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The Effects of Magnesium and Vitamin E Co-Supplementation on Hormonal Status and Biomarkers of Inflammation and Oxidative Stress in Women with Polycystic Ovary Syndrome

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Abstract

Synergistic approach of magnesium and vitamin E may benefit clinical symptoms of patients with polycystic ovary syndrome (PCOS) through improving their metabolic profiles and reducing oxidative stress and inflammation. This study was designed to determine the effects of magnesium and vitamin E co-supplementation on hormonal status and biomarkers of inflammation and oxidative stress in women with PCOS. This randomized, double-blind, placebo-controlled trial was conducted among 60 women with PCOS, aged 18–40 years old. Participants were randomly divided into two groups to take 250 mg/day magnesium plus 400 mg/day vitamin E supplements or placebo ($n = 30$ each group) for 12 weeks. Fasting blood samples were taken at baseline and after the 12-week intervention to quantify related variables. Magnesium and vitamin E co-supplementation resulted in a significant reduction in hirsutism (β − 0.37; 95% CI, − 0.70, − 0.05; $P = 0.02$) and serum high-sensitivity C-reactive protein (hs-CRP) (β − 0.67 mg/L; 95% CI, − 1.20, − 0.14; $P = 0.01$), and a significant increase in plasma nitric oxide (NO) (β 3.40 μmol/L; 95% CI, 1.46, 5.35; $P = 0.001$) and total antioxidant capacity (TAC) levels (β 66.32 mmol/L; 95% CI, 43.80, 88.84; $P < 0.001$). Overall, magnesium and vitamin E co-supplementation for 12 weeks may benefit women with PCOS on hirsutism, serum hs-CRP, plasma NO, and TAC levels. Clinical trial registration number http://www.irct.ir: IRCT20170827339 41N8

Keywords Supplementation · Hormonal status · Inflammation · Oxidative damage

Introduction

Polycystic ovary syndrome (PCOS) is the most common metabolic disorder presented with hyperinsulinemic- and hyperandrogenic-related disorders. This complex metabolic disorder affects nearly 6% of women in reproductive age [1]. Earlier, investigators have documented a systemic low-grade inflammation in women diagnosed with PCOS, which subsequently leads to long-term consequences of PCOS, including enhanced risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [2, 3]. On the other hand, oxidative damage is closely linked with inflammation and further clinical and metabolic disorders in women diagnosed with PCOS [4].

The pathophysiology of PCOS might be associated with the deficiency of essential micronutrients such as magnesium and vitamin E in patients with insulin resistance and oxidative stress. Current evidence has shown that women suffering from PCOS have lower values of magnesium and vitamin E than normal individuals [5, 6]. In addition, few studies conducted in individuals with no PCOS have suggested that combined magnesium and vitamin E intake might be useful to improve metabolic profiles. A meta-analysis study conducted by Simental-Mendia et al. [7] showed that magnesium intake could reduce C-reactive protein (CRP) levels. Furthermore, magnesium supplementation for 12 weeks resulted in a considerable reduction of high-sensitivity C-reactive protein (hs-CRP) and an elevation of total antioxidant capacity (TAC) among diabetic patients with foot ulcer [8]. In another meta-analysis, vitamin E supplementation decreased CRP levels [9]. Recently, there is a growing interest to use the combination approach including combined magnesium and vitamin E, which might improve metabolic profiles in a number of

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diseases with metabolic abnormalities. Due to the synergistic impact of vitamin E and magnesium [10, 11], a further important question will be whether combined vitamin and micronutrient would provide a better protection against disease. The basis of this approach relies on a clinical correlation between vitamin E and cellular magnesium as well as tissue glucose metabolism [12].

Considering the antioxidant and anti-inflammatory effects of magnesium with vitamin E, we hypothesized that magnesium plus vitamin E might be useful on metabolic profiles in women with PCOS. However, data on studies investigating the impact of magnesium plus vitamin E on hormonal profiles, and biomarkers of inflammation and oxidative stress among women with PCOS, are scarce. Therefore, this study evaluates the effects of magnesium with vitamin E co-supplementation on metabolic profiles in women with PCOS.

Methods

Trial Design and Participants

This randomized, double-blinded, placebo-controlled clinical trial is registered in the Iranian clinical trials website (http://www.irct.ir: IRCT2017082733941N8), has followed the Declaration of Helsinki guideline, and informed consent was given by all participants. The study protocol was approved by the Ethics Committee of Arak University of Medical Sciences (AUMS). This study was conducted among 60 women with PCOS, diagnosed based on the Rotterdam Criteria [13], aged 18–40 years, who referred to the Kosar Clinic in Arak, Iran, between October 2017 and January 2018. The main exclusion criteria were as follows: pregnancy, adrenal hyperplasia, androgen-secreting tumors, hyperprolactinemia, thyroid dysfunction, diabetes and other metabolic disorders at enrollment, and antioxidant and/or anti-inflammatory supplements within 3 months prior to the enrollment in the study.

Study Design

All patients were matched for BMI and age. They were then randomly allocated into two groups to receive either 250 mg/day magnesium oxide (Twenty First Century Pharmaceutical Company, AZ, USA) plus 400 IU/day vitamin E (Zahravi Pharmaceutical Company, Tabriz, Iran) ($n = 30$) or placebo (Barij Essence Pharmaceuticals, Kashan, Iran) ($n = 30$) for 12 weeks. The placebos were matched in color, shape, size, packaging, smell, and taste with the vitamin E and magnesium capsules. The compliance rate was assessed by measuring serum magnesium levels. Intake of the magnesium, vitamin E, and placebo capsules was monitored through asking participants to return the medication containers. To increase the compliance rate, all patients received brief daily cell phone reminders to take the supplements. Patients were requested to have their regular physical activity and not to take any extra nutritional supplements during the 12-week trial. All patients completed a 3-day food record and three physical activity records at the baseline of the study, weeks 3, 6, and 9, and the end of the intervention. Daily macro- and micronutrient intakes were calculated by analyzing food records using the Nutritionist IV software (First Databank, San Bruno, CA).

Anthropometric Measures

Patient's weight and height were measured after an overnight fasting, using a standard scale (Seca, Hamburg, Germany), at both the onset of the study and after the 12-week intervention. BMI was calculated as weight in kilogram divided by height in meters squared.

Clinical Assessments

Hirsutism was determined using a modified Ferriman–Gallwey scoring system, as the clinical outcome [14].

Biochemical Assessment

Fasting blood samples were collected at the beginning and end of the trial, at the Arak reference laboratory. Serum total testosterone and sex hormone-binding globulin (SHBG) were measured using Elisa kits (DiaMetra, Milano, Italy) with inter- and intra-assay coefficient of variations (CVs) less than 7%. Serum hs-CRP concentrations were measured using an ELISA kit (LDN, Nordhorn, Germany) with the intra- and inter-assay CVs less than 7%. Other biomarkers were assessed as follows: plasma nitric oxide (NO) using the Griess method [15], TAC using ferric reduction antioxidant power method developed by Benzie and Strain [16], glutathione (GSH) applying Beutler et al.'s method [17], and malondialdehyde (MDA) concentrations using the thiobarbituric acid reactive substance method [18] with the inter- and intra-assay CVs less than 5%.

Sample Size

Sample size was calculated using the standard formula for clinical trials, considering type one error (α) of 0.05 and type two error (β) of 0.20 (power = 80%). According to a previously published study [19], we used 1.93 mg/L as the effect size (d) of hs-CRP and 2.4 mg/L as standard deviation (SD). Using this information, 25 individuals were required to be included in each treatment group. Considering 5 probable dropouts in each group, the final sample size was determined as 30 patients in each group.

Randomization

Randomization was conducted using computer-generated random numbers. Randomization and allocation were concealed from the researchers and patients until the final analyses were completed. The randomized allocation sequence, enrolling patients, and allocating them into intervention groups were performed by a trained staff at the clinic.

Statistical Methods

Anthropometric measures and dietary intakes were compared between intervention groups, using independent samples *t* test. Multiple linear regression models were used to assess treatment effects on the study outcomes after adjusting for confounding variables including the baseline values, age, and BMI. The effect sizes were presented as the mean differences with 95% confidence intervals. Paired-samples *t* test was used to detect within-group differences. The normality of model residual was tested using the Kolmogorov-Smirnov test. The *P* value of < 0.05 was considered as statistically significant. All statistical analyses were conducted using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, IL, USA).

Results

In the current study, all 60 subjects (intervention ($n = 30$) and placebo ($n = 30$)) completed the trial (Fig. 1). Overall, the compliance rate in this study was high, such that more than 90% of the capsules were consumed throughout the study in both groups. No side effects were reported following co-administration of magnesium and vitamin E capsules in patients with PCOS throughout the study.

Mean age, height, weight, and BMI at baseline and end-of-trial were not statistically different between intervention groups **(**Table 1**).**

Mean dietary macro- and micronutrient intakes were also not statistically different between the two groups throughout the trial (data not shown).

After the 12-week intervention, magnesium and vitamin E co-supplementation significantly reduced hirsutism (β − 0.37; 95% CI, − 0.70, − 0.05; $P = 0.02$) and serum hs-CRP (β − 0.67 mg/L; 95% CI, − 1.20, − 0.14; $P = 0.01$), and significantly increased serum magnesium (β 0.17 mg/dL; 95% CI, 0.12, 0.21; $P < 0.001$), plasma NO (β 3.40 μmol/L; 95% CI, 1.46, 5.35; $P = 0.001$), and TAC levels (β 66.32 mmol/L; 95% CI, 43.80, 88.84; $P < 0.001$) compared with the placebo (Table 2). Serum total testosterone, SHBG, plasma GSH, and MDA levels did not significantly change with magnesium and vitamin E co-supplementation. Within-group changes demonstrated a significant reduction in hirsutism ($P = 0.02$), and a significant increase in serum magnesium ($P < 0.001$), SHBG ($P = 0.004$), plasma NO ($P < 0.001$), TAC ($P < 0.001$), and GSH ($P = 0.03$) in the magnesium and vitamin E group. In addition, within-group change showed a significant increase in serum hs-CRP ($P = 0.03$) in the placebo group.

Discussion

We evaluated the effect of co-administration of magnesium and vitamin E, to our best knowledge for the first time, on metabolic status in patients with PCOS. The results showed that taking magnesium and vitamin E supplements together for 12 weeks had beneficial effects on hirsutism, hs-CRP, NO, and TAC levels.

Effects on Hormonal Profiles

Women with PCOS are susceptible to multiple metabolic disorders [20, 21]. The current study demonstrated that magnesium and vitamin E co-supplementation for 12 weeks was associated with a significant reduction in hirsutism, but did not affect serum total testosterone and SHBG levels. Our previous study demonstrated that magnesium-zinc-calcium-vitamin D co-supplementation after 12 weeks to women with PCOS significantly decreased hirsutism, but did not affect other hormonal profiles [22]. In addition, vitamin E (400 IU/day) and omega-3 (1000 mg/day) co-supplementation for 12 weeks to women with PCOS significantly improved total and free testosterone levels, but did not affect other endocrine parameters [23]. In another study, coenzyme Q10 (200 mg/day) with or without vitamin E (400 IU/day) supplementation for 8 weeks to women with PCOS had beneficial effects on serum total testosterone levels, but did not influence SHBG concentrations [24]. A cross-sectional study demonstrated an inverse association between serum α-tocopherol and circulating testosterone, estradiol, and SHBG levels in smoker men [25]. Elevated androgen level which is a hallmark of PCOS in a self-perpetuating cycle promotes hyperandrogenism and results in neuroendocrine abnormality [26]. Previous evidence showed that reducing androgens is attributed to the restoration of ovulatory functions, decreasing hirsutism, and improving health-related quality of life [27, 28]. The absence of beneficial effects of magnesium and vitamin E co-supplementation on total testosterone and SHBG may be due to low-dose magnesium and vitamin E used as well as short-duration intervention. A number of potential mechanisms through which magnesium and vitamin E may improve ovarian functions are proposed including the antioxidant and anti-inflammatory activities of magnesium and vitamin E, as well as their effects on improved insulin sensitivity [24, 29, 30].

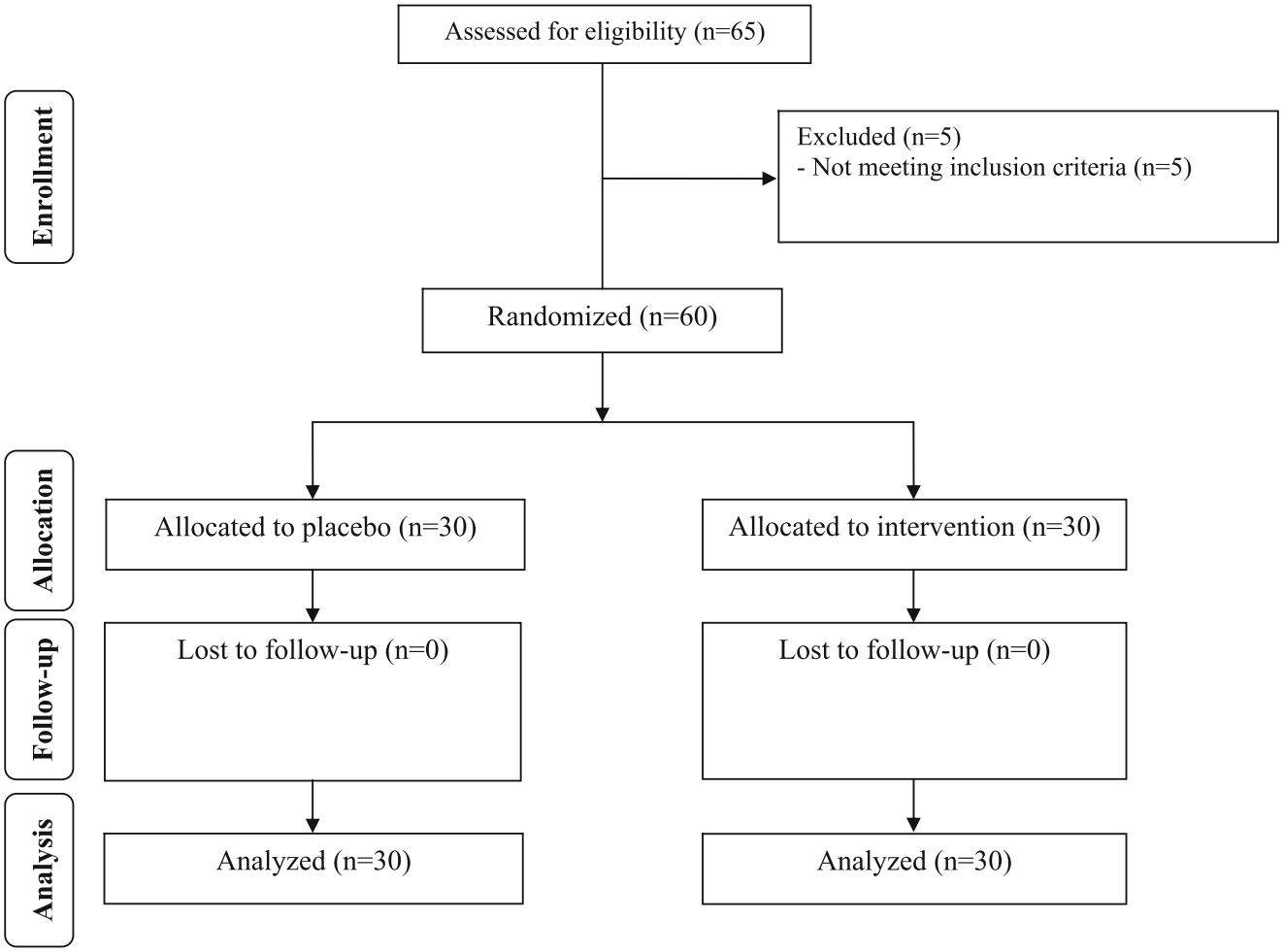

Fig. 1 Summary of patient flow diagram

Effects on Biomarkers of Inflammation and Oxidative Stress

The co-supplementation of magnesium and vitamin E for 12 weeks was found to significantly decrease serum hs-CRP and increase plasma NO and TAC levels in patients with PCOS, but did not affect plasma GSH and MDA levels. We have previously showed that taking magnesium plus zinc supplements for 12 weeks by women with PCOS had beneficial effects on hs-CRP and TAC levels [19]. In addition, a meta-analysis conducted by Simental-Mendia et al. [7] showed that magnesium supplementation could decrease CRP levels in people with high inflammation (CRP levels > 3 mg/dL). A 4-week magnesium supplementation to rugby players and people with sedentary lifestyle significantly decreased oxidative damage [31]. However, magnesium supplementation at a dosage of 250 mg/day as magnesium oxide after 8 weeks to middle-aged overweight women did not influence inflammatory markers [32]. Moreover, the administration of 440 mg magnesium supplements as magnesium oxide 3 times per week for 6 months to hemodialysis patients did not influence CRP concentrations [33]. Anti-inflammatory and antioxidative effects of vitamin E have been previously reported. In a meta-analysis conducted by Saboori et al. [9], vitamin E supplementation significantly reduced CRP levels. Furthermore,

Table 1 General characteristics of study participants

	Placebo group ($n = 30$)	Magnesium plus vitamin E group ($n = 30$)	P^1
Age (years)	26.0 ± 3.7	27.2 ± 7.1	0.42
Height (cm)	159.5 ± 4.9	159.9 ± 4.8	0.71
Weight at study baseline (kg)	70.9 ± 10.3	69.4 ± 10.7	0.58
Weight at end-of-trial (kg)	70.7 ± 10.4	69.2 ± 10.6	0.57
Weight change (kg)	− 0.1 ± 0.6	− 0.2 ± 0.3	0.62
BMI at study baseline (kg/m^2)	27.9 ± 4.2	27.1 ± 4.2	0.48
BMI at end-of-trial (kg/m^2)	27.8 ± 4.2	27.0 ± 4.1	0.47
BMI change (kg/m^2)	− 0.1 ± 0.2	− 0.1 ± 0.1	0.63

Data are means ± SDs

[1] Obtained from independent-samples *t* test

Table 2 Hormonal status and biomarkers of inflammation and oxidative stress at baseline and after the 12-week intervention in subjects with polycystic ovary syndrome

Variables	Placebo group ($n = 30$)			Magnesium plus vitamin E group ($n = 30$)			Difference in outcome measures between magnesium plus vitamin E and placebo treatment groups[1]	
	Baseline	Week 12	P^2	Baseline	Week 12	P^2	β (95% CI)	P^3
Magnesium (mg/dL)	1.89 ± 0.12	1.88 ± 0.11	0.59	1.94 ± 0.20	2.10 ± 0.15	< 0.001	0.17 (0.12,0.21)	< 0.001
Total testosterone (ng/mL)	1.2 ± 0.5	1.2 ± 0.6	0.80	1.4 ± 0.8	1.3 ± 0.7	0.26	0.02 (− 0.09, 0.14)	0.63
SHBG (nmol/L)	48.5 ± 15.1	49.2 ± 15.2	0.57	51.4 ± 26.4	62.9 ± 36.3	0.004	− 0.03 (− 0.13,0.07)	0.56
FAI	0.09 ± 0.05	0.09 ± 0.05	0.46	0.15 ± 0.16	0.11 ± 0.11	0.08	0.12 (− 0.01, 0.27)	0.08
mF-G scores	13.8 ± 3.8	13.8 ± 3.8	0.57	14.9 ± 2.9	14.6 ± 2.5	0.02	− 0.37 (− 0.70, − 0.05)	0.02
hs-CRP (mg/L)	3.5 ± 1.5	3.7 ± 1.5	0.03	3.7 ± 1.9	3.1 ± 1.7	0.05	− 0.67 (− 1.20, − 0.14)	0.01
NO (μmol/L)	36.6 ± 5.6	37.0 ± 5.8	0.34	34.4 ± 2.3	38.7 ± 4.0	< 0.001	3.40 (1.46, 5.35)	0.001
TAC (mmol/L)	513.7 ± 81.7	514.5 ± 77.3	0.90	522.4 ± 30.6	590.7 ± 52.2	< 0.001	66.32 (43.80, 88.84)	< 0.001
GSH (μmol/L)	481.1 ± 101.2	483.8 ± 94.2	0.50	508.1 ± 69.1	519.4 ± 47.7	0.03	12.14 (− 0.17, 24.46)	0.05
MDA (μmol/L)	2.4 ± 0.5	2.5 ± 0.5	0.15	2.7 ± 0.2	2.6 ± 0.2	0.11	− 0.10 (− 0.28, 0.08)	0.27

Data are mean ± SDs

[1] "Outcome measures" refers to the change in values of measures of interest between baseline and week 12. β (difference in the mean outcome measures between treatment groups (magnesium plus vitamin E group = 1 and placebo group = 0))

[2] Obtained from paired-samples *t* test

[3] Obtained from multiple regression model (adjusted for baseline values of each biochemical variables, age, and baseline BMI)

FAI, free androgen index; *GSH*, total glutathione; *hs-CRP*, high-sensitivity C-reactive protein; *mF-G*, modified Ferriman–Gallwey; *MDA*, malondialdehyde; *NO*, nitric oxide; *SHBG*, sex hormone-binding globulin; *TAC*, total antioxidant capacity

vitamin E supplementation at a dosage of 200 mg/day for 12 weeks to workers significantly reduced biomarkers of oxidative stress [34]. However, no significant changes in biomarkers of oxidative damage were observed following the administration of 400 IU/day vitamin E for 8 weeks to patients with chronic obstructive pulmonary disease [35]. Synergistic anti-inflammatory effects of vitamin E plus magnesium might boost their impact on clinical and biochemical symptoms. It is now obvious that PCOS is a pro-inflammatory condition linking with oxidative stress [36]. Impaired antioxidative defense and increased inflammatory markers such as CRP contribute to insulin resistance and the promotion of atherosclerosis which increase the risk of CVD [37]. Anti-inflammatory effects of magnesium supplements may be due to its antagonism to calcium [38] and blocking nuclear factor-kappa B (NF-κB) [39]. In addition, anti-inflammatory and antioxidative effects of vitamin E may be explained by suppressing NF-κB and JAK-signal transducer and activator of transcription 6 (STAT6) or JAK-STAT3 signaling pathways in various types of cells [40].

This study had a few limitations. In the present study, we did not evaluate circulating vitamin E before and after supplementation. Further, this study did not assess gene expression related to inflammatory cytokines and biomarkers of oxidative stress.

Conclusions

In summary, the current study demonstrated that taking magnesium and vitamin E supplements together for 12 weeks by patients with PCOS has beneficial effects on hirsutism, hs-CRP, NO, and TAC, but did not affect serum total testosterone, SHBG, plasma GSH, and MDA levels.

Author's Contributions ZA and MS contributed in conception, design, statistical analysis, and drafting of the manuscript. ZA supervised the study.

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Compliance with Ethical Standards

This randomized, double-blinded, placebo-controlled clinical trial is registered in the Iranian clinical trials website (http://www.irct.ir: IRCT2017082733941N8), has followed the Declaration of Helsinki guideline, and informed consent was given by all participants. The study protocol was approved by the Ethics Committee of Arak University of Medical Sciences (AUMS).

Competing Interests The authors declare that they have no conflict of interest.

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