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Review Article

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Therapeutic Interventional Probiotic Approach and the Treatment of Chronic Kidney Disease (CKD) Associated Uremia

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ABSTRACT

Chronic kidney disease is a heterogeneous disorder characterized by progressive renal malfunction triggered by low Glomerular filtration rate (GFR) with increased morbidity and associated mortality. Intestinal microbiota dysbiosis has recently emerged as an important player in progressing chronic renal disease complications by increasing uremic toxins. Recently, the interest in developing new research initiatives focusing on therapeutic modulation of the intestinal microbiome through a probiotics approach, preserving kidney functionality by maintaining the physiological balance of intestinal microbiota, decreasing uremic toxins production, and improving the kidney-gut axis functionality has been considered as a comprehensive therapeutic approach in controlling and managing chronic kidney disease and associated complications within vitro or in vivo trial analysis. This review shed light on highlighting and exploring chronic kidney disease symptomatic triggers, uremic toxins generation and utilization of strain specified probiotic therapeutically approach exploring its significant efficiency through a wide range of randomized controlled trial analysis within chronic kidney disease patients (CKD) on HD and PD therapy which significantly reported low inflammatory biomarkers and improved dysregulated intestinal microbiota, increased uremic toxin excretion (IS and PCS), improved homeostatic regulatory mechanism and quantifies health furthermore delaying the progression towards kidney failure emerging probiotic approach as a new therapeutically CKD management tool.

INTRODUCTION

Chronic Kidney Disease (CDK) is characterized by gradually progressive decrease in kidney structure and function may arises from any one or more of these underlying conditions as (1) GFR less than 60 mL/min/1.73 m2; (2) albuminuria (i.e, urine albumin ≥30 mg per 24 hours or urine albumin-to-creatinine ratio [ACR] ≥30 mg/g); [1], renal tubular disorders; or (3) history of kidney transplantation; (4) or inflammatory biomarkers of progressive renal malfunctioning such as proteinuria, erythrocyturia, or frequent malformations diagnosed through scanning and labs testing being persistent and underlying for maximum of 3 months [2], Glomerular filtration rate (GFR) presents as a substantially significant variable which diversified CKD into five stages based on GFR [3]. Chronically progressive renal malfunctioning generally advances gradually, even though the vast majority of individuals affected remain

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asymptomatic until the disease progresses and the condition worsens, with anticipated GFR progressing to 30 mL/min per 1.73 m2. Kidney structural dysfunction and impairment entail prolonged periods of time of several months and years [4].

Emerging Role of Probiotics

Probiotics conceptual commencement was first put forward in the year XX with Metchnikoff's investigation [5], In accordance with (ISAPP), "Probiotics are referred as biologically active microbes, that when delivered in an appropriate proportion, offered health advantages to the host and are capable to endure the digestive system (GIT), and improves or restores intestinal microbial equilibrium" Lactobacillus Acidophillus, Streptococcus thermophiles with Bifidobacteria longum considered the most frequently researched probiotics [6, 7](Figure 1).

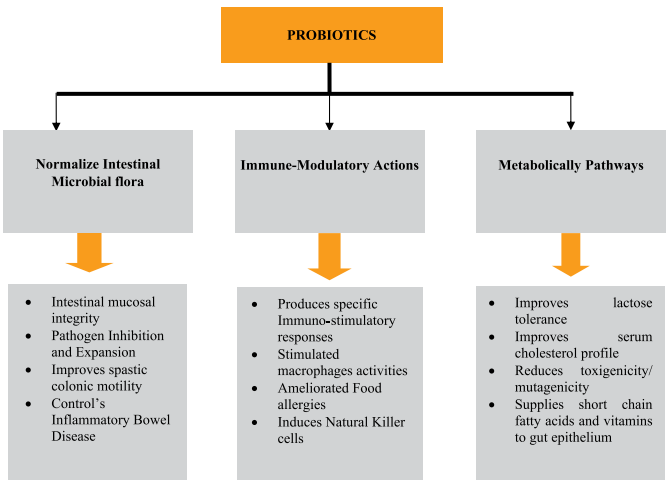

Figure 1: Probiotics Mechanism of Action on Health

Several probiotics have anti-inflammatory advantageous implications as follows: [8] Improved gut mucosa by enhancing gastric mucosal integrity, Microbicide peptidases (AMP's) and probiotic's associated defensive mechanisms, Anti-inflammation impact as well as enhanced immunological response and Competing for micronutrients and bile acids metabolically reactions [9]. There are various sources of probiotics [10](Figure 2).

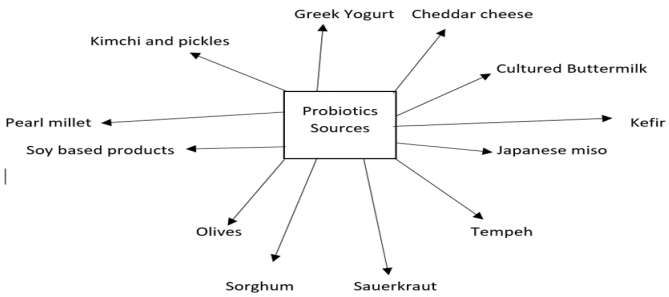

Figure 2: Sources of Probiotics

Probiotics and CKD

Probiotics administration to patients having chronic kidney disease aimed at removing URS, which is the end product of protein metabolism, and lowering the transformation of amino acids into TMAO. Probiotic supplemental therapeutic intervention resulted in p-cresol excretion, potentially reducing the plasma p-cresol levels within hemo-dialysis patients [11]. An experimental analysis demonstrated five-week probiotic therapeutic intervention reduces indoxyl glucuronidase activity in maintained hemodialytic patients (MHD) [12, 13]. Additionally, probiotics' supplementation to eight MHD patients was administered in the form of oral *L. Acidophilus* for 1 to 6 months reduces serum dimethylamine as well as nitrosodimethylamine levels, two significant potential URS that potentially increase CKD mortality [14]. Recent demonstration that probiotic supplementation probably mitigated chronic inflammatory consequences where inflammatory biomarkers negatively correlated with Kidney functioning [15]. Chou *et al.* demonstrated that therapeutic interventional treatment with probiotics within a mouse model increases short-chain fatty acids (SCFAs) within the plasma cells and protects mice from acute kidney injury (AKI) associated with ischemia reperfusion by modulating the gut macrobiotic inflammatory reactions [16]. Natarajan and his colleagues in the year 2014 noticed a decline in the C-reactive protein levels within twenty-two maintained hemodialytic patients (MHD) only after therapeutic interventional supplementation with probiotics for 50 days [17]. In view of the validation of its probable efficacy in an experimental human model, a double-blinded multi-centered trial on forty-two patients with CKD(stage III-IV)showed that the probiotic cocktail resulted in a substantial decrease in blood urea percentiles with probable reduction in plasma creatinine levels, which was additionally observed [18, 19]. Probiotics mechanism of cascade focuses on restoring gut motility by modifying disrupted gut microbial flora, by modulating GIT tract sensations, as well as improving motility movements associated with bowel functions within the gut tract of CKD patients [20]. Different studies were conducted on the probiotic strain against CKD(Table 1).

Table 1: Review of Clinical Experimental Analysis of Probiotic Supplementation as a Targeted Therapeutic Approach Against CKD

Probiotic Strain	Study Type	Dosages	Participants	Treatment Duration	Outcomes/Remarks	References
L.Acidophilus, B. bifidium, Prebiotic inulin fiber, Omega 3 fatty acids (B-vitamins and VitaminE)	Randomized Experimental Human Research Analysis	Nutri-health (1 capsule each day), 2.0× 1012 CFUs	Eighteen patients with CKD (Stage 1-3)	Eight Weeks	Probiotic supplementation was effective in improving glomerular filtration rate (GFR) and strengthening healthy bacterial colonies *(B. bifidium)*	[21]

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L. Acidophilus, L. Casei, L. Lactis, B. bifidum, and *B.infantis*	Randomized Experimental Human Clinical Research Study	Probiotic sachets 6 × 1010 CFUs (2 times each day; morning and evening in 250ml of water taken with meals.	Hundred patients with CKD (Stage 1-3)	Twelve weeks	Probiotic supplementation is effective in dramatically reducing BUN and creatinine levels within overweight and obese individuals with high blood urea profiles, and RFTs and LFTs analysis verified no serum toxicity.	[22]
L. casei, L. cidophilus, L. bulgarigus, L. rhamnosus, B. breve, B. longum, S. thermophilus, and fructo-oligosaccharide	Randomized Experimental Clinical Research Analysis	Familact (500mg) (2 capsules each day after meal)	Sixty-six patients with CKD stage III–IV	Six weeks	Symbiotic probiotic treatment resulted in a notable reduction in mean blood urea levels in patients with CKD stage III, with no serum toxicity verified	[23]
L.acidophilus, B. bifidium, Inulin, Fructo-and galacto-oligosaccharidases	Randomized Experimental Clinical research study	(a) Initial twenty-one days' Interventional phases: (7 g of prebiotic powder + 1 probiotic tablet in the morning with a meal). (b) Last twenty-one days Interventional phases: (7 g of prebiotic powder + 1 probiotic tablet at night with meals)	Thirty-one patients with CKD	Eighteen weeks	Probiotic-mediated symbiotic approach effectively resulted in statistically noteworthy and probably potential clinical reduction in blood serum levels of Indoxyl Sulfate and p-cresyl sulphate within CKD patients	[24]
L.bulgaricus and *S. thermophilus*	Cross-sectional transverse research analysis	Probiotic yogurt (1 time each day)	Eight Hundred and Eighty-eight Patients with CKD stage (III-V)	Five years	Probiotic-supplemented yogurt markedly reduces inflammatory markers (CRP, fibrinogen, and coagulation factor VIII) within CKD patients	[25]

Probiotics' Effectiveness in Patients with Dialysis (Stage 5D)

Due to the exaggerated decline of residual renal functionality, ESKD symptomatic consequences, along with dialysis complications, could trigger dysbiotic intestinal microflora. Consequently, various investigations evaluated the implications of probiotic therapy in individuals with PD or HD. Constipation-associated dysphasia, causing irregular bowel motility, is a frequently experienced symptomatic sign within patients with HD (62.5%) or PD (28.9%) [26]. Slow transit constipation with bowel obstruction via the gastrointestinal tract causes Blind-loop syndrome (bacterial overgrowth within the stools), which plays a triggering role in the genesis of the dysbiotic gut microflora. Luo *et al.* and Hu *et al.* evaluated and correlated gut microflora genomic sequences of 16S Ribosomal ribonucleic acid within healthy subjects, CKD patients (stage I-III), CKD patients (HD and PD), among the Chinese population. Notably significant distinction within intestinal microbial diversification before and following dialysis, and conclusively figured out that patients with HD and PD are hindered metabolic, inter- and intra-cellular signalling pathways [27, 28]. The randomized control research trial analysis of probiotic therapy within HD and PD patients presented (Table 2).

Table 2: Review of Clinical Trial Analysis of Probiotic Supplementation in Patients with Maintained Hemodialysis and Peritoneal Dialysis

Probiotic Strain	Study Type	Dosages	Participants	Treatment Duration	Outcomes/Remarks	References
L.acidophilus and *B. bifidum*	Double-blinded, placebo-controlled, randomized allocated research analysis	Probiotic supplementation forming 2×109 CFU's	Sixty-two subjects within two intervention groups (Experimental group n=Forty CKD patients on (HD); Control group n=Twenty-two healthy volunteers)	Thirty-five days	Probiotic supplemental therapy is effective in improving dysbiotic intestinal microflora, reducing fecal uremic toxicants (IS), and strengthening glomerular filtration rate (GFR) within CKD patients.	[29]
S.thermophilus, L. acidophilus and *B. longum*	Randomly allocated, double-blinded, prospective analysis	RenadylTM forming 30 billion CFU's (2 capsules 3 times each day with meals)	Twenty-two patients with CKD on HD therapy	Six months	Probiotic supplemental therapy efficiently displayed noticeable improvement in symptomatic gastrointestinal disturbances (IBS and IBD) and possesses a marked reduction in inflammatory bio-markers (IL-6 and IL-18) stabilizing QOL appropriately, validating its use for ESKD patients undergoing HD therapy	[30]

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B. bifidum BGN4 and *B. longum BORI*	Randomly allocated, double-blinded, control analysis	Robiotic supplemental strains forming 2.0 ×1010 CFUs (2 times/day)	Twenty-two patients with CKD on HD therapy	Three months	Probiotic therapeutic regimen efficiently enhances systemic anti-inflammatory responses, with the regulatory T-cells' action potential possessing a probable decline in pro-inflammatory phagocytic leukocyte production within the CKD patients.	[31]
B.longum, L. bulgaricus, and *S. thermophilus*	Randomly allocated control analysis trial	Probiotic therapeutic supplementation forming 1 × 109 CFUs (2 times/day)	One hundred and sixteen patients with CKD on PD therapy	Two months	Probiotic supplementation efficiently reduces malnourishment scores, decreases inflammatory bio-markers (IL-6), subsequently lowering fecal uremic toxicants (IS) and stabilizing QOL within PD patients	[32]
L. acidophilus and *B. lactis* + prebiotic (inulin)	Multi-centered, double-blinded, placebo-controlled research analysis	Synbiotic Gel/ placebo therapy	Forty patients (2 groups of 20 patients each) with CKD on HD therapy	Two months	Synbiotic supplementation therapy efficiently improves GIT tract symptomatic disturbances, reduces inflammatory biomarkers (Plasma C-reactive proteins), and improves quality of life within CKD patients.	[33]

Future Prospects of Probiotic Therapy

Probiotics' propensity to adhere to gastrointestinal cellular epithelium and their microbicide efficiency has been analyzed within in-vitro studies showing a positive probable effect with the dosage range of 16 × 109 CFU to 2.0 × 1012 CFU within uremic rats and human trial analysis [12]. L. plantarum supplementation for eight weeks has been shown to considerably decrease the oxidized glutathione quantities within hyperglycemic patients having a GFR of more than >90 mL per minute and albuminuria of more than 300mg per day [34]. Probiotic treatment with B. pasteuri and L. sporogenes within a mouse model decreases significant levels of blood urea nitrogen and serum creatinine percentiles [35]. Future trends of using probiotics entailed a vast array of experimental clinical trial demonstrations owing to its markable positive health implication within CKD patients thus potentially improving intestinal integrity, modulating gut motility, increases fecal uremic toxins excretion and reduces endo-toxins levels and pro-inflammatory biomarkers further strengthening gastro-intestinal permeability, bowel motility, preserving residual kidney functionality within patients with permanent kidney disease outlined probiotic supplementation as promising therapeutically functional approach for patients with Chronic Kidney disease in near future.

CONCLUSION

Chronic renal disease triggers progressive decline of renal structural and functional capabilities owing to decreased glomerular filtration rates, which causes excessive accumulation of uremic toxicants within the blood that significantly contributes to End-stage renal disease. Recent research based on in-vitro and in-vivo experimental trials with probiotic supplemental therapy markedly reduces pro-inflammatory cytokines, improves gut dysbiosis and irregular bowel movements, frequently attenuating kidney fibrosis lesions and scarring, presenting as a promising therapeutic interventional approach within the CKD populace. However, additional research investigations of various strain-specific probiotic treatment trials on a larger scale within hemodialysis and peritoneal dialysis patients with chronic kidney disease, primarily evaluating therapeutic outcomes, are further needed to comprehend the role of dysbiotic microbiota and Chronic kidney disease-related complications within HD and PD patients.

Authors Contribution

Conceptualization: SI, MKN
Methodology: FH, MAI, NA
Formal analysis: SI, MKN
Writing review and editing: SI, NA, ZS, SG, NFA, MKN, QAS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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