ORIGINAL ARTICLE

The effects of probiotic supplement on hemoglobin in chronic renal failure patients under hemodialysis: A randomized clinical trial

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Background: Chronic inflammation is one of the causes of anemia in chronic renal failure patients under hemodialysis. Probiotics probably establish a balance between pro- and anti-inflammatory cytokines. The study was conducted to determine the effects of probiotic supplementation on hemoglobin (Hb) in hemodialysis patients. **Materials and Methods:** A parallel clinical trial was conducted in which patients were randomly allocated into two groups. The intervention group (n = 18) was given a 500 mg probiotic supplement (a capsule) every day whereas the control group (n = 18) received placebo (a capsule), both for 3 months. Hb levels and C-reactive protein (CRP) levels were measured for three periods. The data were analyzed in SPSS-16 using statistical tests including the t-test and repeated-measures ANOVA. **Results:** In the probiotic supplementation group, the mean Hb was 9.22 ± 1.04 mg/dl before the intervention and reached 10.85 ± 1.177 mg/dl afterward, while in the placebo group, the mean Hb level was 9.38 ± 0.97 mg/dl before the intervention and reached 10.03 ± 1.97 mg/dl afterward ($P > 0.05$). During the study, the placebo caused to increase of Hb temporary, but in longer term, the effect of probiotic was more manifested. Hb levels increased in both groups although the change was not statistically significant ($P > 0.05$). The findings showed no significant differences between the two groups in either the pre- or post-intervention CRP levels ($P = 0.239$). **Conclusion:** Probiotic supplementation decreased Hb fluctuations in hemodialysis patients but did not result in a significant increase in Hb levels. Similar studies are therefore recommended to be conducted with a prolonged duration of the study or an increased probiotic dose with larger sample size to complete the results of the present study.

Key words: Chronic renal failure, hemodialysis, hemoglobin, probiotic

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INTRODUCTION

Chronic kidney disease (CKD) is a major health problem worldwide.[1,2] The progression of chronic renal failure toward end-stage renal disease is on the rise. This disease is becoming a global pandemic.[3] Anemia is a common and costly complication of chronic renal failure.[4] It is considered one of the risk factors for cardiovascular complications in these patients,[4,5] increases mortality, decreases quality of life, and affects cognitive function and physical capacity.[6,7] Decreased erythropoietin production by the kidney is the main cause of anemia in these patients.[8] However, several other factors also contribute to the development of anemia in end-stage renal disease, such as the decreased lifespan of red blood cells in the uremic environment, reduced iron absorption from the intestine, chronic blood loss in each hemodialysis session, and inflammation.[9] CKD is recognized as a chronic inflammatory disease. Studies showed that the levels of inflammatory markers are increased in chronic kidney patients compared to healthy population.[10] Inflammation is quite common in hemodialysis patients and has a prevalence of 40%–60%.[11]

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Anemia is one of the harmful effects of inflammation in these 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.[12] In addition, inflammation is considered to be one of the main factors affecting hemoglobin (Hb) fluctuations in chronic renal failure patients, and high C-reactive protein (CRP) levels also predict Hb fluctuations in these patients.[13] Various parameters are used to monitor the progression of inflammation. CRP level is a sensitive marker in the evaluation of inflammation.[14] Given the role of inflammation in anemia and the Hb fluctuations in these patients, a treatment strategy that can affect chronic inflammation can be examined in clinical studies for the better modification of anemia. Probiotics are nonpathogenic microorganisms that, if used alive and in sufficient numbers, will have health benefits for their host through establishing microbial balance in the intestine.[15] With the fluctuations of the intestinal bacteria, probiotics can establish a balance between pro- and anti-inflammatory cytokines in the body.[16] The moderating effect of probiotics on inflammation has been approved for some inflammatory diseases, including diabetes,[17] nonalcoholic fatty liver,[18] chronic inflammation of the intestine,[19,20] pregnancy,[21] rheumatoid arthritis,[22] and obesity[23] and also for patients admitted to ICUs.[24]

Studies have obtained various results; however, despite the chronic inflammatory process noticed in hemodialysis patients and the essential role of chronic inflammation in anemia, no studies have yet been conducted on the effects of probiotics on Hb (index of anemia) with a focus on the moderating effects of probiotics on inflammation in the databases examined. Furthermore, the evidence indicates that Asians have a lower intake of dairy products such as probiotics.[25]

The present study was therefore conducted to determine the effects of probiotic supplementation on Hb in hemodialysis patients.

MATERIALS AND METHODS

Design and setting

The present study was a clinical trial with two parallel groups that it was conducted after being approved by the Ethics Committee (Ethical Code: 562089303182) and obtaining a formal approval for its proposal. All the patients received the necessary information about the study and submitted their written informed consent for participating in the study. The study recruitment started and ended at date August 23, 2014, November 22, 2014, respectively. The study was designed and supervised by the researchers and through coordination with Golestan University of Medical Sciences Vice-Chancellor for Research and Technology, Iran. This study recorded and approved by the Iranian Registry of Clinical Trials (code: 2013072710325N2).

Study population

The population surveyed in this study suffered from chronic renal failure and underwent hemodialysis in two hemodialysis centers including 5 Azar Hospital in Gorgan and Imam Hosein Hospital, Shahroud. They received 12,000 units of erythropoietin alpha injection per week but had Hb levels lower than 110 mg/dL over the past 3 months. The sample size was determined according to Moojerloo *et al*.'s study.[26] The study criteria consisted of being over 17 years in age, undergoing three 4-h dialysis sessions per week, positive CRP results, absence of a severe hyperparathyroidism, absence of active bleeding and surgery in the past 3 months, absence of Hb disorders, absence of anemia due to iron, folate, or vitamin B12 deficiencies, absence of active infections, absence of immune system disorders, absence of malignancies, not being an alcoholic, not being under treatment with antibiotics, not taking corticosteroids and not being infected with HIV, and eligibility criteria obtained by probiotics food recall questionnaire.

Randomization and study intervention

Convenience sampling and simple randomly allocation was used to designate the patients to intervention or control groups. The patients were randomly allocated to Groups A and B (n = 18 for each) using two sets of random numbers with codes 1–36 and were assigned probiotic capsules in one group and placebos in the other [Figure 1]. The study was double blinded, so that neither the patients nor the evaluators had any information about either of the two groups. Indeed the participants did not know which groups they belonged to (probiotic or placebo group). The intervention group received a 500 mg daily oral dose of probiotics and the control group received a placebo that was similar to the

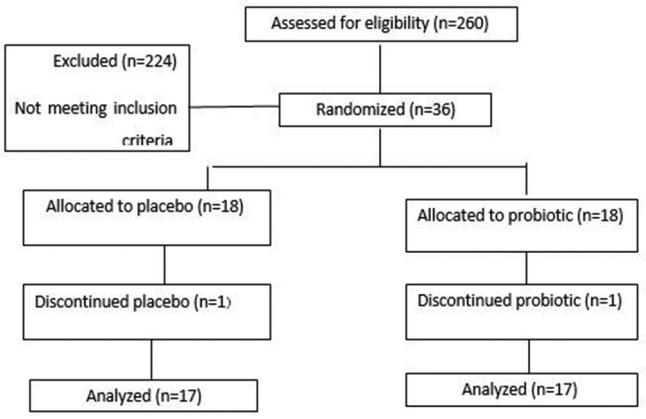

Figure 1: Flowchart of random allocation

probiotic supplements and contained starch. The probiotic supplements contained seven strains, *Lactobacillus acidophilus*, *Bifidobacterium* and *Streptococcus thermophilus* (i.e. beneficial bacteria) produced in the form of 500 mg capsules by Zist Takhmir Company in Iran. The strains used in this probiotic supplement included the followings:

1. *L. acidophilus* (3 × 1010 CFU/g)
2. *Lactobacillus casei* (3 × 109 CFU/g)
3. *Lactobacillus rhamnosus* (7 × 109 CFU/g)
4. *Lactobacillus bulgaricus* (5 × 108 CFU/g)
5. *Bifidobacterium breve* (2 × 1010 CFU/g)
6. *Bifidobacterium longum* (1 × 109 CFU/g)
7. *S. thermophilus* (3 × 108 CFU/g).

The patients completed a 24-h probiotic food recalls questionnaire designed by researchers of the project in the form of a questionnaire examining their probiotic diet on 2 weekdays and 1 day of the weekend to ensure that they did not consume probiotic food products. Its validity assessed through faculty members and experts. The reliability of the questionnaire was assessed through Cronbach's alpha.

Participants' diet, levels of activity, and medications used did not change during the study and all the patients received the necessary training on these subjects. The erythropoietin dose received by each patient did not increase during the study. Both groups received daily folic acid supplements and monthly vitamin B12 supplements and received no other additional supplements. The study exclusion criteria consisted of taking antibiotics during the study, hospitalization, need for surgery, medication therapy changes, dialysis schedule changes, and patient's unwillingness to continue participation in the study, a diagnosis of malignancy during the study, and active bleeding during the study and the need for blood transfusion. The researcher kept in touch with the patients over the phone throughout the study and also visited them during their hemodialysis sessions.

Follow-up and study endpoints

The study was carried out over the course of 12 weeks. The data collection tools used included a questionnaire and a laboratory instrument. The questionnaire covered participants' demographic information and disease and medication history, collected through interviews, observations, and patient records. The initial variable was Hb concentration (index of anemia) measured by Sysmex cell counter (Kx-21N model). The Sysmex Kx-21N is an automated blood cell counter intended for *in vitro* diagnostic use in clinical laboratories. It is a reliable and a compact, fully automated hematology analyzer with simultaneous analysis of 18 parameters in whole blood mode and capillary blood mode. This analyzer counts blood cells as routine in a few minutes.[27,28]

The secondary variable was CRP level determined quantitatively by BT-3500 Autoanalyzer that Pars Azmoon kit was used for measuring CRP levels. The test is a reliable tool with sensitivity, specificity, and positive predictive value of 98.18, 61.58, and 94.1, respectively.[29] The normal range of CRP was determined as lower than 10 mg/L; CRP levels >10 mg/L were taken as a case of positive CRP. Arterial line blood sampling was performed for the laboratory tests before starting the dialysis, and storage conditions were identical for all the samples throughout the study. During the 12 weeks of the study, Hb levels and CRP were measured on days 0, 30, 60, and 90 of the intervention in both groups. It should be noted that the last Hb measurement was carried out in the first hemodialysis session and after receiving the last dose of the probiotic capsules or the placebo. One of the researchers' colleagues performed affairs such as generating the random allocation sequence, enrolling the participants, and assigning participants to intervention.

Statistical analysis

The data obtained were analyzed in SPSS-16 (SPSS Inc. Released 2007. SPSS for Windows, ver. 16.0. Chicago, IL, USA) using statistical tests including the independent *t*-test for comparing Hb and CRP level between two groups at baseline. The ANOVA was used for comparing Hb and CRP levels between groups. Repeated-measures ANOVA between the intervention and placebo groups was used to compare of mean Hb within groups including time effect, interaction of time, and intervention. Mauchly's sphericity test was used to validate ANOVA, but it was not appropriate. Therefore, a Greenhouse–Geisser correction was used. The level of significance was considered at $P < 0.05$ in the study.

RESULTS

The majority of participants were male (55.6%), under diploma (77.8%), the age range of 47–60 years (41.7%), and upper 39-month dialysis duration (30.6%) [Table 1]. The prevalence of Hb levels lower than the target levels (110 mg/dL) was 20% in the hemodialysis patients examined. The study was conducted on 36 patients, including 20 men (55.5%) and 16 women (44.5%), who were assigned through simple random allocation to either the intervention group consisting of 10 men (55.5%) and 8 women (44.5%) or the control group consisting of 10 men (55.5%) and 8 women (44.5%), with a similar gender distribution in both groups. With a mean age of 54.17 ± 13.60 in the intervention group and 61.50 ± 8.68 in the control group, the overall mean age of participants was 57.8 years and the two groups were not significantly different in terms of their age distribution ($P > 0.05$). Before the intervention, the mean Hb level was 9.2235 ± 1.0483 in the probiotic supplement group and 9.3882 ± 0.9738 in the control group and the two groups were not significantly different in terms of their mean preintervention Hb levels ($P > 0.05$). 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 9.3588 ± 1.1843, 9.6882 ± 1.5555, and 10.8588 ± 1.774, respectively, in the probiotic supplement group and 10.0353 ± 1.9792 in the 3rd month in the control group and there were no statistically significant differences between the mean postintervention Hb levels in the probiotic group and the placebo group [Table 2]. The process of Hb changes during the study showed an increasing trend in the probiotic supplement group while the control group did not follow this trend and showed fluctuations instead [Figure 2].

Repeated-measures ANOVA (Greenhouse–Geisser correction) between the two groups showed time effect ($P \leq 0.001$), but interaction of time and intervention was not significant ($P \leq 0.254$). The study indicated that 1 month after consumption of probiotic capsule, the level of Hb of intervention group has increased while the Hb of control group decreased [Figure 3]. After the 2nd month, the level of Hb of both groups has increased while the level of Hb of intervention group was further. Indeed, the placebo caused to increase of Hb temporary, but in longer term, the effect of probiotic was more manifested.

Table 1: Demographic information of hemodialysis patients

Variable	*n* (%)
Gender	
Male	20 (55.6)
Female	16 (44.4)
Age (years)	
33-46	8 (22.2)
47-60	15 (41.7)
Up 60	13 (36.1)
Graduate	
Under diploma	28 (77.8)
Diploma and undergraduate	7 (19.4)
Postgraduate	1 (2.8)
Hemodialysis duration (months)	
6-12	9 (25)
13-25	8 (22.2)
26-38	8 (22.2)
Up to 38	11 (30.6)

Serum CRP levels were controlled quantitatively in the intervention and control groups before the intervention and then 30, 60, and 90 days after the beginning of the intervention alongside Hb levels. The findings showed no significant differences between the two groups in either the pre- or post-intervention CRP levels ($P = 0.239$) [Table 3].

Although the findings showed no significant differences in the CRP levels in the intervention and control groups before and after the intervention [Table 3], an unexpected rising trend was noticed for CRP levels in the intervention group. The outliers of CRP levels were excluded from both groups and the statistical analysis was performed once again. The justification for excluding the outliers was that the patients with outliers of CRP levels might possess intervening factors not yet detected by the researcher that may affect the results of the study. The outliers pertained to four individuals, two of whom belonged to the intervention group and two to the control group. After excluding the outliers and re-analyzing the data, postintervention CRP levels increased once again in both groups; however, there were no significant differences between the two groups in this regard [Table 4].

DISCUSSION

The daily intake of probiotic supplements for 90 days was well tolerated in chronic renal failure patients under

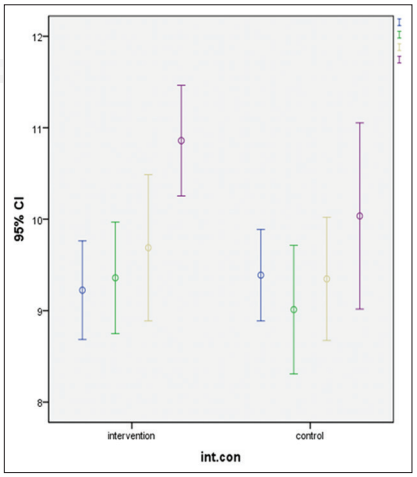

Figure 2: Hemoglobin changes in probiotic and placebo groups

Table 2: Mean and standard deviation of patient's hemoglobin before and after intervention in probiotic and placebo groups

Group	Hb (mg/dl)	Mean±SD		*P*
		Probiotic assumption (*n*=18)	Placebo assumption (*n*=18)	
Before intervention	Mean Hb of 3 months	9.22±1.04	9.38±0.97	0.857
After intervention	Hb 1 month after intervention	9.35±1.18	9.01±1.36	0.435
	Hb 2 months after intervention	9.68±1.55	9.34±1.31	0.494
	Hb 3 months after intervention	10.85±1.17	10.03±1.97	0.152
P		0.757		

Hb = Hemoglobin; SD = Standard deviation

Table 3: Mean and standard deviation of C-reactive protein serum before and after intervention in two groups

Group	CRP (mg/L), mean±SD			
	Before intervention	1 month after intervention	2 months after intervention	3 months after intervention
Intervention group (n=18)	57.68±32.09	62.26±38.33	65.41±38.94	73.22±41.89
Control group (n=18)	74.49±50.15	63.30±44.35	78.45±61.71	76.73±60.27
P	0.239	0.942	0.467	0.836

CRP = C-reactive protein; SD = Standard deviation

Table 4: Mean and standard deviation C-reactive protein serum after excluding the outliers C-reactive protein in two groups

Group	CRP (mg/L), mean±SD			
	Before intervention	1 month after intervention	2 months after intervention	3 months after intervention
Intervention group	49.99±23.47	55.74±27.88	59.07±30.03	66.02±34.58
Control group	56.56±20.83	56.48±31.77	71.98±56.21	71.70±55.73
P	0.424	0.947	0.427	0.740

CRP = C-reactive protein; SD = Standard deviation

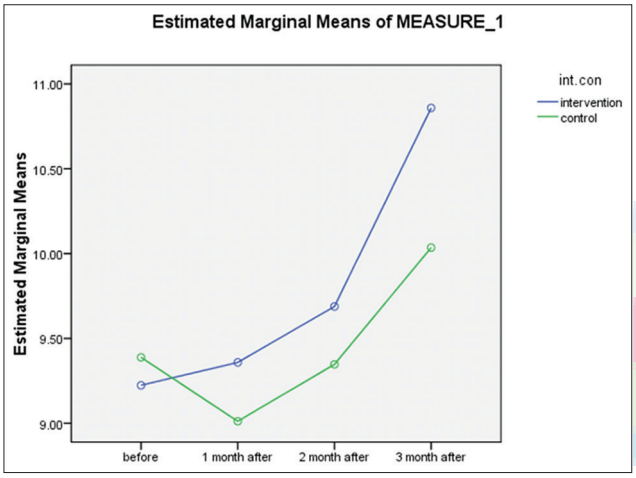

Figure 3: Hemoglobin level in probiotic and placebo group in baseline and 1, 2, and 3 months later

hemodialysis and no complications developed. The results of the study showed increased Hb levels in the probiotic supplementation and placebo groups after the intervention; however, the rate of increase was higher in the intervention group (probiotic supplementation) compared to in the placebo group. In addition, Hb levels fluctuated in the placebo group throughout the study, while they followed only an increasing trend and showed no fluctuations and in longer term the effect of probiotic was more manifested. Nevertheless, the increase in Hb levels was not significantly different between the intervention and control groups. A study on rats indicated that probiotic supplementation has increased Hb levels of the rats.[30] Ranganathan *et al.* studied the effects of *Bifidobacterium* and *L. acidophilus* probiotic supplementation on Stage 3 and 4 chronic renal failure patients for 6 months, but due to the small sample size (n = 16), the researchers could not accurately report hematological parameters such as Hb levels.[31] Cox *et al.* studied the effects of single strain *Bifidobacterium*, two strains of *L. acidophilus* and two strains of *Bifidobacterium* on hematological parameters in healthy individuals and showed that hematological parameters changed very slightly in the healthy individuals in the intervention and control groups after the 150-day probiotic supplementation, and the pre- and post-intervention difference was not statistically significant.[32] The present study showed that, at baseline, as common markers of inflammation, CRP levels were higher than normal in all the patients and ranged from a minimum of 22.8 mg/L to a maximum of 225 mg/L. Given the initial serum levels of CRP in these patients, the study's assumption about the high rate of inflammation in hemodialysis patients who have an uncompensated anemia despite their erythropoietin injections was confirmed; it is clear that the present study was conducted in a particular group of hemodialysis patients. The study had assumed that probiotic supplementation could decrease CRP levels in these patients, but the results showed that after 90 days of probiotic supplementation, CRP levels had not changed significantly in the 1st, 2nd, and 3rd month of the study in the probiotic and control groups. In addition, CRP levels increased in both intervention and control groups after the intervention. The effects of probiotic yogurt on CRP inflammatory marker and interleukin (IL-6) levels in type 2 diabetic patients indicated that the probiotic yogurt used contained *L. acidophilus* and *Bifidobacterium*; no significant differences in CRP and IL-6 levels between the probiotic and ordinary yogurt groups.[33] The effects of 7 days of probiotic supplementation with seven strains of *L. acidophilus* and *Bifidobacterium* on patients with acute conditions showed a significant decrease in CRP levels in the probiotic group.[24] In addition, the effects of Renadyl probiotic dietary supplements on CRP in dialysis patients for 60 days showed a decreased CRP level after their treatment although the decrease was not statistically significant.[34] Probiotic yogurt containing *L. acidophilus* and

Bifidobacterium in pregnant women decreased significantly the levels of CRP after 9 weeks of probiotic yogurt consumption.[21] Shadnoush *et al.* showed that 8 weeks of probiotic yogurt consumption significantly reduced CRP levels in patients with inflammatory bowel disease[19] that are incongruent with our study. Overall, the present study found no significant increase in Hb levels or decrease in serum CRP levels after the consumption of probiotics. Gohel *et al*. found that Probiotic had no significant effect on Hb and hematological parameters.[35] In the study, CRP was measured as an inflammatory indicator with an assumption that if the probiotic decreases inflammatory indicator, the Hb level will increase. However, probiotic did not decrease the level of CRP and consequently Hb did not increase significantly.

Limitation

Inadequate doses of probiotics can be a potential obstacle for the mentioned study. The dose of probiotics prescribed for the patients appears to not have been sufficient for the objectives of the study. In addition, it seems that duration of the study was not adequate because the Hb plot from 2 to 3 months after intervention had an increase in the intervention than control group. Therefore, if the intervention be continued for 4 or 5 months, the probiotic indicates a significant effect.

CONCLUSION

Probiotic supplementation did not cause a significant increase in Hb levels in hemodialysis patients but decreased Hb fluctuations in them. In addition, given the growing increase in CRP levels in this group of hemodialysis patients, hemodialysis patients who do not reach the target Hb levels despite their erythropoietin injections seem to need further investigations and the performance of primary paraclinical measures checking for foci of latent infection and potential malnutrition and then, if necessary, to also be checked for other inflammatory markers.

Given that only a small number of human studies have been conducted on the effects of probiotics on hematological parameters including Hb and inflammatory markers in chronic renal failure patients, similar studies are recommended to be conducted with increased study durations and a control of other inflammatory markers including IL-6 for assessing the effects of probiotics on hematologic parameters in these patients.

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Conflicts of interest

There are no conflicts of interest.

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