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**Research Article**

# The effect of synbiotic supplement on inflammation, gastrointestinal symptoms and quality of life in hemodialysis patients: a randomized, double-blind, placebo-controlled clinical trial.

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## ABSTRACT:

**Introduction:** The prevalence of chronic kidney disease is increasing throughout the world. It is possible that synbiotic supplementation in kidney diseases might affect on intestinal nitrogenous metabolites. Therefore, the aim of this study was to evaluate the effects of synbiotic supplementation on serum concentrations of inflammatory marker, gastrointestinal symptom, quality of life and bowel habit in Iranian HD patients.

**Methods:**This randomized double-blind placebo-controlled clinical trial was performed among 48 Iranian hemodialysis patients. Participants consumed either two capsules of synbiotic or placebo for 8 weeks of intervention. Quality of life, bowel habits and biochemical markers of hemodialysis patients were assessed. Analysis of covariance was used to compare the results of synbiotic and placebo groups.

**Results:** The synbiotic supplementation improved non-significantly the quality of life of patients in compare to placebo group. Furthermore, the effects of synbiotic consumption on bowel habits did not show any significant results. However, the placebo group had significant reduction in defecation frequency ($p=0.01$). Synbiotic supplementation resulted in beneficial improvement in total white blood cells and its differentiation ($p<0.05$).

**Discussion**: Administration of synbiotic in hemodialysis patients could be used as a safe approach for improving quality of life score and gastrointestinal problems in this particular group.

## INTRODUCTION:

Nowadays, chronic kidney disease (CKD) is considered as a health concern of communities that has an important effect on involved individuals and societies. It is shown that the prevalence of CKD is increasing throughout the world and it seems that CKD will become as a major public health problem over the next decade (1). Kidney disease is classified among the first five main diseases in the United States, so that now it is affected more than 20 million US adults (2). Previous studies have shown that many CKD patients are suffering from cardiovascular problems (3-5). It is estimated that the rate of mortality due to cardiovascular diseases in hemodialysis patients (HD) is more than five-times higher in compare to general population (5-

7). Recently, high levels of inflammatory markers are considers as a novel risk factor for cardiovascular diseases (8). Several studies have asserted that CKD and end stage renal disease (ESRD) patients have disturbed levels of inflammatory markers including interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) (9).

Furthermore, about 53% (8%-57%) of CKD andHD patients suffer from constipation and therefore significantly lower levels of health-related quality of life (HRQoL) due to this problem (10-12). Among the available therapies targeting constipation including laxative usage,oral sorbents, olive oil and flaxseed oil, bixalomer (new phosphorus binder) and iron-based phosphate binder (13-15) recently modification of gut microflora has been attracted a great interest. It has been propounded that abnormal intestinal flora (disbiosis) is the main cause of constipation and inflammation among HD patients Intestinal microflora is considered as a highly active society of organisms that performs several functions. The integrity and proper function of the microbiome is critical for good health. It has been established that intestinal microbiome dysfunction is contributed in pathogenesis of various chronic diseases such as inflammation, diabetes (16), cardiovascular diseases (17), obesity(18) and chronic kidney disease (CKD) (19).

Synbiotics contain both of probiotics (living microorganisms such as Bifidobacterium) and prebiotics (non-digestible food adjuncts such as inulin that are selectively fermented by probiotics). Recently, synbiotics are prescribed in order to intestinal environment and bowel habit improvement, decreasing intestinal nitrogenous metabolites and mitigating intestinal inflammatory states (20-22). However, the results of previous studies are inconsistent in this regard. Nakabayashi and colleagues showed that the synbiotics supplementation (Lactobacillus casei strain Shirota, Bifidobacterium breve strain Yakult and galactooligosaccharides) could have significant effects on bowel habits and constipation in HD patients (23). While, a clinical trial performed among American HD patients with 180 billion CFUs per day probiotic formulation failed to show statistically significant changes in markers of inflammation and oxidative stress, and quality of life (24).

Based on our literature review, we hypothesized that if different types of probiotic strains in combination with compatible prebiotic are used in HD patients, it would be possible to detect more improvement in gastrointestinal symptoms as well as quality of life in these patients. Therefore, to evaluate this hypothesis, a double-blind, randomized, placebo-controlled clinical trial was designed to determine whether supplementation with synbiotic will further improve inflammatory markers, gastrointestinal symptoms and quality of life in Iranian HD patients.

## METHODS:

### Participants:

Participants involved with end-stage renal failure (stage V of chronic kidney disease) were enrolled from HD in the dialysis center of the Noor and Saint Aliasghar, Isfahan, Iran. Patients who performed HD treatment 3-times a week; at least 4 hours each time were selected regardless of their age, sex and race for this study. Participants were selected bases on following inclusion criteria: not being pregnant or lactating, lack of addiction to alcohol or drugs abuse, no history of active malignancies except skin cancer and severe chronic conditions (including cardiovascular, pulmonary and hepatic disease), lack of gastrointestinal, hepatitis, HIV disease and psychiatric problems. Furthermore, participants who had severe edema, suffering from infections during 4 past weeks, consumed prebiotic or probiotics productions, immune suppressive drugs, antibiotics or anticoagulant agents were not selected for study entrance. The protocol study was explained for the participants and then all patients signed written informed consents. Participants were excluded if they were not willing to continue study, reported any side effects

due to synbiotic supplementation and dishonesty in answering to questions.

**Study design:**

This 8-week randomized double-blind placebo-controlled clinical trial was performed during October 2015 to December 2015 in the dialysis center of the Noor and Saint Aliasghar, Isfahan, Iran. The adequate sample size of this study was calculated using the available formula for parallel-desined studies ($n=[(Z1-\alpha/2 + Z1-\beta)\times(S_1^2+S_2^2)]/(\mu_1-\mu_2)^2$. To obtained the maximum adequate sample size for each group we used the difference mean of Indoxyl sulfate ($\mu_1-\mu_2=7$ mg/L), type I error of 5%, study power of 80%, $S_1=5.1$ mg/L, $S_2=8.3$ mg/L. The adequate sample size for each group of intervention and control was obtained 15 patients. Due to potential losses during study period, we recruited 24 patients in each group. The HD patients were selected through convenience sampling method. Before the study entry, eligible participants were entered in a one-week run-in period. The demographic information, physical activity questionnaire, medical history, medications, quality of life using SF36 QOL form (25-27), constipation and colon habits by FAIRFAX COLON & RECTAL SURGERY questionnaire were completed and anthropometric indices were measured during run-in period. For evaluation of quality of life, a standardized Persian version of the SF-36 questionnaire was used. This questionnaire has 36 questions, 35 of which are classified in 8 categories. These include: physical functioning (10 questions), physical role functioning (4 questions), bodily pain (2 questions), general health perception (5 questions), vitality (4 questions), social functioning (2 questions), mental health (5 questions) and emotional role functioning (3 questions).

These eight sections are categorized in two overall components: mental and physical, of which physical component includes: physical functioning, physical role functioning, vitality, bodily pain and general health perception. While the mental component consists of general health perception, vitality, social functioning, mental health and emotional role functioning with general health perception and vitality being the common sections (28). A the end of run-in period, participants were randomly allocated to block 1 or block 2 using stratified block randomization based on sex, age (± 5 years) and HD duration (± 6 month). To perform this study in a double-blinded nature, the placebo and synbiotic capsules were encoded as A and B by a third person and then all patients were randomly assigned to either group A or B. At the first day of study entry, 7 milliliter fasting blood samples were taken from all patients (before the start of HD) and 2 packs of placebo or synbiotic capsules were distributed for the first 4-week of study (each pack contains 30 capsules of supplement). The synbiotic capsules (as GeriLact brand; ZIST TAKHMIR Company, Tehran; Iran) contains $1\times10^9$ CFU of Lactobacillus casei strain, Lactobacillus acidophilus strain, Lactobacillus rhamnosus strain, Lactobacillus bulgaricus strain, Bifidobacterium breve strain, Bifidobacterium longum strain and Streptococcus thermophilus strain as probiotic and fructooligosaccharide (FOS) as prebiotic as well as lactose, Mg stearate and talc as filling materials in each serving size (2 capsules). Placebo capsules were produced in a same shape, color, odor and packing (as GeriLact brand; ZIST TAKHMIR Company, Tehran; Iran) and contains maltodexterin. Patients were instructed to keep the capsules in refrigerator at 2-8 $^{\circ}$C and consume 2 capsules per day, between the main meals. In addition, participants were asked to lessen the consumption of foods that probably contain probiotic strains (fermented foods such as yogurt, cheese and kefir). At the end of week 4, participants were asked about regular consumption of supplements, willingness to continue the study and possible side effects of supplements and after that 2 packs of placebo or synbiotic capsules were rendered for the second 4-week of study. At the end of week 8, SF36 QOL form, constipation and colon behavior questionnaire and physical activity questionnaire

were completed by all patients. At the end of study (week 8), overnight fasting blood samples were drawn from all patients too.

**Anthropometric measurements:**

At the start of study, height was measured while patients were standing in a straight position without shoes by using a standard tape; nearest to 0.5 cm. For those patients who were not able to stand in a normal position, ulna length (from olecranon to styloid process) was measured and then by using available formula, the height of subject was estimated. At the beginning and the end of study, weight and were measured. At each visit, patients were weighed before and after HD while were wearing light cloths; using a digital scale; nearest to 0.1 kg. Body mass index (BMI) was calculated by following formula: weight (kg)/(height (m))$^2$.

Gastrointestinal symptoms assessment:

To evaluate the GI symptoms and defecation pattern of HD patients a questionnaire which was described by Nakabayashi et al (29) was completed. Upper and lower abdominal pain, borborygmi, and flatus were scored as often, sometimes, or almost never. Ease of defecation was scored as difficult, easy, or very easy. Defecation frequency was scored as follows: once per 3 days; once per 2 days; once per day; and twice per day. Bristol stool scale was used to determine the stool shape of patients based on following items: (30, 31) separate hard lumps that hardly pass; lumpy, sausage-shaped; sausage-shaped which have cracks; sausage-shaped, smooth and soft; soft blobs which pass easily; fluffy pieces with ragged edges, a mushy stool; and watery stools.

**Physical activity levels:**

Participants reported their physical activity level using a validated physical activity questionnaire at the baseline and end of study. Theduration of each physical activity (in minutes) was multiplied by the metabolic equivalent of task (MET coefficient) and finally reported as Met.hour/day (32).

**Adherence assessment:**

Participant's compliance was assessed through face to face visits in HD section weekly. Researchers asked about the potential side effects of supplements from each patient and consulted them in order to solve the problems. At the end of week 8, the exact number of consumed capsules was assessed.

**Laboratory analysis:**

Biochemical analyses was performed at weeks 0, and 8 after an overnight fasting (12 h). Fasting blood samples were taken from each patient and plasma and serum of specimens were frozen at -70°C at the day of sampling until they were analyzed. Commercially available enzymatic reagents (Pars Azmoon) were used for serum levels of alkaline phosphatase (ALP) assessment. Fasting blood glucose concentrations were measured by using glucose oxidase. Serum creatinine was measured by colorimetric method and serum BUN was assessed by enzymatic colorimetric method by using commercially available kits (Pars Azmoon Co., Tehran, Iran).Whole anti-coagulated blood was used for WBC measurement and WBC count was performed by automated particle Coulter Counters within 24 hours after blood sample collection. Whole blood sample was used for total WBC count.

**Statistical Analyses**

Normal distribution of continuous data was assessed by histogram curves and Kolmogorov-Smirnov test. Demographic variables were analyzed by using $\chi^2$, Fisher exact test, or independent sample t-test, as appropriate. We used analysis of covariance (ANOCVA) to compare the endpoint values of postoperative continuous outcomes between the two groups by adjusting the potential confounders including baseline value of the outcomes, sex, age, duration on HD, and metabolic equivalent tasks (MET). We analyzed the data according to intention to treat principle. Wilcoxon signed-ranks test was used for comparison of values in likert scale or non-numerical variables before and after SYN administration. Continuous and categorical data

are reported as means ± standard deviations and frequency (%), respectively. Statistical analysis was performed using SPSS software (version 18.0, Chicago, IL). For all analyses P values less than 0.05 was considered statistically significant.

## RESULTS

Forty-eight patients were included in the study and were randomly assigned into the 2 groups, synbiotic (n = 24) or placebo (n = 24). A flow chart of study design is depicted in Fig. 1. Eighty-seven percent of patients completed 8 wk of treatment and had end-of-study clinical and laboratory assessments. General characteristics of study population are shown in Table 1. Among the participants, 17.4% were smokers and 34.8% were female. The age range of participants in synbiotic and placebo group was 32-80 and 36-84 years, respectively. The baseline anthropometric measurements, physical activity, biochemical markers, score of quality of life and bowel habits of both groups were not statistically different from each other (Table 1).

At the end of study the mean quality of life score for synbiotic group was 58.48 (range: 22-97) and for HD patients it was 56.43(range: 16-94). The comparison of the different sections of the quality of life score between the two groups over the eight of intervention was showed in Table 2. Based on the presented results, there are no significant differences between synbiotic and placebo groups after eight weeks of intervention. However, the adjusted mean values of some aspects of quality of life score including vitality, social functioning, mental health, emotional role functioning, mental component summary and total Quality of life score was insignificantly higher among synbiotic groups after 8 weeks of intervention.

The effects of synbiotic supplementation on bowel habits of HD patients are presented in Table 3. Although the synbiotic consumption had no significant effects on bowel habits, the defecation frequency (times per week) in placebo group statistically decreased after 8 weeks of intervention (p=0.01). However, the bowel habits of synbiotic group had non-significant slight increase after synbiotic supplementation. The comparison of adjusted end point values of biochemical markers between synbiotic and placebo group are shown in Table 4. At the end of study, a significant increase in total count white blood cells and plackets and a significant decrease in lymphocytes were observed in synbiotic in compare to placebo group. Although fasting blood sugar decreased in synbiotic group this reduction did not reach to statistically significant level (p value=0.2). None of the patients completing the 8 week of study had any serious adverse events, which indicated good tolerance of participants to the treatment. Two minor adverse events were reported; one patient complained of moderate nausea and one of increase appetite, in the synbiotic and placebo groups, respectively, both of them were resolved without reoccurrence.

## DISCUSSION

Our results have shown that administration of synbiotic supplementation may improve the defecation frequency in HD patients, although it could not affect the quality of life significantly.

The administration of synbiotic did not cause any significant changes on other GI symptoms that we evaluated in our patients. Total white blood cell count and plackets had a significant increase whereas lymphocytes had significant decrease in synbiotic consumption in compare to placebo group.

In the present study, we were not able to demonstrate the significant positive effects of synbiotic supplementation on quality of life. Our results confirm the results of a recent 6-month crossover clinical trial evaluating the effectsof Strain-Specific Probiotic in dialysis patients that similar to our study used SF-36 QOL questionnaires (24). However, there are clinical trial studies that could document the beneficial effects of synbiotic consumption on quality of life. An open label, dose escalation study in CKD stages 3-4 patients showed statistically significant improvements in physical functioning (QOL measure), trends toward significant reduction in pain (QOL), and no significant changes in mental,

emotional, and social well-being. This inconsistency in results might be due to different target group of participants and study duration which in the mentioned study was pre-dialysis subjects and 6 month duration, respectively (33). A previous multicenter trial in cohort of CKD stages 3-4 patients that used a simple customized self-assessment of QOL questionnaire showed that improvement in total score of quality of life could be achieved when study subjects were treatedwith the study formulationat 90billionCFU/day dosage (34). Ranganathan and colleagues (34) in a 6 month pilot-scale crossover trial have found that overall QOL improved in all Patients with CKD during probiotic treatment from a mean of 6.68 to a mean of 7.77 ($p<0.05$). The authors concluded that SF-36 questionnaire can be the most appropriate tool for quality of life assessment. Generally, the quality of life in HD patients is low and to improve this score in this specific group of patients a long period of time is needed (27). In this context, it is shown that abnormal defecation which is prevalent among HD patients is one of the symptoms that could reduce the quality of life in HD patients (23). In the current study, a non-significant increase in mental component summary and quality of life in HD patients might be attributed to statistically non-significant gastrointestinal habits improvement. It is possible that with longer period of intervention in the present study, we could document a significant improvement in quality of life and bowel habits of HD patients.

The results of current study failed to show any significant effect of synbiotic supplementation on bowel habits of HD patients. However, defecation frequency in placebo group had a statistically reduction at the end of study. Similarly, in non-dialyzed stage 3-4 CKD patients, Guida et al. found no effect of synbiotics on defecation frequency, stool shape, ease of defecation, superior abdominal pain, inferior abdominal pain, borborygmi, and flatulence (31). Another study also reported no significant changes in any of these GI symptom scores among HD patients over 2 week of intervention. However, a slight increase of stool quantity [e] was observed after the beginning of the synbiotic treatment. This lack of significancy in results of bowel habits might be due to applied prebiotic type, probiotic component and their dose in the consumed synbiotic. Furthermore, in the current study, We asked all participants to cease laxative consumption before the start of study. not all the subjects had a background of hard stools before the study entrance and this issue might affect on final results of bowel habits after 8 weeks of synbiotic supplementation. Our results demonstrated that synbiotic treatment tends to increase fecal volume and normalize stool form even in the absence of laxative usage. Moreover, synbiotic treatment did not adversely affect abdominal symptoms including abdominal pain.

The results of current study demonstrated significant changes in white blood cell count, placket and lymphocyte levels in synbiotic group. It must be noticed that sometimes increasing in total white blood cells might be not associated with increased inflammation. We observed a significant decrease in lymphocytes which are involved in inflammation and a non significant increase in neutrophils which have phagocytic action. Therefore, it seems that this increasing in total white blood cells might be resulted in lowering inflammation. However, due to lack of more information about the effects of synbiotic supplementation on other inflammatory biomarkers, these results must be interpreted with cautious. Furthermore, previous studies have emphasized that total white blood cell count must be considered as a preliminary indicator in inflammation detection.

The main strength of the present study was randomized allocation of patient to either synbiotic or placebo groups. Furthermore, due to well defined inclusion and exclusion criteria just eligible participants with the lowest discrepancies were assigned to experimental groups.

The present study also has some limitations. We did not measured fecal bacterial loads before and

after synbiotic treatment. In addition, we could not followe the study participants after the end of 8 week to assure the stability of the results obtained during supplementation period.

## CONCLUSIONS

Administration of synbiotic in hemodiyalis patients at the dose of 180 billion CFUs per day appears safe and well tolerated. Trends toward improvement were documented in QOL, bowel habit and abdominal symptoms. However, none of them reached to a statistical significance level. In addition, synbiotic supplements induced significant increase in placket and total WBC count and significant decrease in lymphocytes at the end of study. For more definitive results, especially to confirm the trends observed, further randomized placebo-controlled clinical trials with a larger sample size and longer follow up duration is necessary.

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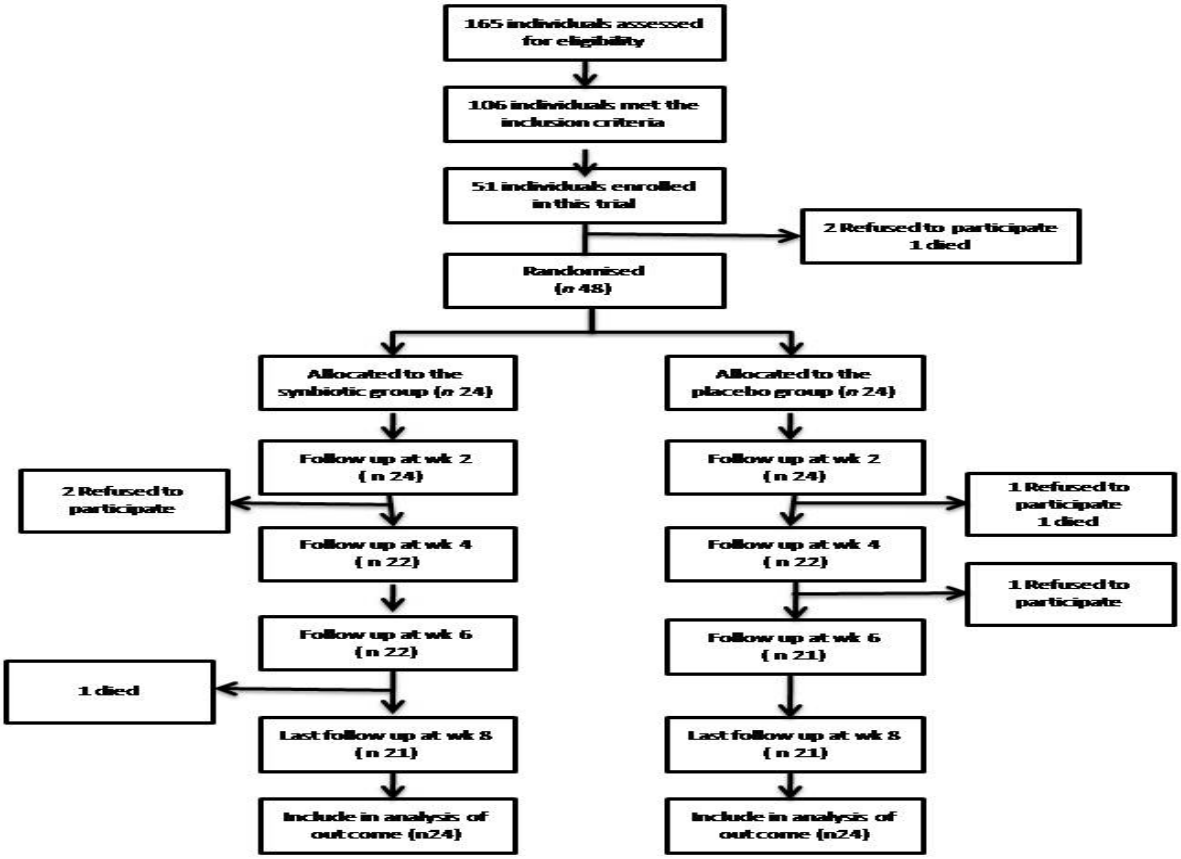


**FIGURE 1. Consolidated Standards of Reporting Trials flow diagram of the study participants.**

**Table legends:**

**Table 1:** General characteristics of study population between synbiotic and placebo groups at baseline[1]

| | Synbiotic group (n 24) | Placebo group (n 24) | Total (n 48) | P |
|---|---|---|---|---|
| Age (y) | 58.30±11.3 | 69.74±42.87 | 60.04±31.4 | 0.26 |
| Sex (M %) | 14(60.8) | 16(69.5) | 30(65.2) | 0.54 |
| Duration on HD (y) | 50.60±40.6 | 52.93±46.51 | 51.74±43.1 | 0.86 |
| Smoking | 6(26%) | 2(8.7%) | 8(17.4%) | 0.12 |
| Metabolic characteristics | | | | |
| Height (cm) | 163.58±7.8 | 161.37±9.9 | 162.57±8.8 | 0.47 |
| Weight (kg) | 69.21±12.3 | 68.40±14.5 | 68.77±13.3 | 0.87 |
| BMI (kg/m2) | 24.81±3.1 | 24.62±5.8 | 24.72±4.6 | 0.92 |
| MET (Met.h/d) | 30.50±9.4 | 28.99±5.9 | 29.75±7.8 | 0.52 |
| Serum biochemistry tests | | | | |
| Serum creatinine (mg/dL) | 8.50±2.3 | 8.4±2.4 | 8.46±2.3 | 0.91 |
| BUN (mg/dL) | 65.00±16.9 | 70.47±22.3 | 67.80±19.8 | 0.36 |
| FBS (mg/dL) | 129.77±57.9 | 137.87±92.96 | 133.91±77.0 | 0.73 |
| ALP (IU/L) | 500.14±69.8 | 628.83±184.46 | 565.91±99.6 | 0.52 |
| WBC(cell/l) | 7.21±1.8 | 6.17±2.1 | 6.68±2.0 | 0.08 |
| Quality of life | 57.14±23.4 | 65.16±18.5 | 60.97±21.4 | 0.22 |
| Bowel habit | | | | |
| Defecation frequency (times/week) | 7.23±5.3 | 8.63±5.9 | 7.93±5.6 | 0.41 |
| Defecation score[2] | 19.22±10.5 | 20.04±9.8 | 19.63±10.1 | 0.79 |
| Ease of defecation (score)[3] | 1.78±0.6 | 1.86±0.7 | 1.82±0.6 | 0.68 |
| Abdominal symptoms | | | | |
| Borborygmus (score)[4] | 1.86±0.8 | 2.00±0.7 | 1.93±0.78 | 0.58 |
| Flatulence (score)[4] | 1.95±0.9 | 2.36±0.8 | 2.15±0.8 | 0.11 |

| | | | | |
|---|---|---|---|---|
| Flatus (score)[5] | 1.68±0.7 | 1.81±0.8 | 1.75±0.7 | 0.55 |

Table abbreviations: BMI: body mass index; MET: metabolic equivalent tasks; BUN: blood urea nitrogen; FBS, fasting blood sugar; ALP: alkaline phosphatase; WBC: white blood cell
1 Values are mean ± SD [2] Scores 0 (very hard stool)–30 (watery stool) [3] Scores 1 (difficult), 2 (easy) and 3 (very easy) [4]Scores 1 (frequent), 2 (occasional) and 3 (almost never). [5]Score1 Score 2 score3??/

**Table 2:** Mean values of the effect of synbiotic supplement versus placebo on aspects of quality of life between the two groups[1]

| | Synbiotic group(n 24) | | Placebo group(n 24) | | P[2] |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Quality of life indices | | | | | |
| Physical Functioning | 52.27 | 0.32 | 55.5 | 0.34 | 0.48 |
| Physical Role Functioning | 29.29 | 9.7 | 34.02 | 10.3 | 0.75 |
| Bodily Pain | 70.66 | 6.5 | 72.64 | 6.8 | 0.84 |
| General Health Perception | 47.30 | 3.6 | 51.73 | 3.9 | 0.43 |
| Vitality | 59.63 | 4.3 | 53.23 | 4.6 | 0.33 |
| Social Functioning | 73.82 | 5.4 | 70.67 | 5.7 | 0.70 |
| Mental Health | 66.79 | 4.2 | 62.62 | 4.4 | 0.52 |
| Emotional Role Functioning | 58.83 | 9.8 | 45.28 | 10.3 | 0.37 |
| Physical Component Summary | 52.93 | 3.3 | 53.93 | 3.6 | 0.84 |
| Mental Component Summary | 61.41 | 3.7 | 58.44 | 4.1 | 0.61 |
| Quality of life | 58.48 | 3.4 | 56.43 | 3.7 | 0.70 |

1 Values are mean ± SD 2 Based on ANCOVA test adjusted for baseline values of the outcome, sex, age, and duration on HD, metabolic equivalent tasks

**Table 3:** The baseline and final values of the effect of synbiotic supplement versus placebo on different aspects of gastrointestinal behavior between the two groups[1]

| | Synbiotic group (n 24) | | | Placebo group (n 24) | | |
|---|---|---|---|---|---|---|
| | Baseline | Final | P[2] | Baseline | Final | P[2] |
| Bowel habits | | | | | | |
| Defecation frequency (times/week) | 7.2,7.0(1-24) | 7.3,7.0(1.5-24) | 0.97 | 8.6,7.0(1-24) | 6.4,7.0(1-10.5) | 0.01 |
| Defecation score[3] | 19.2,20(0-300 | 19.8,20(10-30) | 0.90 | 20.0,25(0-30) | 21.4,20(10-30) | 0.23 |
| Ease of defecation (score)[4] | 1.7,2(1-3) | 1.9,2(1-2) | 0.52 | 1.8,2(1-3) | 1.7,2(1-2) | 0.52 |
| Abdominal symptoms | | | | | | |
| Borborygmus (score)[5] | 1.8,2(1-3) | 2.0,2(1-3) | 0.45 | 2,2(1-3) | 1.9,2(1-3) | 0.49 |
| Flatulence (score)[5] | 1.9,2(1-3) | 2.2,2(1-3) | 0.14 | 2.3,3(1-3) | 2.2,2(1-3) | 0.25 |
| Flatus (score)[5] | 1.6,2(1-3) | 1.9,2(1-3) | 0.08 | 1.8,2(1-3) | 1.7,2(1-3) | 0.44 |

1Values are shown as mean, median (min–max). 2 P-values were obtained using Wilcoxon signed-rank test
[3]Scores 0 (very hard stool)–30 (watery stool), [4] Scores 1 (difficult), 2 (easy) and 3 (very easy). [5] Scores 1 (frequent), 2 (occasional) and 3 (almost never).

**Table 4:** The Mean values of the effect of synbiotic supplement versus placebo on Serum biochemistry tests between the two groups[1]

| | Synbiotic group(n 24) | | Placebo group(n 24) | | P[2] |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| FBS (mg/dL) | 109.3 | 12.6 | 129.4 | 12.6 | 0.27 |
| BUN (mg/dL) | 65.52 | 4.3 | 69.8 | 4.3 | 0.50 |
| Serum creatinine (mg/dL) | 8.5 | 0.4 | 8.3 | 0.4 | 0.78 |
| ALP (IU/L) | 515.5 | 138.3 | 574.0 | 138.2 | 0.77 |
| WBC(cell/L) | 7.5 | 0.4 | 6.1 | 0.4 | 0.03 |
| Placket(cell/L) | 205.3 | 15.0 | 150.7 | 15.1 | 0.01 |
| lymphocytes(cell/L) | 24.1 | 1.8 | 30.4 | 1.8 | 0.02 |
| Eosinophils(cell/L) | 3.9 | 0.6 | 2.6 | 0.5 | 0.11 |
| Monocytes(cell/L) | 1.93 | 0.1 | 2.2 | 0.2 | 0.28 |
| Neutrophils(cell/L) | 69.9 | 1.8 | 65.0 | 1.9 | 0.07 |

Table abbreviations: FBS: fasting blood sugar; BUN: blood urea nitrogen; ALP: alkaline phosphatase; WBC: white blood cell. 1 Values are mean ± SD 2 Based on ANCOVA adjusted for baseline values of the outcome, sex, age, and duration on HD, metabolic equivalent tasks