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Effects of selenium supplementation on glucose homeostasis, inflammation, and oxidative stress in gestational diabetes: Randomized, double-blind, placebo-controlled trial

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ABSTRACT

Objective: To our knowledge, no reports are available indicating the effects of selenium supplementation on metabolic parameters, inflammatory factors, and oxidative stress in gestational diabetes mellitus (GDM). The aim of this study was to assess the effects of selenium supplementation on metabolic status in pregnant women with GDM who were not on oral hypoglycemic agents.
Methods: This randomized, double-blind, placebo-controlled clinical trial was performed with 70 women with GDM. Patients were randomly assigned to receive either 200 μg selenium supplements as tablet (n = 35) or placebo (n = 35) for 6 wk from weeks 24 to 28 of gestation. Fasting plasma samples were taken at study baseline and after 6 wk of intervention to quantify related variables.
Results: Selenium supplementation, compared with placebo, resulted in a significant reduction in fasting plasma glucose (−10.5 ± 11.9 versus +4.5 ± 12.9 mg/dL; $P < 0.001$), serum insulin levels (−1.98 ± 11.25 versus +5.26 ± 9.33 μIU/mL; $P = 0.005$), homeostasis model of assessment (HOMA)-insulin resistance (−0.84 ± 2.76 versus +1.47 ± 2.46; $P < 0.001$) and a significant increase in quantitative insulin sensitivity check index (+0.008 ± 0.03 versus −0.01 ± 0.01; $P = 0.009$). Additionally, a significant decrease in serum high-sensitivity C-reactive protein (hs-CRP) levels (−791.8 ± 2271.8 versus +500.5 ± 2563.3 ng/mL; $P = 0.02$) was seen after the administration of selenium supplements compared with placebo. Additionally, we observed a significant elevation in plasma glutathione (+52.14 ± 58.31 versus −39.93 ± 153.52 μmol/L; $P = 0.002$) and a significant reduction in plasma malondialdehyde levels (−0.01 ± 0.36 versus +0.67 ± 1.90 μmol/L; $P = 0.04$) after consumption of selenium supplements compared with placebo. We did not find any significant effect of taking selenium supplements on HOMA β-cell function, lipid profiles, plasma nitric oxide, or total antioxidant capacity concentrations.
Conclusion: Selenium supplementation in pregnant women with GDM demonstrated beneficial effects on glucose metabolism, hs-CRP levels, and biomarkers of oxidative stress.

Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy that has been defined as impaired insulin metabolism and carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy [1]. Requirement for selenium is increased during pregnancy [2]. Selenium is involved in inhibiting the expression of

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cyclooxygenase (COX)-2 and P-selectin [3], therefore, its nutritional inadequacy during pregnancy might increase the risk for GDM. Mean serum levels of selenium are less than normal in healthy Iranian women [4]. On the other hand, the prevalence of GDM in Iranian pregnant women is 4.7% [5]. It is associated with short- and long-term health complications for the mother, fetus, and the neonate [6]. Additionally, previous studies have reported that hyperglycemia in patients with diabetes could result in increased oxidative stress and nitrosative stress [7]. Poor glycemic control in these patients has been associated with the depletion of serum antioxidant activity [8].

Several dietary [9,10] and nondietary [11,12] strategies have been proposed for management of GDM. Some studies have reported a significant inverse association between body selenium status and plasma glucose levels in patients with GDM [13,14]. Others have shown that selenium supplementation in pregnant women might result in decreased oxidative stress and improved pregnancy outcomes [15,16]. Dietary sources of selenium are nuts, cereals, meat, mushrooms, fish, and eggs [17]. Selenium is an important component of the enzymes that protect cells from the adverse effects of free radicals [18]. Selenium is also involved in the production of thyroid hormones and has been shown to contain anti-inflammatory effects [19]. Current data supports the beneficial effect of selenium on hypertension [20], coronary artery disease [21], certain cancers [22], and inflammatory diseases [23]. Others have examined the efficacy of selenium supplementation in cancers [24]. Some studies have indicated [25] a significant decrease in serum insulin levels and insulin resistance in centrally obese women after supplementation with 200 μg/d selenium added to a hypocaloric diet enriched with legumes; however, no significant effect on lipid profiles, inflammatory factors, and biomarkers of oxidative stress have been reported. Additionally, selenium supplementation has resulted in increased erythrocyte and plasma total antioxidant status (TAS), erythrocyte-reduced glutathione (GSH) and glutathione peroxidase (GPx) in patients with epilepsy and refractory epilepsy [26].

Selenium supplementation might affect glucose homeostasis, inflammation, and oxidative stress by inhibiting the production of advanced glycation end products [3] and decreased free radical production and lipid hydroperoxides [27]. Therefore, we hypothesized that selenium supplementation might affect the metabolic status of pregnant women with GDM. We are not aware of any studies that examined the effect of selenium supplementation on glucose homeostasis, lipid profiles, inflammatory factors, and biomarkers of oxidative stress in women with GDM. This study aimed to investigate the effect of selenium supplementation on the metabolic profile of women with GDM who were not on oral hypoglycemic agents (OHAs).

Materials and methods

Participants

This randomized, double-blind, placebo-controlled trial was conducted in Arak, Iran, from February to April 2014. For estimating sample size, we considered type 1 (α) and type 2 errors (β) of 0.05 and 0.20 (power = 80%), respectively, and homeostasis model of assessment-insulin resistance (HOMA-IR) as a key variable. Based on a previous study [25], SD of HOMA-IR was 0.4 and the difference in mean (d) of HOMA-IR was 0.3. We reached the sample size of 28 women for each group using the suggested formula for parallel clinical trials. In the present study, we included pregnant women, primigravida, ages 18 to 40 y who were carrying singleton pregnancies who had been diagnosed with GDM by "one-step" 2-h 75-g oral glucose tolerance test (OGTT) at 24 to 28 wk gestation. None of the participants were taking OHAs. Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment [28]. Pregnant women without a previous diagnosis of glucose intolerance were screened. Diagnosis of GDM was done based on the American Diabetes Association criteria [29]: Those whose plasma glucose met one of the following criteria were considered to have GDM: fasting ≥92 mg/dL, 1-h ≥180 mg/dL, or 2-h ≥153 mg/dL. In all, 1200 pregnant women attending maternity clinics affiliated with the Arak University of Medical Sciences, Arak, Iran, were screened for GDM. Seventy pregnant women met the inclusion criteria (1110 were excluded because they did not have GDM and 20 others were not included because they were diagnosed with GDM class A2, and required insulin therapy: fasting plasma glucose [FPG] >105 and blood sugar 2-h postprandial >120 mg/dL). Women with intrauterine fetal death (IUFD), premature preterm rupture of membrane (PPROM), placenta abruption, preeclampsia, eclampsia, chronic hypertension, hypo- or hyperthyroidism, urinary tract infection, smokers, and those with kidney or liver diseases or those taking estrogen therapy and stressful life conditions were not included in the present study. We excluded women who required commencing insulin therapy during intervention (FPG >105 and blood sugar 2-h postprandial >120 mg/dL). In all, 70 pregnant women were recruited in the present study and after stratification for preintervention body mass index (BMI; <30 and ≥30 kg/m^2) and weeks of gestation (<26 or ≥26 wk), they were randomly assigned to consume either selenium supplements (n = 35) or placebo (n = 35) for 6 wk. Random assignment was done by the use of computer-generated random numbers. Randomization and allocation were concealed from the researcher and participants until the main analyses were completed. A trained midwife at the maternity clinic did the randomized allocation sequence, enrolled participants, and assigned participants to interventions. The study was conducted according to the guidelines of the Declaration of Helsinki. The present study was approved by the ethics committee of Arak University of Medical Sciences and registered on the Iranian registry of clinical trials website (IRCT201403175623 N18). All participants provided informed written consent before recruitment.

Study design

Women were randomly assigned to take either 200 μg selenium supplements as tablet or placebo daily for 6 wk during weeks 24 to 28 of gestation. Selenium supplements and placebos were manufactured by Nature Made Pharmaceutical Company (Northridge, CA, USA) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. The appearance of the placebo, such as color, shape, size, and packaging, were identical to the selenium capsules. Selenium supplements and placebos were packed in identical packages and coded by the producer to guarantee blinding. Participants were asked not to alter their routine physical activity or usual dietary intakes throughout the study and not to consume any supplements other than the one provided to them by the investigators. All the women were also consuming 400 μg/d folic acid from the beginning of pregnancy and 60 mg/d ferrous sulfate from the second trimester. To assess compliance, participants were asked to bring the medication containers. Compliance was checked through counting unused capsules. To increase compliance, all patients received short messages on their cell phones reminding them to take the supplements daily. All participants provided three dietary records (one weekend day and two weekdays) and three physical activity records to ensure they maintained their usual diet and physical activity during the intervention. Both dietary and physical activity records were taken at weeks 2, 4, and 6 of the intervention. The dietary records were based on estimated values of household measurements. To obtain nutrient intakes of participants based on these 3-d food diaries, we used Nutritionist IV software (First Databank, San Bruno, CA, USA) modified for Iranian foods. After being diagnosed with GDM, the women were first instructed about a healthy diet; however, they were not given a specific menu and they were only participating in a nutritional education class that focused on the basics of healthy diet.

Assessment of anthropometric and biochemical variables

Data on prepregnancy weight and height (measured values) were taken from the women's preexisting medical records. A trained midwife at the maternity clinic performed the anthropometric measurements at study baseline and 6 wk after the intervention. Body weight was measured in an overnight fasting state, without shoes, and while minimally clothed by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretched tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. BMI was calculated as weight in kg divided by height in m^2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice with a 10-min interval between the two measurements via a sphygmomanometer (ALPK2, Zhejiang, China). The average of these two measurements was considered as the participant's final BP. As the intervention was completed at least 6 wk before expected delivery, required information on cesarean delivery, newborns' hyperbilirubinemia and newborns' weight, height, and head circumference were collected using data from their medical records at the center or the hospital.

At baseline and after 6 wk of intervention, 10 mL venous blood samples were taken after overnight fasting at Arak reference laboratory. FPG levels were measured on the day of blood collection. Blood samples were immediately