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**Original Research Article**

# Role of rhubarb and α-keto analogues of essential amino acids supplementation in halting progression of chronic kidney disease

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## ABSTRACT

**Background:** Chronic kidney disease (CKD) is an emerging chronic disease due to rapidly increasing incidence of diabetes and hypertension worldwide. Newer drugs are being searched which can stop nephron damage and are cost effective. This study was undertaken to compare the efficacy and safety profile of rhubarb and α-keto analogues of essential amino acids supplementation in patients of chronic kidney disease.
**Methods:** A prospective comparative study was conducted in patients of chronic kidney disease attending Renal Clinic of a tertiary care centre. Randomization of patients was done into three interventional groups: conservative management along with placebo was given in first group (Control); conservative management along with Rhubarb capsule (350 mg, thrice daily) was given in second group (Rhubarb) and conservative management along with α-keto analogues of essential amino acids (600 mg, thrice daily) was given in third group (KAA). The treatment was given for 12 weeks. Clinical and biochemical parameters were assessed at 0, 4, 8 and 12 weeks of treatment.
**Results:** Patients of all three groups showed gradual improvement in clinical features and biochemical parameters as compared to their pre-treated values which was more marked in KAA supplemented group. There was reduction in: fasting blood glucose (12.51%, 19.15% and 20.78%), PPBG (14.80%, 19.00% and 20.89%), serum creatinine (25.00%, 30.54% and 39.52%), blood urea (25.55%, 33.64% and 38.09%), and 24-hour total urine protein (TUP) (19.80%, 30.18% and 38.34%) in Group I, II and III respectively. There was increase in: haemoglobin level (12.64%, 14.99% and 19.77%), 24-hour total urine volume (TUV) (19.41%, 28.82% and 33.32%) and GFR (22.6%, 46.5% and 49.2%) in Group I, II and III respectively. Rhubarb and KAA supplementations were safe and well-tolerated.
**Conclusions:** KAA is more effective than Rhubarb as add on therapy with conservative management in patients of chronic kidney disease.

**Keywords:** α-keto analogues of essential amino acids, Conservative management, Chronic kidney disease, Rhubarb

## INTRODUCTION

Chronic kidney disease (CKD) includes a spectrum of different pathophysiologic processes associated with abnormal kidney function as well as continuous decline in glomerular filtration rate (GFR).[1] Worldwide, CKD is 12th leading cause of death and 17th cause of disability.[2] This is an underestimate as patients with CKD more likely die due to cardiovascular disease (CVD) than reaching end-stage renal disease (ESRD). With increasing prevalence of CKD, CKD related CVD, ESRD and the consequent cost burden of renal replacement therapy (RRT) has to be realized. The prevalence of CKD in India is approximately 17.2% with ~6% have CKD

stage 3 or worse.[3] Rhubarb is a member of genus Rheum in the family Polygonaceae. Important derivatives from Rhubarb are anthraquinones like rhein, emodin, aloe-emodin.[4] Rhein and rhaponticin are potential candidates for hypoglycaemic effect.[5] Rhein decreases the lipid level and protects against diabetic nephropathy progression.[6] Emodin decreased the gluconeogenesis of renal tubular cells and reduced the ATP content of epithelial mitochondria. Both the Na+/K+- ATPase and Ca2+-ATPase activities of the epithelial cells were decreased during the administration of emodin in an in-vitro study.[7] Rhubarb supplementation is effective along with conservative management in patients of chronic kidney disease.[8]

Keto amino acids (KAA)/α-Keto analogues of essential amino acids are nitrogen free analogues of essential amino acids. The use of KAA along with a low or very low protein diet allows a reduced intake of nitrogen while avoiding the harmful consequences of inadequate dietary protein intake and malnourishment.[9-15] α-keto amino acid reduced proteinuria, improved renal function and nutritional status in diabetic nephropathy patients.[16] KAA halted progression of type 2 diabetic nephropathy by regulating inflammatory mediators such as tumor necrosis factor-α, C-Reactive Protein and adiponectin.[17] The aim of our study was to compare the efficacy and safety profile of rhubarb and α-keto analogues of essential amino acids supplementation in patients of chronic kidney disease.

## METHODS

The approval for study was taken from Institutional Ethics Committee and registered on 03/09/2012 under Clinical Trial Registry of India with number CTRI/2012/09/002947. Study design was randomized, prospective, double blinded and parallel group. Study period was from June 2012 to September 2013. Study was done in chronic kidney disease patients attending Nephrology Clinic of a tertiary care centre of North India. Written and informed consent was taken from all patients enrolled in the study. The diagnosis of CKD was made on the basis of detailed clinical history, physical examination and investigations. Patients having chronic kidney disease (Stage 1-4), age 20-60 years and of either sex were included in the study. Patients on dialysis, end stage renal disease (ESRD), pregnant, terminally ill, immuno-compromised or severe renal pathology like malignancy were excluded from the study.

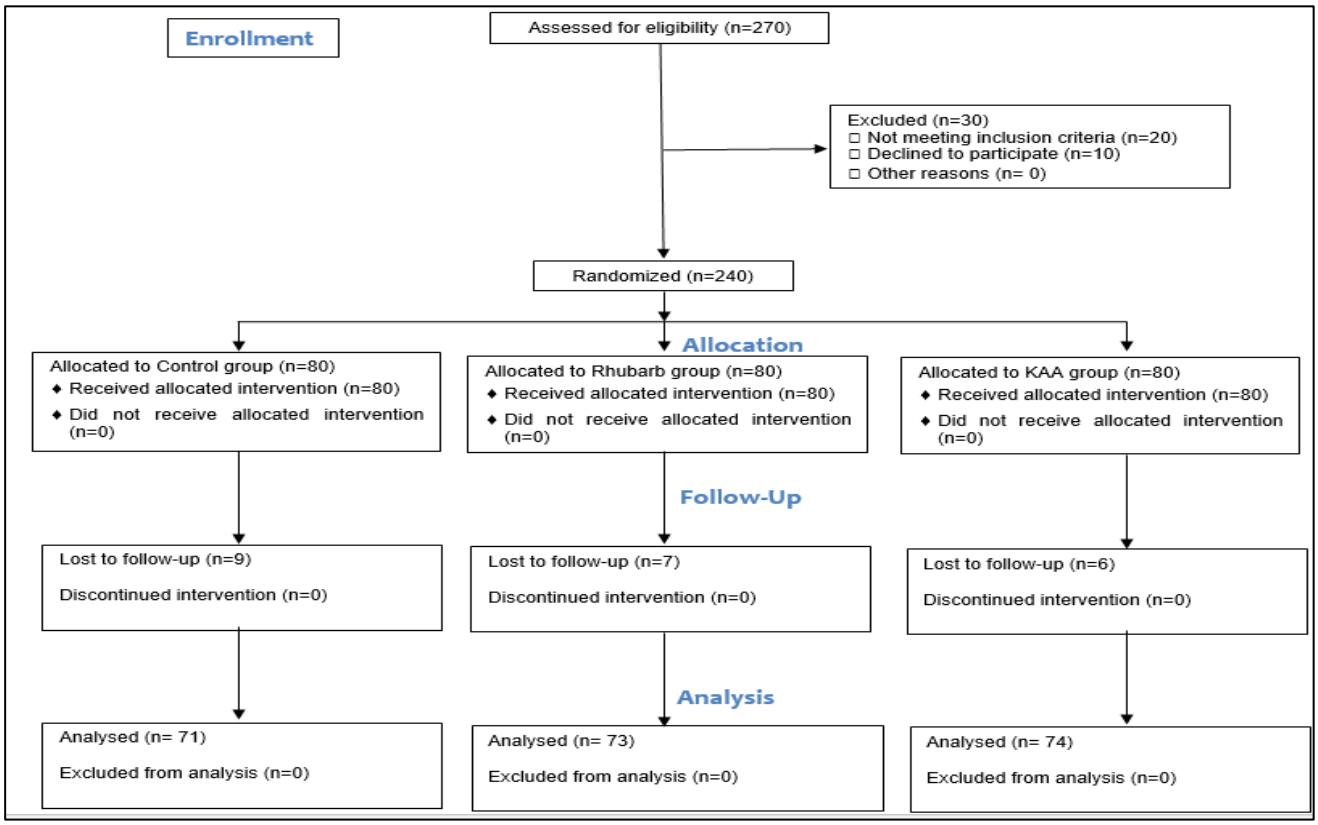


**Figure 1: Enrolment, allocation and follow-up of patients.**

n = (z2/e2) pq where z = level of confidence interval at 95%, so z=1.96; e= acceptable error; p=prevalence (prevalence assumed as 17.2% according to SEEK-India cohort study); q=1-p. Hence, sample size (n) = ((1.96*1.96)/ (0.09*0.09))* (0.172*0.828)=67.54.[3] So, sample size of 68 is minimum required for each group.

Taking into consideration a 15% dropout rate, 80 patients were recruited in each group. The power of the study using the study results (GFR) is 100%. A total of 270 patients were assessed, 240 patients were enrolled, out of which 218 patients completed the study. Nine patients of Group I, 7 patients of Group II and 6 patients of Group III were excluded from the study as they failed to report on subsequent visits. Enrolled patients were randomized into three groups at a ratio of 1:1:1 using table generated by random allocation software.

Patients were included in the study after final diagnosis, applying inclusion and exclusion criteria. Group I (Control) patients received conservative management along with placebo; Group II (Rhubarb) patients received conservative management along with Rhubarb (350 mg capsule) thrice daily and Group III (KAA) was given conservative management along with α-keto analogues of essential amino acids (600 mg) thrice daily (Figure 1).

All the three groups received treatment for 12 weeks. Conservative management included renal diet, telmisartan (40 mg OD), torsemide (20 mg BD), calcium carbonate (650 mg TDS), Calcitriol (0.25 µg OD), Erytropoietin (2000U s.c. twice a week), ferrous fumarate 350 mg OD, Vitamin B12 15 µg OD, Folic acid 1.5 mg OD, sodium bicarbonate (650 mg TDS). Regular follow-up of patients with haemogram and renal function tests was done at 0, 4, 8 and 12 weeks of treatment. The primary outcome in this study was assessed by serum creatinine, blood urea, 24-hour total urine protein (TUP), 24-hour total urine volume (TUV) and GFR while secondary outcomes were haemoglobin level, blood glucose-fasting and post-prandial, serum potassium and serum calcium. All adverse events were recorded on standard adverse drug reaction (ADR) reporting forms of CDSCO at each visit. ADRs causality assessment was done using Naranjo's Scale and severity assessment by Modified Hartwig and Siegel Scale.[18,19] Other routine laboratory tests like liver function tests (LFT), ECG and Chest X ray were performed wherever required. The values were expressed as mean±SD. Statistical significance between pre-and post-treatment values in each group was calculated using Student's Paired T-test. Statistical significance between groups was calculated using ANOVA followed by Post-Hoc Tukey HSD test. $P < 0.05$ was considered significant. Statistical analysis was done using SPSS-20 software. The effect size calculated using improvement in serum creatinine was 0.2.

## RESULTS

Eighty patients were enrolled in each group. Seventy-one patients in Group I, 73 in Group II and 74 patients in Group III completed the study. The distribution of patients was almost similar and no significant difference ($p>0.05$) was seen between the groups. None of the patient required dialysis and there was no mortality in any group. As per GFR (mL/min per 1.73 $m^2$), patients belonged to CKD stage 3 and 4 (Table 1).

**Table 1: Baseline demographic characteristics of patients.**

| | Group-I (Control) | Group-II (Rhubarb | Group-III (KAA) | Total |
|---|---|---|---|---|
| Number | 71 | 73 | 74 | 218 |
| Sex(M/F) | 41/30 | 42/31 | 44/30 | 127/91 |
| Mean age, years | 45.09±11.61 | 45.30±10.91 | 45.74±11.21 | 45.3±11.1 |
| **Stage of Chronic Kidney Disease (GFR in ml/min)** | | | | |
| 3 (30-59) | 19 | 20 | 22 | 61 (27.98%) |
| 4 (15-29) | 52 | 53 | 52 | 157 (72.02%) |
| **Underlying cause of CKD** | | | | |
| Diabetic nephropathy | 32 (45.07%) | 32 (43.83%) | 32 (43.24%) | 96 (44.04%) |
| Hypertensive nephropathy | 13 (18.30%) | 14 (19.17%) | 15 (20.27%) | 42 (19.26%) |
| Chronic glomerulonephritis | 8 (11.26%) | 7 (9.58%) | 8 (10.81%) | 23 (10.55%) |
| Tubulointerstitial nephritis | 6 (8.45%) | 5 (6.84%) | 4 (5.40%) | 15 (6.88%) |
| Autosomal dominant polycystic kidney disease | 3 (4.22%) | 4 (5.47%) | 4 (5.40%) | 11 (5.04%) |
| Unknown | 9 (12.67%) | 11 (15.06%) | 11 (14.86%) | 31 (14.22%) |

The baseline clinical features were almost similar in all the three groups. There was gradual improvement in clinical features in all the three groups after 12 weeks of treatment but it was more marked in KAA group as compared to Rhubarb group (Table 2). There was progressive decrease in both systolic and diastolic blood pressure towards normal in all the three the groups. KAA group showed most significant decrease in both systolic and diastolic blood pressure (Table 3). The total leucocyte count (TLC), differential leucocyte count (DLC), platelet count, serum sodium, potassium and calcium remained within normal limits at the end of 12 weeks of treatment in all three groups.

**Table 2: Signs and symptoms of patients.**

| Signs and Symptoms | Group I (Control) | | Group II (Rhubarb) | | Group III (KAA) | |
|---|---|---|---|---|---|---|
| | 0 week | 12 weeks | 0 week | 12 weeks | 0 week | 12 weeks |
| Anorexia | 65 | 3 | 66 | 3 | 65 | 2 |
| Nausea | 54 | 9 | 55 | 8 | 53 | 5 |
| Vomiting | 59 | 7 | 58 | 6 | 57 | 5 |
| Weakness | 58 | 0 | 58 | 0 | 59 | 0 |
| Weight loss | 21 | 3 | 19 | 2 | 20 | 1 |
| Headache | 46 | 5 | 45 | 4 | 44 | 2 |
| Pruritus | 35 | 2 | 37 | 1 | 37 | 0 |
| Swelling over body | 50 | 0 | 49 | 0 | 51 | 0 |
| Oliguria | 55 | 0 | 54 | 0 | 53 | 0 |
| Burning during micturation | 28 | 0 | 30 | 0 | 31 | 0 |
| Fever | 33 | 0 | 32 | 0 | 30 | 0 |
| Anaemia | 65 | 55 | 66 | 54 | 64 | 50 |
| Hypertension | 60 | 12 | 58 | 8 | 61 | 6 |
| Dyspnoea | 35 | 2 | 34 | 1 | 33 | 0 |

**Table 3: Comparison of blood pressure, haemogram and renal function tests between rhubarb and α-keto analogues of essential amino acids (KAA) groups before and after 12 weeks of treatment.**

| Parameter | Group | 0 week Mean ± SD | 12 weeks Mean ± SD | % Improvement after 12 weeks | 95% Confidence Interval |
|---|---|---|---|---|---|
| SBP (mm Hg) | I | 150.40±17.62 | 136.62±16.45$^{b}$ | (-)9.16% | 1.058 to 1.145 |
| | II | 152.97±20.60 | 132.60±8.79$^{b}$ | (-)13.31% | 1.114 to 1.194 |
| | III | 156.78±22.86 | 130.85±9.58$^{c1}$ | (-)16.53% | 1.154 to 1.243 |
| DBP (mm Hg) | I | 87.32±10.43 | 85.98±9.65 | (-)1.53% | 0.977 to 1.055 |
| | II | 88.63±11.42 | 84.73±9.31$^{b}$ | (-)4.40% | 1.006 to 1.088 |
| | III | 88.02±12.40 | 83.80±10.71$^{c1}$ | (-)4.79% | 1.005 to 1.097 |
| Hb% (g/dL) | I | 7.91±1.93 | 8.91±1.48$^{c}$ | (+)12.64% | 0.828 to 0.951 |
| | II | 7.87±2.06 | 9.05±1.58$^{c}$ | (+)14.99% | 0.808 to 0.934 |
| | III | 7.84±1.10 | 9.39±0.87$^{c1}$ | (+)19.77% | 0.803 to 0.868 |
| FBG (mg/dL) | I | 130.05±42.90 | 113.78±14.31$^{c}$ | (-)12.51% | 1.049 to 1.239 |
| | II | 132.60±45.55 | 107.20±18.03$^{c1}$ | (-)19.15% | 1.129 to 1.348 |
| | III | 131.28±44.31 | 104.00±8.46$^{c3}$ | (-)20.78% | 1.162 to 1.363 |
| PPBG (mg/dL) | I | 184.95±61.17 | 157.56±23.20$^{c}$ | (-)14.80% | 1.075 to 1.275 |
| | II | 182.30±62.05 | 147.65±15.46$^{c1}$ | (-)19.00% | 1.134 to 1.337 |
| | III | 181.28±55.22 | 143.40±12.83$^{c3}$ | (-)20.89% | 1.172 to1.357 |
| B.Urea (mg/dL) | I | 107.16±35.85 | 79.78±24.79$^{b}$ | (-)25.55% | 1.206 to 1.495 |
| | II | 108.89±42.65 | 72.25±26.89$^{c}$ | (-)33.64% | 1.329 to 1.708 |
| | III | 106.73±27.72 | 66.07±19.29$^{c1}$ | (-)38.09% | 1.477 to 1.768 |
| S.Cr. (mg/dL) | I | 4.44±1.64 | 3.33±1.37$^{c}$ | (-)25.00% | 1.172 to 1.520 |
| | II | 4.06±2.08 | 2.82±1.24$^{c1}$ | (-)30.54% | 1.228 to 1.681 |
| | III | 4.68±1.86 | 2.83±1.10$^{c1}$ | (-)39.52% | 1.455 to 1.879 |
| TUP (g/day) | I | 3.03±1.29 | 2.43±0.97$^{b}$ | (-)19.80% | 1.086 to 1.430 |
| | II | 3.18±1.57 | 2.22±1.28$^{c}$ | (-)30.18% | 1.203 to 1.714 |
| | III | 3.34±0.88 | 2.06±0.61$^{c2}$ | (-)38.34% | 1.481 to 1.777 |
| TUV (mL/day) | I | 1454.36±221.53 | 1736.76±176.04$^{c}$ | (+)19.41% | 0.802 to 0.874 |
| | II | 1451.69±303.74 | 1870.14±258.78$^{c2}$ | (+)28.82% | 0.732 to 0.822 |
| | III | 1457.46 ±179.48 | 1943.23±204.1$^{c3}$ | (+)33.32% | 0.723 to 0.778 |
| GFR (mL/min) | I | 19.0±1.17 | 23.3±1.63$^{b}$ | (+)22.6% | 0.798 to 0.834 |
| | II | 19.1±2.37 | 28.0±3.51$^{c1}$ | (+)46.5% | 0.655 to 0.711 |
| | III | 19.7±1.86 | 29.4±3.68$^{c3}$ | (+)49.2% | 0.646 to 0.695 |

Values are mean ± SD; p<0.05 was considered significant; ap<0.05, bp<0.01, cp<0.001 compared to 0 week value of respective group; 1p<0.05, 2p<0.01, 3p<0.001 compared to control group. I=Control; II=Rhubarb; III=KAA; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; Hb%= Haemoglobin percent; FBG= Fasting Blood Glucose; PPBG= Post-prandial Blood Glucose; B. Urea= Blood Urea; S.Cr.=Serum creatinine; Na+= Serum sodium; K+= Serum potassium; Ca2+= Serum calcium; TUP=24 Hour Total Urine Protein; TUV=24 hour total urine volume; GFR = Glomerular Filtration Rate; (+) Increase, (-) Decrease.

There was progressive improvement in various biochemical parameters in all three groups. KAA group showed maximum improvement among the three groups. As compared to control group, KAA group showed significant increase in haemoglobin percent ($p<0.05$), decrease in fasting and post-prandial blood glucose ($p<0.01$), decrease in blood urea ($p<0.05$), decrease in serum creatinine ($p<0.05$), decrease in TUP ($p<0.01$), increase in TUV ($p<0.001$) and increase in GFR ($p<0.001$) than Rhubarb group after 12 weeks of treatment (Table 3).

The adverse drug reactions occurrence was not significantly different between Rhubarb and KAA group. According to Modified Hartwig and Siegel Scale, the adverse drug reactions were mild (no hospitalization, no change of therapy and no additional treatment) in severity in both groups. No adverse event was of acute onset (within 60 minutes). On Naranjo's Scale, the ADRs were possible (Score = 1-4) in 12 cases and probable (Score = 5-8) in 11 cases with Rhubarb group while possible (Score = 1-4) in 15 cases and probable (Score = 5-8) in 7 cases with KAA group (Table 3).

## DISCUSSION

Globally, chronic kidney disease (CKD) is an emerging chronic disease due to rapidly increasing incidence of diabetes and hypertension worldwide.[20,21] CKD causes premature morbidity and mortality and hampers quality of life. In India, CKD is a problem for both health sector and economy. More than 1 lakh new patients enter Renal Replacement Therapy (RRT) annually in India.[22] Because of limited resources, only 10% of Indian ESRD patients receive RRT. The monthly cost for hemodialysis is $300, whereas CAPD is $600. The cost of renal transplant is $8900 for first year, which declines later to $3000 annually. Among available options, renal transplant is the preferred choice as it is cost effective and offers better quality of life but only a fraction of Indians can afford it.[22]

Conservative management is very useful in preventing CKD and its progression to ESRD. It declines the rate of deterioration in renal function. It provides only symptomatic relief. So, newer drugs are being searched which can stop nephron damage, delay the development of ESRD and are cost effective.

At 0 week, all the three groups were similar and not significantly different in respect to number, age distribution, mean age, gender, stage, cause, clinical and biochemical parameters of patients. As per the CKD registry of India, the mean age for CKD in India was 50.1 ±14.6 years, with M:F ratio of 70:30 and diabetic nephropathy the leading cause of CKD.[23] In present study the mean age was 45.3±11.1 years, with M:F ratio of 58:42 (127/91) and diabetic nephropathy was the leading cause of CKD (Table 1).

In previous studies, it has been reported that rhubarb has beneficial effect in CKD patients.[24,25] Rhubarb contains various phytoconstituent among which rhein and emodin are important. Rhein inhibits cellular hypertrophy and extracellular matrix (ECM) deposition by decreasing the transforming growth factor-beta 1 (TGF-β1) and fibronectin expression in renal tissue.[6] In mesangial cells, TGF-β1 stimulates the glucose uptake through upregulation of GLUT 1 expression. Emodin has inhibitory effect on the expression of c-myc mRNA and hence cell cycle down regulation in cultured rat mesangial cells, which might be the reason why emodin inhibits mesangial cell proliferation.[26] Rhubarb decreases the production of various cytokines from macrophages and human mesangial cells.[27,28] Rhubarb also possess laxative effect which increases excretion of nitrogenous wastes from the body.[29,30] Rhubarb showed beneficial effects in nephropathy patients at a dose of 1000 mg/day.[25] So, Rhubarb dose used in our study was 350 mg TDS daily.

α-keto-analogues of the essential amino acids are useful in the treatment of uremia.[31] KAA by taking nitrogen from non-essential amino acids get transaminated and hence decrease the formation of urea by re-using the amino group.[11] Ketoacids reduce protein degradation and urinary protein excretion. Keto-acid supplementation produce reduction of plasma urea, urea synthesis and urea excretion and an improvement in nitrogen balance in patients of chronic renal failure.[32] KAA have good glycemic control, improved insulin sensitivity and reduce hyperinsulinemia.[12] Chen N et al showed significant reduction in TNF-α, CRP and adiponectin on keto acid supplementation in type 2 diabetic nephropathy.[17] KAA showed beneficial effects in CKD stage 4, 5 at dose of 60 mg/kg BW/day.[13] So, KAA dose used in our study was 600 mg TDS daily.

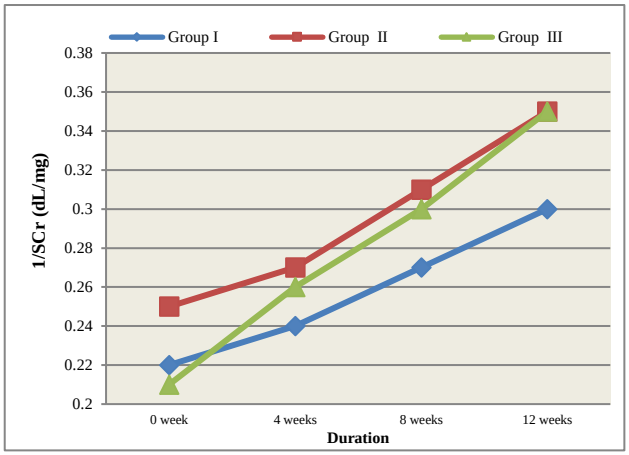


**Figure 2: Progression rate of renal failure in the three groups.**

The progression rate of decline in renal function can be assessed using the slope of the reciprocal serum creatinine versus the time. The slope was steepest in KAA group followed by Rhubarb and control groups. This showed that KAA prevented progression of renal failure more than rhubarb (Figure 2).

The results showed that adverse drug reactions occurrence was not significantly different between rhubarb and keto amino acid treated group. According to Ye R et al, there was no side effect of rhubarb administration at a dose of 8-12 g/day for 3 weeks in 30 patients of nephropathy.[24] Walser M et al showed that KAA supplementation at a dose of 6-14 g/day for 15-60 days in 10 patients of severe uremia produced no toxicity.[14] Mitch WE et al found no side effect or toxicity of KAA supplementation in patients of nephropathy.[15] So, the ADRs might be the manifestations of underlying renal pathology or due to other co-administered drugs. The results in present study are in accordance with those reported in earlier studies. So, supplementation of Rhubarb or α-Keto analogue of essential amino acid along with conservative management produces improvement in clinical features as well as biochemical parameters in patients of Chronic Kidney Disease. The data from this study shows that KAA 600 mg TDS is more effective than Rhubarb 350 mg TDS in patients of chronic kidney disease. The drawback of this study is its limited period of study. Longer duration of follow-up is needed in further studies to see the long-term effect of rhubarb and KAA in chronic kidney disease patients.

## CONCLUSION

Supplementation of Rhubarb or α-keto-analogues of the essential amino acids along with conservative management produces improvement in clinical features as well as biochemical parameters and safe in patients of chronic kidney disease.

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