The effects of synbiotic supplementation on metabolic factors and systemic inflammation in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study

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Abstract

Background: Type 2 diabetes is a common metabolic disorder in the world, and it has become a challenge for the health system. Some studies have indicated the desirable effects of synbiotics on metabolic factors in patients with diabetes. Aim: This study aimed to determine the effect of synbiotic supplementation on metabolic factors and systemic inflammation in patients with type 2 diabetes mellitus.

Methods: In this randomized, double-blind controlled trial, 50 patients with type 2 diabetes randomly allocated to the synbiotic (containing Bacillus coagulans + Lactobacillus rhamnosus + Lactobacillus acidophilus and fructooligosaccharide) or placebo groups to received one sachet daily for 12 weeks. Glycemic index, Lipid profile, and hs-CRP measured at the beginning of the study and the end of the 12th week.

Results: After 12 weeks, supplementation means a change of Hip circumference (HC) significantly decreased in the synbiotic group compared to the placebo group (-0.85±1.89 vs. 1.23±3.98). Although systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of trial declined in the synbiotic group compared to baseline, respectively p=0.03, p=0.01. Analysis of covariance demonstrated that synbiotic supplementation during 12 weeks significantly reduced glycemic factors including fasting blood glucose (FBG), insulin, homeostatic Model Assessment for Insulin Resistance (HOMA-IR), β-cell function (HOMA-β) ($p<0.05$) and inflammatory index, hs-CRP ($p<0.05$) compared to placebo.

Conclusion: The current study indicated Synbiotic supplementation could improve glycemic index, systemic inflammation and blood pressure in patients with type 2 diabetes. So correcting the intestinal microbial flora can be a new therapeutic approach to treating this disease.

Trial registration: IRCT, IRCT20100524004010N27. Registered 7 January 2019, https://www.irct.ir/trial/36535

Background

Diabetes mellitus (DM) is one of the most common and crucial metabolic diseases in the world. The rapid increase in the prevalence of diabetes is the most severe and challenging health problem of the 21st century worldwide [1]. Type 2 diabetes is a multifactorial disorder and various factors involved in this disorder, such as genetic, epigenetic, environmental and lifestyle factors [2, 3]. Macro- and microvascular complications occur in patients with poorly controlled diabetes that have irreversible on the body. Microvascular complications include nephropathy neuropathy and retinopathy, and macro-vascular complications can be attributed to cardiovascular disease, which is one of the most critical risk factors for the death of these patients [4]. It demonstrated that in type 2 diabetes, abrupt metabolic pattern balance, although increase serum concentration of inflammatory cytokines and oxidative stress [5].

Nowadays, many studies are underway to investigate the benefits of functional foods, which one of the important aspects of this research is the anti-diabetes effects of these foods [6]. Probiotics are living microorganisms that, when existed insufficient amounts, have beneficial effects to the host [7]. Probiotics are digestive-resistant micro-organisms that have the ability to adherence to gastrointestinal and already have been proved probiotics is necessary for the balance of population pathogenic bacteria [8]. These compounds are recommended for the prevention and treatment of various conditions and diseases. Their mechanism of action is multifactorial, but most of its function is due to the regulation of immune function [9]. Probiotics can be effective in controlling blood sugar by blocking the production of reactive oxygen species, antioxidant properties and increasing the bioavailability of diabetes drugs [10]. In addition, certain species of probiotics enhance the function of the gut barrier [11] and may reduce the displacement and leakage of microorganisms and their derivatives, including lipopolysaccharides into the portal vein [12]. Recently the effect of probiotics has been investigated in various fields. Human studies have shown that use from probiotic supplements or products containing it improves fasting plasma glucose [13–15] and glycosylated hemoglobin [14, 16], but one study indicated that probiotics did not have any effects on glycemic indexes [17].

The main concern with probiotics application is these microorganisms are vulnerable to gastric acid and bile acids, but Bacillus coagulans is a spore-forming bacterium, can survive through the gastric and duodenal environment [7]. The aim of this study was to assess the effects of bacillus coagulans and fructooligosaccharide as a synbiotic supplement on metabolic factors and systemic inflammation in patients with type 2 diabetes.

Material

Participants and Ethics Statements

This study was a randomized double-blind, placebo-controlled trial which was on patients with type 2 diabetes, the participants were recruited from the diabetes clinic of Imam Hossein hospital in Tehran, Shahid Beheshti University of Medical Sciences. Type 2 diabetes was diagnosed according to fasting blood glucose (FBG) of > 126 mg/dL or 2-h postprandial glucose concentrations of > 200 mg/dL[18]. Patients with type 2 diabetes who were volunteer, BMI in the rage of 18.5–30 kg/m^2, aged 40–70 years included in the study. Exclusion criteria were pregnancy, insulin administration, consuming synbiotics and/or probiotics supplements within the past 3 months, changing the type and dosage of medications during the study, liver disease, renal failure, hypo- or hyperthyroid and inflammatory disease. This study was approved by the ethics committee of National Nutrition and Food Technology Research Institute (NNFTRI) of Shahid Beheshti University of Medical Sciences and it was registered at Iranian Registry of Clinical Trials, with the registration number of IRCT20100524004010N27, hence performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Study Design

At the beginning of the study, all volunteers completed the written informed consent then block randomization was conducted to allocate the participants in symbiotic or placebo group. The bottle of sachets encoded by A and B by the company, researchers and patients were not aware of the type of supplement. Placebo and symbiotic sachet were the same in color, size, packaging, and shape, and they were produced by the same pharmaceutical company (Magnolia Co, Iran). A technician did a randomized allocation of people to the groups. Symbiotic and placebo groups were received one sachet daily for 12 weeks. Each 2 g sachet contained 10^{11} spores of B. coagulans GanedenBC30 (GBI-30, 6086) + 10^{10} cfu Lactobacillus rhamnosus GG + 10^{9} cfu Lactobacillus acidophilus and 500 mg fructooligosaccharide (FOS) + 0.7% Natural Orange flavor (Magnolia Co, Iran). Placebo sachets were filled by 2 g of starch + 0.7% Natural Orange flavor (Magnolia Co, Iran).

Dietary Assessment

Dietary intake was assessed at the baseline and end of the study using a three-day food record (Two workday and one weekend). Researchers were interviewed by patients about the report their intake and then all measures converted to the gram and analyzed for macro- and micronutrients by Nutritionist IV (N4) software.

Anthropometric And Blood Pressure Assessments

The anthropometric measurements including weight, waist circumference (WC) and hip circumference (HP) were measured at baseline and end of the trial also body mass index (BMI) was computed before and after supplementation. Participants' weight was measured without shoes and wearing light clothes to the nearest 0.1 kg, using Seca digital scale digital scales, also Height was measured barefoot to the nearest 1 cm, using a meter attached to the wall. The waist circumference was determined in the middle area of the iliac crest and the last gear and hip circumference in the largest environment with the Seca head circumference meter. All measurements conducted by a person who was a nutritionist. Also, blood pressure variables including systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured twice after a 10-minute respite by a digital blood pressure monitor with 1 mmHg precision. the average of two values included in analysis.

Biochemical Assessments

Glucose was measured using Pars Test kit (Parsazmun, Tehran, Iran) and by enzymatic colorimetric method (GOD-PAP method). In this method, glucose oxidation is measured by enzymatic oxidation by glucose oxidase. The resulting color intensity increases with the concentration of glucose in the serum. The red wavelength was 495 nm. Serum insulin concentration was measured using ELISA method (Dmeditec, Germany) with a sensitivity of 1.76 µLu / ml. Triglyceride (TG) concentration was measured using Pars Test kit (Parsazmun, Tehran, Iran) enzymatically. Total cholesterol (TC) and high-density

lipoprotein cholesterol (HDL-C) concentration was measured by the enzymatic method using Pars Test Kit (Parsazmun, Tehran, Iran). Low-density lipoprotein cholesterol (LDL-C) concentration was also calculated using Friedewald's formula: LDL-C (MF) = Total cholesterol -TG/6 - (HDL-C). Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR) formula (HOMA-IR = [FBG (mg / dL) × Fasting Insulin (μU / ml)] / 405). Also insulin sensitivity was calculated using the quantitative insulin sensitivity check index (QUICKI) formula (QUICKI = 1 / [log fasting insulin (μU / ml) + log fasting glucose (mg / dl)) and the function of β-pancreatic cells was calculated using the HOMA-β model (HOMA-β = 360 × Insulin (μU / ml) / Fasting glucose (mg / dl) – 63). Finally the concentration of the hs-CRP was measured by using ELISA kit (IBL ,Germany, REF: EU59151).

Statistical Analysis And Sample Size

In this study that is anticipated symbiotic supplementation causes 20 mg/dl reduction in FBG according previous study [15], also with consideration 80% power (1–β) and α = 0.05, the minimum sample was calculated in each group 22 subjects and with considering 10% dropout the sample size increased to 25 subjects in each group. Mean ± standard deviation (SD) and frequency (percent) used for reporting quantitative and qualitative variables, respectively. The Normal distribution of variables was examined by the Kolmogorov-Smirnov test. For comparing qualitative and quantitative confounder variables between two groups Chi-square and Independent sample t-test were used, respectively. To determine differences for quantitative variables within groups paired-samples t-test and between groups, independent samples t-test were applied. Analysis of covariance was performed to comparing the quantitative variables between two groups and adjustment the effects of baseline and confounder variables. P-value < 0.05 consider as significant statistically. All analysis was done with the Statistical Package for Social Science version 21 (SPSS Inc.,Chicago, Illinois, USA).

Results

In this study, 50 patients with type 2 diabetes participated, 25 of them in the synbiotic group and 25 in the placebo group. During the study, five patients were excluded from the synbiotic group due to their lack of willingness to cooperate, insulin injection and substitution in the drug. In the placebo group, two persons were excluded from the study due to a lack of willingness to cooperate and changes in the type of drug used (Fig. 1). Totally 20 patients (12 women and 8 men) in the synbiotic group and 23 patients (14 women and 9 men) in the placebo group at the completed study. This study was carried out from October 2018 to February 2018.

Table 1 shows the general characteristics of patients in both groups. The mean age of patients in the symbiotic and placebo group was 59.10 ± 9.71 and 60.39 ± 6.74, respectively. There were not any significant differences in general information between two groups (Table 1).

Table 1

Baseline characteristics of participants in both groups

variables	Symbiotic groups	Placebo group	P value
Age(year)	9.71 ± 59.10	6.74 ± 60.39	0.612
Gender (%) Men Women	12 (60%) 8 (40%)	14 (61%) 9 (39%)	0.954
Smoking (%) Yes No	0 (0%) 20 (100%)	3 (13%) 20 (87%)	0.236
Hypoglycemic agents (%) Yes No	16 (83%) 4 (17%)	21(90%) 2 (10%)	0.780
Lipid lowering drugs (%) Yes No	12 (52%) 11 (48%)	10 (50%) 10 (50%)	0.460
Blood pressure lowering drugs (%) Yes No	15 (65%) 8 (35%)	13 (65%) 7 (35%)	0.650
All variables analyzed by except age which were analyzed by t-independent test, p:0.05			

Dietary intakes of subjective in both groups at baseline and end of the trial presented in Table 2. Statistical analysis between two groups at the beginning and end of the trial did not show any significant difference also the amounts of changes in dietary intake within groups during the intervention were not significantly.

Table 2
Dietary intakes in the symbiotic and placebo group

Nutrient	Time of assessment	Symbiotic group	Placebo group	P**
Energy (kcal/d)	Baseline	494.9 ± 1930.5	671.8 ± 1852.8	0.664
	End of study	469.5 ± 1977.2	566.7 ± 1810.06	0.303
	P*	0.497	0.565	
Carbohydrate (g/d)	Baseline	72.67 ± 257.36	109.76 ± 247.35	0.731
	End of study	72.01 ± 256.62	86.60 ± 233.84	0.358
	P*	0.191	0.161	
Protein (g/d)	Baseline	24.99 ± 76.64	18.23 ± 65.02	0.091
	End of study	26.12 ± 82.79	22.05 ± 73.54	0.215
	P*	0.187	0.064	
Fat (g/d)	Baseline	23.29 ± 72.5	27.89 ± 72.49	0.999
	End of study	20.72 ± 74.05	21.28 ± 69.04	0.440
	P*	0.719	0.290	
Vitamin E)mg/d)	Baseline	8.87 ± 20.74	7.90 ± 21.19	0.863
	End of study	7.96 ± 22.33	7.17 ± 20.84	0.523
	P*	0.332	0.732	
Vitamin C)mg/d)	Baseline	94.99 ± 131.88	72.03 ± 117.07	0.565
	End of study	106.92 ± 145.45	72.11 ± 118.57	0.390
	P*	0.604	0.898	

P*: p-value for comparison within groups
P **: p-value for comparison between groups

The mean ± standard deviation of anthropometric measurements and blood pressure of patients in the two groups at the beginning and end of the study is shown in Table 3. Differences in weight, BMI, waist circumference and hip circumference between two groups were not significant differences between the two groups at the beginning and end of the study ($P > 0.05$). Within-group analysis for all anthropometric measurements did not show any significant changes in synbiotic and placebo groups ($P > 0.05$). Although the mean changes of hip circumference were significantly different in the synbiotic group compared to the placebo group ($P = 0.012$). Between-group analysis showed that end of trial DBP significantly decreased in the synbiotic group compared to the placebo group ($p = 0.01$), although within-

group analysis demonstrated that SBP declined significantly in the synbiotic group (p = 0.03), other analysis did not show any significant change in blood pressure values (Table 3).

Table 3
Anthropometric indexes and blood pressure in both groups

Variables	Time	Symbiotic group	Placebo group	P*
Weight (kg)	Baseline	71.13 ± 15.96	72.63 ± 10.35	0.713
	End of trial	70.93 ± 16.04	72.81 ± 10.80	0.650
	P**	0.725	0.537	0.531
	Mean change	-0.2 ± 2.50	0.18 ± 1.43	0.472
	P***			
BMI (Kg/m^2)	Baseline	27.32 ± 4.34	28.27 ± 2.54	0.398
	End of trial	27.20 ± 4.10	28.32 ± 2.54	0.299
	P**	0.558	0.679	0.458
	Mean change	-0.11 ± 0.89	0.04 ± 0.56	0.585
	P***			
WC(Cm)	Baseline	87.70 ± 8.82	90.13 ± 3.96	0.266
	End of trial	87.00 ± 9.39	90.26 ± 3.98	0.161
	P**	0.197	0.779	0.788
	Mean change	-0.7 ± 2.34	0.13 ± 2.20	0.173
	P***			
HC(Cm)	Baseline	97.55 ± 8.41	95.78 ± 3.87	0.396
	End of trial	96.70 ± 8.31	97.02 ± 4.54	0.879
	P**	0.060	0.067	0.012
	Mean change	-0.85 ± 1.89	1.23 ± 3.98	0.828
	P***			
SBP (mm/Hg)	Baseline	11.70 ± 0.92	12.23 ± 1.49	0.171
	End of trial	11.10 ± 0.91	11.97 ± 1.65	0.299
	P**	0.03	0.379	0.403
	Mean change	-0.6 ± 1.14	-0.26 ± 1.41	0.254
	P***			
DBP (mm/Hg)	Baseline	7.15 ± 0.87	7.52 ± 1.12	0.238
	End of trial	6.55 ± 0.75	7.18 ± 0.76	0.010
	P**	0.010	0.127	0.393
	Mean change	-0.60 ± 0.94	-0.33 ± 1.02	0.804
	P***			

P*: p-value for comparison between group by independent t test
P**: p-value for comparison within group by paired t test
P***: p-value for comparison by Ancova (adjusted for baseline values)
BMI: Body mass index, WC: Waist circumference, HC: Hip circumference, SBP: Systolic blood pressure, DBP: Diastilic blood pressure.

Mean baseline, end of the trial and mean changes values of lipid profile including TC, TG, LDL-C, and HDL-C in the placebo and synbiotic group presented in Table 4, comparison between two groups did not show any significant difference except TG at baseline (p = 0.004). Although analysis of covariance demonstrated that supplementation with synbiotic did not any effect on lipid profile (p > 0.05).

Table 4
Biochemical profile in both group

Variables	Groups	assessment time			P**	P***
		baseline	End of study	Mean change		
Triglyceride (mg/dl)	symbiotic	47.17 ± 173.00	46.23 ± 168.15	37.70 ± 4.85-	0.545	0.589
	placebo	52.32 ± 126.39	44.21 ± 121.13	36.67 ± 5.26-	0.499	
	P*	0.004	0.120	0.971		
Total cholesterol (mg/dl)	symbiotic	46.68 ± 180.95	34.52 ± 169.50	42.31 ± 11.45-	0.241	0.064
	placebo	47.29 ± 179.82	47.87 ± 174.27	31.06 ± 5.04-	0.444	
	P*	0.938	0.684	0.571		
HDL-C (mg/dl)	symbiotic	9.55 ± 34.76	5.29 ± 32.57	8.33 ± 2.19-	0.254	0.068
	placebo	2.96 ± 31.05	4.06 ± 32.10	3.81 ± 1.04	0.202	
	P*	0.109	0.744	0.122		
LDL-C (mg/dl)	symbiotic	180.87 ± 52.69	170.56 ± 40.33	-16.82 ± 56.44	0.331	.0.073
	placebo	52.55 ± 174.05	54.05 ± 166.90	34.75 ± 7.65-	0.276	
	P*	0.678	0.805	0.519		
FBG (mg/dl)	symbiotic	39.17 ± 163.00	32.48 ± 146.85	39.12 ± 16.75-	0.066	0.009
	placebo	40.26 ± 144.43	40.40 ± 147.65	14.54 ± 3.21	0.300	
	P*	0.136	0.944	0.041		
Insulin (Mu/ml)	symbiotic	7.25 ± 16.87	4.56 ± 9.80	16.32 ± 10.50-	< 0.0001	0.024
	placebo	5.78 ± 16.99	4.46 ± 18.27	6.30 ± 1.33	0.338	
	P*	0.925	< 0.0001	0.003		
HOMA-IR	symbiotic	2.82 ± 6.50	2.08 ± 3.68	2.62 ± 2.82-	< 0.0001	< 0.0001

Variables	Groups	assessment time			P**	P***
		baseline	End of study	Mean change		
	placebo	2.43 ± 5.98	2.86 ± 6.73	2.27 ± 0.75	0.128	
	P*	0.519	< 0.0001	< 0.0001		
HOMA-β	symbiotic	74.30 ± 46.37	45.32 ± 22.93	-28.98 ± 44.84	0.009	< 0.0001
	placebo	66.52 ± 99.31	46.37 ± 94.63	48.19 ± 4.68-	0.645	
	P*	0.166	> 0.0001	0.096		
QUICKI	symbiotic	0.017 ± 0.296	0.025 ± 0.323	0.025 ± 0.026	< 0.0001	0.948
	placebo	0.015 ± 0.299	0.014 ± 0.294	0.013- ±0.004	0.101	
	P*	0.650	> 0.0001	> 0.0001		
hs-CRP (ng/ml)	symbiotic	6.53 ± 3.01	4.12 ± 3.05	-2.41 ± 2.48	< 0.0001	0.001
	placebo	5.53 ± 2.04	6.47 ± 6.47	0.89 ± 3.21	0.146	
	P*	0.219	0.042	0.001		

P*: p-value for comparison between group by independent t test
P**: p-value for comparison within group by paired t test
P***: p-value for comparison by Ancova (adjusted for baseline values)

After supplementation with synbiotic, within-group analysis showed that insulin, HOMA-IR, HOMA-B, and QUICKI significantly decreased (respectively, p = < 0.001, p = < 0.001, p = < 0.001, p = < 0.001), although statistical analysis showed that mean changes of FBG (p = 0.041), insulin (p = 0.003), HOMA-IR (p = < 0.001) and QUICKI (p = > 0.001) significantly decreased in synbiotic group compared to placebo group. Insulin (p = < 0.0001), HOMA-IR (p = < 0.0001), HOMA-B (p = 0.009) and QUICKI (p = < 0.0001) decreased at the end of the trial compared to baseline in the synbiotic group. Analysis of covariance has been shown that symbiotic supplementation in comparison placebo significantly decreased FBG, insulin, HOMA-IR, and HOMA-B, respectively p = 0.009, p = 0.024, p = < 0.0001, p = < 0.0001 (Table 4).

The mean and standard deviation of hs-CRP in baseline and end of the trial is expressed in Table 4, the analysis indicated that hs-CRP decreased in synbiotic compared to placebo (p = 0.042), although at end of trial hs-CRP declined in the synbiotic group compared a baseline (p = p = < 0.0001). Analysis of covariance indicated that synbiotic as compared to placebo attenuated hs-CRP (p = 0.001).

Discussion

In this study, receiving synbiotic supplementation (fructooligosaccharide and bacillus coagulans) compared with placebo have desirable effects on insulin resistance, glycemic indexes, hs-CRP and diastolic blood pressure in patients with type 2 diabetes but did not have a significant effect on lipid profile.

Up to our knowledge this is first study that evaluated the effects of bacillus coagulans on type 2 diabetes patients. The findings of this study are consistent with the result of the Malaguarnera et al. [19] they showed that synbiotic supplementation could improve the HOMA-IR index But did not any effect on serum insulin levels in the subjects after 6 months of intervention. The results of this study were consistent with the findings of Thorburn [20], and Englyst et al. [21], In these studies supplementation with oligophytic enzymes reduced the levels of insulin levels. In fact, these studies have shown that foods containing indigestible carbohydrates have a hypoglycemic effect.

The findings of the present clinical trial showed that the concentration of serum triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol in the synbiotic group did not change significantly compared to the baseline and the placebo group. Our results were consistent with the findings of Malaguarnera et al. [19]. In this mentioned study, there was no significant difference in TG and TC concentrations between the two groups at the end of six months of supplementation with bifidobacterialangum and fructo-oligosaccharide with lifestyle modification (exercise and diet). Only serum LDL concentration in the treatment group decreased significantly after 6 months of intervention compared to the placebo group. In another study conducted by Ebrahimi et al. [22] in 2017 on obese patients with type 2 diabetes, serum concentrations of triglyceride, total cholesterol, and LDL-cholesterol in the synbiotic supplemented group did not change significantly compared to the placebo group after 12 weeks of supplementation. However, the serum concentration of HDL-cholesterol was considerably higher in the synbiotic group than in the placebo group after treatment [22]. Also, Assam et al. did not observe any significant change in lipid profile concentration in the synbiotic group after six weeks in patients with diabetes mellitus [23], The results of this study are in line with the present study.

Human study about the effect of synbiotic supplementation on lipid profile is rare and animal studies have been reported controversy results. In a study by Wang et al. [24], 5-week administration of Lactobacillus Plantarum M2 to cholesterol-rich rats showed a significant decrease in serum TC, LDL, and TG levels, but did not affect HDL concentration. The results of earlier studies were also the same as our study results and consistent with Wang's [25–27]. The contradictory findings in lipid profile concentrations can be attributed to differences in strains used, culture media used for the strains, dosage used in the studies, study designs and treatment periods in the studies. The mechanism of the effect of probiotics is still unclear. Some studies indicated that health promotion effects of synbiotics attributed to inhibition of pathogenic bacteria proliferation, the rectification of intestinal flora, reduction of disease risk. The beneficial effects of prebiotics on serum lipid profiles are via short-chain fatty acids (SCFA). Butyrate inhibits the synthesis of cholesterol in the liver. Acetate, as a cholesterol precursor, stimulates its

synthesis in the liver, and propionate probably reduces the rate of cholesterol synthesis in the liver by reducing the use of acetate to synthesize cholesterol. The primary mechanism in reducing serum TG is to decrease lipogenic activity in the liver [28–31].

This study showed that taking synbiotic supplements compared to placebo significantly decrease in the serum concentration of hs-CRP. The findings of the present study were in line with the findings of previous studies. A study by Kekkonen et al. [32] demonstrated that three weeks consume milk containing Lactobacillus rhamnosus, sherman and a species of freadenreichii had desirable effects on hs-CRP. However, in this study expressed that other probiotics such as bifidobacteria and lactobacillus lactis, could not change hs-CRP. Therefore, the type of bacterial strains used and even the duration of the intervention may cause differences in these results. Some other studies also showed that synbiotic supplementation could decrease hs-CRP concentration [19, 33, 34]. The proposed mechanism for the effect of probiotics and prebiotics on serum levels of hs-CRP is due to the extrahepatic effects of these supplements by reducing adipose tissue mass and subsequently decreasing IL-6 by adipose tissue, hepatocyte stimulation is lessened, resulting in lower amounts of hs-CRP being synthesized. Also, modification of the gut microbial flora by using probiotics and prebiotics is effective in reducing endotoxemia and proinflammatory cytokines by maintaining intestinal mucosal integrity and reducing intestinal permeability.

This study showed that taking synbiotic supplements compared to placebo reduced diastolic blood pressure. In addition, systolic and diastolic blood pressure were also significantly decreased within the synbiotic group. A study by Bahmani et al. [35] showed that 120 grams of synbiotic-enriched bread in patients with diabetes mellitus for eight weeks did not have any significant effect on systolic and diastolic blood pressure. The findings of this study are comparable to the present study. In another study by Mahboobie et al. [36] synbiotic supplements containing 6 bacterial strains with fructooligosaccharide for 12 weeks in person with diabetes. In this study, systolic and diastolic blood pressure did not change significantly in the intervention group compared to the placebo group. The conflicting results of synbiotic supplementation and its effects on systolic and diastolic blood pressure may be due to different doses of supplementation in studies, duration of intervention, type of disease, and various bacterial species. However, the precise mechanism of how probiotics and prebiotics work on blood pressure is unclear. A possible mechanism for improving blood pressure could be the change in the composition of the microbial flora, the reduction of inflammatory mediators and the increase in nitric oxide levels.

It is essential to use a probiotic which can survive extreme conditions of the gastric and duodenal environment. Bacillus coagulans is a spore-forming bacterium, which could tolerate this condition.

The present study had some limitations that should be noted for future research. First, all of the patients consuming oral hypoglycemic agents; thus, we cannot attribute all hypoglycemic effects to the symbiotic supplement. Second, due to exclusion criteria considered in this study could limit the generalizability of the results.

Conclusion

Summary findings of this randomized, double-blind controlled trial showed that taking synbiotic (Bacillus coagulans, Lactobacillus rhamnosus, Lactobacillus acidophilus and fructooligosaccharide) supplements for 12 weeks could decrease FBG, serum insulin levels, insulin resistance, diastolic blood pressure, hs-CRP, and increased QUICKI compared to the placebo group. synbiotic supplementation did not cause significant changes in serum levels of lipid profile and systolic blood pressure compared to the control group.

Abbreviations

SBP
Systolic blood pressure
DBP
Diastolic blood pressure
HOMA-IR
homeostatic Model Assessment for Insulin Resistance
HOMA-β
β-cell function
DM
Diabetes mellitus
FBG
Fasting blood glucose
WC
Waist circumference
HP
Hip circumference
QUICKI
Quantitative insulin sensitivity check index
BMI
Body mass index
TG
Triglyceride
TC
Total cholesterol
HDL-C
High-density lipoprotein cholesterol
LDL-C
Low-density lipoprotein cholesterol

Declarations

Authors contribution

A.V, O.NP and G.S designated the study, analyzed and interpreted the data and drafting study; G.S and O.NP supervised the study; M.S diagnose patients; M.H perform laboratory tests; A.V, K.A, E.H writing the manuscript; G.S, I.K O.NP revised the content of manuscript, analysis and final of the version to be published. All authors read and approve the final manuscript.

Acknowledgment

No applicable.

Competing interest

The authors declare that they have no competing interest.

Availability of data and materials

Please contact authors for data request.

Consent for publication

No applicable.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of the National Nutrition and Food Technology Research Institute of Shahid Beheshti University of Medical Sciences. Written informed consents were obtained from all participants.

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Figures

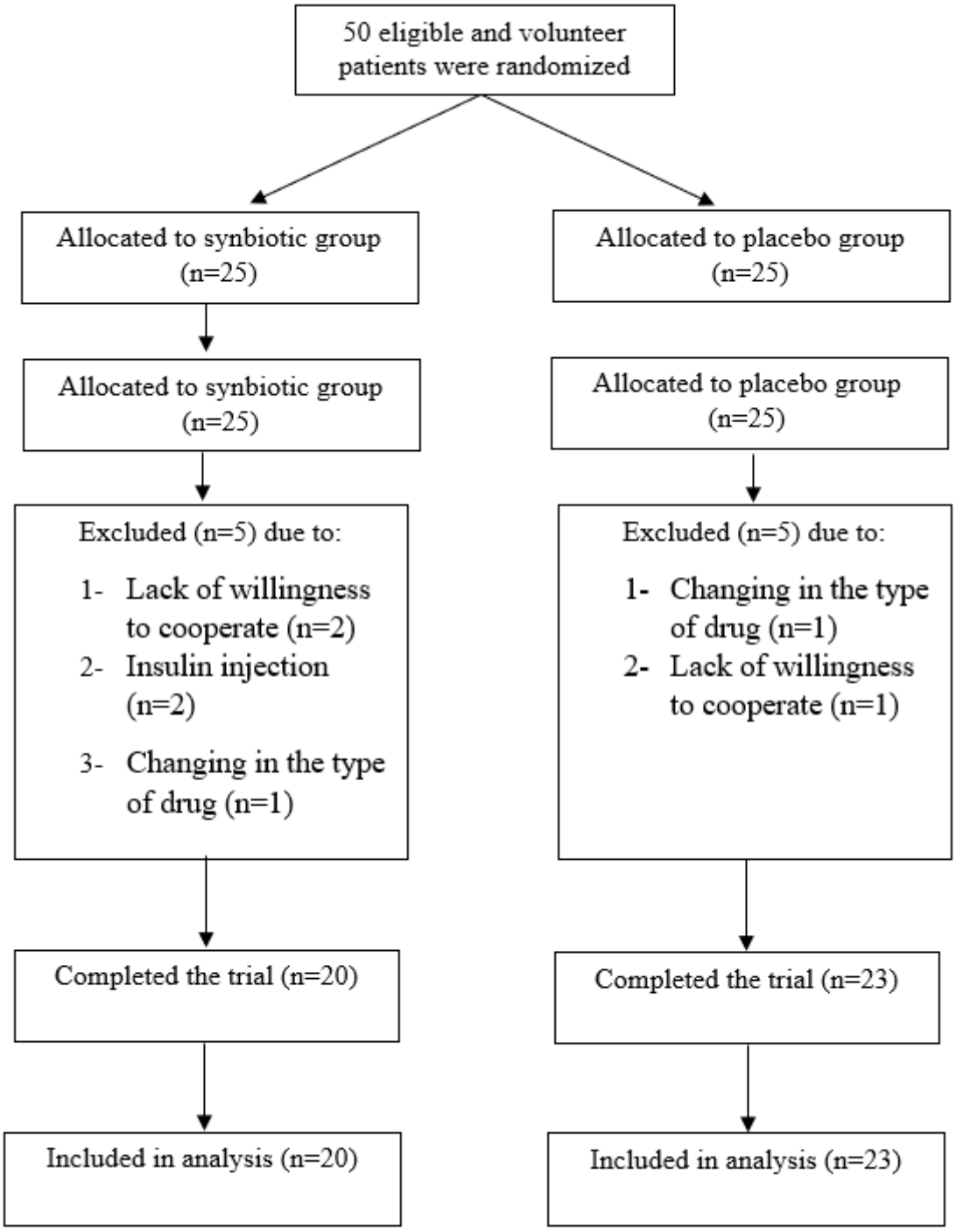

Figure 1

Flow diagram of the study participants