Specific Probiotics for Chronic Kidney Disease: A Review

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Abstract

Chronic kidney disease (CKD) is a global health issue with a high economic cost to health systems and one of the risk factor for cardiovascular disease (CVD). All stages of CKD are associated with decreased quality of life. CKD is usually asymptomatic until later stages. Probiotics are living micro-organism very well known for a role they in the prevention and reduction of risk factors for several diseases and are also capable of enhancing certain vital physiological functions. A normal human digestive tract contains about 400 types (strains) of probiotic bacteria that control and reduce the growth of harmful bacteria and promote a healthy digestive system. The application of probiotics to kidney health is an emerging area of medicine that has only recently come into attention of scientists. In CKD patients there is a build-up of poisonous wastes in the bloodstream due to the overloaded and impaired kidneys. Certain probiotic microorganisms can utilize urea, uric acid, creatinine and other toxins as nutrients for growth which helps eliminate them as fecal matter. Probiotic organisms transform the colon into a blood cleansing organ in cases where kidney fails to remove toxins from blood. Thus probiotics are new hope for CKD patients and can be used to delay progression of disease. We aim to compile the data of various researches and clinical trials being conducted to evaluate benefits of probiotics in CKD patients.

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Keywords: Chronic Kidney Disease (CKD), Probiotics and Uremic Toxins.

Introduction

According to the World Health Organization, kidney disease and disease of the urinary tract cause 850,000 deaths worldwide every year. Globally, Chronic kidney disease (CKD) is the 12th leading cause of death and the 17th leading cause of disability. CKD has a high global prevalence with a consistent estimated global prevalence of between 11 to 13% with the majority stage 3. [1] The study done in Delhi showed the prevalence of CKD is 0.785% or 7852/million adult population in India [2]. CKD usually gets worse slowly, and symptoms may not appear until kidneys are badly damaged. In the late stages of CKD, nearing kidney failure, symptoms noticed that are caused by waste and extra fluid building up in body.[3] Accumulated wastes cause a condition generally known as azotemia. This condition can become fatal if not medically treated. In addition, related complications of that waste build up can include high blood pressure, anaemia, weak bones, poor nutritional health and nerve damage.

The definition and classification of chronic kidney disease (CKD) keeps on updating, current international guidelines define this condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1·73 m2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause.[4] To facilitate assessment of CKD severity, the National Kidney Foundation developed criteria (as part of its Kidney Disease Outcomes Quality Initiative (NKF KDOQI™)) to stratify CKD patients:

- Stage 1: normal eGFR ≥ 90 mL/min per 1.73 m2 and persistent albuminuria
- Stage 2: eGFR between 60 to 89 mL/min per 1.73 m2

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- Stage 3: eGFR between 30 to 59 mL/min per 1.73 m2
- Stage 4: eGFR between 15 to 29 mL/min per 1.73 m2
- Stage 5: eGFR of < 15 mL/min per 1.73 m2 or end-stage renal disease[5]

Aim of chronic kidney disease treatment is to delay progressive loss of kidney function and prevent or manage complications. Four interventions clearly delay chronic kidney disease progression, including management of hypertension; use of a renin angiotensin aldosterone system (RAAS) blocker, an ACE-I, or ARB for hypertension and albuminuria; control of diabetes; and correction of metabolic acidosis [6]. The widely accepted fact that people with CKD have altered gut flora is becoming an area of interest because it impacts the patient in a myriad of ways. In the forefront is gastrointestinal (GI) health and uremic toxins. Restoring balance of intestinal flora favourably impacts the CKD patient and improves any GI issues such as constipation or diarrhea as well as promotes healthy digestion and improved immunity [7]. Probiotics are emerging solution for modifying the altered gut flora for benefits of CKD patients.

World Health Organization and the Food and Agriculture Organization of the United Nations, defined probiotics as "live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host." Some of the popularly used probiotic microorganisms are Lactobacillus rhamnosus, Lactobacillus reuteri, bifidobacteria and certain strains of Lactobacillus casei, Lactobacillus acidophilus-group, Bacillus coagulans, Escherichia coli strain Nissle 1917, certain enterococci, especially Enterococcus faeciumSF68, and the yeast Saccharomyces boulardii.[8]

Certain probiotic microorganisms can utilize urea, uric acid and creatinine and other toxins as nutrients for growth. Overloaded and impaired kidneys lead to build up of these poisonous wastes in the bloodstream. Probiotic microorganisms multiply and metabolize larger quantities of uremic toxins, facilitating the increased diffusion of these toxins from the circulating blood into the bowel across the lining of the intestinal walls. Ultimately, these microbes are excreted in the feces (normally microbes make up 50% of feces by weight). This process is known as "Enteric Dialysis" [10]

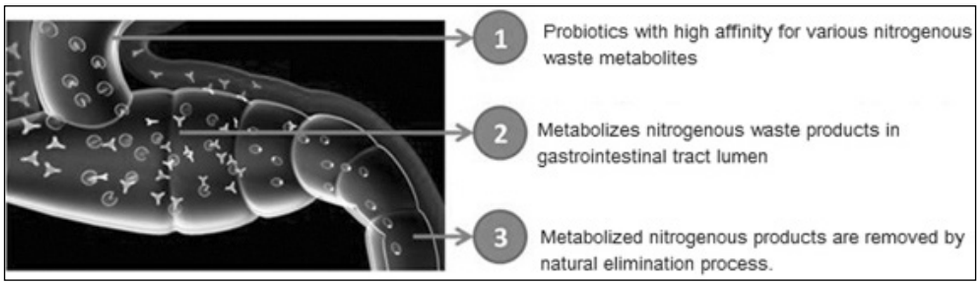


Figure 1: Process of Enteric Dialysis.

Country	Category
Japan	Functional food and nutraceuticals
Europe	Functional food
China	Functional food
Brazil	Functional food
New Zealand and Australia	Functional food
USA	Dietary supplements, drugs, Biological product, Medical food and Live biotherapeutic agent
India	Functional food, drugs
Malaysia	Functional food
Canada	Natural health product

Table no.1: Categories of Probiotics in different countries.[9]

Intestinal bacteria can benefit health by breaking down toxins, synthesizing vitamins, and defending against infection. They may also play a role in preventing such diseases as peptic ulcers, colorectal cancer, and inflammatory bowel disease. Probiotic organisms with the aid of microbes can indirectly removes toxic wastes and helps eliminate them as fecal matter. Thus probiotics can used to reduce the burden of toxic waste in CKD patients and improve quality of life. Limited clinical data is available for use of probiotics in CKD patients. Aim of this review is to summarise all clinical trials regarding benefits of probiotics in CKD patients.

Clinical evidence:

For the exact combinations of Renadyl™ (Streptococcus thermophilus KB19 + Lactobacillus acidophilus KB27 + Bifidobacterium longum KB31)

Ranganathan N et al, 2014, studied health status and level of satisfaction of customers with CKD using

Renadyl™. Survey questionnaires along with stamped and addressed return envelopes were mailed out to 523 current and 475 former customers of Renadyl™ from Kibow Biotech Inc. Results were tabulated and analyzed using SAS V9.2 and MS Excel. A total of 147 responses were received (16% response rate, 57 female, 84 male, age 7-94 years). Majority was over 50 years of age, retired, in at least stage III of kidney disease, with one or several comorbid conditions. Overwhelming majority (over 75%) was satisfied with safety, perceived efficacy and performance of Renadyl™, and with Kibow's services. Safety of Renadyl™ in all stages of CKD and with a variety of comorbid conditions, established in prior studies, was corroborated. It does not interfere with any other medical treatments, including dialysis. At the same time, it provides at least some beneficial effect with regard to the overall quality of life and maintaining or improving kidney health in particular. [11]

Ranganathan N et al, 2014, studied effect of Strain-Specific Probiotic Formulation (Renadyl™) in Dialysis Patients by randomized, double-blind, placebo-controlled crossover study. The primary objective of study was to assess the safety and efficacy of Renadyl™ measured through improvement in quality of life or reduction in levels of known uremic toxins. Secondary goal was to investigate the effects on several biomarkers of inflammation and oxidative stress. Two 2-month treatment periods separated by 2-month washout and crossover, with physical examinations, venous blood testing, and quality of life questionnaires completed at each visit. Data were analyzed with SAS V9.2. Twenty two subjects (79%) completed the study. Observed trends were as follows (none reaching statistical significance): decline in WBC count (−0.51×109/L, = 0.057) and reductions in levels of C-reactive protein (−8.61 mg/L, ◎ = 0.071) and total Indoxyl glucuronide (−0.11 mg%, ◎ =0.058). Renadyl™ appeared to be safe to administer to ESRD patients on haemodialysis. Stability in QOL assessment is an encouraging result for a patient cohort in such advanced stage of kidney disease. [12]

Ranganathan N et al, 2013, studied dose Escalation, safety and impact of a Strain-Specific Probiotic (Renadyl™) on Stages III and IV Chronic Kidney Disease Patients. During the screening (T0), each patient was examined and the baseline values were obtained, after which the patient was initiated on the dose of 1 capsule containing 30 billion CFU thrice daily with meals (90 billion CFU/day). At the end of month 1 (T1), the dose was increased to 2 capsules (180

Figure 2: Creatinine – Means by visit

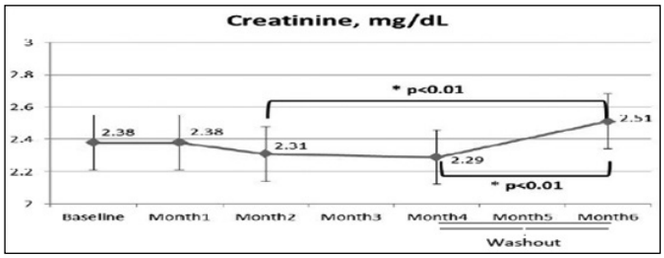


Figure 3: C-reactive Protein – Means by visit

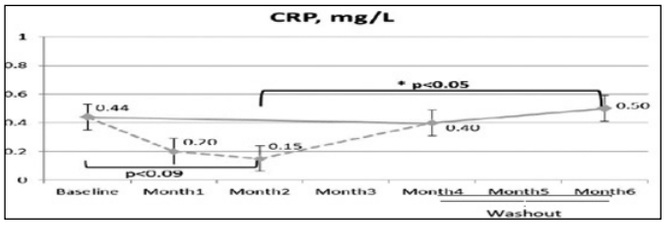


Figure 4: Hemoglobin – Means by visit

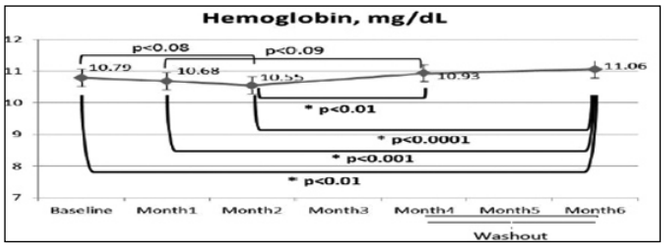


Figure 5: Blood Urea Nitrogen – Means by visit

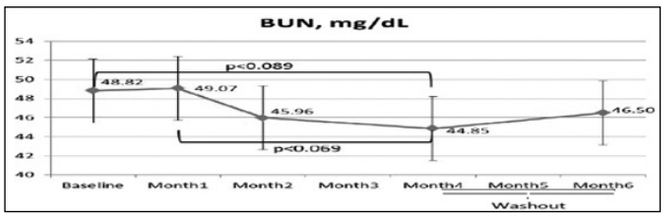


Figure 6: Potassium – Means by visit

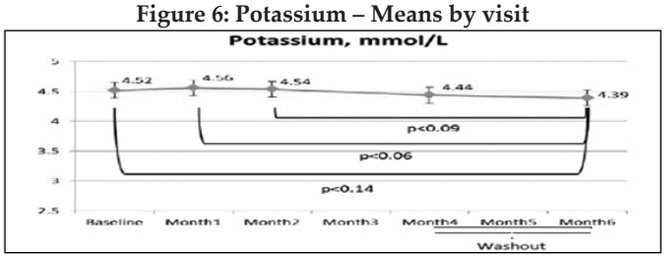
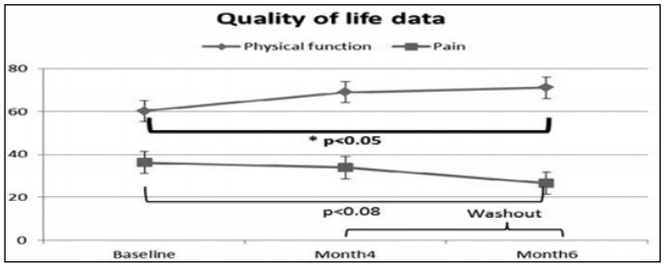


Figure 7: Quality of life data – Means by visit



billion CFUs/day), and at month 2 (T2) – to the maximum of 3 capsules (270 billion CFUs/day) thrice daily with meals. After two months on the maximum dose (T3 and T4), the treatment was discontinued (T4) and the washout period began. Two months later, each patient came for the follow-up visit (T5) and completed the study. Out of 31 participants, 28 (90%) completed the study, with additional 2 participants lost to the follow-up. No significant adverse events were noted with dose escalation. Statistically significant changes were observed in creatinine (months 2 to 6: -0.23 ± 0.09 mg/dL, p<0.05) (Figure 2), C - reactive protein (CRP) (mos. 2 to 6: -0.28 ± 0.14 mg/L, p<0.05) (Figure 3), haemoglobin (baseline to month 6: 0.35 ± 0.13 mg/dL, p<0.01, months 1 to 6: 0.46 ± 0.13 mg/dL, p<0.001, months 2 to 4: 0.35 ± 0.13 mg/dL, p<0.01, months 2 to 6: 0.58 ± 0.13 mg/dL, p<0.0001) (Figure 4) and haematocrit (baseline to month 6: 1.17%, p<0.05, months 1 to 4: 1.00%, p<0.05, months 1 to 5: 1.69%, p<0.001, months 2 to 5: 1.36%, p<0.005). In addition, trends not reaching statistical significance were observed in BUN (baseline to month 4: -3.56 ± 2.07 mg/dL, p<0.09; months 1 to 4: -3.81 ± 2.07 mg/dL, p<0.07) (Figure 5), potassium(months 1 to 6: 0.21 ± 0.11 mmol/L, p<0.06, months 2 to 6: 0.19 ± 0.11mmol/L, p<0.09) (Figure 6), haemoglobin (baseline to month 2: 0.23 ± 0.13 mg/dL, p<0.08, months 1 to 4: 0.23 ± 0.13 mg/dL, p<0.09, months 4 to 6:0.23 ± 0.13 mg/dL, p<0.09) and CRP (baseline to month 2: 0.23 ± 0.14mg/L, p<0.095). QOL results indicated improvement in physical functioning (baseline to month 6, p<0.05) (Figure 7), a trend toward reduction of pain (baseline to month 6, p<0.08), with no significant change in mental, emotional and social well-being.[13]

Ranganathan N et al, 2010, studied the effect of Probiotic Dietary Supplementation for Promoting Healthy Kidney Function in Patients with Chronic Kidney Disease by randomized, double-blind, placebocontrolled crossover trial. Trial of a probiotic bacterial formulation was conducted in four countries, at five institutions, for 6 months on 46 outpatients with CKD stages 3 and 4: USA (n=10), Canada (n=13), Nigeria (n=15), and Argentina (n=8). Outcomes were compared using biochemical parameters: blood urea nitrogen (BUN), serum creatinine, and uric acid. General well-being was assessed as a secondary parameter by a quality of life (QOL) questionnaire on a subjective scale of 1-10. Oral ingestion of probiotics (90 billion colony forming units [CFUs]/day) was well tolerated and safe during the entire trial period at all sites. BUN levels decreased in 29 patients (63%, P<0.05), creatinine levels decreased in 20 patients (43%, no statistical significance), and uric acid levels decreased in 15 patients (33%, no statistical significance). Almost all subjects expressed a perceived substantial overall improvement in QOL (86%, P<0.05). The main outcomes of this preliminary trial include a significant reduction of BUN, enhanced well-being, and absence of serious adverse effects, thus supporting the use of the chosen probiotic formulation for bowel-based toxic solute extraction. QOL and BUN levels showed statistically significant differences in outcome (P<0.05) between placebo and probiotic treatment periods at all four sites (46 patients).[14]

Ranganathan N et al, 2009, studied the effect Probiotic dietary supplementation in patients with stage 3 and 4 chronic kidney disease by prospective, randomized, double-blind, crossover, placebo-controlled, 6-month pilot scale trial in Canada,. The patients were randomized into two study arms: Group A and Group B. Group A received the placebo; Group B received probiotic bacteria in the formulation, KB. After 3 months, the crossover was made. Group A received probiotic bacteria; Group B received the placebo. Physical examination and complete laboratory testing were performed at each visit. The following tests were included: blood biochemistry, haematology, liver function and urine protein to creatinine ratio, ALT, CRP, ammonia, adherence and quality of life assessment based on the patient diary card. In addition, feces samples were collected at the beginning, the middle (3 months), and the end (6 months) of the study. Fecal samples were analyzed for total aerobes (TAE), total anaerobes (TAN), Bifidobacteria (BIF), Lactobacillus (LAC), Streptococcus (STRP) and pH. Study product/placebo for the subsequent period was dispensed at each visit. No wash-out period was considered because of the cross-over design of this study. Among the 13 patients who completed the trial, the mean change in BUN concentration during the probiotic treatment period (-2.93 mmol/L) differed significantly (p =0.002) from the mean change in BUN concentration during the placebo period (4.52 mmol/L). In addition, the mean changes in uric acid concentration were moderate during the KB period (24.70 mmol/L) versus during the placebo period (50.62 mmol/L, p =0.050), and the changes in serum creatinine concentration were insignificant. Neither gastrointestinal nor infectious complications were noted in any subject with improved QOL. Thus orally administered probiotic bacteria selected to metabolize nitrogenous wastes may be tolerated for as long as 6 months. No

Figure 8: Average relative changes in chosen biochemical

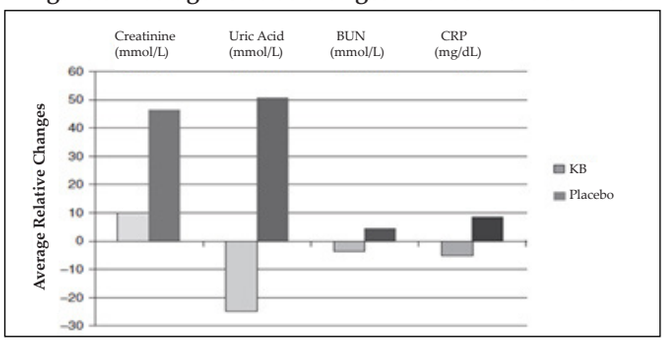


Figure 9: Fecal microbial profiles

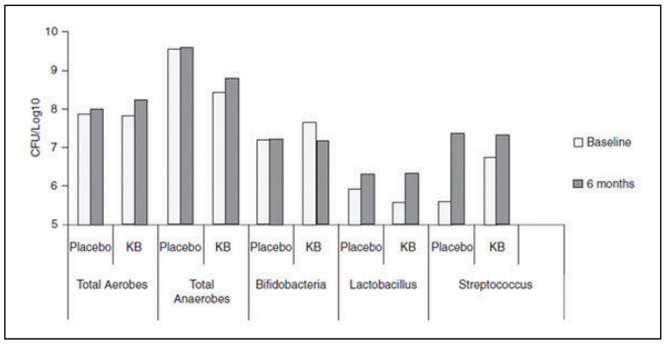
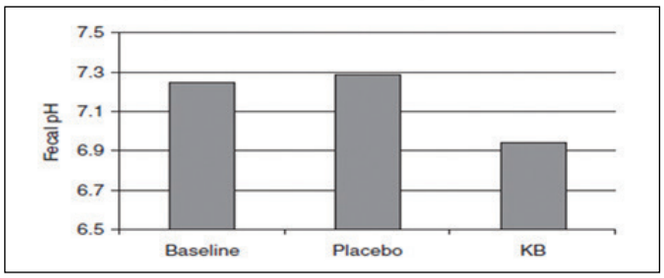


Figure 10: Observed fecal pH values



significant changes were observed in the microbiological profiles between placebo and probiotic treatment groups after 90 days (Figure 9). Fecal pH of the probiotic bacteria cohort (pH = 6.94) was significantly lower than the placebo cohort (pH =7.29) with a p-value of >95% (Figure 10). [15]

For similar combination of probiotic and prebiotics:

Boregs et al, 2018, studied the effect of Probiotic Supplementation in Chronic Kidney Disease, by a randomized, double-blind, placebo-controlled trial. Objective was to evaluate the effects of probiotic supplementation on the gut microbiota profile and inflammatory markers in chronic kidney disease patients undergoing maintenance haemodialysis (HD). Forty-six HD patients were assigned to receive 1 of 2 treatments: probiotic (n =23; Streptococcus thermophilus, Lactobacillus acidophilus, Bifidobacteria longum, 90 billion colony-forming units per day) or placebo (n = 23) daily for 3 months. Blood and feces were collected at baseline and after intervention. The inflammatory markers (C-reactive protein and interleukin-6) were analyzed by immunoenzymatic assay (enzyme-linked immunosorbent assay). Uremic toxins plasma levels (indoxyl sulfate, p-cresyl sulfate, and indole-3-acetic acid) were obtained by Reversed-Phase High-Performance Liquid Chromatography. Routine laboratory parameters were measured by standard techniques. Fecal pH was measured by the colorimetric method, and the gut microbiota profile was assessed by Denaturing Gradient Gel Electrophoresis analysis. Sixteen patients remained in the probiotic group (11 men, 53.6±11.0 year old, 25.3±4.6 kg/m2) and 17 in the placebo group (10 men, 50.3 ± 8.5 year old, 25.2 ±5.7 kg/m2). After probiotic supplementation there was a significant increase in serum urea (from 149.6 ±34.2 mg/dL to 172.6 ± 45.0 mg/dL, P = .02), potassium (from 4.4 ± 0.4 mmol/L to 4.8 ± 0.4 mmol/L, P = .02), and indoxyl sulfate (from 31.2 ±15.9 to 36.5 ± 15.0 mg/dL, P = .02). The fecal pH was reduced from 7.2 ± 0.8 to 6.5 ± 0.5 (P = .01). These parameters did not change significantly in placebo group. Changes in the percentage delta (D) between groups were exhibited with no statistical differences observed. The inflammatory markers and gut profile were not altered by supplementation. Thus aprobiotic supplementation failed to reduce uremic toxins and inflammatory markers. Therefore, probiotic therapy should be chosen with caution in HD patients. [17]

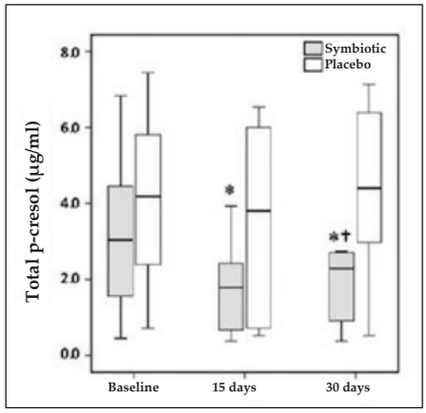


Figure 11: Box plot of p-Cresol plasma concentrations in the symbiotic (n =22) and placebo (n = 12) groups at different times of the study. *p < 0.01 vs baseline, +p < 0.01 vs placebo.

Guida et al, 2017, studied the effect of a Short-

Course Treatment with synbiotics on Plasma p-Cresol Concentration in Kidney Transplant Recipients(KTR) by single-center, parallel-group, double-blinded, randomized (2:1 synbiotic to placebo) study. Objective was to investigate effects of synbiotics on accumulated p-cresol (uremic toxin) both because of increased production by their dysbiotic gut microbiome and because of reduced elimination by the transplanted kidneys. Thirty-six KTRs (29 males, mean age 49.6 ± 9.1 years) with transplant vintage > 12 months, stable graft function, and no episode of acute rejection or infection in the last 3 months were given 5 g powder of Synbiotic (Probinul Neutro, CadiGroup, Rome, Italy) or placebo dissolved in water three times a day far from meals. at home for 30 days. The total plasma p-Cresol measured by high-performance liquid chromatography at baseline and after 15and 30 days of placebo or synbiotic treatment. After 15 and 30 days of treatment, plasma p-Cresol decreased by 40% and 33% from baseline (both $p < 0.05$), respectively, in the synbiotic group, whereas it remained stable in the placebo group. After 30 days of treatment, no significant change was observed in either group in renal function, glycemia, plasma lipids, or albumin concentration. Treatment was well tolerated and did not induce any change in stool characteristics. The results of this pilot study suggest that treatment with synbiotics may be effective to lower plasma p-Cresol concentrations in KTRs.[16]

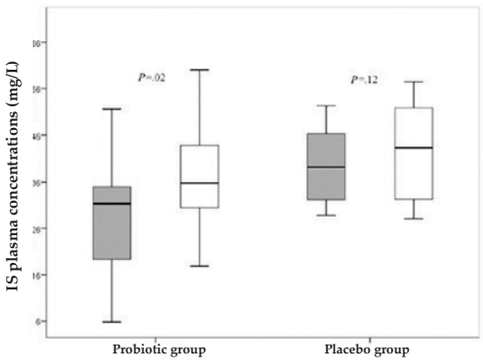


Figure 12: Representation of Indoxyl sulfate (IS) plasma concentrations in chronic kidney disease patients on haemodialysis, before (shaded bar) and after (open bar) interventions.

Pavan M, 2016, studied the Influence of prebiotic and probiotic supplementation on the progression of chronic kidney disease, a randomized control and open-label trial. The objective was to investigated whether prebiotic and probiotic supplementation along with low protein diet retards the progression of CKD. 24 stable CKD stage III to V patients, who are not on renal replacement therapy were randomly assigned to 2 groups: low protein diet + prebiotic + probiotic supplementation (N.=12), receiving 3 tablets of prebiotic + probiotic supplementation daily for 6 months, and the control group receiving low protein diet only (N.=12). After 12 months the declining GFR during prebiotic and probiotic supplementation were significantly lower (-11.6±8.6 vs. -3.4±4.6 mL/min per 1.73 m2 per year, 95% CI -6.45 - -9.86, P<0.001) than those with low protein diet alone. Thus Prebiotic and probiotic supplementation along with low protein diet delayed the progression of CKD.[18]

Rossi M et al, 2016, studied Synbiotics Easing Renal Failure by a randomized, double–blind, placebo–controlled, crossover trial. The objective of study was to evaluate whether synbiotic (pre- and probiotic) therapy alters the gut microbiota and reduces serum concentrations of microbiome–generated uremic toxins, IS (Indoxyl sulfate) and PCS (p-cresol sulfate), in patients with CKD. 37 predialysis adult participants with CKD(eGFR=10–30 ml/min per 1.73 m2) underwent a 2-week run–in period followed by randomization in a 1:1 ratio to either synbiotic supplements or placebo for 6 weeks. Thereafter, participants underwent a further 4-week washout period followed by crossover to the alternative intervention. Of 37 individuals randomized (age =69±10 years old; 57% men; eGFR=24±8 ml/min per 1.73 m2), 31 completed the study. Synbiotic therapy did not significantly reduce serum IS (-2 μmol/L; 95% confidence interval [95% CI], -5 to 1 μmol/L) but did significantly reduce serum PCS (-14 μmol/L; 95% CI, -27 to -2 μmol/L). Decreases in both PCS and IS concentrations were more pronounced in patients who did not receive antibiotics during the study (n=21; serum PCS, -25 μmol/L; 95% CI, -38 to -12 μmol/L; serum IS, -5 μmol/L; 95% CI, -8 to -1 μmol/L). Synbiotics also altered the stool microbiome, particularly with enrichment of Bifidobacterium and depletion of Ruminococcaceae. Except for an increase in albuminuria of 38 mg/24 h (P=0.03) in the synbiotic arm, no changes were observed in the other secondary outcomes. Thus In patients with CKD, synbiotics did not significantly reduce serum IS but did decrease serum PCS and favourably modified the stool microbiome.[19]

Viramontes D et al, 2014, studied Effect of a Symbiotic Gel (Lactobacillus acidophilus, Bifidobacterium lactis and Inulin) on Presence and Severity of Gastrointestinal Symptoms in

Haemodialysis Patients, by a double-blinded, pla-

cebo-controlled, randomized, clinical trial. The objective was to assess the effect of a symbiotic gel on presence and severity of gastrointestinal symptoms (GIS) in haemodialysis patients. Twenty-two patients were randomized to the intervention group (nutritional counselling 1 symbiotic gel) and 20 patients were randomized to the control group (nutritional counselling 1 placebo), during 2 months of follow-up. After a 2-month treatment, intervention group had a significant reduction in prevalence and monthly episodes of vomit, heartburn, and stomach ache, as well as a significant decrease in GIS severity compared with control group. Moreover, intervention group had a greater yet not significant decrease in the prevalence of malnutrition and a trend to reduce their C-reactive protein and tumour necrosis factor a levels compared with control group. No symbiotic-related adverse side effects were shown in these patients. Clinical studies with longer follow-up and sample size are needed to confirm these results. It is thus concluded that administration of a symbiotic gel is a safe and simple way to improve common GIS in dialysis patients.[20]

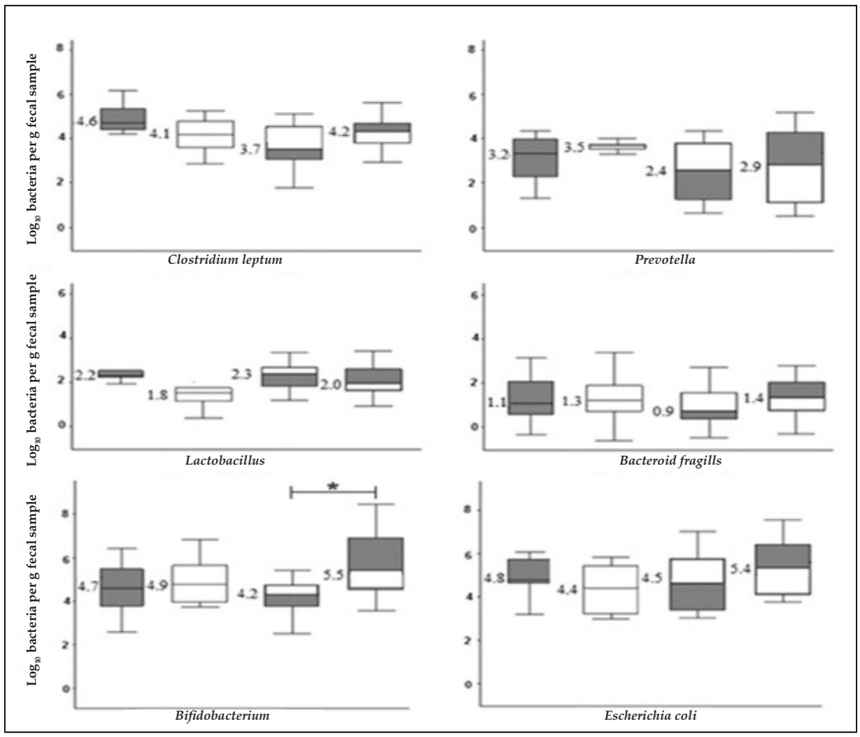


Figure 13: Box plots of bacterial groups quantified by EvaGreen real-time PCR in patient with end stage renal disease.

Wand et al, 2015, studied the effect of probiotics on serum levels of cytokine and endotoxin in peritoneal dialysis patients, by a randomised, double-blind, placebo-controlled trial. The objective was to evaluate the impact of oral probiotics on serum levels of endotoxemia and cytokines in peritoneal dialysis (PD) patients. From July 2011 to June 2012, a randomised, double-blind, placebo-controlled trial was conducted in PD patients. The intervention group received one capsule of probiotics containing 109 cfu Bifobacterium bifidum A218, 109 cfu Bifidobacterium catenulatum A302, 109 cfu Bifidobacterium longum A101, and 109 cfu Lactobacillus plantarum A87 daily for six months, while the placebo group received similar capsules containing maltodextrin for the same duration. Levels of serum TNF-α, interferon gamma, IL-5, IL-6, IL-10, IL-17, and endotoxin were measured before and six months after intervention. 39 patients completed the study (21 in the probiotics group and 18 in the placebo group). In patients receiving probiotics, levels of serum TNF-α, IL-5, IL-6, and endotoxin significantly decreased after six months of treatment, while levels of serum IL-10 significantly increased. In contrast, there were no significant changes in levels of serum cytokines and endotoxin in the placebo group after six months. In addition, the residual renal function was preserved in patients receiving probiotics. In conclusion, probiotics could significantly reduce the serum levels of endotoxin, pro-inflammatory cytokines (TNF-α and IL-6), IL-5, increase the serum levels of anti-inflammatory cytokine (IL-10), and preserve residual renal function in PD patients.[21]

Campieri et al, 2001, studied the Reduction of oxaluria after an oral course of lactic acid bacteria at high concentration. The objective was to investigate the hypothesis whether oxaluria can be reduced by means of reducing intestinal absorption through feeding a mixture of freeze-dried lactic acid bacteria. Six patients with idiopathic calcium-oxalate urolithiasis and mild hyperoxaluria (>40 mg/24 h) received daily a mixture containing 8 x 10(11) freeze-dried lactic acid bacteria (L. acidophilus, L. plantarum, L. brevis, S. thermophilus, B. infantis) for four weeks. The 24-hour urinary excretion of oxalate was determined at the end of the study period and then one month after ending the treatment. The ability of bacteria to degrade oxalate and grow in oxalate-containing media, and the gene expression of

Ox1T, an enzyme that catalyzes the transmembrane exchange of oxalate, also were investigated. The treatment resulted in a great reduction of the 24-hour excretion of oxalate in all six patients enrolled. Mean levels +/- SD were 33.5 +/- 15.9 mg/24 h at the end of the study period and 28.3 +/- 14.6 mg/24 h one month after treatment was interrupted compared with baseline values of 55.5 +/- 19.6 mg/24 h ($P < 0.05$). The treatment was associated with a strong reduction of the fecal excretion of oxalate in the two patients tested. Two bacterial strains among those used for the treatment (L. acidophilus and S. thermophilus) proved in vitro to degrade oxalate effectively, but their growth was somewhat inhibited by oxalate. One strain (B. infantis) showed a quite good degrading activity and grew rapidly in the oxalate-containing medium. L. plantarum and L. brevis showed a modest ability to degrade oxalate even though they grew significantly in oxalate-containing medium. No strain expressed the Ox1T gene. Thus the biological manipulation of the endogenous digestive microflora can be a novel approach for the prevention of urinary stone formation.[22]

Cruz-Mora J et al, 2014, studied Effects of a Symbiotic on Gut Microbiota in Mexican Patients of End-Stage Renal Disease, a random, placebo controlled trial. The objective was to test whether additional intake of symbiotic gel affects specific modifications of gut microbiota in patients with end-stage renal disease (ESRD). Eighteen patients with ESRD diagnosis with renal replacement therapy (hemodialysis) were randomly assigned to 2 treatment groups: (1) test group (nutritional counselling 1 symbiotic) and (2) control group (nutritional counselling 1 placebo). Clinical history and the evaluation of Gastrointestinal Symptom Rating Scale were performed. Gut microbiota composition was analyzed by real-time polymerase chain reaction from fecal samples. All subjects were followed for 2 months. Bifidobacterial counts were higher in the second samples (mean: 5.5±1.72 log10 cells/g) than in first samples (4.2±0.88 log10 cells/g) in the patients of the test group ($P = .0344$). Also, lactobacilli counts had a little decrease in the test group (2.3 ± 0.75 to 2.0±0.88 log 10 cells/g) and the control group (2.2±0.90 to 1.8±1.33 log 10 cells/g), between the first and the second samples. Gastrointestinal symptoms scores (scale 8-40) were reduced in the test group (start 12 [10-14] and end 9 [8-10]) compared with control group (start 11 [8-21] and end 11 [9-15]).Thus Short-term symbiotic treatment in patients with ESRD can lead to the increase of Bifidobacterium counts, maintain the intestinal microbial balance.[23]

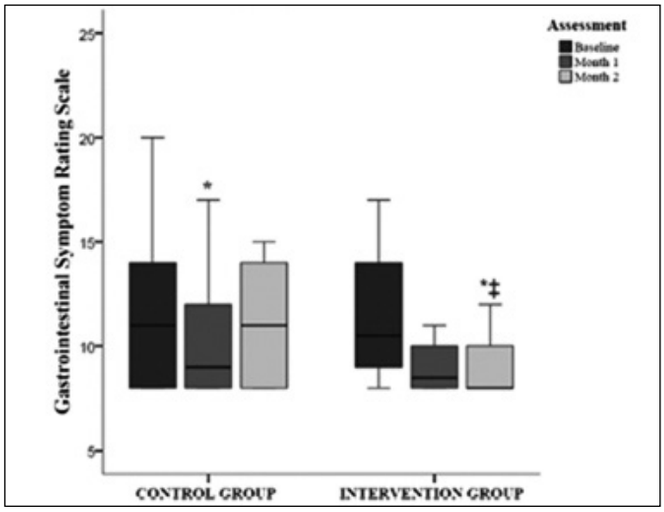


Figure 14: Gastrointestinal symptom rating scale during the study. *P ≤ .05 versus baseline; *P⚜ ≤ .05 versus control.

The first sample of control group (black; n 5 10), the second sample of control group (white; n 5 10), the first sample of test group (black and white; n 5 8), and the second sample of test group (white and black; n 5 8). The mean counts are presented by numbers. Boxes show the upper (75%) and the lower (25%) percentiles of the data. Whiskers indicate the highest and the smallest values. Significant difference (P 5 .0344), is indicated by asterisk. PCR, polymerase chain reaction.

Simenhoff ML et al, 1966, studied Biomodulation of the toxic and nutritional effects of small bowel bacterial (SBBO) overgrowth in end-stage kidney disease using freeze-dried Lactobacillus acidophilus. In this study, 8 haemodialysis patients were treated with a course of oral Lactobacillus acidophilus (LBA) in an attempt to alter this SBBO. LBA treatment was effective in lowering 2 compounds generated in vivo. Serum dimethylamine (DMA) levels dropped from 224 +/- 47 to 154 +/- 47 micrograms/dl at the end of LBA treatment ($p < 0.001$). Nitrosodimethylamine, a carcinogen, levels also decreased significantly from 178 +/- 67 (untreated) to 83 +/- 49 ng/kg (after LBA treatment). Patients nutritional status, assessed as serum albumin, body weight, caloric intake, midarm muscle area (MAMA) and appetite improved modestly, but not significantly. LBA changed small bowel pathobiology by modifying metabolic actions of SBBO, reducing in vivo generation of toxins and carcinogens and promoting nutrition with no adverse side effects.[24]

From the clinical trials it is clear that probiotics can reduce nitrogenous waste load in CKD patients only if it can metabolise these waste. Thus ability of probiotics to utilise nitrogenous waste is key for enteric dialysis.

Summary of clinical data:

Author and Journal	Methodology	Results	Conclusion
Ranganathan Natarajan et al, 2014 BioMed Research International	Patient no: 22 Design: randomized, double-blind, placebo-controlled crossover study Duration: 2 months Indication: end-stage renal disease	decline inWBC count (change of −0.51 × 109/L, ◎ < 0.057) and reductions in the levels of total indoxyl glucuronide (−0.11mg%, ◎ < 0.058) and C-reactive protein (−8.62mg/L, ◎ < 0.071).	Renadyl™ in ESRD patients at the dose of 180 billion CFUs per day appears safe and well tolerated.
Natarajan Ranganathan Adv Ther (2010)	Patient no: 46 Design: randomized, double-blind, placebocontrolled crossover trial Duration: 6 months Indication: CKD	Blood urea nitrogen decreased in 29 patients (63%, P<0.05), creatinine levels decreased in 20 patients (43%, no statistical significance), and uric acid levels decreased in 15 patients (33%, no statistical significance)	Chosen probiotic formulation can be used for bowel based toxic solute extraction.
Ranganathan N et al, Current medical research and opinion	Patient no: 16 Design: : A prospective, randomized, double-blind, crossover, placebo-controlled Duration: 6 months Indication: CKD	The mean change in BUN concentration during the probiotic treatment period (2.93 mmol/L) differed significantly (p = 0.002) from the mean change in BUN concentration during the placebo period (4.52 mmol/L). In addition, the mean changes in uric acid concentration were moderate during the KB period (24.70 mmol/L) versus during the placebo period (50.62 mmol/L, p = 0.050)	Probiotics decrease level of BUN and improve quality of life in CKD patients
Ranganathan N et al, Journal of Nephrology & Therapeutics	Patient no: 31 Design: open label, dose escalation observational study Duration: 6 months Indication: CKD	The primary goal was met, as no significant adverse events were noted during the dose escalation phase. The secondary goal was also met, as QOL measure of physical functioning improved (base to month 6, p<0.05) and a strong trend in reduction of pain was observed (base to month 6, p<0.08).	Highest dose of 270 CFUs per day, appears safe and well-tolerated. Statistically significant improvements were noted in creatinine, C-reactive protein, hemoglobin, and physical functioning. Trends toward reduction were noted in BUN and pain. Other markers of inflammation and oxidative stress exhibited a lot of variation.

Author and Journal	Methodology	Results	Conclusion
Guida B et al,2017 Journal of the American College of Nutrition	Patient no: 36 Design: single-center, parallel-group, double-blinded, randomized (2:1 synbiotic to placebo) study. Duration: 1month Indication: plasm p-cresol in kidney Transplant Recipients(KTR)	33% decrease in level of plasma p-cresol from baseline($p<0.05$) after 30 days	Treatment with synbiotics may be effective to lower plasma p-Cresol concentrations in KTRs
Dehghani H et la, 2016 Iranian Journal of Kidney disease	Patient no: 66 Design: A randomized controlled trial Duration: 6 weeks Indication: Chronic Kidney disease(CKD)	Blood urea nitrogen level showed reduction from 40.80 ± 22.11 mg/dL to 36.14 ± 20.52 mg/dL, P = .01	Synbiotic supplement could reduce blood urea nitrogen in CKD
Pavan M et al, 2016 Italian Journal of urology and nephrology	Patient no: 24 Design: a randomized control and open-label Duration: 12 months Indication: CKD	The declining GFR during prebiotic and probiotic supplementation were significantly lower (-11.6±8.6 vs. -3.4±4.6 mL/min per 1.73 m2 per year, 95% CI -6.45 - -9.86, P<0.001) than those with low protein diet alone	Progression of CKD can be delayed with pro and pre biotic supplements.
Rossi M et la, 2016 Clinical Journal of American Society	Patient no: 37 Design: randomized, double-blind, placebo-controlled, crossover trial Duration: 11 months Indication: CKD	Serum p-cresyl sulfate(PCS) reduce from-27 to -2 micro mol/L Altered stool microbe with depletion of Ruminococcaceae and enrichment of Bifidobacterium.	CKD patients are benefited by synbiotics.
Viramontes-Hörner D et al, 2015 Journal of Renal Nutrition.	Patient no: 42 Design: A double-blinded, placebo-controlled, randomized, clinical trial Duration: 2months Indication: GIT symptoms Haemodialysis patients Strains: L. acidophilus, B.lactis	Decrease in GI symptoms severity in patients taking probiotics	Probiotic improves common GI symptoms in Haemodialysis patients
Wang IK et al, 2015 Beneficial Microbes Journal	Patient no: 39 Design: randomised, double-blind, placebo-controlled trial Duration: 6 months Indication: Peritoneal dialysis (PD) patient Strains: B.bifidum, B.catenulatum, B.longum, L.plantarum	Decrease in serum levels of cytokines and endotoxin in patients receiving probiotics	Probiotics can preserve renal function in PD patients

Author and Journal	Methodology	Results	Conclusion
Campieri C et al, 2001 Kidney international journal	Patient no: 6 Duration: 4 weeks Indication: Hyperoxaluria Strains: L.acidophilus, L.plantarum, L.brevis, S.thermphilus, B.infantis	Fecal excretion of oxalate in two patients	Digestive flora can be new approach to prevent urinary stone formation.
Cruz-Mora J et al, 2014 Journal of Renal Nutrition.	Patient no:18 Design: Random Duration: 2 months Indication: End-stage renal disease(ESRD) Strains: L. acidophilus, B.lactis	High Bifidobacterial count(p=0.0344) Reduction in GI symptoms as compare to control.	Bifidobacterium can maintain intestinal microbial balance in ESRD pateints.
Simenhoff ML et al, 1966 Mineral and electrolyte journal.	Patient no: 8 Indication: Small bowel bacterial overgrowth(SBBO) in ESRD Strains: L.acidophilus	Drop in levels of serum dimethylamine(DMA) (p<0.001) and nitrsodimethylamine	L.acidophilus reduces generation of toxins and carcinogens and promoting nutrition with no adverse side effects in SBBO.

Like "no two individuals are same", not all probiotics have same efficacy of cleansing blood and it varies. Only specific strain of probiotics can benefit CKD patients. S.thermophilus (KB19), L.acidophilus (KB27) and B.longum (KB31) microbes are screened, selected and grown under uremic conditions, so that they have a higher affinity for uremic toxins. These microbes are specifically from classes already approved for human consumption and are Generally Recognized as Safe (GRAS) under US FDA. As per independent Agency Report S.thermophilus (KB19), L.acidophilus (KB27) and B.longum (KB31) have 78-95% urea hydrolysis efficacy while the generic strains of these three probiotics have only 2-18% efficacy.

Conclusion:

CKD is the leading cause of death globally. Diuretic, phosphate & potassium binders and RAAS inhibitors are commonly used in treatment of CKD. Probiotics is new approach in management of CKD. It not only improves the levels of uremic toxins in blood but also provide benefits to patient by restoring the gut altered microbial balance. Here we conclude, probiotics in CKD patients have been clinically tested and shown to be safe, effective and delay progression of CKD. A specific importance needs to be given to strain of probiotic micro-organism. Only specific strain can be beneficial for improving quality of life and to decrease uremic toxin in CKD patients.

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