Original Article

The Effect of Synbiotic and Probiotic Supplementation on Mental Health Parameters in Patients Undergoing Hemodialysis: A Double-blind, Randomized, Placebo-controlled Trial

Abstract

Introduction: The purpose of this double-blind clinical trial, was to examine the effect of supplementation with the synbiotic and probiotic on the mental health, quality of life, and anemia in HD patients. **Methods:** Seventy-five HD patients were randomly assigned to receive the synbiotic (n = 23) as 15 g of prebiotics, 5 g of probiotic powder containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and *Bifidobacterium longum* (2.7 × 107 CFU/g each); probiotics (n = 23) as 5 g probiotics similar to the synbiotic group with 15 g of maltodextrin as placebo; and placebo (n = 19) as 20 g of maltodextrin. Serum hemoglobin (Hb) and albumin (Alb) were measured. Beck depression and anxiety index (BDI/BAI) was used to assess symptoms of depression and anxiety. The health-related quality of life (HRQoL) was assessed using the questionnaire SF-36. **Results:** From baseline to 12 weeks, synbiotic and probiotic supplementation resulted in a significant decrease in BDI and BAI score in comparison to the placebo ($P < 0.05$). Between and intergroup comparison showed no significant changes between the groups in terms of HRQoL. However, the serum Hb level increased significantly in the synbiotic and probiotic group compared to the placebo group ($P < 0.001$). **Conclusion:** Overall, 12 weeks of synbiotic and probiotic supplementation resulted in an improvement in mental health and anemia compared with the placebo, whereas they failed to enhance the quality of life in HD patients.

Keyword: *Hemodialysis, hemoglobin, mental health, probiotic, quality of life, synbiotic*

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Introduction

End-stage kidney disease (ESKD) patients endure many problems due to medical condition as well as psychological disorders that exert a negative impact on their disease progression. Anxiety and depression are the most prevalent psychiatric diseases in hemodialysis (HD) patients and the level of anxiety in these patients has been reported to be 27%–45.7%.[1] Moreover, the prevalence of severe depression and mild-to-moderate depression in these patients has been stated as 22% and 25%, respectively.[2] Restrictions such as fluid and dietary intake, financial problems, diminished physical activity, long-term dependency on renal replacement therapy (RRT), and frequent admittances to the hospital, make the HD patients susceptible to depression.[3] Besides, increased mortality among HD patients with depression and poor health-related quality of life (HRQoL)[4,5] which is even worse than the patients with other chronic diseases has been reported. It is worth noting that depression and HRQoL are closely interrelated among HD patients,[6,7] and depression negatively affect HRQoL in HD patients.[8] On the other hand, anemia and hypoalbuminemia have been demonstrated to have an association with depression and low quality of life[2,9] in different populations of patients, including patients with renal failure, pulmonary disease, cancer, and heart failure.[10] Thus, the interventions improving depression and anemia in HD patients might also effectively improve HRQoL in this population.

In recent years, emerging evidence has revealed a link between the brain, gut microbiota, and immune system, as well as in the study of gut microbial differences as a possible source of inflammatory activity in psychiatry disorders.[11] There is evidence indicating that modulation of

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intestinal microbiota by supplementation of probiotics may results in improvement of mood and psychological disorders in the healthy population,[12] patients with chronic fatigue syndrome[13] and autism spectrum diseases,[14] and hemodialysis patients.[15]

Besides, inflammation is considered to be one of the main factors affecting hemoglobin (Hb) fluctuations in chronic kidney disease (CKD) patients. The production of proinflammatory cytokines during the process of inflammation has an inhibitory effect on the production of red blood cells and reduces the response to erythropoietin in erythrocyte precursor cells in the bone marrow.[16] Since depressive disorders and anemia have been attributed to systemic inflammations, the probiotic strain including *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium lactis,* and *Bifidobacterium longum*, which have been shown to reduce inflammatory markers, may have a beneficial effect on psychological outcomes and serum hemoglobin level in HD patients. Therefore, the current study aimed to compare the effect of synbiotic and probiotics versus placebo on anemia, depressive and anxiety symptoms, and quality of life among HD patients.

Materials and Methods

Trial design

The present study was a double-blind, randomized, placebo-controlled trial carried out between January and July 2018 in Ahvaz Jundishapour University of Medical Sciences. The protocol of the study was according to the Declaration of Helsinki and was approved by the Ethics Committee of Ahvaz Jundishapour University of Medical Sciences (IR.AJUMF.REC.1395.812). This trial was registered in Iran Registry of Clinical Trials (IRCT2017041233393N1, http://www.irct.ir).

Randomization

Randomization was performed using computer-generated random numbers. Randomization and allocation were concealed from the researchers and patients. A nutritionist at the hemodialysis center conducted the randomized allocation sequence, enrolling patients, and allocating them to interventions.

Sample size

The sample size was determined according to serum IL-6 level [one of the primary outcomes which has been reported elsewhere[17] in a previous study of peritoneal dialysis patients receiving the probiotic supplement.[18] A sample size of 22 patients per group was ascertained with a mean difference of 0.6, a standard deviation of 0.8 for serum IL-6 level, and the possibility of 80% at the level of a $\alpha = 0.05$. To allow for up to 3 dropouts in each group, 25 patients per group were determined as the final sample size.

Patient recruitment criteria

Around 75 permanent hemodialysis (HD) patients aged 30 to 65, with the arteriovenous fistula, undergoing thrice-weekly HD, attending dialysis center of Emam Khomeini hospital, Ahvaz, Iran for at least 3 months before starting the study, were enrolled in this study. Dialysis duration was 3–4.5 h per session, with a blood flow of 250 mL/min and a dialysate flow of 500 mL/min. Patients with a previous kidney transplant or likely to receive a transplant, medically diagnosed severe infections, liver disease, malignancy, amputated limbs, inflammatory bowel disease, pregnancy and patients using catabolic drugs, antioxidant vitamin supplements, pre, pro and synbiotic, and antibiotics within 1 month of study commencement, were excluded from the study.

Protocol

Firstly, patients were matched based on sex, duration of dialysis, and age. They were randomly assigned to one of the three groups to receive synbiotics ($n = 25$) or probiotics ($n = 25$) or placebo ($n = 25$). We advised patients to consume synbiotic, probiotic, and placebo in four separate doses (5 g per serving). According to the buffering capacity of the food on the survival of probiotic microbes during gastrointestinal transit, the patients were asked to take the capsules with or just before their lunch. They were requested not to change their routine physical activity, and not to take any anti-inflammatory medications and supplements during the 12-week intervention. A 3-day 24 h food recall (1 weekend day and 2 weekdays) and international physical activity questionnaire (IPAQ) were completed by all patients at study baseline and weeks 3, 6, 9, and 12 of intervention. To obtain macro- and micronutrient intakes of participants based on the 3-day food recalls, we used Nutritionist IV software (First Databank, San Bruno, CA) modified for Iranian foods. Physical activity was described as metabolic equivalents (METs) in hours per day. To measure the METs for each subject, we calculated the times (in an hour per day) reported for each physical activity by its related METs coefficient using standard tables.

Intervention

Tak Gen Zist Pharmaceutical Company (Tehran, Iran) that was approved by the Food and Drug Organization of the Ministry of Health and Medical Education provided the probiotic, synbiotic, and placebo product and supplement packaging. The synbiotic supplement contained freeze-dried *Lactobacillus acidophilus* strain T16, *Bifidobacterium bifidum* strain BIA-6, *Bifidobacterium lactis* strain BIA-7, *Bifidobacterium longum* strain BIA-8 (2.7×10^7 CFU/gr each) per 5 g sachet and 15 g of prebiotics includes 3 different fiber types a) 5 g fructo-oligosaccharides (FOS) b) 5 g galacto-oligosaccharides (GOS) c) 5 g of inulin per three 5 g

sachets. The probiotic supplement contained the probiotics, the same as a synbiotic group per 5 g sachet and 15 g placebo per three 5 g sachets. Excipients used in the probiotic supplements were as follows: maltodextrin, plum flavor, and malic acid. The prebiotic product was composed of prebiotics and 0.2% plum flavor. The placebo product contained only excipients. The maltodextrin, used as the major placebo substance generally, was identically packaged as the intervention supplements to maintain blinding. The synbiotic, probiotic, and placebo were administered as 5 g packaged sachets, to be taken four times a day with their meals. All treatments were administered for 3 months. The placebo sachet was matched to the study synbiotic and probiotic products for color, solubility, texture, and taste. The dose of the pro- and synbiotic was according to WHO guidelines and studies on the pro- and synbiotic studies.[19,20]

Treatment adherence

Every 4 weeks, patients were given enough supplements to last until their next scheduled visit and were instructed to return all the unused supplements at each visit. During the study, by asking patients to return the remaining supplements, we monitored the consumption of synbiotic, probiotic supplements, and placebos. Besides, a short message was sent to the cell phones of all patients every day to remind them to use the supplements. In addition, to monitor the treatment adherence, at baseline and the end of the study, stool samples were collected to investigate the changing of fecal microbiota colonies. No serious adverse effects were seen during the study.

Outcomes and other covariates assessment

The nutritionist of HD center who was blind to the intervention assignment measured weight and height in the beginning and the end of the study. Weight was measured using the Seca scale with an accuracy of 0.5 kg in the fasting state with minimal clothing without shoes in the beginning and at the end of the study. Height was measured with an accuracy of 0.5 cm without shoes at the beginning of the study. We used the validated Persian version of Beck depression inventory II (BDI-II)[21,22,25] to evaluate the depression symptoms at baseline and the end of the study.

The health-related quality of life (HRQoL) was assessed using the questionnaire SF-36.[17] This questionnaire has been generally used and validated in ESKD patients. The questionnaire comprises 36 items evaluating 8 domains of HRQoL. Each scale was scored with a range from 0 to 100. The total SF-36 score is calculated based on mathematical averaging of the scale components. The higher score indicates a better state of HRQoL. The SF-36 questionnaire was given to patients to complete during routine HD treatment. It was read for cases that were unable to read.

At week 0, 3, 6, 8, and 12 of supplementation, 5 mL venous blood samples were collected after 10–12 h of fasting, before the midweek dialysis treatment using the slow flow/stop pump technique. Then, blood samples centrifuged at 3000 g for 10 min and serums were isolated to measure hemoglobin (Hb) and albumin levels. Dialysis Kt/V was determined using the 1993 Daugirdas equation.

Statistical analysis

The normal distribution of the variables was examined by Shapiro–Wilk's W-test. Continuous variables were shown as means and standard deviations. To compare variables before and after the intervention within each group, paired *t*-test or the Wilcoxon signed-rank test for skewed variables was used. At baseline and end of the study, differences between groups of normally distributed variables were examined using analysis of variance (ANOVA), and differences between groups of nonparametric variables were examined with the Kruskal-Wallis test for continuous data. Duncan's multiple comparisons were used to compare between groups only if the treatment was significant. Repeated-measures ANOVA between groups was applied to compare the mean serum Hb levels within groups for time effect, the interaction of time, and intervention. The *P*-value of 0.05 was considered statistically significant and analysis was performed in SPSS 23.0.

Results

Characteristics of patients

The baseline characteristics of the 75 participants and the consort flow chart of the study are shown in our previous report.[23] Of the 75 HD patients who commenced the study, 10 patients (2 synbiotic, 2 probiotic, and 6 control) withdrew from the study. A total of 65 (23 synbiotic, 23 probiotic, and 19 control) patients who met the inclusion and exclusion criteria were finaly analysed. The information regarding age, body mass index, BMI (kg/m^2), gender, Kt/V, hemodialysis vintage, comorbidities, history of hypertension, and type 2 diabetes mellitus (T2DM) were also recorded. No significant differences in the baseline characteristics were seen between groups, the details were described elsewhere.[23] Repeated-measures ANOVA (Greenhouse–Geisser correction) between groups presented no significant differences in dietary intake within or between groups ($P > 0.5$) for the 5 different times, the details were described elsewhere.[23] No adverse effects, particularly gastrointestinal symptoms, were noted during the study. The consumption of the synbiotic or probiotic supplement compared to the placebo altered the global profile of the fecal microbiota of patients.

Primary outcomes

Effects of synbiotic and probiotic supplementation on mental health

The statistical analysis demonstrated that mean BAI and BDI score significantly decreased in the probiotic and synbiotic group over 12 weeks ($P < 0.05$). At week 12, significant changes in the BAI and BDI score were seen

between the groups (P = 0.049, P = 0.012, respectively). Pairwise comparisons between all groups revealed that the alteration in BDI score in the synbiotic and probiotic groups was significantly greater than the control group (P < 0.05). The mean BAI and BDI score were significantly different between groups at the end of the study (P = 0.004, P = 001, respectively). The synbiotics and probiotic treatment significantly decreased the BAI and BDI in comparison to the placebo (P < 0.05) [Table 1].

Effects of synbiotic and probiotic supplementation on quality of life

The HRQoL score presented a small upward trend in the synbiotic and probiotic groups and showed a small downward trend in the control group. However, the changes were not statistically different (P > 0.05) during the study in all groups. Besides, the mean HRQoL at the end of the study was not significantly different between groups (P > 0.05). There was no significant difference in the mean change of HRQoL score in all groups (P > 0.05) [Table 1].

Effects of synbiotic and probiotic supplementation on serum level of hemoglobin

Before the intervention, the mean Hb level in the synbiotic (10.57 [1.30]), probiotic (10.31 [1.30]) and the placebo (10.74 [1.43]) group were not significantly different (P > 0.05). After the intervention, the mean Hb level obtained sequentially with the 3 months measurements. The Hb was in the 1st, 2nd, and 3rd month after intervention in the synbiotic group 10.94 (1.18), 11.1 (1.45), and 11.38 (1.1), respectively, in the probiotic group 10.7 (1.20), 10.8 (0.86), and 11.16 (1.36), respectively and the control group 10.36 (1.03), 9.7 (0.99), and 10.74 (0.93), respectively. There was a significant difference between the mean post-intervention Hb levels in the synbiotic and probiotic group in comparison to the control group (P < 0.001, P = 0.005, respectively). The process of Hb changes during the study showed an increasing trend in the probiotic and synbiotic group while the placebo group did not follow this trend and showed fluctuations instead [Figure 1].

Repeated measures ANOVA (Greenhouse–Geisser correction) among the three groups showed time effect (P = 0.004), moreover, the interaction of time and intervention was significant (P = 0.007). The study indicated that 1 month after consumption of synbiotic and probiotic supplementation, the level of Hb of the synbiotic

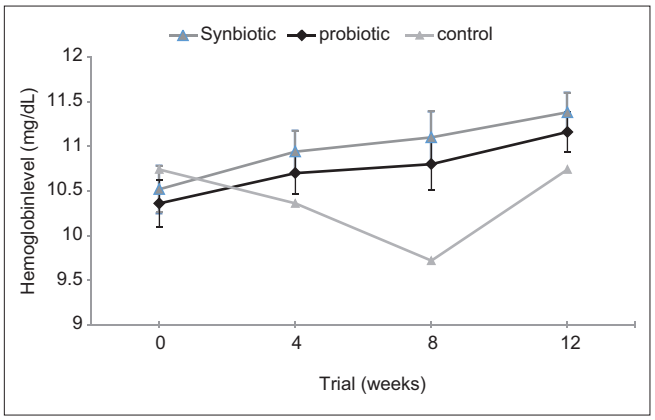

Figure 1: Hemoglobin level in synbiotic, probiotic, and control group in baseline and 4, 8, and 12 weeks later

Table 1: Clinical variables at baseline and end of 6 months interventions in HD patient

Parameters	Baseline	P1	Week 12	P1	Changes	P2	P3
BAI, score							
Synbiotic (*n*=23)	16.8 (2.5)	0.41	14.85 (2.4)	0.004	-2.00 (2.2)	<0.001	0.049
Probiotic (*n*=23)	17.24 (3.05)		15.1 (2.9)		-2.14 (1.87)	<0.001	
Placebo (*n*=19)	17.87 (2.47)		17.1 (2.25)		-0.76 (2.28)	0.106	
BDI, score							
Synbiotic (*n*=23)	17.18 (2.03)	0.60	15.34 (1.93)	0.001	-1.84 (1.66)	<0.001	0.012
Probiotic (*n*=23)	17.87 (2.67)		15.75 (2.28)		-2.11 (2.6)	<0.001	
Placebo (*n*=19)	17.86 (2.6)		17.54 (1.92)		-0.096 (3.07)	0.877	
HRQOL, a total score							
Synbiotic (*n*=23)	49.52 (12.45)	0.96	53.60 (20.84)	0.26	4.08 (23.2)	0.388	0.47
Probiotic (*n*=23)	48.55 (15.49)		50.66 (17.09)		2.10 (22.11)	0.639	
Placebo (*n*=19)	48.77 (13.02)		45.50 (13.85)		-3.27 (20.34)	0.429	
Albumin, gr/dL							
Synbiotic (*n*=23)	3.99 (0.55)	0.77	4.06 (0.42)	0.36	0.068 (0.39)	0.392	0.11
Probiotic (*n*=23)	3.95 (0.55)		3.92 (0.50)		-0.024 (0.46)	0.798	
Placebo (*n*=19)	4.06 (0.53)		3.85 (0.60)		-0.208 (0.54)	0.068	

BAI- Beck Anxiety Index; BDI- Beck Depression Index; HRQOL- Health Related Quality Of Life. All Results are presented as the mean (SD). P1: P value refer to comparisons between groups (Kruskal-Wallis test or ANOVA as appropriated). P2: P value refer to comparisons between week 0 and week 12 within groups (Wilcoxon or paired t-test as appropriate). P3: P value refer to comparisons of mean differences between pre- and postintervention between groups (Kruskal-Wallis test or ANOVA as appropriate)

and probiotic groups have increased while the Hb of the control group decreased [Figure 1]. After the 2nd month, the level of Hb of the control group increased while the level of Hb of intervention groups was further.

Discussion

Psychological problems including depression and anxiety are considered to be correlated with a higher risk of mortality and morbidity in ESKD patients.[24] The recent evidence on the role of gut microbiota in the pathogenesis of some diseases has led researchers to propose probiotics as potential therapeutic agents in mood disorders.[16] Although the beneficial effects of probiotics and/or prebiotics on renal function, inflammation, and reduction of uremic toxins in HD patients have been widely investigatedmuch less has been published on their effects on psychological comorbidities. However, in our previous study, we showed that synbiotic supplementation resulted in greater improvement in depression symptoms and serum BDNF level compared to the probiotic supplementation in HD patients with or without depression symptoms.[15]

Effect on mental health

In the present study, a self-report rating scale, BDI was used to measure depression. The depression and anxiety scores significantly decreased from the baseline after 12 weeks of probiotic and synbiotic supplementation. The results of human trials on the efficacy of probiotics in the management of depression and anxiety are, however, conflicting. Although the mood-improving effects of probiotics have been reported by a few earlier trials,[13,16,26-29] no beneficial influence has been found in the other experiments[22,30-36] or meta-analysis reports.[37] These controversial observations can be attributed to differences in the study population, sample size, intervention duration, probiotic strain, and administration dose. Moreover, there is an established association between microbiota abnormalities, inflammation, and depression[38,49] supporting the idea that antidepressant effects of probiotic and synbiotic treatments found in this study arise from their gut-modulatory, anti-inflammatory, and immune-regulatory properties which have been shown in our previous studies.[23,40] Moreover, the probiotic might improve symptoms of depression by enhanced serum tryptophan and reduced serotonin levels.[39] Furthermore, the probiotic treatment probably helps decrease symptoms of depression in those with elevated inflammatory status.[38] Thus, in the present study, the HD patients with persistent inflammation showed a significant decrease in BDI score by probiotic and synbiotic supplementation in comparison to the placebo group. At the end of the intervention, the BDI and BAI, of probiotic and synbiotic treatments were similar but significantly lower than those of placebo. Data from the last three trials failed to indicate the antidepressant effects of prebiotics[16,41,42]; the antianxiety capacity of prebiotics was only observed in a trial by Silk *et al*.[42] of patients with irritable bowel syndrome (IBS). In the current study, however, prebiotics in combination with probiotics could exert psychotropic-like effects. One possible explanation is that the health benefits of prebiotics mainly arise from their ability to stimulate the growth or activity of beneficial intestinal microbiota, which have been shown to decrease in HD patients compared with healthy subjects. Probiotic supplementation can compensate for the reduction of beneficial commensal bacterial species.[43,44] The use of prebiotics along with probiotics, therefore, seems to be more effective in modulation of gut dysbiosis and gut-brain axis function, which may, in turn, lead to improvement of metabolic brain disorders such as depression.

Effect on quality of life score

Mental health status can also be correlated to the weakened quality of life in CKD patients.[43] Although several previous trials have indicated an increase in quality of life following probiotic supplementation in healthy elders[33] or IBS patients,[30] no beneficial effect was found in this study. This finding is consistent with the results of the study conducted on dialysis patients showing no improvement of QOL by daily consumption of a probiotic formulation for two 2-month periods separated by a 2-month washout period.[45] Compared with the general population or other patients, CKD patients should deal with more complicated health issues, which may worsen their life quality. Moreover, these trials[42-46] have been performed in regions with different social and economic conditions making it difficult to make a comparison.

Effect on serum hemoglobin level

Anemia and low Hb level associated with declining renal function is another common complication of CKD that may negatively affect the quality of life.[50] The mean Hb level showed a significant increasing trend in patients supplemented with probiotic or synbiotic formulations, while Hb level variability was observed in the placebo group. Considering the potential role of inflammation in CKD-anemia and Hb fluctuation, [47,48] the anti-inflammatory activity of probiotic strains observed in our previous studies [23,40] may explain these findings. In the study conducted by Fukushima *et al*.,[51] the serum Hb level of enterally fed elderly in-patients under probiotic treatment significantly improved which was also accompanied by a decrease in the inflammatory blood parameter, TNF-α (tumor necrosis factor-alpha). In another trial, however, a 12-week supplementation of hemodialysis patients with a multi-strain probiotic preparation did not affect the hemoglobin status; the inefficacy of probiotics in the improvement of inflammation was considered responsible for this result.[50] Probiotic administration also showed no positive effect on Hb level in HIV patients and healthy elders in the other trials.[52,53]

To our knowledge, this is the first randomized clinical trial that investigated the effect of both synbiotic and probiotic

in mental health improvement in HD patients. The strengths of this study include firstly, evaluation and comparing the effects of synbiotic and probiotic supplementation for a better life in HD patients. Secondly, potential dietary confounders were controlled for by evaluation five times dietary intake during the study applied by a qualified dietitian who was blinded, along with the participants, to the intervention, however, the data were reported elsewhere.[23] Thirdly, the use of three diverse prebiotics promoted fermentation with the entire colon; FOS and GOS can be completely fermented in the proximal part and inulin may help the extension of fermentation to the distal part.[54] Finally, we evaluated the compliance of our intervention by fecal microbial counting.

On the other hand, the study had some limitations. In our previous work,[23] conventional culturing methods were applied to evaluate the fecal microbiome of the study population which prohibited us to achieve a reliable profile. Molecular analysis of gut microbiota in future studies may be helpful to address the possible mechanism of such effects. Furthermore, the short duration of the study restricted the statistical power for the detection of alterations in HRQoL score in intervention groups.

In total, probiotics, especially in combination with prebiotics, implied a potential capacity to promote the health status of hemodialysis patients through the improvement of comorbid depression, anxiety symptoms, and hemoglobin level. It is worth noting that there is no other report on the possible influence of probiotic and/or synbiotic formulation on the mental status of these patients. The mood-improving effects found in the probiotic and synbiotic groups were, therefore, not related to these interfering factors.

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Conflicts of interest

There are no conflicts of interest.

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