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Effects of selenium supplementation on glucose homeostasis and free androgen index in women with polycystic ovary syndrome: A randomized, double blinded, placebo controlled clinical trial

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ABSTRACT

Background/objectives: Insulin resistance (IR) is a main pathophysiologic feature in polycystic ovary syndrome (PCOS) patients which is triggered by elevated oxidative stress in these patients. Selenium, an essential micronutrient, is a major constituent of antioxidant enzymes such as glutathione peroxidase. Recently, decreased plasma selenium concentrations were reported in PCOS patients. So, the present study was carried out in order to assess whether selenium consumption can improve the metabolic response to insulin and reduce the insulin resistance in these women.
Subjects/methods: A total of 53 PCOS patients (diagnosed by Rotterdam criteria), 18–42 years old, participated in this randomized, double-blind and placebo controlled trial for 12 weeks (selenium, $n = 26$; placebo, $n = 27$). The effects of daily administration of 200 μg selenium or placebo on serum glucose, total testosterone (tT), sex hormone binding globulin (SHBG) and free androgen index (FAI) in fasting state were evaluated.
Results: At the end of the study, insulin resistance was significantly increased in selenium recipients when compared with the placebo group (2.05 ± 0.39 when compared with 1.81 ± 0.25, $p = 0.017$). Also, selenium supplementation resulted in marginally significant increase ($p = 0.056$) in insulin level when compared with the placebo group. There were no statistically significant changes in other study endpoints, when comparing the two groups.
Conclusion: This study showed that selenium supplementation in PCOS patients may worsen insulin resistance in them. Until the results of larger studies become available, indiscriminate consumption of selenium supplements in PCOS patients will warrant caution.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders in women which affects up to 10% of women of reproductive age [1] and has considerable economic burden [2]. Together with being a reproductive system problem characterized by hyperandrogenism and anovulation, it is a metabolic disorder usually accompanied by insulin resistance [3]. Insulin resistance has a pivotal role in the pathophysiology of PCOS [3]. Women with PCOS are more likely to develop impaired glucose tolerance (IGT), type 2 diabetes mellitus (T2DM), dyslipidemia and cardiovascular disease (CVD) than healthy women [4,5].

Selenium is an essential trace element which is a main part in antioxidant proteins including glutathione peroxidases (GPXs) [6]. Considering the main antioxidant role of selenium, it has been thought to be useful in prevention and treatment of diseases which are related to increased oxidative stress including PCOS [7–9]. Also, selenium has been shown to act as an insulin-mimetic [10]. Based on previous studies, selenium can inhibit the expression of COX-2 and P-selectin [11] and by inhibition of inflammatory cytokines like TNF-a and IL-1, can improve insulin function [12]. Recently, lower concentrations of plasma selenium in PCOS patients when compared with healthy women, was reported [8]. Therefore, it seems

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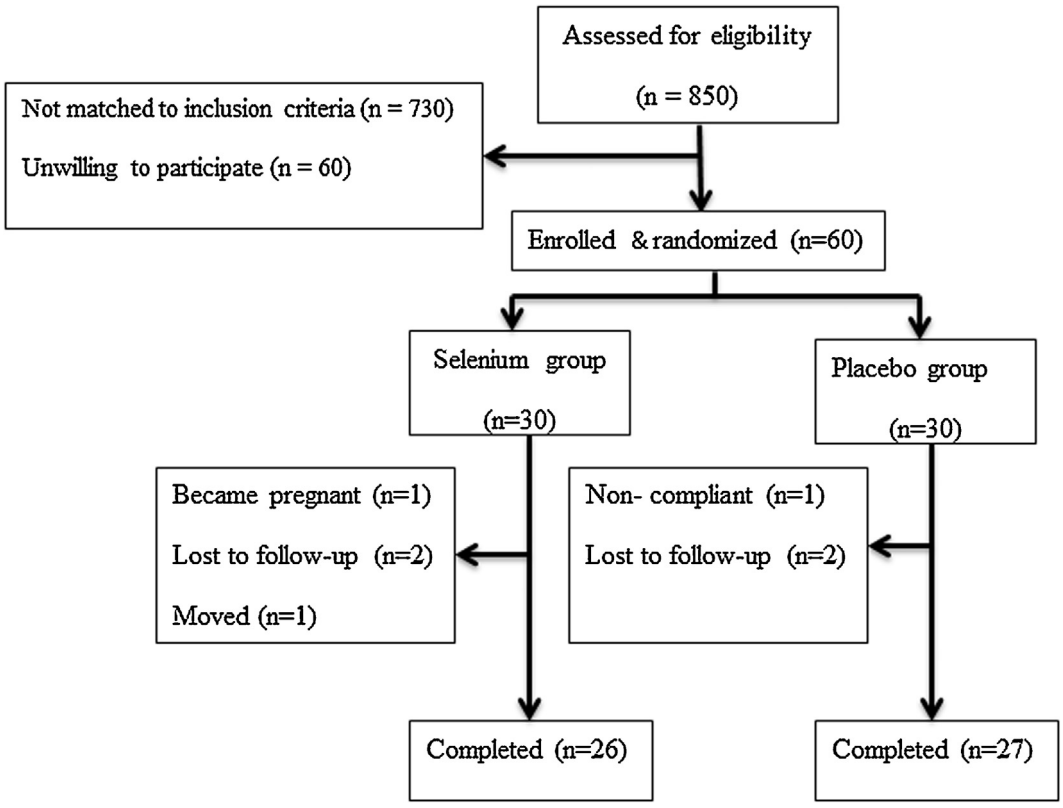

Fig. 1. Diagram representing flow of patients.
From 60 women who were enrolled in this study, 26 in selenium group and 27 in placebo group completed the trial. In selenium group, 4 patients discontinued the trial (1 became pregnant, 2 were lost to follow-up and one moved) and in placebo group 3 women did not complete the study (1 Non-compliant, 2 lost to follow up).

that selenium supplementation in these patients could be valuable. However, selenium has a narrow therapeutic window and the results of selenium supplementation in different patient groups are conflicting [7,13–15]. Data on the effect of selenium supplementation on glucose metabolism and free androgen index in PCOS patients are scarce, with only 2 studies identified [15,16]. Therefore, the present study was carried out. The main objective was to test the hypothesis that selenium supplementation can improve glucose homeostasis in PCOS patients. The effects of selenium on total testosterone, SHBG and free androgen index were considered as secondary outcomes.

2. Methods and materials

2.1. Study participants

The participants were selected from PCOS patients attending Valie-Asr Reproductive Health Research Centre of Tehran University of Medical Sciences (TUMS) according to inclusion criteria as follow: 18–45 years old women with diagnosed PCOS (based on Rotterdam criteria) that were inclined to participate in our study. On the basis of Rotterdam criteria PCOS is diagnosed if at least two of the following features are confronted [17]:

1. Ovulatory dysfunction: which is described by having eight or fewer menstrual periods in a year, or less than 26 days or more than 35 days interval between 2 menstrual period.
2. Clinical/biochemical hyperandrogenism.
3. Polycystic ovaries which are the presence of 12 or more follicle (2–9 mm) or an ovarian volume of more than 10 cm^3 on ultrasonography.

We excluded women who had congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors and hyperprolactinemia. Also participants with diabetes, hypo/hyperthyroidism, renal dysfunction, liver disease or cardiovascular disease were excluded from the study. Volunteers that were consuming any medications that affect their metabolic and hormonal profile (such as metformin, oral contraceptives, ovulation induction agents and corticosteroid drugs) and selenium supplement in the past 3 months and using tobacco were excluded. A total of 850 patients were screened and at the end 60 patients met the study criteria and were entered the study.

Sample size was calculated by the standard equation suggested for parallel clinical trials. To detect a change of 1.2 in the homeostasis model assessment of insulin resistance (HOMA-IR) as key variable by considering type one error (α) of 0.05 and type two error (β) of 0.20 (power = 80%), 25 women in each group were required. Based on a previous study standard deviation of 1.48 was assumed [18]. This study was approved by the ethical committee of Tehran University of Medical Sciences. All participants gave written informed consent. The trial was registered on Iranian Registry of Clinical Trial (Registration ID: IRCT2014110519813N1). The guidelines of the Declaration of Helsinki were followed in this study.

2.2. Study design

This study was a randomized, double blinded, placebo controlled clinical trial and was carried out from September 2014 to January 2015. The study population was 60 PCOS patients that were randomly allocated to the placebo or selenium groups using computer generated random number list. Randomization and allocation were concealed from the researchers and participants until