Protective Effect of Probiotic Against Progression of Chronic Kidney Disease: A Randomized Clinical Study

Waleed Khaild Rahman[1], Ihsan Salah Rabea[2], Mudhfar Mohammed Meizel[3]

[1]Al-Diwaniyah Health Office, Ministry of Health and Environment, Al-Diwaniyah, Iraq, [2]Department of Clinical Pharmacy, Faculty of Pharmacy, University of Kufa, Al-Najaf, Iraq, [3]Department of Medicine, Medical College, Alqadisiyah University, Al-Diwaniyah, Iraq

Abstract

Background: Chronic kidney disease (CKD) is a gradual, irreversible disease with severe global health implications. By raising the level of urea toxins in the body, gut microbiota dysbiosis may hasten the onset of chronic renal disease. Probiotics have been recognized to keep the intestinal microbiota's physiological equilibrium. In an effort to develop alternatives to chronic hemodialysis, much research has been carried out, especially for elderly patients who face psychological challenges. **Objectives:** The goal of this study is to assess the therapeutic benefits of probiotics on CKD patients. **Materials and Methods:** This randomized clinical trial was carried out at the Dialysis Center of Al-Diwaniyah Medical Hospital in Diwaniyah Governorate. Forty-two patients with end-stage renal disease on regular hemodialysis were enrolled, with 21 patients receiving oral probiotic supplementation in addition to standard care, and 21 patients receiving only standard care. Blood samples were collected at the baseline and after eight weeks, and several biomarkers were measured, including estimated glomerular filtration rate, creatinine, urea, phosphorus, albumin, and indoxyl sulfate. **Results:** The results showed that there was a significant difference in the mean difference of blood urea (P = 0.008) and serum phosphorus (P = 0.004) among groups, and the significant level was attributed to the probiotic group. However, the other biomarkers were not affected by the treatment. **Conclusion:** The use of oral probiotics for 8 weeks in Iraqi patients on hemodialysis can improve urea and phosphorus levels and safeguard the intestinal epithelial barrier in CKD patients.

Keywords: CKD, dysbiosis, phosphorus, probiotics, urea

Introduction

Chronic kidney disease (CKD) is characterized by signs of structural or functional renal impairment for 3 months or more with negative effects on health; typically, it affects several metabolic pathways and progresses in an irreversible manner.[1] The major result of CKD is end-stage renal disease (ESRD), which has a considerable impact on health-related quality of life and utilization of medical assistance.[2] CKD is characterized by structural damage to nephrons that cannot be reversed.[3] It is manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (eGFR) that persists for more than 3 months and can progress to ESRD necessitating renal replacement therapy (RRT).[4,5]

A significant public health issue on a global scale is CKD. It raises the danger of cardiovascular disease and causes death.[6] The estimated global prevalence of CKD is 8%–16%, with the highest rates observed in the UK and Singapore (both 16%), while in the United States, CKD affects 15% of the adult population, with approximately 1.9 million individuals receiving RRT.[7]

In CKD, progressive damage or loss of functioning nephrons can occur due to primary kidney disease, secondary complications of systemic disorders such as hypertension or diabetes mellitus, or acute kidney injury resulting in irreversible damage. The colon adapts as the major excretory organ to maintain body homeostasis

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Address for correspondence: Dr. Waleed Khaild Rahman, Al-Diwaniyah Health Office, Ministry of Health and Environment, Al-Diwaniyah, Iraq.
E-mail: ph.waleedkhaild99@gmail.com

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in CKD, leading to severe consequences for the gut environment. Accumulation of serum urea during CKD increases urea influx into the intestinal lumen, where urease-producing bacteria hydrolyze it into ammonia and ammonium hydroxide, resulting in increased intestinal pH, mucosal irritation, and structural alterations to the gut barrier.[8,9] The damaged "leaky gut" allows translocation of bacteria and toxins into the systemic circulation, promoting chronic inflammation, adverse cardiovascular outcomes, and CKD progression.[10-13]

Additionally, a number of elements, including nutritional consumption, emotional stress, and drugs, might affect how CKD progresses.[14] The role of the gut microbiota in the onset and progression of CKD was recently discovered.[15] Urea toxins, such as indole-3 acetic acid, p-cresyl sulfate (PCS), and indoxyl sulfate, which disrupt epithelial tight junctions and enhance intestinal wall permeability via endotoxemia and systemic inflammation,[16] are increased by intestinal microbiota dysbiosis.[17] In turn, renal endothelial dysfunction, fibrosis, and tubular damage are brought on by intestinal endotoxins, which may pass through the intestinal wall and enter the bloodstream, promote microinflammation in the kidney, and speed up the loss of renal function.[18,19]

Probiotic supplementation has been more popular as an adjuvant therapy for CKD in recent years due to its affordability and patient acceptability. Many researchers have examined whether probiotics can reduce the progression of CKD by controlling the modification of the gut flora and lowering the urea toxin. However, the treatment regimens of probiotics varied among many randomized controlled studies (RCTs).

Probiotics have been shown to reduce inflammatory biomarkers in CKD patients, according to some researchers,[20] whereas others found no discernible differences.[21] It is challenging to directly compare studies because of a multitude of confounding factors, including sample size, strain diversity, and treatment duration. Therefore, a strategy based on evidence-based research is required to assess the therapeutic effects of probiotics on CKD. Trials have been conducted to limit the influx of uremic toxins from the intestine, which may potentially decrease CKD progression.[22]

The aim of the present study is to assess the therapeutic benefits of probiotics on CKD patients.

Materials and Methods

A randomized clinical study was conducted at the Dialysis Center of Al-Diwaniyah Medical Hospital, Diwaniyah Government in Iraq, spanning from October 1, 2022, to January 20, 2023. The study enrolled 42 patients with ESRD who were undergoing regular hemodialysis. Of these, 21 patients were assigned to receive oral supplementation with probiotic from Desma company in addition to standard care, whereas the other 21 patients received only standard care. Blood samples were collected at baseline and after 8 weeks to measure parameters such as eGFR, creatinine, urea, phosphorus, albumin, and indoxyl sulfate. Data were recorded using a data extraction sheet. Clinical trial registration No. NCT05540431.

The primary objective of the study was to investigate whether there is a significant association between renal function tests and the use of probiotic. As a secondary objective, the present study explored whether demographic characteristics had any impact on the protective effect of probiotic. The inclusion criteria for the study were patients aged >18 and <75 years old, who had been on regular hemodialysis for at least 1 month, of both genders, able to communicate in Arabic language or through their caregiver, and able to provide informed consent. Patients who did not meet these criteria were excluded from the study.

Ethical approval

Ethical approval was obtained from the Scientific Committee at the Faculty of the Pharmacy, University of Kufa registration number 30\4847\2022, Al-Diwaniyah general health institution, and the nephrology centers in Al-Diwaniyah Teaching Medical General Hospital. Written consent was obtained from all patients prior to the commencement of the study.

Statistical analysis

Statistical analysis was performed using the statistical package for social sciences (SPSS) version 23 and Microsoft Office Excel 2010. Categorical variables were expressed as numbers and percentages, whereas quantitative variables were evaluated for normality distribution using the Kolmogorov–Smirnov test. Normally distributed numeric variables were expressed as mean and standard deviation, whereas non-normally distributed numeric variables were expressed as median and inter-quartile range. The following statistical tests were used: (1) Chi-square test for association between categorical variables when less than 20% of cells had expected counts of less than 5, (2) independent samples *t* test for difference in means between two groups when numeric variables were normally distributed, or Mann–Whitney *U* test for non-normally distributed variables, and (3) paired *t* test to compare means before and after treatment. Overall, the study utilized rigorous statistical analysis to analyze the collected data.

Results

Out of 100 dialysis patients screened for eligibility, only 42 patients met the inclusion criteria and 28 of them were enrolled in the study. Of the remaining 14 patients, 5 did not complete the study, 3 were noncompliant, 3 were lost

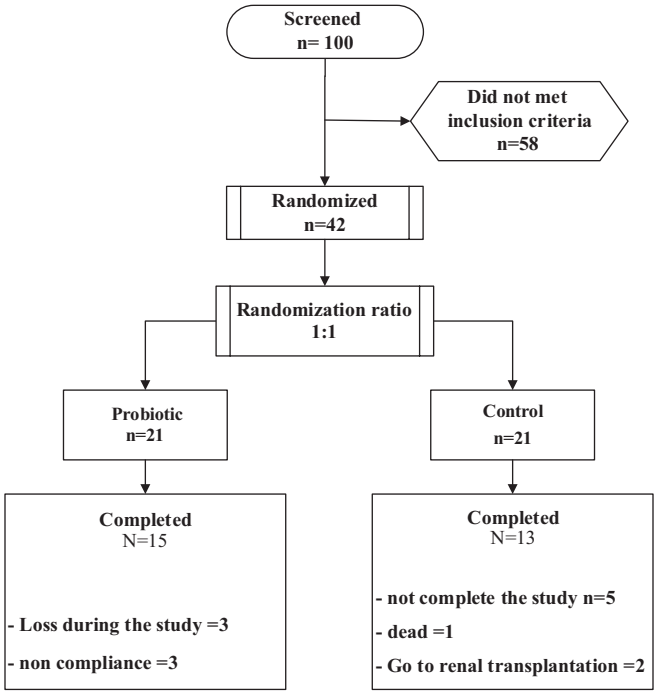

Figure 1: Patient distribution in the study. *N* represents the number of patients

during the study, 2 were scheduled for transplantation, and 1 patient died during the study period, as presented in Figure 1.

The study [Table 1] presents the general characteristics of patients enrolled. The mean age for the control group and probiotic group were 46.08 ± 12.79 years and 45.47 ± 16.43 years, respectively (P = 0.915), with no significant difference. There was also no significant difference in the duration of dialysis since onset for the control group and probiotic group, which were 4 (4.5) years and 4 (6) years, respectively (P = 0.742). Mean length of dialysis sessions for the control group and probiotic group were 3.12 ± 0.36 h and 3.23 ± 0.37 h, respectively (P = 0.405), and the frequency of sessions per week showed no significant difference between groups, with 2.77 ± 0.73 and 2.93 ± 0.46, respectively (P = 0.474). The proportion of males in the control group and probiotic group was higher than that of females, but there was no significant difference in gender distribution (P = 0.778). Table 1 shows the frequency distribution of patients according to body mass index. However, there was no significant difference in residency distribution between the control group and probiotic group (P = 0.750). The

Table 1: General characteristics of patients enrolled in the present study

Characteristic	Control group *n* = 13	Probiotic group *n* = 15	*P*
Age (years)			
Mean ± SD	46.08 ± 12.79	45.47 ± 16.43	0.915 I
Range	25–63	20–69	NS
Duration since dialysis (years)			
Median (IQR)	4 (4.5)	4 (6)	0.742 M
Range	1–10	1–13	NS
Session length (h)			
Mean ±SD	3.12 ± 0.36	3.23 ± 0.37	0.405 I
Range	2.5–4	3–4	NS
Sessions per week			
Mean ± SD	2.77 ± 0.73	2.93 ± 0.46	0.474 I
Range	1–4	2–4	NS
Gender			
Male	8 (61.5%)	10 (66.7%)	0.778 C
Female	5 (38.5%)	5 (33.3%)	NS
BMI (kg/m^2)			
Underweight	6 (46.2%)	3 (20.0%)	†
Normal weight	4 (30.8%)	11 (73.3%)	
Overweight	2 (15.4%)	0 (0.0%)	
Obese	1 (7.7%)	1 (6.7%)	
Residency			
Urban	2 (15.4%)	3 (20.0%)	0.750 C
Rural	11 (84.6%)	12 (80.0%)	NS
Education level			
Illiterate	5 (38.5%)	4 (26.7%)	†
Primary	7 (53.8%)	7 (46.7%)	
Secondary	0 (0.0%)	0 (0.0%)	
Tertiary	1 (7.7%)	4 (26.7%)	

n: number of cases, **SD**: standard deviation, **IQR**: inter-quartile range, **BMI**: body mass index, **I**: independent samples *t* test, **M**: Mann–Whitney *U* test, **C**: Chi-square test, **NS**: not significant, †: more than 20% of cells have an expected count of more than 5

frequency distribution of patients according to education level is also presented in Table 1.

Table 2 displays the frequency distribution of patients and control subjects based on smoking and chronic medical illnesses. Control group and probiotic group had 1 (7.7%) and 4 (26.7%) smokers, respectively. The control group had 8 (61.5%) cases of essential hypertension, whereas the probiotic group had 13 (86.7%) cases. Urinary tract infection was found in 3 (23.1%) and 3 (20.0%) of the control group and probiotic group, respectively. Diabetes mellitus was found in 4 (30.8%) and 5 (33.3%) of the control group and probiotic group, respectively. Control group had 3 (23.1%) cases of ischemic heart disease while the probiotic group had 1 (6.7%). Control group had 1 (7.7%) case of heart failure while the probiotic group had 2 (13.3%). Renal stone was found in 1 (7.7%) of the control group while the probiotic group had none. The control group had 1 (7.7%) case of epilepsy while the probiotic group had none. Benign prostatic hyperplasia was found only in probiotic group 2 (13.3%).

Table 3 displays the biochemical parameters prior to the initiation of treatment. The baseline eGFR showed no significant difference between the control and probiotic groups, 6.54 ± 2.03 and 6.13 ± 2.07 mL/min/1.73 m^2, respectively ($P = 0.606$). Baseline blood urea was also not significantly different among the control and probiotic groups, 131.15 ± 32.85 and 133.93 ± 29.45 mg/dL, respectively ($P = 0.815$). However, no significant difference was observed in baseline serum creatinine between the two groups, control and probiotic groups, 8.98 ± 1.55 and 9.54 ± 2.17 mg/dL, respectively ($P = 0.444$).

Furthermore, baseline serum albumin showed no significant difference between the control and probiotic groups, 3.46 ± 0.39 and 3.63 ± 0.33 g/dL, respectively ($P = 0.219$). Additionally, no significant difference was observed in baseline serum phosphorous between the control and

Table 2: The frequency distribution of patients and control subjects according to smoking and chronic medical illnesses

Characteristic	Control group *n* = 13 (%)	Probiotic group *n* = 15 (%)	*P*
Smoking	1 (7.7)	4 (26.7)	†
Essential hypertension	8 (61.5)	13 (86.7)	†
Urinary tract infection	3 (23.1)	3 (20.0)	†
Diabetes mellitus	4 (30.8)	5 (33.3)	†
Ischemic heart disease	3 (23.1)	1 (6.7)	†
Heart failure	1 (7.7)	2 (13.3)	†
Renal stone	1 (7.7)	0 (0.0)	†
Epilepsy	1 (7.7)	0 (0.0)	†
Benign prostatic hyperplasia	0 (0.0)	2 (13.3)	†

n: number of cases, †: more than 20% of cells have an expected count of more than 5

Table 3: Biochemical parameters before starting treatment

Characteristic	Control group *n* = 13	Probiotic group *n* = 15	*P*
Estimated GFR (mL/min/1.73 m^2)			
Mean ± SD	6.54 ± 2.03	6.13 ± 2.07	0.606 I
Range	4.00–11.00	3.00–11.00	NS
Blood urea (mg/dL)			
Mean ± SD	131.15 ± 32.85	133.93 ± 29.45	0.815 I
Range	77.00–183.00	100.00–195.00	NS
Serum creatinine (mg/dL)			
Mean ± SD	8.98 ± 1.55	9.54 ± 2.17	0.444 I
Range	6.75–11.43	6.25–13.92	NS
Serum albumin (g/dL)			
Mean ± SD	3.46 ± 0.39	3.63 ± 0.33	0.219 I
Range	2.70–4.10	3.10–4.20	NS
Serum phosphorus (mg/dL)			
Mean ± SD	4.82 ± 1.36	5.93 ± 2.27	0.134 I
Range	2.40–7.90	2.40–10.10	NS
Serum indoxyl sulfate (ng/mL)			
Mean ± SD	519.18 ± 139.17	547.96 ± 138.56	0.589 I
Range	184.50–760.37	300.42–825.18	NS

n: number of cases, **SD**: standard deviation, **GFR**: glomerular filtration rate, **I**: independent samples *t* test, **NS**: not significant

Table 4: Comparison of the mean difference (post-value minus pre-value) of biochemical markers between the probiotic group and the control group

Characteristic	Control group *n* = 13	Probiotic group *n* = 15	*P*
Estimated GFR			
Mean ± SD	0.08 ± 2.72	-0.27 ± 1.49	0.676 I
Range	-6.00 to 4.00	-4.00 to 2.00	NS
Blood urea			
Mean ± SD	47.33 ± 41.73	1.45 ± 41.89	0.008
Range	-63.92 to 99.00	-50.00 to 120.00	I**
Serum creatinine			
Mean ± SD	1.09 ± 4.71	0.50 ± 1.16	0.669 I
Range	-2.39 to 14.53	-1.57 to 2.06	NS
Serum albumin			
Mean ± SD	0.49 ± 0.73	0.19 ± 0.41	0.176 I
Range	-1.11 to 2.02	-0.50 to 1.00	NS
Serum phosphorus			
Mean ± SD	1.30 ± 2.37	-0.87 ± 1.20	0.004
Range	-3.61 to 5.90	-2.80 to 0.40	I**
Serum indoxyl sulfate			
Mean ± SD	-93.42 ± 166.82	-166.35 ± 188.66	0.292 I
Range	-436.05 to 195.78	-454.38 to 236.58	NS

n: number of cases, **SD**: standard deviation, **I**: independent samples *t* test, **NS**: not significant, **: significant at $P \leq 0.01$

probiotic groups, 4.82 ± 1.36 and 5.93 ± 2.27 mg/dL, respectively ($P = 0.134$). Lastly, there was no significant difference in baseline serum indoxyl sulfate between the control and probiotic groups, 519.18 ± 139.17 and 547.96 ± 138.56 ng/mL, respectively ($P = 0.589$).

Table 4 shows the comparison of the mean difference of post-value from pre-value in serum levels of biochemical markers among groups. There was no significant difference in mean difference of eGFR among the groups ($P = 0.676$). However, there was a significant difference in the mean difference (1.45 ± 41.89) of blood urea among groups, with the probiotic group showing the highest reduction level ($P < 0.01$). There was no significant difference in mean difference (0.50 ± 1.16) of serum creatinine ($P = 0.669$) or serum albumin ($P = 0.176$) among the groups. There was a significant difference in mean difference of serum phosphorus, with the probiotic group showing the highest reduction level ($P = 0.004$). Finally, there was no significant difference in mean difference of serum indoxyl sulfate among the groups ($P = 0.292$).

Discussion

This study aimed to investigate if oral probiotic could decrease uremic toxins and improve renal function tests in patients with ESRD undergoing regular hemodialysis. The present study compared eGFR, serum urea, creatinine, serum albumin, serum phosphorus, and indoxyl sulfate levels in the groups at baseline and after eight weeks of follow-up.

In the probiotic group, there was a significant decrease in serum urea and phosphorus throughout the follow-up period ($P \leq 0.01$). Our findings were supported by previous studies by Miranda Alatriste *et al.*[23] and Mady *et al.*,[24] which also reported a decrease in urea and phosphorus levels respectively.

It is well known that the kidneys cannot excrete waste products such as urea and creatinine in ESRD. Instead, their excretion relies mainly on hemodialysis procedures.[25] As urea has a lower molecular weight than creatinine, it needs less hemodialysis time to be dialyzed.[26] This could explain the nonsignificant decrease in creatinine levels in both groups. Five studies[20,27-30] with 126 subjects who received the probiotics supplementation and 124 subjects who received placebos reported changes in serum creatinine. After probiotic supplementation, no significant changes were found between the probiotic and placebo groups. Studies of Pavan[28] and Rossi[30] had a larger weight in the analysis of serum creatinine. However, no significant differences of serum creatinine were found in subgroup analyses.

Regarding albumin levels, most ESRD patients suffer from hypoalbuminemia due to several reasons such as a low-protein diet, protein loss through urine, and dialysate, especially with high flux filters. However, the current study found a nonsignificant decrease in albumin levels. This could be due to the frequent monitoring of albumin levels in both groups, and intravenous albumin treatment was administered to patients with hypoalbuminemia. Additionally, the majority of dialysis patients suffer from malnutrition associated with anorexia and poor protein intake.

The study also revealed an increase in eGFR in the control group and a decrease in the probiotic group,

but the changes did not reach significant levels in either group. These insignificant changes may be due to the need for longer durations of probiotic use to show beneficial effects or the need for a larger sample size.

Chronic kidney disease is characterized by renal function deterioration that causes a progressive retention of a large amount of various uremic toxins. The uremic toxin indoxyl sulfate is difficult to remove by regular hemodialysis, and even hemodiafiltration has limited success in removing it.[31,32] Methods such as decreasing the indoxyl sulfate concentration on the dialysate side, increasing the flow rate of the dialysate, and increasing the size of the dialyzer can be used, but their clinical efficacy is unclear.[33,34] Limiting protein intake can reduce indoxyl sulfate production, and a low-protein diet supplemented with ketoanalogues has been shown to decrease serum indoxyl sulfate levels.[35,36]

Furthermore, the study revealed a decrease in indoxyl sulfate levels in the control group and probiotic group, but the changes did not reach significant levels in either group. These insignificant changes may be due to the need for longer durations of probiotic use to show beneficial effects or the need for a larger sample size.[37]

The current study has several limitations. Firstly, the sample size was restricted as only a small number of patients met the inclusion criteria out of a total of 100 patients in the center. Secondly, the study was open-label due to concerns about gastrointestinal upset, which may have influenced the tolerability and adverse effects. Thirdly, the study was novel with few comparable studies or references. Finally, the study was conducted in a single center and cannot be generalized the results to all centers treating hemodialysis patients in Iraq.

In conclusion, oral probiotic showed promise in reducing uremic toxins in Iraqi patients on maintenance hemodialysis, but larger, longer-term studies with multiple centers and a greater number of patients are needed to confirm its nephroprotective effect. Further research is also needed to determine its potential benefits in pre-dialyzed patients.

Availability of data and materials

The corresponding author can provide access to the database upon reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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