Synbiotic Supplementations for Azotemia in Patients With Chronic Kidney Disease

A Randomized Controlled Trial

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Introduction. Chronic kidney disease (CKD) is a progressive and irreversible impairment of kidney function; if it progresses to the end-stage of CKD, dialysis or kidney transplant is needed. In general, there are no definitive treatment to slow the progression of CKD. This study aimed to determine the effect of synbiotic supplementations on azotemia in patients with CKD.

Materials and Methods. A randomized controlled trial was conducted on 66 patients with CKD (stages 3 and 4). The participants were randomly divided into 2 groups to receive synbiotic supplement, 1000 mg/d, and placebo (2 capsules a day) for 6 weeks. At the beginning and end of the study, blood parameters and kidney function were evaluated.

Results. Of the 66 patients studied, 16 patients (24.2%) were women and 50 (75.8%) were men. The mean age and body mass index of the participants were 61 ± 7.65 years and 28.52 ± 4.06 kg/m^2, respectively. The level of blood urea nitrogen showed a significant reduction following the intake of synbiotic supplement (from 40.80 ± 22.11 mg/dL to 36.14 ± 20.52 mg/dL, P = .01). Serum creatinine, uric acid, and other indicators of kidney function showed no significant change.

Conclusions. The intake of synbiotic supplement could reduce blood urea nitrogen in patients with CKD in stages 3 and 4; however, it had no effect on the other markers of kidney function.

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INTRODUCTION

Chronic kidney disease (CKD) is an irreversible progressive disorder, in which the body's ability to maintain the balance of fluids and electrolytes is lost. Other terms related to kidney failure include "azotemia," which means the accumulation of nitrogenous waste products in the blood, and "uremia," meaning azotemia associated with a clinical syndrome.[1] About 500 million people worldwide are suffering from CKD.[2-5] In Iran, the incidence of CKD was 18.9% based on a recent study performed on a large population of 10063 men over 20 years.[4,6] A rapid increase in the prevalence of CKD, high costs of treatment, and the major role CKD plays in the increased risk of cardiovascular diseases, all have led to the global attention and health care focus on CKD.[7-9]

At present, the most effective treatment for CKD and uremia is dialysis or kidney transplantation. Because of the high-cost, time consuming, and complex technology-dependent nature of renal replacement therapies, only 15% of uremic patients in the world have the ability to undergo dialysis, so that every year, 80000 Americans die due to

the different complications of dialysis. Also, due to the shortage of kidney donors, high costs of transplant surgery, and high risk of organ rejection, there is little chance for most patients worldwide to receive a kidney allograft.[5] Although limiting the protein content of the diet can also reduce the uremic toxins uremic symptoms, and complications of CKD,[1,10] protein-energy malnutrition, particularly hypoalbuminemia caused by it, can cause increased morbidity and mortality in these patients.[10-14]

Synbiotics are synergistic combinations of probiotics and prebiotics. Probiotics are live microorganisms that, if consumed by human or animal, by effecting on the intestinal flora, will create beneficial effects on the health of the host.[15-17] The main effect of probiotics is characterized by stabilization and adjustment of the intestinal flora.[16] Prebiotics are selective indigestible carbohydrated food sources that stimulate the growth and reproduction of bacteria such as *Bifidobacterium* and *Lactobacilus*.[18] In uremic patients, due to the intake of antibacterial drugs (absorbing phosphorous and potassium), abnormal bowel movements (as a result of fluid-restricted diet and lack of enough fiber in the diet due to food restriction), and abnormally high levels of urea and creatinine diffused into the bowel, the composition of the intestinal flora is disturbed. Hence, in these patients, more uremic toxins are produced by the intestinal bacteria.[13,19] It is believed that the probiotic bacteria including *Lactobacilus* and *Bifidobacterium* species, which produce lactic acid, are helpful to maintain the balance between the different species of microorganisms in the intestine. These bacteria produce organic acids that can reduce the pH of the gastrointestinal tract through inhibiting the sensitive bacteria to acids, such as enteric species, which produce urease enzyme.[19]

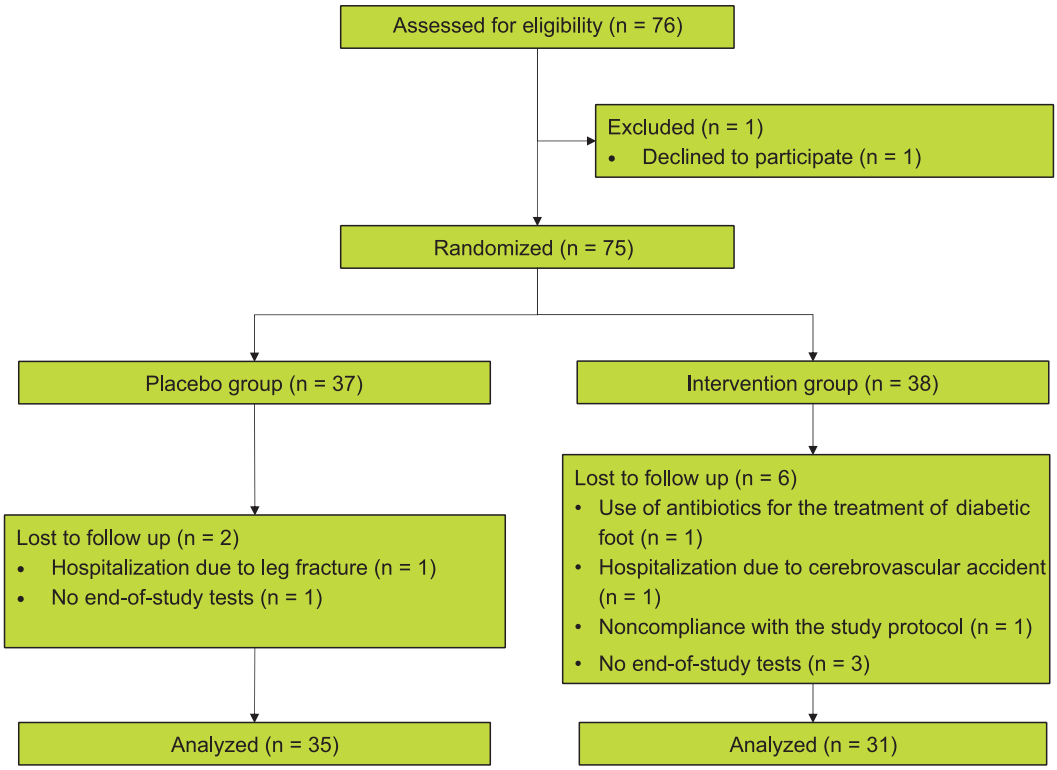
Ammonia production is reduced by blocking the activity of urease. On the other hand, ammonia has a weak base; thus, reducing the intestinal pH increases the ratio of ionized ammonia to nonionized ammonia and reduces the nonionic inactive diffusion. As a result, less ammonia is absorbed into the portal vein and is mainly excreted through the feces. In addition, the reduction of intestinal pH in turn reduces the decomposition of nitrogenous substances (proteins and amino acids), and decrease ammonia production.[20] Also, the activity of probiotics in the digestive tract leads to better digestion, increases the bio-availability, and enhances the nutritional value of some nutrients and vitamins.[15,21-23] Correction of micronutrients' status in the patients with CKD improves the quality of life in these people.[24] One way to slow down the progression of CKD is lowering the blood pressure and controlling the blood sugar in these patients.[25] The use of probiotics has beneficial effects on the blood pressure, lipid and glycemic profiles, and blood levels of inflammatory biomarkers, as well as the markers of kidney function. This can, therefore, slow down the progression of CKD and reduce cardiovascular complications as the main cause of death in these patients.[26,27]

Considering the increasing prevalence of kidney failure, concurrent with the increased prevalence of diabetes mellitus, hypertension, and atherosclerosis, and also a lack of human research in this regard, this study aimed to determine the effect of synbiotic supplement on azotemia in patients with CKD in order to prevent the progression of the disease along with pharmaceutical treatments.

MATERIALS AND METHODS

This study was a randomized controlled double-blinded clinical trial. The study population included patients with CKD, referring to the clinics affiliated with Yazd University of Medical Sciences (Yazd, Iran) in 2013. Inclusion criteria were an age between 35 and 75 years and suffering from CKD stage 3 or 4 (glomerular filtration rate [GFR], 15 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2). Exclusion criteria were as follows: pregnancy in women, use of antibiotics and lactulose 14 days before the start of the study, alcohol dependence, and hepatitis or HIV infection. Attrition criteria were the use of antibiotics and lactulose during the study and starting treatment with hemodialysis. The allocation flowchart of the present study is shown in the Figure.

During an early interview with the participants, a questionnaire about their general characteristics was completed that included data on sex, age, education, occupation, and underlying diseases. The weight of patients was measured using a Trillion balance with the accuracy of 100 g. The patients' height without shoes was measured using a stadiometer with the accuracy of 0.5 cm. The participants were divided into two groups of case and control. During the 6-week intervention, the case group received daily 2 Familact capsules



Study flowchart.

(Zist Takhmir, Tehran, Iran), 500 mg (containing 7 strains of probiotics; *Lactobacilus casei*, *Lactobacilus acidophilus*, *Lactobacilus bulgarigus*, *Lactobacilus rhamnosus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Sterptococus thermophilus*, and prebiotic Fructooligosaccharides), after the meal, and the control participants received daily 2 capsules of placebo, 500 mg. For blinding, placebo was produced in similar color and appearance of the supplement capsules, as well as the shape of packaging (Zist Takhmir, Tehran, Iran). To differentiate the two types of capsules, a small code was written on the box of the capsules ('A' or 'B'), and neither the patients nor the person delivering the capsule to the patients were informed of the codes and type of supplement capsules.

At the beginning and end of the study. The amounts of blood urea nitrogen, uric acid, and creatinine of serum and urine were measured by the colorimetric method using Biosystem diagnostic kits and an autoanalyzer (Prestige SPA Plus, Japan). The 24-hour urine volume was determined by a calibrated container. Then, the 24-hour urine creatinine clearance and GFR were calculated.[1]

Analysis of data was performed using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, IL, USA). A *P* value less than .05 was considered significant.

RESULTS

The total of 76 patients with CKD stages 3 and 4 were enrolled, of whom 66 (86.8%) completed the study, and 9 were excluded for reasons listed in Figure 1. Comparison of the frequency distribution of the characteristics of the participant in the case and control groups is shown in Table 1. There was no significant differences between the two groups in terms of the basic characteristics, including age and body mass index.

Table 2 indicates the results kidney function tests studied before the intervention in the case and control groups, which indicates no significant different between the two groups. The results of comparing the variables before and after the intervention for the two groups are indicated in Table 2. As shown, the mean blood urea nitrogen in the case group after the intervention has been reduced significantly ($P = .01$), but the mean serum creatinine, serum uric acid, creatinine clearance, and GFR before and after the intervention had no

Table 1. Characteristics of the Participants in the Intervention and Control Groups*

Characteristic	All	Intervention Group	Control Group	*P*
Age, y	61.00 ± 7.65	63.00 ± 6.52	60.00 ± 8.33	.09
Sex				
Female	16 (24.2)	8 (25.8)	8 (22.8)	
Male	50 (75.8)	23 (74.2)	27 (77.2)	.50
Employment				
Self-employed	8 (12.1)	3 (9.7)	5 (14.3)	
Unemployed	41 (62.1)	19 (61.3)	22 (62.9)	
Housekeeper	17 (25.8)	9 (29.0)	8 (22.8)	.76
Level of education				
Illiterate	17 (25.8)	10 (32.3)	7 (20.0)	
Primary school	25 (37.8)	11 (35.5)	14 (40.0)	
Middle school	5 (7.6)	2 (6.5)	3 (8.6)	
Diploma	14 (21.2)	6 (19.4)	8 (22.8)	
Academic	5 (7.6)	2 (6.5)	3 (8.6)	.34
Body mass index, kg/m^2	28.52 ± 4.06	28.75 ± 4.35	28.34 ± 3.84	.70
Underlying disease				
Diabetes mellitus	65 (98.5)	31 (100)	34 (97.1)	
Hypertension	55 (84.6)	26 (83.8)	29 (82.8)	
Hypperlipidemia	53 (80.3)	27 (87)	26 (74.2)	
Heart disease	6 (9.0)	3 (9.7)	3 (8.6)	
Gastrointestinal disease	4 (6.0)	2 (6.4)	2 (5.7)	.44
Chronic kidney disease stage				
Stage 3	45 (68.2)	21 (67.7)	24 (68.6)	
Stage 4	21 (31.8)	10 (32.3)	11 (31.4)	.57

*Values are mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.

Table 2. Kidney Function Parameters Before and After the Intervention in the Intervention and Control Groups

Parameter	Intervention Group			Control Group			*P* for Changes*
	Before	After	*P*	Before	After	*P*	
Blood urea nitrogen, mg/dL	40.80 ± 22.11	36.14 ± 20.52	.01	37.22 ± 21.95	39.62 ± 27.56	.17	.006
Serum creatinine, mg/dL	2.00 ± 0.70	1.90 ± 0.70	.07	2.15 ± 1.02	2.18 ± 1.14	.72	.15
Serum uric acid, mg/dL	5.89 ± 1.70	5.72 ± 1.49	.49	5.30 ± 1.00	5.51 ± 1.15	.13	.18
Creatinine clearance, mL/min /1.73 m^2	28.24 ± 13.32	32.96 ± 19.87	.08	33.46 ± 19.33	36.63 ± 20.52	.10	.62
Glomerular filtration rate, mL/min /1.73 m^2	41.35 ± 15.74	43.25 ± 17.49	.31	41.40 ± 16.91	39.51 ± 17.64	.32	.90

*Comparison of the intervention and control groups after the intervention

significant differences between the two groups.

Table 2 shows a significant reduction the in mean blood urea nitrogen (P = .006). There was also a negative net change in the mean serum creatinine and blood uric acid in the case group, and a positive net change in average of these variables in the control group. The net changes in the mean of creatinine clearance and GFR in both groups were positive; however, these changes were not significant in any of the two groups.

DISCUSSION

This study showed that taking a synbiotic supplement, 500 mg, twice daily for 6 weeks resulted in a significant reduction in the mean blood urea, compared to placebo. In 2 studies conducted by Ranganathan and colleagues, probiotic supplementation in patients with CKD led to significant reduction in blood urea nitrogen levels.[19,28] In the study of Liu and coworkers, significant reduction in venous ammonia levels was reported in the patients with hepatic encephalopathy after receiving the probiotic sachet (*Pediacoccus pentoseceus*, *Leuconostoc mesenteroides*, *Lactobacillus paracasei*, and *Lactobacillus plantarum*) together with fermentable bioactive fiber.[29] Another study by Ranganathan and colleagues on the effect of different probiotic diets on the improvement of

azotemia in nephrectomized rats showed that 16 weeks of daily feeding of these rats with a diet containing *Bacillus pasteurii* led to a reduction in their urea level. They further reported that by inclusion of probiotic supplements in the diet of uremic rats, the rate of progression of azotemia was decreased and survival was increased.[3]

Nitrogenous waste products, including ammonia, are produced in many tissues; however, they often are produced due to urease activity of gut bacteria present. They are then absorbed through the intestinal epithelium and enter the portal venous blood flow. Ammonia is converted into urea in the liver, and then transferred to the kidneys and excreted through the urine. It is believed that lactic acid-producing probiotic bacteria, including *Lactobacillus* and *Bifidobacterium* species, can produce organic acids that reduce the gastrointestinal tract pH, and thereby, lead to inhibiting acid sensitive bacteria such as enteric species that produce the urease enzyme.[19] Ammonia production is reduced by blockage of the activity of urease. However, ammonia has a weak (unstable) base, thus reduces intestinal pH, increases the proportion of ionized to nonionized ammonia, and reduces nonionic inactive diffusion. Hence, less ammonia is absorbed into the portal vein, and more ammonia is excreted in the feces. In addition, the reduction of intestinal pH itself reduces decomposition of nitrogenous substances (proteins and amino acids) and decrease ammonia production.[20]

In our investigation of the mean serum creatinine, there was no significant difference between the two groups at baseline; however, in the case group, mean serum creatinine was reduced after the intervention. In Patel and colleagues' study, creatinine levels in the rats that received *Bacillus pasteurii* or *Lactobacillus sporogenes* showed 40% reduction, but serum creatinine levels in the rats fed with the other diets showed no significant difference compared with the placebo group.[30] In the study of Ranganathan and colleagues, the mean serum creatinine in patients with CKD, after taking probiotic supplements, had no significant difference.[19,28] Nonetheless, in another study by the same researchers, prescription of probiotic capsule containing *Streptococcus thermophilus*, *Lactobacillus acidophilus*, and *Bifidobacterium longum* for uremic pigs resulted in a significant reduction in the mean serum creatinine.[31]

Also, in the present study, it was found that although taking synbiotic supplementation decreased mean uric acid in the case group, the difference was not significant. In the findings of Ranganathan and colleagues, after taking probiotic supplementation, no significant changes were observed in the blood uric acid levels of the cases.[19] In another clinical trial by the same investigators, the average of the changes of uric acid concentration in the course of taking probiotic supplements versus taking placebo was reported as moderate.[28] Prakash and colleagues showed that the bacteria produced through genetic engineering in vitro were able to significantly reduce the uric acid concentration; these bacteria also reduced plasma uric acid level in the laboratory animals.[32]

Bacterial cells use nitrogenous wastes such as urea, uric acid and creatinine as a food source for their metabolism; however, they do not produce ammonia as a byproduct, and therefore, reduce the concentration of these toxins in uremic patients.[19,33,34] In this study, the reasons for lack of changes in serum creatinine and uric acid could be short duration of the study, lack of enough time to unfold the effects of synbiotic supplements, difference in the type and dose of probiotic bacteria used, and difference in the response of individuals. On the other hand, levels of uremic toxins and serum creatinine, in addition to the kidney functional factors, were affected by factors such as diet, energy intake, metabolic acidosis, disorder in fat metabolism, physical activity, and blood pressure changes.

This study found that sysbiotic supplement increased creatinine clearance and GFR in the CKD patients; however, this increase was not significant. The results of Ranganathan colleagues' study showed that probiotic C (*Bacillus pasteurii*) and D (*Lactobacillus sporogenes*) diets were more effective in increasing the creatinine clearance of rats than the other diets.[3] However, in the study of Rathi and colleagues, taking probiotic-prebiotic supplement improved GFR in most of the patients.[35]

Diabetes mellitus and high blood pressure have been identified as the most important factors of CKD. Active immunity and inflammation are involved in the pathogenesis of diabetes mellitus, and its microvascular complications similar to those of nephropathy. In addition to inflammation, many researchers have suggested dyslipidemia

as a factor influencing renal damages in diabetic patients.[36] Several studies have shown that the use of probiotics has beneficial effects on the blood pressure, lipid and glycemic profile, and the blood levels of inflammatory biomarkers and the kidney function indexes.[27] Probiotics also regulate the balance of intestinal flora and reduce the production and absorption of uremic toxins derived from the intestine, which can lead to a reduction in renal fibrosis, delay in the progression of CKD, and improve azotemia.[37,38]

It is possible that lack of achieving a significant results in terms of changes in creatinine clearance and GFR can be due to the short duration of the study, differences in the types of bacteria used, the low dose of synbiotic supplements, a low sample size, and the difference in individuals' responses. On the other hand, almost all individuals in the present study were patients with a long history of diabetes mellitus. In fact, this may be effective on the metabolic memory and the long-term effects such as epigenetic alterations induced by glucose. Changes in the expression of genes in these patients may be responsible for the lack of improvement of renal factors in this study. Also inflammatory cytokines and oxidative stress may be responsible for the escalation of renal damages in these patients.[39]

CONCLUSIONS

This study showed that taking a synbiotic supplement, 500 mg, twice a day for 6 weeks, could reduce blood urea nitrogen in patients with CKD at stages 3 and 4; however, it had no effect on the other indicators of kidney function.

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CONFLICT OF INTEREST

None declared.

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