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The Effect of Probiotic Yogurt Containing *Lactobacillus rhamnosus* and *Bifidobacterium bifidum* on Disease Activity and Disability in Patients with Systemic Lupus Erythematosus: A Randomized Controlled Trial

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease with relapsing and remitting periods. It has been reported that alterations of gut microbiota can affect disease activity in SLE. Probiotics which can modify the gut microbiota may be useful to control disease activity. Therefore, the effect of probiotic yogurt was evaluated on SLE disease activity.

In this triple-blind, randomized, controlled trial, the patients were randomized and divided into 2 groups. The patients had Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) ≤6 and were on a stable dose of immunosuppressant in the last 3 months. The intervention group was given 200 g of probiotic yogurt containing *Lactobacillus rhamnosus* and *Bifidobacterium bifidum* for 13 weeks. The control group was given 200 g of yogurt without bacteria for 13 weeks. Demographic measurements, SLEDAI, and Health Assessment Questionnaire (HAQ) were analyzed before and after the intervention. The probiotic group (19 patients) and the control group (14 individuals) were compared. At the beginning and baseline of the trial, the probiotic and control groups' average energy intake, micronutrients, and macronutrients did not differ significantly.

In the probiotic group, the amount of protein, cholesterol, magnesium, zinc, selenium, and iron intake increased significantly after intervention. There are no significant changes in SLEDAI score and disability (HAQ) between case and control groups at the end of the study.

Consumption of probiotic yogurt containing *L. rhamnosus* and *B. bifidum* did not have a significant short-term effect on SLEDAI and disability in SLE patients.

Keywords: Health assessment questionnaire; Probiotic; Systemic lupus erythematosus disease activity index; Systemic lupus erythematosus

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Disease Activity, Disability, Systemic Lupus Erythematosus, Probiotics

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with a relapsing and remitting course, characterized by a tendency to flare.[1] SLE is associated with different clinical manifestations affecting various tissues.[2] Effective diagnosis and management as a clinical challenge is influenced by various factors (heterogeneity of disease presentation and organ involvement in various patients and the variability of disease activity).[3] There is an increased risk of organ damage with disease activity over time, however, remission remains the purpose of SLE treatment.[4]

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is a widely used measure for assessing the overall disease activity of SLE.[5] Measurement of disease activity in SLE is crucial for evaluating outcomes among SLE patient groups, responses to new drugs, and assessing disease longitudinally for clinical trials[6] SLEDAI is a complicated tool composed of 24 clinical and laboratory variables and needs training and knowledge for its application.[7] Individual organ system involvement due to flares was recorded with SLEDAI-2K, which requires a ≥4-point increase in SLEDAI-2K compared to the previous visit.[8]

SLE compromises patients' daily activities to the extent that about two-thirds of them experience permanent or periodic inability to perform activities at home or work.[9] The level of disability is evaluated through a health assessment questionnaire (HAQ).

Changes in the composition of gut microbiota can contribute to the development of autoimmune disorders, such as SLE.[10,11] Dysbiosis as a crucial internal environmental factor has also been demonstrated to be linked with SLE.[12] SLE patients have special patterns of gut microbiome dysbiosis which are related to disease activity.[13] *Ruminococcus gnavus* is observed abundantly in SLE gut dysbiosis and causes specific autoantibody responses which are directly linked with the overall anti-double-stranded DNA (anti-dsDNA) levels, SLE disease activity index, and progression of lupus nephritis.[13] Because of the failure of new biotherapies, physicians are searching for adjuvant therapies that might be used without side effects. Gut microbiota regulation is known as an effective therapeutic factor for SLE.[14] As the gut microbiota might cause SLE progression, probiotics may be helpful to control disease activity.[15]

Probiotics through short-chain fatty acids (SCFAs) produced by probiotics, regulate inflammation by regulating immune factors, phagocytosis, and migration of immune cells.[16] According to the reports, SCFAs inhibit the production of proinflammatory cytokines (tumor necrosis factor-alpha [TNF-α], interleukin [IL]-1β, and IL-6) and increase the expression of IL-10 in mouse leukemic monocyte/macrophage cell lines.[17]

The SCFAs, such as propionate and butyrate, inhibit the expression of adhesion molecules and chemokines that are induced by stimuli. This suppresses the recruitment of monocytes, macrophages, and neutrophils, suggesting that they have anti-inflammatory effects.[18] Furthermore, SCFAs can impede the actions of histone deacetylases while activating G-protein coupled receptors in intestinal epithelial cells and immune cells. This helps to reduce inflammation in the gut. The inhibitory effect of butyrate on nuclear factor-kappa B (NF-κB) activation has been presented in reports.[19]

The most common types of microbes, that are used as probiotics, are lactic acid bacteria and *Bifidobacteria*.[20] It has been shown that the consumption of a combination of 5 *Lactobacillus* spp. in female MRL/lpr mice decreases disease activity, enhances renal function, and prolongs survival. *Lactobacillus* spp. increases regulatory T cells (Tregs) in the kidney while suppressing pathogenic helper T cells such as T_H17.[21]

Concerning dysbiosis in SLE and the effect of probiotics on immune responses, this study aims to investigate the effect of L. rhamnosus and *Bifidobacterium bifidum* on disease activity and HAQ in SLE patients.

MATERIALS AND METHODS

Study Subject

This triple-blind, randomized, and controlled trial study was conducted on patients diagnosed with SLE according to the American College of Rheumatology 1997 criteria[22] on 33 patients in the Rheumatology Research Center, Shariati Hospital, Tehran.

In this study, 60 patients with lupus were enrolled. Twenty-seven patients were excluded due to various reasons, including starting antibiotic therapy, being pregnant, having health problems, changing their medications, changing their physical activity level, and having surgery. The patients were randomized and

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divided into 2 groups: the intervention group (18 women and 1 man) and the control group (14 women) by using the random numbers generated by the computer. Patients confirmed a written satisfaction form to enroll in the study. The inclusion criteria were age between 20 and 60 years, body mass index (BMI) of 25 to 40 kg/m^2, SLEDAI≤6, following a stable medication regimen (at least the last 3 months). The exclusion criteria comprised a history of inflammatory diseases (e.g., pancreatitis, inflammatory bowel disease, or myocarditis), lactation or pregnancy, smoking, changes in the dosage of drugs, consumption of alcoholic beverages, kidney and liver diseases, digestive tract disorders, lactose intolerance, food supplement consumption, having taken antibiotics, being on a weight-reduction diet, and use of probiotic products 1 month before the intervention.

Preparation and Consumption of Probiotic Yogurt

The intervention group was given 200 g probiotic yogurt containing 10^6 colony-forming units (cfu) of both *L. rhamnosus* and *B. bifidum* (Domino Dairy Industries, Iran) every day for 13 weeks. To count the probiotic bacteria in yogurt samples, we used de Man, Rogosa and Sharpe (MRS) agar medium, for this purpose, first, appropriate dilutions of the sample were prepared in a sterile saltwater solution. After culturing, the plates were transferred to an incubator at 37°C and colony counting was done after 72 hours. The control group was given 200 g of yogurt without the bacteria every day for 13 weeks. The subjects and investigators were unaware of which yogurt contained the *Lactobacillus* and *Bifidobacterium* species. The allocation of groups was blinded to investigators and patients. The taste and appearance of both types of yogurts were similar. There was no adverse effect of probiotic yogurt consumption in our studies.

Study Design and Measurements

Information on food consumption, demographic characteristics, and clinical characteristics were collected before and after the trial.

Anthropometric Assessment

Demographic data, such as age, sex, and BMI, were measured at the beginning and end of the study. Body weight was examined according to a Seca scale, Hamburg, Germany, under light clothing conditions with an accuracy of 0.1 kg. Height was measured via a stillness meter (Seca) with an accuracy of 0.1 cm, without shoes. BMI was calculated by dividing body weight in kilograms by the square of height in meters.

Assessment of Food Intake and Physical Activity

The patients' food intake was evaluated by three 24-hour food diaries and food reminders. To get a 24-hour food reminder, 2 days in the middle of the week and 1 day at the weekend were selected.

Measurement of food intake was conducted using Nutritionist IV software. The physical activity registration questionnaire was also used to evaluate the activity level of the participants on 1 day in the middle of the week and 1 day on the weekend, according to Table 2.

Assessment of Disease Severity

It is a physician-administered tool for assessing 16 clinical conditions and 8 laboratory features in the last 10 days.[23] The SLEDAI evaluates 24 patients' clinical details and lab variables of the last 10 days. The scores from 0 to 5 indicate mild activity, 6 to 10 indicate moderate activity, 11 to 19 indicate high activity, and 20 indicate very high activity.[24] SLEDAI was measured before and after the intervention.

Assessment of Disease Related-disabilities

The HAQ disability index consists of 20 questions categorized into 8 groups.

The disability index evaluates 8 categories of daily activities, which include 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. Each question was rated on a 4-point scale: 0 for no difficulty, 1 for some difficulty, 2 for much difficulty, and 3 for unable to do.[25] After calculating the score, then they were divided by 8 to derive the HAQ (score range 0–3).[25,26] We measured the HAQ at the beginning and the end of the study.

Sample Size Calculation

The standard deviations (SD) for high-sensitivity C-reactive protein (hs-CRP) in both the control and intervention groups were found to be 5.93. Using the recommended formula for parallel clinical trials, we determined that each group required a sample size of 17 patients.[27]

Using this formula and accounting for a 20% dropout rate in each group, we needed a sample size of 20 persons per group.

Statistical Analysis

The quantitative variables were represented as mean values with standard deviation, while categorical variables were expressed as frequency and percentage. After assessing the normality distribution of quantitative variables by the Kolmogorov-Smirnov test, the independent *t* test, or Mann-Whitney U test, and chi-square or Fisher's exact tests, were used to compare quantitative and categorical variables between probiotic and control groups, respectively. Also, to compare variables before and after the intervention the paired *t* test, Wilcoxon tests, analysis of covariance (ANCOVA), and Quade's ANCOVA were used. The generalized estimating equations method was used to adjust the effect of potential cofounders. Considering the per-protocol approach, the analyses were conducted using R software, version 4.2.3. The *p* values <0.05 were considered statistically significant.

RESULTS

Demography and Clinical Characteristics

Demography and medication data of probiotic and control groups are shown in Table 1. BMI and medications in the 2 groups were unchanged before and after the study.

Assessment of Dietary Intake and Physical Activity

Table 2 shows the results for dietary intake and physical activity. The mean intake of energy, micronutrients, and macronutrients was not significant in either probiotic or placebo groups at the baseline and end of the study. In the intervention group, the amount of protein, cholesterol, magnesium, zinc, selenium, and iron intake increased significantly after intervention (p=0.007, 0.041, 0.001, 0.001, 0.026, and 0.020, respectively). The mean intake of energy, micronutrients, and macronutrients were not significantly different in either probiotic or placebo groups at the beginning and end of the study. The results of this study indicated that physical activity in both probiotic (38.74±2.9 to 38.44±2.6) and control groups (38.63±3.8 to 38.44±2.6) did not have statistically significant differences before and after the intervention (p=0.601 and 0.797, respectively).

The Influence of *L. rhamnosus* and *B. bifidum* on SLEDAI Score

We evaluated the effect of *L. rhamnosus* and *B. bifidum* on SLEDAI, which is shown in Table 3. Our analysis showed SLEDAI ≤6. SLEDAI increased from 3.26±2.42 to 3.37±2.50 in the probiotic group and decreased in the placebo group from 2.93±2.84 to 2.86±2.91. These differences were not statistically significant (p=0.246). Eighteen subjects were active clinical and other active serological.

The clinical characteristics before and after the study were the same except for one case shown in Table 4. All these findings showed there were no significant differences in proteinuria, ulcer, loss of hair, low complement, arthritis, anti-dsDNA, and fever in the intervention and placebo groups between the baseline and the end of the study. Response to treatment was considered by clinical activity, serology, and activity (SLEDAI).

The Influence of *L. rhamnosus* and *B. bifidum* on Health Assessment Questionnaire

In this study, we analyzed the effect of the consumption of probiotic yogurt on the HAQ index (Table 3). Our results have demonstrated no changes in the probiotic group (0.17±0.33 vs 0.17±0.35) and an increase in the placebo group (from 0.29±0.46 to 0.39±0.62), but differences were not significant between the 2 groups (p=0.074). The questions related to the HAQ are shown in Table 5. The 2 groups under study showed only 2 questions with a minor change.

Table 1. Comparison of demographic and clinical characteristics of study participants in the 2 experimental groups at baseline

Variable		Total n=33	Probiotic group n=19 (58%)	Placebo group n=14 (42%)	*p*
Demographic characteristics					
Age at study onset, y		42.03±10.7	43.26±12.5	40.36±7.8	0.412§
Duration of disease, y		13.87±8.67	15.94±8.96	11.00±7.66	0.119§
Gender, women		32(97.0%)	18 (94.7%)	14 (100%)	0.999*
BMI, kg/m^2		26.23±4.64	26.38±4.3	26.02±5.19	0.830§
Education	Under diploma/diploma	20 (60.6%)	11 (57.9%)	9 (64.3%)	0.710*
	College education	13 (39.4%)	8 (42.1%)	5 (35.7%)	
Job-status	Housekeeper	20 (60.6%)	11 (57.9%)	9 (64.3%)	0.710*
	Employed	13 (39.4%)	8 (42.1%)	5 (35.7%)	
Race	Fars	19 (58%)	11 (57.9%)	8 (57.1%)	0.966*
	Others	14 (42%)	8 (42.1%)	6 (42.9%)	
Marital status, married		22 (66.7%)	14 (73.7%)	8 (57.1%)	0.459*
Comorbidity present		18 (54.5%)	12 (63.2%)	6 (42.9%)	0.247*
Current medication					
Prednisolone		27 (81.8%)	16 (84.2%)	11 (78.6%)	0.999*
Hydroxychloroquine		28 (84.8%)	16 (84.2%)	12 (85.7%)	0.999*
Mycophenolate 500		8 (24.2%)	6 (31.6%)	2 (14.3%)	0.416*
Alendronate		8 (24.2%)	5 (26.3%)	3 (21.4%)	0.999*
Pantoprazole		5 (15.2%)	4 (21.1%)	1 (7.1%)	0.366*
Azathioprine		6 (18.2%)	4 (21.1%)	2 (14.3%)	0.490*

BMI: body mass index; §Based on independent *t* or Mann-Whitney tests; *based on chi-square or Fisher's exact tests.

Table 2. Comparison of nutrition intakes and physical activity in the two experimental groups at baseline and throughout the study.

Variable	Probiotic group n=19 (58%)	Placebo group n=14 (42%)	*p*	Variable	Probiotic group n=19 (58%)	Placebo group n=14 (42%)	*p*
Energy, kcal				**Cholesterol, mg/day**			
Baseline	1838.31±149.9	1913.43±188.3	0.211§	Baseline	138.62±61.0	136.01±71.4	0.911§
End of study	1848.21±102.7	1876.43±145.6	0.890‡	End of study	188.55±85.1	158.96±74.5	0.317‡
Change*	9.89±27.54	−37.00±41.01	0.332§	Change*	49.93±22.63	22.95±28.03	0.455§
p	0.724†	0.551†	—	*p*	0.041†	0.428†	—
Protein, g/day				**DHA-Omega 3, g/day**			
Baseline	50.83±8.3	51.50±9.4	0.832	Baseline	0.03±0.1	0.02±0.1	0.603
End of study	58.04±8.2	55.33±9.9	0.362	End of study	0.01±0.03	0.01±0.02	0.714
Change*	7.21±2.46	3.83±3.01	0.855	Change*	−0.02±0.02	−0.01±0.02	0.858
p	0.007	0.225	—	*p*	0.260	0.168	—
Fat, g/day				**EPA-Omega 3, g/day**			
Baseline	78.15±18.2	86.82±13.5	0.144	Baseline	0.01±0.03	0.006±0.02	0.504
End of study	82.26±10.3	88.81±15.4	0.145	End of study	0.009±0.03	0.003±0.008	0.413
Change*	4.11±5.47	1.99±4.67	0.942	Change*	−0.002±0.01	−0.003±0.01	0.864
p	0.463	0.678	—	*p*	0.857	0.887	—
Carbohydrate, g/day				**Vitamin A, Re/day**			
Baseline	230.32±30.8	236.66±41.0	0.615	Baseline	525.02±537.4	424.69±235.6	0.743
End of study	224.76±27.0	220.47±36.7	0.655	End of study	544.53±499.5	474.21±361.6	0.895
Change*	−5.56±7.98	−16.19±14.54	0.499	Change*	19.50±172.34	49.52±111.96	0.894
p	0.495	0.286	—	*p*	0.999	0.826	—
Diet fiber, g/day				**Vitamin D, µg/day**			
Baseline	12.97±2.8	12.73±3.7	0.837	Baseline	0.29±0.2	1.17±3.1	0.477
End of study	13.84±2.5	14.63±2.5	0.359	End of study	0.54±0.57	1.14±2.9	0.560
Change*	0.87±0.86	1.90±0.99	0.423	Change*	0.25±0.15	−0.03±1.20	0.548
p	0.327	0.096	—	*p*	0.124	0.778	—
PUFA, g/day				**Calcium, mg/day**			
Baseline	26.18±5.7	25.79±4.1	0.855	Baseline	413.32±99.9	429.99±123.4	0.671
End of study	25.83±5.0	25.87±4.2	0.783	End of study	433.29±112.4	475.32±87.5	0.425
Change*	−0.35±1.55	0.08±1.27	0.913	Change*	19.97±39.26	45.33±35.42	0.648
p	0.778†	0.950†	—	*p*	0.617	0.198	—
SFAs, g/day				**Sodium, mg/day**			
Baseline	15.77±3.5	18.91±6.9	0.122	Baseline	718.16±267.1	757.91±338.4	0.708
End of study	16.22±2.8	18.89±5.2	0.071	End of study	653.51±256.3	832.14±275.1	0.047
Change*	0.45±1.19	−0.35±1.55	0.743	Change*	−64.65±88.15	74.23±124.29	0.355
p	0.305	0.822	—	*p*	0.473	0.561	—
Potassium, mg/day				**Selenium, mg/day**			
Baseline	1652.79±278.9	1654.00±338.7	0.991	Baseline	0.03±0.01	0.05±0.07	0.343
End of study	1735.63±175.9	1789.64±270.9	0.406	End of study	0.04±0.01	0.05±0.02	0.086
Change*	82.84±65.16	135.64±100.70	0.649	Change*	0.01±0.005	−0.007±0.02	0.770
p	0.220	0.201	—	*p*	0.026	0.506	—

Table 2. Continued...

Variable	Probiotic group n=19 (58%)	Placebo group n=14 (42%)	*p*	Variable	Probiotic group n=19 (58%)	Placebo group n=14 (42%)	*p*
Magnesium, mg/day				**Iron, mg/day**			
Baseline	200.82±25.4	200.99±52.8	0.990	Baseline	9.66±1.4	10.13±1.7	0.401
End of study	232.69±40.4	205.54±40.4	0.112	End of study	10.66±1.1	9.63±1.7	0.038
Change*	31.87±9.87	4.55±18.82	0.585	Change*	1.00±0.39	−0.50±0.64	0.038
p	0.001	0.813	—	*p*	**0.020**	0.442	—
Zinc, mg/day				**Physical activity: MET, h/week**			
Baseline	6.54±0.8	7.12±1.3	0.130	Baseline	38.74±2.9	38.63±3.8	0.923
End of study	7.89±1.1	7.40±1.3	0.232	End of study	38.44±2.6	38.39±2.3	0.840
Change*	1.35±0.31	0.29±0.47	0.057	Change*	−0.30±0.60	−0.24±0.91	0.953
p	<0.001	0.553	—	*p*	0.601	0.797	—

* Change (pre vs post, mean±standard error of the mean); † based on paired *t* or Wilcoxon tests; § based on independent *t* or Mann-Whitney tests; ‡ based on ANCOVA or Quade's ANCOVA (baseline value was included as a covariate)

; † based on repeated measure analysis GEE adjusted by iron and sodium change. DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; Re: retinol; PUFA: polyunsaturated fatty acid; SFA: saturated fatty acid; MET: metabolic equivalent.

Table 3. Effect of 13 weeks of probiotic yogurt on Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Health Assessment Questionnaire in patients with systemic lupus erythematosus

	Groups	Follow up Times		Change	*p*†
		Baseline	End of study		
Systemic Lupus Erythematosus Disease Activity Index	Probiotic	3.26±2.42	3.37±2.50	0.11±0.11	0.317
	Placebo	2.93±2.84	2.86±2.91	−0.07±9.07	0.317
	p	0.522	0.246	0.244	—
Health Assessment Questionnaire	Probiotic	0.17±0.33	0.17±0.35	0.00±.008	0.999
	Placebo	0.29±0.46	0.39±0.62	0.09±.05	0.109
	p	0.253	0.054	0.074	—

Based on paired *t* or Wilcoxon tests

Table 4. Comparison of the clinical characteristics before and after the study in the two groups

	Total n=33	Probiotic group n=19 (58%)	Placebo group n=14 (42%)	*p*
SLEDAI				
Proteinuria	9 (27.3%)	5 (26.3%)	4 (28.6%)	0.999
Ulcers	2 (6.1 %)	0 (0%)	2 (14.3 %)	0.172
Hair loss	3 (9.1%)	1 (5.3 %)	2 (14.3 %)	0.561
Low complement	10 (30.3%)	7 (36.8%)	3 (21.4%)	0.455
Arthritis	3 (9.1%)	2 (10.5%)	1 (7.1%)	0.999
Anti-dsDNA	11 (33.3%)	9 (47.4%)	2 (14.3%)	0.067
Fever	1 (3%)	0 (0.0%)	1 (7.1%)	0.424

dsDNA: double-stranded DNA; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

Table 5. Effect of 13 weeks of consumption of Probiotic yogurt on Health Assessment Questionnaire in systemic lupus erythematosus patients at baseline and end of the study

Health Assessment Questionnaire		Total n=33	Probiotic group n=19 (58%)	Placebo group n=14 (42%)	*p*
1. Dress yourself, including tying shoelaces and doing buttons	No difficulty	29 (87.9%)	19 (100.0%)	10 (71.4%)	0.024
	Some difficulty	4 (12.1%)	0 (0.0%)	4 (28.6%)	
2. Shampoo your hair	No difficulty	32 (97%)	19 (100.0%)	13 (92.9%)	0.424
	Some difficulty	1 (3.0%)	0 (0.0%)	1 (7.1%)	
3. Stand up from an armless chair	No difficulty	30 (90.9%)	18 (94.7%)	12 (85.7%)	0.561
	Some difficulty	3 (9.1%)	1 (5.3%)	2 (14.3%)	
4. Get in and out of bed	No difficulty	30 (90.9%)	18 (94.7%)	12 (85.7%)	0.561
	Some difficulty	3 (9.1%)	1 (5.3%)	2 (14.3%)	
5. Cut your meat	No difficulty	33 (100.0%)	19 (100.0%)	14 (100.0%)	NA
	Some difficulty	0 (0.0%)	0 (0.0%)	0 (0.0%)	
6. Lift a full cup or glass to your mouth	No difficult	33 (100.0%)	19 (100.0%)	14 (100.0%)	NA
	Some difficulty	0 (0.0%)	0 (0.0%)	0 (0.0%)	
7. Open a new carton of milk	No difficult	30 (90.9%)	17 (89.5%)	13 (92.9%)	0.999
	Some difficulty	3 (9.1%)	2 (10.5%)	1 (7.1%)	
8. Walk outdoors on flat ground	No difficulty	27 (81.8%)	17 (89.5%)	10 (71.4%)	0.363
	Some difficulty	6 (18.2%)	2 (10.5%)	4 (28.6%)	
9. Climb up five stairs	No difficulty	23 (69.7%)	15 (78.9%)	8 (57.1%)	0.257
	Some difficulty	10 (30.3%)	4 (21.1%)	6 (42.9%)	
10. Wash and dry your entire body	No difficulty	33 (100.0%)	19 (100.0%)	14 (100.0%)	NA
	Some difficulty	0 (0.0%)	0 (0.0%)	0 (0.0%)	
11. Take a bath	No difficulty	31 (93.9%)	19 (100.0%)	12 (85.7%)	0.172
	Some difficulty	2 (6.1%)	0 (0.0%)	2 (14.3%)	
12. Get on and off the toilet	No difficult	27 (81.8%)	16 (84.2%)	11 (78.6%)	0.999
	Some difficulty	6 (18.2%)	3 (15.8%)	3 (21.4%)	
13. Reach and get down a 5 lb. object (for example, a bag of sugar from just above your head)	No difficulty	28 (84.8%)	18 (94.7%)	10 (71.4%)	0.138
	Some difficulty	5 (15.2%)	1 (5.3%)	4 (28.6%)	
14. Bend down to pick up clothing from the floor	No difficulty	29 (87.9%)	16 (84.2%)	13 (92.9%)	0.620
	Some difficulty	4 (12.1%)	3 (15.8%)	1 (7.1%)	
15. Open car doors	No difficulty	33 (100.0%)	19 (100.0%)	14 (100.0%)	NA
	Some difficulty	0 (.0%)	0 (0.0%)	0 (0.0%)	
16. Open jars which have been previously opened	No difficulty	31 (93.9%)	18 (94.7%)	13 (92.9%)	0.999
	Some difficulty	2 (6.1%)	1 (5.3%)	1 (7.1%)	
17. Turn taps on and off	No difficulty	32 (97.0%)	19 (100.0%)	13 (92.9%)	0.424
	Some difficulty	1 (3.0%)	0 (0.0%)	1 (7.1%)	
18. Run errands and shop.	No difficulty	26 (78.8%)	16 (84.2%)	11 (78.6%)	0.999
	Some difficulty	6 (18.2%)	3 (15.8%)	3 (21.4%)	
19. Get in and out of a car	No difficulty	29 (87.9%)	18 (94.7%)	11 (78.6%)	0.288
	Some difficulty	4 (12.1%)	1 (5.3%)	3 (21.4%)	
20. Do chores such as vacuuming, housework, or praying.	No difficulty	25 (75.8%)	16 (84.2%)	9 (64.3%)	0.238
	Some difficulty	8 (24.2%)	3 (15.8%)	5 (35.7%)	

DISCUSSION

The role of the human gut microbiota in the maintenance of a healthy physiological condition, as well as its connection to the improvement of disease, remains to be clarified. Studies show that intestinal microbes could initiate and amplify autoimmune diseases, like rheumatoid arthritis and SLE.[28] Intestinal microbiota dysbiosis might induce immune system imbalance and intensification of SLE.[15] The SLE etiology is not known; however, several factors (hormonal, environmental, and genetic factors) may contribute to the disease. One of the environmental factors that may contribute to the development of SLE is the microbiome.[29] Medications that treat specific diseases or modulate the immune system can affect the gut microbiome.[29] The term dysbiosis can refer to a reduction in beneficial bacteria, an excessive growth of harmful bacteria, or a reduction in bacterial diversity.

It has been reported that the disease severity in SLE patients has been linked to changes in gut microbial composition and function.[30] In both SLE patients and lupus-prone animals, dietary supplement intake is significantly related to disease activity and microbiota.[31] As a result, supplementation with probiotics might be helpful to immune function and intestinal health in SLE.

It has been reported that a special microbial signature with more severe dysbiosis was observed in SLE patients which is associated strongly with the SLEDAI score, showing the role of gut microbiota in the severity and activity of the disease.[32] For example, the SLEDAI score in SLE patients showed a negative correlation with the abundance of *Firmicutes* and *Bifidobacterium*, while SLE activity reported a positive correlation with *Streptococcus* bacteria.[33] In SLE patients, we have seen reduced commensal bacteria (e.g., *Firmicutes* and *Bacteroidetes*) and an increase in detrimental bacteria.[34] Consumption of Bifidobacterium bifidum, which is less abundant in the gut microbiota of SLE patients, prevents $CD4^+$ T-lymphocyte overactivation in patients with SLE.[35]

A probiotic with immunoregulatory properties can ameliorate inflammatory and autoimmune diseases. Some strains induce mostly IL-10 production, promote Treg development, and control excess immune responses.[36] Administration of probiotics can reduce the severity of SLE by decreasing inflammation.[37] The results of our research demonstrated that the consumption of *Lactobacillus* and *Bifidobacterium* did not affect disease activity according to the SLEDAI index. In research by Hatakka et al after consumption of 2 capsules/day of *L. rhamnosus* for 12 months, no changes were observed in the inflammatory mediators or in disease activity in rheumatoid arthritis.[38] Widhani et al studied the effect of symbiotics on inflammatory mediators and SLEDAI scores in SLE patients. They have described that the symbiotics supplementation suppressed the increased high sensitivity C-reactive protein (hs-CRP), decreased IL-6 expression, increased the *Firmicutes/Bacteroidetes*, and meliorated SLEDAI 2K scores.[39] So, based on our results and Widhani et al study, if probiotics are taken in a symbiotic form, a combination of prebiotics and probiotics, SLEDAI may decrease. Prebiotics selectively stimulated the growth of probiotics resident in the gut and, therefore, changed the colonic microflora to a healthier composition.[41]

Since this disease is chronic and generalized, it affects patients' quality of life in all aspects in the long term.[41] The HAQ might give a better idea of a patient's functional status than lab values or physicals.[42] In SLE, as survival has steadily improved over the last few decades, long-term treatment objectives have expanded to include improving disability reduction.[43] The effect of probiotics on HAQ has not been examined in SLE patients, but some rheumatic autoimmune diseases like rheumatoid arthritis can cause an improvement in HAQ. According to the report by Pineda et al taking *L. rhamnosus* and *L. reuteri* supplements in patients with RA, who did not receive intra-articular steroids within 1 month before or during the research (3 months) resulted in improved HAQ scores.[44] While Hatakka et al demonstrated no significant improvement in HAQ after the intake of *L. rhamnosus* among RA patients for 12 months.[38] The results of our research show that the HAQ value was unchanged in the probiotic group. Concerning the Hatakka et al study, the prolonged use of probiotic capsules did not affect the disease activity. According to our results and the Pineda et al study, it seems that past medications can change the effect of probiotics.[45]

This is the first clinical trial examining the effects of probiotic yogurt administration on HAQ.

The small sample size was due to the limitation. The power for SLEDAI and HAQ was calculated (50% and 99%, respectively). Our study suggests that the sample size of other studies should be increased.

Our study showed that the use of probiotics yogurt did not have a significant short-term effect on disease activity (SLEDAI) and disability (HAQ) scores in SLE patients. It might be decreased SLEDAI and HAQ if synbiotics are consumed instead of probiotics. Furthermore, past medication usage by patients and follow-up time (>3 months) should be considered. We suggest conducting studies on SLE patients with active disease and elevated SLEDAI scores for more impactful results.

STATEMENT OF ETHICS

This study was conducted based on the guidelines of the Declaration of Helsinki, was approved by the Ethics Committees of Tehran University of Medical Sciences (IR.TUMS.DDRI.REC.1399.059) and registered in the Iranian Registry of Clinical Trials (IRCT20240821062833N1).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Upon reasonable request via r.banaki@gmail.com.

AI ASSISTANCE DISCLOSURE

Not applicable.

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