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The Effects of Selenium Supplementation on Clinical Symptoms and Gene Expression Related to Inflammation and Vascular Endothelial Growth Factor in Infertile Women Candidate for In Vitro Fertilization

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Abstract

This study was performed to determine the effects of selenium supplementation on clinical symptoms and gene expression related to inflammatory markers in infertile women with polycystic ovary syndrome (PCOS) who were candidate for in vitro fertilization (IVF). Thirty-six women candidate for IVF were recruited in this randomized double-blinded, placebo-controlled trial. They (n = 18/group) were randomly assigned into intervention groups to take either 200 μg/day of selenium or placebo for 8 weeks. RT-PCR findings indicated that selenium supplementation downregulated gene expression of interleukin-1 (IL-1) ($P < 0.004$) and tumor necrosis factor alpha (TNF-α) ($P = 0.02$) in lymphocytes of patients with PCOS compared with the placebo. In addition, selenium supplementation upregulated gene expression of vascular endothelial growth factor (VEGF) ($P = 0.001$) in lymphocytes of patients with PCOS compared with the placebo. Selenium supplementation had no significant effect on clinical symptoms and gene expression of IL-8 ($P = 0.10$) and transforming growth factor beta (TGF-β) ($P = 0.63$). Overall, our findings documented that selenium supplementation for 8 weeks to infertile women candidate for IVF improved IL-1, TNF-α, and VEGF gene expression, though selenium had no effect on clinical symptoms and, IL-8 and TGF-β gene expression. Clinical trial registration number: http://www.irct.ir: IRCT20170513033941N23.

Keywords Selenium · Gene expression · Inflammatory markers · Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder in reproductive-aged women. The main cause of PCOS remains unknown and is likely multifactorial. Insulin resistance and a low-grade inflammation play critical roles in the pathological process of this syndrome [1]. Women suffering from PCOS are often subfertile secondary to ovulatory dysfunction, impaired oocyte quality, and low endometrial receptivity [2]. In vitro fertilization (IVF) recommended as an assisted reproduction technology for PCOS-related infertility when patients do not respond to ovulation induction agents [3]. PCOS women undergoing IVF treatment are known to possess a higher risk of developing some complication including increased cancelation rate and ovarian hyperstimulation syndrome [4, 5]. Some evidence suggested that inflammatory cytokine profiles influence oocyte fertilization and correlate with pregnancy success in women who conceive using IVF setting [6]. In addition, it is reported that the serum concentration of some growth factor such as vascular endothelial growth factor (VEGF) is associated with embryo quality in these women [7].

Earlier, in a meta-analysis study by Ju et al. [8], it has been reported that supplementation with selenium improved inflammation and oxidative stress. Few studies investigated

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the effects of selenium supplementation among PCOS patients. Previously, we observed that taking selenium supplementation in subjects with PCOS had beneficial effects on glycemic and lipid profiles [9]. Moreover, an experiment by Zhang et al. [10] showed that selenium deficiency exacerbated uterine tissue destruction and increased the mRNA expression of inflammatory cytokines in the mice model of endometritis. Interestingly, selenium administration in this study led to a decrease in tumor necrosis factor-α (TNF-α), interleukin-(IL-) 1β and IL-6 gene expression.

Selenium has both anti-inflammatory and anti-oxidant properties. It may alleviate the inflammatory gene expression by inhibiting the activation of mitogen-activated protein (MAP) kinase and nuclear factor-kappaB (NF-κB) pathways [11]. Hence, this study aimed to evaluate the effects of selenium supplementation on clinical symptoms and gene expression related to inflammatory biomarkers and VEGF in women with PCOS candidate for IVF.

Methods

Trial Design and Participants' Characteristics

This randomized, double-blinded, placebo-controlled trial was registered by Iranian website for clinical trials registration (http://www.irct.ir: IRCT20170513033941N23). Between February and August 2018, 40 infertile women with PCOS, at age 18 to 40 years, who were candidate for IVF without prior IVF, were randomly enrolled in this investigation. To confirm PCOS diagnosis, Rotterdam criteria was used [12]. Subjects with metabolic abnormalities such as diabetes, impaired glucose tolerance, and thyroid dysfunction were excluded from the trial. This study was approved by the research ethics committee of Shahid Beheshti University of Medical Sciences (SUMS), Tehran, Iran. All individuals signed written informed consent.

Intervention

At first, patients were matched according to BMI (< 25 and ≥ 25 kg/m^2), age (< 30 and ≥ 30 y), dosage of medication used and ovarian reserve (anti-Müllerian hormone) of PCOS. Then, subjects were randomly allocated into intervention groups to intake either 200 μg/day selenium as selenium yeast (Nature Made, California, USA) ($n = 18$) or placebo (Barij Essence, Kashan, Iran) ($n = 18$) for 8 weeks. Due to a lack of evidence about the appropriate dosage of selenium for infertile patients with PCOS candidate for IVF, we used the abovementioned dose of selenium based on a previous study in patients with PCOS [9]. Placebos and selenium supplements were exactly matched in terms of appearance, smell, shape, and packaging. To randomize enrolled patients, computer-generated random numbers were used. Allocation and randomization were concealed from both the participants and researchers until final analyses completion. Adherence to the placebos and supplements, during the trial, was checked by asking participants to bring the medication containers back. Patients completed dietary records at weeks 0, 4, and 8 of the trial.

Assessment of Outcomes

TNF-α gene expression was measured as the primary outcome and other gene expression associated with inflammation were considered as the secondary outcomes. Fasting blood samples (15 mL) were collected at the initiation and end of the 8-week investigation at Mahdieh Hospital (Tehran, Iran).

Isolation of Lymphocyte Cells

Lymphocyte cells were extracted from blood samples, using 50% percoll (Sigma-Aldrich, Dorset, UK). Viability test and cell count were done using trypan blue, DNA, and RNA extraction [13].

RNA Extraction and Real-Time PCR

RNA was extracted from blood samples using RNX-plus kit (Cinnacolon, Tehran, Iran). RNA suspension was frozen at − 20 °C until cDNA was derived. Following the extraction of total RNAs from each sample, RNA was quantified using a UV spectrophotometer. Using Moloney murine leukemia virus reverse transcriptase (RT), isolated RNA was reverse transcribed to cDNA library. IL-1, IL-8, transforming growth factor beta (TGF-β), TNF-α, and VEGF were carried out on lymphocytes, using SYBR green detection and Amplicon Kit and applying quantitative RT-PCR and Light Cycler technology (Roche Diagnostics, Rotkreuz, Switzerland) (Table 1). The primers of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were used as a housekeeping gene.

Statistical Methods

Kolmogorov-Smirnov test was used to assess the normality of data. To determine the differences in gene expression of inflammation and anthropometric measures between intervention groups, independent samples t test was applied. Differences in proportions were evaluated by Fisher's exact test. To control confounding variables, including dosage of medication used, we used analysis of covariance (ANCOVA). The P values of < 0.05 were considered statistically significant. Statistical analyses were done using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

Table 1 Specific primers used for real-time quantitative PCR

Gene	Primer	Product size (bp)	Annealing temperature (C)
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG R: TCTTCCTCTTGTGCTCTTGCTGG	126	61.3
IL-1	F: GCTTCTCTCTGGTCCTTGG R: AGGGCAGGGTAGAGAAGAG	174	56
IL-8	F: GCAGAGGGTTGTGGAGAAGT R: ACCCTACAACAGACCCACAC	150	56
TNF-α	F: GTCAACCTCCTCTCTGCCAT R: CCAAAGTAGACCTGCCCAGA	188	52
TGF-β	F: TTGAGACTTTTCCGTTGCCG R: CGAGGTCTGGGGAAAAGTCT	227	56
VEGF	F: CTTCTGAGTTGCCCAGGAGA R: CTCACACACACACAACCAGG	216	54

GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IL-1, interleukin-1; IL-8, interleukin-8; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor

Results

Two dropouts were reported in each intervention group, due to personal reasons. Overall, 36 participants [infertile women with PCOS candidate for IVF receiving selenium ($n = 18$) and placebo ($n = 18$)] completed the study (Fig. 1). Compliance rate in this study was more than 90%. No side effects were reported following the supplementation of selenium in women with PCOS in this study.

Anthropometric measures were not statistically different between intervention groups (Table 2). Moreover, following selenium supplementation, IVF outcomes including endometrial thickness, number of oocytes retrieved, number of fertilized oocytes, fertilization rate, pregnancy rate, and number of embryo were not significantly different between supplemented and placebo groups.

The average of dietary intakes of energy, carbohydrates, fats, proteins, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol, total dietary fiber, selenium, zinc, magnesium and manganese was also not significantly different between the two groups throughout the treatment (Table 3).

RT-PCR findings indicated that selenium supplementation downregulated gene expression of IL-1 ($P < 0.004$) and TNF-α ($P = 0.02$) in lymphocytes of patients with PCOS compared with the placebo (Fig. 2). Selenium supplementation had no significant effect on gene expression of IL-8 ($P = 0.10$) in lymphocytes of patients with PCOS.

Selenium supplementation upregulated gene expression of VEGF ($P = 0.001$) in lymphocytes of patients with PCOS compared with the placebo (Fig. 3). There was no significant effect of selenium supplementation on the gene expression of TGF-β ($P = 0.63$) in lymphocytes of patients with PCOS. In addition, when we adjusted the analysis for dosage of medication used, findings did not change (for IL-1, $P < 0.001$; for TNF-α, $P = 0.03$; for IL-8, $P = 0.07$; for VEGF, $P = 0.001$; and for TGF-β, $P = 0.69$).

Discussion

In the present study, we investigated the effects of selenium supplementation clinical symptoms and gene expression related to inflammatory markers for 8 weeks in infertile women with PCOS who were candidate for IVF treatment. We found that supplementation with selenium improved gene expression of IL-1, TNF-α, and VEGF, but did not affect the gene expression of other cytokines including IL-8 and TGF-β.

Previously, it is stated that the concentrations of inflammatory markers such as TNF-α and IL-6 are elevated in follicular fluid from PCOS patients undergoing IVF [14]. TNF-α is an inflammatory cytokine which mediates insulin resistance and is capable of promoting hyperandrogenism in PCOS patients [1]. This cytokine involves in both physiological and pathological conditions in reproductive tissues. Exaggerated TNF-α activity may promote epithelial apoptosis, favors pelvic implantation, and impairs trophoblast cell fusion [15]. In IVF treatment, TNF-α levels correlates with the poor quality of oocyte and the reduced rates of fertilization [16]. In addition, IL-1 which is a key player in the local and systemic inflammation has been known to stimulate the generation of reactive oxygen species and activation of NF-κB pathways [17]. The current research showed that selenium supplementation for 6 weeks downregulated the gene expression of TNF-α and IL-1, but did not affect IL-8 and TGF-β mRNA expression in PCOS patients who were candidate for IVF. Few studies have reported that deficiency of trace elements may have effect on reproductive health [18, 19]. Among trace elements, selenium and zinc play an important role in sexual development, menstrual cycle, and ovulation [20]. In addition, there is a correlation between these nutrients and their derivatives and spontaneous abortions and congenital malformations [20]. In another study, it was seen a lack of selenium in IVF patients [21]. Few studies have reported the effects of selenium supplementation on metabolic profiles in patients with PCOS. In a study conducted by Razavi et al.

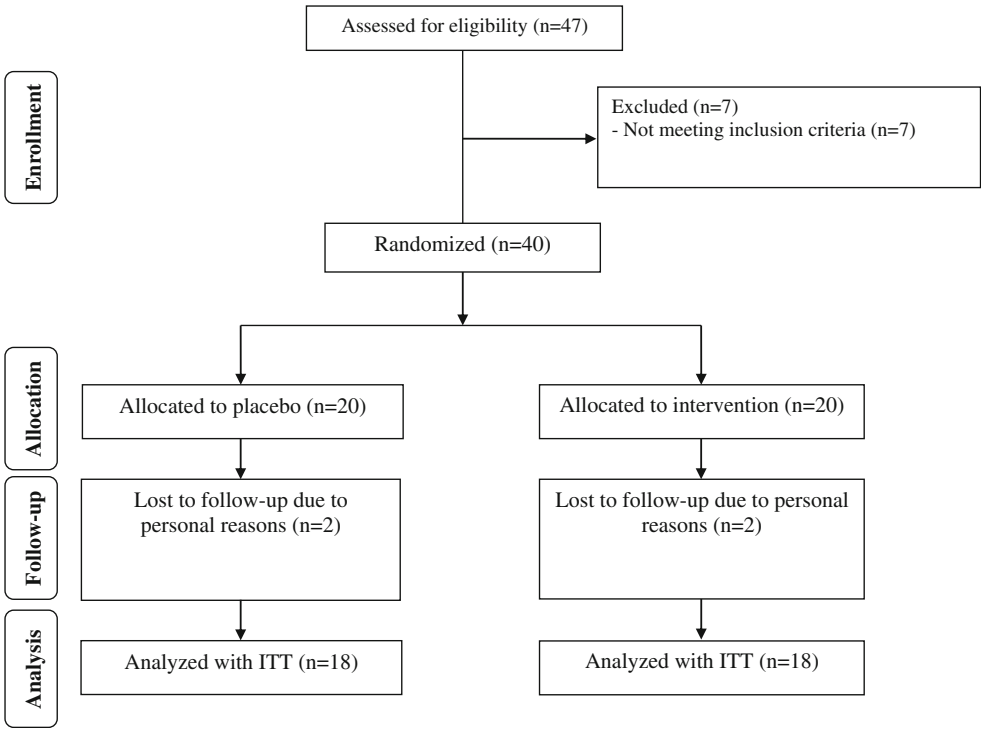

Fig. 1 Summary of patient flow diagram

[22], selenium supplementation at a dosage of 200 μg/day for 8 weeks to patients with PCOS significantly improved few reproductive outcomes, and biomarkers of inflammation and oxidative stress. In addition, we have previously shown that selenium and probiotic co-supplementation for 12 weeks to women with PCOS had beneficial effects on mental health parameters, total testosterone, hirsutism, and few biomarkers of inflammation and oxidative stress [23]. Also, selenium significantly decreased oxidative stress through transient receptor potential cation channel subfamily V member 1 channels in the neutrophils of patients with PCOS [24]. However, taking 200 μg/day selenium supplements for 12 weeks by women

Table 2 General characteristics of study participants

	Placebo group ($n = 18$)	Selenium group ($n = 18$)	P^1
Age (y)	32.6 ± 3.5	32.1 ± 4.7	0.28
Height (cm)	163.9 ± 2.6	165.6 ± 3.1	0.07
Weight at study baseline (kg)	76.8 ± 6.5	74.5 ± 8.0	0.35
Weight at end-of-trial (kg)	77.0 ± 6.5	74.5 ± 8.1	0.32
Weight change (kg)	0.2 ± 0.8	0.1 ± 1.3	0.69
BMI at study baseline (kg/m^2)	28.6 ± 2.5	27.2 ± 3.1	0.14
BMI at end-of-trial (kg/m^2)	28.7 ± 2.5	27.2 ± 3.2	0.13
BMI change (kg/m^2)	0.1 ± 0.3	0.03 ± 0.5	0.69
Gonal-F therapy (IU/day)	240.5 ± 70.7	256.1 ± 45.3	0.43
Outcomes of IVF at end-of-trial			
Endometrial thickness (mm)	9.0 ± 1.6	9.6 ± 2.0	0.30
No. of oocytes retrieved (n)	17.7 ± 4.3	16.0 ± 5.4	0.31
Fertilization rate, % (n)	61.1 (11/18)	66.7 (12/18)	0.73†
Pregnancy rate, % (n)	27.8 (5/18)	33.3 (6/18)	0.71†
No. of embryo (n)	10.7 ± 2.3	11.9 ± 2.3	0.12

Data are means ± SDs; BMI, body mass index

[1] Obtained from independent t test

[†] Obtained from Fisher's exact test

Table 3 Mean dietary intakes of study participants throughout the study

	Placebo group (n = 18)	Selenium group (n = 18)	P^1
Energy (kcal/d)	2296 ± 298	2198 ± 310	0.33
Carbohydrates (g/d)	319.4 ± 69.9	303.6 ± 55.8	0.45
Protein (g/d)	82.1 ± 14.7	83.2 ± 18.2	0.85
Fat (g/d)	80.4 ± 11.1	76.3 ± 13.5	0.33
SFAs (g/d)	25.0 ± 4.2	24.4 ± 5.1	0.71
PUFAs (g/d)	24.3 ± 3.2	22.8 ± 5.7	0.30
MUFAs (g/d)	20.9 ± 4.9	21.1 ± 5.4	0.89
Cholesterol (mg/d)	229.1 ± 121.2	189.3 ± 73.4	0.24
TDF (g/d)	19.2 ± 5.0	19.8 ± 3.7	0.67
Selenium (μg/d)	55.2 ± 11.0	54.3 ± 8.0	0.79
Zinc (mg/d)	10.3 ± 2.4	9.8 ± 2.8	0.50
Magnesium (mg/d)	259.2 ± 52.2	254.3 ± 48.0	0.77
Manganese (mg/d)	2.1 ± 0.9	1.9 ± 0.7	0.32

Data are means± SDs; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; TDF, total dietary fiber

[1] Obtained from independent t test

with PCOS resulted in a marginally significant increase in insulin concentrations [25]. Previously, our supporting study indicated that a 6-week selenium supplementation in women with gestational diabetes mellitus (GDM) reduced the gene expression of TNF-α [26]. In addition, selenium administration led to a decrease in TNF-α and IL-1 gene expression chicken with lead-induced spleen damage [27]. Moreover, selenium supplementation downregulated inflammatory mediators TNF-α, IL-1B, and IL-6 gene expression in *Staphylococcus aureus*-stimulated bovine mammary endothelial cells [28]. However, 2 weeks' supplementation with selenium did not change plasma concentrations of inflammatory markers including TNF-α levels in patients undergoing hematopoietic stem cell transplantation [29]. Given the negative influences of the pro-inflammatory environment presenting in polycystic ovaries, the alleviating of inflammation improves endometrium function and enhance insulin action [30]. Selenium supplementation may decrease gene expression of inflammatory cytokines through the suppressing of phosphorylation in NF-κB and MAPK pathways [31]. In addition, modifying the cellular redox tone by selenoproteins mediate the signaling of NF-κB and MAPK which in turn resulted in reduced protein synthesis of inflammatory mediators [32]. Moreover, an in vitro study indicated that selenoproteins inhibit histone acetylation of TNF-α gene promoters in macrophage cell which may explain the regulation of inflammatory gene expression by selenium [33].

In the present study, we demonstrated that selenium supplementation for 6 weeks, upregulated VEGF mRNA expression in PCOS women candidate for IVF. Similarly, VEGF expression was increased by selenium supplementation in GDM women [26]. In addition, the administration of herbal extract enriched with selenium increased the expression of VEGF in rat model of Alzheimer's disease [34]. Moreover, topical application of selenium upregulated VEGF mRNA expression in diabetic rats [35]. Although, selenium administration did not change VEGF gene expression in an animal model of epilepsy [36]. VEGF is a regulator of angiogenesis which increases vascular permeability and induces capillary formation. It is also implicated in reproductive performance [37]. The abnormal gene expression of VEGF has been suggested to be associated with low implantation rates and the lack of clinical pregnancy after IVF attempt [38]. Decreased gene expression of VEGF also increases susceptibility to pre-

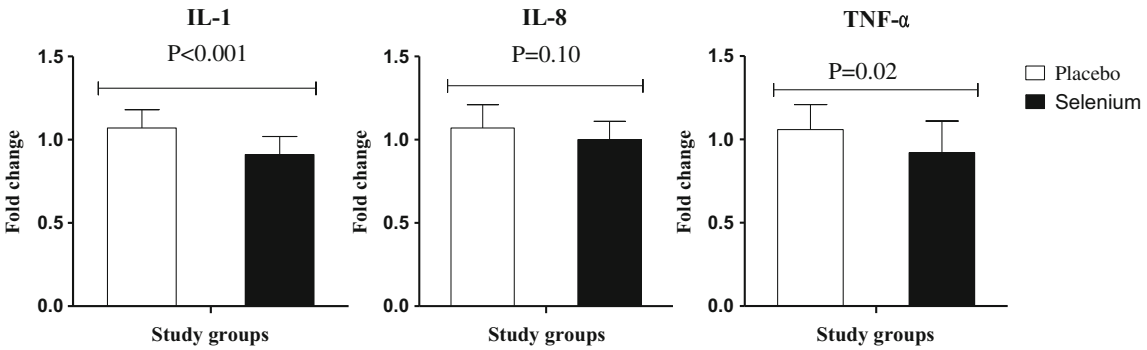

Fig. 2 Effect of the 8-week supplementation with selenium or placebo on expression ratio of IL-1, IL-8, and TNF-α gene in lymphocytes of polycystic ovary syndrome women candidate for in vitro fertilization

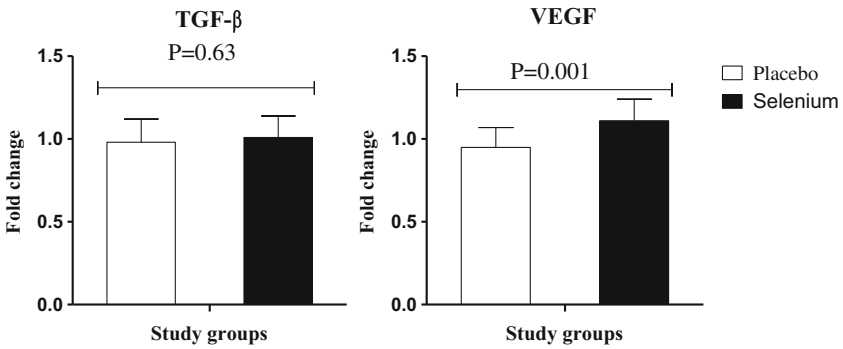

Fig. 3 Effect of the 8-week supplementation with selenium or placebo on expression ratio of TGF-β and VEGF gene in lymphocytes of polycystic ovary syndrome women candidate for in vitro fertilization. IL-1, interleukin-1; IL-8, interleukin-8; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor

eclampsia during pregnancy [39]. The higher levels of VEGF mRNA expression are associated with better endometrial blood flow which in turn lead to successful implantation and embryo transfer following IVF [40, 41]. Selenium may exert regulatory effects on VEGF gene expression through thioredoxin reductase action and balancing oxidation state [42].

Overall, our findings documented that infertile women with PCOS, who were candidate for IVF benefited from selenium supplementation for 8 weeks in terms of improving the gene expression of IL-1, TNF-α, and VEGF, though selenium had no effect on clinical symptoms and gene expression of IL-8 and TGF-β.

Authors' Contributions ZA helped in conception, design, and statistical analysis of the manuscript. ZH, NH, SZ-M, MM, EA, and M-HP contributed in data collection and manuscript drafting. ZA supervised the study.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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