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ORIGINAL RESEARCH

The Effects of Synbiotic Supplementation on Glycemic Status, Lipid Profile, and Biomarkers of Oxidative Stress in Type 1 Diabetic Patients. A Placebo-Controlled, Double-Blind, Randomized Clinical Trial

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Background and Objective: The aim of the present study was to evaluate the effects of synbiotic on glycemic status, lipid profile, and biomarkers of oxidative stress in type 1 diabetes mellitus (T1DM) patients.

Materials and Methods: In this double-blind clinical trial, 50 T1DM patients were randomly allocated to intervention (n = 25) and control (n = 25) groups and received either synbiotic powder (*Lactobacillus sporogenes* GBI-30 (probiotic), maltodextrin and fructooligosaccharide (prebiotic)) or placebo 2 g per day for 8 weeks. Fasting blood samples were collected before and after the intervention to measure fasting blood glucose (FBG), insulin concentration, hemoglobin A1c (HbA1c), lipid profile, and biomarkers of oxidative stress such as total antioxidant capacity (TAC) and hs-C-reactive protein (hs-CRP).

Results: Supplementation with synbiotic resulted in a significant decrease in the mean serum levels of HbA1c and hs-CRP ($p = 0.01$ and $p = 0.004$, respectively), and marginally significant decrease in FBG ($p = 0.05$) in the intervention group post- intervention. Also, the mean changes of FBG and hs-CRP were significantly lower in the intervention group compared with the control group ($p = 0.03$ and $p = 0.005$, respectively). There were no significant changes found in lipid profile in intervention group post-intervention ($p \geq 0.05$). The mean serum levels of insulin and TAC were significantly increased in the intervention group post-intervention ($p = 0.001$). There was a significant increase in the mean changes of TAC ($p = 0.005$) in the intervention group compared with the control group.

Conclusion: The 8-week synbiotic supplementation in T1DM patients may be effective in improvement of FBG, HbA1c, insulin, hs-CRP, and TAC.

Keywords: type 1 diabetes mellitus, synbiotic, glycemic status, lipid profile, inflammation

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the progressive destruction of beta-pancreatic cells and the insufficiency of insulin production by these cells.[1] Genetic background and environmental factors are involved in the process of this disease.[2] The progression of disease is slow and may start before the diagnosis of T1DM. The disease progress is mostly occurred in early childhood or

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adolescence,[3,4] when the autoantibodies against beta cells appeared in the peripheral circulation.[5] T1DM is characterized by chronic hyperglycemia along with accelerated protein glycosylation.[6] The chronic hyperglycemia can induce the high levels of bioactive molecules including superoxide free radicals, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) initiate early atherosclerosis by the formation of oxidized low-density lipoprotein (LDL), foam cells and proliferation of smooth muscle cells.[7] In fact, some epidemiological studies found a positive relationship between high levels of blood sugar, lipid dysfunction and cardiovascular diseases.[8]

The incidence of T1DM is increased by 3–4% annually.[9] About 26,000 infants, children, and adolescents in the United States suffer from the disease.[10] Over 85% of patients are under 20 years old.[11] The increasing prevalence of diabetes in adolescents and young adults has become a major health problem.[12] Such a rapid changes and decreases in the age of affliction are not due to genetics. Therefore, it is suggested that the recent increase in diabetes may be due to changes in the living environment affecting exposure to pathogenic microbes, as well as the composition of microbial flora in the gut regulating immunity and metabolism.[13] The intestinal mucus is considered as a defense barrier and breaking down of this defense barrier[11,14] lead to invading bacteria and toxins to the gastrointestinal tract, organs, and tissues.[15] Gut microbiomes play a key role in health.[16] The main benefits of the microbiota for the host include carbohydrate fermentation and digestion, vitamin synthesis, expansion of intestinal lymphoid tissues, eliciting specific immune responses and preventing the accumulation of pathogens.[17] According to the health hypothesis, the sudden changes in human intestinal microflora are probably one of the causative factors of increased incidence of autoimmune diseases.

A new version of the "Health Hypothesis" suggests that reduced exposure to environmental and/or intestinal stimuli, including germs, is responsible for an increased incidence of childhood autoimmune diseases.[18] In T1DM children, variations in the intestinal microflora have been reported; for instance, in children with T1DM in Spain, a reduced butyrate-producing bacteria with anti–inflammatory impacts was observed.[16]

Probiotic, the Greek word, meaning "for life"[19] has been shown to activate monocytes, macrophages, and dendritic cells in vitro that affect the immune system.[20] In addition, prebiotics which are non-digestible carbohydrates consumed by the intestinal bacteria for fermentation,[21] are used in medicine to produce short-chain fatty acids (SCFAs)[22] such as inulin or fructooligosaccharides (FOS), which stimulate the growth and metabolism of probiotics in the intestine. A mixture of prebiotics and probiotics as synbiotic has beneficial effects against several diseases.[23] Several studies also suggest that the use of synbiotic foods may help control metabolic profiles, inflammatory factors, and oxidative stress biomarkers. Nevertheless, such effects have been mainly observed in animal models or nondiabetic patients.[24] The hypoglycemic effects of *Lactobacillus* and *Bifidobacterium* have been investigated in several human studies. Several clinical trials have suggested that probiotic and synbiotic compounds alleviate or prevent elevated blood glucose in diabetic and non-diabetic subjects.[25] Previous studies have reported that the synergistic effects of synbiotic supplements on the intestine and immune system are significantly stronger than probiotics and prebiotics alone.[26] Recently, few studies have also reported that synbiotic and probiotic intake can improve insulin sensitivity and reduce inflammatory factors.[27] The effects of synbiotic use in T1DM have not been investigated by any study so far. The aim of the present study was to evaluate the impacts of synbiotic supplementation on glycemic control, lipid profile, and biomarkers of oxidative stress in T1DM Patients.

Materials and Methods

In this double-blind clinical trial, the patients with type 1 diabetes referred to an endocrinologist's clinic in Ahvaz city, were selected. The inclusion criteria were as the age of 4 to 18 years old, males and females, body mass index <95% percentile (according to BMI for age chart for children under 18) and at least 1 year diagnosed with T1DM. The exclusion criteria were as: kidney disease, coronary artery disease, acute and chronic pulmonary inflammation, short bowel syndrome, allergies, lactation or pregnancy, traveling for more than 2 weeks, smoking, using dietary supplements, anti–inflammatory drugs, using any antioxidant supplements since last 3 months, using immunosuppressive drugs, antibiotics and synbiotic products, following specific diets, changing diet and weight loss.

All patients had a confirmed diagnosis of T1DM (FBG ≥126 mg/dl or 2 hr glucose) 2 hpp (≥200 mg/dl or HbA1c ≥6.5%).[28] The study protocol was confirmed by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref No. IR.AJUMS.REC.1396.1032) and was recorded in the Iranian Registry of Clinical Trials website (IRCT20180310039020N1).

Study Design

In this study, 50 families announced their child's readiness to participate in the study, of which 44 patients completed

the study (Figure 1). Patients were randomly (block design based on the combined analysis) divided into two intervention and control groups (25 subjects in each group). The subjects in the intervention group received 2 g of synbiotic powder (containing 10^9 CFU *Lactobacillus sporogenesis* GBI-30 as probiotic and maltodextrin and fructooligosaccharide as prebiotic) in one glass of water as once daily after a main meal for 8 weeks. The subjects in the control group received 2 g of starch powder with a glass of water once daily for 8 weeks. Both the supplement and placebo powder were provided by the "Parsilact Company," Shiraz, Iran. The placebo and supplement were matched in terms of shape, color, size, and taste. The dosage of supplement was as 80% probiotic and 20% prebiotic. The patients were asked to avoid using any probiotic products during the study and parents were contacted weekly to control the usage of supplements.

Anthropometric and Nutritional Assessments

A three-day food record (including two working days and one weekend day) was completed pre and post-intervention. The dietary analysis was performed using the "Nutritionist 4" software, and the mean intakes of macronutrients and energy intake were calculated and compared with International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines.[29] Also, the body weight was measured using the "Seca" scale with an accuracy of 0.5 kg and the height was measured using the tape meter with an accuracy of 0.1 cm. The BMI was calculated as weight/height^2, kg/m^2. According to the standard deviation scores (SDS) of weight, height and BMI calculated using the World Health Organization (WHO) data, SDS of patients were calculated.[30,31] The physical activity was also evaluated by IPAQ questionnaire.[32]

Biochemical Measurements

A 5 mL blood sample was collected from each subject after 12 hrs of fasting and before insulin administration pre- and post-intervention. The FBG was immediately measured by the enzymatic method using laboratory kits (Pars Azmoon, Tehran, Iran) and an auto-analyzer. HbA1c was measured by enzymatic method using nycocard laboratory kits (Norway). All samples were stored in a freezer (Snijders, Germany) at −80°C until the analysis. Insulin, hs-CRP and TAC were measured by enzyme-linked immunosorbent assay (ELISA) method using kit (Tarvand Sina, Esfehan, Iran). Also, the serum levels of TG, cholesterol, and HDL-c was measured by the colorimetric method using the laboratory kits of Pars Azmoon (Tehran, Iran). The LDL-c and VLDL-c were calculated by the following formula (Friedewald formula):[33]

$$\mathrm{LDL-c(mg/dL)} = \mathrm{TC(mg/dL)} - \mathrm{HDL-c(mg/dL)} - \mathrm{TG(mg/dL)}/5(\mathrm{VLDL})$$

Statistical Analysis

Considering the FBG as the primary outcome[21] and the 90% of power study and the withdrawal rate of % 15, the sample size calculated as 25 subjects in each group. All data were presented as mean ± SD for the quantitative variables or number (percentage) for the qualitative variables. The data were tested using Kolmogorov-Smirnoff-test for normal distribution with SPSS 20 software. The Chi-square test was used to compare the qualitative variables. The Independent sample *t*-test was used to compare quantitative variables between two groups. The Paired-sample test was also used to identify within-group differences (before and after intervention). Results with $P < 0.05$ were considered statistically significant.

Results

Forty-four subjects (22 in the intervention group and 22 in the control group as 23 females and 21 males) completed the study with the mean age of 10.36 ± 2.50. There were no adverse effects were reported during the study. Table 1 showed that there were no significant difference in terms of demographic characteristics, the standard deviation scores (SDS) of weight, height and BMI, physical activity, using insulin (data not shown), and duration of diabetes between the two intervention and control groups at baseline ($p \geq 0.05$). Moreover, no significant differences were observed in dietary intakes including calories, protein intake, carbohydrates, fat, cholesterol, saturated fat, and dietary fiber between groups pre- and post-intervention ($p \geq 0.05$) (Table 2). According to acceptable macronutrient distribution range recommended by the ISPAD guidelines (2018), energy contribution of macronutrients was normal. Dietary fiber intakes of patients were lower than recommended (children >2 years old, Age in years +5 = grams of fiber per day).[29]

Glycemic Control

No significant differences were seen in FBG, insulin, and HbA1c between 2 groups at baseline ($p \geq 0.05$). At the end of the study, there was a significant reduction ($p = 0.01$) in

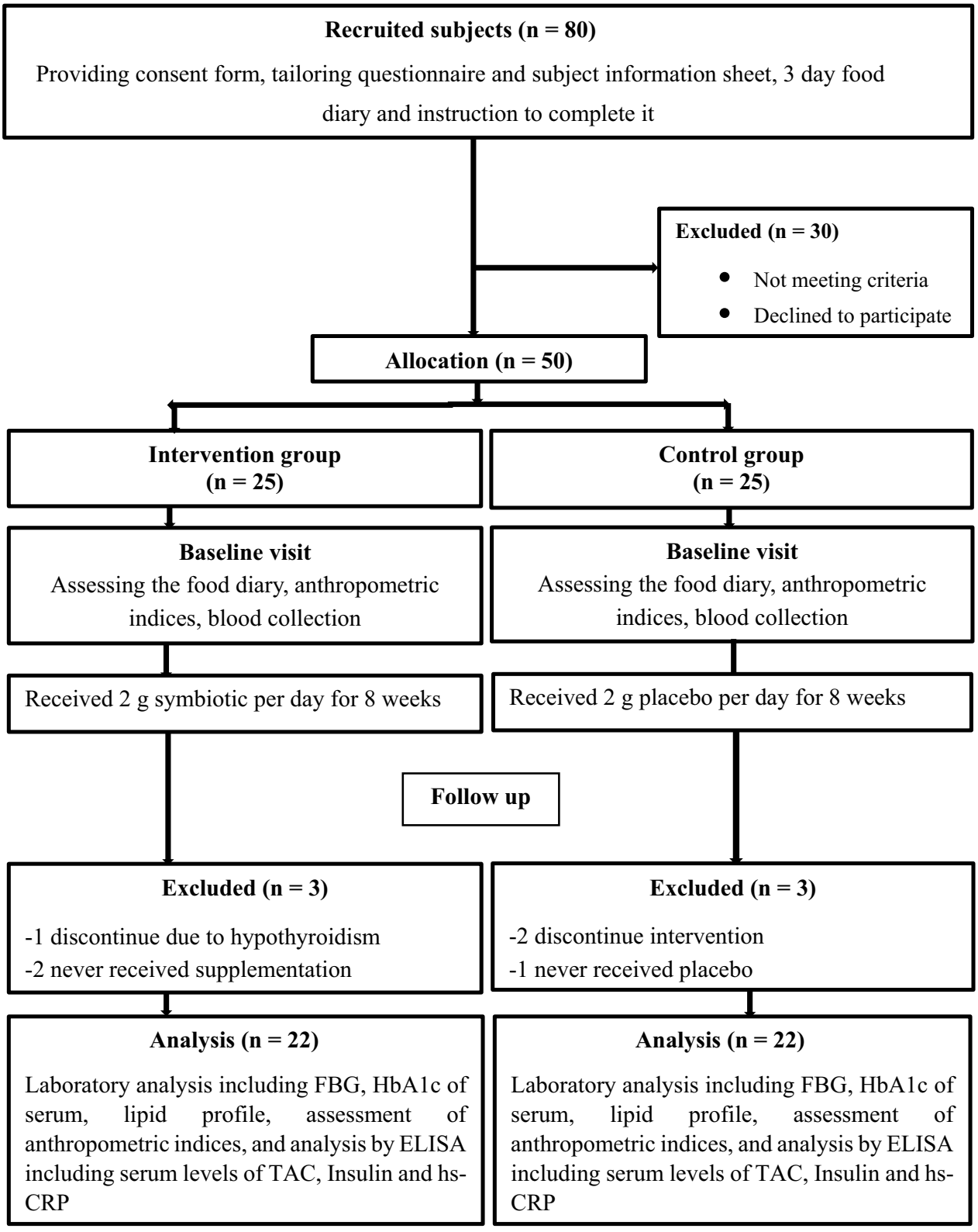

Figure 1 Flow diagram of the study.
Abbreviations: FBG, fasting blood glucose; HbA1c, hemoglobin A1c; hs-CRP, hs-C-reactive protein; TAC, total antioxidant capacity; ELISA, enzyme-linked immunosorbent assay.

Table 1 The Characteristics of Subjects at Baseline

Variable	Control Group (n=22)	Intervention Group (n=22)	*P-value	SDS (Z score)
Age (years)	10.04 ± 2.08	10.36 ± 2.53	0.65	
Gender Female (N) (%) Male (N) (%)	 12 (54) 10 (45)	 11 (50) 11 (50)	1.00[a]	
Weight (kg)	34.90 ± 13.56	43.20 ± 17.94	0.09	
Z-score for weight	−0.14 ± 1.75	0.39 ± 1.78	0.32	−2,+1
Height (m)	137.65 ± 18.01	144.38 ± 21.48	0.26	
Z-score for height	−0.04 ±2.45	0.45 ± 2.04	0.46	−2,+3
BMI (kg/m^2)	17.86 ± 3.45	19.77 ± 4.18	0.20	
Z-score for BMI	−0.02 ±1.44	0.54 ±1.04	0.13	−2,+1
Disease duration (years)	4.04 ± 1.36	4.45 ± 1.96	0.42	

Notes: Values are expressed as means ± SD. $P<0.05$ was considered as significant. *$P<0.05$ was considered as significant using independent *T*-test between the two groups at baseline. [a]$P<0.05$ was considered as significant using Chi-square test.
Abbreviation: SDS, standard deviation scores.

the mean serum levels of HbA1c (8.90±1.95 vs 8.61±1.85%, respectively, for baseline and after the intervention) in the intervention group. However, the decrease in the mean serum levels of FBG showed a marginal trend toward significant (199.72±81.10 vs 163.68±75.88 mg/dl; $p = 0.05$) (Table 3). Also, the mean changes of FBG were significantly lower in the intervention group compared with the control group (−36.04±81.87 vs 9.31±45.34, respectively; $p = 0.03$). Also, after adjusting for confounding factors, the results did not change in terms of significance; except for HbA1c after adjusting, there was a significant decrease ($p = 0.03$) (Table 3).

Lipid Profile

The results of this study showed that there were no significant difference ($p \geq 0.05$) in the mean levels of lipid profile such as triglyceride (TG), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL_{-c}), low-density lipoprotein cholesterol (LDL_{-c}), and very low-density lipoproteins (VLDL) between two groups at baseline and after the intervention. Also, after adjusting for confounding factors, the results did not change in terms of significance (Table 3).

Biomarkers of Stress Oxidative and Inflammatory Status

According to results of Table 4, there were no significant difference ($p \geq 0.05$) in the mean levels of TAC and hs-CRP between two groups at baseline. At the end of the study, synbiotic supplementation significantly reduced serum levels of hs-CRP (3054.64±3009.89 vs 1807.10±2258.92 ng/mL, respectively; $p = 0.004$) in the intervention group.

In addition, the mean changes of serum levels of hs-CRP were significantly lower in the intervention group compared with the control group (−1247.54±1793.66 vs 25.28±858.14 ng/mL, respectively; $p = 0.005$). The results of this study showed that in intervention group the mean of TAC was increased significantly ($p = 0.001$) post-intervention compared with baseline (94.16±14.29 to 101.12±14.35 mmol/lit, respectively). Consumption of synbiotic, compared to the control, resulted in a significant increase in the mean changes of TAC ($p = 0.005$) (Table 4).

Discussion

According to this study, 8-week synbiotic supplementation in T1DM patients improved FBG, HbA1c, insulin, hs-CRP, and TAC. The earlier studies investigated the impact of the synbiotic supplementation in type 2 diabetes and to our best of knowledge, the current study was the first study to investigate synbiotic supplementation among patients with T1DM.

Dietary Fibers and Microbiota

The microbiota can be altered through the intake of certain dietary ingredients including fiber and prebiotics. There are several studies showing an increase in the gut

Table 2 Mean ± SD of Energy, Macronutrients Intake at Baseline and Post-Intervention

Variable	Baseline	Post-Intervention	**P-value	ISPAD
Energy (kcal/d)				
Control group	1616.86 ± 150.59	1617.63 ± 147.89	0.78	
Intervention group	1655.81 ± 150.65	1667.77 ± 165.20	0.26	
*P-value	0.39	0.29		
Carbohydrate (g/d)				
Control group	203.66 ± 20.76	203.95 ± 20.16	0.61	
Intervention group	212.62,± 23.90	213.26 ± 24.09	0.14	
*P-value	0.19	0.17		
Carbohydrate (%)				
Control group	50	50	0.77	45–50
Intervention group	51	51	0.46	
*P-value	0.59	0.69		
Protein (g/d)				
Control group	62.91 ± 13.72	62.99 ± 13.87	0.62	
Intervention group	70.38 ± 17.07	70.27 ± 16.87	0.66	
*P-value	0.11	0.12		
Protein (%)				
Control group	15.5	15.5	0.65	15–20
Intervention group	17	16.8	0.51	
*P-value	0.31	0.20		
Fat (g/d)				
Control group	59.76 ± 3.18	59.57 ± 3.30	0.66	
Intervention group	60.57 ± 3.50	60.45 ± 3.62	0.68	
*P-value	0.42	0.40		
Fat (%)				
Control group	33	33	0.60	<35
Intervention group	33	32.5	0.58	
*P-value	0.12	0.26		
Cholesterol (mg/d)				
Control group	191.83 ± 59.71	189.17 ± 54.99	0.14	
Intervention group	185.40 ± 56.79	185.50 ± 56.97	0.76	
*P-value	0.71	0.82		
Saturated fat (g/d)				
Control group	13.91 ± 2.81	13.59 ± 2.47	0.41	<10
Intervention group	13.88 ± 2.35	13.57 ± 2.69	0.02	
*P-value	0.96	0.97		
Dietary fiber (g/d)				
Control group	9.39±2.70	9.08±2.41	0.20	15.04
Intervention group	9.33±2.77	9.04±2.43	0.20	15.36
*P-value	0.94	0.95		
Dietary fiber (g/1000 kcal)				
Control group	5.81± 1.67	5.61±1.49	0.20	
Intervention group	5.78±1.75	5.42±1.46	0.10	
*P-value	0.96	0.66		

Notes: Values are expressed as means ± SD. *$P<0.05$ was considered as significant at baseline and post-intervention using independent *T*-test between two groups. **$P<0.05$ was considered as significant using paired *T*-test.

Abbreviation: ISPAD, International Society for Pediatric and Adolescent Diabetes.

Table 3 Glycemic Status and Lipid Profile at Baseline and Post-Intervention

Variables	Intervention Group (n=22)	Control Group (n=22)	P-value*	P-value**	P-value***
FBG (mg/dl)					
Baseline	199.72±81.10	162.31±68.11	0.10		
End	163.68±75.88	171.63±73.89	0.72		
P-value	0.05	0.34			
Difference	−36.04±81.87	9.31±45.34		0.03	0.02
Insulin (µg/mL)					
Baseline	6.37±6.32	5.97±5.02	0.81		
End	10.90±8.20	7.57±7.12	0.15		
P-value	<0.001	0.18			
Difference	4.52±4.53	1.59±5.46		0.06	0.06
HbA1c (%)					
Baseline	8.90±1.95	9.60±2.23	0.27		
End	8.61±1.85	9.08±2.59	0.96		
P-value	0.01	0.08			
Difference	−0.28±0.52	−0.52±1.36		0.44	0.03
LDL-c (mg/dl)					
Baseline	79.81±13.55	74.45±17.06	0.25		
End	81.86±15.01	79.31±17.90	0.61		
P-value	0.14	0.06			
Difference	2.04±6.34	4.86±11.47		0.31	0.31
HDL-c (mg/dl)					
Baseline	54.13±9.47	49.13±8.02	0.06		
End	56.04±9.29	51.22±8.24	0.07		
P-value	0.26	0.12			
Difference	1.90±7.73	2.09±6.16		0.93	0.06
VLDL-c (mg/dl)					
Baseline	16.75±6.20	14.93±2.48	0.21		
End	15.65±9.67	15.00±3.73	0.77		
P-value	0.36	0.92			
Difference	−1.10±5.53	0.06±3.26		0.40	0.30
TG (mg/dl)					
Baseline	83.77±31.03	74.68±12.44	0.21		
End	78.27±48.39	75.00±18.69	0.77		
P-value	0.36	0.92			
Difference	−5.50±27.68	0.31±16.30		0.40	0.40
CHOL (mg/dl)					
Baseline	156.90±21.55	156.81±21.46	0.98		
End	158.63±21.32	158.31±21.26	0.96		
P-value	0.65	0.69			
Difference	1.72±17.59	1.50±17.70		0.92	0.93

Notes: Values are expressed as means ± SD. *P*<0.05 was considered as significant using paired *T*-test. **P*<0.05 was considered as significant using independent *T*-test between the two groups before and post-intervention. ***P*<0.05 was considered as significant changes using independent *T*-test between the two groups post-intervention. ****P*<0.05 was considered as significant using analysis of covariance (ANCOVA) between the two groups post-intervention after adjusting for confounding factors.
Abbreviations: FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; CHOL, total cholesterol; HDL, high-density; LDL, low-density lipoprotein cholesterol.

microbiota diversity and population (specifically the Clostridia class) and the reduction of the gut pH and transit time by consumption of fiber and whole grain.[34,35] The transit time in the upper intestine has a key role in the regulation of satiety and appetite, glycemic control and the hormone signaling in the gut.

Table 4 The Mean ± SD of Hs-CRP and TAC at Baseline and Post-Intervention

Variables	Intervention Group (n=22)	Control Group (n=22)	P-value*	P-value**
Hs-CRP (ng/mL)				
Baseline	3054.64±3009.89	2267.73±2087.29	0.31	
End	1807.10±2258.92	2293.01±1899	0.44	
P-value	0.004	0.89		
Difference	−1247.54±1793.66	25.28±858.14		0.005
TAC (mmol/lit)				
Baseline	94.16±14.29	100.07±11.49	0.33	
End	101.12±14.35	92.37±4.27	0.002	
P-value	0.001	0.08		
Difference	6.96±8.61	−7.70±11.58		0.005

Notes: Values are expressed as means ± SD. *P*<0.05 was considered as significant using paired *T*-test. **P*<0.05 was considered as significant using Independent *T*-test between the two groups at baseline and post-intervention. ***P*<0.05 was considered as significant changes using Independent *T*-test between the two groups post-intervention

Abbreviations: hs-CRP, Hs-C-reactive protein; TAC, total antioxidant capacity.

On the other hand, the transit time in the lower intestine (colon) mainly determine the gut microbiota.[36] It is indicated that the short-chain fatty acid (SCFA) production through the fermentation of non-digestible carbohydrates may impact on the appetite suppressing effects. It was found that increasing the colonic production of the SCFA propionate can significantly increase postprandial concentrations of the anorexigenic gut hormones peptide YY and glucagon-like peptide-1 (GLP-1), and sharply diminish the energy intake in humans.[37] More dietary fiber intake is associated with increased diversity of the gastrointestinal microbial community.[38]

Diabetes and Microflora Composition

Several studies found that the permeability of butyrate is increased in the patients with DM. The butyrate is secreted by the intestinal epithelial cells and mainly supply the energy for them. Therefore, the disturbance of the butyrate secretion can be a factor impairing the tight barrier function of intestinal epithelial cells.[39] Kieler et al in a study reported that the diversity of gut microbiota was lower in the diabetic cats than in the lean cats. There are growing evidence to support the presence of dysbiosis in the gut microbiota of T2DM patients. It is suggested that in general, the balance between beneficial and harmful bacteria is disturbed in the patients with DM, so that the population of beneficial bacteria decrease and that of harmful bacteria increase.[40] Therefore, it may be concluded that the diabetes condition can affect the composition of microbiota.

Anti-Metabolic Effects of Synbiotic

In a double-blinded clinical trial T2DM patients consumed 200 mL/d of a synbiotic shake containing 10^8 UFC/mL *Lactobacillus acidophilus*, 10^8 UFC/mL *Bifidobacterium bifidum* and 2 g oligofructose for 30 days and the results showed that the intervention significantly reduced the levels of FBG, which was almost similar to the results of our study. Also, a significant increase was observed in HDL-c which was not concurred with the present study. Similar to the present study, no significant change was observed in other lipid profile factors.[21] In another study, Ekhlasi et al, studied the effects of synbiotic and vitamin E supplementation on 60 patients with nonalcoholic fatty liver disease and found a significant decrease in FBG, insulin concentrations, TG, and TC in the synbiotic and synbiotic + vitamin E groups. Furthermore, the intake of synbiotic plus Vitamin E supplements led to a more significant decrease in LDL-C compared with control group.[15] In agreement to this study, in two other clinical trials, no significant changes were observed in LDL-c, TC, HDL-c, and TG.[24,41] The quantity and type of bacteria used in different studies as well as the duration of the intervention, target population, and type of disease may be factors influenced in the results of the studies.

It is indicated that synbiotic produces short-chain fatty acids, carbon disulfide, and methyl acetate, which can increase lipolytic activity.[24] It has been suggested that probiotics and prebiotics might counteract the development of the metabolic syndrome through replacing the aggravating bacteria in the gut, which in turn can improve serum lipid levels and insulin resistance.[26] Previous studies suggested some possible mechanisms. Synbiotics can increase the

GLP-1 and GLP-2 hormones. The GLP-1 reduces blood sugar and GLP-2, a proglucagon-derived peptide, reduces intestinal permeability. GLP-1 and GLP-2 secretion can lead to weight loss, hypoglycemia, and HbA1c depletion.[42] The loss of gut microbiota balance can affect on various organs such as adipose tissue, skeletal muscle, and liver, so it may affect on insulin resistance and glycemic status.

The Effects of Synbiotic on Inflammatory and Antioxidant Parameters

Systemic inflammation is common in the diabetes patients. It may lead to various complications including the cardiovascular disease in diabetes patients. There is no treatment strategy for reducing inflammation in diabetes patients has been established yet.[34,43] In a study by Asgharian et al, 80 patients with nonalcoholic fatty liver received a capsule containing synbiotic for 8 weeks. There was no significant difference reported in CRP index in any of the intervention and control groups in this study.[43] In agreement with the findings of the present study, after synbiotic supplementation in T2DM patients, there was a significant decrease in CRP in the intervention group compared with the control group.[44] In the study carried out by Malangwara et al, LDL-c and hs-CRP were found to be significantly improved in 66 patients after 24 weeks of supplementation with synbiotic. In terms of hs-CRP as an inflammatory factor, the results were consistent with our study. But the LDL-c had the opposite effect.[44] Regarding with the oxidative stress biomarkers, consuming bread-containing synbiotic for 8 weeks did not improve TAC in patients with type 2 diabetes.[45] Raygan et al in a study for 12 weeks in patients with diabetic CHD investigated the effects of vitamin D and probiotics. Unlike our study, the supplementation did not influence the FBG but similar to our study, the TAC and fasting insulin were improved.[46] Sonigisepp et al, observed a significant improvement in TAC after 3-week probiotic supplementation in healthy subjects.[47] The results of this study were more similar to the results of our study. In the study of Bahmani et al, the effect of synbiotic supplementation in type 2 patients was investigated and unlike our study, there was no effect observed on TAC.[45] There are other contradictory results have been observed in various studies. It is suggested that having a different population, using different dosages of synbiotic, duration of intervention, size effect of synbiotic, dosage of bacterial strain, and the type of prebiotic may be considered as possible reasons for different findings.

Free radicals can cause several complications of diabetes. There are many factors in diabetes which can increase the amount of these radicals including glucose autoxidation, leukocyte activation, etc.[48] With 12 weeks of probiotic supplementation in patients undergoing hemodialysis, Soleimani et al observed a significant increase in the TAC of these patients.[49] The precise mechanism behind the hypoglycemic effect and improvement of total antioxidant index by synbiotic have not been fully elucidated. It is indicated that lipopolysaccharide (LPS) derived from the outer membrane of Gram-negative bacteria increases the production of pro-inflammatory cytokines. One of the proposed mechanisms to explain how gut microbiota affects blood glucose is their effects on epithelial integrity of intestine, short-chain fatty acid production and its effect on energy homeostasis and blood glucose. Another mechanism is the conversion of primary bile acids to secondary ones by intestinal bacteria and activation of GLP1 by intestinal L cells.[50] Improvement of metabolic profiles, biomarkers of inflammation and oxidative stress by probiotics may be due to their effects on increasing concentrations of GSH, scavenging superoxide and hydroxyl radicals, reduced inflammatory signaling and decreased adiposity. Therefore, the beneficial effect of probiotics on biomarkers of oxidative stress is probably due to butyrate production in the intestine, and an increase in glutamate-cysteine-ligase activity.[51] In further researches can investigate the effects of synbiotic supplementation on microflora composition and other biomarkers of oxidative stress in type 1 diabetes.

Strengths and Limitation of the Study

This study was the first study to evaluate synbiotic supplementation in patients with (T1DM). The limitation of this study was its sample size.

Conclusion

It is suggested that supplementation with synbiotic for 8 weeks in patients with T1DM can improve FBG, HbA1c, insulin, hs-CRP, and TAC. So, this supplement can be used along with other diabetes control treatments.

Abbreviations

BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1C; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein density; SD, standard deviation; TC, total cholesterol; TG, triglyceride; Hs-CRP, Hs-C-reactive protein; TAC, total antioxidant capacity.

Compliance with Ethical Standards

The design of this study was done according to the guidelines of the Helsinki Declaration and all procedures involving human patients were approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code. IR.AJUMS.REC.1396.1032). In present study, a parent or legal guardian provided written informed consent before initiating the study.

Data Sharing Statement

The datasets are not publicly available because of lack of agreement for disclosing individual raw data in public but are available from the corresponding author on reasonable request.

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Disclosure

The authors have declared that there are no conflicts of interest in this work.

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