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Nephro Update

Beneficial effect of probiotic supplementation in patients with chronic kidney disease

- Probiotics are an emerging solution for improving the altered gut flora of CKD patients.
- Oral ingestion of probiotics is well tolerated and safe and significantly reduces blood urea nitrogen, creatinine, and uric acid levels.
- Probiotics reduce the levels of uremic toxins in the blood along with a proven benefit to the patient by restoring the altered microbial balance of the gut.
- Probiotics reduce inflammatory markers resulting from altered gut flora, in experimental studies.

ISSUE 1

Expert Opinion

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- In CKD patients, due to impaired kidney function, there is an accumulation of toxins in the bloodstream.
- The concentration of uremic toxins increase as the disease progresses to end stage kidney disease (ESKD).
- Recent studies have demonstrated the importance of gut microbiota in the progression of CKD.
- Blood urea nitrogen, uric acid, creatinine, and other toxins can be used as nutrients by some probiotic microorganisms for growth, which helps eliminate them.
- Probiotics are a novel approach in the management of patients with CKD and can be used in delaying the progression of the disease.
- Probiotics not only reduce the levels of uremic toxins in the blood, but they also provide benefit to the patient by restoring the altered microbial balance of the gut.

Introduction

According to the World Health Organization (WHO), kidney disease and disease of the urinary tract account for 850,000 annual deaths worldwide. Chronic kidney disease (CKD) is the 12th leading cause of mortality and the 17th leading cause of disability worldwide. The global prevalence of CKD is high, estimated as 11-13%, with the majority of the cases at CKD stage 3.[1] It is estimated that the prevalence of CKD in India is between 13% to 17%.[2]

Role of gut microbiota in the progression of CKD

CKD usually progresses gradually, and symptoms may not appear until the kidneys are severely damaged. In late stages of CKD, kidney failure results with symptoms of uremic toxin and fluid accumulation in the body.[1]

The bowel provides a unique opportunity to remove or modify uremic toxins in a therapeutic regimen. Uremic toxins comprise of over 100 different metabolites, most of which diffuse into the bowel due to the kidney's inability to filter these toxic metabolites.[3]

Several factors, e.g., underlying etiology of kidney disease, degree of proteinuria, diet, blood pressure control, medications, etc. may influence the progression of CKD.

Recent studies have demonstrated the importance of gut microbiota in the progression of CKD and development of uremic symptoms. Dysbiosis of the intestinal microbiota increases uremic toxins like indole-3 acetic acid, p-cresyl sulfate (PCS) and indoxyl sulfate, which damage the epithelial tight junctions and increase intestinal wall permeability via endotoxemia and systemic inflammation. As a result, intestinal endotoxins may pass through the intestinal wall into the bloodstream, causing microinflammation in the kidney and renal endothelial dysfunction, fibrosis, and tubular damages, accelerating the decline of renal function.[4]

Effect of probiotics in CKD patients

Restoring the balance of intestinal flora benefits CKD patients and improves any gastrointestinal symptoms like constipation or diarrhea. Probiotics also promotes healthy digestion and improved immunity.[1]

Probiotics are an emerging solution for improving the altered gut flora of CKD patients.[1]

Probiotics supplementation has emerged as an adjuvant therapy for CKD in recent years, with increasing patient acceptance. Many studies have been conducted to determine whether probiotics can slow down the progression of CKD by altering the intestinal flora and reducing urea toxins.[4]

A normal healthy bowel contains 1-2 kg of microbes, which amounts to several hundred trillion colony forming units (CFU). As a result, the consumption of 90 billion CFU every day is clinically safe.[5]

Lactobacillus and Bifidobacterium species help to maintain the proper balance of microorganisms in the intestine. They produce organic acids, which may lower pH in microenvironments of the gastrointestinal tract, and thus inhibit acid sensitive bacteria, including enteric pathogenic species.[3]

The *L. acidophilus* strain has been used for the eradication of small bowel bacterial overgrowth in dialysis patients. Similarly, several *Bifidobacterium* strains are widely prescribed in Japan for patients with kidney failure (primarily for the removal of phenol, indole, and related aromatic metabolic uremic toxins). *Streptococcus thermophilus* is a urease producing microbe that is mainly present in fermented foods.[3] Probiotic supplementation containing five spore-forming species of *Bacillus*, including *B. coagulans*, has resulted in a significant reduction in intestinal permeability as evidenced by significant reductions in endotoxins, triglycerides, and proinflammatory cytokines.[6]

Ranganathan N *et al.,* in 2009, conducted a pilot clinical trial to evaluate biochemical and clinical effects of an oral probiotic dietary supplements in CKD patients. The pilot study addressed the potential use of probiotic supplements to help maintain a healthy kidney function. Each enteric-coated capsule contained a mixture of *L. acidophilus, B. longum, and S. thermophilus*, for a total of 1.5 X 10^{10} CFU. Two capsules were administered three times a day with meals (9 X 10^{10} CFU/day). The study reported that the mean change in blood urea nitrogen (BUN) concentration was significantly different in the probiotic treatment period (-2.93 mmol/L) as compared to the placebo period (4.52 mmol/L). Furthermore, the mean change in uric acid concentration was moderate during the probiotic treatment period (24.70 µmol/L) as compared to the placebo period (50.62 µmol/L, $p = 0.050$). The study concluded that oral administration of probiotic regimen in patients with CKD was well tolerated, with decrease in BUN and uric acid, potentially contributing to an improved quality of life.[5]

Another study by Ranganathan N *et al.*, in 2010, showed that oral ingestion of probiotics (9 X 10^{10} CFUs/day) was well tolerated and safe during the 6-month treatment period, at all the sites where the study was conducted. BUN, creatinine, and uric acid levels decreased in 63%, 43%, and 33% of patients with CKD stages 3 and 4, respectively (Table 1). Majority of the subjects reported a significant overall improvement in quality of life (86%, $p < 0.05$).[3]

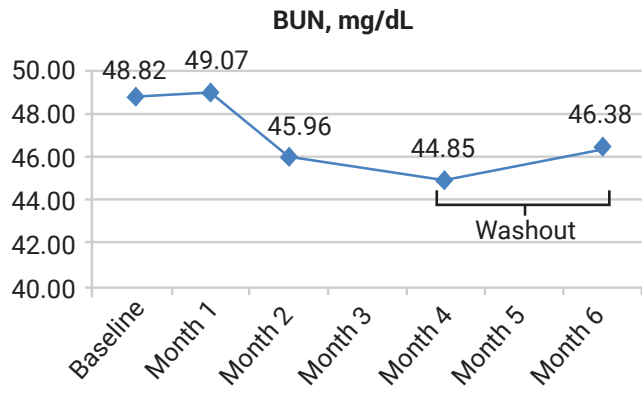
Table 1: Percentage of patients showing improvement with probiotics

Site	No. of patients	No. of patients with decreased levels (%)			No. patients with improved quality of life ratings (%)
		Creatinine	Uric acid	BUN	
Argentina	8	4(50)	4(50)	4(50)	7(88)
Canada	13	7(54)	4(31)	13(77)	11(85)
Nigeria	15	5(33)	5(33)	7(47)	13(87)
USA	10	4(40)	2(20)	5(50)	8(80)
Total	46	20(43)	15(33)	29(63)	39(85)

Pavan M demonstrated that combination of prebiotic and probiotic supplementation containing *Streptococcus thermophilus, Lactobacillus acidophilus, Bifidobacterium longum* and fructo- oligosaccharides, along with low protein diet significantly decreased glomerular filtration rate (GFR) decline, i.e. potentially delaying progression of CKD and thus the need for dialysis. A recent meta-analysis included 11 interventions that administered probiotics using different species and strains. In nine of these studies, uremic toxins (p-cresyl sulfate and indoxyl sulfate) decreased after intervention.[7] In a systematic review and meta-analysis, Jia L *et al.,* demonstrated that probiotics supplementation may reduce the levels of p-cresyl sulfate and increase the levels of IL-6, thereby protecting the intestinal epithelial barrier of patients with CKD.[4]

Administration of probiotic formulation containing *S. thermophilus, L. acidophilus and B. longum strains* for 4 months in CKD Stage 3 and 4 patients, reaching the highest dose of 270 billion CFUs per day, appears to be safe and well-tolerated. Statistically significant improvements were reported in creatinine, C-reactive protein, and hemoglobin levels, and physical functioning. Furthermore, the levels of urea showed a decline with probiotic administration. The levels declined until month 4, suggesting that probiotic formulation can reduce the toxic levels of renal dysfunction. Upon discontinuation of probiotic, the urea concentrations increased again, indicating that it was indeed the bacterial strains in the formulation that were able to metabolize uremic toxins (Figure 1).[8]

Figure 1: Change in blood urea nitrogen



In conclusion, probiotics are a novel approach in the management of patients with CKD. Probiotics not only reduce the levels of uremic toxins in the blood, but they also provide benefit to the patient by restoring the altered microbial balance of the gut. Use of probiotics in patients with CKD have been clinically tested and shown to be safe, effective and may help in delaying progression of CKD in at least some patients.[1]

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