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Original Article

Probiotic and synbiotic supplementation could improve metabolic syndrome in prediabetic adults: A randomized controlled trial

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ABSTRACT

Aims: Modulation of the gastrointestinal microbiome is suggested to contribute to the progression of metabolic syndrome associated diseases. This study was designed to assess the effects of probiotics and synbiotics on metabolic syndrome in individuals with prediabetes.
Methods: 120 adults with prediabetes were enrolled in a double-blind, placebo-controlled randomized parallel-group clinical trial. Participants were randomized to a multi-species probiotic or inulin-based synbiotic or placebo. Blood samples and anthropometric measures were collected at baseline, 12 and 24 weeks after treatment. The primary outcome measures were the changes between groups in metabolic syndrome and its components' prevalence.
Results: A significant trend for a reduction in the prevalence of hyperglycemia in probiotic and synbiotic groups ($p = 0.01$ and 0.005 respectively), and hypertension in probiotic group ($p = 0.04$) was found. The decreases in metabolic syndrome prevalence were significant after taking probiotic and synbiotic supplementation as compared with placebo ($p = 0.02$). Also, the prevalence of low HDL-cholesterol level was decreased during the study in the probiotic group compared with placebo ($p = 0.02$).
Conclusions: The potential benefits of using probiotic and synbiotic for metabolic syndrome management in prediabetes have been supported by the results in the current study which might provide an important strategy to combat metabolic syndrome-associated diseases.

1. Introduction

The term of metabolic syndrome is used to describe a combination of metabolic disorders that all together, increase the risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases [1]. The components of metabolic syndrome are including the presence of central obesity, dyslipidemia, glucose intolerance and hypertension [2]. The worldwide prevalence of metabolic syndrome is variable, ranging from 10% to 84%, depending on geographical origins and composition of the studied population [3]. Metabolic syndrome prevalence has been increased substantially in the last two decades which should be a priority for public health [4]. It is estimated that people with metabolic syndrome are twice as likely to die and three times as likely to have a heart attack or stroke compared with people without the syndrome [5]. Moreover, compared with persons without metabolic syndrome, those with the syndrome have an approximately 5-fold increase in diabetes risk. However, when metabolic syndrome combines with prediabetes, the risk is increased even more [6]. Indeed, two clinical constructs for identifying individuals at high risk of developing type 2 diabetes are metabolic syndrome and prediabetes. Thus, effective treatment of these at-risk individuals is imperative for the prevention of type 2 diabetes [7].

To date, the intestinal microbiota has been interested in its equivocal impact on health and is an emerging investigative field [8]. The connection between metabolic syndrome and gut microbiota is now acknowledged and some of the therapeutic strategies have been proposed to improve the composition of the gut microflora in order to promote optimal metabolic health [9].

Current investigations suggest that manipulation of the gut microbiota by probiotics, prebiotics, and synbiotics could be a promising approach for the management of metabolic syndrome

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[10]. Probiotics reside in the human intestine and colon and exert actions such as modulating gastrointestinal micro-flora and immunologic responses. Prebiotics are non-digestible oligosaccharides that beneficially affect by stimulating the growth or activity of beneficial bacteria in the colon [11]. In combination, probiotics and prebiotics create synbiotics, which can provide even more benefits than probiotics or prebiotics alone. Certain probiotic species and prebiotic types have been partially demonstrated to improve glycemic markers and lipid profiles in obese, type 2 diabetes mellitus and dyslipidemic rodents and human subjects [12,13]. However, it is not known whether probiotic species, prebiotics or synbiotics can improve metabolic syndrome in individuals at risk of type 2 diabetes.

Hence, well-designed clinical trials addressing the efficacy and efficiency of these products on metabolic syndrome and its components are needed. For this reason and also because of conflicting results of previous studies, the present study has been designed to investigate the effects of supplementation with probiotics and synbiotic on metabolic syndrome in subjects with prediabetes who are at risk of diabetes and cardiovascular diseases.

2. Methods

2.1. Participants

Prediabetic individuals aged between 35 and 70 years were recruited from the first relatives of type 2 diabetic patients in the outpatient clinic of Isfahan Endocrine and Metabolism Research Center between June 2016 and March 2017. Eligibility criteria included male and female adults with fasting plasma glucose between 100 mg/dl and 125 mg/dl and/or 2 h postprandial serum glucose levels between 140 mg/dl and 199 mg/dl following a 2-hour 75-g glucose tolerance test and/or glycated hemoglobin (HbA1C) between 5.7% and 6.4%, according to ADA definition for prediabetes [14]. Exclusion criteria included smoking, use of steroids and other agents that may influence lipid metabolism, diabetes mellitus, hypo- and hyperthyroidism, cardiovascular events within the last 6 months, major systemic diseases, gastrointestinal problems, liver disease, renal failure, using probiotic, prebiotic or synbiotic during the past 3 months, antibiotic or laxatives use in the past 3 months or during the treatment period, pregnancy, having food allergies, and participation in any other clinical trials within the last 6 months.

2.2. Study design

The original protocol consisted of a 24-week intervention period with a 36-week follow-up, as previously reported [15]. The current study was an adaptation of the original intervention and was conducted as a 24-week (without follow-up), randomized, double-blind, placebo-controlled, three-arm, parallel-group clinical trial.

2.3. Sample size

For the primary outcome, we estimated that we would need to enroll 87 patients to detect a reduction in the frequency of the metabolic syndrome of 15% [16] by probiotic or synbiotic as compared with placebo with the statistical power of 80%, allowing for a type I (α) error of 0.05. However, allowing for a loss to follow-up of 30%, 120 patients were required to undergo randomization.

2.4. Randomization

The randomization sequence was generated using a computer-generated list of random numbers to create a series of sequentially numbered envelopes containing equal assignments to placebo, probiotic or synbiotic. Recruited participants were enrolled and assigned a three-digit number in chronological order by a person not involved in the study. Participants were then randomized to one of the three groups by blocking stratified sampling method according to age and gender. The study pharmacist was responsible for delivery of the blinded supplements. The supplements, which were assigned letter A, B or C, were otherwise identical and the participants, laboratory staff, outcome assessors, and data analysts were blinded for assignment to interventions. An unrestricted randomization scheme was followed. The randomization numbers were contained in sealed, opaque envelopes kept by office staffs who were not involved in outcome measurements. The blinding code was provided to the investigators after the statistical analyses were completed.

2.5. Intervention

Participants were supplemented with 6 g/d of either probiotic containing the freeze-dried *Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium lactis,* and *Bifidobacter longum* (1.5×10^9 for each) with maltodextrin as filler, synbiotics comprising the mentioned-above probiotics plus inulin as prebiotic, or placebo including maltodextrin for 24 weeks. The supplements were prepared and packaged in Tak Gen Zist Pharmaceutical Company, Tehran, Iran in sachet form. The participants were advised not to modify their dietary and/or physical activity habits during the study. The researchers were in weekly contact with participants and if there were any concerns or side effects during the intervention, the participant was excluded from the study. Compliance was assessed based on returned sachet counts. If a participant had missed more than 10% of supplement dose at follow-ups, it defined as noncompliance and he or she was excluded from the study.

2.6. Ethical aspects

This study was conducted according to the ethical guidelines provided by the National Health and Medical Research Council and the Declaration of Helsinki. The original study protocol was approved by the Isfahan University of Medical Sciences and the Research Ethics Committee (approval no. IR. MUI.REC.1394.3.813). All identifiable information collected from participants was coded. All participants provided signed, written informed consent. This trial was registered with the Iranian Clinical Trials Register (trial registration no.: IRCT201511032321N2).

2.7. Assessments

Assessments were done at the beginning and repeated at 12-weeks and 24-weeks of intervention periods.

2.7.1. Anthropometric variable

Waist circumference was measured at the midpoint between the lowest rib and the iliac crest to the nearest 0.1 cm using a flexible tape. All the measurements were taken by one person to decrease the error rate.

2.7.2. Blood pressure

Blood pressure for each participant was measured by a trained nurse on three occasions using a mercury sphygmomanometer to the nearest 1 mm Hg in the sitting position after at least 5 min of rest. The mean of three measurements with a minimum of 5 min between the occasions was recorded according to American Heart Association guidelines [17].

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2.7.3. Laboratory tests

Participants who had met the inclusion criteria were instructed to arrive at Isfahan Endocrine and Metabolism Research Center for laboratory testing between 7:00 and 9:00 a.m. after a 12-hour overnight fast and not to do vigorous physical activity for the previous 48 h. We measured the fasting plasma glucose level by using the glucose oxidase (GOD) method. Plasma lipid and lipoprotein concentrations (i.e., high-density lipoprotein cholesterol, and triglycerides) were measured using a photometric assay kit (Pars Azmoun Co., Tehran, Iran). All of the intra- and inter-assay coefficients of variation were <10%.

2.8. Metabolic syndrome definition

The metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria (NCEP ATP-III); the presence of three or more of the following criteria: waist circumference≥102 cm for men and ≥88 cm for women, fasting triacylglycerol ≥150 mg/dl, HDL-cholesterol <40 mg/dl for men and <50 mg/dl for women, blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic, or drug treatment for hypertension, and fasting plasma glucose ≥100 mg/dl [18].

2.9. Statistical analysis

The analysis was based on intention-to-treat. Continuous variables were summarized as means ± SD and categorical variables as proportions. The baseline data in the three groups were compared using one-way ANOVA and chi-square test. For categorical variables, the chi-square test was used to analyze the association between groups at each time and the Cochrane test was used to compare the trend of changes in each group. Generalized estimation equation (GEE) was applied to evaluate and compare the effect of the interventions on categorical outcomes between groups. Two-sided p-values of less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed with the use of a statistical software package (SPSS-15).

3. Results

120 participants were randomly assigned to an intervention, with 40 participants to undergo probiotics, 40 participants to undergo synbiotic and 40 participants to undergo placebo. 35 participants lost to follow-up the study. The attrition rates were 37% for the probiotic group, 28.6% for the synbiotic group and 34.4% for the placebo group. The major causes of attrition were using antibiotic during the study, low compliance, disinclination, GI complication, and traveling. Finally, 85 participants completed the 24-weeks' intervention including 27 in probiotic, 30 in synbiotic and 28 in placebo groups (Fig. 1).

The baseline demographic, anthropometric and biochemical characteristics were not different between the three groups (Table 1).

81 out of 120 participants (67.5%) had the metabolic syndrome at the baseline of study (22 in the probiotic group, 26 in the synbiotic group and 33 in the placebo group, $p = 0.38$). We observed a significant trend for a reduction in the prevalence of hyperglycemia (FPG≥100) in probiotic and synbiotic groups ($p = 0.01$ and 0.005 respectively), and hypertension (≥130 mmHg systolic or ≥85 mmHg diastolic, or drug treatment for hypertension) in probiotic group ($p = 0.04$). There was a reduction in the other components in probiotics and synbiotic groups during intervention period as well, although it was not significant (Table 2). On the other hands, the differences in metabolic syndrome between the three groups were seen at 12 weeks and 24 weeks ($p = 0.04$ and 0.032 respectively). The change in metabolic syndrome prevalence, as it has been shown in Fig. 2, revealed a decreasing trend for all treatment groups which was significant after taking probiotic and synbiotic supplements as compared with placebo ($p = 0.02$). For hypertriglyceridemia, a significant difference between probiotic and synbiotic groups compared to placebo at 24 weeks of intervention was observed ($p = 0.02$). Also, the prevalence of low HDL-cholesterol was reduced during the study in probiotic group compared with placebo (Table 2). During the study, no serious adverse events were registered. The only reported adverse event (14.1%) was mild gastrointestinal complications including flatulence, dysphagia, and dyspepsia (2 in the probiotic group, 5 in the synbiotic group and 5 in the placebo group).

4. Discussion

The available evidence suggesting the employ of probiotics, prebiotics or synbiotics are not strong enough and, therefore, the therapeutic use of these supplements for metabolic disorders has not been recommended yet [18,19]. Also, only a small number of studies focusing on human interventions were designed to analyze the effects of probiotic and/or synbiotic administration in prediabetes population who are at risk of diabetes and cardiovascular diseases [5]. The outcome of this study revealed that the treatment by probiotic and synbiotic decreased metabolic syndrome prevalence during the study period (17% and 23% respectively) which the changes were significant compared to placebo. This outcome leads to improve the current knowledge in clinical practice about metabolic abnormalities. The results of this study showed that the trend of reduction in metabolic syndrome through synbiotic administration has occurred in the first 12 weeks. Therefore, it seems that 12weeks period may be sufficient to observe synbiotic effects on metabolic syndrome improvements in prediabetic subjects. In our subjects, according to the National Cholesterol Education Program's Adult Treatment Panel III definition, the prevalence of the metabolic syndrome was 67.5% at baseline. It has been documented that approximately 70% of individuals with prediabetes meet clinical criteria for the metabolic syndrome which is in agreement with current study [20]. In the Iranian adult population, according to the population-based studies in different cities of Iran, the prevalence of metabolic syndrome from 2003 to 2016 has been 31–37% [21]. The prevalence of metabolic syndrome in Isfahan province, according to Isfahan Healthy Heart Program (IHHP) in 2015, has been reported as 20.7% [22]. So, there is an emerging high prevalence of metabolic syndrome in prediabetic subjects compared with general population. Consequently, as the overlap between prediabetes and metabolic syndrome creates a tension for diabetes, it is important to identify the prediabetes patients with metabolic syndrome because these patients have a particularly adverse metabolic state [23]. Therefore, to reduce the risk of diabetes and cardiovascular events in individuals with prediabetes, screening and early detection and treatment of risk factors for metabolic syndrome are strongly recommended.

The reversal of the metabolic syndrome is usually due to a significant reduction in at least one of the components [24]. The results of this study showed that in 26% of the patients with hyperglycemia and 21% of the patients with hypertension who underwent probiotic therapy, the disorder resolved within 24 weeks which is a statistically significant improvement. Moreover, the prevalence of low HDL-cholesterol improved through probiotic supplementation in compared with placebo. These results were in agreement with most prior studies. It has been shown that oral administration of probiotics could decrease serum glucose levels and modulate lipid metabolism in animal models [25–27]. Some researchers have investigated the effects of probiotics on serum

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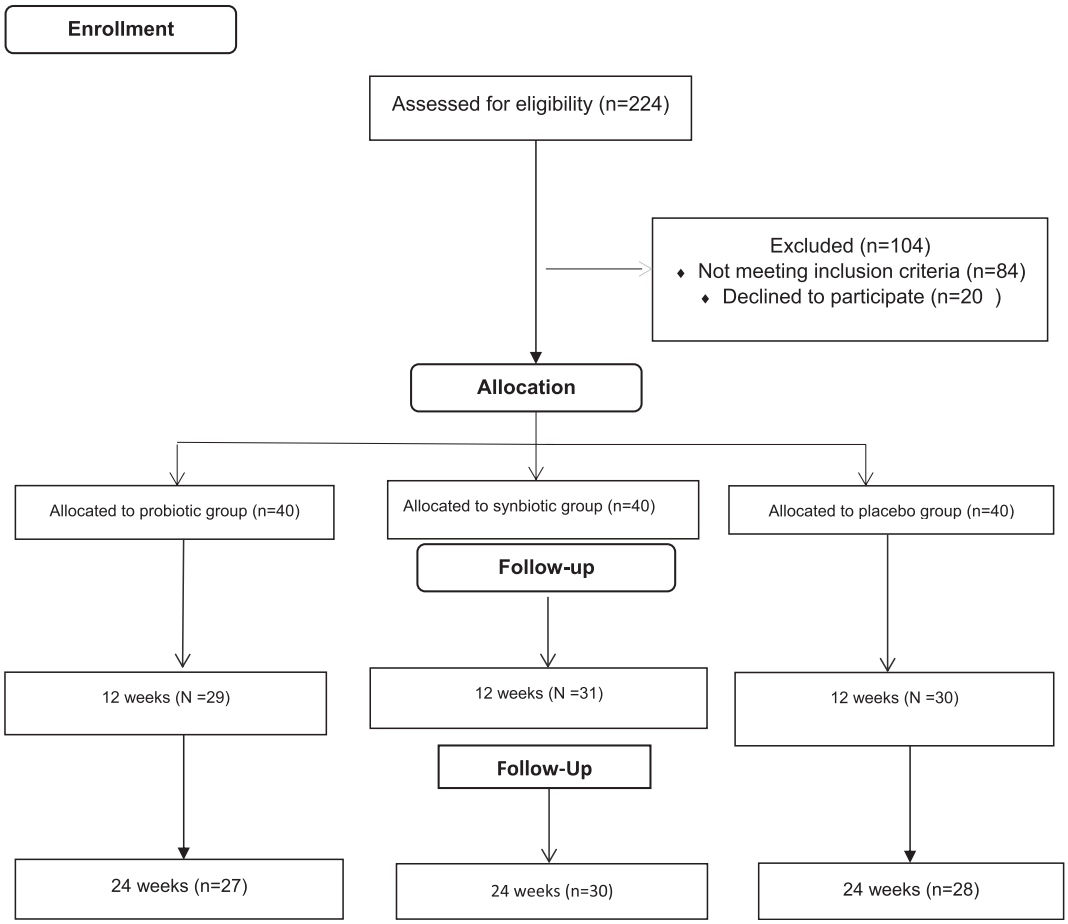

Fig. 1. Flowchart according to the consolidated standards of reporting trials.

Table 1
Baseline characteristics presented by the three groups.

		Probiotic (n = 40)	Synbiotic (n = 40)	Placebo (n = 40)	P- value
Age (years)		52.9 ± 6.3	52.97 ± 6.8	52.97 ± 5.9	0.91
Gender	Male N (%)	15 (48)	17 (43)	18 (43)	0.96
	Female N (%)	25 (52)	23 (57)	22 (57)	
Education (years)		11.8 ± 3.8	11.1 ± 3.8	10.5 ± 3.3	0.22
Waist circumference (cm)		96.23 ± 9.4	97.43 ± 9.7	98.76 ± 8.8	0.47
Fasting Plasma Glucose (mg/dl)		107.19 ± 7.6	107.93 ± 8.5	104.56 ± 8.2	0.44
Systolic Blood Pressure (mmHg)		122 ± 10	119 ± 12	123 ± 13	0.39
Diastolic Blood Pressure (mmHg)		79 ± 6	79 ± 5	82 ± 7	0.23
HDL-C (mg/dl)[a]		46.11 ± 10.8	42.41 ± 9.8	43.00 ± 9.3	0.22
Triglyceride (mg/dl)		157.57 ± 72.9	148.05 ± 52.6	150.40 ± 53.2	0.73

[a] High density lipoprotein cholesterol.

glucose and lipid profiles in human subjects too, but the results have not been consistent [28–30]. These discrepancies may have been caused by using various probiotic strains. It seems that using multispecies probiotic may be more effective than single-strain on metabolic disorders [31].

We used 4-strain probiotics including *Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium lactis,* and *Bifidobacterium longum* in this study.

Interestingly, certain probiotics share common beneficial properties and it should be kept in mind that different bacteria may affect different sections of the intestines. The *Lactobacillus* and *Bifidobacterium* strains cannot individually account for all of the effects attributed to probiotics. In humans, it may be expected that probiotic action of *Lactobacillus* strains is primarily targeting the small intestine, while that of *Bifidobacterium* strains is directed more towards the colon [32].

The administration of probiotics combining *Bifidobacterium* and *Lactobacillus* strains seems to improve glucose tolerance, increase the production of SCFAs and of butyrate that stimulate the intestinal production of GLP-1 [33].

The present study was the first to test the effects of our synthetic synbiotic which was created for the first time in Iran. There are few data on the relationships of synbiotic supplementation and metabolic syndrome, particularly in Iran. In the current study, synbiotic could resolve hyperglycemia in 21.4% of the subjects in which the improvement is statistically significant.

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Table 2
The frequency of metabolic syndrome and its components in the three groups at the intervention periods.

components	Groups	At baseline (n = 120)	At 12 weeks (n = 90)	At 24 weeks (n = 85)	p-value[a]	p-value[c]
Central Obesity[e]	Probiotic N (%)	23 (62.2%)	16 (55.2%)	16 (61.5%)	0.13	0.42
	Synbiotic N (%)	25 (61%)	18 (56.2%)	16 (53.3%)	0.89	
	Placebo N (%)	30 (66.6%)	22 (75.8%)	20 (71.4%)	0.22	
	p-value[b]	0.84	0.18	0.36		
Hyperglycemia[f]	Probiotic N (%)	31 (83.8%)	20 (68.9%)	15 (57.7%)	0.01*	0.47
	Synbiotic N (%)	32 (78%)	18 (56.25%)	17 (56.6%)	0.005*	
	Placebo N (%)	38 (84.4%)	22 (75.8%)	17 (60.7%)	0.14	
	p-value[b]	0.70	0.25	0.95		
Hypertension[g]	Probiotic N (%)	15 (40.5%)	11 (37.9%)	5 (19.2%)	0.04*	0.18
	Synbiotic N (%)	13 (31.7%)	8 (25%)	8 (26.6%)	0.40	
	Placebo N (%)	22 (48.8%)	14 (48.3%)	10 (35.7%)	0.27	
	p-value[b]	0.27	0.17	0.39		
Hypertriglyceridemia[h]	Probiotic N (%)	17 (45.9%)	13 (44.8%)	9 (34.6%)	0.05	0.26
	Synbiotic N (%)	16 (40%)	13 (41.9%)	8 (27.6%)	0.18	
	Placebo N (%)	22 (50%)	14 (50%)	17 (62.9%)	0.37	
	p-value[b]	0.65	0.82	0.02*		
Low HDL −C[i]	Probiotic N (%)	17 (47.2%)	11 (39.3%)	12 (48%)	0.56	0.02*
	Synbiotic N (%)	30 (83.3%)	19 (59.4%)	22 (73.3%)	0.15	
	Placebo N (%)	30 (66.6%)	19 (65.5%)	21 (75%)	0.47	
	p-value[b]	0.05	0.11	0.07		
Metabolic Syndrome[d]	Probiotic N (%)	22 (59.4%)	15 (51.7%)	11 (42.3%)	0.23	0.02*
	Synbiotic N (%)	26 (63.4%)	13 (40.6%)	12 (40%)	0.09	
	Placebo N (%)	33 (73.3%)	21 (72.4%)	20 (71.4%)	0.91	
	p-value[b]	0.38	0.04*	0.032*		

*$p < 0.05$ that is defined as statistically significant.
[a] Obtained based on Chochran test (within group analysis).
[b] Obtained based on Chi-square test (between group analysis at each study time point).
[c] Resulted from GEE for comparing the changes over time between study groups.
[d] Defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria.
[e] Waist circumference≥102 cm for men and ≥88 cm for women.
[f] Fasting plasma glucose ≥100 mg/dl.
[g] Blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic, or drug treatment for hypertension.
[h] Fasting triacylglycerol ≥150 mg/dl.
[i] HDL-cholesterol <40 mg/dl for men and <50 mg/dl for women.

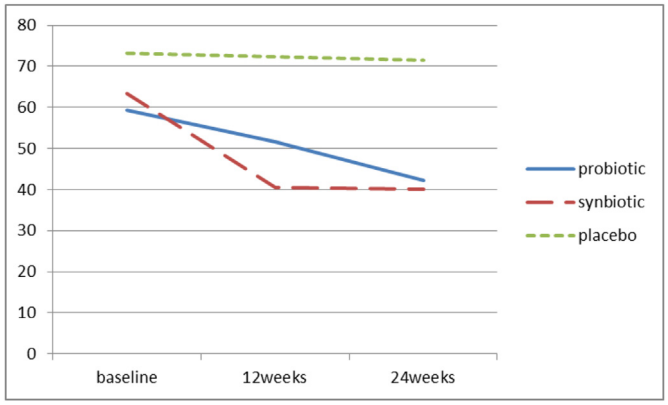

Fig. 2. The trend of metabolic syndrome in the three groups during the study period.

Our synbiotic was included the above-mentioned probiotics plus inulin as prebiotic. Prebiotics enhance the growth of beneficial bacteria such as *Bifidobacteria* or *Lactobacilli*. Moreover, they contribute to reducing body weight and adipocyte size by modulating appetite and by promoting the production of GLP-1, peptide YY and the decrease of ghrelin, and fatty acid storage [34]. However, data regarding effects of prebiotics on body weight, satiety, GLP-1, and peptide YY production seem to be controversial [35]. We found that the prevalence of other components of metabolic syndrome has been declined in intervention period by probiotic and synbiotic when measured on the basis of clinical targets using the biological thresholds outlined in NCEP ATP-III. Although the differences in the prevalence of these components were not statistically significant, they might be significant by using more sample size.

However, additional studies are needed to clarify whether probiotics or synbiotics can be used in prediabetes patients as a therapeutic or preventive agent for metabolic syndrome or not.

5. Strengths

This study has several strengths, including the dosage and length of intervention that was estimated as appropriated based on the existing literature of probiotic and synbiotic intervention trials within related research fields. The implications of our study are strengthened because of being a placebo-controlled, double-blind, randomized study. Furthermore, we reported data on the metabolic syndrome in prediabetes patients, which have a synergistic cardiovascular and diabetes risk.

6. Limitations

Although the sample size in this study provided sufficient power to distinguish statistically significant effects in the main outcome variables, some of the changes were near to be significant that if we used the more sample size it was possible to get better results.

7. Conclusion

The results of this study demonstrated the potential benefits of using probiotic and synbiotic to metabolic syndrome management in prediabetes patients. Since metabolic syndrome can lead to type 2 diabetes mellitus and other chronic diseases with significant public health impacts, the use of probiotic and synbiotic might

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provide an important tool in public health strategies to combat metabolic syndrome-associated diseases. Overall, the results of this trial add to the current knowledge base while suggesting potential benefits of functional foods that can be applied in the context of clinical practice.

However, more clinical studies are still needed to reach definitive conclusions on the potential applications of the human gut microbiome in the treatment of the patients with metabolic syndrome-associated diseases.

Author disclosure statement

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Author contributions

MA, AA, AF, and NK conceptualized the study and are the writing group. NK and MTE were main researchers. AF and NK developed the statistical design and analysis. All of the authors have seen and approved the final version of the manuscript.

Trial registration

Iranian Registry of Clinical Trials: IRCT201511032321N2, Date registered February 27, 2.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.07.016.

References

[1] Sayon-Orea C, Martínez-González MA, Ruiz-Canela M, Bes-Rastrollo M. Associations between yogurt consumption and weight gain and risk of obesity and metabolic syndrome: a systematic review–. Advances in Nutrition 2017;8(1). 146S-54S.
[2] Mazidi M, Rezaie P, Kengne AP, Mobarhan MG, Ferns GA. Gut microbiome and metabolic syndrome. Diabetes & Metabolic Syndrome: Clin Res Rev 2016;10(2):S150–7.
[3] Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. World J Gastroenterol: WJG. 2014;20(43):16079.
[4] Alberti K, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009;120(16):1640–5.
[5] He M, Shi B. Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. Cell Biosci 2017;7(1):54.
[6] Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2012;59(7):635–43.
[7] Garvey WT, Ryan DH, Henry R, Bohannon NJ, Toplak H, Schwiers M, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. Diabetes Care 2014;37(4):912–21.
[8] Barko P, McMichael M, Swanson K, Williams D. The gastrointestinal microbiome: a review. J Vet Intern Med 2018;32(1):9–25.
[9] O'Connor S, Chouinard-Castonguay S, Gagnon C, Rudkowska I. Prebiotics in the management of components of the metabolic syndrome. Maturitas 2017;104:11–8.
[10] Hur KY, Lee M-S. Gut microbiota and metabolic disorders. Diabetes & metabolism journal 2015;39(3):198–203.
[11] Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev 2004;17(2):259–75.
[12] Asemi Z, Khorrami-Rad A, Alizadeh S-A, Shakeri H, Esmaillzadeh A. Effects of synbiotic food consumption on metabolic status of diabetic patients: a double-blind randomized cross-over controlled clinical trial. Clin Nutr 2014;33(2):198–203.
[13] Sun J, Buys NJ. Glucose-and glycaemic factor-lowering effects of probiotics on diabetes: a meta-analysis of randomised placebo-controlled trials. Br J Nutr 2016;115(7):1167–77.
[14] Buysschaert M, Bergman M. Definition of prediabetes. Medical Clinics 2011;95(2):289–97.
[15] Kassaian N, Aminorroaya A, Feizi A, Jafari P, Amini M. The effects of probiotic and synbiotic supplementation on metabolic syndrome indices in adults at risk of type 2 diabetes: study protocol for a randomized controlled trial. Trials 2017;18(1):148.
[16] Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, et al. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. N Engl J Med 2011;365(24):2277–86.
[17] Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves JW, Hill MN, et al. Recommendations for blood pressure measurement in humans: an AHA scientific statement from the Council on high blood pressure research professional and public education subcommittee. J Clin Hypertens 2005;7(2):102–9.
[18] Floch MH, Walker WA, Madsen K, Sanders ME, Macfarlane GT, Flint HJ, et al. Recommendations for probiotic use—2011 update. J Clin Gastroenterol 2011;45:S168–71.
[19] Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. Microb Pathog 2012;53(2):100–8.
[20] Nóvoa FJ, Boronat M, Saavedra P, Díaz-Cremades JM, Varillas VF, La Roche F, et al. Differences in cardiovascular risk factors, insulin resistance, and insulin secretion in individuals with normal glucose tolerance and in subjects with impaired glucose regulation: the Telde Study. Diabetes Care 2005;28(10):2388–93.
[21] Ostovar R, Kiani F, Sayehmiri F, Yasemi M, Mohsenzadeh Y, Mohsenzadeh Y. Prevalence of metabolic syndrome in Iran: a meta-analysis. Electron Physician 2017;9(10):5402.
[22] Mohammadian-Hafshejani A, Sarrafzadegan N, Sadeghi M. Some facts about the metabolic syndrome in Iran. ARYA Atheroscler 2017;13(2):95–6.
[23] Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult US population, 1999–2010. J Am Coll Cardiol 2013;62(8):697–703.
[24] Ilanne-Parikka P, Eriksson JG, Lindström J, Hämäläinen H, Keinänen-Kiukaanniemi S, Laakso M, et al. Prevalence of the metabolic syndrome and its components: findings from a Finnish general population sample and the Diabetes Prevention Study cohort. Diabetes Care 2004;27(9):2135–40.
[25] Yadav H, Jain S, Sinha P. Antidiabetic effect of probiotic dahi containing Lactobacillus acidophilus and Lactobacillus casei in high fructose fed rats. Nutrition 2007;23(1):62–8.
[26] Kumar R, Grover S, Batish VK. Hypocholesterolaemic effect of dietary inclusion of two putative probiotic bile salt hydrolase-producing Lactobacillus plantarum strains in Sprague–Dawley rats. Br J Nutr 2011;105(4):561–73.
[27] Mohania D, Kansal VK, Shah D, Nagpal R, Kumar M, Gautam SK, et al. Therapeutic effect of probiotic dahi on plasma, aortic, and hepatic lipid profile of hypercholesterolemic rats. J Cardiovasc Pharmacol Therapeut 2013;18(5):490–7.
[28] Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition 2012;28(5):539–43.
[29] Jung S-P, Lee K-M, Kang J-H, Yun S-I, Park H-O, Moon Y, et al. Effect of Lactobacillus gasseri BNR17 on overweight and obese adults: a randomized, double-blind clinical trial. Kor J Fam Med 2013;34(2):80–9.
[30] Delzenne NM, Kok N. Effects of fructans-type prebiotics on lipid metabolism–. Am J Clin Nutr 2001;73(2). 456s-8s.
[31] Sayin SI, Wahlström A, Felin J, Jäntti S, Marschall H-U, Bamberg K, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. Cell Metabol 2013;17(2):225–35.
[32] Amar J, Chabo C, Waget A, Klopp P, Vachoux C, Bermúdez-Humarán LG, et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. EMBO Mol Med 2011;3(9):559–72.
[33] Yadav H, Lee J-H, Lloyd J, Walter P, Rane SG. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. J Biol Chem 2013;288(35):25088–97.
[34] Parnell JA, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter Bacteroidetes and Firmicutes in lean and obese JCR: LA-cp rats. Br J Nutr 2012;107(4):601–13.
[35] Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. Br J Nutr 2014;111(7):1147–61.