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The effects of symbiotic therapy on anthropometric measures, body composition and blood pressure in patient with metabolic syndrome: a triple blind RCT

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Abstract

Background: Increase in prevalence of obesity and type 2 diabetes which are of the main risk factors of metabolic syndrome, is not only the result of changes in genetic, diet or physical activity, but also an imbalance of micro flora may play an important role. Therefore, alteration of micro flora using pre/probiotic is considered as a new strategy for treatment of metabolic disorders.

Methods: The current study is a triple blind randomized controlled trial. 46 patients from both sexes, who fulfilled inclusion criteria, randomly categorized into intervention or placebo group. The intervention and placebo groups consumed 2 probiotic capsules or 2 placebo capsules during 3 months, respectively. Both groups received a weight loss diet, according to their adjusted ideal body weight. Anthropometric, body composition, blood pressure and nutritional measurements were done in the beginning, at 6th week, and at the end of the study. T-test and paired-t test were used for statistical analysis.

Results: 40 patients completed the study. BMI, WC, HC, fat mass, lean mass and blood pressure were reduced in all participants ($p< 0.05$). Systolic blood pressure in symbiotic group was less than placebo group, significantly ($p< 0.05$). The trend of weight loss in symbiotic group continued at least for 12 weeks while it was stopped at week 6 in placebo group.

Conclusion: Symbiotic supplement with the weight loss diet had synergistic effects on improvement in systolic blood pressure and anthropometric measurements. Based on our findings, symbiotic can postpone plateau phase of weight loss and it may prevent resistance to further weight loss.

Keywords: Metabolic syndrome, Gut micro flora, Symbiotic, Body composition.

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Introduction

Metabolic syndrome is a complex of disorders caused by multiple interrelated factors that increase the risk of type 2 diabetes and cardiovascular diseases. Obesity is the main risk factor for metabolic syndrome (1). The prevalence of obesity and obesity-related disorders is increasing worldwide(2). In the last decade, it has been shown that the gut microbiota may play an important role in the development of obesity, obesity-associated inflammation, insulin resistance and metabolic syndrome, through its interactions with host genetic, dietary and environmental factors (2, 3). Gut-derived endotoxin can cause the inflammation leading to metabolic syndrome (MetS) and oxidative stress (3,4). There are some evidences that have been shown changes in the gut microbiota correlated with energy intake (5).

Recent studies established the role of dietary strategies like application of probiotics and prebiotics as biotherapeutics in weight

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management (1,6). In the other words, obesity can be targeted in developing various therapies. Some possible mechanisms for those strategies are improvement in microbial balance, decrease in food intake through their effect on appetite, decrease in abdominal adiposity, increase in mucosal integrity through increased glucagon like peptide-2 (GLP-2) and decrease in inflammatory tone.

Moreover, because of the role of body composition and central adiposity on insulin resistance, some authors have investigated the effect of pre/probiotic therapy on insulin resistance and inflammatory biomarkers through their effects on body composition (7-9).

There are some animal studies that introduced pre/probiotic therapy as a new strategy to treat obesity (4, 10-12), but data in humans are currently scarce. Moreover, there is not any consistency on the information about the effects of microbiota modification on metabolic disorders.

On the other hand, some investigators have been shown that the use of probiotic alone, cannot be so effective, because the probiotic bacteria arrive to the colon before they can be active, metabolically (13).

Some authors have been shown that combination of probiotic and prebiotic lead to better improvement than each of them, alone (13,14); however, there is not enough knowledge about symbiotic therapy, particularly in patients with metabolic syndrome. So, we investigated the effects of a symbiotic supplement on anthropometric measurements, body composition and blood pressure in patients with metabolic syndrome.

Methods

Study population

The study protocol was approved by the Ethics Committee of the Iranian National Institute of Nutrition and Food Technology under number 51530 and it was registered in Iranian Registry of Clinical Trials with IRCT2013111115368N1. It was a triple blind randomized clinical trial. A total of 46 volunteers from both sexes aged 25-70, with BMI≥ 25 kg/m2, who had at least three determinant of metabolic syndrome, were recruited from health centers located in district 2 of Tehran. The patients fulfilled inclusion criteria including: FBS≥ 100mg/dl, waist circumference≥ 90cm and 80cm for male and female, respectively, blood pressure≥ 130/85mmHg, not smoking, not pregnant or lactating, without a diagnosis of thyroid disorders or kidney disease, not taking multivitamin-mineral supplements, omega-3, oral contraceptive peel, estrogen, progesterone, corticosteroids or insulin, not consuming green tea or fiber powder, not being a vegetarian, not taking any kind of antibiotic drugs within the past 1 month before the study. Exclusion criteria were: taking antibiotic during study, consuming energy less than 800 or more than 4200 Kcal/daily according to 3 d dietary recalls, consuming less than 2/3 of symbiotic/placebo capsules, missing any inclusion criteria during the study. The entire participants consumed their current medication during the study. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee at Shahid Beheshti University of Medical Sciences (SBMU). Written informed consent was obtained from all subjects.

Data collection

Anthropometric measurements, blood pressure and information on food intake (through 3 d dietary recalls) were collected at three intervals: at the beginning of the trial, at the end of week 6 and at the end of week 12. At the end of each interval, body weights were measured (floor scale; Seca, Hamburg, Germany) with 0.1 kg accuracy without shoes and with minimum clothing. Weight was measured in the fasting state. The subjects' heights were measured, with 0.1 cm accuracy, with non-stretchable tape (Seca). BMI was determined by dividing body weight by height squared (kg/m^2). Waist and hip circumference were meas-

ured by a non-stretchable meter with 0.5cm accuracy.

For measuring the body composition, we used bioelectric impedance analysis (BIA) method by Body Scan- Quad Stat 4, made in England. The patients were told to be fasted and don't smoke from 12-14 hours before the test, but they should drink a glass of water 10-15 minutes before the test.

At each interval, 3 d dietary recalls were taken from each volunteer. The amount of food consumed was converted to grams using household measures. Through weekly follow-ups by phone, and through periodical visits of the patients in diet therapy clinic of SBMU at each interval, a nutritionist checked the subjects' compliance with the study protocol and assessed dietary recalls in person.

Nutritionist IV was used in performing nutrient calculations for the 3 d dietary recalls. The database of this software is built upon the Nutrient Database Bank for Standard Reference from the US Department of Agriculture and other sources. The database was modified with reference to the existing national Iranian food composition table, developed by the Iranian National Institute of Nutrition and Food Technology.

Subjects were assigned into two groups (symbiotic or placebo) through stratified random sampling method according to BMI (25-29.9kg/m^2, 30-34.9kg/m^2, 35kg/m^2 or more). Each group consisted of 23 individuals. Both groups received a diet based on their adjusted ideal body weight. Symbiotic and placebo capsules were white, 250 mg made by Protexin Company (England). Each symbiotic capsule was consisted of *Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus bulgaricus*, FOS (Fructooligosaccharide - Prebiotic), Magnesium stearate (source: mineral and vegetable), Vegetable capsule (hydroxypropyl methyl cellulose) TVC: 200 million CFU TVC: 2×10^8 CFU. The placebo was made of maltodextrine. Both symbiotic and placebo were packed in identical capsules and coded by the producer to guarantee blinding. The participants were asked to take 2 capsules, daily (1 capsule after breakfast and 1 capsule after dinner). The patients were asked to avoid consuming any other probiotic and fermented products. The study was a triple blind one. That is, in addition to patients and authors, the evaluator of the results was also not aware of the assigned treatments. Taking capsules was monitored once per week through phone interviews.

We used physical activity questionnaire to assess physical activity of patient at first and the end of study. Reproducibility and validity of this questionnaire was confirmed in a study of Kelishadi, et al. in Iran(15). The volunteers were told not to alter their exercise routine for the duration of the study (12 weeks).

Statistical analysis

The statistical tests were conducted using SPSS 11.5. The Kolmogorof–Smirnov test was used to test the normality of the distribution of variables. Student t-test and paired t-test and analysis of variance for repeated measurement were used to comparison between and within each group.

Multiple comparisons were conducted by the Bonferroni post hoc test. $p< 0{\cdot}05$ was considered as statistically significant.

Results

From a total of 46 participants, 40 (87%) cases completed the study. So, there were 20 cases in each group. Based on Kolmogorof–Smirnov test, the distribution of anthropometrics, body composition, physical activity and food intake were normal and the parametric tests ($p< 0.05$) including t-test, paired t-test and analysis of variance for repeated measurement were used for their analysis. For systolic and diastolic blood pressure, Mann-Whitney U and Friedman tests were used because of their abnormal distribution.

The Chi-square test showed that there were 6 (%26.09) male and 17 (%73.91)

Table 1. Anthropometric, body composition and blood pressure before, during and at the end of the study

Variables	In the beginning		At week 6		At week 12	
	Symbiotic	Placebo	Symbiotic	Placebo	Symbiotic	Placebo
Weight (Kg)*	81.3±13.50	84±11.60	79.3±13.70 [a]	82.4±11.27 [a]	77.7±13.73 [a,b]	82.2±11.43 [a]
BMI (Kg/m^2)*	32±4.08	32.7±5.39	31.2±4.22 [a]	32.1±5.26 [a]	30.6±4.26 [a,b]	32±5.23 [a]
WC (cm)*	106.5±9.73	106.9±7.41	102.9±9.83 [a]	104.8±7.90 [a]	99.2±10.11 [a,b]	104.2±8.21 [a]
HC (cm)*	112.6±11.04	115.4±11.30	110.9±11.13 [a]	114.1±11.12 [a]	108.8±10.82 [a,b]	113.4±11.13 [a]
Fat mass (%)	48.4±6.77	49.6±9.35	-	-	45.4±7.71 [a]	47.3±9.61 [a]
Lean mass (%)	51.5±6.77	50.3±9.35	-	-	54.5±7.71 [a]	52.6±9.61 [a]
Systolic Blood Pressure (mmHg) ‡	14±1	14.2±1	12.7±1 [c]	14±2	12±1 [a,b,c]	13.7±2 [a]
Diastolic Blood Pressure (mmHg) ‡	9±1	9.7±1	8±1	8±2	8±1 [a]	8±2 [a]

*Mean ± SD, ‡ Median ± Interquartile ranges
[a] significant difference from the beginning of the study within each group (p<0.001).
[b] significant difference between week6 and week12 within each group (p<0.001).
[c] significant difference between two groups (p<0.001).

Table 2. Current medications and probiotic products consumption before, during and at the end of the study

Variables	In the beginning N (%)		At week 6 N (%)		At week 12 N (%)	
	Symbiotic	Placebo	Symbiotic	Placebo	Symbiotic	Placebo
Glucose reducer drugs(Yes)	16(80)*	19(95)	16(80)	19(95)	16(80)	19(95)
Lipid reducer drugs(Yes)	13(65)	14(70)	13(65)	14(70)	13(65)	14(70)
Blood pressure reducer drugs(Yes)	18(90)	15(75)	18(90)	15(75)	18(90)	15(75)
Prebiotic products (Yes)	3(15)	2(10)	3(15)	2(10)	3(15)	2(10)

female in symbiotic group and 7 (%30.4) male and 16 (%69.6) female in placebo group. There was no significant difference between the two groups for sex. The mean±SD age for the symbiotic and placebo groups were 57.1±7.2 years and 60.8±7.7 years, respectively that did not show any significant difference between the two groups (p= 0.06).

Table 1 shows the mean±SD of anthropometric measurements, body composition and the median and interquartile range of blood pressure of the volunteers. These variables had a similar distribution between the two groups at the beginning of the study. Body composition was measured in the beginning and at the end of the study, while the other measurements were also assessed in the middle of the study (week 6). Analysis for repeated measurement showed that weight, BMI, WC and HC were reduced significantly within each group at week 6 and 12. Moreover, there were significant reduction in these parameters between week 6 and week 12, only in symbiotic group (p< 0.05). At the end of the study, the percent of lean mass, fat mass, systolic and diastolic blood pressures were reduced in both groups, significantly (p< 0.05). Moreover, according to t-test, systolic blood pressure in the symbiotic group was significantly lower than the placebo group at week 6 and at week 12 (p< 0.05). Furthermore, there was a significant reduction in systolic blood pressure between week 6 and week 12, only in the symbiotic group (p< 0.05).

Table 2 shows the status of taking medications and probiotic products consumption. There was not any significant difference between the two groups in the beginning of the study. Their distribution remained unchanged until the end of the study.

Table 3. Food intake and physical activity measurements before, during and at the end of the study (Mean ± SD)

Variables	In the beginning		At week 6		At week 12	
	Symbiotic	Placebo	Symbiotic	Placebo	Symbiotic	Placebo
Total calorie intake (Kcal)	2458.1±525.90	2390.9±399.25	2227±343.73 [a]	2238±431.97 [a]	2127.7±262.49 [a]	2052.7±282.16 [a]
Carbohydrate (% energy)	58.2±8.19	57.5±7.74	58.8±7.46	58±7.60	56.3±6.27	58.1±9.44
Protein(% energy)	16.1±3.43	15.5±3.25	16.2±3.63	14.5±2.74	16.3±3.24	14.4±3.21
Fat(% energy)	25.5±7.93	26.8±6.16	24.9±5.86	27.3±6.80	27.2±6.42	27.4±9.33
SAFA(mg)	16.9±6.01	16.7±7.42	17±5.33	17.6±6.07	16.9±5.38	15.4±6.40
PUFA(mg)	15.9±8.69	14.5±6.02	11.8±7.12 [a]	15±11.35	14.2±6.86	14.8±8.40
MUFA(mg)	19.9±7.20	19.9±6.18	17.4±6.32	18.6±7.78	18.9±6.21	18.7±5.40
Cholesterol(mg)	169.3±119.88	220.9±146.32	166.1±136.60	184.4±130.15	158±106.24	195.9±123.89
Dietary fiber(g)	13.7±7.24	13.8±6.69	12.1±6.58	11±5.15	12.4±8.12	11.3±5.12
Physical activity (MET/day)	35.9±4.07	37±2.98	-	-	35.6±4.19	36.8±3.16

[a] significant difference from the beginning of the study within each group (p<0.05).

Table 3 shows mean±SD for food intake and physical activity. All of the measurements were assessed 3 times except for physical activity that was measured in the beginning and at the end of the study. Independent t-test did not show any difference between the two groups at the beginning of the study for intakes of total calorie, macronutrients, SFA, PUFA, MUFA, cholesterol, dietary fiber (based on the 3 d dietary recalls) and physical activity level ($p<0.05$). Using analysis of variance for repeated measurement, total calorie intake was reduced significantly after 12 weeks in both groups. The percent of PUFA from total calorie was reduced after 6 weeks in symbiotic group, significantly. The other variables did not show any significant difference from the beginning of the study until the end of it.

Discussion

Our study showed that consumption of symbiotic supplement for 12 weeks, compared with the placebo, reduces systolic blood pressure. In earlier studies, the beneficial effects of probiotics on blood pressure have been attributed to its releasing effect of bioactive peptides, such as the angiotensin converting enzyme-inhibitory peptides (16, 17). This mechanism has been confirmed with the consumption of both Bifidobacterium longum and L. acidophilus (16). Although in our study both systolic and diastolic blood pressure were reduced significantly within each group after 12 weeks, the significant difference between two group were seen only in systolic blood pressure. It was agreed with the findings of Sharafedtinov, et al that showed probiotic can reduce blood pressure in obese people with high blood pressure (18); however, the effect of pre/probiotic on blood pressure is controversial. Some authors have not shown any beneficial effect on blood pressure (19-21). This inconsistency may be as a result of different clinical properties of participants. To our knowledge, there is no study available on adult patients with metabolic syndrome. Furthermore, it may be due to different interventions, i.e. use of prebiotic, probiotic or symbiotic component in different dosage, and different duration in various studies.

We also found a reduction in percent of fat mass and an enhancement in percent of lean mass after 12 weeks. But we did not find any difference between the two groups of study. It should be noted that all of our participants followed a weight loss diet according to their adjusted ideal body weight. So, we found a significant reduction in anthropometric measurements in both groups. Calorie intake of patients in both groups decreased significantly at the end of study, according to the 3 d dietary recalls. It shows that our participants followed their weight loss diet, appropriately. One of the interesting points of our study was that the trend of weight loss in placebo group was stopped after 6 weeks but patients in symbiotic group continued to lose body until the end of week 12, significantly. This finding shows that the symbiotic supplement accompanied with a weight loss diet, may delay weight loss plateau phase. Sanchez et al showed a similar finding, only among healthy obese women (9).

Weight loss until resistance to further weight loss may be detrimental for some physiological reasons such as adaptive reduction in thermogenesis or for some psychobiological variables like depression; this emphasizes the relevance of caution and reasonable objectives when prescribing a weight reduction program for obese individuals (22, 23). According to our results, symbiotic supplement may have an important role in prevention of resistance to lose further weight.

Weight loss diets in obese subjects can significantly alter the species composition of the gut microbiota (24). On the other hand, Dietary pre/probiotic consumption was found to be associated with subjective improvements in satiety (25). The patients who consumed symbiotic lost weight for a longer period of time, compared with patients consumed placebo; it may be explain

by the effect of symbiotic on appetite. Appetite suppression, lipid metabolism regulation and increase of energy expenditure are the main mechanisms by which anti-obesity effects of pre/probiotic components are exerted (26).

Zarrati, et al. suggested that the weight-loss diet plus a probiotic yogurt had more synergistic effects on fat percentage and body weight among overweight and obese individuals compared with the weight-loss diet without the probiotic yogurt (8); however, it was conducted on healthy people. Moreover, they used a probiotic food while we used a symbiotic supplement.

By the way, some authors have shown that consumption of pre/probiotic causes no significant difference in anthropometric measurements (9, 19, 27). Therefore, it needs more investigations. The connection between gut microbiota and energy homeostasis, and its role in the pathogenesis of obesity-related disorders, like metabolic syndrome, are increasingly recognized (20). Evidences show that the relationship between diet, inflammation and insulin resistance are, in part, mediated by the composition of intestinal bacteria (28).

Some experimental models have shown that gut microbiota manipulation is in favor of treatment of different metabolic disorders (6). Some human and animal studies also suggest that the count of specific bacteria is inversely related to fat mass, diabetes, and the low levels of inflammation associated with obesity (29). Lee, et al. suggested that the change in body composition had a positive correlation with endotoxin level and the population of gut Lactobacillus plantarum (30). Some studies indicated that the gut microbiota differs in lean and obese individuals, and in individuals with different food habits (28). So, it seems that improving or normalizing the dysbiosis of the gut microbiota may benefit obesity and associated co-morbidities (5). Dietary strategies like pro/prebiotic consumption, seem to be appropriate without any adverse health effects (1). Metagenomic studies have shown that the human gut microbiota helps the fermentation of indigestible carbohydrates to short-chain fatty acids. It provides excess energy to the body and lead to the obese phenotype. So, alteration in the ratio of Bacteroidetes and Firmicutes (induced by pro/prebiotic or symbiotic) lead to changes in fermentation patterns and it may be helpful in the treatment of obesity pandemic (31). Although we did not investigate patients' microbiota in our study, Lee SJ, et al. suggested that there are a correlation between endotoxin level and weight reduction; it indicates that pre/ probiotics may prevent production of endotoxin, and may improve gut microbiota dysbiosis associated with obesity (30). Moreover, there are several mechanisms connecting gut microflora to host energy metabolism including increased energy harvesting from the diet, regulation of tissue-free fatty acid composition and uptake, storage and oxidation, regulation of appetite through gut peptide, secretion, and modulation of intestinal barrier by glucagon-like peptide-2 secretion, activation of innate immunity and hepatic fibrogenesis through the lipopolysaccharide (LPS)-toll-like receptor-4 axis ; however, data in humans are currently scarce.

The strong points of our study were as below. Firstly, triple blind design of the study was a positive point in our design. Secondly, the use of a multispecies symbiotic supplement in our study increased the probability of bacterial survival until entering to the colon. Thirdly, measurement of body composition using BIA method, in addition to anthropometric measurements was another positive aspect of this study. A limitation of our study was that we did not investigate microflora. So, further studies should be conducted with due regard to this limitation on more participants.

Conclusion

The impact of the weight loss diet accompanied with the symbiotic supplement on anthropometric measures and blood pressure, may offer a novel means for the

prevention and management of risk factors of metabolic syndrome. Moreover, this strategy may delay weight loss plateau phase and prevent resistance to further weight loss.

Conflict of interest

Authors have nothing to disclose. We declare that there are no conflicts of interest.

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