Iran Red Crescent Med J. 2018 November; 20(11):e67270. doi: 10.5812/ircmj.67270.

Published online 2018 November 3. **Research Article**

Effect of Prebiotic on Anthropometric Indices in Women with Polycystic Ovarian Syndrome: A Triple-Blind, Randomized, Controlled Clinical Trial

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Received 2018 February 08; **Revised** 2018 May 19; **Accepted** 2018 September 30.

Abstract

Background: Polycystic Ovary Syndrome (PCOS) increases the risk of cardiovascular diseases and diabetes, and obesity can accelerate this trend.
Objectives: This study aimed at determining the effect of prebiotics on anthropometric indices in patients with this syndrome.
Methods: This controlled clinical trial was conducted with 62 women from 18- to 45-year-old in the city of Tabriz, Iran, during years 2016 to 2017. Participants were assigned to prebiotic and control groups, using the random blocks method. The intervention group had a daily intake of 20 g of resistant Dextrin, dissolved in a glass of water for three months, and the placebo group had a daily intake of 20 g of Maltodextrin, dissolved in a glass of water for three months. Participants' Body Mass Index (BMI), weight, waist circumference, and hip circumference were measured before, and three and six months after the intervention.
Results: There was no significant difference between the groups in terms of baseline values ($P > 0.05$). Three months after the intervention, mean (SD) waist circumference, hip circumference, weight, and BMI was 78.11 (9.7), 100.85 (7.7), 65.31 (10.9), and 24.41 (4.2) in the prebiotic group and 86.54 (12.3), 108.72 (10.7), 73.25 (14.7), and 27.73 (5.7) in the control group, respectively. Six months after the intervention, mean (SD) anthropometric indices was 78.11 (7.9), 101.45 (7.2), 65.70 (10.3), and 24.54 (3.9) in the prebiotic group and 86.4 (12.6), 108.54 (10.8), 73.8 (14.7), and 27.65 (5.5) in the control group, respectively. According to the Analysis of Variance (ANOVA) test, and with controlled baseline values, all anthropometric indices were significantly lower in the prebiotic group compared to the control group at three ($P < 0.001$) and six months ($P < 0.001$).
Conclusions: This study confirmed the positive and significant effects of prebiotics in reducing anthropometric indices, three and six months after the intervention in women with PCOS.

Keywords: Body Mass Index, Cardiovascular Disease, Diabetes, Obesity, Prebiotics, Polycystic Ovary Syndrome, Waist Circumference

1. Background

Polycystic Ovary Syndrome (PCOS) is a common problem in the general population and affects 2% to 20% of the female population (1). This syndrome leads to the incidence of acne, hirsutism, and infertility (2), and over time, causes metabolic disorders associated with obesity (3), which cause chronic diseases, such as diabetes type II and cardiovascular diseases (3, 4).

Pathophysiology of this disease is unknown, yet genetics is more commonly considered (5), although environmental factors that lead to insulin resistance and obesity in these women are also assumed to be (6) involved, since obesity inhibits the release of ovule, due the production of male hormones and facilitation of the development of this syndrome.

Previous studies have shown that obesity is increasing among women with PCOS (7), and by producing inflammatory cytokines, this fat is associated with insulin resistance and reduced ovulation (8). Insulin resistance, in turn, leads to hyperinsulinemia, simulation of ovarian androgen production, and inhibition of follicle production (9). Obesity exacerbates insulin resistance and hyperandrogenism and increases symptoms of this syndrome (10). Therefore,

weight loss, through exercise and nutrition, can increase the body's response to ovulation, stimulating medications and leading to natural pregnancy in these women (11).

A few studies have shown that consumption of dairy products reduces insulin resistance due to lactobacilli and other beneficial intestinal bacteria (12). Prebiotics have been known as carbohydrates that are indigestible or have little digestibility against human digestive enzymes and stimulate growth or increase the activity of beneficial intestinal bacteria, such as lactobacilli and bifidobacteria (13, 14). Metabolic effects of intestinal microbes include regulation of hormone production from cholesterol, peptides, and amino acids, and also prevention of inflammation (15). These hormones have a key role in regulating the metabolism of the body and include stimulating alpha-melanocyte, neuropeptide Y, ghrelin (the internal factor stimulating secretion of growth hormone that has a role in regulating metabolism and energy), insulin, and leptin (energy storing an indicator of the body that has a role in regulating metabolism and appetite), and so on (16).

Prebiotics appear to be suitable for patients with PCOS, due to benefits in improving blood lipids, insulin resistance, and regulating body weight (14). One of this prebiotics is Nutirose, which has been marketed as FBNutriose (derived from wheat starch) and FMNutriose (derived from corn starch). In addition, both of these are also found as 6Nutriose and 10Nutriose (17).

2. Objectives

Given that previous studies have shown the beneficial effects of prebiotics on gastrointestinal diseases, infections, diabetes, immune system, and intestinal microbes, with subsequent beneficial effects on metabolic parameters associated with obesity, inflammations, glucose tolerance disorder, diabetes, abnormal level of lipids in blood plasma (14, 18), and considering the prevalence of this syndrome among women (1), the present study was conducted to determine the effect of prebiotics on anthropometric indicators in women with PCOS. This study was the first research conducted to determine the effect of prebiotics on anthropometric indices in women with PCOS.

3. Methods

3.1. Study Design and Participants

The present randomized, triple-blind clinical trial (participant, data collector and data analyzer had no knowledge of the type of intervention received by groups) was conducted on 62, 18- to 45-year-old women, attending clinics affiliated to Tabriz University of Medical Sciences, during years 2016 to 2017.

The inclusion criteria were confirmation of PCOS diagnosis by a research colleague (AA; endocrinologist), age range of 18 to 45 years old, reading and writing abilities to complete the questionnaires, BMI between 25 and 40, lack of probiotics, prebiotics, vitamins and minerals, and omega-3 consumption during the study, and three months before the intervention. Exclusion criteria included having other androgenic disorders, such as adrenal hyperplasia or androgen-secreting adrenal tumors, based on a research colleague examination, having thyroid gland diseases and Cushing's syndrome, based on a research colleague examination, taking hormonal contraceptives or use of hormone therapy, pregnancy or lactation, prior surgery to remove one or both of the ovaries, smoking and alcohol, strenuous physical activity (refers to activities where the person is not able to talk while being performed, due to increased breathing rate and respiration), and use of dietary supplements.

3.2. Sample Size

Based on a study conducted by Amini et al. (19), and given M1 = 26.25, and assuming 25% reduction in BMI due to intervention (M2 = 20) and SD1 = SD2 = 6.90, with α = 0.05 and power = 90%, the sample size was determined as 27 women per group, which was increased to 31 women per group, taking into account possible withdrawals.

3.3. Sampling

Sampling began after obtaining the necessary permissions from the Ethics Committee (IR.TBZMED.REC.1395.286) of Tabriz University of Medical Sciences and registration in IRCT (code: IRCT2016062810324N33). Sampling was conducted at women's hospitals' clinics (Alzahra and Taleghani), endocrine clinic of Imam Reza Hospital, Sina Hospital clinic, and health centers in the city of Tabriz. All four mentioned hospitals are educational and governmental hospitals. Al-Zahra Hospital is a specialized referral center that provides services in the fields of obstetrics and gynecology, oncology, neonatal, and perinatology. Taleghani hospital is a general hospital, which provides various services, including general surgery, NICU, neonatal, delivery, obstetrics, and gynecology. Imam Reza and Sina Hospitals are general hospitals and have various specialty and super specialty wards. Health centers were public, governmental, or private first-level referral centers.

The researcher selected women attending these centers, according to eligibility and purposive sampling method. Women, who consented to participate were assessed in terms of Rotterdam criteria (two out of three criteria for diagnosis of PCOS, which includes menstruation cycle disorders (amenorrhea and oligomenorrhea), clinical or biochemical hyperandrogenism, or sonographic signs of PCOS), and patients that satisfied these criteria were referred to the project collaborator (an endocrinologist) for final confirmation for inclusion. With a final

diagnosis of PCOS, the study objectives and method were fully explained for participants and informed written consent was obtained from them. Then, a demographic questionnaire was completed by the participants; their waist circumference, hip circumference, and height were measured using a tape measure; their weight using Seca scales, and the results were recorded. After completion of a three-month therapy, the researcher phoned the participants and asked them to attend the infertility department and clinic of Alzahra Hospital, and their weight, waist circumference, hip circumference was measured and recorded in the relevant checklist. Three months after completion of the intervention (six months after the start of intervention), the researcher phoned the patients again and asked them to attend the infertility department and clinic of Alzahra Hospital, and measured and recorded their weight, waist circumference, and hip circumference once again.

3.4. Random Allocation and Intervention

Participants were assigned to intervention and control groups, using the random block method with blocks of four and six and sequence of 1:1. To conceal allocation, prebiotic or placebo were packed the same and placed in similar envelops. Each participant was given three large envelops, with the same number, each containing 30 sachets of 20 g of prebiotic (polysaccharide from corn, wheat, and other edible starches with fibrous properties) (NUTRIOSE 06 FM; Roquette) or placebo (Maltodextrin, which is an easily digestible carbohydrate compound with no fibrous property) (Jiujiang Huirong Trade Company Limited). The second envelope was given after the end of the first month for use in the second month, and the third envelope was given after the end of the second month for use in the third month. The treatment period lasted for three months. Prebiotic and placebo were used by dissolving in a glass of water. Participants were taught how to use their medication and were given the researcher's phone number to contact and ask questions and receive instructions. For greater assurance, a checklist was given to the subjects to record the first day of intake, and continue ticking prebiotics intake until the end of the treatment period to avoid forgetting their daily intake. Over the three months of the intervention, prebiotic intake was followed-up by weekly telephone contact (once every seven days to ensure intake of prebiotic over the week). In case of any problems, participants were able to contact the researcher.

3.5. Data Collection

In the present study, a questionnaire was used for personal-social details, and a checklist for recording weight, waist circumference, and hip circumference. The personal-social questionnaire contained questions on the social level, obstetrics, and infertility (including name, surname, age, marital status, occupation, monthly income, the woman and husband's education, housing status, number of pregnancies, parity, number of miscarriages, live children, history of infertility, and its duration, as shown in Table 1). To control the potential confounding factor of diet, dietary intakes were evaluated using a three-day food diary (two weekdays and one weekend) at baseline. Dietary intakes were analyzed with the Nutritionist 4 software (First Databank, Inc., Hearst Corporation), using the database from tables of content and nutritional value of Iranian food products. A checklist was also used to record the side effects.

Weight (in kg) was measured with a reliable weighing scale (Seca, Germany) while participants were wearing light clothing and no shoes. A measuring tape measured Height, waist, and hip circumference (in cm). All measures were conducted by one person (the first author of this article). The measured values were recorded in a checklist by the researcher.

For the validity of the personal-social questionnaire and checklist, content and face validities were used so that they were given to faculty members, and their reforming views were implemented based on the feedback received.

3.6. Data Analysis

The obtained data were analyzed with the SPSS Statistics Software. Homogeneity of groups, in terms of demographic details, was assessed using the Chi-Square, round Chi-Square, Independent T, and Fisher's Exact tests. Normal distribution of quantitative data was assessed using the K-S test and all variables had a normal distribution. Body mass index was found using weight (kg) over a square of height (m). To compare the two groups in terms of BMI, weight, waist circumference, and hip circumference three and six months after the intervention, Analysis of Covariance (ANCOVA) test was used, after adjusting for baseline values. P values of < 0.05 were considered significant at all stages and calculations were performed according to ITT.

4. Results

Overall, 150 females aged 18 to 45 years old were observed at Tabriz hospitals and clinics from October, 2016 to May, 2017, of whom 38 were excluded from the study due to the use of infertility therapies, 20 patients due to the lack of eligibility criteria, and 30 patients due to reluctance to participate, and finally, 62 patients participated in the study. Participants were randomly assigned to intervention (31 women) and control (31 women) groups. From the intervention group, one woman used her medication for only one month due to food allergy, yet attended Alzahra Hospital three months and six months after the intervention for controlling her weight and anthropometric indices. From the placebo group, one woman refrained from

taking the medication due to sensitivity, yet attended three months and six months after the intervention for controlling her weight and anthropometric indices (Figure 1).

There was no significant difference between the two groups in terms of socio-demographic/obstetrics characteristics (P > 0.05). The socio-demographic, obstetrics, and diet status of participants are shown in Table 1.

In the prebiotic group, mean (SD) waist circumference was 81.72 (10.2) before the intervention and 78.11 (9.7) three months after the intervention. In the control group, mean (SD) waist circumference was 84.90 (11.90) before the intervention and 86.54 (12.3) three months after the intervention. No significant differences were found between the two groups before the intervention (P = 0.256), yet according to the ANCOVA test, the two groups were significantly different in terms of waist circumference after the intervention (adjusted mean difference = -5.35; Confidence Interval 95% = -6.80 to -3.90; P < 0.001). Six months after the intervention, mean (SD) waist circumference was 78.11 (7.9) in the prebiotic group and 86.4 (12.6) in the control, which was significantly lower in the intervention group compared to the control group (-5.25; -6.76 to -3.74; P < 0.001).

In the prebiotic group, mean (SD) hip circumference was 103.37 (7.8) before the intervention and 100.85 (7.7) three months after the intervention. In the control group, mean (SD) hip circumference was 105.88 (9.9) before the intervention and 108.72 (10.7) three months after intervention. No significant differences were found between the two groups before the intervention (P = 0.274), yet hip circumference was significantly reduced in the intervention group compared to the control after the intervention (-5.45; -7.24 to -3.66; P < 0.001). Six months after the intervention, mean (SD) hip circumference was 101.45 (7.2) in the prebiotic group and 108.54 (10.8) in the control, which was significantly lower in the intervention group compared to the control group (-4.76; -6.78 to -2.76; P < 0.001).

In the prebiotic group, mean (SD) weight was 67.62 (11.0) before the intervention and 65.31 (10.9) three months after the intervention. In the control group, mean (SD) weight was 72.2 (14.5) before the intervention and 73.25 (14.7) three months after the intervention. No significant differences were found between the two groups before the intervention (P = 0.168), yet weight was significantly reduced in the intervention group compared to control after the intervention (-3.37; -4.41 to -2.34; P < 0.001). Six months after the intervention, mean (SD) weight was 65.70 (10.3) in the prebiotic group and 73.8 (14.7) in the control, which was significantly lower in the intervention group compared to the control group (-2.92; -4.07 to -1.77; P < 0.001).

In the prebiotic group, mean (SD) BMI was 25.59 (4.4) before the intervention and 24.41 (4.2) three months after the intervention. In the control group, mean (SD) BMI was 27.30 (5.6) before the intervention and 27.73 (5.7) three months after the intervention. No significant differences were found between the two groups before the intervention (P = 0.188), yet BMI was significantly reduced in the intervention group compared to the control after the intervention (-1.29; -1.68 to -0.89; P < 0.001). Six months after the intervention, mean (SD) BMI was 24.54 (3.9) in the prebiotic group and 27.65 (5.5) in the control, which was significantly lower in the intervention group compared to the control group (-1.18; -1.60 to -0.75; P < 0.001) (Table 2 and Figure 2).

5. Discussion

The present study was conducted to determine the effect of prebiotic on anthropometric indices (waist circumference, hip circumference, weight, and BMI) in women with PCOS during years 2016 and 2017, and the prebiotic showed positive effects in reducing anthropometric indices, including waist circumference, hip circumference, weight, and BMI.

In the study conducted by Yang et al. (20), 28 g of green tea and 18 g of inulin, three times a day, for eight weeks, significantly decreased waist circumference, hip circumference, weight, and BMI. In the study conducted by Sanchez et al. (21), inulin and oligosaccharide significantly decreased weight in the first 12 weeks in the female group. In the study conducted by Liber and Szajewska (12), 8 g of oligo-fructose for 12 weeks was shown to have no significant difference in BMI. In the study conducted by Aliasgharzadeh et al. (22), 10 g of resistant dextrin for eight weeks significantly decreased weight and BMI. In the study conducted by Dehghan et al. (23), 10 g of oligo-fructose enriched inulin for eight weeks significantly decreased weight and BMI. In the study conducted by Khajebishak et al. (24) on the role of intestinal microbiota on health and a short review on the probiotic and prebiotic supplements in obesity prevention showed the positive effect of prebiotics on weight loss and a decrease of BMI. In the study conducted by Aliasgharzadeh et al. (25), 10 g of oligo-fructose enriched inulin for eight weeks significantly decreased weight and BMI.

The mechanism by which prebiotics cause weight loss and reduced anthropometric indices are unknown. However, some studies have shown that prebiotics rapidly and completely ferments on the colon, and by reaching the liver through the portal vein, cause modulation of cholesterol metabolism, and reduce hepatocytes' triglyceride storing capacity, leading to metabolism and consumption of triglycerides in the body. Previous studies have also shown that intestinal fermentation of prebiotics leads to modulation of secretion of gastrointestinal system hormones (glucagon 1 and 2-like peptide), and these hormones increase satiety and reduce accumulation of ghrelin (with the appetite-stimulating property), and therefore

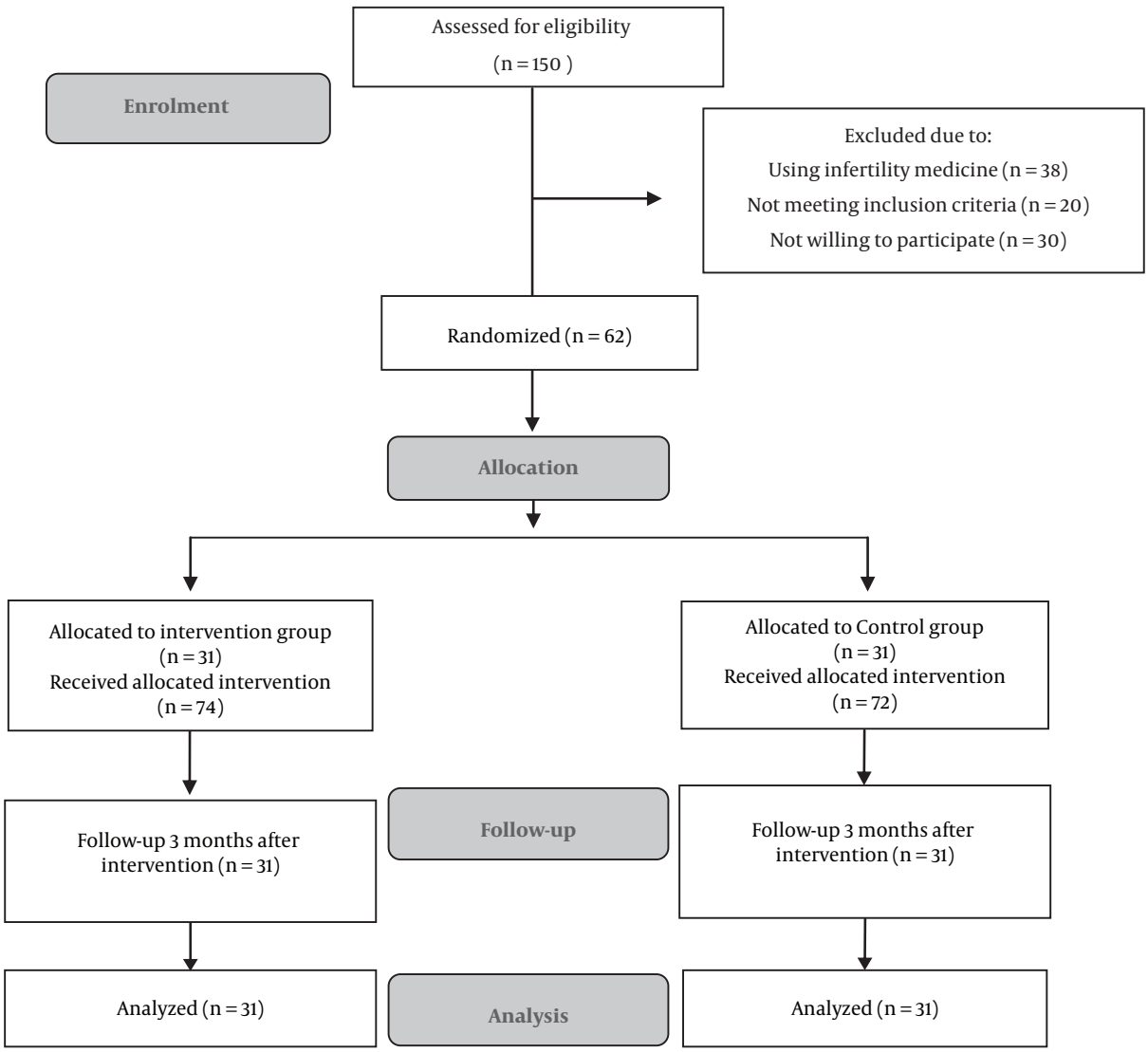

Figure 1. Study flow chart

can have a role in weight loss (25).

One of the strong points of the present study was three months and six months follow-up periods. Observing all principles of randomized controlled trial, including randomization, allocation concealment, and blinding in order to prevent selection and detection biases was another strong point of this study. The limitations of the present study include lack of a specific food regimen for patients with PCOS and controlling of dietary intakes only at the beginning of the intervention. It is recommended that studies should be conducted, in which food intake is controlled during the intervention and an appropriate regimen is concurrently provided with prebiotics. Since in the present study, resistant dextrin, as a prebiotic had a positive effect in reducing anthropometric indices in patients with PCOS while receiving prebiotics, and given the side-effects of weight loss medications on patients bodies, prebiotics are recommended as an alternative weight loss therapy for patients with PCOS.

5.1. Conclusion

The present study results showed the positive and significant effects of prebiotics in reducing anthropometric indices in females with PCOS. Given their negligible side-

Table 2. Comparison of Anthropometric Indices at Different Time Points by the Study Groups (N = 62)[a]

Variable	Intervention Group[b]	Control Group[b]	Comparison Between Groups	
			MD (95% CI)[c]	P Value
BMI				
Before intervention	25.6 ± 4.4	27.3 ± 5.6	-1.7 (-4.3 to 0.9)	0.188
3 months after intervention	24.4 ± 4.2	27.7 ± 5.7	-1.3 (-1.7 to -0.9)	< 0.001
6 months after intervention	24.5 ± 3.9	27.6 ± 5.5	-1.2 (-1.6 to -0.7)	< 0.001
Weight				
Before intervention	67.6 ± 11.0	72.2 ± 14.5	-4.58 (-11.1 to 2.0)	0.167
3 months after intervention	65.3 ± 10.9	73.2 ± 14.7	-3.37 (-4.4 to -2.3)	< 0.001
6 months after intervention	65.7 ± 10.3	73.1 ± 14.7	-2.92 (-4.1 to -1.8)	< 0.001
Buttocks circumference				
Before intervention	103.4 ± 7.8	105.9 ± 9.9	-2.51 (-7.1 to 2.0)	0.274
3 months after intervention	100.8 ± 7.7	108.7 ± 10.7	-5.45 (-7.24 to -3.7)	< 0.001
6 months after intervention	101.4 ± 7.2	108.5 ± 10.8	-4.76 (-6.78 to -2.8)	< 0.001
Waist circumference				
Before intervention	81.7 ± 10.2	84.9 ± 11.9	-3.2 (-8.8 to 2.5)	0.265
3 months after intervention	78.1 ± 9.7	86.5 ± 12.3	-5.3 (-6.8 to -3.9)	< 0.001
6 months after intervention	78.1 ± 9.2	86.4 ± 12.6	-5.2 (-6.8 to -3.78)	< 0.001

[a] For comparison groups before intervention, Independent *t* test was used and for comparison after intervention groups, ANCOVA was used by adjusting the baseline score.
[b] Values are expressed as mean ± SD.
[c] Adjusted mean difference (confidence interval of 95%).

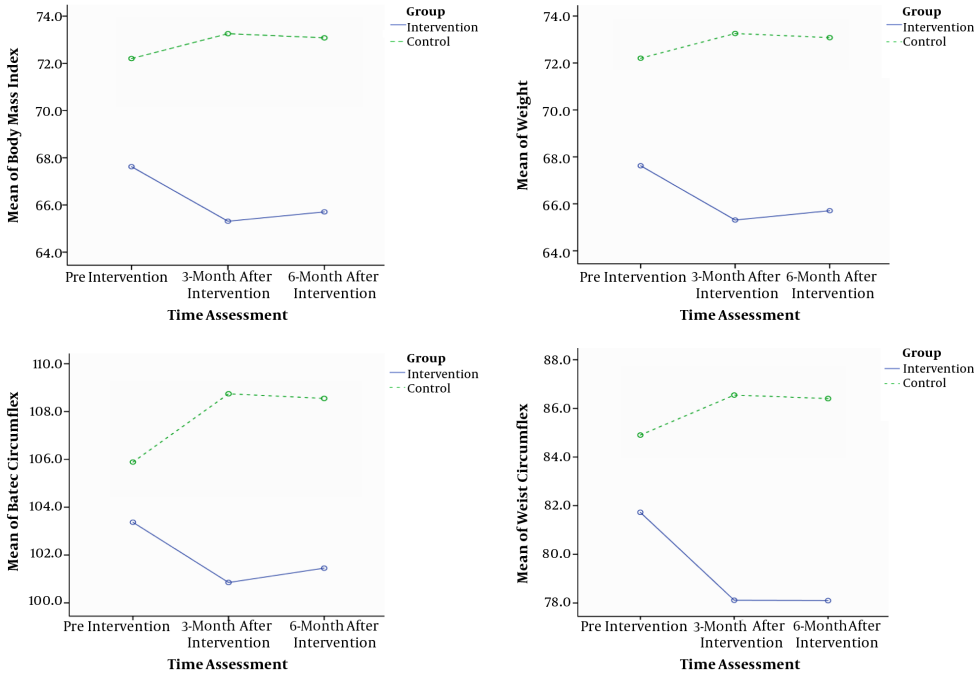

Figure 2. Trend in the mean of anthropometric indices (BMI, weight, waist circumference, and hip circumference) according to repeated measure ANOVA by study group

effects, prebiotics appears to be a suitable alternative to weight loss medications in these patients. However, for better and more definitive conclusion, further trials with larger sample sizes are recommended.

Acknowledgments

The researcher and her colleagues express their gratitude to the Research center of Tabriz University of Medical Sciences, all participants in our study and all staff of Alzahra, Taleghani and Sina Hospitals and their clinics.

Footnotes

Authors' Contribution: Sevda Gholizadeh made a substantial contribution to the conception of the study, the recruitment of women and the data collection, and drafted the manuscript. Mojgan Mirghafourvand was involved in the design of the study and performed the analysis. Parvin Dehghan, Sakineh Mohammad, and Akbar Aliasgarzadeh supervised the study and made a substantial contribution to the conception of the study. All authors revised the article, gave their comments, and approved the final version.

Ethical Considerations: This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1395.286).

Funding/Support: This study was funded by the Tabriz University of Medical Sciences.

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Table 1. Socio-Demographic and Obstetrics Characteristics and Diet Status of the Participants[a]

Characteristics	Prebiotic Group, N = 31	Placebo Group, N = 31	P Value
Age, y	28 ± 6.3	26 ± 6.2	0.111[b]
Marital status			0.610[d]
Single	15 (48.4)	13 (41.9)	
Married	16 (51.6)	18 (58.1)	
Job			0.005[d]
House keeper	9 (34.6)	19 (73.1)	
Work outside	17 (65.4)	7 (26.9)	
Income			0.685[c]
Enough	7 (25.9)	6 (22.2)	
Completely enough	15 (55.6)	15 (55.6)	
Inadequate	5 (18.5)	6 (22.2)	
Level of education			0.096[c]
Primary school	1 (3.2)	1 (3.2)	
Secondary school	0 (0.0)	4 (12.9)	
High school	1 (3.2)	3 (9.7)	
Diploma	8 (25.8)	6 (19.4)	
University	21 (67.7)	17 (54.8)	
Husband's education			0.183[c]
Primary school	0 (0.0)	2 (10.0)	
Secondary school	1 (6.3)	4 (20.0)	
High school	0 (0.0)	1 (5.0)	
Diploma	7 (43.8)	2 (10.0)	
University	8 (50.0)	11 (55.0)	
Home status			0.361[e]
Personal	26 (89.7)	19 (73.1)	
Rented home	1 (3.4)	2 (7.7)	
Parents home	2 (6.9)	5 (19.2)	
Number of pregnancy			0.334[e]
0	11 (55.0)	10 (50.0)	
1	8 (40.0)	7 (35.0)	
2	0 (0.0)	3 (15.0)	
4	1 (5.0)	0 (0.0)	
Number of parity			1.000[e]
0	11 (55.0)	12 (60.0)	
1	8 (40.0)	8 (40.0)	
3	1 (5.0)	0 (0.0)	
Number of children			1.000[e]
0	11 (55.0)	12 (60.0)	
1	8 (40.0)	8 (40.0)	
3	1 (5.0)	0 (0.0)	
Number of abortion			0.182[e]

0	19 (95.0)	15 (75.0)	
1	1 (5.0)	5 (25.0)	
Infertility			0.003[d]
Yes	1 (3.0)	10 (32.0)	
No	30 (96.0)	21 (67.0)	
Calorie, Kc	2780 (996.6)	3081 (900.4)	0.385[b]
Protein, Gm	123 (51.9)	118 (40.8)	0.660[b]
Carbohydrate, Gm	376 (148.0)	423 (135.6)	0.200[b]
Fiber, Gm	28 (8.9)	29 (17.4)	0.676[b]
Total fat, Gm	573 (371.4)	520 (338.2)	0.562[b]
Saturated fatty acid, Gm	33 (17.4)	35 (13.7)	0.722[b]
Unsaturated fatty acid, Gm	19 (16.4)	26 (36.4)	0.394[b]
Cholesterol, mg	519 (361.4)	459 (335.8)	0.501[b]

[a] Values are expressed as No. (%), unless age that expressed as mean ± SD.
[b] Independent *t* test.
[c] Liner by Liner Association.
[d] Fishers Exact test.
[e] Chi-Square test.