Effect of a Symbiotic Gel (*Lactobacillus acidophilus* + *Bifidobacterium lactis* + Inulin) on Presence and Severity of Gastrointestinal Symptoms in Hemodialysis Patients

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Objective: The study aimed to assess the effect of a symbiotic gel on presence and severity of gastrointestinal symptoms (GIS) in hemodialysis patients.

Design: A double-blinded, placebo-controlled, randomized, clinical trial was designed. The study was conducted at 2 public hospitals in Guadalajara, Mexico.

Subjects and Intervention: Twenty-two patients were randomized to the intervention group (nutritional counseling + symbiotic gel) and 20 patients were randomized to the control group (nutritional counseling + placebo), during 2 months of follow-up.

Main Outcome Measure: Presence and monthly episodes of GIS were assessed by direct interview and severity by using the self-administered GIS questionnaire. Additionally, biochemical parameters, inflammatory markers, and nutritional status (dietary intake, subjective global assessment, anthropometry, and body composition) were evaluated.

Results: After a 2-month treatment, intervention group had a significant reduction in prevalence and monthly episodes of vomit, heartburn, and stomachache, as well as a significant decrease in GIS severity compared with control group. Moreover, intervention group had a greater yet not significant decrease in the prevalence of malnutrition and a trend to reduce their C-reactive protein and tumor necrosis factor α levels compared with control group. No symbiotic-related adverse side effects were shown in these patients. Clinical studies with longer follow-up and sample size are needed to confirm these results.

Conclusions: We concluded that administration of a symbiotic gel is a safe and simple way to improve common GIS in dialysis patients.

Introduction

MALNUTRITION IS ONE of the most prevalent consequences in dialysis patients, particularly in countries like ours, where more than 80% have malnutrition, evaluated as any malnutrition degree according to subjective global assessment (SGA).[1] In addition, inflammation, another common condition in these patients, plays a significant role exacerbating malnutrition due to an increase in rest energy expenditure, inhibition of muscular, and hepatic protein synthesis and, consequently, decreasing somatic and visceral protein storage. It has been established that both malnutrition and inflammation are associated with atherosclerosis progression and with an increased risk of all cause and cardiovascular morbidity and mortality in dialysis patients.[2,3]

Etiology of malnutrition and inflammation in dialysis patients is complex. However, in recent times, altered gut microflora, one common problem with negative effects on nutritional and inflammatory status has become an area of considerable interest.[4,5] Uremic patients show greatly increased counts of pathogenic microorganisms in

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the intestine, and the absorption of proteins (and other nutrients) is hampered, so that more substrate enters the intestine; thus, more generation and absorption of uremic toxins occur, which worsens the uremic and nutritional status and accentuates gastrointestinal symptoms (GIS).[5] Moreover, intestinal bacterial overgrowth enhances bacterial translocation and production of gut-derived endotoxins, which may increase systemic inflammation.[4]

Probiotics are live microorganisms that enhance intestinal tract health by decreasing the counts of pathogenic microorganisms and, thus, the uremic toxins production. Prebiotics are nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of probiotics. Finally, combinations of probiotics and prebiotics (symbiotic) may result in synergistic effects on gastrointestinal function, which indirectly may benefit inflammatory and nutritional status of dialysis patients.[6]

Although there is evidence of the beneficial effects of oral supplementation with prebiotics and probiotics in the general population,[7,8] few studies have demonstrated the benefits of these dietetic compounds in dialysis patients[9] and, particularly, none in our country, where malnutrition seems to be more prevalent than in other countries.[1] The purpose of this study was to assess the effect of a symbiotic on GIS in hemodialysis patients; additionally the effect on inflammatory and nutritional markers was evaluated.

Methods

Study Population

Adult clinically stable hemodialysis patients with arteriovenous fistula, aged 18 years and older, and receiving thrice-weekly hemodialysis for at least 3 months before start the study, attending at 2 public hospitals in Jalisco (México), were evaluated for enrollment in this study. Patients with the following criteria were excluded: usual intake of probiotics, omega-3 fatty acids, pentoxifylline, and immunosuppressive and/or nonsteroidal antiinflammatory drugs; medical illnesses that affect nutritional and inflammatory status (cancer, decompensated heart failure, chronic liver diseases, intestinal malabsorption, active infections, and acquired immunodeficiency syndrome); filters reuse; and renal transplant antecedent. After inclusion, those patients who developed any of the diseases described previously or met any of the exclusion criteria as well as patients with lack of treatment adherence (<80%) and voluntary dropout the study were eliminated. Ethic approval was granted by the Research Ethic Committee of both hospitals (Registration numbers: 044/10 and 265/12).

Study Design and Treatment Period

A double-blinded, placebo-controlled, randomized, clinical trial was designed. Once the eligibility criteria had been met and informed consent was obtained, eligible patients were randomly allocated to receive nutritional counseling + symbiotic gel (intervention group) or nutritional counseling + placebo (control group) during 2 months of follow-up. Nutritional counseling consisted in an individualized dietary prescription, based on Kidney Disease Outcomes Quality Initiative recommendations,[10] provided by only 1 experienced dietician (D.V.H.), that included energy (30-35 kcal/kg/day) and protein intake (1.1-1.2 g/kg/day), as well as potassium, phosphorus, and sodium restriction, according with biochemical blood parameters. The symbiotic gel (Nutrihealth; Nutrimentos Inteligentes, S.A. de C.V, Guadalajara, Jalisco, México) contained a mix of probiotics (*Lactobacillus acidophilus NCFM* and *Bifidobacterium lactis Bi-07*) for a total of 11×10^6 colony-forming units; 2.31 g of a prebiotic fiber (inulin); 1.5 g of omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids); and vitamins (complex B, folic acid, ascorbic acid, and vitamin E). The placebo had identical color, size, and flavor to the interventional product. At baseline and every month, both groups received 2 boxes with 14 gels each. Subjects of both groups consumed 1 gel/day in fasting. To evaluate the treatment adherence, there was a monthly count of the empty package.

Every month, tolerability and safety of the symbiotic gel were evaluated by direct interview by the same experienced dietician (D.V.H.), who was blinded to the intervention treatment. Additionally, the nephrologist in charge of patients was aware of any side effect.

Gastrointestinal Symptom Assessment

By direct interview (D.V.H.), presence and monthly episodes of anorexia, nauseas, vomit, heartburn, stomachache, bloating, constipation, and diarrhea were evaluated. To assess the severity of GIS, we used the self-administered GIS questionnaire (GSQ).[11] The GSQ contains 8 items, rated in 5 categories relating to severity (1 = none, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe). The GSQ data are presented as total scores (8-40); the higher the score, the more pronounced the symptoms. All patients answered the GSQ based on the month preceding the assessment.

Nutritional and Biochemical Assessment

Dietary intake was monthly assessed by two 24-h dietary recall (D.V.H.). Participants were requested to remember all food and fluids consumed the day before the assessment. Dietary recalls information was processed using the software Nutrikcal (Consinfo SC, Mexico City, México), and average nutrient consumption was calculated.

Nutritional status was evaluated at baseline and at the second month of treatment using the original version of SGA,[12] which evaluates weight loss, dietary intake, GIS, functional capacity, and physical examination, including subcutaneous fat and muscle stores. According to SGA results, nutritional status was classified into 3 categories: well nourished, moderate or mild malnutrition, and severe malnutrition.

Weight, height, mid-arm muscle circumference, and tricipital and subscapular skinfold thickness were measured according to the International Society for the Advancement of Kinanthropometry guidelines.[13] Body mass index and mid-arm muscle and fat areas were calculated.[14,15] Body composition was measured 30 minutes after hemodialysis by multifrequency whole body bioimpedance spectroscopy assessment using the Body Composition Monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany).

Biochemical analysis was monthly performed in a central laboratory. Serum glucose, urea, blood urea nitrogen, creatinine, lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol [c-HDL], and low-density lipoprotein cholesterol[c-LDL]), and electrolytes (sodium, potassium, phosphorus, and calcium) were undertaken by usual methods; serum albumin was determined by the green bromocresol method. At baseline and second month of treatment, C-reactive protein (CRP) was determined by a high-sensitivity chemiluminescent immunoassay.

Monthly, serum samples were obtained and stored at −80°C until determination of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) by enzyme-linked immunosorbent assay (ELISA) using high-sensitivity kits (Human TNF-alpha Quantikine ELISA Kit and Human IL-6 Quantikine ELISA Kit; R&D Systems, Minneapolis, MN) (A.S.R., J.A.B.).

Statistical Methods

Data management and statistical analyses were performed using statistical software SPSS version 10.0 (IBM Corporation, IL). Data are presented as mean ± standard deviation, median (percentiles 25%-75%), or percentages, as appropriate. For intragroup comparisons, repeated measure analysis of variance on ranks (Friedman test) and Wilcoxon test were used in the case of dimensional variables, and McNemar test in the case of categorical variables. Intergroups comparisons were performed using U de Mann–Whitney test for dimensional variables and χ^2 test or Fisher exact test for categorical variables. Values of $P \leq .05$ were considered significant.

Results

Patients

One hundred eight subjects were considered eligible to participate in this clinical trial. Nevertheless, only 42 patients met inclusion criteria and signed informed consent. At the end of the study, 4 patients were eliminated because they did not receive thrice-weekly hemodialysis, and there was a voluntary dropout of 3 patients, 2 of the control group and 1 of the intervention group because of diarrhea. For the analysis of TNF-α and IL-6, we only could include 23 patients because of lack of feasible samples (Fig. 1).

Patient demographic information is listed in Table 1. There was no significant difference between participants allocated to either the intervention or control group at baseline in age, genre, family history of disease, etiology of chronic kidney disease, and time on hemodialysis.

Gastrointestinal Symptoms

Presence and monthly episodes of GIS during the study are presented in Table 2. A statistically significant difference was shown between the intervention group and the control group in the presence of vomit, heartburn, and stomachache at the end of the study. There was only a significant reduction in the presence of bloating at the first and the second month of treatment in the intervention group versus baseline. Monthly episodes of all of the GIS (except anorexia) reduced in the intervention group during the treatment period, showing a significant difference only in the case of bloating and constipation. There were also fewer episodes of vomit, heartburn, and stomachache at the second month in the intervention group compared with the control group. As depicted in Figure 2, severity of GIS significantly diminished at first month in the control group but increased at the end of the study. In contrast, severity of GIS in the intervention group significantly decreased at the second month of treatment. A statistically significant difference was shown between the intervention group and the control group at the end of the study.

Nutritional and Biochemical Evaluation

There was a significant reduction in energy intake at the end of the study in both groups (Table 3). There was also a significant decrease in total carbohydrate and protein intake in the control group at the second month of treatment compared with baseline.

Data from the SGA (Table 3) showed a trend to improve nutritional status at the end of the study in both treatment groups. Nevertheless, the intervention group had a greater yet not significant decrease in the prevalence of moderate malnutrition compared with the control group (8.3 vs. 17.7%).

Regarding the anthropometric and body composition measurements (Table 3), we observed a significant reduction in lean tissue mass (kilogram) and BCM in the control group. Also, there was a significant decrease in mid-arm fat area and BCM in the intervention group. The rest of the analyzed variables remained globally unchanged throughout the study in both treatment groups.

Most of the biochemical variables remained unchanged during follow-up in both treatment groups (Table 4). In the control group, we only observed a significant increase in sodium levels at first month of treatment, whereas in the intervention group, sodium, c-LDL, and c-HDL levels significantly increased during the study. There was a statistically significant difference between control group and intervention group in glucose and c-LDL levels at the first month of treatment. Regarding the inflammatory markers, CRP levels were significantly higher at baseline in the intervention group compared with the control group. At the second month of treatment, CRP levels had a trend to decrease in

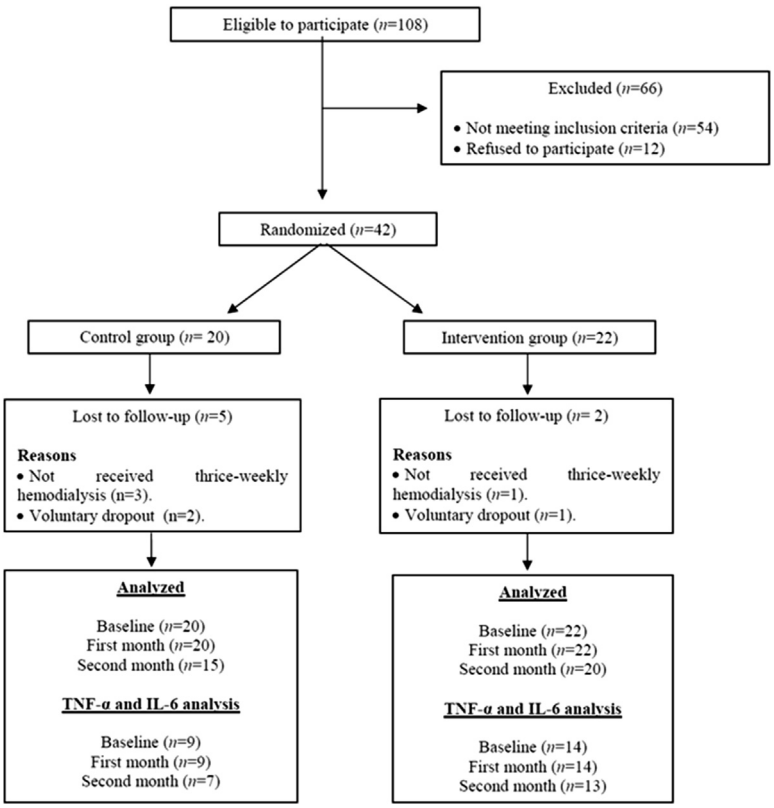

Figure 1. The Consolidated Standards of Reporting Trials (CONSORT) flowchart of participant progression throughout the study.

the intervention group, whereas IL-6 and TNF-α concentrations remained unchanged in both groups (Table 4).

Discussion

A combination of symbiotic supplementation and nutritional counseling for 2 months significantly reduces presence, monthly episodes, and severity of common GIS in hemodialysis patients as well as shows a trend to decrease inflammation and to maintain nutritional status and dietary intake.

Many randomized, placebo-controlled, clinical trials in healthy population have shown that both probiotics and symbiotics can significantly improve GIS.[7,8] On the other hand, few studies have demonstrated the beneficial effects of prebiotics and probiotics in dialysis patients by evaluating changes in biochemical parameters, quality of life, and uremic toxins.[9] Therefore, to our knowledge, this is the first placebo-controlled, randomized, clinical trial in hemodialysis patients, which showed that a symbiotic improves presence, monthly episodes, and severity of GIS, especially vomit, heartburn, and bloating. We have previously demonstrated in a subgroup of this study, that intake of a symbiotic significantly increase bifidobacteria counts in hemodialysis patients.[16] For that reason, we suggest that this beneficial effect on GIS is attributed to the modification of the intestinal microflora by the symbiotic.

Although both groups had nutritional counseling, there was a significant decrease in energy intake in both groups. However, during the follow-up, reduction in dietary intake

Table 1. Patient Demographic Characteristics

Variable	Control Group (n = 20)	Intervention Group (n = 22)
Sex, % (n)		
Men	80.0 (16)	72.7 (16)
Women	20.0 (4)	27.3 (6)
Age (y)	39.0 ± 16.0	40.6 ± 17.1
Family history, % (n)		
Diabetes	75.0 (15)	63.6 (14)
Hypertension	50.0 (10)	50.0 (11)
Obesity	55.0 (11)	31.8 (7)
Heart failure	15.0 (3)	13.6 (3)
Dyslipidemia	10.0 (2)	9.1 (2)
Cancer	10.0 (2)	31.8 (7)
Kidney disease	20.0 (4)	22.7 (5)
CKD etiology, % (n)		
Diabetes	15.0 (3)	18.2 (4)
Uric acid nephropathy	—	4.5 (1)
Renal polycystosis	15.0 (3)	—
Unknown	70.0 (14)	63.6 (14)
Hypertension	—	13.6 (3)
Time on hemodialysis (y)	5.5 ± 3.4	4.6 ± 2.1

CKD, chronic kidney disease.

Values expressed as mean ± standard deviation or percent (number).

Table 2. Presence (%, [*n*]) and Monthly Episodes (Mean ± SD) of Gastrointestinal Symptoms During the Study

	Control Group			Intervention Group		
Variable	Baseline (n = 20)	Month 1 (n = 20)	Month 2 (n = 15)	Baseline (n = 22)	Month 1 (n = 22)	Month 2 (n = 20)
Anorexia						
% (n)	15.0 (3)	20.0 (4)	26.7 (4)	13.6 (3)	9.1 (2)	15.0 (3)
Mean ± SD	0.9 ± 2.6	2.5 ± 7.0	4.1 ± 8.9	2.1 ± 7.0	0.7 ± 2.9	2.8 ± 7.8
Nausea						
% (n)	35.0 (7)	25.0 (5)	26.7 (4)	18.2 (4)	13.6 (3)	10.0 (2)
Mean ± SD	4.5 ± 8.7	1.7 ± 3.3	3.6 ± 8.9	3.1 ± 8.2	0.3 ± 1.0	1.7 ± 6.7
Vomit						
% (n)	20.0 (4)	30.0 (6)	26.7 (4)	13.6 (3)	22.7 (5)	0.0 (0)*
Mean ± SD	1.0 ± 2.7	0.4 ± 1.7	0.6 ± 1.5	1.6 ± 5.2	0.4 ± 0.9	0.0 ± 0.0*
Heartburn						
% (n)	25.0 (5)	30.0 (6)	40.0 (6)	18.2 (4)	18.2 (4)	5.0 (1)*
Mean ± SD	1.5 ± 3.9	1.0 ± 1.7	3.1 ± 5.5	2.5 ± 6.9	1.6 ± 6.3	0.2 ± 0.8*
Stomachache						
% (n)	20.0 (4)	20.0 (4)	20.0 (3)	18.2 (4)	9.1 (2)	0.0 (0)*
Mean ± SD	2.4 ± 6.8	0.5 ± 1.3	0.8 ± 2.2	2.1 ± 5.6	0.2 ± 0.8	0.0 ± 0.0*
Bloating						
% (n)	35.0 (7)	30.0 (6)	26.7 (4)	54.5 (12)	18.2 (4)†	10.0 (2)†
Mean ± SD	2.5 ± 3.9	1.5 ± 2.5	3.6 ± 6.7	9.9 ± 12.2	1.0 ± 3.1†	0.3 ± 0.9†
Constipation						
% (n)	35.0 (7)	20.0 (4)	20.0 (3)	27.3 (6)	9.1 (2)	5.0 (1)
Mean ± SD	5.1 ± 9.1	1.7 ± 4.8	1.6 ± 4.3	5.0 ± 9.2	0.6 ± 2.5†	0.3 ± 1.3†
Diarrhea						
% (n)	25.0 (5)	15.0 (3)	20.0 (3)	13.6 (3)	13.6 (3)	5.0 (1)
Mean ± SD	0.9 ± 1.6	0.4 ± 1.3	1.0 ± 3.0	1.2 ± 4.3	0.6 ± 1.8	1.4 ± 6.2

SD, standard deviation.

Values expressed as percent (number) or as mean ± SD to facilitate data interpretation. Nevertheless, statistical analysis was made with nonparametric tests.

*$P \leq .05$ versus control group.

†$P \leq .05$ versus baseline.

of protein and carbohydrates was significantly higher in the control group, which could mean that the symbiotic maintains dietary intake of these nutrients. Also, several longitudinal studies have shown that dietary intake decrease as kidney disease and time in dialysis progress.[17,18] Hence, this could partially explain the reduction in dietary intake in both groups. Patients included in the study received no continual nutritional advice before the inclusion to the study, and, when some restrictions to control serum potassium and phosphorus were applied, they significantly decreased nutritional intake, particularly when milk and beans were restricted. Additionally, study population attending these health institutions comes from the lowest social strata in Mexico, which in turn may dramatically limit access and variety of foods.[19]

Data from the SGA showed a clinically important improvement (without statistical significance) in nutritional status because of the fact that prevalence of malnutrition decreased in both treatments groups. Nevertheless, intervention group had a greater decrease compared with control group, where food intake and functional capacity were the main SGA components that contributed to this improvement (data not shown); the increase on food intake may be related with the beneficial effect of the symbiotic on GIS. Some studies have confirmed that nutritional counseling enhances nutritional status of both chronic kidney disease and dialysis patients.[1,20] The outcomes of these studies strengthen the beneficial effect of conventional nutritional counseling on nutritional status observed in the present clinical trial.

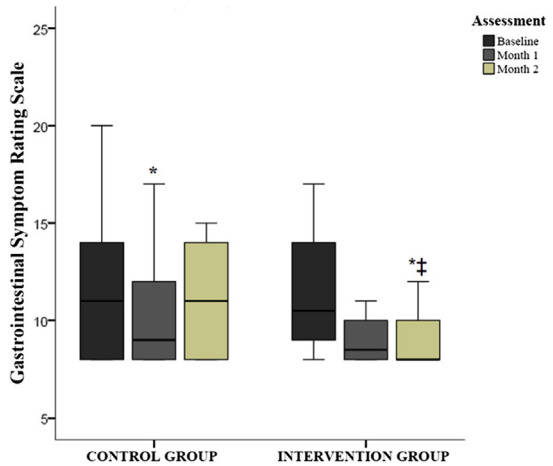

Figure 2. Gastrointestinal symptom rating scale during the study. *$P \leq .05$ versus baseline; ‡$P \leq .05$ versus control.

Table 3. Results of Nutritional Assessment During Follow-up

	Control Group			Intervention Group		
Variable	Baseline (n = 20)	Month 1 (n = 20)	Month 2 (n = 15)	Baseline (n = 22)	Month 1 (n = 22)	Month 2 (n = 20)
Energy (kcal)	1,557.1 ± 534.6	1,421.6 ± 318.3	1,229.8 ± 311.9*	1,433.2 ± 503.5	1,367.7 ± 638.2	1,237.2 ± 351.7*
Energy (kcal/kg)	25.1 ± 10.4	22.6 ± 7.6	19.4 ± 6.7	25.3 ± 13.8	24.2 ± 15.1	22.0 ± 10.5*
Carbohydrate (g)	221.6 ± 83.6	194.0 ± 47.7	166.5 ± 51.6*	190.6 ± 69.4	180.6 ± 83.3	164.8 ± 46.1
Lipid (g)	50.5 ± 20.7	48.6 ± 17.5	44.1 ± 16.9	50.4 ± 23.1	52.2 ± 35.5	44.4 ± 21.1
Protein (g)	57.8 ± 18.0	54.9 ± 12.6	44.5 ± 10.3*	57.8 ± 18.0	48.9 ± 14.5	47.6 ± 14.4
Protein (g/kg)	0.9 ± 0.3	0.8 ± 0.2	0.7 ± 0.2	0.9 ± 0.5	0.8 ± 0.3	0.8 ± 0.3
Fiber (g)	11.5 (8.3-17.5)	10.7 (6.9-15.2)	8.9 (5.8-13.5)	11.5 (8.3-17.5)	10.7 (7.1-12.6)	9.7 (6.5-13.1)
Dry weight (kg)	64.6 ± 12.4		65.4 ± 13.5	63.0 ± 18.7		61.9 ± 17.8
Height (cm)	164.1 ± 6.7			164.7 ± 10.3		
Dry BMI (kg/m^2)	24.0 ± 4.7		24.4 ± 5.0	22.9 ± 5.5		22.7 ± 5.4
TSF (mm)	10.9 ± 6.2		11.6 ± 5.3	10.7 ± 6.7		9.4 ± 5.3
SSF (mm)	13.8 ± 8.8		14.6 ± 9.7	13.6 ± 8.6		11.7 ± 6.8
MAMA (cm^2)	47.9 ± 9.9		49.7 ± 12.5	46.7 ± 12.5		45.4 ± 13.2
MAFA (cm^2)	14.9 ± 9.8		16.0 ± 8.6	15.6 ± 11.7		12.6 ± 9.1*
OH (L)	0.6 ± 1.9		1.0 ± 2.0	1.1 ± 2.6		1.3 ± 2.1
TBW (L)	31.8 ± 5.9		30.6 ± 5.3	31.3 ± 6.1		30.6 ± 5.7
E/I	0.8 ± 0.1		0.8 ± 0.1	0.8 ± 0.2		0.8 ± 0.1
LTM (kg)	35.3 ± 10.2		31.9 ± 6.2*	34.0 ± 8.8		32.6 ± 6.9
FAT (kg)	22.3 ± 12.1		24.6 ± 10.2	21.3 ± 13.8		21.5 ± 13.0
BCM (kg)	19.2 ± 6.9		16.9 ± 4.0*	18.7 ± 6.3		17.3 ± 4.6*
Nutritional status (SGA)						
A	60.0 (12)		73.3 (11)	72.7 (16)		95.0 (19)
B	35.0 (7)		26.7 (4)	22.7 (5)		5.0 (1)
C	5.0 (1)		0.0 (0)	4.5 (1)		0.0 (0)

A, well nourished; B, moderate or mild malnutrition; C, severe malnutrition; BMI, body mass index; BCM, body cell mass; E/I, extracellular/intracellular water index; FAT, fat tissue; LTM, lean tissue mass; MAFA, mid-arm fat area; MAMA, mid-arm muscle area; OH, overhydration; SGA, subjective global assessment; SSF, subscapular skinfold; TBW, total body water; TSF, triceps skinfold.

Values expressed as mean ± standard deviation, median (percentile 25, 75) or percent (number).

*$P \leq .05$ versus baseline.

Anthropometric and body composition measurements did not show important changes in both treatment groups. However, it must be notice that in the intervention group lean body mass variables remained unchanged, whereas in the control group, these variables significantly decreased. It has been demonstrated that omega-3 fatty acids are capable to preserve lean body mass in patients with advanced cancer.[21,22] Therefore, intake of a symbiotic added with omega-3 better maintains muscle and lean tissue mass in these hemodialysis patients.

Symbiotic supplementation also appeared to have beneficial effects only on serum levels of CRP. The present investigation is the first randomized clinical trial that examined the effects of a symbiotic added with omega 3 and vitamins on CRP, TNF-α, and IL-6 levels, independent predictors of cardiovascular mortality in dialysis.[23,24] Our data demonstrated that the intervention group showed a trend to decrease plasma CRP levels. Omega 3 and vitamin C supplementation has been found to have effective benefits in reducing CRP serum concentrations in hemodialysis patients.[25–27] Furthermore, it has been suggested that bacterial overgrowth (dysbiosis) in the gut and an increased translocation of living bacteria and bacterial components have the potential to activate innate immunity and systemic inflammation.[28] Thus, using a symbiotic to manipulate the microbiota with the addition of anti-inflammatory nutrients, such as omega 3 and vitamin C, like in the present study, may have a therapeutic potential to correct the inflammatory status in hemodialysis patients.

Low levels of total cholesterol and c-HDL have been related to an increased risk of death in dialysis patients, opposite to the general population, which does not mean that high cholesterol is good for dialysis patients. Rather, the high cholesterol levels in some patients may suggest that they experience a lesser degree of 2 complications of kidney disease: malnutrition and inflammation.[29] Therefore, the outcomes on lipid profile observed in the intervention group may be related with an improvement on nutritional and inflammatory status.

This study was limited by the sample size and the period of follow-up, which were therefore underpowered to detect statistically significant differences in several of the studied variables that yielded clinically significant effect sizes. Although the sample size is identified as a limitation of this study, it must be noted that statistical differences were apparent and sufficient to support the aims of this study. Given the small sample size and the short period of follow-up, caution should be taken in extrapolating these data to the general dialysis population until more comprehensive studies are conducted in a larger dialysis population.

Table 4. Results of Biochemical Variables During the Study

Variable	Control Group			Intervention Group		
	Baseline (n = 20)	Month 1 (n = 20)	Month 2 (n = 15)	Baseline (n = 22)	Month 1 (n = 22)	Month 2 (n = 20)
Albumin (g/dL)	3.7 ± 0.2	3.7 ± 0.3	3.7 ± 0.2	3.7 ± 0.3	3.7 ± 0.2	3.7 ± 0.3
Glucose (mg/dL)	88.3 ± 10.8	86.9 ± 21.6	87.6 ± 8.2	98.6 ± 22.5	99.3 ± 17.9*	103.1 ± 33.6
Total cholesterol (mg/dL)	140.4 ± 28.1	137.1 ± 26.5	130.6 ± 17.9	161.5 ± 39.6	155.1 ± 30.3	150.3 ± 34.9
Triglycerides (mg/dL)	125.0 ± 67.6	122.6 ± 50.3	137.8 ± 84.6	149.7 ± 74.7	147.1 ± 71.0	146.6 ± 97.3
c-HDL (mg/dL)	31.7 ± 7.5	33.7 ± 9.8	31.1 ± 11.0	29.1 ± 7.1	32.8 ± 6.0†	39.2 ± 9.3†
c-LDL (mg/dL)	65.6 ± 18.6	63.1 ± 24.4	63.9 ± 22.6	76.6 ± 21.2	83.6 ± 22.9*	82.4 ± 26.0†
Phosphorus (mg/dL)	4.4 ± 1.3	4.6 ± 1.6	4.5 ± 1.3	4.7 ± 1.5	4.6 ± 1.8	5.1 ± 1.4
Potassium (mg/dL)	5.1 ± 0.8	5.0 ± 0.9	4.9 ± 0.6	4.6 ± 0.8	4.9 ± 0.8	5.0 ± 1.1
Sodium (mg/dL)	135.0 ± 4.3	136.7 ± 4.7†	137.4 ± 5.0	135.1 ± 3.1	137.6 ± 4.2†	137.0 ± 2.8†
Calcium (mg/dL)	8.9 ± 0.7	8.8 ± 1.2	9.2 ± 0.9	9.1 ± 0.8	9.1 ± 0.7	8.7 ± 0.9
Urea (mg/dL)	139.2 ± 38.1	130.2 ± 45.1	131.5 ± 43.8	137.9 ± 65.7	146.0 ± 57.4	148.6 ± 41.6
BUN (mg/dL)	61.3 ± 22.4	63.5 ± 17.0	62.2 ± 21.0	66.5 ± 30.3	69.8 ± 26.7	69.4 ± 19.4
Creatinine (mg/dL)	11.4 (10.2-13.2)	12.1 (9.7-14.5)	10.4 (9.0-13.2)	9.8 (7.5-12.9)	10.4 (8.7-12.7)	11.4 (9.9-13.0)
CRP (mg/dL)	2.2 (1.0-9.1)	—	5.0 (0.6-9.9)	9.1 (1.7-14.1)*	—	6.3 (1.8-11.3)
	n = 9	n = 9	n = 7	n = 14	n = 14	n = 13
TNF-α (pg/mL)	1.6 (0.2-6.9)	0.1 (0.04-9.5)	3.1 (0.0-3.7)	2.6 (0.1-5.5)	2.9 (0.9-5.5)	2.9 (0.9-6.7)
IL-6 (pg/mL)	1.3 (0.2-3.0)	2.0 (1.2-3.1)	0.6 (0.2-3.6)	1.8 (0.8-3.9)	1.2 (0.4-3.9)	2.0 (1.2-3.9)

BUN, blood urea nitrogen; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; IL-6, interleukin 6; LDL, low-density lipoprotein cholesterol; TNF-α, tumor necrosis factor-α.

Values expressed as mean ± standard deviation or median (percentile 25, 75).

*$P \leq .05$ versus control group.

†$P \leq .05$ versus baseline.

In summary, findings of the present study show that a symbiotic gel could be a useful alternative or complementary treatment to improve common GIS in hemodialysis patients, as well as to maintain dietary intake in this population. However, this investigation highlights the need for larger scale research to determine definitely the effect of symbiotics on nutritional status and inflammatory biomarkers in hemodialysis patients.

Practical Applications

Intake of a symbiotic gel, added with vitamins and omega-3 in combination with nutritional counseling, improves presence and severity of common GIS in hemodialysis patients. These findings will be the basis to widely recommend the use of symbiotics as an alternative therapy of GIS in these patients, which secondarily will improve their nutritional status and quality of life.

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References

1. Martín-Del-Campo F, González-Espinoza L, Rojas-Campos E, et al. Conventional nutritional counseling maintains nutritional status of patients on continuous ambulatory peritoneal dialysis in spite of systemic inflammation and decrease of residual renal function. *Nephrology.* 2009;14:493-498.

2. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis.* 2003;42:864-881.

3. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen G, Bergstrom J. Are there two type of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol Dial Transpl.* 2000;15:953-960.

4. Kotanko P, Carter M, Levin NW. Intestinal bacterial flora—a potential source of chronic inflammation in patients with chronic kidney disease. *Nephrol Dial Transpl.* 2006;21:2057-2060.

5. Schepers E, Glorieux G, Vanholder R. The gut: the forgotten organ in uremia? *Blood Purif.* 2010;29:130-136.

6. Chow J. Probiotics and prebiotics: a brief overview. *J Ren Nutr.* 2002;12:76-86.

7. Guyonnet D, Schlumberger A, Mhamdi L, Jakob S, Chassany O. Fermented milk containing *Bifidobacterium lactis* DN-173 010 improves gastrointestinal well-being and digestive symptoms in women reporting minor digestive symptoms: a randomised, double-blind, parallel, controlled study. *Br J Nutr.* 2009;102:1654-1662.

8. Nova E, Viadel B, Wärnberg J, Carreres JE, Marcos A. Beneficial effects of a synbiotic supplement on self-perceived gastrointestinal well-being and immunoinflammatory status of healthy adults. *J Med Food.* 2011;14:79-85.

9. Evenepoel P, Meijers B, Bammens B, Verbeke K. Uremic toxins originating from colonic microbial metabolism. *Kidney Int.* 2009;76(suppl):S12-S19.

10. National Kidney Foundation. Nutrition guidelines in chronic renal failure. *Am J Kid Dis.* 2000;35(suppl. 2):S1-S141.

11. Li Y, Dong J, Zuo L. Is subjective global assessment a good index of nutrition in peritoneal dialysis patients with gastrointestinal symptoms? *Perit Dial Int.* 2009;29(suppl):S78-S82.

12. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *J Parenter Enteral Nutr.* 1987;11:8-13.

13. ISAK (International Society for the Advancement of Kinanthropometry). International Standards for Anthropometric Assessment. 1st ed. Underdale, SA, Australia: The International Society for the Advancement of Kinanthropometry; 2001.

14. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr.* 1981;34:2540-2545.

15. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA.* 1994;272:205-211.

16. Cruz-Mora J, Martínez-Hernández NE, Martín del Campo-López F, et al. Effects of a symbiotic on gut microbiota in Mexican patients with end-stage renal disease. *J Ren Nutr.* 2014;24:330-335.

17. Davies SJ, Phillips L, Griffiths AM, Naish PF, Russell GI. Analysis of the effects of increasing delivered dialysis treatment to malnourished peritoneal dialysis patients. *Kidney Int.* 2000;57:1743-1754.

18. Johansen KL, Kaysen GA, Young BS, Hung AM, da Silva M, Chertow GM. Longitudinal study of nutritional status, body composition, and physical function in hemodialysis patients. *Am J Clin Nutr.* 2003;77:842-846.

19. García-García G, Nuñez-Martinez MG, Obrador GT. Prevalence of malnutrition in low-income Mexican CAPD patients. *Perit Dial Int.* 2003;23:501-504.

20. Campbell KL, Ash S, Davies PS, Bauer JD. Randomized controlled trial of nutritional counseling on body composition and dietary intake in severe CKD. *Am J Kidney Dis.* 2008;51:748-758.

21. Read JA, Beale PJ, Volker DH, Smith N, Childs A, Clarke SJ. Nutrition intervention using an eicosapentaenoic acid (EPA)-containing supplement in patients with advanced colorectal cancer. Effects on nutritional and inflammatory status: a phase II trial. *Support Care Cancer.* 2007;15:301-307.

22. Ryan AM, Reynolds JV, Healy L, et al. Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg.* 2009;249:355-363.

23. Lobo JC, Stockler-Pinto MB, Farage NE, et al. Reduced plasma zinc levels, lipid peroxidation, and inflammation biomarkers levels in hemodialysis patients: implications to cardiovascular mortality. *Ren Fail.* 2013;35:680-685.

24. Barreto DV, Barreto FC, Liabeuf S, et al. Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease. *Kidney Int.* 2010;77:550-556.

25. Gharekhani A, Khatami MR, Dashti-Khavidaki S, et al. Potential effects of omega-3 fatty acids on anemia and inflammatory markers in maintenance hemodialysis patients. *Daru.* 2014;22:1-11.

26. Saifullah A, Watkins BA, Saha C, Li Y, Moe SM. Oral fish oil supplementation raises blood omega-3 levels and lowers C-reactive protein in haemodialysis patients-a pilot study. *Nephrol Dial Transplant.* 2007;22:3561-3567.

27. Biniaz V, Sadeghi Shermeh M, Ebadi A, Tayebi A, Einollahi B. Effect of vitamin C supplementation on C-reactive protein levels in patients undergoing hemodialysis: a randomized, double blind, placebo-controlled study. *Nephrourol Mon.* 2013;6:e13351.

28. Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int.* 2013;83:1010-1016.

29. Cheung AK. Is lipid control necessary in hemodialysis patients? *Clin J Am Soc Nephrol.* 2009;4(Suppl 1):S95-S101.