Hahn et al. study reported a reduced serum level of urea and nitrogen in patients who were given ketoanalogues as compared to those who were only on low protein diet.[13] Di Iorio et al. study recently revealed, ketoanalogues is associated with reduction of final nitrogenous acid production by 53%, 67% at six, twelve months respectively. This consequently

reduces clearance burden on kidneys by 120%, 138% after six and twelve-month follow-up respectively which ultimately slows down disease progression in CKD patients.[14] A recent prospective, randomized, controlled trial by Garneata et al. have proved the safety and role of ketoanalogues in delaying the need for dialysis in CKD patients.[15]

Besides reducing the decline in GFR, studies have also revealed the beneficial effects of ketoanalogues on blood pressure, vascular calcification, bone health, fluid retention, metabolic acidosis prevention in such patients.[8,16] More trials are compulsory to asses safety as well as efficacy of ketodiet in pregnant, post renal transplant, associated comorbidities and the exact time of initiation of this therapy in CKD patients.[8] Studies have also revealed the financial benefits of keto-analogues by reducing the need of renal replacement therapy.[17,18]

The strength of our study is it provides insights for use and future studies on efficacy and safety of ketoanalogues in our patients as few studies to the best of our knowledge are carried out in Pakistan. Limitations of our study are single center study and patient were only followed up for six months.

Conclusion

Alpha keto-analogues slows down the progression of disease in non-dialysis dependent CKD patients. This is an emerging therapy which may be used to defer dialysis in CKD patients but its use is still controversial. Further trials and studies are essential to be carried out to reach to a consensus level about the use of keto-analogues in such patients.

Authors Contribution

BS: Idea conception, study designing, data analysis, results and interpretation, manuscript writing and proof reading

K: Idea conception, study designing, data collection, manuscript writing and proof reading

ZA: Idea conception, study designing, data collection, data analysis, results and interpretation

MSU: Idea conception, data collection, data analysis, results and interpretation, manuscript writing and proof reading

WA: Idea conception, study design, data interpretation and proof reading

REFERENCES

1. Albert Li, Lee HY, Lin YC. Effect of Ketoanalogues on Chronic Kidney Disease Deterioration: A Meta-Analysis. Nutrients 2019; 11: 957. doi: 10.3390/nu11050957
2. MacRae C, Mercer SW, Guthrie B, Henderson D. Comorbidity in chronic kidney disease: a large cross-sectional study of prevalence in Scottish primary care. British Journal of General Practice. 2021; 71: e243-9. doi: 10.3399/bjgp20X714125
3. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney International Supplements. 2022; 12: 7-11. doi: 10.1016%2Fj.kisu.2021.11.003
4. Chen TK, Knicely DH, Grams ME. Kidney Disease Diagnosis and Management. JAMA. 2019; 322: 1294-304. doi: 10.1001/jama.2019.14745
5. Ruwanpathirana T, Senanayake S, Gunawardana N, Munasinghe A, Ginige S, Gamage D, et al. Prevalence and risk factors for impaired kidney function in the district of Anuradhapura, Sri Lanka: a cross-sectional population-representative survey in those at risk of chronic kidney disease of unknown aetiology. BMC Public Health. 2019; 19: 763. doi: 10.1186%2Fs12889-019-7117-2
6. Chen HY, Sun CY, Lee CC, Wu IW, Chen YC, Lin YH, et al. Ketoanalogue supplements reduce mortality in patients with pre-dialysis advanced diabetic kidney disease: A nationwide population-based study. Clinical Nutrition. 2021; 40: 4149-60. doi: 10.1016/j.clnu.2021.01.045
7. 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. Journal of Renal Nutrition. 2020; 30: 189e99. doi: 10.1053/j.jrn.2019.07.005
8. Koppe L, Cassani de Oliveira M, Fouque D. Ketoacid analogues supplementation in chronic kidney disease and future perspectives. Nutrients. 2019; 11: 2071. doi: 10.3390/nu11092071
9. Wang YC, Juan SH, Chou CL, Hsieh TC, Wu JL, Fang TC. Long Term Effects of Ketoanalogues on Mortality and Renal Outcomes in Advanced Chronic Kidney Disease Patients Receiving a low protein diet Nutrients. 2020; 12: 2708. doi: 10.3390%2Fnu12092708
10. Umar S, Sabir S, Altaf A, Raja KM, Siddiqi FA, Saleem S, et al. Efficacy of Alpha Keto-Analogues in the Management of Chronic Kidney Disease. Pakistan Armed Forces Medical

Journal. 2022; 72: 292-5. doi: 10.51253/pafmj.v72i1.6154

11. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney disease. Kidney International. 2019; 96: 1048-50. doi: 10.1016/j.kint.2019.07.012
12. Lee TW, Jang HN, Kim Y, Bae E, Cho HS, Park DJ, et al. Nephrology Dialysis Transplantation. 2017; 32: iii592. doi: 10.1093/ndt/gfx172.MP444
13. Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. Cochrane Database of Systematic Reviews. 2018; 10: CD001892. doi: 10.1002%2F14651858.CD001892.pub5
14. Alkhatib L, Diaz LV, Varma S, Chowdhary A, Bapat P, Pan H, et al. Lifestyle Modifications and Nutritional and Therapeutic Interventions in Delaying the Progression of Chronic Kidney Disease: A Review. Cureus. 2023; 15: e34572. doi: 10.7759/cureus.34572
15. Prakash S. Low-protein diet and very low-protein diet in chronic kidney disease and the role of ketoanalogs in disease retardation. Journal of Renal Nutrition and Metabolism. 2019; 5: 51-3. doi: 10.4103/jrnm.jrnm_58_19
16. Milovanova L, Fomin V, Moiseev S, Taranova M, Milovanov Y, Lysenko L, et al. Effect of essential amino acid ĸetoanalogues and protein restriction diet on morphogenetic proteins (FGF-23 and Klotho) in 3b-4 stages chronic ĸidney disease patients: A randomized pilot study. Clinical and Experimental Nephrology. 2018; 22: 1351-9. doi: 10.1007/s10157-018-1591-1
17. Praditpornsillpa K, Garneata L, Lin YC, Pradelli L, Susantitphong P, Wu CH, et al. Economic Analysis of a Ketoanalogue-Supplemented Very Low-Protein Diet in Patients in Chronic Kidney Disease in Taiwan and Thailand. Journal of Renal Nutrition. 2023; 33: 269-77. doi: 10.1053/j.jrn.2022.09.004
18. Praditpornsilpa K, Garneata L, Lin YC, Povero M, Pradelli L, Susantitaphong P, et al. EE225 What Is the Economic Impact of Delaying Kidney Replacement Therapy Through Ketoanalogue-Supplemented Low Protein Diet in Advanced Chronic Kidney Disease?. Value in Health. 2022; 25: S97. doi: 10.1016/j.jval.2022.09.474