

## Efficacy of Alpha Keto-Analogues in The Management of Chronic Kidney Disease

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### ABSTRACT

**Objective:** To determine the efficacy of alpha keto-analogues in the management of chronic kidney disease at a tertiary care hospital.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** Nephrology Department, Armed Forces Institute of Urology, Rawalpindi from Jul to Dec 2020.

**Methodology:** A total of 300 patients of chronic kidney disease stage 3 and 4, not dependent on hemodialysis were included in the study. They were divided into two groups with matched age, gender and duration of chronic kidney disease. Group-I received the routine treatment of chronic kidney disease with low protein diet while group-II received alpha keto-analogue in standard dose in addition to routine treatment of chronic kidney disease with low protein diet. Estimated glomerular filtration rate was assessed at the baseline and after six months.

**Results:** Out of 300 patients 151 (50.3%) were males while 149 (49.7%) were female patients. 110 (36.7%) patients had stage-3 disease while 190 (63.3%) had stage-4 chronic kidney disease. Mean difference of eGFR in group-I was  $3.17 \pm 3.19$  mL/min/ $1.73\text{m}^2$  while mean difference of eGFR in group-II was  $1.16 \pm 1.52$  mL/min/ $1.73\text{m}^2$  ( $p$ -value $<0.001$ ).

**Conclusion:** Alpha keto-analogues emerged as an efficacious short-term option in reducing the progression of chronic kidney disease in our study. Use of this option in addition to routine treatment and low protein diet was related to significant improvement in renal functions.

**Keywords:** Alpha keto-analogues, Chronic kidney disease, Estimated glomerular filtration rate.

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## INTRODUCTION

Epidemiological data suggest that chronic renal failure is highly prevalent in all parts of the world with pattern clearly showing increased incidence in the last decade.<sup>1,2</sup> Treatment of this chronic debilitating condition involve a multidisciplinary and multimodality approach ranging from dietary modifications to kidney transplant.<sup>3,4</sup> Various metabolic pathways get affected in chronic renal failure leading to multiple biochemical and hematological abnormalities.<sup>5,6</sup> Multiple options have been in practice to slow down the progression of chronic kidney disease and offer the patient an optimum quality of life.

Alpha keto-analogues have been used to slow the progression of CKD or even to halt the process of further decline in renal function. A study was conducted in 2017 on anemic patients of CKD and they showed the effect of addition of alpha keto-analogues on renal replacement therapy and mortality. They concluded

that addition of alpha keto-analogue reduced the risk of starting dialysis therapy for long term. Progression of CKD was also observed to be slowed down in these patients.<sup>7</sup> Another study revealed that there was an additional benefit in terms of delay in progression of disease and reduction in proteinuria.<sup>8</sup>

Burden of chronic kidney disease is enormous in our part of the world and is still on the rise.<sup>9</sup> A recent local study published by Alam *et al*, regarding safety and efficacy of Nigella sativa oil as an add-on therapy to alpha-keto analogue in patients with CKD concluded that N. sativa oil supplementation along with alpha-keto analogue is more efficacious and safe in delaying the progression of CKD.<sup>10</sup> We planned this study with the objective to determine the efficacy of alpha keto-analogues in management of chronic kidney disease at a tertiary care hospital of Pakistan.

## METHODOLOGY

This quasi-experimental study was conducted at the department of Nephrology in Armed Forced Institute of Urology Rawalpindi from July to December 2020. Sample size was calculated by WHO sample size

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calculator by taking population progression of CKD patients to dialysis as 75.2%.<sup>11</sup> Non-probability consecutive sampling technique was used to gather the sample. Diagnosis and staging of CKD were done as per National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/KDOQI) 2002.<sup>12</sup>

**Inclusion Criteria:** All the patients of CKD stage 3 and 4 who were not dependent on any type of dialysis were included in the study.

**Exclusion Criteria:** The patients who had few sessions of any kind of renal replacement therapy were excluded from the study. Patients who were candidates for renal transplant, patients with any renal or extra renal malignancies or those who were not compliant to low protein diet were also the part of exclusion criteria.

Ethical Review Board Committee of the hospital granted ethics approval for this study (Nephro-Adm-Trg-1IRB/2020/101). Written informed consent was taken from all the participants of this study. Non-dialysis dependent CKD patients presenting at Nephrology OPD were included in the study. Group-I received the routine treatment of chronic kidney disease with low protein diet while group-II received alpha keto-analogue in standard dose in addition to routine treatment of chronic kidney disease with low protein diet. Venous blood was taken from the participants between 9-11 a.m. after 12 hours of fasting. Serum creatinine, urea and electrolytes levels were measured for all the participants. Urinary creatinine levels were also measured. The creatinine clearance was calculated by comparing the creatinine level in a 24-hours urine sample with the creatinine level in the blood.<sup>13</sup> eGFR was calculated as  $eGFR (mL/min) = [(140-age) \times Wt / (0.814 \times S.Cr \text{ in } \mu\text{mol/L})] \times (0.85 \text{ if female})$ .<sup>14</sup> Change in eGFR at baseline and after six months was compared in both the groups.

Statistical Package for Social Sciences (SPSS) version 23 was used for the data analysis. Mean and standard deviation were calculated for age and duration of illness. Frequency and percentages were calculated for gender of the patients. Independent sample t-test was applied to compare the eGFR in both the groups at baseline and after three months of designated management. The *p*-value of  $\leq 0.05$  was considered statistically significant.

## RESULTS

Study population was all the non-dialysis dependent CKD patients. They were divided into two equal

groups. Out of 300 patients 151 (50.3%) were males while 149 (49.7%) were female patients.

Table-I summarized the general characteristics of the patients of CKD included in the study. Out of 110 (36.7%) patients had stage 3 disease while 190 (63.3%) patients had stage 4 chronic kidney disease. Mean age of patients in group-I was  $48.439 \pm 7.35$  years while mean age of patients in group-II was  $49.422 \pm 6.51$  years.

**Table-I: Characteristics of patients with chronic kidney disease included in the study (n=150).**

Parameters	n (%)
<b>Age</b>	
Mean Age in group-I	48.439 ± 7.35 years
Mean age in group-II	49.422 ± 6.51 years
Duration of illness	
Mean duration of CKD in group-I	4.1 ± 3.455 years
Mean duration of CKD in group-II	4.3 ± 1.276 years
<b>Gender</b>	
Male	151 (50.3%)
Female	149 (49.7%)
<b>Stage of Disease</b>	
Stage 3	110 (36.7%)
Stage 4	190 (63.3%)

Table-II showed that mean difference of eGFR in group-I was  $3.17 \pm 3.19$  mL/min/1.73 m<sup>2</sup> while mean difference of eGFR in group-II was  $1.16 \pm 1.52$  mL/min/1.73m<sup>2</sup> (*p*-value <0.001).

**Table-II: Difference in e-Glomerular filtration rate in both the groups at base line and after six months of designated treatment.**

Parameter	Group-I	Group-II	<i>p</i> -value
Difference in e-Glomerular filtration rate (Mean ± SD)	3.17 ± 3.19 mL/ min/ 1.73m <sup>2</sup>	1.16 ± 1.52 mL/min/ 1.73m <sup>2</sup>	<0.001

## DISCUSSION

Usually CKD is considered as an irreversible condition in which clinicians can only slow down the process of deterioration of kidney function but cannot stop it and eventually renal replacement therapy or transplant remains the ultimate solution. Number of methods has been used to slow down this process but still researchers have been trying hard to find the best way to deal with this problem. We designed this experimental study to determine the efficacy of alpha keto-analogues in management of chronic kidney disease at a tertiary care hospital of Pakistan.

Feiten *et al*, did a study by making two groups of patients of CKD and administering one group with conventional low protein diet and supplementing the

other group with keto-acids in addition to conventional low protein diet. They showed that electrolyte status and blood urea nitrogen were attained better with the combination of very-low-protein diet and keto-acids. Thus, this combination can be offered to these patients with confidence.<sup>15</sup> Both our groups were having low protein diet and group-II had alpha keto-analogue in addition to low protein diet and that was more beneficial in terms of reduction in eGFR.

Chewcharat *et al*, in their meta-analysis concluded that addition of ketoanalogues to routine dietary modification could effectively improve and preserve eGFR and help in managing almost all the clinical parameters among patients of chronic kidney disease without causing serious adverse effects.<sup>16</sup> We only studied eGFR based on creatinine clearance and our results were similar to results generated by Chewcharat *et al*.

Another study published in 2016 evaluated this phenomenon from another angle and studied the effect of conventional dietary modifications for CKD supplemented with keto-analogues in CKD pre-dialysis patients on vascular stiffness and AVF Maturation. They concluded that very low protein diets supplemented with keto-analogues appear to improve the native AVF primary outcome, decreasing the initial vascular stiffness, possible by preserving vascular wall quality in CKD patients through a better serum phosphate levels control and the limitation of inflammatory response.<sup>17</sup> Our objective was not to study the AVF outcome but metabolic effects were clearly better in combination group as compared to the group only receiving standard treatment and low protein diet.

Li *et al*, in their recent meta-analysis concluded that restricted protein diet supplemented with ketoanalogues was found to significantly delay the progression of chronic kidney disease particularly in patients with an estimated glomerular filtration rate (eGFR) >18 mL/min/1.73m<sup>2</sup>.<sup>18</sup> Our results supported their findings and we also concluded that alpha keto-analogues were good short term option in reducing the progression of chronic kidney disease. Use of this option in addition to routine treatment and low protein diet was related to significant improvement in renal functions in six-month time.

#### LIMITATIONS OF STUDY

There were few limitations in our study. Patients of CKD were enrolled from Nephrology Unit of one hospital only therefore not the representative of entire population. Follow up time was six months only which make it very

difficult to predict the long term efficacy and adverse effects of alpha keto-analogues.

#### CONCLUSION

Alpha keto-analogues emerged as an efficacious short-term option in reducing the progression of chronic kidney disease in our study. Use of this option in addition to routine treatment and low protein diet was related to significant improvement in renal functions in three-month time.

**Conflict of Interest:** None.

#### Authors' Contribution

SU: Design analysis interpretation, SS: Design analysis interpretation, NMA: Interpretation, KMR: Interpretation, FAS: Interpretation, SS: Interpretation, MNA: Interpretation, HS: Interpretation.

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