Original Research Article

Effectiveness of probiotics (Procite®) supplementation on uremic toxins in non-dialysis chronic kidney disease patients: A real-world retrospective analysis

ABSTRACT

Background: Gut dysbiosis is linked to chronic kidney disease (CKD) and cardiovascular disease progression. By addressing dysbiosis, probiotics may enrich the gut microbiota, boost immunological response, restore intestinal permeability, and promote anti-inflammatory effects, possibly benefiting CKD patients. Probiotics have the potential to slow progression. A small number of studies have suggested that supplementation of probiotics may decrease CKD progression.

Aim: To determine the effectiveness of Procite® (probiotics) supplementation in lowering uremic toxins in CKD patients.

Study design: A real-world retrospective analysis

Methodology: A real-world retrospective analysis was conducted in a tertiary care hospital and included patients aged 18-75 years, with CKD stages 3-5, not on dialysis. Patients (n=51) who had taken Procite® (which contains 70 billion colony-forming units (cfu) of probiotic strains) for at least 3 months were included in the analysis. Patient records were evaluated from baseline (day 0) and at 1 month and 3 months post-probiotic supplementation. Clinical and laboratory parameters, including serum creatinine and blood urea, were assessed to evaluate efficacy and safety outcomes.

Results: A total of 51 CKD patients (M; F-39;19) with a mean age of 50.43 ± 14.7 years. Mean serum creatinine at baseline, 1 and 3 months after probiotic were 4.23 ± 2.14, 4.15 ± 1.96 and 4.06 ± 2.03, respectively. The reduction in serum creatinine was not statistically significant. At 3 months, 80.39% patients' serum creatinine was stable, 15.68% improved, and 3.92% worsened. The blood urea at baseline, 1 and 3 months were 45.66± 16.8, 41.17 ± 12.6 and 38.74 ± 12.7, respectively. Blood urea was significantly lower after 1 month (-4.49, P=0.003) and 3 months (-6.92, P<0.001). There were no specific adverse events.

Conclusion: Supplementation of Procite® (Probiotics) in CKD leads to lowering blood urea, serum creatinine and stabilising the progression of the condition. Probiotics can be helpful to adjuvant therapy in the management of CKD.

Keywords: chronic kidney disease, probiotic, blood urea, serum creatinine, uremic toxins

1. INTRODUCTION

Chronic kidney disease (CKD) is identified as a substantial contributor to global mortality and morbidity and a major risk for cardiovascular disease by the Global Burden of Disease Collaboration.1 Between 1990 and 2017, the global all-age prevalence of CKD increased by 29.3%, while the global all-age mortality rate from CKD scaled by 41.5% [1]. In India, the prevalence of CKD and the mortality rate from CKD are transitioning at an analogous pace [1]. CKD is distinguished by a progressive decrease in glomerular filtration rate and/or development of proteinuria, followed by progressive retention of organic waste products referred to as uremic toxins (UT) [2]. Uremic toxicity deleteriously impacts several organ systems and metabolic pathways [3].

CKD being a complex condition, it necessitates a multimodal strategy combining non-pharmacological and pharmaceutical therapies with advanced stages necessitating kidney replacement therapy [4]. However, despite the standard care, the outcomes of patients of CKD and End stage renal disease (ESRD) remains poor [4,5].

Novel therapeutics are being investigated in an attempt to enhance outcomes in advanced CKD. In recent years, there has been a surge of interest in the impact of gut microbiota on disease and health, including renal conditions [6]. It has recently been established that CKD is associated with dysbiotic gut microbiota, and intestine dysbiosis plays a significant role in renal physiology and pathology, including uremic toxin accumulation and systemic inflammation [6,7,8]. In addition to providing fuel for good bacteria in the gut, prebiotics may also improve transit time (alleviate constipation), improve diarrhoea, aid in calcium absorption, and improve immune function [9,10]. Thus, the implementation of therapies that alter the gut microbiota, such probiotics, has become a promising tactic to lower uremic toxins and enhance therapeutic outcomes [9,11].

Probiotics containing Lactobacilli strains have the potential to slow progression. A small number of randomized studies have suggested, that supplementation of probiotics may decrease CKD progression by lowering uremic toxins [11,12,13].

Procite® is a novel probiotic with varied probiotic strains (Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus plantarum, Streptococcus thermophilus and Bifidobacterium lactis). There exists a paucity of data on the beneficial outcomes of Procite® (probiotics) supplementation in CKD patients in actual real-world practice in India. Therefore, the present study was to determine the effectiveness of Procite (probiotics) supplementation in lowering uremic toxins in CKD patients in real-world practice.

2. MATERIAL AND METHODS

This retrospective study was conducted in the Nephrology Department of a tertiary care hospital. It reviewed patients of either gender, aged 18-75 years, with CKD stages 3 to 5 who were receiving standard care but were not on dialysis. Only those patients who had taken Procite®—which contains 70 billion colony-forming units (cfu) of probiotic strains (Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus plantarum, Streptococcus thermophilus, and Bifidobacterium lactis)—for at least 3 months were included in the analysis. The Procite® probiotic capsule (containing 70 billion cfu) was administered as one capsule once a day in addition to standard of care. Patient records were evaluated from baseline (day 0) and at 1 month and 3 months following probiotic supplementation. Clinical and laboratory parameters, including serum creatinine and blood urea, were assessed to evaluate efficacy and safety outcomes.

2.1 Efficacy parameters

1) Change in serum creatinine levels post-treatment from baseline- The difference in the serum creatinine levels pre and post probiotic supplementation at1 month and 3 months was analysed and compared.

2) Change in blood urea levels post-treatment from baseline- The difference in the blood urea levels pre and post probiotic supplementation at 1 month and 3 months was analysed and compared.

3) Outcomes- The outcomes were based on the changes in the serum creatinine at 3 months post-probiotic supplementation from baseline. Patients having creatinine level within 25% range were termed as “stable”, those with creatinine level decreased more than 25% from baseline were termed as “improved”, and those with creatinine level increased more than 25% from baseline were termed as “worsened”.

2.2 Safety assessment

The patients were followed up for any probiotic related adverse events. Patient reported specific adverse reactions were also recorded.

2.3 Statistical method for analysis

The study data were analyzed in SPSS software (v.20). Data normality was assessed using the Kolmogorov-Smirnov test. A descriptive analysis of characteristics factors and efficacy variables was carried out. For numerical and ordinal data, mean with standard deviation and median with interquartile range were calculated. The change in the pre and post assessment variables over the time points was assessed using repeated measures ANOVA. Bonferroni post hoc test was used for multiple comparison between the timepoints. A P-value less than 0.05 was considered statistically significant.

3. RESULTS

3.1 Baseline characteristics

The mean age of the patients was 50.43 ± 14.7 years. Out of 51 patients, there were 39 males (76.47%). The male-to-female ratio was 3.25:1. Based on eGFR, the CKD staging of the patients were as follows: 5.8 % were in stage 3A, 9.8% in stage 3B, 43.1% in stage 4 and 41.2 % in stage 5.

3.2 Efficacy outcomes

3.2.1 Change in serum creatinine levels post-treatment from baseline

The mean serum creatinine levels at baseline, 1 month and 3 months after probiotic supplementation were 4.23 ± 2.14, 4.15 ± 1.96 and 4.06 ± 2.03, respectively. (Table 1)

The change (reduction) in serum creatinine after probiotic supplementation at 1 month (-0.11, *P*=0.83) and 3 months (-0.21, *P*=0.27) compared to baseline was not statistically significant. (Figure 1)

Table 1. Comparison of pre and post probiotic supplementation change in serum creatinine levels

Parameter	Number	Mean (± SD)	Median (Interquartile range)	Mean difference from baseline (± SD)	P value
Serum Creatinine Baseline	51	4.26 (± 2.14)	3.41 (2.68-5.43)	0 (± 0)	0.127
Serum Creatinine 1-Month	51	4.159 (± 1.96)	3.56 (2.54-5.91)	-0.11 (± 0.71)	
Serum Creatinine 3-Month	51	4.061 (± 2.02)	3.56 (2.26-5.74)	-0.21 (± 0.86)	

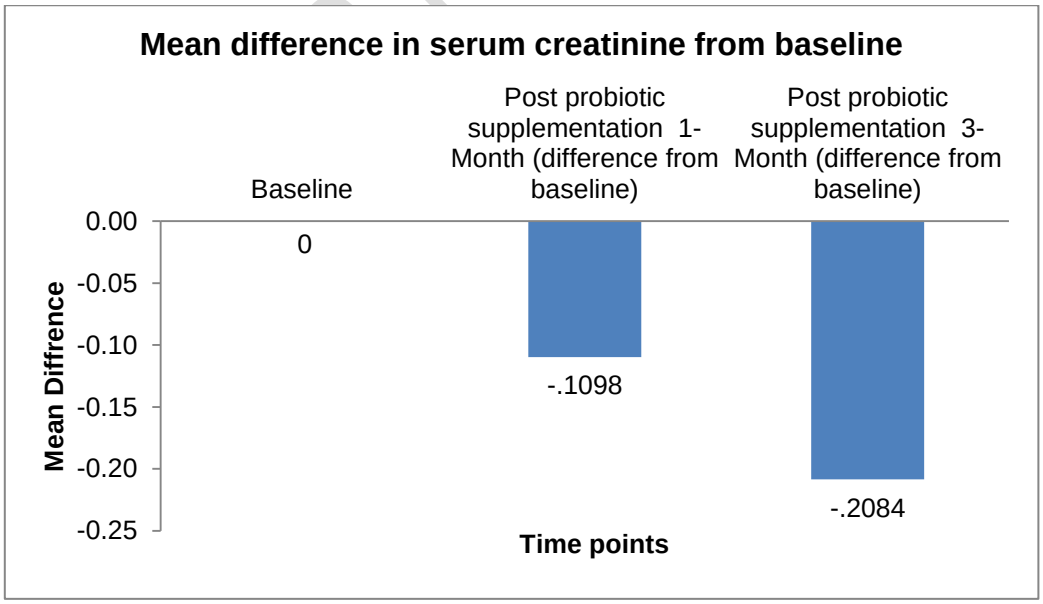

Figure 1. Change in serum creatinine levels post-treatment (Post probiotic supplementation) from baseline

3.2.2 Change in blood urea levels post-treatment from baseline

The blood urea levels at baseline, 1 month and 3 months post-supplementation were 45.66± 16.8, 41.17 ± 12.6 and 38.74 ± 12.7, respectively. (Table 2)

The change (reduction) in the mean difference of blood urea from baseline over the time points (post probiotic supplementation 1 month and 3 months) was significant (F=14.6, *P*<0.001).

On post hoc analysis by Bonferroni test, the blood urea levels were significantly reduced after 1 month (mean difference =-4.49, *P*=0.003) and 3 months (mean difference =-6.92, *P*<0.001) post- probiotic supplementation compared to baseline. (Figure 2)

Table 2. Comparison of pre and post probiotic supplementation change in blood urea

Parameter	Number	Mean (± SD)	Median (Interquartile range)	Mean difference from baseline (± SD)	P value
Blood Urea Baseline	51	45.66 (± 16.89)	46.0 (34.20-52.00)	0 (± 0)	<0.001
Blood Urea 1-Month	51	41.17 (± 12.64)	40.1 (32.2-49.2)	-4.490 (± 9.132)	
Blood Urea 3-Month	51	38.74 (± 12.17)	38.0 (27.4-48.2)	-6.920 (± 11.28)	

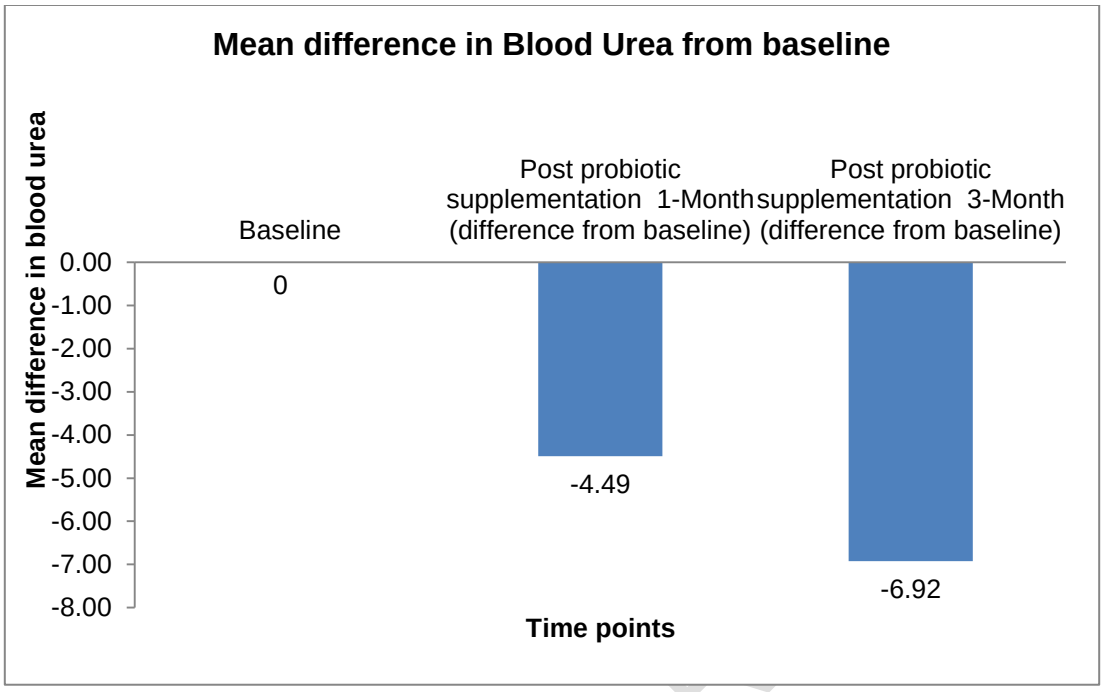

Figure 2. Change in blood urea levels post-treatment (Post probiotic supplementation) from baseline

3.2.3 Outcomes based on serum creatinine changes at 3 months post-treatment

At 3 months post probiotic supplementation, the majority (n=41, 80.39%) of CKD patients' serum creatinine was stable, 15.68% (n=8) improved (creatinine level decreased >25% from baseline), and 3.92% (n=2) worsened (creatinine level increased >25% from baseline. (Table 3)

Table 3. Outcomes based on serum creatinine changes post 3-months probiotic supplementation

Parameter		Number	Percentage
Outcomes- based on serum creatinine changes post 3-months probiotic supplementation	Stable (Creatinine level did not change within ± 25 %	41	80.39%
	Improved (Creatinine level decreased >25% from baseline)	08	15.68%
	Worsened (Creatinine level increased >25%)	02	3.92%

3.2.4 Safety assessment

No specific adverse events were reported or linked to probiotic supplementation

4. DISCUSSION

The results of the present study demonstrated that supplementation of probiotics (Procite®) in CKD lowers uremic toxins and stabilises the condition.

Uremic toxins, which are important in the pathogenesis of CKD and CVD.3 Despite standard treatment, clinical outcomes are unsatisfactory [4,5], necessitating the exploration of innovative adjuvant therapies such as probiotics due to the relationship of CKD with dysbiotic gut microbiotia. In this study, an attempt was made to retrospectively explore the effectiveness of Procite® (probiotics) supplementation in lowering uremic toxins in CKD patients in real-world practice.

In the present study, Procite® supplementation caused a minor reduction in creatinine level at 1 month (-0.11 and 3 months (-0.21) compared to baseline, but the reduction was not statistically significant (P>0.05). At 3-months post Procite® supplementation, the majority (80.39%) of CKD patients' serum creatinine was stable and in 15.68% it was improved, indicating CKD stabilisation and a potential delay in its progression Similar findings have been reported in research done by Saxena et al.,[12] with probiotics (Enzobiotics), which did not change creatinine levels after 90 days of treatment [12].

In the present study, we also found that Procite® supplementation resulted in a significant decrease in urea levels at (-4.49, P=0.003) and 3 months (-6.92, P0.001) compared to baseline, indicating a possibility for improvement and a delay in its progression. The finding of a reduction in urea levels is consistent with previous research using probiotic supplements [14]. A prospective randomized case control study evaluated the role of probiotics in CKD. There was significant improvement in renal parameters such as creatinine, urea and uric acid in both interventional (case) and non-interventional (control) groups with more improvement in the probiotic group than in control group [15].

Thongprayoon et al.,[11] conducted a comprehensive review and meta-analysis of 5 RCTs involving 161 CKD patients, and their findings showed that short-term probiotic treatment had no discernible effects on serum creatinine or eGFR. However, probiotic use potentially reduces uremic toxins in CKD patients [11].

The relationship between gut dysbiosis and chronic kidney disease (CKD) is reciprocal and encompasses not only the condition itself but also its aftermath and complications.[8] As CKD advances, renal function diminishes, causing uremic toxins to be retained. These urea-containing molecules build up in the gut and bloodstream, encouraging the colonisation of microbes that can use urea as an energy source. This altered gut microenvironment causes dysbiosis and, eventually, leaky gut syndrome [16]. By addressing dysbiosis, probiotics may enrich the gut microbiota, boost immunological response, restore intestinal permeability, and promote anti-inflammatory effects, possibly benefiting CKD patients [17].

Thus, the present study's findings support the hypothesis that probiotic microbiome restoration may provide beneficial effects in CKD patients by reducing uremic toxin

production in the gut, as evidenced by the potential reduction in uremic toxins in CKD patients treated with Procite probiotics supplementation.

Features of Procite® and evidence for probiotic strains - Each capsule of Procite® contains 70 billion (bn) colony forming units (cfu) of freeze-dried probiotic strains (six strains - Lactobacillus acidophilus 10 bn cfu, Lactobacillus rhamnosus 10 bn cfu, Lactobacillus casei 10 bn cfu, Lactobacillus plantarum 10 bn cfu, Streptococcus thermophilus 20 bn cfu and Bifidobacterium lactis 10 bn cfu). All six strains are whole genome sequenced equivalents of clinically validated and characterized strains with a history of extensive use. Lactobacillus acidophilus and Lactobacillus rhamnosus have been shown to significantly reduce the levels of uremic toxins in dialysis patients [18,19]. Streptococcus thermophiles combinations have also demonstrated significant efficacy in CKD as evidenced by reductions in the accumulation of circulating uremic toxins [20]. Lactobacillus casei had slowed the decline of renal function in individuals with stage 3–5 CKD in placebo-controlled study [21]. Lactobacillus plantarum has shown to increase iron absorption [22]. Overall, all six strains have distinct advantages and help to restore gut microbial balance in CKD patients. The composition (number of strains), quantity of probiotics (bn cfu) and frequency of administration are debatable. In a study of stage 3 and 4 CKD patients was to confirm the safety and tolerability of several doses of Renadyl™ (90, 180, 270 billion colony-forming units, showed stabilizing Creatinine. The escalation efficacy was demonstrated in statistically significant changes of serum creatinine (months 2 to 6: -0.23 mg/dL, $p<0.05$) [23].

The present study of Procite® with six strains, 70 billion cfu and once-daily dosing demonstrated safety while also confirming effectiveness in terms of blood urea reduction in a real-world adjuvant scenario. One single arm research with 45 billion cfu and twice-daily probiotic treatment showed a reduction in blood urea of -2.97 mg/dl on day 90 (blood urea - baseline 52.11 mg/dl to 49.14 on day 90) [24]. While acknowledging limitations of cross study comparison, the magnitude of blood urea reduction appears to be greater with once daily Procite® of -6.92 mg/dl in the present study, while -2.97 in the referred study [24].

Furthermore, the current study's results show that once-a-day administration has the potential for greater ease and compliance. Procite® can also be used twice a day in selected patients as needed (as a health supplement, the recommended dosage of Procite® is one or two capsules per day with or post meal).

Limitations of the study

First and foremost, this was pilot research with a small sample size (limiting statistical power for detection of changes in the primary outcome) and a single hospital setting (limited generalizability of the study findings). A larger population research from multicentric sites might yield more conclusive results. Second, the study only looked at specific uremic markers (creatinine and urea levels) for short-term outcomes. Significant declines in C-reactive protein, indoxyl sulfate, and p-cresyl sulfate levels have often been noted when probiotics have been administered to patients with CKD [25,26]. We haven`t looked at these parameters in our pilot study. Use of antibiotics during the study also reduces the efficacy of the Probiotics and also causes mild deterioration in kidney function were not accounted. Furthermore, randomized control studies with a robust design are required to confirm these beneficial outcomes with Procite® supplementation.

5. CONCLUSION

Supplementation of Procite® (Probiotics) in CKD leads to lowering blood urea, serum creatinine and stabilising the CKD. Probiotics can be helpful to adjuvant therapy in the management of CKD. Furthermore, randomised control trials with long duration of follow up are required to validate these beneficial results.

ETHICAL APPROVAL (NOT APPLICABLE)

This was a secondary data analysis and hence IEC approval was not required.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as large language models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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