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The Effects of Synbiotic Supplementation on Metabolic Status in Women With Polycystic Ovary Syndrome: a Randomized Double-Blind Clinical Trial

Mansooreh Samimi[1] · Adeleh Dadkhah[1] · Hamed Haddad Kashani[2] · Maryam Tajabadi-Ebrahimi[3] · Elahe Seyed Hosseini[2] · Zatollah Asemi[4]

Abstract

Data on the effects of synbiotic supplementation on glycemic control, lipid profiles, and atherogenic index of plasma (AIP) of women with polycystic ovary syndrome (PCOS) are limited. The purpose of this study was to assess the effects of synbiotic supplementation on glycemic control and lipid profiles in women with PCOS. A prospective, randomized, double-blind, placebo-controlled trial was done at the Naghavi Hospital affiliated to Kashan University of Medical Sciences, Kashan, Iran, between April 2017 and June 2017. Sixty women with PCOS were randomized to intake synbiotic capsule containing *Lactobacillus acidophilus* strain T16 (IBRC-M10785), *Lactobacillus casei* strain T2 (IBRC-M10783), and *Bifidobacterium bifidum* strain T1 (IBRC-M10771) (2×10^9 CFU/g each) plus 800 mg inulin ($n = 30$) or placebo ($n = 30$) for 12 weeks. Fasting blood samples were taken at baseline and after the 12-week intervention to determine related variables. Compared with the placebo, synbiotic supplementation resulted in a significant reduction in serum insulin concentrations (-2.8 ± 4.1 vs. $+1.8 \pm 6.4$ μIU/mL, $P = 0.002$) and homeostasis model of assessment-insulin resistance (-0.7 ± 1.0 vs. $+0.4 \pm 1.5$, $P = 0.002$), and a significant elevation in the quantitative insulin sensitivity check index ($+0.01 \pm 0.01$ vs. -0.01 ± 0.03, $P < 0.001$). In addition, significant decreases in serum triglycerides (-16.2 ± 31.4 vs. $+5.8 \pm 23.1$ mg/dL, $P = 0.003$), VLDL-cholesterol concentrations (-3.3 ± 6.3 vs. $+1.1 \pm 4.6$ mg/dL, $P = 0.003$), and AIP (-0.05 ± 0.08 vs. -0.003 ± 0.10 mg/dL, $P = 0.03$) were seen following the supplementation of synbiotic compared with the placebo. Overall, we found that synbiotic supplementation to women with PCOS for 12 weeks had beneficial effects on markers of insulin resistance, triglycerides, VLDL-cholesterol concentrations, and AIP, but did not influence other lipid profiles. Trial registration: www.irct.ir: IRCT201604015623N71.

Keywords Synbiotic supplementation · Probiotic bacteria · Polycystic ovary syndrome · Glycemic control · Lipid profiles

Introduction

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine disorder among women in the reproductive age, which is commonly characterized by hyperinsulinemia, dyslipidemia, hyperandrogenism, and ovulatory dysfunction [1]. PCOS may cause increased risk of metabolic disorders, including type 2 diabetes mellitus (T2DM), gestational diabetes (GDM), cardiovascular diseases (CVD), endometrial cancer, and other pregnancy-related complications [2]. Many studies indicating gut microbiota could affect the nutrient composition and amino acid utilization by the host [3–5]. The gut bacteria perturbations may also altered metabolism of fatty acids in adipose tissue and liver, gut peptide YY modulation, and secretion of glucagon-like peptide-1 [3, 6]. Additionally, the bacteria produce various amino acids that could be used as precursors for the synthesis of fatty acids, which in turn may lead to obesity [6]. Obese women can intense functional hyperandrogenism and insulin resistance [7].

✉ Zatollah Asemi
asemi_r@yahoo.com

[1] Department of Gynecology and Obstetrics, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran

[2] Anatomical Sciences Research Center, Kashan University of Medical Sciences, Kashan, Iran

[3] Science Faculty, Islamic Azad University, Central Branch, Tehran, Iran

[4] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

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It has reported that gut bacterial flora in obese patients are significantly different from normal individuals [8]. Several studies have also reported that probiotic bacteria have a potential effect on treatment of metabolic disease [9, 10]. The beneficial effects of probiotics, such as modulation of adiposity and insulin resistance, have been deep-rooted in different gut problems [11]. Other researchers have demonstrated that the consumption of probiotics can cause catabolism of specific amino acids [10, 12]. Earlier, we reported the beneficial effects of probiotic in the treatment of metabolic profiles of women with PCOS [13]. Moreover, another study has indicated that probiotic intake could prevent the production of endotoxins and compositions that lead to synthesis of adipose tissue [8]. Others also showed the lipid-lowering effects of probiotics. For instance, *Lactobacillus fermentum* was significantly reduced LDL-cholesterol and triglyceride values in healthy individuals [14]. To our knowledge, there are insufficient data regarding the role of synbiotic on metabolic profiles of women with PCOS. Only few limited studies have evaluated the influence of probiotic on weight loss, insulin resistance, and lipid profiles in patients with PCOS [13, 15]. The aim of current study was to assess the effects of synbiotic supplementation on glycemic control and lipid profiles in women with PCOS.

Methods

Participants

The present randomized, double-blind, placebo-controlled clinical trial, registered in the Iranian registry of clinical trials (http://www.irct.ir: IRCT201604015623N71), was carried out among 60 patients with PCOS diagnosed according to the Rotterdam criteria [16] and aged 18–40 years who were referred to the Naghavi Hospital affiliated to Kashan University of Medical Sciences (KAUMS), Kashan, Iran, between April 2017 and June 2017. The research was approved by the research ethics committee of KAUMS. Smokers, intake of probiotics, and/or synbiotics supplements within the last 3 months, pregnant women, other common causes of hyperandrogenism, and/or anovulation, including Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, and thyroid dysfunction, were excluded in the study.

Study Design

Participants were randomized into two groups to receive either one synbiotic capsule containing *Lactobacillus acidophilus* strain T16 (IBRC-M10785), *Lactobacillus casei* strain T2 (IBRC-M10783), and *Bifidobacterium bifidum* strain T1 (IBRC-M10771) (2×10^9 CFU/g each) plus 800 mg inulin ($n = 30$) and placebo ($n = 30$) per day for 12 weeks. Subjects in the placebo group received the placebo that contained starch but no bacteria. Shape and size of synbiotics and placebo capsules were similar and manufactured by Tak Gen Zist Pharmaceutical Company, Tehran, Iran, and Barij Essence, Kashan, Iran, respectively. Randomization assignment was conducted using computer-generated random numbers. Randomization and allocation concealment were conducted by the researchers and participants and were carried out by a trained midwife member at the gynecology clinic. All participants were advised to maintain their routine dietary habits without any changes in their other lifestyle factors such as physical activity during the study. All women completed 3-day food records and three physical activity records as metabolic equivalents (METs) at weeks 0, 3, 6, 9, and 12 of the treatment.

Treatment Adherence

To assess the compliance, subjects were asked to bring the medication container. To increase the compliance, participants received a short message on their cell phones to intake the supplements daily.

Assessment of anthropometric measures

At baseline and after the 12-week intervention, all subjects underwent standard anthropometric measurements: height and weight (Seca, Hamburg, Germany). BMI was calculated as weight in kg divided by height in meters squared [17].

Assessment of Outcomes

The primary outcomes were markers of glycemic control. The secondary outcomes were markers of cardio-metabolic risk, including lipid profiles and atherogenic index of plasma (AIP) [18].

Biochemical Assessment

Ten-milliliter fasting blood samples were taken at weeks 0 and 12 of the intervention. To determine fasting plasma glucose (FPG), serum triglycerides, VLDL-, total-, LDL-, and HDL-cholesterol concentrations, we used enzymatic kits (Pars Azmun, Tehran, Iran) [19]. All inter- and intra-assay coefficient variances (CVs) for FPG, lipid concentrations were lower than 5%. Circulating levels of serum insulin were quantified using an ELISA Kit (Monobind, CA, USA) with the intra- and inter-assay CVs 3.0 and 4.6%, respectively [20]. The homeostatic model of assessment for insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were determined according to suggested formulas [21]. AIP was calculated based on suggested formulas [18].

Statistical Methods and Sample Size

The Kolmogorov-Smirnov test was applied to control the normal distribution of variables. Independent-sample *t* test was used to determine changes in anthropometric measures and dietary intakes between the two groups. To determine the effects of synbiotic supplementation on glycemic control and markers of cardio-metabolic risk, we used one-way repeated-measure ANOVA. To assess if the magnitude of the change depended on the baseline values of biochemical parameters, maternal age, and baseline BMI, we adjusted all analyses for these variables to avoid the potential bias using analysis of covariance (ANCOVA). $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, IL, USA).

To calculate sample size, we applied the standard formula suggested for clinical trials by considering type one error (α) of 0.05 and type two error (β) of 0.20 (power = 80%). Based on a prior study [22], we used 1.86 as SD and 1.5 as the difference in mean (*d*) of HOMA-IR as key variable. Based on this, we needed 25 participants in each group. Assuming 5 dropouts in each group, the final sample size was determined to be 30 participants per group.

Results

As demonstrated in the study flow diagram (Fig. 1), during the intervention phase of the study, two subjects were excluded from the each group [withdrawn due to personal reasons (n = 2)]. However, as the analysis was done based on ITT principle, all 60 subjects with PCOS were included in the final analysis.

Mean age, height, baseline weight, and BMI as well as their means after the 12-week intervention of the participants were not significant between synbiotic supplements and placebo groups (Table 1).

Considering the 3-day dietary records obtained during the intervention, there was no statistically significant difference in terms of dietary macro- and micro-nutrient intakes between synbiotic supplements and placebo groups (data not shown).

Compared with the placebo, synbiotic supplementation resulted in a significant reduction in serum insulin concentrations (-2.8 ± 4.1 vs. $+1.8 \pm 6.4$ μIU/mL, $P = 0.002$), HOMA-IR (-0.7 ± 1.0 vs. $+0.4 \pm 1.5$, $P = 0.002$), and a significant elevation in QUICKI ($+0.01 \pm 0.01$ vs. -0.01 ± 0.03, $P < 0.001$) (Table 2). In addition, significant decreases in serum triglycerides (-16.2 ± 31.4 vs. $+5.8 \pm 23.1$ mg/dL, $P = 0.003$), VLDL-cholesterol concentrations (-3.3 ± 6.3 vs. $+1.1 \pm 4.6$ mg/dL, $P = 0.003$), and AIP (-0.05 ± 0.08 vs. -0.003 ± 0.10 mg/dL, $P = 0.03$) were seen following the supplementation of synbiotic compared with the placebo.

When we controlled the analyses for baseline levels of biochemical variables, age and baseline BMI, FPG became significant ($P = 0.04$), AIP became non-significant ($P = 0.06$) and other findings did not change (Table 3).

Discussion

We found that synbiotic supplementation to women with PCOS for 12 weeks had beneficial effects on markers of insulin resistance, triglycerides, VLDL-cholesterol concentrations, and AIP, but did not influence other lipid profiles. To our knowledge, this study is the first report of synbiotic supplementation on glycemic control, lipid concentrations, and AIP among women with PCOS. It must be kept in mind that in the current study, observed changes in markers of insulin metabolism in the synbiotic group compared with the placebo were within the permitted standard ratios. Hyperinsulinemia and insulin resistance in women with PCOS can result in the progression to T2DM and CVD later in life [2]. Therefore, synbiotic supplementation due to its decreasing effects on markers of insulin resistance may be useful to decrease complications related to metabolic disorders. However, observed changes at triglycerides and VLDL-cholesterol levels in our study were statistically significant, but did not affect other lipid profiles. Long-term interventions and higher dosage of probiotic and inulin might result in greater changes in lipid profiles.

PCOS is associated with carbohydrate intolerance, insulin resistance, and increased lipid concentrations [23]. The current study supported that synbiotic supplementation for 12 weeks to women with PCOS resulted in a significant reduction in serum insulin levels, HOMA-IR, and a significant elevation in QUICKI compared with the placebo, but did not affect FPG. We have previously indicated that taking probiotic supplements had favorable effects on markers of insulin resistance in patients with PCOS [13] and diabetic hemodialysis patients [24]. In our previous study in women with PCOS, the rate of decreased insulin, HOMA-IR, and triglycerides was 16, 18, and 12%, respectively, whereas in the current study, the rate of decreased insulin, HOMA-IR, and triglycerides was 27, 30, and 12%, respectively. Furthermore, in that study, probiotic supplementation could not affect AIP, whereas in the current study, synbiotic intake significantly decreased AIP. Shoaei et al. [15] also indicated that probiotics could significantly reduce fasting glucose and insulin levels in women with polycystic ovary syndrome. Furthermore, Firouzi et al. [25] observed that taking multi-strain probiotics for 12 weeks by patients with T2DM modestly improved HbA1c and fasting insulin levels, but did not affect lipid concentrations. Improvements in markers of insulin metabolism in the current study were in accordance with several studies reported previously [26, 27]. In addition, a systematic review

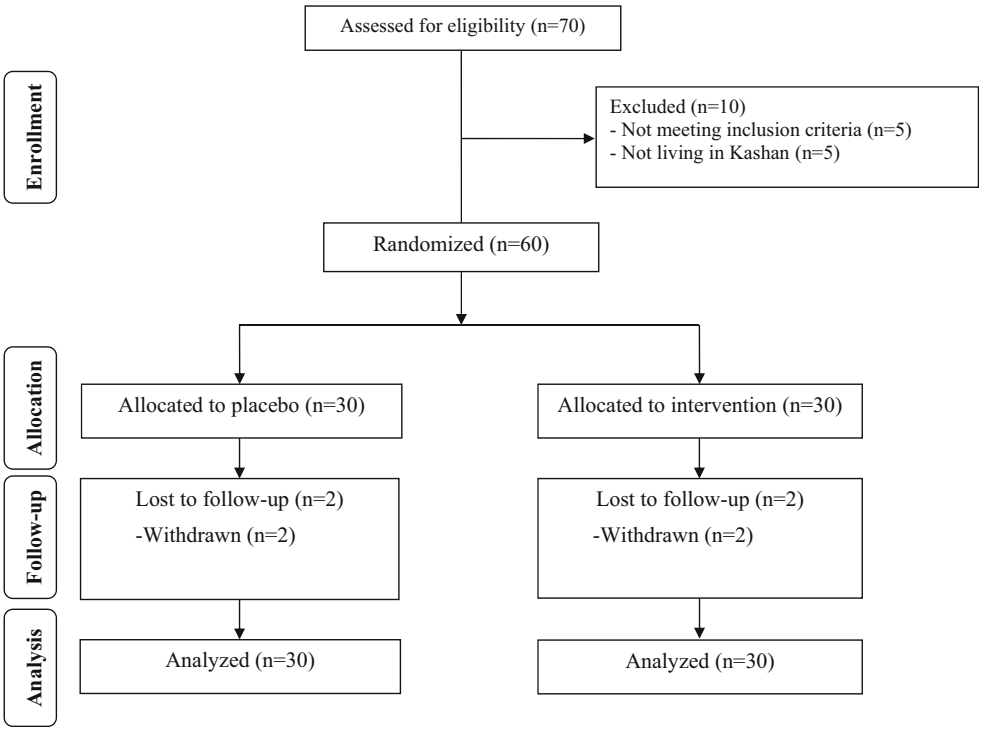

Fig. 1 Summary of patient flow

documented that some prebiotics and synbiotics have immunomodulatory function and directly controlled hyperglycemia and HOMA-IR [28]. Another study also reported probiotic supplementation for 16 weeks to pregnant women could prevent GDM [29]. Our previous study have showed a significant decrease in insulin concentrations and HOMA-IR and a significant increase in QUICKI without no change in FPG following the 12-week supplementation of probiotics in patients with multiple sclerosis [30]. However, a 8-week supplementation with probiotics in women with PCOS has showed no significant change in insulin resistance markers [15]. Obesity, hyperinsulinemia and T2DM are important metabolic characteristics of PCOS and common factors influencing liver function and generating nonalcoholic fatty liver disease [31]. In addition, subjects with PCOS have an 11-fold increased risk of metabolic syndrome compared with control subjects, even in the same age range [32]. Probiotics and synbiotics may increase glucagon-like peptide 1 secretion from enteroendocrine L-cells to improve insulin metabolism and decrease glucotoxicity [33]. In addition, synbiotics may improve insulin metabolism through the modification of gut flora, the reduction of endotoxin levels, elevation of fecal pH [34], and the reducing production of pro-inflammatory cytokine [35].

This study exhibited that taking synbiotic supplements by women with PCOS for 12 weeks was associated with a significant reduction in serum triglycerides, VLDL-cholesterol concentrations, and AIP compared with the placebo, but did not influence other lipid profiles. In line with our findings, Letexier et al. [36] reported that a 3-week supplementation with 20 g inulin in healthy subjects had beneficial effect on the treatment of hypertriglyceridemia. A meta-analysis study

Table 1 General characteristics of study participants

	Placebo group ($n = 30$)	Synbiotic group ($n = 30$)	P^a
Age (year)	27.3 ± 6.1	27.0 ± 5.6	0.87
Height (cm)	164.5 ± 6.8	163.8 ± 5.9	0.67
Weight at study baseline (kg)	74.4 ± 14.0	73.3 ± 11.5	0.75
Weight at end of trial (kg)	74.3 ± 14.2	73.2 ± 11.5	0.75
Weight change (kg)	− 0.1 ± 0.9	− 0.1 ± 1.3	0.95
BMI at study baseline (kg/m^2)	27.5 ± 5.3	27.3 ± 3.8	0.85
BMI at end of trial (kg/m^2)	27.4 ± 4.3	27.2 ± 3.8	0.85
BMI change (kg/m^2)	− 0.1 ± 0.3	− 0.1 ± 0.5	0.94

Data are means ± SDs

[a] Obtained from independent *t* test

Table 2 Glycemic control and lipid profiles at baseline and after the 12-week intervention in subjects with polycystic ovary syndrome

	Placebo group ($n = 30$)			Synbiotic group ($n = 30$)			
	Baseline	End of trial	Change	Baseline	End of trial	Change	P^a
FPG (mg/dL)	94.0 ± 5.7	92.8 ± 8.1	− 1.2 ± 6.6	92.2 ± 6.2	88.0 ± 7.2	− 4.1 ± 9.1	0.16
Insulin (μIU/mL)	12.1 ± 6.3	13.9 ± 5.2	1.8 ± 6.4	12.9 ± 4.2	10.1 ± 3.9	− 2.8 ± 4.1	0.002
HOMA-IR	2.8 ± 1.4	3.2 ± 1.2	0.4 ± 1.5	3.0 ± 1.1	2.3 ± 0.9	− 0.7 ± 1.0	0.002
QUICKI	0.33 ± 0.03	0.32 ± 0.01	− 0.01 ± 0.03	0.32 ± 0.01	0.34 ± 0.02	0.01 ± 0.01	< 0.001
Triglycerides (mg/dL)	138.2 ± 37.9	144.0 ± 47.2	5.8 ± 23.1	146.4 ± 56.3	130.3 ± 39.3	− 16.2 ± 31.4	0.003
VLDL-cholesterol (mg/dL)	27.6 ± 7.6	28.8 ± 9.4	1.1 ± 4.6	29.3 ± 11.2	26.0 ± 7.9	− 3.3 ± 6.3	0.003
Total cholesterol (mg/dL)	168.3 ± 27.7	173.8 ± 28.5	5.5 ± 27.2	164.5 ± 23.7	163.2 ± 29.0	− 1.3 ± 27.3	0.33
LDL-cholesterol (mg/dL)	91.9 ± 27.9	93.8 ± 31.0	1.9 ± 31.7	90.8 ± 19.8	90.7 ± 31.1	− 0.1 ± 27.0	0.78
HDL-cholesterol (mg/dL)	48.8 ± 8.3	51.3 ± 16.1	2.5 ± 13.1	44.4 ± 8.8	46.4 ± 8.5	2.0 ± 4.2	0.84
AIP	0.44 ± 0.16	0.43 ± 0.22	− 0.003 ± 0.10	0.49 ± 0.20	0.43 ± 0.16	− 0.05 ± 0.08	0.03

All values are means ± SDs

AIP atherogenic index of plasma, *FPG* fasting plasma glucose, *HOMA-IR* homeostasis model of assessment–insulin resistance, *HDL-cholesterol* high-density lipoprotein-cholesterol, *LDL-cholesterol* low-density lipoprotein-cholesterol, *QUICKI* quantitative insulin sensitivity check index, *VLDL-cholesterol* very low density lipoprotein-cholesterol

[a] *P* values represent the time × group interaction (computed by analysis of the one-way repeated-measure ANOVA)

has showed that synbiotic supplementation to diabetic patients significantly decreased triglycerides and total cholesterol levels [37]. Mikelsaar et al. [14] also observed that a 8-week administration of dairy Kefir containing *L. fermentum* ME-3 significantly reduced triglyceride concentrations in healthy individuals. The consumption of *L. fermentum* ME-3 kefir after a standard breakfast for 2 weeks in healthy subjects resulted in a significantly reduced postprandial triglyceride response [38]. In addition, an 8-week treatment of T2DM patients with synbiotic bread containing *Lactobacillus sporogenes* and inulin for 8 weeks has showed a significant reduction of triglycerides and VLDL-cholesterol levels [39]. However, Schaafsma et al. [40] demonstrated that synbiotic supplementation for 3 weeks in male volunteers significantly reduced total-, LDL-, and LDL-/HDL-cholesterol, whereas it did not affect triglyceride levels. In the current study, the absent of beneficial effects of synbiotic supplementation on other lipid profiles might be explained by different study designs, characteristics of study people, different dosages of probiotic bacteria and inulin used, types and quality of probiotic bacteria and inulin used, and duration of the intervention. Life-long lipid metabolic dysfunction in subjects with PCOS

Table 3 Adjusted changes in metabolic variables in PCOS patients

	Placebo group ($n = 30$)	Synbiotic group ($n = 30$)	P^a
FPG (mg/dL)	− 0.7 ± 1.3	− 4.6 ± 1.3	0.04
Insulin (μIU/mL)	1.6 ± 0.8	− 2.5 ± 0.8	0.001
HOMA-IR	0.3 ± 0.2	− 0.6 ± 0.2	< 0.001
QUICKI	− 0.009 ± 0.004	0.009 ± 0.004	0.001
Triglycerides (mg/dL)	4.6 ± 4.6	− 15.0 ± 4.6	0.004
VLDL-cholesterol (mg/dL)	0.9 ± 0.9	− 3.0 ± 0.9	0.004
Total cholesterol (mg/dL)	6.2 ± 4.4	− 2.0 ± 4.4	0.19
LDL-cholesterol (mg/dL)	1.9 ± 5.0	− 0.2 ± 5.0	0.76
HDL-cholesterol (mg/dL)	2.5 ± 1.8	2.0 ± 1.8	0.85
AIP	− 0.006 ± 0.01	− 0.05 ± 0.01	0.06

All values are means ± SEs

AIP atherogenic index of plasma, *FPG* fasting plasma glucose, *HOMA-IR* homeostasis model of assessment–insulin resistance, *HDL-cholesterol* high-density lipoprotein-cholesterol, *LDL-cholesterol* low-density lipoprotein-cholesterol, *QUICKI* quantitative insulin sensitivity check index, *VLDL-cholesterol* very low density lipoprotein-cholesterol

[a] Obtained from repeated-measure ANOVA adjusted for baseline values of biochemical variables, age, and baseline BMI

exaggerates the risk for CVD with aging [41]. Furthermore, surrogate outcomes, such as carotid intima changes are increased in PCOS due to dyslipidemia [42]. Synbiotics may improve triglycerides, VLDL-cholesterol values, and AIP by lipolysis of triglycerides and transform triglyceride-rich particles into small [43], suppressing nuclear factor-kappaB [44], and the effects on gut microbiota-short-chain fatty acid (SCFA)-hormone axis [45].

Limitations

Our study due to the limited funding supports facing some limitations; we could not assess the effect of synbiotics on the SCFA of patient fecal, and also, our follow-up was in the limited time. Longer follow-up probiotic administration may affect other lipid profiles.

Conclusion

Overall, we found that synbiotic supplementation to women with PCOS for 12 weeks had beneficial effects on serum insulin, HOMA-IR, QUICKI, triglycerides, VLDL-cholesterol concentrations, and AIP, but did not affect FPG, total-, LDL-, and HDL-cholesterol levels.

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Compliance with Ethical Standards

Ethical Responsibilities of Authors This paper is our original unpublished work and it has not been submitted to any other journal for reviews.

Availability of Data and Materials The primary data for this study is available from the authors on direct request.

Ethics Approval and Consent to Participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Consent for Publication Not applicable.

Competing Interests The authors declare that they have no competing interests.

Abbreviations AIP, Atherogenic index of plasma; PCOS, Polycystic ovary syndrome; VLDL, Very-low-density lipoprotein; CFU, Colony forming units; T2DM, Type 2 diabetes mellitus; CVD, Cardiovascular diseases; GDM, Gestational diabetes mellitus; FPG, Fasting plasma glucose; METs, Metabolic equivalents; CVs, Coefficient variances; HOMA-IR, Homeostatic model of assessment for insulin resistance; QUICKI, Quantitative insulin sensitivity check index; SCFA, Short-chain fatty acids; NF-κB, Nuclear factor-kappaB

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