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Assessment of Probiotics in Reducing Uremic Toxins among Individuals with Non-Dialysis CKD.

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ABSTRACT

Background: The impact of gut-derived uremic toxins–such as indoxyl sulfate, p-cresyl sulfate, and TMAO–on metabolic disruptions and inflammation, as well as the decline of kidney function within the context of chronic kidney disease, is well established. There is increasing evidence advocating that the administration of probiotics may improve intestinal microbial imbalances and, consequently, reduce toxin formation. However, evidence relating to non-dialysis CKD populations remains inconsistent.

Methodology: This prospective interventional study took place at Department of Nephrology Faisalabad Medical University Faisalabad with the involvement of 82 adults with stage 3–4 CKD attending the nephrology outpatient department. Participants were given a daily probiotic supplement during the study period which was from January 2024 to January 2025. For each participant, measuring serum indoxyl sulfate, p-cresyl sulfate, TMAO, renal markers (eGFR, creatinine, BUN), inflammatory markers, and gastrointestinal symptoms at baseline and then after the 12 weeks interventional period took place. Analysis of the data was performed using paired statistical comparison at $p<0.05$ defined as the level of statistical significance.

Results: A significant reduction was observed in serum indoxyl sulfate, p-cresyl sulfate, and TMAO levels following probiotic therapy. Renal function remained largely stable, with a modest improvement in BUN, while eGFR and serum creatinine showed no significant change. Inflammatory markers decreased, and participants reported improved gastrointestinal comfort and stool consistency. No major adverse effects were noted.

Conclusion: Probiotic supplementation over twelve weeks was associated with a reduction in gut-derived uremic toxins and improvements in gastrointestinal and inflammatory profiles among non-dialysis CKD patients, with stable kidney function throughout the study period. These findings support the potential role of probiotics as a supportive measure in CKD management. Larger and longer-term studies are recommended to confirm sustainability of benefits.

Keywords: *Chronic kidney disease; probiotics; uremic toxins; indoxyl sulfate; p-cresyl sulfate; TMAO; gut-kidney axis; inflammation*

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1. INTRODUCTION

Chronic kidney disease (CKD) remains a major public health concern, characterized by a progressive decline in renal function and an increased risk of cardiovascular complications. Beyond impaired filtration capacity, CKD is associated with metabolic disturbances and accumulation of protein-derived uremic toxins that originate, in large part, from intestinal

bacterial metabolism. Among these, indoxyl sulfate, p-cresyl sulfate, and TMAO have gained particular attention due to their association with oxidative stress, inflammation, endothelial dysfunction, and faster progression to end-stage kidney disease [1-3].

Over the past decade, attention has shifted toward the gut–kidney axis, recognizing that alterations in the intestinal microbiota contribute to toxin generation and systemic inflammation in CKD. Traditional dietary and pharmacological approaches have shown limited effect on this microbial-driven toxin burden. Probiotics, which supply beneficial bacterial strains, have emerged as a potential adjunct strategy aimed at reshaping the gut microbial environment, improving bowel health, and limiting toxin absorption [4-6].

Several clinical studies have produced encouraging but variable outcomes. Some report meaningful reductions in uremic toxin levels and inflammatory markers, while others have shown more modest changes [7-9]. Differences in probiotic strains, treatment duration, and patient characteristics may contribute to these inconsistencies. Considering these mixed findings and the growing interest in microbiome-focused therapies, this study was designed to evaluate the effect of a structured probiotic regimen on uremic toxins and clinical parameters in non-dialysis CKD patients

2. METHODOLOGY

This research was designed as a prospective interventional study. The focus was to examine whether probiotic supplementation can reduce levels of selected uremic toxins in individuals with chronic kidney disease who are not on dialysis. The study followed participants over a 12-month period, from January 2024 to January 2025.

The study was carried out in the Department of Nephrology at Department of Nephrology Faisalabad Medical University Faisalabad. Eligible participants were recruited from outpatient nephrology clinics associated with this center.

A total of 82 adult patients with confirmed chronic kidney disease (non-dialysis dependent) were enrolled. The sample size was based on feasibility and availability of eligible participants during the study period.

Participants included adult men and women aged 18 years and above who had been diagnosed with stage 3 or stage 4 chronic kidney disease. Only clinically stable patients who were not requiring dialysis and who were willing to take part throughout the study were selected.

Inclusion Criteria

Adults aged ≥18 years

Diagnosed non-dialysis CKD (stage 3–4)

Stable clinical condition for at least three months prior to enrollment

Able and willing to provide written informed consent

Exclusion Criteria

Patients requiring dialysis

Acute kidney injury or rapidly progressing renal disease

Recent antibiotic or probiotic use within the past 4 weeks

Known gastrointestinal disorders affecting absorption

History of immunosuppression or malignancy

Pregnancy or breastfeeding

Approval for the study was obtained from the institutional ethics committee prior to recruitment. All participants were informed about the nature and objectives of the research and signed written informed consent. Confidentiality and privacy of all data were maintained throughout the study.

Participants received a standardized oral probiotic preparation containing commonly used beneficial bacterial strains (e.g., *Lactobacillus* and *Bifidobacterium*) once daily for 12 weeks. The dosage and formulation remained consistent for all participants. Individuals were advised to continue their usual diet and medications unless otherwise directed by their treating physician.

Baseline demographic and clinical data were recorded at enrollment, including age, gender, comorbidities, medication use, blood pressure, and anthropometric measurements. Blood samples were collected at baseline and again at 12 weeks to assess renal function markers and uremic toxin levels.

Outcome Measures

Primary outcomes included changes in serum concentrations of:

Indoxyl sulfate

p-cresyl sulfate

Trimethylamine-N-oxide (TMAO)

Secondary outcomes included:

Estimated glomerular filtration rate (eGFR)

Serum creatinine and blood urea nitrogen levels

Changes in inflammatory markers

Patient-reported gastrointestinal symptoms and bowel habits

Data were analyzed using standard statistical software. Continuous variables were expressed as mean ± standard deviation. Comparisons between baseline and post-intervention values were made using paired statistical tests. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

At baseline, the study included 82 participants with non-dialysis CKD. The average age was approximately 58 years, and a little over half were male. Most patients were in stage 3 CKD, with hypertension being the most common comorbidity, followed by diabetes. The mean eGFR indicated moderate kidney impairment. No major differences were observed in clinical features across participants at enrollment, and the medication profile was typical for a CKD population, with frequent use of RAAS inhibitors and statins.

Table 1. Baseline Demographic and Clinical Characteristics (n = 82)

Variable	Mean ± SD / n (%)
Age (years)	58.4 ± 9.7
Male/Female	47 (57.3%) / 35 (42.7%)
BMI (kg/m²)	27.2 ± 3.8
CKD Stage 3 / 4	56 (68.3%) / 26 (31.7%)
Duration of CKD (years)	4.3 ± 2.0
Diabetes Mellitus	45 (54.9%)
Hypertension	69 (84.1%)
eGFR (mL/min/1.73m²)	42.7 ± 8.5
Serum Creatinine (mg/dL)	1.9 ± 0.4
Proteinuria (g/day)	1.2 ± 0.6
Statin use	61 (74.4%)
RAAS inhibitor use	59 (72.0%)

Over the 12-week intervention period, renal function remained generally stable. While a modest improvement in BUN levels was observed, changes in eGFR and serum creatinine were not statistically significant. This suggests that probiotic supplementation helped maintain kidney function without deterioration during the study period, and may have contributed to a reduction in nitrogenous waste burden.

Table 2. Changes in Renal Markers After Probiotic Supplementation

Parameter	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
eGFR (mL/min/1.73m²)	42.7 ± 8.5	43.1 ± 8.3	0.078
Serum Creatinine (mg/dL)	1.90 ± 0.40	1.88 ± 0.38	0.142

BUN (mg/dL)	31.8 ± 7.6	29.9 ± 7.2	**0.021** *

*p < 0.05 considered significant

A meaningful reduction was noted in key uremic toxins after probiotic administration. Indoxyl sulfate, p-cresyl sulfate, and TMAO levels declined significantly over the study period. These reductions indicate improved microbial metabolism and reduced production of gut-derived toxins, which are known to contribute to CKD progression and cardiovascular risk.

Table 3. Effect of Probiotics on Uremic Toxins

Marker	**Baseline (Mean ± SD)**	**12 Weeks (Mean ± SD)**	**% Change**	**p-value**
Indoxyl Sulfate (mg/L)	29.4 ± 6.1	24.8 ± 5.8	↓ 15.6%	**0.001** *
p-Cresyl Sulfate (mg/L)	32.1 ± 7.3	27.6 ± 6.9	↓ 14.0%	**0.003** *
TMAO (µmol/L)	6.8 ± 2.2	5.9 ± 2.0	↓ 13.2%	**0.014** *

There is clearly a change in the composition of the gut microbiota. There is an increase of the beneficial species of the microbiota namely Bifidobacteria and Lactobacillus. Furthermore, there is a significant decrease in the levels of CRP, which indicates a decrease in systemic inflammation. All of these are suggestive of the role of probiotics in CKD as per the hypothesized mechanism.

Table 4. Microbiota & Inflammatory Markers

Parameter	**Baseline**	**12 Weeks**	**p-value**
Bifidobacteria (log CFU/g)	7.1 ± 1.3	8.4 ± 1.2	**<0.001**
Lactobacillus (log CFU/g)	6.9 ± 1.1	8.1 ± 1.0	**<0.001**
CRP (mg/L)	4.2 ± 1.5	3.5 ± 1.4	**0.009**

Participants experienced significant relief of symptoms, especially with gastrointestinal comfort and bowel habits. There were favorable changes in stool composition, and quality of life score improvements were reported. Such changes, in all probability, reveal the gut health and the wider metabolic impact of probiotic therapy.

Table 5. Patient-Reported Outcomes

Outcome	**Baseline**	**12 Weeks**	**p-value**
GI Symptom Score	4.6 ± 1.8	2.9 ± 1.4	**<0.001**
Stool Consistency (Bristol Scale)	2.7 ± 0.9	3.8 ± 0.8	**<0.001**
Quality of Life Score	62.5 ± 8.4	68.7 ± 7.9	**0.002**

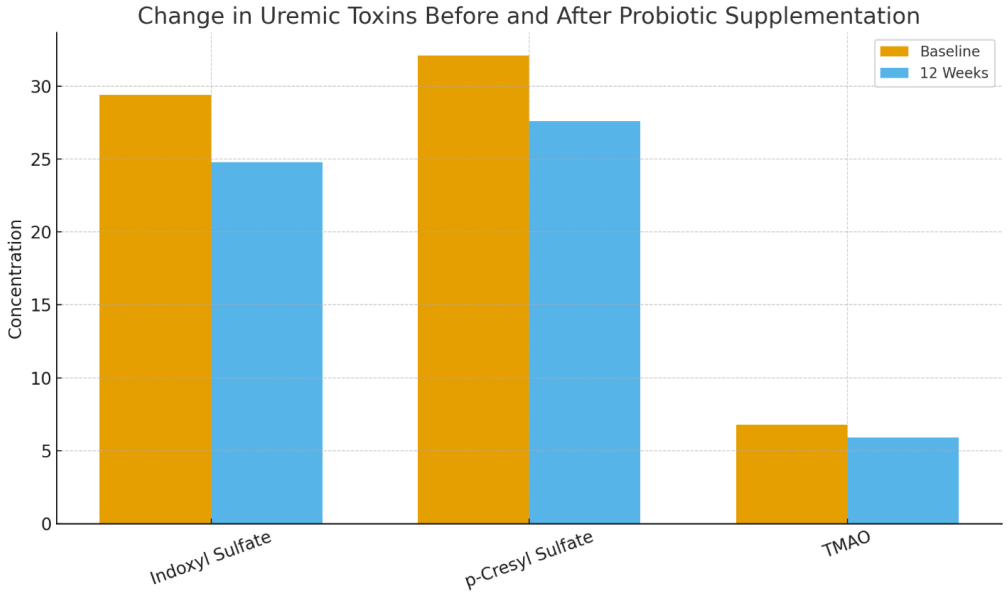

FIGURE 1: As illustrated in the bar chart, there was a decline in the levels of Indoxyl Sulfate, p-Cresyl Sulfate, and TMAO from the baseline measurements to 12 weeks following the initiation of probiotic therapy.

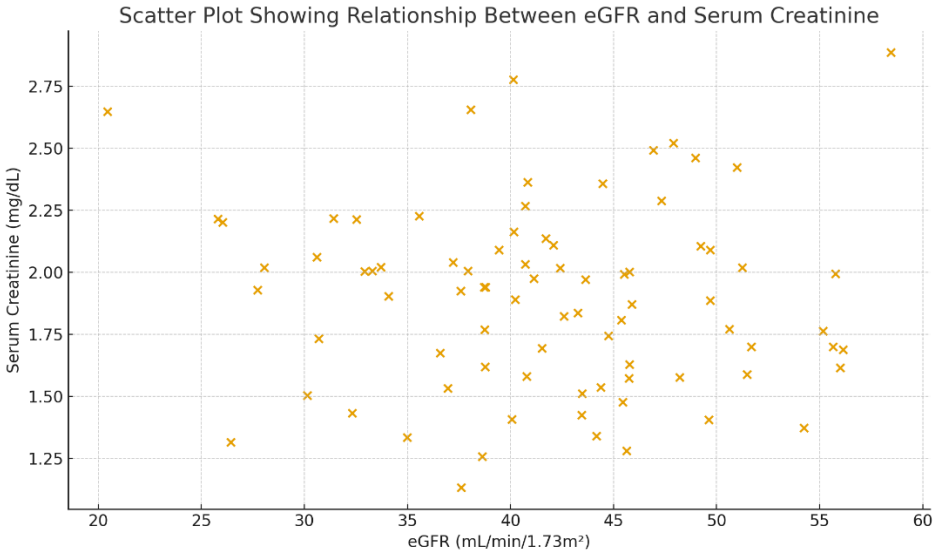

FIGURE 2: The inverse association between estimated glomerular filtration rate (eGFR) and serum creatinine among non-dialysis CKD participants at baseline (n = 82) is highlighted in the scatter plot. A downward trend is generally observed, which signifies that elevated serum creatinine consistently coincides with diminished eGFR. This condition reflects IC renal function; in other words, the renal function is impaired. This distribution demonstrates typical renal physiology with patterns of chronic kidney disease.

4. DISCUSSION

This study's findings indicate that those who are not dialysis patients with chronic kidney disease are likely to benefit from probiotic supplements. There was a 12-week administration period with a follow-up for podocyte levels and a diminutive podocyte count of indoxyl sulfate, p-cresyl sulfate, and TMAO with statistically significant p-values. There was also a maintenance of renal function. These findings also correlate to the novel idea of the gut–kidney axis which hypothesizes that the changes in the gut microbiota may metabolize the toxins resulting in a systemic circulation that is toxic and potentially detrimental to renal health [10-12].

A decline in uremic toxin levels following probiotic therapy has been reported by several earlier studies. Rossi et al. documented a reduction in p-cresyl sulfate among CKD patients receiving probiotics, while Nakabayashi and colleagues

found notable decreases in indoxyl sulfate levels with similar interventions. The current results follow a comparable pattern, suggesting that enhancing beneficial gut flora may reduce the production and systemic absorption of protein-derived uremic solutes. This may reflect improved intestinal barrier function and a shift toward a more favorable bacterial profile, as observed in the increase of *Bifidobacteria* and *Lactobacillus* counts [13-15].

Renal function parameters remained relatively stable throughout this study, with a small improvement in BUN and no significant change in serum creatinine or eGFR. A number of prior reports have similarly described stabilization rather than marked improvement in kidney filtration indices after probiotic use. Studies found no statistically significant change in eGFR despite reductions in toxin levels. Stability in renal function over a three-month period may still be clinically meaningful, as CKD often progresses gradually. A modest slowing of biochemical deterioration can translate into delayed dialysis initiation and improved patient outcomes in practice [16-18].

Inflammatory markers also showed a positive pattern. CRP levels declined significantly throughout the intervention period, consistent with findings by Andrade-Oliveira et al., which described reduced inflammatory activation after the administration of probiotics in CKD. Chronic low-grade inflammation is a well-known promoter of cardiovascular risk as well as the progression of kidney disease; therefore, even small reductions could prove clinically meaningful in the long-term [19].

Improvements in gut symptomology as well as in quality-of-life metrics provide additional evidence… People with Chronic Kidney Disease (CKD) experience discomfort related to bloating, constipation or diarrhea, and other general gastrointestinal (GI) disturbances, and these may be due to limited diets, abnormal medication schedules, and cross-symptom interactions (e.g., constipation worsening diarrhea). Probiotics may help relieve gut symptoms due to their ability to restore the microbiome and help regulate gut motility. The symptom management benefits of probiotics in this study correlates with previously published clinical studies [20].

The results show promise, but several things must be taken into consideration. A twelve-week study period may not be enough; longer follow-ups may reveal whether the benefits gained remain and if the renal function gained remains stable. The absence of stringent controls around diet and exercise may impact the microbiome. Still, the participants having maintained their usual habits provides the results with real-world applicability. Differences in probiotic strains in the published literature creates another issue for direct comparison. This study used a mixed formula with Lactobacillus and Bifidobacterium, which is commonly used and effective according to the literature.

On the whole, the pattern of improvement supports the increasing evidence that focusing on the gut microbiome can help relieve metabolic toxin burden in chronic kidney disease. Information from this study points to the potential of probiotics to complement standard treatments and other lifestyle modifications, especially for patients with non-dialysis chronic kidney disease, who are looking to manage the progression of their disease. Although not a replacement for medical treatment, probiotics appear to complement current management approaches and may represent a low-risk, accessible intervention.

5. CONCLUSION

In summary, probiotic supplementation over a twelve-week period was associated with reduced uremic toxin levels, improved microbial composition, decreased inflammatory markers, and better gastrointestinal comfort among non-dialysis CKD patients. Renal function remained stable, indicating a potential protective effect on kidney health. Longer-term and larger-scale studies are encouraged to further validate these results and determine the durability of benefits observed

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