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The Effects of Selenium Supplementation on Gene Expression Related to Insulin and Lipid Metabolism, and Pregnancy Outcomes in Patients with Gestational Diabetes Mellitus: a Randomized, Double-Blind, Placebo-Controlled Trial

Maryam Karamali[1] · Fatemeh Dastyar[1] · Mohammad Hossein Badakhsh[1] · Esmat Aghadavood[2] · Elaheh Amirani[2] · Zatollah Asemi[2]

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Abstract

This study was performed to evaluate the effects of selenium supplementation on gene expression related to insulin and lipid metabolism, and pregnancy outcomes in patients with gestational diabetes mellitus (GDM). The current randomized, double-blind, placebo-controlled clinical trial was conducted in 36 patients with GDM. Participants were randomly divided into two groups to intake either 200 μg/day selenium supplements as selenium yeast or placebo ($n = 18$ each group) for 6 weeks. Selenium supplementation upregulated peroxisome proliferator-activated receptor gamma ($P = 0.03$) and glucose transporter 1 (GLUT-1) ($P = 0.01$) in lymphocytes of subjects with GDM compared with the placebo. Selenium supplementation did not affect gene expression of low-density lipoprotein receptor (LDLR) and lipoprotein(a) [Lp(a)]. Supplementation with selenium had a significant decrease in incidence of newborns' hyperbilirubinemia (5.6% vs. 33.3%, $P = 0.03$) and newborns' hospitalization (5.6% vs. 33.3%, $P = 0.03$) compared with the placebo. Overall, we found that selenium supplementation for 6 weeks among patients with GDM significantly increased PPAR-γ and GLUT-1 expression, but did not affect gene expression of LDLR and LP(a). It also reduced incidence of newborns' hyperbilirubinemia and newborns' hospitalization. Clinical trial registration number: http://www.irct.ir: IRCT20170513033941N35.

Keywords Selenium supplementation · Gestational diabetes mellitus · Gene expression · Pregnancy outcomes

Introduction

Gestational diabetes mellitus (GDM) is defined as newly recognized diabetes during pregnancy that is not clearly existed before [1]. It is a common endocrine disorder occurred in pregnant women. According to the epidemiological studies, the highest prevalence of GDM regardless of screening criteria belongs to East-Asia with a range of 11.1–11.7% and the lowest prevalence is attributed to Australia with a range of 3.6–3.7% [2]. Numerous evidence demonstrated that women with GDM have an elevated future risk of type 2 diabetes mellitus and cardiovascular disease [3]. Moreover, GDM is illustrated to be associated with increased risk of obstetrical consequences such as cesarean section, macrosomia, shoulder dystocia, birth injury, and prematurity [4]. In long term, the babies of mothers with GDM are prone to obesity and metabolic disorders [5]. In GDM women, dietary modification and glucose monitoring therapy as the primary therapeutic strategy is reported to reduce the risk of several adverse outcomes, including gestational hypertension and neonatal outcomes [6].

GDM is associated with lower selenium levels compared with normal glucose tolerance pregnant women [7]. In addition, based on the results of several animal studies, selenium deficiency is linked to altered expressed levels of genes related to insulin signaling, inflammation, and lipid metabolism such as peroxisome proliferator-activated receptor-γ (PPAR-γ) and low-density lipoprotein receptor (LDLR) [8]. Some evidence emphasize on the role of inappropriate mRNA transcript levels of these genes and others involved in glucose and lipid homeostasis in pregnancies complicated by GDM [9, 10].

✉ Zatollah Asemi
asemi_r@yahoo.com

[1] Department of Gynecology and Obstetrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

[2] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

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Previously, a meta-analysis indicated that selenium supplementation improved insulin levels and insulin sensitivity in patients with metabolic disorders, while did not affect other measurement of glycemic control and serum lipids [11]. Few studies have investigated the effects of selenium supplementation on expression levels of genes related to carbohydrate and lipid metabolism. Earlier, we verified that an 8-week selenium supplementation at a dosage of 200 μg/day to women with polycystic ovary syndrome (PCOS) who were candidate for in vitro fertilization (IVF) improved mRNA transcript levels of PPAR-γ and glucose transporter 1 (GLUT-1), and downregulated LDLR expression, while did not improve lipoprotein(a) [LP(a)] expression [12]. There are several animal studies showing selenium administration improved gene expression of GLUT-4, insulin receptor substrate-1 (IRS-1), and PPAR-γ [13, 14]. In addition, some studies have been conducted regarding the effectiveness of selenium supplementation on pregnancy complications. A meta-analysis conducted by Xu et al. [15] elucidated that selenium supplementation to pregnant women significantly decreased the incidence of preeclampsia. Moreover, it was observed that low selenium status during pregnancy is associated with miscarriage [16] and preterm delivery [17]. However, taking selenium supplements at a dosage of 200 μg/day by HIV-infected pregnant women between 12 and 27 weeks of gestation until 6 months after delivery did not favorably influence pregnancy outcomes [18].

Selenium is capable of alleviating inflammatory response via the inhibition of nuclear factor kappa B (NF-κβ), toll-like receptors (TLR), and mitogen-activated protein kinases (MAPK) p38 pathways and by which modulate the expression levels of PPAR-γ and reduce insulin resistance [19]. In addition, it can counteract reactive oxygen species and free radicals by its antioxidant activity and may reduce oxidative damage associated with pregnancy [20]. Therefore, the present study is aimed to examine the effects of selenium supplementation on gene expression related to insulin and lipid metabolism, and pregnancy outcomes in GDM women.

Methods

Trial Design and Participants

This study, registered in the Iranian website for clinical trials (http://www.irct.ir: IRCT20170513033941N35), was a randomized, double-blind, placebo-controlled clinical trial. The current study was conducted in 36 patients with GDM class A1 that needed diet therapy at 24–28 weeks' gestation referred to the Akbarabadi Clinic in Tehran, Iran, between July 2018 and March 2019. The investigation was performed in accordance with the Declaration of Helsinki and informed consent was taken from all participants. The study was approved by the ethics committee of Iran University of Medical Sciences (IUMS). Eligible subjects were primigravida, aged 18–40 years who were diagnosed with GDM by a "one-step" 2-h 75-g oral glucose tolerance test. Diagnosis of GDM was done based on the criteria of the American Diabetes Association [21]: those whose plasma glucose met one of the following criteria were considered as having GDM: fasting ≥ 92 mg/dL, 1-h ≥ 180 mg/dL, or 2-h ≥ 153 mg/dL. Subjects with clinical characteristics at enrollment such as thyroid disorders, smokers, preeclampsia, eclampsia, those with kidney or liver diseases, and required commencing insulin therapy during intervention, taking selenium supplements or other antioxidants 3 months before the intervention were our exclusion criteria.

Study Design

Participants were randomly allocated into two groups to receive either 200 μg selenium as selenium yeast free other supplements such as zinc and copper (Nature Made, California, USA) ($n = 20$) or placebo (Barij Essence, Kashan, Iran) ($n = 20$) per day for 6 weeks. Selenium supplements and placebos (cellulose) tablets were identical in shape and size. Although the duration of intervention was 6 weeks, all patients were followed up until the end of pregnancy. Patients were requested not to change their routine physical activity or usual diets throughout the study and not to take any antioxidant medications or supplements that might affect their nutritional status during the 6-week intervention. Randomization assignment was conducted using computer-generated random numbers. Allocation concealment and randomization were conducted by the researchers and patients and were done by a trained staff at the gynecology clinic. Consumption of selenium supplements and placebos throughout the study was checked through asking subjects to return the medication containers. Furthermore, a short message was sent to the cell phones of all patients every day to remind participants to use the supplements. A 3-day food record at weeks 0, 3, and 6 of the intervention was completed by all participants using Nutritionist IV software (First Databank, San Bruno, CA) modified for Iranian foods. A trained staff at the clinic took anthropometric measurements at baseline and after the 6-week intervention. Body weight was quantified after an overnight fast using a digital scale (Seca, Hamburg, Germany). Polyhydramnios was diagnosed using the sonographic estimation method at end-of-trial. On the basis of this measurement, polyhydramnios was defined as an amniotic fluid index (AFI) in excess of 25 cm [22]. Newborns' hyperbilirubinemia was considered when the total serum bilirubin levels were at 15 mg/dL or more among infants who were 25 to 48 h old, 18 mg/dL in infants who were 49 to 72 h old, and 20 mg/dL in infants older than 72 h [23].

Assessment of Outcomes

Gene expression of PPAR-γ was considered as the primary outcome and gene expression of GLUT-1, LDLR, LP(a), and pregnancy outcomes was considered as the secondary outcomes.

Isolation of Lymphocyte

At baseline and after the 6-week intervention, 15 mL fasting blood samples were collected in the anticoagulant ethylenediaminetetraacetic acid tubes. Then, lymphocytes were extracted from blood samples of subjects with GDM at Akbarabadi reference laboratory, Tehran, Iran, using 50% percoll solution (Sigma-Aldrich, Dorset, UK) by centrifugation for 20 min and 3000 rpm at 4 °C. The cells of lymphocytes which were at the interface of percoll and serum were removed using a pasteur pipette and washed a few times with phosphate buffer saline [24]. Samples were taken for cell count and viability testing by trypan blue, RNA, and DNA extraction [24].

Total RNA Extraction

To RNA extraction, the RNX-plus (Cinnacolon, Tehran, Iran) was used. Total RNA was isolated from all samples according to recommended protocol by manufacture. The total RNA was precipitated at room temperature for 15 min. The pellet including total RNA was washed using 75% ethanol and centrifuge at 7500*g* for 8 min. After drying ethanol, the RNA pellet resuspended in 50 μl or less of TE buffer. The concentration of total RNA was calculated based on OD 260/280 ration measurements as a means to address purity of RNA [24]. Following the extraction of the total RNAs from each sample, RNA quantification was performed by UV spectrophotometer. Each sample OD 260/280 ratio between 1.7 and 2.1 was intended that shows no contamination with both protein and DNA [24]. The first-strand cDNA synthesis can be performed as an individual reaction or as a series of parallel reactions with different RNA templates [24]. The isolated RNA was reverse transcribed to cDNA library using moloney murine leukemia virus reverse transcriptase. Reverse transcription was performed with random primers.

Gene Expression

Gene expression of PPAR-γ, GLUT-1, LDLR, and LP(a) was evaluated by quantitative RT-PCR in lymphocytes, using the LightCycler technology (Roche Diagnostics, Rotkreuz, Switzerland) with SYBR green detection and Amplicon Kit (Table 1). Glyceraldehyde-3-phosphate dehydrogenase primers were applied as housekeeping gene. As template, approximately 50 ng cDNA was applied in a quantitative real-time RT-PCR, and the signals were detected using a real-time PCR system. To design primers, Primer Express Software (Applied Biosystems, Foster City) and Beacon designer software (Takaposizt, Tehran, Iran) were used. Relative transcription values were calculated by the method of Pffafi.

Statistical Analyses

Using a formula suggested for clinical trials, having 17 subjects in each group were adequate while considering a type one error (α) of 0.05 and type two error (β) of 0.20 (power = 80%), 0.150-fold change as SD and 0.145-fold change as the mean distinction (d) of gene expression of PPAR-γ as a primary outcome [12]. Assuming 20% dropouts in each group, the final sample size was determined to be 20 patients in each group.

To confirm whether the study variables had normally distributed or not, we used the Kolmogorov-Smirnov test. To detect changes in anthropometric measures, dietary intakes, gene expression related to insulin and lipid, and pregnancy outcomes between the two groups, we used independent samples t test. The P value of < 0.05 was considered statistically significant. All statistical analyses used the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

Among individuals in the selenium and placebo groups, two persons due to personal reasons were excluded (Fig. 1). Finally, 36 participants (18 in each group) completed the trial. The compliance rate in our study was high; participants reported that more than 90% of selenium and placebo capsules was consumed during the course of the trial. No side effects were reported following the intake of selenium in patients with GDM throughout the study.

Mean age, height, weight, and BMI at baseline as well as mean weight and BMI after intervention were not statistically different between the two groups (Table 1). Supplementation with selenium had a significant decrease in incidence of newborns' hyperbilirubinemia (5.6% vs. 33.3%, $P = 0.03$) and newborns' hospitalization (5.6% vs. 33.3%, $P = 0.03$) compared with the placebo (Table 2). We did not find a significant difference in polyhydramnios, gestational age, cesarean section rate, need of insulin therapy after intervention, maternal hospitalization, newborn's birth size, and Apgar scores when comparing the two groups (data not shown).

Based on the 3-day dietary records obtained throughout the trial, we observed no significant change in dietary macro- and micronutrient intakes (data not shown).

Selenium supplementation upregulated gene expression of PPAR-γ ($P = 0.03$) and GLUT-1 ($P = 0.01$) in lymphocytes of subjects with GDM (Fig. 2).

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
PPAR-γ	F: ATGACAGACCTCAGACAGATTG R: AATGTTGGCAGTGGCTCAG	210	54
GLUT-1	F: TATCTGAGCATCGTGGCCAT R: AAGACGTAGGGACCACACAG	238	62.1
LDLR	F: ACTTACGGACAGACAGACAG R: GGCCACACATCCCATGATTC	223	57
Lp(a)	F: GACACAGCACGTTCATTCCA R: ACACCCCCCTACAATGCTTC	200	55

GAPDH, glyceraldehyde-3-phosphate dehydrogenase; *GLUT-1*, glucose transporter 1; *Lp(a)*, lipoprotein(a); *LDLR*, low-density lipoprotein receptor; *PPAR-γ*, peroxisome proliferator-activated receptor gamma

Selenium supplementation did not affect gene expression of LDLR ($P = 0.64$) and Lp(a) ($P = 0.43$) in lymphocytes of subjects with GDM (Fig. 3).

Discussion

In the present study, we examined the effects of 6-week selenium supplementation on gene expression related to insulin and lipid metabolism, and pregnancy outcomes in women with GDM. We found that selenium supplementation significantly improved PPAR-γ and GLUT-1 expression, but did not affect gene expression of LDLR and LP(a). It also improved few pregnancy outcomes including newborns' hyperbilirubinemia and newborns' hospitalization.

Effects on Gene Expression

GDM is accompanied by disturbances in maternal metabolism which interference with the placental metabolism and affects fetal outcomes [25]. The results of current study indicated that selenium supplementation upregulated PPAR-γ and GLUT-1

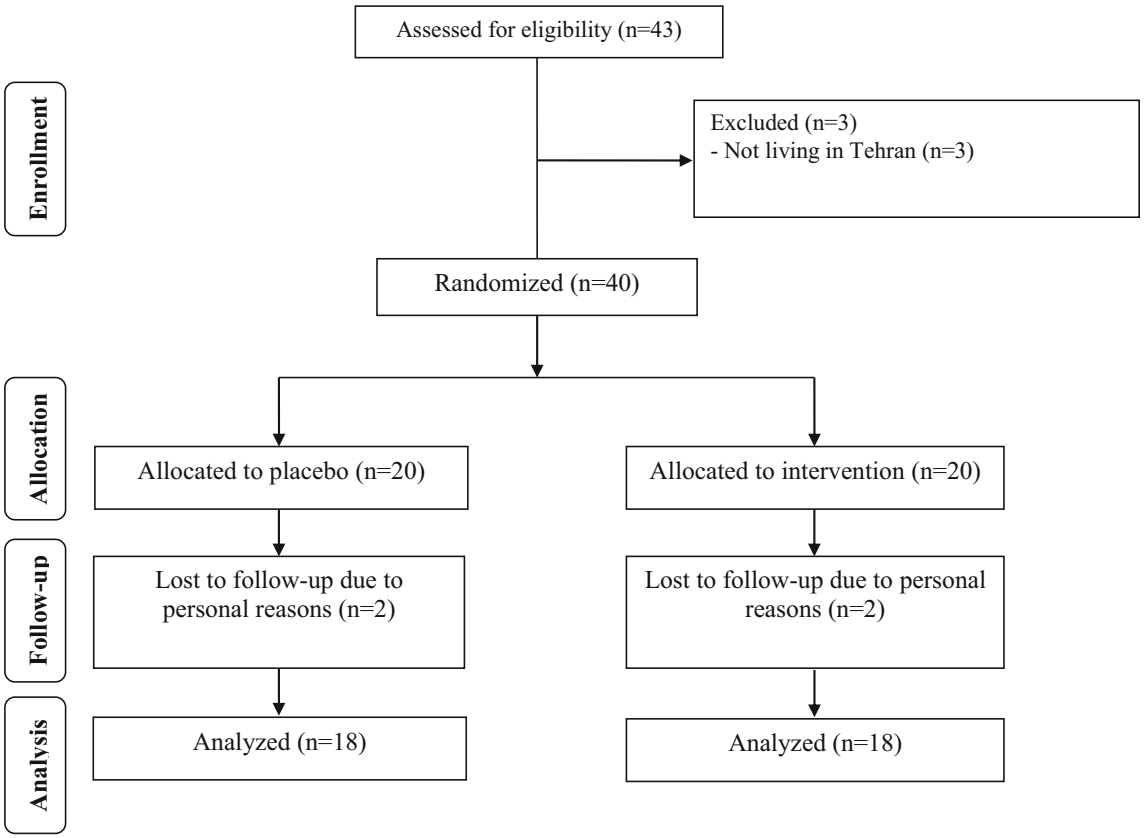

Fig. 1 Summary of patient flow diagram

Table 2 General characteristics of study participants and pregnancy outcomes

	Placebo group ($n = 18$)	Selenium group ($n = 18$)	P^1
Age (years)	29.5 ± 3.9	28.0 ± 4.1	0.26
Height (cm)	160.1 ± 3.2	162.1 ± 6.0	0.22
Weight at study baseline (kg)	67.4 ± 9.1	65.9 ± 11.0	0.68
Weight at end-of-trial (kg)	70.1 ± 9.3	68.5 ± 10.9	0.65
BMI at study baseline (kg/m^2)	26.3 ± 3.4	25.1 ± 3.6	0.30
BMI at end-of-trial (kg/m^2)	27.3 ± 3.4	26.0 ± 3.5	0.27
Pregnancy outcomes			
Newborns' weight (g)	3340.0 ± 462.4	3266.1 ± 436.3	0.62
Newborns' length (cm)	51.3 ± 2.6	49.8 ± 4.0	0.20
Newborns' head circumference (cm)	35.3 ± 1.3	35.0 ± 1.1	0.32
Newborns' hyperbilirubinemia (%)	6 (33.3)	1 (5.6)	0.03†
Newborns' hospitalization (%)	6 (33.3)	1 (5.6)	0.03†

Data are means ± SDs

[1] Obtained from independent *t* test

[†] Obtained from the Pearson chi-square test

expression, while unchanged LDLR and LP(a) expression. Consistent with the results of present study, a 16-week selenium administration in mice led to an elevated gene expression levels of PPAR-γ and GLUT-2 [13]. In addition, Xu et al. [26] reported that a 4-week selenium supplementation (selenium selenite) at a dosage of 180 μg/kg/day combined with low-dose insulin improved blood glucose and HbA1c levels, and increased gene expression of GLUT-4. Moreover, our previous research showed that 200 μg/day selenium supplementation for 8 weeks in women with PCOS candidate for IVF upregulated mRNA transcript levels of PPAR-γ and GLUT-1, and decreased LDLR, but did not affect gene expression of LP(a) [12]. In contrast to our findings about the effects of selenium supplementation on gene expression levels of LP(a), an observational study by Alissa et al. [27], there was a significant association between selenium status and serum Lp(a) values in healthy adult males. Uncontrolled glucose and lipid profiles in pregnant women are associated with adverse clinical consequences for mother and infant [28]. PPAR-γ is a member of a family of nuclear hormone receptors. Activation of PPAR-γ involved in insulin sensitivity, glucose homeostasis, lipid metabolism, adipogenesis, and inflammation [29]. Decreased circulating or mRNA transcript levels of PPAR-γ have been implicated in pregnancies complicated by GDM, preeclampsia, and intrauterine growth restriction. It has been suggested that PPAR-γ may act as a regulator of maternal metabolism and immune function in normal pregnancy. In addition, due to the role in vascular function, it is essential for the progression of a healthy pregnancy [30]. On the other hand, animal studies indicated that GLUT-1 deficiency may play a key role in the incidence of fetal malformations resulting from the hyperglycemia of maternal diabetes [31]. Selenium supplementation inhibits the activity of NF-κβ, TLR, and p38MAPK. It has been suggested that the inhibition of these inflammatory pathways leads to an increase in gene expression levels of PPAR-γ [19, 32]. In addition, GLUT-1 expression is inversely related to extracellular glucose concentrations [33]; therefore, the improvement of glucose homeostasis by selenium may be due to increased gene expression of GLUT-1.

Effects on Pregnancy Outcomes

According to findings of present study, selenium supplementation in women with GDM led to a significant reduction in newborns' hyperbilirubinemia and newborns' hospitalization. Previously, it is reported that dietary selenium intake during pregnancy was negatively correlated with indices of central adiposity in neonate, while it was not associated with birth weight [34]. In addition, 200 μg/day selenium supplementation in HIV-infected gestational women between 12 and 27 weeks of pregnancy until 6 months after delivery did not improve preterm birth, newborns' head circumference and length, and other pregnancy complications [18]. In another study by Bermudez et al. [35], selenium concentrations in both umbilical cord and maternal blood were not related to birth weight from small for gestational age to large for gestational age babies of healthy mothers. In addition, in the present study, we failed to find a significant effect of selenium supplementation on the rate of preeclampsia in GDM mothers. In contrast to our findings, a meta-analysis by Xu et al. [15] indicated that selenium supplementation during pregnancy decreased the risk of preeclampsia. Prior evidence demonstrated that macrosomia is associated with increased perinatal mortality and neonatal morbidity. It also elevates the risk of cesarean section, birth trauma, and shoulder dystocia [36]. Hence,

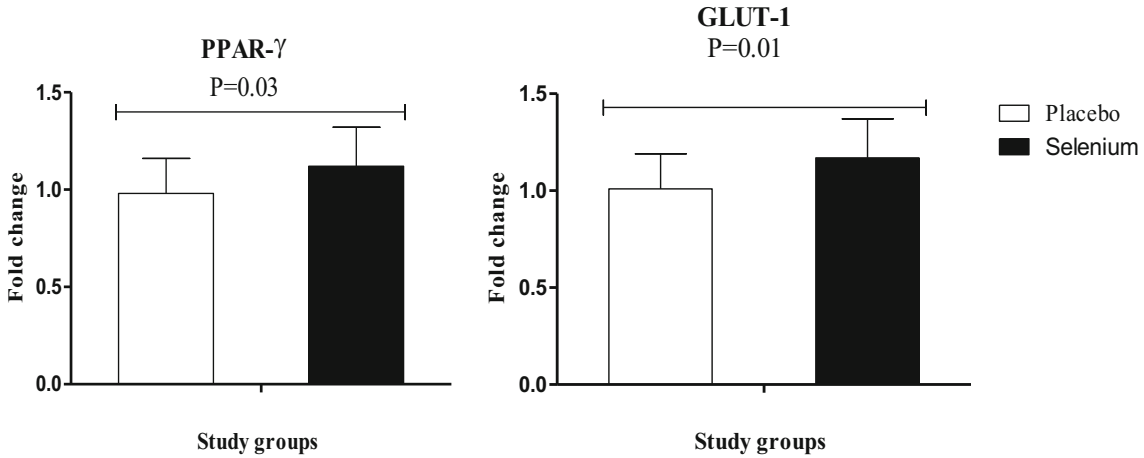

Fig. 2 Fold change (means ± SDs) in gene expression levels of PPAR-γ and GLUT-1 in women with GDM who were received selenium supplements and placebo. *P* value was obtained from independent *t* test. *N* = 18 in each group

reduction in the risk of macrosomia is implicated in long-term health of mother and infant. It is well established that maternal metabolism is a major determinant of placental metabolism, intrauterine environment, and fetal outcomes [25]. In pregnancies affected by diabetes, maternal hyperglycemia and hyperinsulinemia exacerbate the transfer of glucose to fetus and increase fetal overgrowth. In addition, maternal diabetes leads to several alternations in placenta structure and function which ultimately change the nutrient delivery to fetus [37].

In the present study, we observed that selenium supplementation to pregnant women with GDM decreased the rate of infant hyperbilirubinemia. It has been proposed that newborns' hyperbilirubinemia may be a result of depleted antioxidant enzymes and increased oxidative stress during pregnancy which increase radical generation and lipid peroxidation of erythrocyte membrane which finally leads to hemolysis and increased bilirubin levels in neonate [38]. Several studies reported that selenium levels or other antioxidants in neonatal with hyperbilirubinemia were significantly lower than the control group [39, 40]. One mechanism regarding the potential role of selenium supplementation in reducing adverse pregnancy outcomes such as infant hyperbilirubinemia is explained by its antioxidant activity which is applied through the incorporation in the synthesis of glutathione peroxides, selenoprotein P, and thioredoxin reductase [41].

The current study had a few limitations. Due to limited funding, we did not evaluate the effects of selenium supplementation on serum or urine selenium and glutathione peroxidase. In addition, sample size was low. Further studies are needed to confirm our findings with higher sample size.

Conclusions

Overall, we found that selenium supplementation significantly increased PPAR-γ and GLUT-1 expression, but did not affect gene expression of LDLR and LP(a). It also improved few

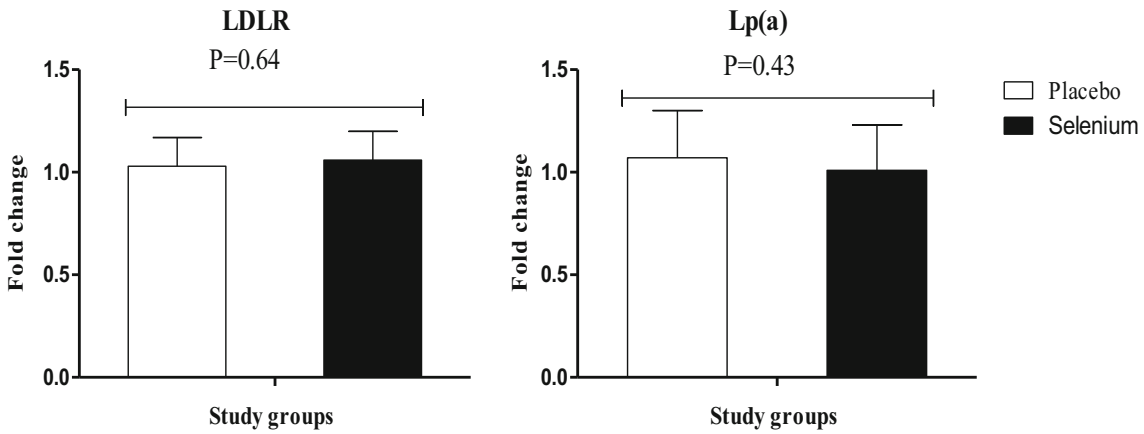

Fig. 3 Change (means ± SDs) in gene expression levels of LDLR and Lp(a) in women with GDM who were received selenium supplements and placebo. *P* value was obtained from independent *t* test. *N* = 18 in each group. GDM, gestational diabetes mellitus; GLUT-1, glucose transporter 1; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein(a); PPAR-γ, peroxisome proliferator-activated receptor gamma

pregnancy outcomes including newborns' hyperbilirubinemia and newborns' hospitalization.

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Author Contributions ZA: Conception, design, and statistical analysis, drafting of the manuscript and supervised the study.

MK, FD, M-HB, EA, and EA: data collection and manuscript drafting.

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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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