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The Impact of Pre Probiotics and Alpha Keto Analogue to Enhancing Non - Dialysis CKD Patient's Management

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ABSTRACT

Background: The critical role of the gut-kidney axis is the main importance of normal homeostasis and the dysregulation of this axis in CKD progression. This new approach helps us to restore the symbiotic intestinal environment using dietary prebiotic, probiotic along with supplementation like alpha-keto analogues followed by a low protein diet which ultimately improves metabolic changes, are promising target strategies to either delay or slow down disease progression.

Result and Discussion: the (30-40) age group 2 females, and the (40-50) age in which males were 11 and females were 8, (50-60) age group having 23 males and 16 females, (60-70) age group having 36 males and 13 females**.** A total of 94 participants (66 males and 28 females) got pre-probiotics as the main intervention, while 56 participants (28 males and 28 females) received both pre-probiotics and alpha keto analogues. Age group analysis shows the distribution of participants across various age groups, with significant improvements noted mostly in older age groups, which makes the intervention acceptable across diverse age groups.

Conclusion: our study provides compelling evidence stating that the use of pre-probiotics along with alpha keto analogues supports the effectiveness of the intervention strategy in improving renal function, slowing down the progression of chronic kidney disease (CKD), and enhancing the quality of life of CKD patients.

Keywords: pre-probiotics, alpha keto analogue, chronic kidney disease

INTRODUCTION

CKD stands for chronic kidney disease which is a syndrome characterized by progressive and irreversible nephron loss and microvascular damages, metabolic changes, chronic inflammation, oxidative stress, and reduced regenerative capacity of the kidneys[1]. The incidence of CKD and its contribution to cardiovascular disease are a worldwide burden with high concern of mortality which is rapidly increasing day by day[2]. One potential explanation for this high prevalence of change in the intestinal biochemical environment is that promotes inflammatory gut dysbiosis which is vulnerable to kidney diseases[3]. Increased levels of ammonia in CKD patients alter the intestinal pH which degrades the tight epithelial junctions of gut[4]. Moreover, impaired intestinal barrier function along intestinal microbiota dysbiosis in patients with CKD causes increase translocation of gut-derived uremic toxins into systemic circulation which leads to the production of pro-inflammatory cytokines and excessive free radicals which enhance CKD progression and greater risk of cardiovascular events[5]. The critical role of the gut-kidney axis is the main importance of normal homeostasis and the dysregulation of this axis in CKD progression. This new approach helps us to restore the symbiotic intestinal environment using dietary prebiotic[6], probiotic[7] along with supplementation like alpha-keto analogues[8] followed by a low protein diet which ultimately improves metabolic changes, are promising target strategies to either delay or slow down disease progression.

Probiotic refers to living microorganisms when consumed in adequate doses they can improve intestinal microbiota profile by gradually increasing beneficial bacteria along with maintaining gut epithelium barrier functioning and competition with pathogens bacteria for survival such as nutrients and regulating host immune responses. Some strains of probiotics also improve host metabolism, mitigate uremic intoxication, and reduce pro-inflammatory markers which delay the progression of renal dysfunction[9]. Prebiotics are defined as non-living, indigestible fibres that may stimulate the growth or activity of probiotics which are beneficial for microorganisms in the gut[10]. Prebiotics that favor the proliferation of health-promoting bacteria are Bifidobacteria, lactobacillus, and streptococcus thermophilus which

modulate the relevant process of CKD by mitigating the production of short-chain fatty acids (SCFAs), which reduce the inflammation[11]. As probiotic strains feed off prebiotic substrates both synergistically act to promote host gastrointestinal health resulting in a reduction of circulating levels of p-cresyl sulfate (p-CS) and indoxyl sulfate (IS) in CKD. These supplements are capable ofrestoring enteric flora which improves cardiometabolic parameters in patients with CKD, such as inflammation, oxidative stress, and more[12]. Proteins are restricted as a high intake of protein causes the progression of CKD. Still, prolonged protein restriction leads to malnutrition and thus causes poor prognosis to improve amino acids in our body alpha-keto analogue (KA) of essential amino acids in the body which improves nutritional deficiencies caused by protein-restricted diet in CKD patients with KA alleviation decrease in glomerular filtration rate (eGFR) as well as maintaining body mass index[13]. Several studies have synthesized data on theeffect of prebiotics, and probiotic in CKD patients and they concluded that through consumption of pre-probiotics helps the host to reduce inflammation and oxidative stress status[14]. Similarly, few studies stated that pre-probiotics have antioxidant effect[15] and Alpha-ketoanalogues also show significant improvement in CKD patients[16]. However, treatment combinations with pre-probiotic and alpha-keto analogueshave not been extensively reviewed in CKD conditions. To the best of our knowledge, no study was conducted to assess the effects on CKD patients. Therefore, the objective of this study was to evaluate the overall efficacy of pre-probiotic and alpha-ketoanalogues among non-dialysis CKD patients.

METHODOLOGY

Research design:
Study design: Prospective observational study

Study site:
The study was conducted in the Department of Nephrology at Delta Hospital, Rajahmundry East Godavari dist., Andhra Pradesh, India and also approved by institutional ethical committee-VIPS/DPP/IRB/08/2022-23.

Study duration:
The study was carried out from September 2022 to February 2023 (6 months).

Source data:
For all patients included in the study their baseline demographic parameters will be documented &baseline investigations as mentioned in proforma will be recorded. The date of starting Pre probiotics & Alpha- keto analogues will be documented. SF-36 scoring will be done at initial visits and at the end of the study period, to assess the impact of pre-probiotics & Alpha- Ketoanalogues on health-related quality of life. Investigations including renal function test will be repeated at the end of the study to assess the role of Pre Probiotics and Alpha-keto analogues in these Patients.

STUDY CRITERIA

Inclusion Criteria:

1. AGE >18 yrs
2. CKD G1-5(ND)

Exclusion Criteria:

1. AGE <18 yrs
2. Patient of CKD G5 (D)
3. Patients who left against medical advice.
3. Pregnant and lactating patients were also avoided in this study.
4. Patients with incomplete medical records or missing essential data.

Method of Data Collection:

- Consent form
- Data collection form.
- Communication with the patients.

Study Protocol:
The study was carried out after receiving approval from the Ethical Committee on September 2022 to February 2023. The patients receiving pre probiotics and alpha-ketoanalague for the management of CKD with eGFR were included in the study. A total of 75 patients were studied over 6 months. The essential data such as, patient's demographics information, past medical history, and clinical data such as serum creatinine, serum urea, serum uric acid, blood urea nitrogen along with SF-36 scoring for quality of life were collected using data collection form. The data entered on

SPSS statistical analysis and questionnaire was used to note the quality of life and statically tests were performed by T-TEST, PAIRED T-TEST, and CRONBACH'S ALPHA. All the data were assessed based on the duration of CKD patients.

Results:
In this study, a total of 150 participants were involved, including 94 males and 56 females. The study indicates that males were dominant compared to females.

Table 1: Age based gender distribution in CKD patients

S. No	Age	Male	Female	P-Value
1.	≤20	0	0	< 0.005
2.	21-30	1	0	
3.	31-40	0	2	
4.	41-50	11	8	
5.	51-60	23	16	
6.	61-70	36	13	
7.	71-80	19	15	
8.	81-90	4	2	

In our study, the 20-90 age group present in that again subdivided into 7 groups (20-30) in which 1 male was presently followed by the (30-40) age group 2 females, and the (40-50) age in which males were 11 and females were 8, (50-60) age group having 23 males and 16 females, (60-70) age group having 36 males and 13 females, (70-80) age group having 19 males and 15 females, (80-90)age group having 4 males and 2 females as shown in Table 1

Table 2: Laboratory Findings

S. No	Parameters	Initial	Final	P-Value
1.	serum creatinine	2.57	2.43	<0.005
2.	serum urea	56.67	43.09	
3.	serum uric acid	8.44	5.38	
4.	serum BUN	31.7	22.2	
5.	eGFR	33.5	33.2	

In our study, initial and final mean values of renal function parameters were collected and analyzed. which says that there was a mean value decrease in serum creatinine levels from 2.57 to 2.43 with significance ($p < 0.005$), indicating improvement in renal function. Although decreases were found in serum urea (from 56.67 to 43.09), similarly serum uric acid (from 8.44 to 5.38), serum uric acid (from 8.44 to 5.38) with statistical significance ($p < 0.005$), and eGFR shows a slight change in mean (from 33.5 to 33.2) showing that minimal impact on glomerular filtration rate with significance ($p < 0.005$). overall we can conclude that with intervention significantly lowered serum creatinine and other renal parameters as shown in Table 2

Table 3: Sub-grouping of patients based on staging of CKD

S.no	Staging	Initial		Final	
		Male	Female	Male	Female
1.	CKD G2	2	2	58	28
2.	CKD G3a	10	4	36	27
3.	CKD G3b	36	18	0	1
4.	CKD G4	44	21	0	0
5.	CKD G5	2	11	0	0

The study assessed to check the impact of intervention on stages of chronic kidney disease (CKD) both in male and female participants. Initially, the staging of participants was noted from CKD stage G2 to G5, and at the end of the follow-up again CKD staging was accessed, and we found that initially in CKD G2, there we 2 males and 2 females, which increased dramatically to 58 males and 28 females post-intervention and for CKD G3a numbers decreased from 10 males to 4 females starting it was 36 males and 27 females. Similarly in CKD G3b, there were 36 males and 18 females initially, dropping to 0 males and 1 female after the intervention. In the CKD G4 stage, the initial count was 44

males and 21 females, both reduced to 0 by the end of the study and for CKD G5 the starting counts of 2 males and 11 females both decreased to o post-intervention, specifically notable in the reduction of participants seen in (G3b to G5) and increased in those classified under less severe stages (G2 AND G3a) which shown in table 3.

Table 4: Treatment Groups

S. No	Treatment	Gender		Total
		Male	Female	
1.	pre-probiotics	66	28	94
2.	Alpha ketoanalogues and pre-probiotics	28	28	56
3.	total	94	56	150

A total of 150 participants, were divided by treatment group. A total of 94 participants (66 males and 28 females) got pre-probiotics as the main intervention, while 56 participants (28 males and 28 females) received both pre-probiotics and alpha keto analogues. This distribution, allows us to check the effect of treatment on various stages of CKD and renal function parameters as shown in Table 4.

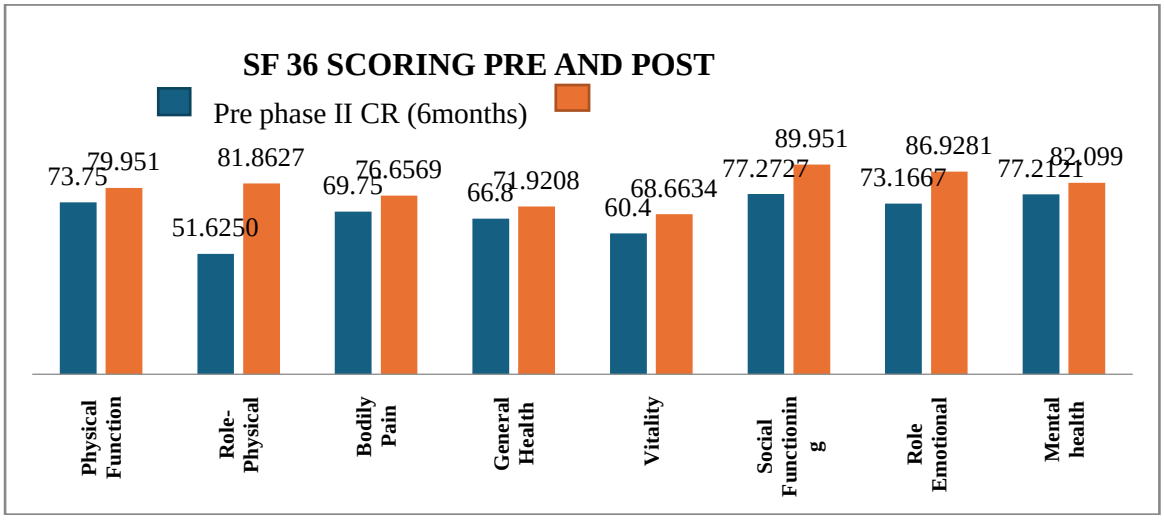

Figure 1: SF 36 pre and post questionnaire scoring

In our study, we used 1 parameter out of 7, which was the quality of life. This parameter mainly focused on physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Initially, data was collected at a specific period, and the final data was taken at the last visit of the subjects, as shown in Table 3. Significant overall improvement was found by analyzing the data in SPSS, as depicted in Figure 1.

Table 5: Cronbach's alpha score

Post Phase II CR (6 months)

SF36 scale (Q. Nos.)	Items	Cronbach's alpha	
		Before	After
Overall	36	0.74	0.80
Physical functioning (3-12)	10	0.84	0.71
Role limitation due to physical health (13-16)	4	0.10	0.36
Role limitation due to emotional problems (17-19)	3	0.13	0.33
Energy/fatigue (23, 27, 29, 31)	4	0.44	0.58
Emotional well-being (24, 25, 26, 28, 30)	5	0.68	0.42
Social functioning (20, 32)	2	0.46	0.30
Pain (21, 22)	2	0.40	0.55
General health (1, 33-36)	5	0.21	0.20
Health change (2)	1	-	-

After analyzing the data and conducting Cronbach's alpha in SPSS, we found significant improvements in various domains of quality of life, except for social functioning and general health.

DISCUSSION

The main purpose of our study was to determine the effectiveness of prebiotics and alpha-keto analogs in treating chronic kidney disease (CKD), a global health issue. Our findings showed that the use of prebiotics along with alpha-keto analogues resulted in a significant reduction in serum creatinine, serum urea, serum uric acid, and serum blood urea nitrogen (BUN), as well as improvements in CKD staging and estimated glomerular filtration rate (eGFR). In this study investigated the efficacy of a comprehensive intervention strategy on renal function, CKD staging, and quality of life of 150 participants. The intervention, which included pro-prebiotic alone or in combination with alpha-keto analogues, demonstrated notable improvements across multiple parameters. Gender analysis provided a predominance of males in our study, indicating a potential gender bias in CKD participants. However, the intervention's effectiveness was observed across both genders, exposing its broad applicability. Age group analysis shows the distribution of participants across various age groups, with significant improvements noted mostly in older age groups, which makes the intervention acceptable across diverse age groups. However further attention may be warranted to address aspects such as social functioning and general health, where improvements were less pronounced.

Gender Analysis

In our study gender distribution aligns with current research indicating a higher prevalence of chronic kidney diseases (CKD) in males compared to females. This observation is compatible with the study which highlighted gender-specific disparities in CKD prevalence and progression rate (Jha et al.,2013)[17]. Further exploration of gender-related factors influencing CKD development and progression is warranted to tailor interventions effectively.

Age Group Analysis

Our findings verified with existing literature demonstrating an age-related increase in CKD prevalence. The disproportionate burden of CKD in older age groups, particularly among males, underscores the need for age-specific management strategies (Bash et al., 2009)[18].understanding age-related risk factors along with implementing targeted intervention is crucial for addressing the growing CKD burden in the aging population.

Renal function parameters

The significant improvements in renal function parameterspost-intervention with pre-probiotic and alpha-keto analogues in CKD with the compliance from recent studies evaluating the efficacy of pre-probiotics (Zirker L et al.,2015)[6], (Fagundes R et al.,2018)[19] and alpha-keto analogues (Laetitia k et al.,2019)[20]in CKD management which suggest a promising therapeutic approach for slowing CKD progression and preserving renal function.

CKD Staging

Our Study's outcomes align with emerging research highlighting the potential use of pre-probiotics (Fagundes R et al.,2018)[7] and alpha-keto analogues modifying CKD progression (Chen H et al.,2021)[8] the substantial reductions in participants in severe CKD stages post-intervention underscore the clinical relevance of our study findings. Our results support the integration of comprehensive treatment strategies targeting various CKD stages to optimize better patient outcomes.

Treatment Group Analysis

The different responses observed between treatment groups underscore the importance of personalized treatment approaches in CKD management (De Mauri A et al., 2022)[21].the synergistic effect observed in participants receiving both pre-probiotic and alpha-keto analogue highlights the potential benefits of combination therapies to slow down CKD progression. Tailoring intervention based on individual patient characteristics and disease severity may enhance treatment efficacy and patient outcomes.

Quality of life (SF36 questionnaire)

Our study aligns with recent research demonstrating the positive results on improving the quality of life in CKD patients (Ranganathan N et al.,2010)[22] the significant improvement across multiple SF36 domains post-intervention shows the holistic benefits in CKD management strategies. Addressing not only physiological parameters but also quality of life aspects is also places essential for optimizing patient well-being and treatment adherence.

CONCLUSION

Our findings regarding renal function parameters showcased a significant decrease in serum creatinine levels, along with improvements in serum urea and uric acid, and renal functions enhanced after post-intervention. Additionally, minimal impact on eGFR was observed, underscoring the intervention's targeted efficacy. CKD staging analysis revealed a striking reduction in participants classified under more severe stages (G3b to G5), coupled with an increase in less severe stages (G2 and G3a) post intervention. The shift towards less severe stages provides us with a potential

halt or reversal of disease progression with the intervention. Quality of life assessment using the SF36 questionnaire demonstrated significant improvement in various areas such as enhanced physical, emotional, and social well-being following the intervention. Finally, our study provides compelling evidence stating that the use of pre-probiotics along with alpha keto analogues supports the effectiveness of the intervention strategy in improving renal function, slowing down the progression of chronic kidney disease (CKD), and enhancing the quality of life of CKD patients. This evidence underscores the importance of comprehensive intervention in managing CKD and improving patient outcomes. Further research is warranted to explore the long-term effects and broader applicability of such intervention in diverse CKD populations.

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