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The probiotic supplementation reduced inflammation in polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders that plaques women today. One of the underlying factors associated with the development of PCOS is elevated inflammation. However, the application of available nutraceutical therapies remains relatively unknown and thus is the focus of the current study. In this manner, we evaluated the effects of probiotic supplement on clinical and immunological parameters of PCOS. Our randomized-control trial, four strains of *Lactobacillus* for a probiotic group and the equivalent dosage with maltodextrin was used as the placebo. To further understand the impacts of immunological parameters towards inflammation in PCOS, we measured interleukin (IL) 6, 10, TNF-α, hs-CRP and clinical manifestations before and after the trial. The probiotic supplementation resulted in a significant increase in IL-10 levels compared with the placebo, after the intervention. However, in both groups, there was a significant decrease in hs-CRP and IL-6 levels. Probiotic supplementation does not make any significant changes in the TNF-α levels. This study observed that *Lactobacillus* supplementation modulates inflammation in PCOS patients.

1. Introduction

Polycystic ovary syndrome is a heterogeneous endocrinopathy disorder in 5–10% of women in their reproductive ages (Deligeoroglou, Kouskouti, & Christopoulos, 2009). The observed clinical and metabolic component of this disease are obesity, menstrual abnormalities, hirsutism, hyperandrogenism, increasing LH (luteinizing hormone) to FSH (follicle-stimulating hormone) ratio, and hyperinsulinemia (Norman et al., 1995). The exact etiology of the polycystic ovary syndrome (PCOS) has not been studied well; however, it appears that the inflammatory pattern, which can be detected by the C-reactive protein (CRP) level and is one of the underlying causes that enhances the progress of this disorder (Giallauria et al., 2008). More specifically, the elevation of CRP levels serves as an indicator for low-grade chronic inflammation and is also positively correlated with the insulin resistance (Toulis et al., 2011). The PCOS patients display 96% higher levels of CRP levels than seen in healthy subjects (Deligeoroglou et al., 2012; Toulis et al., 2011). Moreover, the central obesity that occurs as a result of hyperandrogenemia is regarded to be a vital link between the low-grade inflammation and hyperandrogenemia in this syndrome (Deligeoroglou et al., 2009). Without taking the obesity into consideration, about 50–70% of the PCOS patients have insulin resistance. This percentage increases to 95% for the PCOS patients suffering from obesity (Setji & Brown, 2014).

The exact pathophysiology of this syndrome remains unknown, however hyperandrogenism has been reported to be a central mediator for the development of this syndrome (Setji & Brown, 2014). A novel "microgendermo" hypothesis has suggested a bidirectional correlation

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between sex steroid hormone and gut microbiota components (Flak, Neves, & Blumberg, 2013). Dysbiosis of gut microbiota by a high-fat-sugar diet induces an increase in testosterone levels in PCOS women (Tremellen & Pearce, 2012). Tremellen and Pearce have been shown the rolls of the lipopolysaccharide of gram-negative bacteria to make low-grade-inflammation through "leaky gut" syndrome (Tremellen & Pearce, 2012). In this regard, Guo and colleges raise questions upon the effects of gut microbiota modulation for the treatment of PCOS (Guo et al., 2016). In their study, *Lactobacillus* and fecal microbiota from healthy rats were transplanted into letrozole-induced PCOS rat model which have increased estradiol and estrone levels (Guo et al., 2016). The *Lactobacillus* administration raises the gut barrier, resulting in short-chain fatty acid metabolites that display unique effects to reduce insulin resistance, inflammation, and modulate androgen level (Hulston, Churnside, & Venables, 2015).

It is hypothesized that insulin influences the androgen synthesis in ovarian theca cells, which is considered as the pathogenic cause of the hyperandrogenemia in PCOS (Moghetti et al., 2000). However the full benefits of metformin, an anti-diabetic agent, on PCOS woman with hyperandrogenism disturbance and anovulation problems are unclear (Morin-Papunen et al., 2003). Current treatments for PCOS is the utilization of oral contraceptive pills such as Cyproterone acetate (2 mg), especially for whom have acne, hirsutism, and hyperandrogenism (Morin-Papunen et al., 2003). Further studies have reported that IL-6 is a crucial factor in regulating CRP, insulin resistance, and obesity in PCOS (González, Rote, Minium, & Kirwan, 2009; Kaya et al., 2010). Inflammatory markers such as hs-CRP, TNF-α have been observed to be elevated in the follicular phase of PCOS when compared to control (Puder et al., 2005). Furthermore, probiotics have been observed to display regulatory effects on IL-6, CRP, and insulin resistance in an inflammatory disease, including in PCOS subjects (Shoaei, Heidari-Beni, & Tehrani, 2015). However, the association of oral contraceptives with probiotics have not been studied and is the focus of the current study. We have observed that together oral contraceptives with probiotics significantly reduces inflammation associated with PCOS by reducing CRP and IL-6 as well as weight in PCOS patients.

2. Methods

2.1. Subjects and methods

Our double-blind placebo-controlled trial evaluated the efficacy of probiotics in decreasing the inflammation in PCOS based upon criteria from the Rotterdam trial (Franks, 2006). Inclusion criteria for the current study (Rotterdam criteria) requires the presence of more than two of the following symptoms: oligo/anovulation, hyperandrogenism (symptoms like hirsutism, acne, male pattern alopecia, increasing the free testosterone levels), polycystic ovaries based upon ultrasound evaluation (Franks, 2006). In the current study, we recruited 60 Iranian women between 18 and 45 years old that resided in Tehran and suffered from PCOS. A Stratified blocked randomization was used to assign participants to four blocks based on the subjects' BMI and age. The study exclusion criteria were thyroid dysfunction, hyperprolactinemia, diabetes, history of premature menopause, smoking, and Cushing's syndrome. Individuals who displayed symptoms from the flu or was diagnosed with cancer, autoimmune disease, or who made the significant changes in their routine diet and physical activity during the trial were excluded. Also, all subjects with a history of smoking, professional athletes, and those who were taking any medication other than Cyproterone acetate or any supplement or herbal medicine were also excluded from the study. Lastly participants who had any form of oral antibiotic therapy less than a month from the initiation of the trial were omitted. The subjects were given two capsules per day each capsule consisting of 1×10^9 colony forming units (CFU) of each *lactobacillus* strains (equal to 500 mg) made by Zist Takhmir company under the supervision of Tehran University of Medical Sciences. Two maltodextrin capsules from the same company with the identical texture, color, and size given to the placebo group per day. The trial was conducted for 12 weeks. The four strains of *Lactobacillus* are: *Acidophilus*, *Lactobacillus Plantarum*, *Lactobacillus Fermentum*, and *Lactobacillus Gasseri* were in equal quantity in each capsule. The same company made the same capsule considering the shape and color. All participants were administered the oral contraceptive Cyproterone acetate (ethinylestradiol-anti androgenic therapy) following the 3rd day of completion of their menstrual cycle. The following were carried out at the beginning and the end of the study;

1 A transvaginal ultrasound 7.0-MHz curved-array probe applied for all participants between the 3rd and 5th days of their menstrual cycles to assess the ovaries polycystic phenomenon (> 10, 2–8 mm follicle). The same ultrasound procedure was repeated between the 12th to 14th days of period to evaluate a dominant follicle (Atiomo, Pearson, Shaw, Prentice, & Dubbins, 2000).
2 The anthropometric measurements (body weight, waist, hip, abdominal circumference, height, and BMI) recorded for all subjects at the beginning and end of the study. Body weight measured by Seca scales with an accuracy of 100 g (Seca, Homburg, Germany) and Seca stadiometer with a precision 0.1 cm was determined. Flexible body tape was utilized to measure the waist circumference with an accuracy 0.1 cm on the average waistline between ribs and iliac bone. The same tape measure was used to determined abdominal and hip circumference.
3 The history of menstrual cycles was recorded for each subject for the six months before the starting date of the study as well as during the study.
4 Blood samples were collected at the beginning and end of the trial. The samples were analyzed at Laboratory of Immune Deficiency, Tehran University of Medical Sciences. Five (ml) of venous blood samples were obtained after 12-h of overnight fasting. All blood sample were immediately centrifuged at 1500–2000 for 5 min, then serum samples were collected and stored at −80 °C. The cytokines (IL-6, IL-10, TNF-α) were measured by ELISA (IBM, Germany) following protocols from the manufacturer.
5 High-sensitivity C-reactive protein (hs-CRP) was quantified by a latex-enhanced immunonephelometric assay that has a reported sensitivity of 0.01 mg/L and an intra-assay coefficient of variation of 8.7% (Behring Nephelometer II, Dade Behring, Inc., Newark, DE, USA)

All patients were also evaluated in their early follicular phase (days 3–5) of the menstrual cycle (Moghetti et al., 2000). Every two weeks after randomization all participants received a phone call to evaluate the dose of their capsule consumption during their trials and any possible side-effects of treatment.

Investigators obtained a signed written informed consent from all participants before the study. The study was approved by the ethics committee of National Nutrition and Food Technology Research Institute of Iran and was registered in the Iranian Registry of Clinical Trials (number: IRCT2016081429362N1).

2.2. Statistical analysis

Analysis of Covariance (ANCOVA) used to adjust the mean of some clinical, metabolic and immunological parameters after the trial. For other variables which measured two times in each group, the differences were evaluated using the independent samples *T*-test (for inter-group analysis) and paired samples *t*-test (for intra-group analysis). Blinded-duplicate sampling and (during intervention) decreases systematic error and inter-assay variability. All statistical analyses were done by SPSS (v24.0 for Windows, SPSS, Chicago, IL). P-values < .05 were considered statistically significant.

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