A RETROSPECTIVE COMPARATIVE STUDY ON KETOANALOGUES ON RETARDING PROGRESSION OF CHRONIC KIDNEY DISEASE AND PREVENTING MALNUTRITION

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Abstract: Background:- Patients suffering from CKD may be suggested to follow LPD and VLPD which might cause malnutrition and muscle wastage. Hence, patients in stage 3, 4 and 5 of CKD are prescribed ketoanalogues; nitrogen free analogues of essential amino acids; to prevent malnutrition and retard CKD progression. This study was designed to investigate the efficacy of ketoanalogues in CKD patients.
Methodology:- The study was conducted in KIMS Hospitals, Gachibowli for a period of 6 months. A total of 50 patients were considered of which 25 patients were on ketoanalogues and 25 patients were not on ketoanalogues. Information on demographics, diagnosis, laboratory data and treatment of all patients was obtained. Parameters such as body weight, BMI, eGFR, serum albumin, BUN, serum creatinine, serum potassium, serum chloride and serum sodium were compared to determine efficacy of ketoanalogues. Age group, gender, and common comorbidities were also determined.
Results:- This was a retrospective study where CKD stage 3, 4 and 5 patients were considered. Group 1 showed a slower decline in eGFR, serum. Albumin, BUN, Sr. Creatinine and prevented hyperkalemia, hyperchloremia and dysnatremia. Most common comorbidities found were diabetes and hypertension. The study depicted males are more susceptible to developing CKD than females in both groups. The majority of patients with CKD belonged to the age group 60-69 years.KA have been found to be beneficial in preventing malnutrition by assessing the parameters such as BMI, body weight, and serum albumin levels. KA were prescribed both in powder and tablet dosage forms but tablets was found to be more preferred
Conclusion:- The study depicts that ketoanalogues are effective in retarding CKD progression further to dialysis and prevented the risk of malnutrition in CKD patients when compared to patients not taking ketoanalogues.

Keywords: Ketoanalogue, CKD, low protein diet, very low protein diet, comorbidities, hyperkalemia, hyperchloremia, dysnatremia, diabetes, hypertension.

I. INTRODUCTION:-

CHRONIC KIDNEY DISEASE:-

Chronic renal disease or chronic kidney disease, is a disorder in which kidney functiongradually declines over time. It includes conditions that harm the kidneys and lessen their capacity to filter waste from the blood. Worldwide, CKD is a significant public health issue. End-stage renal disease (ESRD). may eventually result from CKD if it is not well controlled. Inaddition, CKD may exacerbate a wide range of additional illnesses. Kidney disease and cardiovascular disease are tightly related, and when one organ is ill, the other becomes dysfunctional, eventually failing both organs. This condition is frequently known as cardio- renal syndrome (CRS).

KETOANALOGUES:-

The goal of CKD treatment is to prevent or slow further damage to the kidneys. Dietary intervention is the main approach to kidney failure. Dietary protein restriction, with or without supplementation of ketoanalogues of certain amino acids, have long been considered as an attractive intervention to slow progression of CKD.. The principal solutes retained in CKD are the protein-related products that cause hyper-azotemia, acidemia, and hyperphosphatemia; phosphate and sodium also play a relevant role in renal adaptation, causinghyperparathyroidism and extracellular volume expansion, respectively. Generally, nutritional management of CKD requires balancing the nutrients, intake of energy, protein,

sodium, potassium, phosphorus, and fluid. The current strategy for controlling CKD aims to delay the time for dialysis and to relieve symptoms and signs caused by CKD-related comorbidities.

Unfortunately, in many countries nephrologists generally do not examine CKD patients until dialysis is imminent and they have few options for delaying the time to dialysis. However, increasing the time until transition to dialysis therapy may improve patient's quality of life and can reduce the financial strain on the healthcare system. Consequently, postponing dialysis initiation should receive a high priority in majority of patients with advanced CKD. In fact, there is evidence that many patients will be able to postpone the transition to dialysis, reportedly, more than 60 % of all CKD patients can experience a persistently low GFR (i.e., below 25 ml/min/1.73 m2) during the two years prior to initiation of dialysis

Ketoanalogues of amino acids (KAs) are nitrogen-free analogs of essential amino acids.Alpha- Ketoanalogues (KA) of essential amino acids, converted into essential amino acids in the body via transamination, could improve nutritional deficiencies caused by protein-restricted diets in CKD patients. Using KA to supplement a LPD slowed or halted the progression of renal insufficiency in CKD patients. KA formulations may slow down the progression of CKD but solid evidence proving the efficacy of these nutritional supplements is lacking. Ketoanalogues (KAs) are converted into BCAAs in the body via the urea cycle, and they have been used to supplement a low protein diet (LPD) or very low protein diet (VLPD) in the prevention of nutritional deficiencies. "Keto diet" refers to a variety of KA and low- protein diets (LPDs; 0.6 g/kg per day) or very-low-protein diets (VLPDs; 0.3–0.4 g/kg per day), which allow a reduced intake of nitrogen while avoiding the deleterious consequences of inadequate dietary protein intake and malnourishment. These diets have been effective in reducing renal death in selected CKD patients with proven diet adherence and low comorbidity. Nutrition deficiency is one of the major concerns in CKD patients. Restricted protein diets can protect the kidneys and delay CKD deterioration by decreasing albuminuria and alleviating renal fibrosis. However, these diets may lead to malnutrition, contributing to nutrition-related comorbidities.

In advanced CKD, a large number of metabolites produced under normal intake conditions cannot be excreted by unhealthy kidneys, and metabolism dysregulation leads to many harmful effects including protein-energy wasting (PEW), mineral bone disorders, and chronic inflammation. During the past decades, LPDs and VLPDs have been demonstrated to beassociated with a decrease in proteinuria, better control of blood pressure, and slower decline inGFR in advanced CKD patients. Nevertheless, a protein-restricted diet may also increase the risk of branched-chain amino acid (BCAA) deficiency and further PEW status.Hence, how is it best to achieve a proper balance between intake and consumption has become a major issue in CKD management, especially in patients with advanced CKD. KA supplements may increase protein synthesis in muscles and suppress protein degradation, respectively. Studies have reported that KA supplements seem to be advantageous for CKD patients on an LPD or VLPDto slow the progression of CKD.

II. MATERIALS AND METHODS

This observational study was carried out at the NEPHROLOGY department at Krishna Institute of Medical Sciences hospitals, Gachibowli, Hyderabad, Telangana. A sample size of 50 was taken and observed for 6 months. Out of which, 25 patients were on ketoanalogues and 25 patients were not on ketoanalogues.

Selection criteria: The study is carried out based on the following criteria:

- Inclusion criteria

1. Age more than 21 years.
2. All CKD stage 3-5 patients.
3. Patients particularly using ketoanalogues.
4. Patients of both sexes.
5. CKD with comorbidities.
6. Patients with nephrotic syndrome being considered for low-protein diet.

- Exclusion criteria

1. Special category patients (pediatrics, lactating, pregnancy).
2. Patients undergoing dialysis

All the patients who met the inclusion criteria were selected and the relevant data of the patients was obtained from old Medical Record Department (MRD) for consecutive 3 months after getting required permission from Hospital administration.

III. RESULTS

1. DISTRIBUTION BASED ON AGE:-

Age Interval (years)	Group I		Group II	
	N	%	N	%
30-39	03	12	05	20
40-49	05	20	08	32
50-59	05	20	04	16
60-69	05	20	07	28
70-79	06	24	01	04
80-89	01	04	0	0

Table 1: Distribution of subjects based on age

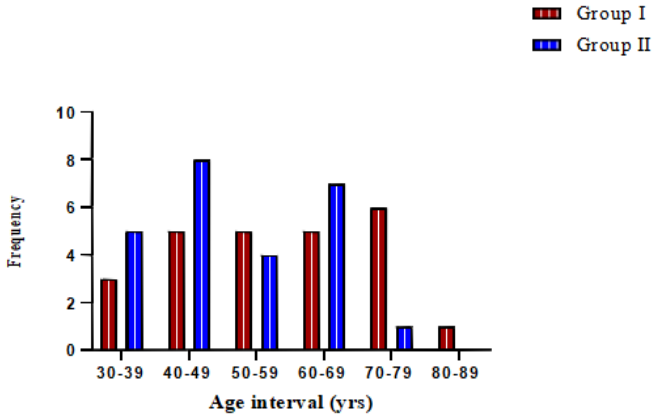


Fig 1: Age based distribution of patients

➢ The majority of patients with CKD taking ketoanalogues belonged to the age group 70-79 years and patients not taking ketoanalogues belonged to age group 40-49 years.

2. DISTRIBUTION BASED ON GENDER:-

Group	Male		Female	
	N	%	N	%
I	17	68	08	32
II	18	72	07	28

Table 2: Distribution of subjects based on gender

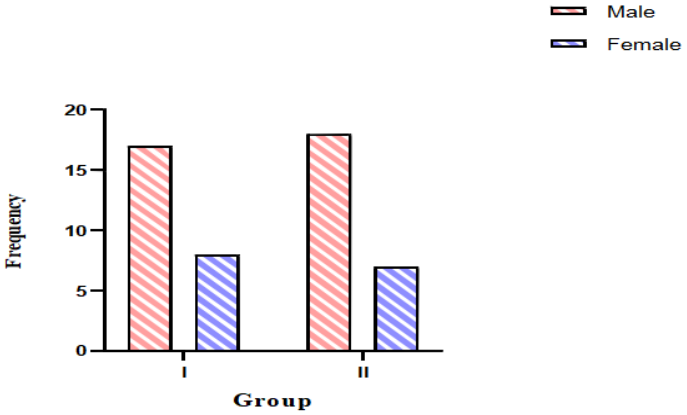


Fig 2 : Gender based distribution of patients.

➢ The gender more susceptible in developing CKD was found to be males in both the groups.

3. DISTRIBUTION BASED ON DIAGNOSIS:-

Diagnosis	Group I		Group II	
	N	%	N	%
CKD stage 3A	01	04	05	20
CKD stage 3B	07	28	08	32
CKD stage 4	08	32	01	04
CKD stage 5	09	36	11	44

Table 3: Distribution of subjects based on diagnosis

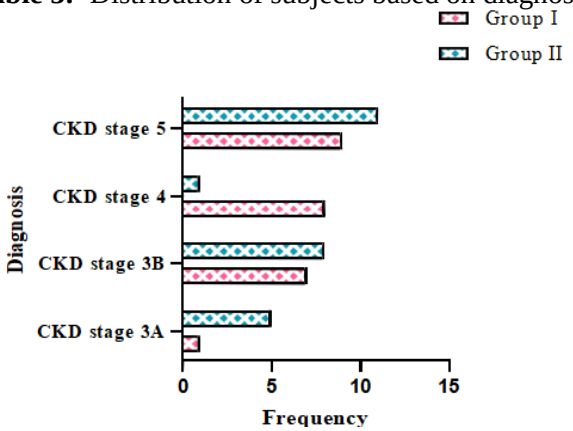


Fig 3: Diagnosis based distribution of patients.

➢ According to the objectives, stage 3, 4 and 5 ckd patients were considered. Ketoanalogues were prescribed in all the stages. However, patients of stage 5 CKD were prescribed ketoanalogues comparatively more than in other stages.

4. DISTRIBUTION BASED ON COMORBID CONDITIONS:-

Comorbidity	Group			
	I		II	
	N	%	N	%
Hypertension	22	88	24	96
Diabetes mellitus	13	52	12	48
Anaemia	01	04	0	0
Hypothyroidism	07	28	05	20

Table 4: Distribution of subjects based on Comorbid conditions

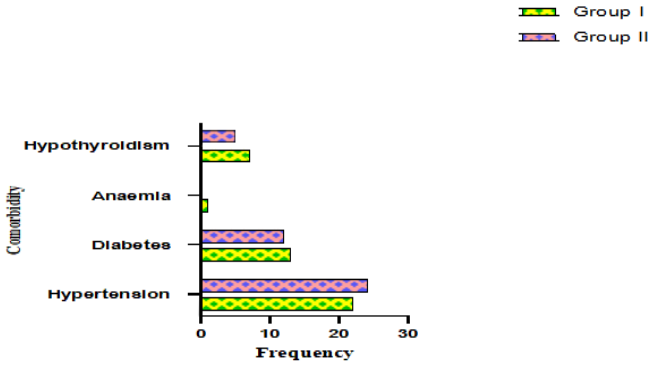


Fig 4: Comorbid condition-based distribution of patients

➢ The most common comorbidities found in CKD patients were hypertension and diabetes followed by hypothyroidism and anemia. This showed how hypertension and diabetes were somehow responsible in causing and aggravating CKD in patients

5. COMPARISON BASED ON eGFR:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	21.29±2.49	21.79±2.51	22.42±2.64	0.2849
II	34.99±3.74	25.82±3.35	18.32±3.07	<0.0001*

Table 5: Comparison of subjects based on eGFR

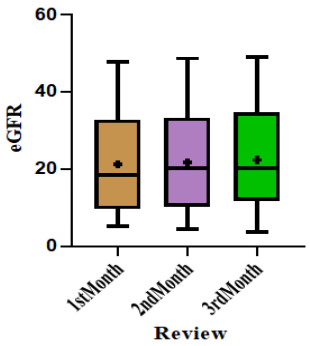


Fig 5(a): eGFR in group I

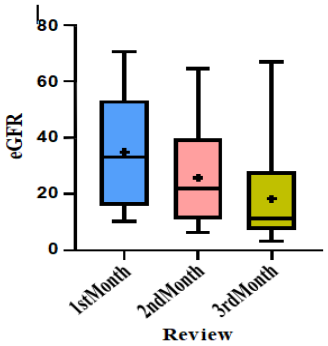


Fig 5(b): eGFR in group II

*Statistically significant difference was found

➢ No significant decline in eGFR was seen in group I whereas there was a rapid decline in eGFR in group II. Ketoanalogues were effective in slowing down the fall in eGFR rates in CKD patients.

6. COMPARISON BASED ON SERUM ALBUMIN:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	3.74±0.22	3.84±0.24	3.78±0.20	0.7609
II	3.50±0.23	3.09±0.23	2.73±0.19	0.0004*

Table 6: Comparison of Serum Albumin

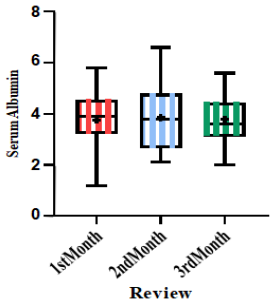


Fig 6(a): Sr Albumin in Group I

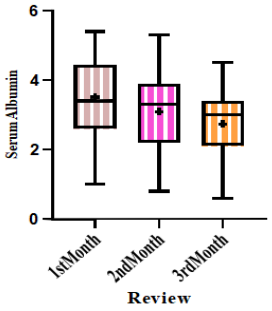


Fig 6(b): Sr Albumin in Group II

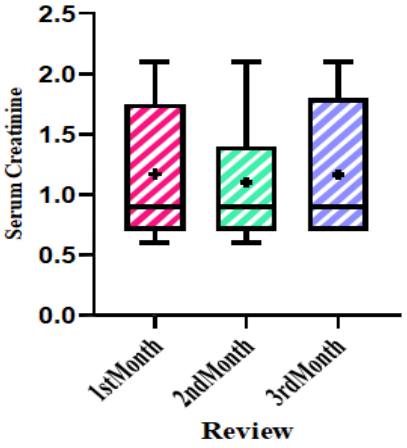
*Statistically significant difference was found

➢ Serum albumin levels were well maintained in group I when compared to group II where decline in levels is seen. It is a marker for malnutrition and decline in albumin levels shows significant malnutrition which is prevented by the use of ketoanalogues.

7. COMPARISON BASED ON SERUM CREATININE:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	1.17±0.10	1.10±0.09	1.16±0.10	0.3459
II	1.34±0.12	2.12±0.22	4.01±0.46	<0.0001*

Table 7: Comparison of Serum Creatinine



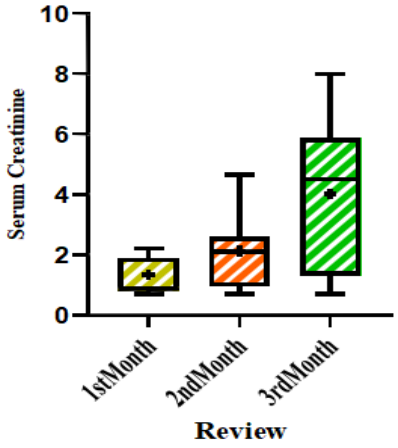


Fig 7(a): Sr Creatinine in Group I **Fig 7(b):** Sr Creatinine in Group II

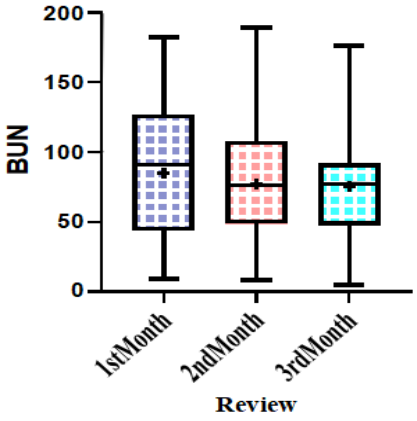
*Statistically significant difference was found

➢ There was no significant change in serum creatinine levels in group I whereas there was a significant increase in serum creatinine levels in group II stating the effectiveness of ketoanalogues in preventing the increase in creatinine levels in CKD patients.

8. COMPARISON BASED ON BUN LEVELS:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	84.74±9.33	76.74±8.74	75.65±8.81	0.1065
II	45.68±8.01	55.76±8.84	63.88±9.55	0.0002*

Table 8: Comparison of BUN



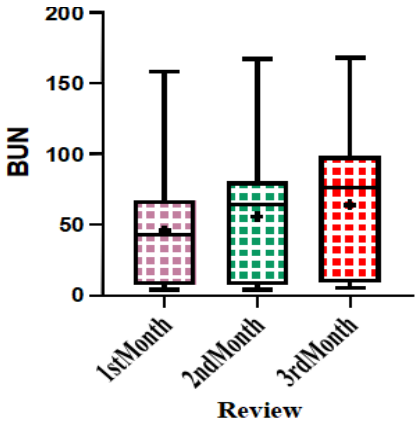


Fig 8(a): BUN Levels in Group I **Fig 8(b):** BUN Levels in Group II

*Statistically significant difference was found

➢ There was no significant change in blood urea nitrogen levels in group I whereas there was a significant increase in blood urea nitrogen levels in group II stating the effectiveness of KA in preventing the increase in BUN levels in CKD patients.

9. COMPARISON BASED ON BODY WEIGHT:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	77.89±3.83	78.13±3.69	79.55±3.66	0.0035*
II	81.67±2.21	76.81±2.30	72.44±2.23	<0.0001*

Table 9: Comparison of Body Weight

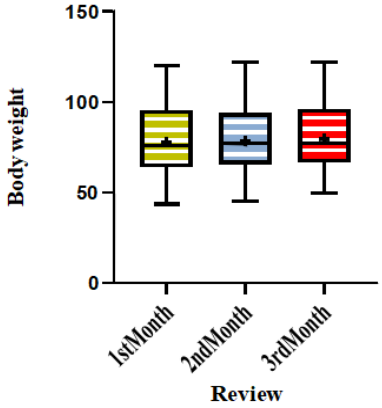


Fig 9(a): Body Weight in Group I

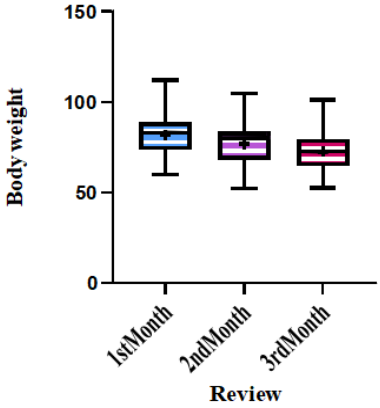


Fig 9(b): Body Weight in Group II

*Statistically significant difference was found

➢ Body weight was maintained in group I and there was a decline in body weight in group II indicating KAs were effective in maintaining body weight and preventing malnutrition.

10. COMPARISON BASED ON BMI:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	29.13±1.29	29.20±1.31	29.64±1.31	0.0705
II	30.37±0.87	28.68±0.87	26.94±0.85	<0.0001*

Table 10: Comparison of BMI

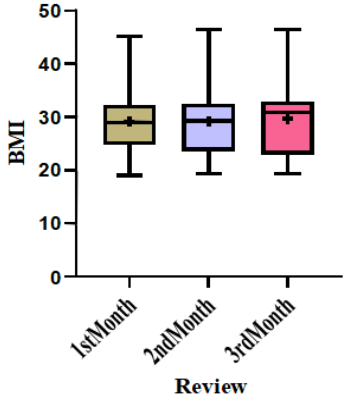


Fig 10(a): BMI in Group I

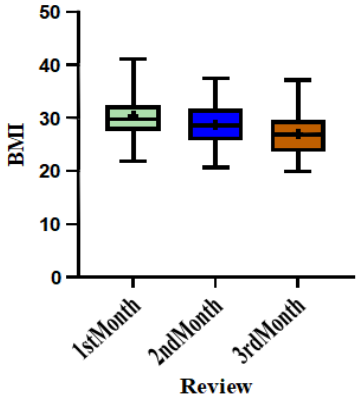


Fig 10(b): BMI in Group II

*Statistically significant difference was found

➢ Body mass index was maintained in group I and there was a decline in body mass index in group II indicating ketoanalogues were effective in maintaining BMI and preventing malnutrition.

11. COMPARISON BASED ON SERUM SODIUM:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	77.89±3.83	78.13±3.69	79.55±3.66	0.0035*
II	81.67±2.21	76.81±2.30	72.44±2.23	<0.0001*

Table: Comparison of Serum Sodium

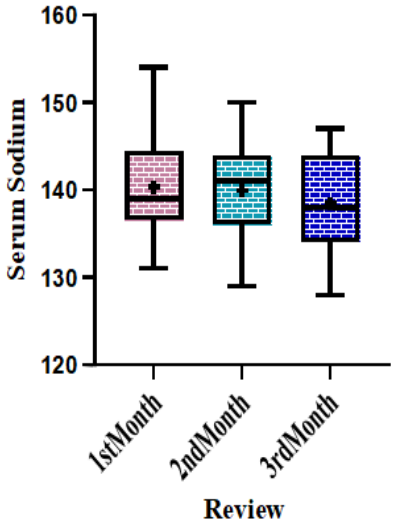


Fig 12(a): Sr Sodium in Group I

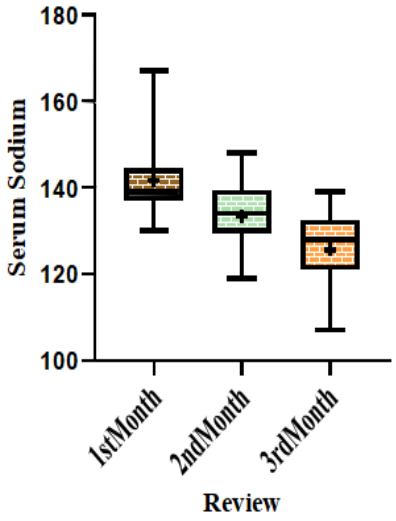


Fig 12(b): Sr Sodium in Group II

*Statistically significant difference was found

➢ Dysnatremia, which is a common complication in CKD patients, is the abnormal levels of serum sodium. No major fluctuations in serum sodium was seen in group I where as there was a decline in serum sodium levels in group II. Ketoanalogues were helpful in preventing serum sodium fluctuations

12. COMPARISON BASED ON SERUM POTASSIUM:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	4.63±0.18	4.62±0.13	4.43±0.10	0.3330
II	4.61±0.17	5.11±0.16	6.01±0.22	<0.0001*

Table 13: Comparison of Serum Potassium

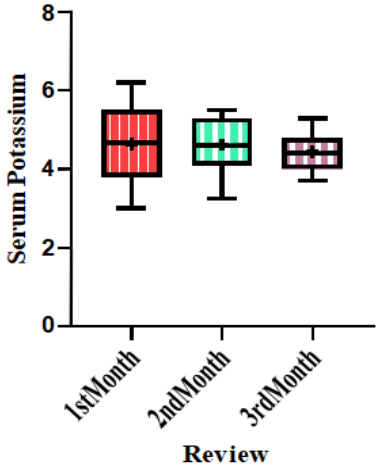


Fig 13(a): Sr Potassium in Group I

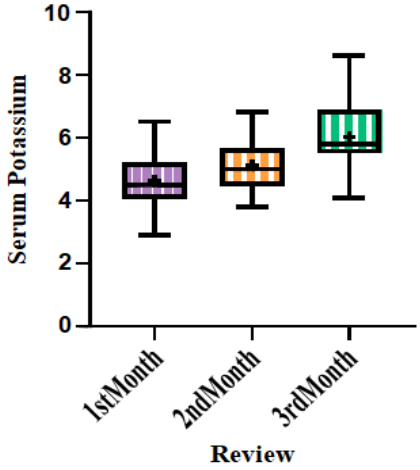


Fig 13(a): Sr Potassium in Group II

*Statistically significant difference was found

➢ Serum potassium levels were well maintained in group I and there was a significant increase in serum potassium levels in group II indicating hyperkalemia, yet another complication of CKD. Ketoanalogues were effective in preventing hyperkalemia in CKD patients.

13. COMPARISON BASED ON SERUM CHLORIDE:-

Group	Review			P value
	1st Month	2nd Month	3rd Month	
I	104.5±1.07	103.3±1.71	99±1.71	<0.0001*
II	100.8±1.74	106.9±1.94	116.9±2.68	<0.0001*

Table 14: Comparison of Serum Chloride

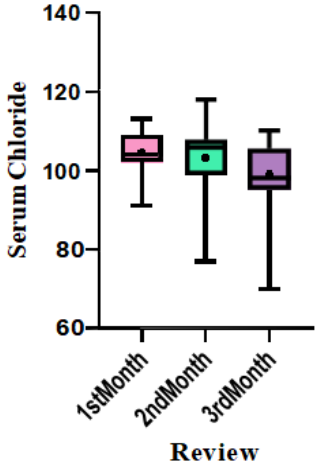


Fig 14(a): Sr Chloride in Group I

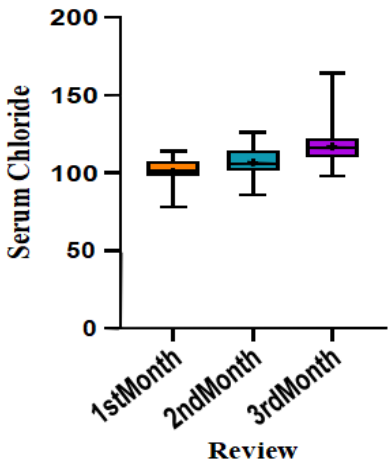


Fig 14(b): Sr Chloride in Group II

*Statistically significant difference was found

- Serum chloride levels were not elevated in group I and there was a significant increase in serum chloride levels in group II indicating hyperchloremia. This portrays that KAs were effective in preventing hyperchloremia in CKD patients

14. DISTRIBUTION BASED ON DOSAGE FORM:-

Dosage Form	N	Percentage
Tablet	15	60
Sachet	07	28
Tablet, Sachet	03	12

Table 15: Distribution based on dosage Form of ketoanalogues prescribed

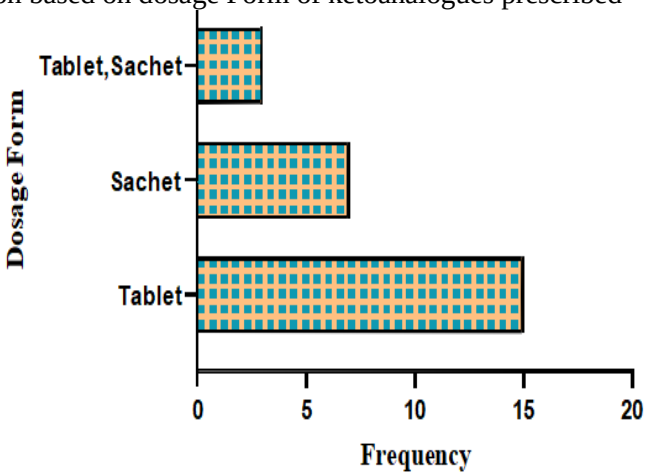


Fig 15:- Prescribed dosage form distribution of ketoanalogues

- The frequently prescribed dosage forms of ketoanalogues were powder forms and tablet forms. However, tablet forms were much more preferred over powder forms due to convenience of adherence and ease of administration. Some patients were prescribed both as well.

IV. DISCUSSION

The present study was conducted with the aim to assess the efficacy of ketoanalogues in retarding CKD progression and preventing malnutrition. In this study, a total of 50 patients were considered out of which 25 were on ketoanalogues (group 1) and 25 patients were not on ketoanalogues (group 2). Our results provide evidence that KA supplementation during LPD may reduce the risk of commencing long-term dialysis or of developing the composite outcome in patients with advanced CKD, especially when used at an appropriate dosage.

In this study,

- Out of 25 patients in the group taking ketoanalogues, majority were belonging to the age group of 70-79 years, out of which number of males was higher than that of females, whereas 25 patients in the group not taking ketoanalogues majority were belonging to the age group of 40-49 out of which number of males was again higher than females. This shows that males were more prone to develop CKD. Group 1 had older population because ketoanalogues were preferably prescribed in later stages of CKD which was found in the geriatric population.
- Majority of the patients in the study had hypertension, diabetes mellitus and hypothyroidism as common co-morbid conditions of which hypertension and diabetes being the highest showed how they affected the development of CKD which is similar to the study conducted by Clare MacRae et.al
- The eGFR showed a significant difference in both the groups i.e slower decline of eGFR was noticed in group 1 and rapid decline in eGFR was noticed in group 2. this proved that ketoanalogues are indeed effective in slowing the decline of eGFR in CKD patients which was similar to the conclusion obtained by Api Chewcharat.
- There was a significant decrease in serum BUN levels in group 1 when compared to the group 2. A study conducted by SF Feiten et.al showed similar results.
- Significant difference of serum creatinine was observed in both the groups I.e group 2 not taking ketoanalogues showed greater creatinine values than group 1 taking ketoanalogues which was common to the results obtained by Albert Li et.al.
- There was no decrease in serum abumin levels in group 1 but group 2 showed a decline in serum albumin levels indicating malnutrition in patients not taking ketoanalogues. This proves that ketoanalogues are affecting in preventing malnutrition in CKD patients. These results were similar to Kullaya Takkavatakarn et.al.
- In our study, we observed significant difference (<0.05) in BMI and body weight in group 1 i.e there was a decline in BMI and body weight in group 2 indicating malnutrition.Zheng Jiang et.al however stated that there was no significant difference in BMI and body weight.
- The p-value for serum electrolytes i.e sodium, potassium and chloride was compared between 2 groups and was found to be statistically significant in group 2 (<0.05) where as no statistical difference was found in group one. Hyperkalemia was a common condition seen in CKD patients, however this condition was not found in patients taking ketoanalogues. Hyperchloremia was also prevented on using ketoanalogues. Dysnatremmia, yet another common condition found in CKD patients, which involves abnormal levels of serum sodium, was also prevented in patients taking ketoanalogues.

V. CONCLUSIONS:-

- In our retrospective study, we concluded that ketoanalogues were beneficial in retarding CKD progression and preventing malnutrition.
- The study showed a slower decline in GFR, a decrease in serum creatinine and BUN levels, and prevent hyperkalemia, hyperchloremia, and dysnatremia in patients taking ketoanalogues compared to patients not taking ketoanalogues.
- The dosage of ketoanalogues depended on the stage of CKD, the patient's comorbidities, and the extent of deterioration in kidney functioning. People with major comorbidities and stage 5 CKD with very less kidney functioning were prescribed higher doses than their counterparts.
- From the results, we can conclude that males are more susceptible to developing CKD than females in both groups. The majority of patients with CKD belonged to the age group 60-69 years. The most common comorbidities associated with CKD patients were hypertension followed by diabetes mellitus.
- We can conclude that Ketoanalogue supplementation was beneficial in preventing malnutrition by assessing the parameters such as BMI, body weight, and serum albumin levels in patients taking ketoanalogues as these levels were well maintained.
- Ketoanalogues were prescribed in both powder and tablet dosage forms, however, tablet forms were mostly preferred due to the convenience of adherence and ease of administration

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