Prev. Nutr. Food Sci. 2023;28(2):121-133
https://doi.org/10.3746/pnf.2023.28.2.121
ISSN 2287-8602

Review

Effect of Selenium Supplementation on Biochemical Markers of Women with Polycystic Ovarian Syndrome: A Systematic Review

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ABSTRACT: Polycystic ovary syndrome (PCOS) is a widespread endocrine disorder among fertile women and may be induced by nutritional deficiencies. In this study, we assess the impact of selenium supplementation (SS) on biochemical markers in women with PCOS. To gather relevant literature, we searched the Web of Science, Cochrane Library, Scopus, Embase, and MEDLINE databases from inception up to July 24, 2022. Subsequently, we included all published full-text randomized clinical trials examining the effects of SS versus placebo on biochemical changes in women with PCOS. Review Manager 5.3 was used to collect and analyze data and assess the risk of bias. Seven articles, comprising 413 women, were ultimately involved in the study. According to the results, SS could increase the level of quantitative insulin sensitivity check index [standardized mean difference (SMD)=0.34, 95% confidence interval (CI)=0.04∼0.65], total antioxidant capacity (SMD=0.89 mmol/L, 95% CI=0.52∼1.26), and glutathione (SMD=1.00 μmol/L, 95% CI=0.22∼1.78). Conversely, SS could decrease triglyceride, cholesterol, fasting plasma glucose, insulin, and the homeostasis model of assessment-insulin resistance levels compared with the placebo. Furthermore, there were no significant differences regarding sex hormone-binding globulin level, testosterone level, malondialdehyde, and body mass index between the two groups. In addition, the results suggest that SS improves biochemical markers in women with PCOS and thus is recommended for treating biochemical disorders among these women in addition to standard treatment.

Keywords: biomarkers, dietary supplements, polycystic ovary syndrome, selenium, systematic review

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a widespread endocrine and metabolic disorder among fertile-aged women (Escobar-Morreale, 2018). The prevalence of PCOS varies depending on the criteria used for its diagnosis. According to the Rotterdam criteria, for example, the prevalence of PCOS among adolescents was reported to be 11.04% around the world (Naz et al., 2019) and projected to be between 3% and 7% among the whole Iranian population (Ghiasi, 2019). PCOS is a heterogeneous disorder with signs and symptoms of hyperandrogenism and ovarian dysfunction (Escobar-Morreale, 2018). These signs and symptoms include subfertility, irregular menstrual cycles, oligoanovulation during reproductive life, and increased possibility of complications during pregnancy, such as gestational diabetes, preeclampsia, intrauterine growth restriction, and cesarean delivery. Other symptoms that may be present in PCOS include hirsutism, acne, and alopecia, which are symptoms of hyperandrogenism, along with insulin resistance and hyperinsulinemia due to obesity (Escobar-Morreale, 2018; Meier, 2018; Louwers and Laven, 2020). Due to these signs and symptoms, women with PCOS often experience a lower quality of life (Upadhyaya et al., 2016; Greenwood et al., 2018). According to Chaudhari et al. (2018), the prevalence of anxiety and depression in women with PCOS was 38.6% and 25.7%, respectively. Studies have found an association between infertility and alopecia in women with PCOS, and anxiety and acne have also been associated with depression in these women (Chaudhari et al., 2018). Additionally, researchers have reported that women with hirsutism experience a lower psychological quality of life (Kolhe et al., 2022).

Received 25 January 2023; Revised 15 April 2023; Accepted 17 April 2023; Published online 30 June 2023
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Unfortunately, PCOS has no definitive cure. It is a lifelong disorder that must be treated individually and based on the real needs of affected women, and in most cases, the treatment is symptom-oriented (Escobar-Morreale, 2018; Aversa et al., 2020). When the first-line treatment approach alone, which is health behavior modification (diet and/or physical activity), cannot improve the signs and symptoms of PCOS, medical treatment is usually recommended. Exercise and low-glycemic-index diets can reduce triglycerides, fasting insulin, total cholesterol, total testosterone, waist circumference, low-density lipoprotein, and homeostasis model of assessment-insulin resistance (HOMA-IR) in women with PCOS (Kite et al., 2019; Szczuko et al., 2021). Nutrition-related signaling pathways contribute significantly to regulating ovarian follicle growth and ovulation rate (Yu et al., 2011). Additionally, different nutrients contribute to the regulation of the insulin signaling pathway and androgen synthesis (Günalan et al., 2018). As previously mentioned, the cause of PCOS is unknown, and polygenic causes and environmental factors contribute to its development (Escobar-Morreale, 2018). Previous research has suggested that a lack of vitamins or minerals could also contribute to PCOS. Furthermore, recent studies have recommended the use of nutritional supplements such as vitamins and minerals to treat PCOS because they contribute to the etiology and occurrence of PCOS. These include vitamins A, B group, D, and E, as well as inositol, calcium, chromium, magnesium, selenium, and probiotics (Szczuko et al., 2016; Günalan et al., 2018; Ghanei et al., 2018).

One of the minerals that has been investigated for its effect on PCOS symptoms is selenium. Selenium, along with selenocysteine and selenomethionine, has a biological function in the body such as regulating thyroid function and strengthening fertility (Mojadadi et al., 2021). Also, these substances have antioxidant properties and anti-inflammatory effects (Hariharan and Dharmaraj, 2020). Inflammation is a strong risk factor for PCOS (Abraham Gnanadass et al., 2021). Selenium also has metabolic functions, including regulating carbohydrate metabolism (Solovyev et al., 2019). Jamilian et al. (2015) found that an 8-week selenium supplementation (SS) program (200 μg/d) resulted in reduced levels of serum insulin, HOMA-IR, serum triglycerides, and very low-density lipoprotein. However, compared with the placebo, this intervention elevated the quantitative insulin sensitivity check index (QUICKI) (Jamilian et al., 2015). Mohammad Hosseinzadeh et al. (2016) showed that insulin resistance increased after 12 weeks of SS (200 μg/d), but there was no change in other laboratory markers. Several studies, including one systematic review, have investigated the impact of SS on biomarkers in women with PCOS (Wu et al., 2022); however, there is still a paucity of information in this regard. In Wu et al.'s (2022) meta-analysis involving five randomized controlled trials (RCTs), no biochemical marker was investigated. Conversely, they used the mean difference (MD) before and after the intervention to evaluate the impact of selenium on biochemical markers. In this study, the impact of SS on biochemical symptoms in women with PCOS, who were divided into intervention and control groups, was assessed. Participants who received selenium made up the intervention group, while those who were given the placebo comprised the control group.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) of RCTs (Moher et al., 2009) in the design and implementation of this study.

Inclusion criteria

***Type of studies*:** All published full-text RCTs investigating the impact of SS versus placebo on biochemical changes among women with PCOS were included in this review. However, we excluded conference abstracts, unpublished RCTs, quasirandomized trials, and observational studies.

***Type of participants*:** Only fertile-aged women diagnosed with PCOS according to the Rotterdam criteria were included in this review. Participants with diseases similar to PCOS, such as congenital adrenal hyperplasia, thyroid disease, hyperprolactinoma, Cushing's syndrome, or androgen-secreting tumors, were excluded.

***Type of interventions*:** Trials that evaluated any dose of selenium alone, combined with probiotics versus placebo, or with no intervention were considered eligible for inclusion.

***Type of outcomes measured*:** The primary outcomes of this study were endocrine hormones such as testosterone and sex hormone-binding globulin (SHBG). Secondary outcomes were lipid profile, glucose hemostasis, and biomarkers of oxidative stress.

Search approaches for identification of studies

The Cochrane Library (Central), Web of Science, Scopus, Embase, and MEDLINE databases were searched from inception up to July 24, 2022. In addition, we hand-searched the references of the selected studies to locate other potentially eligible studies. Some of the MeSH terms used were "women" OR "Woman" OR "Women's Groups" OR "Women's Group" AND "selenium supplements" OR "Aqueous Selenium" OR "Oceanic Selenium" OR "Se Aspatate" OR "Selenimin" OR "selenium TR" OR "Sele-Pak" AND "clinical and biochemical symptoms" OR "symptoms" OR "Signs" AND "polycystic ovary syndrome" OR "Polycystic Ovarian Syndrome".

Data collection and analysis

Data were collected and analyzed following the Cochrane Handbook for Systematic Reviews of Interventions. Two research team members (SFS and RK) screened the study titles and abstracts. To check the eligibility of the studies, the same authors independently assessed the full text of all studies that potentially met the inclusion criteria. Consensus and discussion with the third author (PA) resolved any disagreements.

Data extraction was conducted independently by the two mentioned authors based on the designed data extraction forms, and the differences in the extracted data were resolved by consensus between the authors.

The extracted data included information such as the author's name, publication year, study location, study methods, participants, diagnosis criteria, participants' age, body mass index (BMI), number of women in each group, and the type of intervention received. If a difference existed in the measurement units of the laboratory tests, the ENDMEMO website was used to convert the units.

Assessing the risk of bias

The risk of bias in the selected studies was evaluated using the Review Manager (RevMan) software (Cochrane) according to the Cochrane risk of bias tool. The two authors (SFS and RK) independently assessed seven areas of selection bias: sequence generation, allocation concealment, performance bias, detective bias, attrition bias, reporting bias, and other potential sources of bias. We discussed any conflicts with the third author (PA).

Data synthesis and measurement of the treatment effect

Data management and analysis were conducted using RevMan 5.3. The combined data from primary studies were initially analyzed using a fixed-effect model. For continuous data, the mean and SD and the number of participants in the control and selenium groups were used to calculate the MD or standardized mean difference (SMD) between the groups if the results were reported based on the same or different criteria, respectively. For dichotomous data, the number of events and participants were used to calculate the odds ratio. For all outcomes, $P<0.05$ was considered statistically significant.

Assessment of heterogeneity and subgroup analysis

For this analysis, I^2 less than 25% indicated low heterogeneity, I^2 between 25% and 50% represented moderate heterogeneity, and I^2 over 50% showed a high level of heterogeneity (Higgins and Thompson, 2002). To evaluate heterogeneity between studies, a random-effects model and chi-square tests were used. Forest plots were examined for evidence of heterogeneity based on the weight of the studies. Sensitivity analysis were conducted where possible to examine the causes of heterogeneity. We conducted sensitivity analysis by sequentially removing a single study to test its contribution to heterogeneity in the meta-analysis. We conducted a subgroup analysis based on the intervention duration (12 weeks vs. 8 weeks).

RESULTS

The database search yielded 888 articles. After removing duplicates (n=72), 816 articles were screened, of which nine full-text articles were evaluated for eligibility. At this stage, we excluded two more papers from the study due to duplicate data (Badehnoosh et al., 2018) and wrong outcomes (Heidar et al., 2020). Finally, seven articles were selected for the quantitative and qualitative analysis (Jamilian et al., 2015; Mohammad Hosseinzadeh et al., 2016; Razavi et al., 2016; Jamilian et al., 2018; Shabani et al., 2018; Rashidi et al., 2020; Zadeh Modarres et al., 2022). The study flow diagram of the search and selection process is shown in Fig. 1.

Characteristics of the studies

The reviewed studies were all randomized, double-blind, placebo-controlled trials published between 2015 and 2022. The total number of participants in these studies was 413 women with PCOS, of whom 207 received the intervention, and 206 were given placebos. Sample sizes ranged from 40 to 100 in each study. Table 1 shows the characteristics of the articles involved in the meta-analysis. All selected articles were conducted in Iran and used the Rotterdam criteria for PCOS diagnosis. The mean age of participants was 27.07±4.42 years. In two studies, the intervention group received selenium plus probiotic supplements (Jamilian et al., 2018; Shabani et al., 2018). However, the intervention group in other studies received selenium alone. The dose received in all trials was 200 μg/d for 8 or 12 weeks.

The quality assessment of the papers was conducted by the two reviewers (SFS and RK) according to the Cochran Risk of Bias tool using RevMan software. Fig. 2 shows the risk of bias in the selected articles, which showed no attrition or reporting biases. Twenty-five percent of the studies did not adequately explain the randomization method, allocation concealment, and blinding of the participants and personnel and were categorized as unclear.

Primary outcome measures

***SHBG level*:** Three studies (Mohammad Hosseinzadeh et al., 2016; Jamilian et al., 2018; Rashidi et al., 2020), which comprised 189 participants and measured the SHBG level, were involved in the meta-analysis. The results showed that the SHBG level was significantly higher in the selenium group than the placebo group in these studies

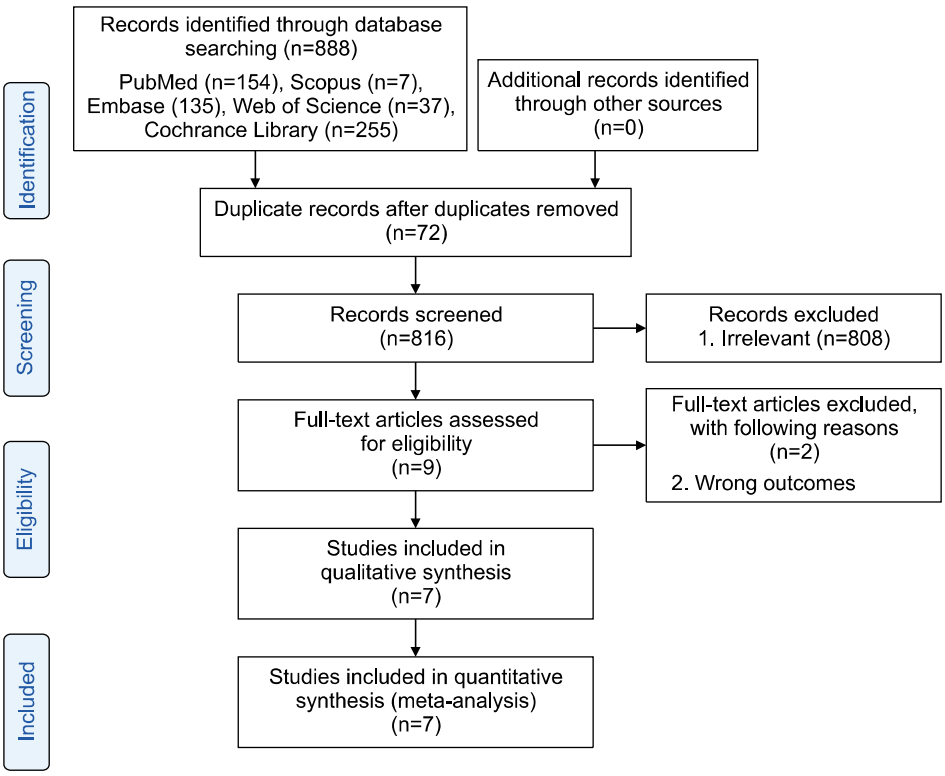

Fig. 1. Flow chart of the literature search process.

[SMD=0.50 nmol/L, 95% confidence interval (CI)=0.20 ~0.80, I^2=55%; Fig. 3]. After removing one paper, the heterogeneity reached 0%, and the intervention and control groups were not significantly different regarding SHBG level (SMD=0.31 nmol/L, 95% CI=−0.04~0.66, I^2=0%, data not shown).

***Total testosterone level*:** Three papers (Mohammad Hosseinzadeh et al., 2016; Jamilian et al., 2018; Rashidi et al., 2020), which comprised 189 participants, were involved in the meta-analysis. One article measured free testosterone levels. However, due to the difference in the hormonal levels of free and total testosterone, we did not include this study in the meta-analysis (Razavi et al., 2016). No significant differences in testosterone levels were observed between groups with high heterogeneity (SMD= 0.19 ng/mL, 95% CI=−0.11~0.49, I^2=87%; Fig. 4). After employing random-effects and sensitivity analysis and removing one paper (Mohammad Hosseinzadeh et al., 2016), there was still moderate heterogeneity, and there were no significant MDs between groups (SMD=−0.15 ng/mL, 95% CI=−0.59~0.29, I^2=36%, data not shown).

Lipid profile

***Triglyceride level*:** To compare triglyceride level, the meta-analysis involved four studies comprising 236 participants (Jamilian et al., 2015; Shabani et al., 2018; Rashidi et al., 2020; Zadeh Modarres et al., 2022). No statistically significant differences were observed between groups (SMD =−0.23 mg/dL, 95% CI=−0.49~0.03, I^2=53%, data not shown). However, after employing sensitivity analysis and removing one paper (Rashidi et al., 2020), there was a statistically significant decrease in the triglyceride level in the selenium group compared with the placebo group (SMD=−0.43 mg/dL, 95% CI=−0.73 to −0.12, I^2= 0%). Based on the intervention duration, the subgroup analysis revealed no difference in triglyceride levels between the two groups. Fig. 5 shows the forest plot of the sensitivity and subgroup analysis of the triglyceride level (mg/dL) in the selenium versus placebo groups after 12 weeks of intervention.

***Cholesterol level*:** As indicated in Fig. 6, the meta-analysis involved four studies. These articles involved 236 women, of whom 119 and 117 were in the selenium and placebo groups, respectively. The cholesterol level was significantly lower in the selenium group than in the placebo group (SMD=−0.30 mg/dL, 95% CI=−0.55 to −0.04, I^2=0%). However, based on the intervention duration, the subgroup analysis revealed no difference between the two groups regarding cholesterol levels.

Glucose hemostasis

***Fasting plasma glucose (FPG)*:** The meta-analysis involved four papers with a total of 223 participants (Jamilian et al., 2015; Mohammad Hosseinzadeh et al., 2016; Shabani et al., 2018; Zadeh Modarres et al., 2022). The results showed no statistically significant differences between the groups (SMD=−0.22 mg/dL, 95% CI=−0.50~0.05, I^2= 93%, data not shown). Given the high heterogeneity, we employed sensitivity analysis and a random-effects model. As shown in Fig. 7, after eliminating one paper (Mohammad Hosseinzadeh et al., 2016), there was a statistically significant decrease in the FPG level in the selenium group

Table 1. Characteristics of studies included in the systematic review

Study	Location	Study type	Age	PCOS criteria	The case group		The control group		Outcome		
					Size	Drug	Size	Drug	Variable	Case	Control
Jamilian et al., 2018	Iran	Randomized, double-blinded, placebo-controlled clinical trial	25.6±3.8	Rotterdam criteria	30	Selenium (200 μg/d) plus probiotic supplements	30	Placebo for 12 wk	BMI (kg/m^2)	24.5±3.3	24.2±3.0
									BDI	14.4±3.7	15.3±4.7
									Total testosterone (ng/mL)	1.1±0.6	1.3±0.4
									SHBG (nmol/L)	49.5±22.1	40.4±18.3
									CRP (mg/L)	2.0±1.5	2.7±1.5
Jamilian et al., 2015	Iran	Randomized, double-blind, placebo-controlled trial	25.4±5.1	Rotterdam criteria	35	Daily selenium supplements (200 μg) as tablets for 8 wk	35	Placebo for 8 wk	BMI (kg/m^2)	24.8±3.6	25.0±4.0
									FPG (mmol/L)	4.68±0.65	5.14±0.46
									Insulin (pmol/L)	50.86±32.83	82.65±82.50
									HOMA-IR	1.85±1.22	3.20±3.42
									Triglyceride (mmol/L)	1.12±0.48	1.41±0.70
									Cholesterol	3.93±0.87	4.25±0.76
									Waist	76.14±8.88	79.60±10.47
									Hip circumference	93.01±8.41	96.25±10.20
Mohammad Hosseinzadeh et al., 2016	Iran	Randomized, double-blind, placebo-controlled trial	29.2±1.0	Based on Rotterdam criteria	26	Selenium (200 μg) as a selenium-enriched yeast tablet for 12 wk	27	Placebo for 12 wk	FPG (mg/dL)	92.73±3.23	88.07±1.87
									Insulin (mu/L)	8.55±1.32	8.43±1.15
									HOMA-IR	2.05±0.39	1.81±0.25
									Total testosterone (ng/mL)	0.78±0.22	0.60±0.04
									SHBG (nmol/L)	71.58±13.98	58.78±10.09
Rashidi et al., 2020	Iran	Randomized, double-blind, placebo-controlled clinical trial	29.4±5.3	Rotterdam criteria	34	Selenium (200 μg/d) for 12 wk	32	Placebo for 12 wk	Testosterone (ng/mL)	0.69±0.31	0.67±0.32
									SHBG (nmol/L)	79.12±72.32	65.47±66.77
									Cholesterol (mg/dL)	187.0±38.1	189.5±30.2
									Triglyceride (mg/dL)	142.1±89.0	121.3±64.4
Razavi et al., 2016	Iran	Randomized double-blind, placebo-controlled trial	25.1±4.5	Rotterdam criteria (2003)	32	Daily selenium tablet (200 μg) as selenium yeast daily for 8 wk	32	Placebo for 8 wk	BMI (kg/m^2)	24.3±3.5	25.1±4.2
									Free testosterone (pg/mL)	2.41±1.46	3.02±1.66
									CRP (ng/mL)	1,472.70±1,444.43	2,765.81±2,372.19
Shabani et al., 2018	Iran	Randomized, double-blind, placebo-controlled trial	27.7±6.9	Rotterdam criteria	30	Selenium (200 μg/d) plus probiotic supplements for 12 wk	30	Placebo for 12 wk	BMI (kg/m^2)	24.5±4.9	25.5±3.8
									FPG (mg/dL)	87.8±7.3	92.9±7.0
									Insulin (μIU/mL)	9.4±3.4	11.6±4.5
									HOMA-IR	2.1±0.8	2.6±1.0
									Triglycerides (mg/dL)	84.3±34.8	102.4±32.4
									Total cholesterol (mg/dL)	158.5±31.1	172.8±30.7
									HDL-cholesterol (mg/dL)	46.2±7.2	45.0±7.9
Zadeh Modarres et al., 2022	Iran	Randomized, double-blind, placebo-controlled trial	32.6±4.6	Rotterdam criteria	20	Selenium supplements (200 μg/d) for 8 wk	20	Starch as placebo daily for 8 wk	BMI (kg/m^2)	25.2±4.2	25.6±2.6
									HOMA-IR	2.7±1.4	3.2±1.5
									FPG (mg/dL)	84.4±7.7	88.5±9.4
									Insulin (μIU/mL)	12.1±5.9	15.2±7.0
									Total cholesterol (mg/dL)	166.3±32.9	174.8±27.0
									Triglycerides (mg/dL)	127.6±48.9	137.3±54.6

PCOS, polycystic ovary syndrome; BMI, body mass index; BDI, beck depression inventory; SHBG, sex hormone-binding globulin; CRP, C-reactive protein; FPG, fasting plasma glucose; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL, high-density lipoprotein.

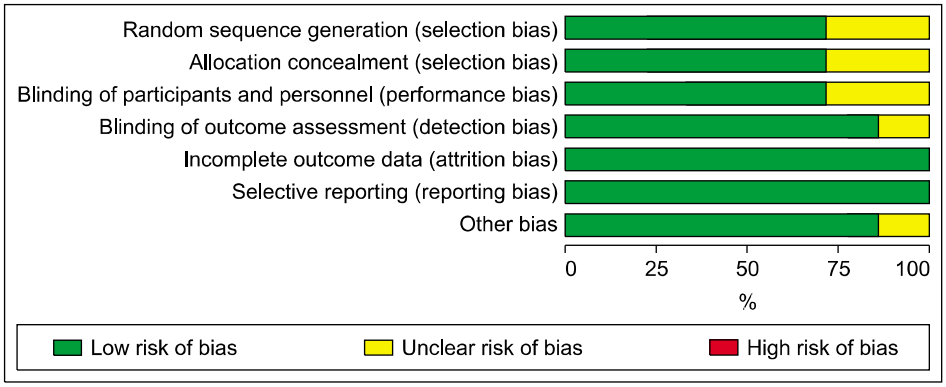

Fig. 2. Risk of bias graph.

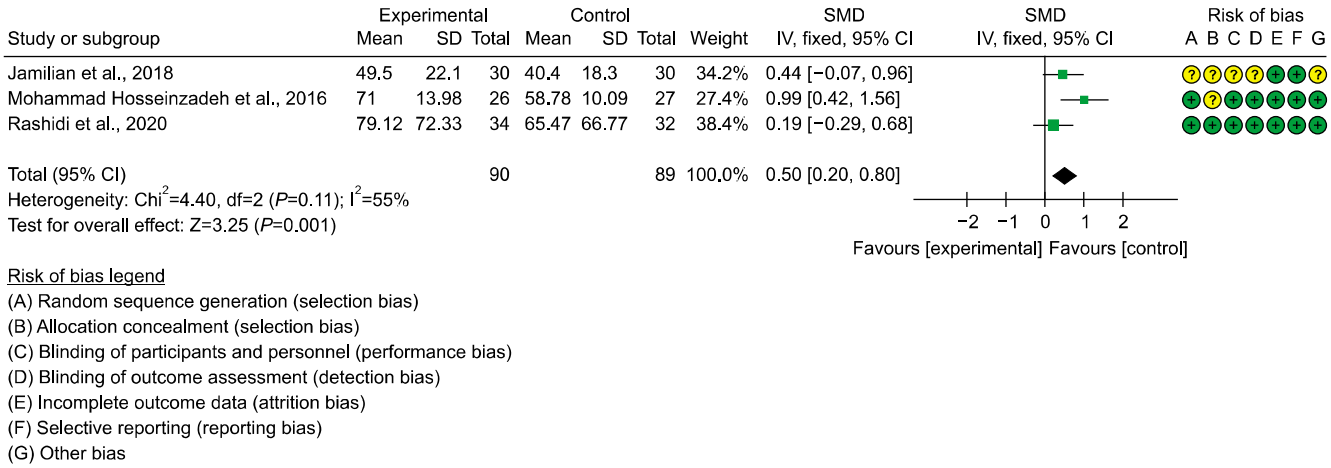

Fig. 3. Forest plot comparing the sex hormone-binding globulin level (nmol/L) between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

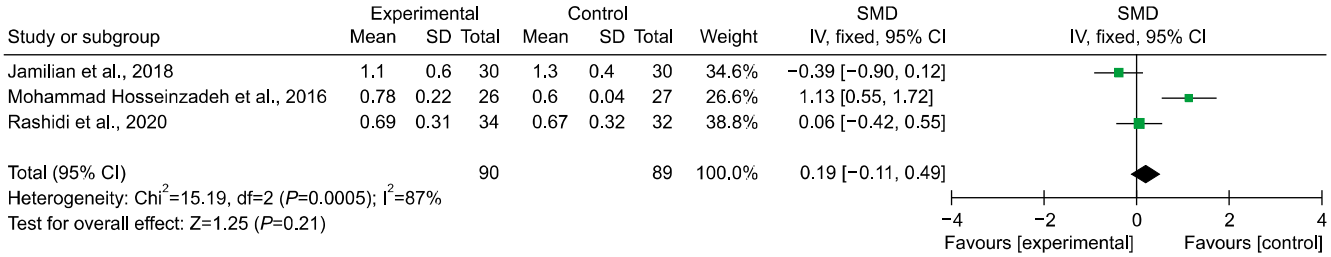

Fig. 4. Forest plot comparing the testosterone level (ng/mL) between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

compared with the placebo group (SMD=−0.69 mg/dL, 95% CI=−1.00 to −0.38; I^2=0%).

***Insulin level*:** As shown in Fig. 8, four studies comprising 223 participants were used in the meta-analysis (Jamilian et al., 2015; Mohammad Hosseinzadeh et al., 2016; Shabani et al., 2018; Zadeh Modarres et al., 2022). The results showed a lower level of insulin in the selenium group than in the placebo group (SMD=−0.36 mIU/L, 95% CI=−0.63 to −0.10, I^2=19%). Additionally, in the subgroup analysis, a significant difference was observed in insulin levels between two groups after 8 weeks of intervention. High heterogeneity was observed in the 12-week interventions, but we could not perform sensitivity analysis because there were only two papers.

***HOMA-IR*:** The meta-analysis involved four papers (Jamilian et al., 2015; Mohammad Hosseinzadeh et al., 2016; Shabani et al., 2018; Zadeh Modarres et al., 2022) comprising 223 participants. No statistically significant differences were observed between the groups regarding the HOMA-IR level (SMD=−0.21, 95% CI=−0.47∼0.06, I^2=79%, data not shown). After employing random-effects and sensitivity analysis and removing one paper, the heterogeneity reached 0%, and the two groups were significantly different (SMD=−0.49, 95% CI=−0.79 to −0.18, I^2=0%). In other words, the HOMA-IR level was statistically lower in the intervention group than in the

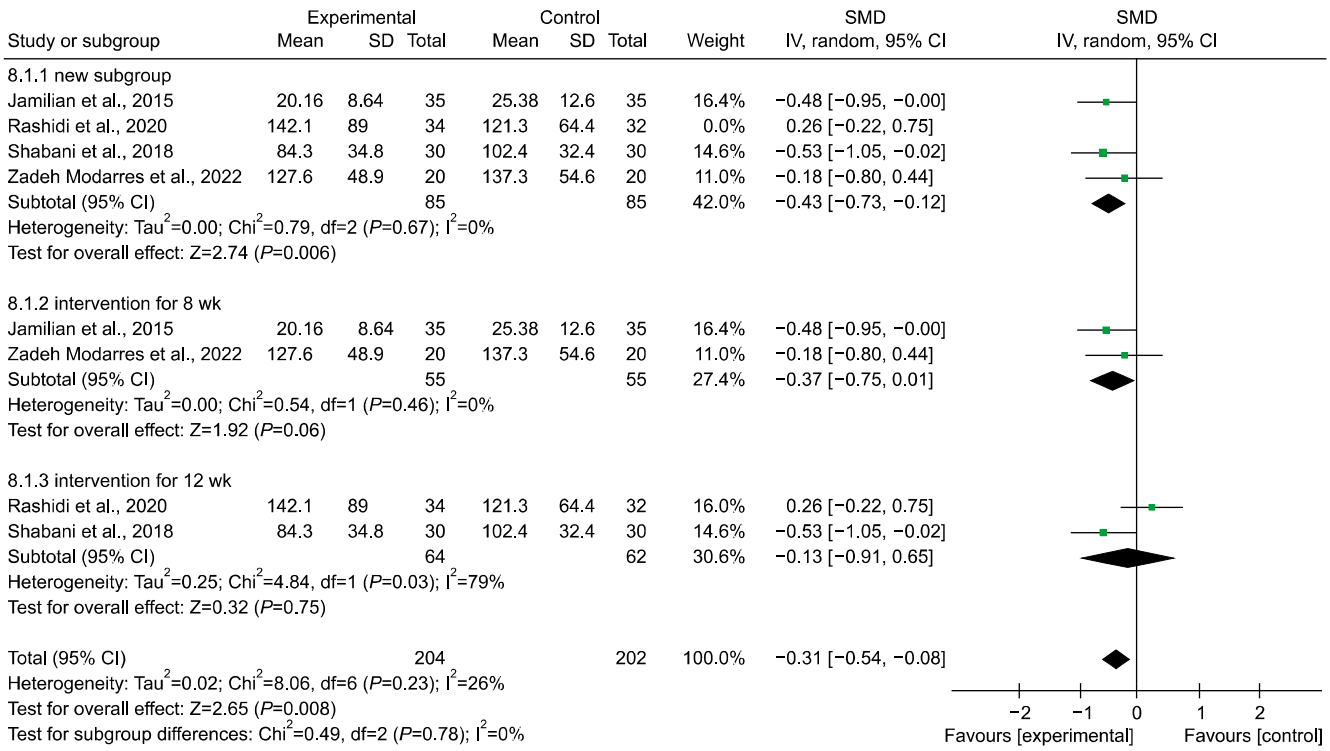

Fig. 5. Forest plot of the sensitivity and subgroup analysis of the triglyceride level (mg/dL) between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

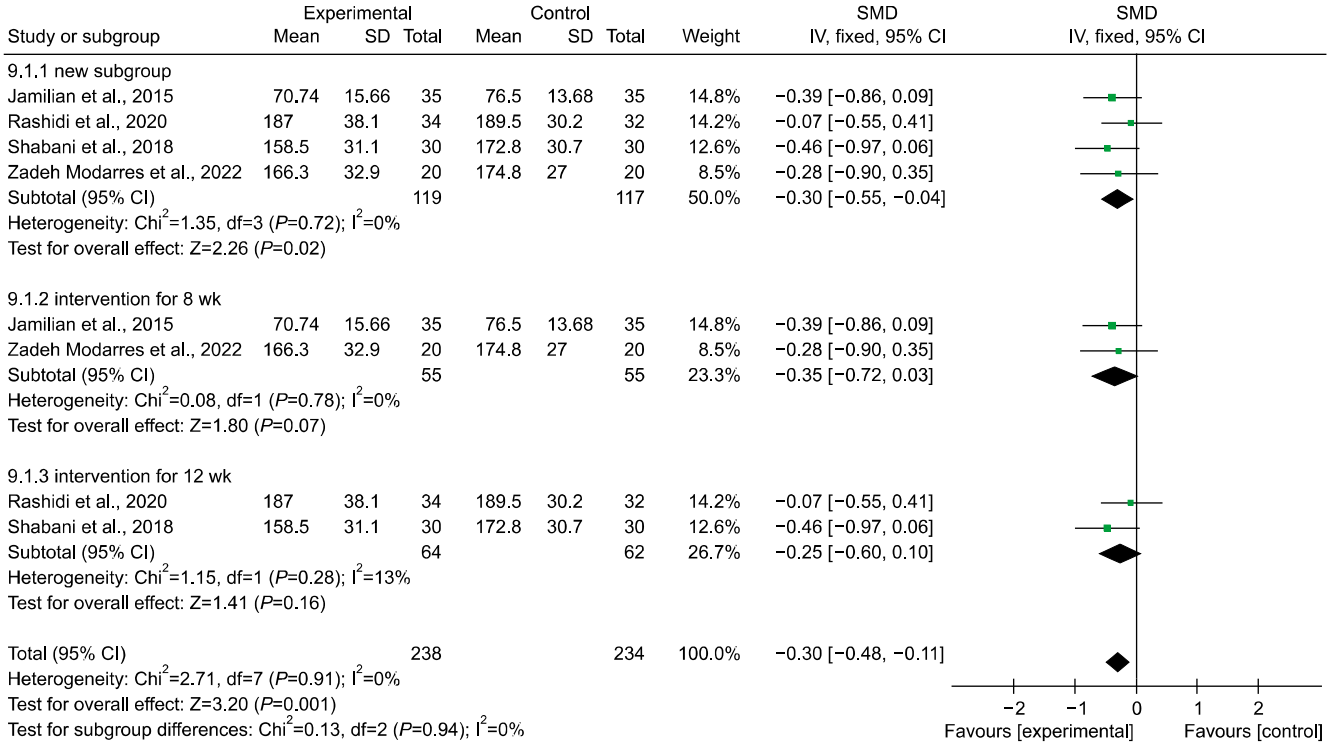

Fig. 6. Forest plot comparing the cholesterol level (mg/dL) between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

placebo group (Fig. 9).

QUICKI

The meta-analysis involved three papers comprising 160 participants (Jamilian et al., 2015; Shabani et al., 2018; Zadeh Modarres et al., 2022). The groups were significantly different regarding the QUICKI level (SMD=0.34, 95% CI=0.04∼0.65, I^2=28%, data not shown), which

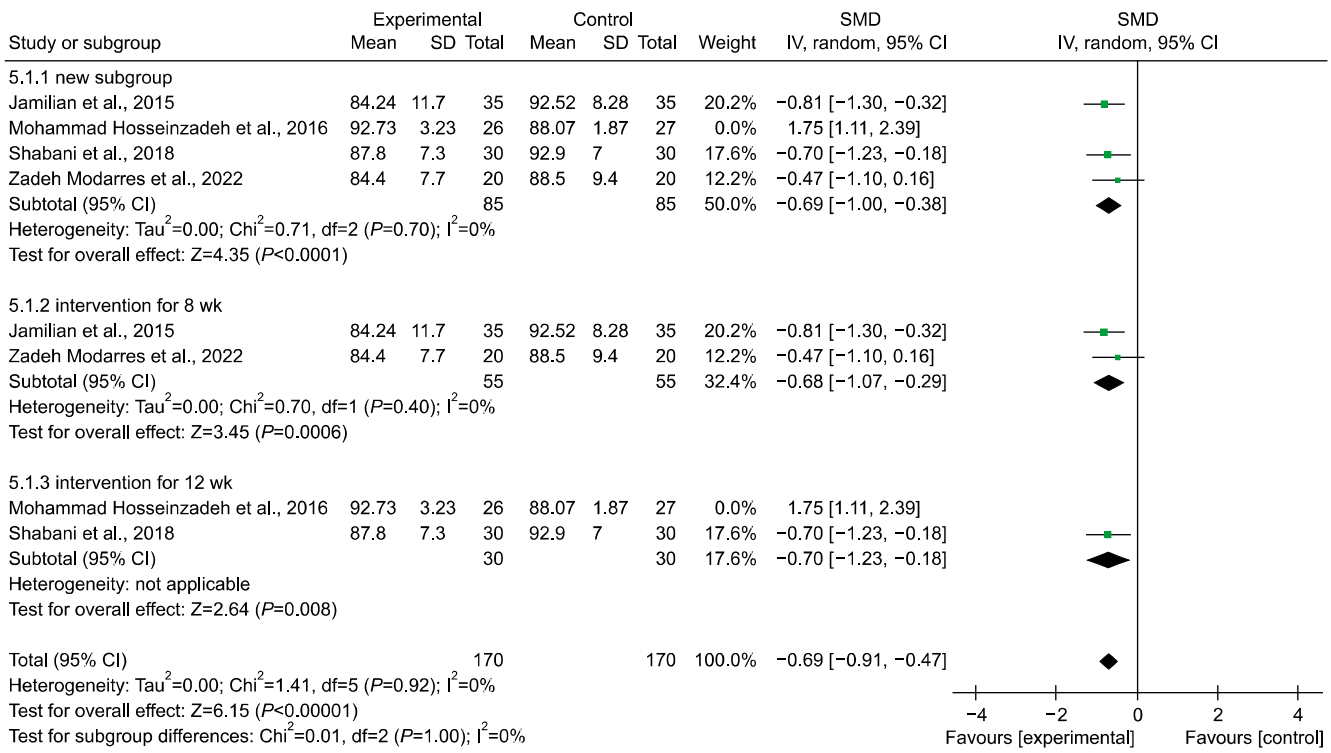

Fig. 7. Forest plot of the sensitivity analysis of the fasting plasma glucose level (mg/dL) between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

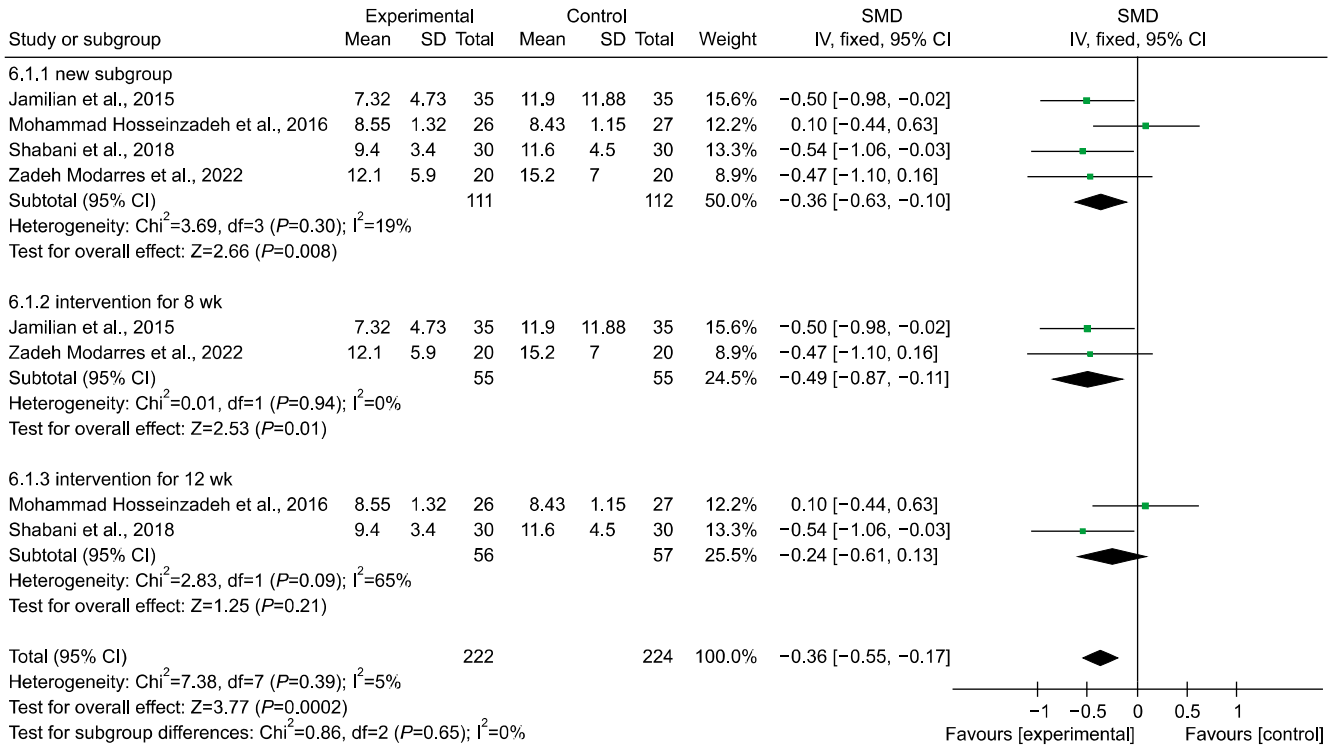

Fig. 8. Forest plot comparing the insulin level (mIU/L) between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

was statistically higher in the intervention group than in the placebo group.

Biomarkers of oxidative stress

***Total antioxidant capacity (TAC)*:** The meta-analysis involved three papers comprising 164 participants (Razavi et al., 2016; Jamilian et al., 2018; Zadeh Modarres et al., 2022). The groups significantly differed regarding TAC level (SMD=0.72 mmol/L, 95% CI=0.40∼1.03, I^2=45%, data not shown). After employing random-effects and

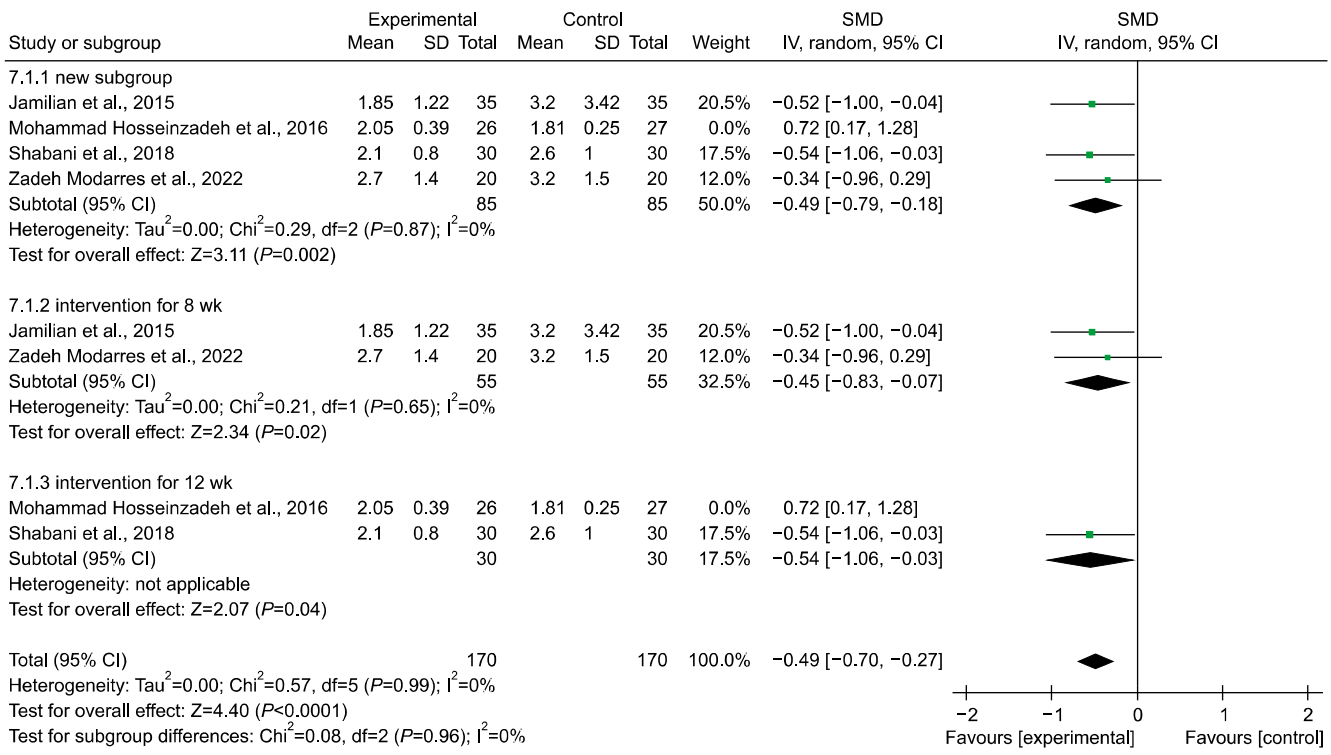

Fig. 9. Forest plot of the sensitivity analysis of the homeostasis model of assessment-insulin resistance level between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

sensitivity analysis and removing one paper (Zadeh Modarres et al., 2022), the heterogeneity was reduced to 0%, and TAC was significantly higher in the intervention group than the placebo group (SMD=0.89 mmol/L, 95% CI=0.52～1.26, I^2=0%, data not shown).

***Glutathione (GSH)*:** The meta-analysis involved three papers comprising 164 participants (Razavi et al., 2016; Jamilian et al., 2018; Zadeh Modarres et al., 2022). The groups were significantly different regarding the GSH level (SMD=0.49 μmol/L, 95% CI=0.18～0.81, I^2=84%, data not shown). After employing random-effects and sensitivity analysis and removing one paper (Razavi et al., 2016), there was still high heterogeneity, and the level of total GSH was statistically higher in the selenium group than in the placebo group (SMD=1.00 μmol/L, 95% CI=0.22～1.78, I^2=79%, data not shown).

***Malondialdehyde (MDA)*:** The results of the meta-analysis involving three papers comprising 164 participants (Razavi et al., 2016; Jamilian et al., 2018; Zadeh Modarres et al., 2022) showed that the MDA level was statistically lower in the selenium group than the placebo group (SMD=−0.54 μmol/L, 95% CI=−0.86 to −0.22, I^2=77%, data not shown). After employing random-effects and sensitivity analysis and removing one paper (Zadeh Modarres et al., 2022), the heterogeneity reached 0%, and there was no difference between the groups regarding the MDA level (SMD=−0.31 μmol/L, 95% CI=−0.66～0.05, I^2=0%, data not shown).

General characteristics

***BMI*:** The meta-analysis involved five articles comprising 304 women (Jamilian et al., 2015; Razavi et al., 2016; Jamilian et al., 2018; Shabani et al., 2018; Zadeh Modarres et al., 2022). No significant difference was observed between the groups regarding their BMI (MD=−0.33 kg/m^2, 95% CI=−1.17～0.52, I^2=0%). Additionally, the subgroup analysis showed no differences between the groups regarding the intervention duration (Fig. 10).

DISCUSSION

In this systematic review, we investigated the impact of SS on the biochemical markers of women with PCOS. We analyzed seven RCTs, comprising 413 women with PCOS. The study revealed that consuming SS was associated with increased QUICKI, TAC, and total GSH levels, as well as reduced triglyceride, cholesterol, FPG, insulin, and HOMA-IR levels. Furthermore, regarding SHBG, testosterone levels, MDA, and BMI, no significant differences were observed between the groups.

Previous studies have suggested that insufficient levels of vitamins or minerals may contribute to PCOS. Recently, women with PCOS were found to have lower concentrations of plasma selenium than healthy women (Coskun et al., 2013). By inhibiting proinflammatory cytokines and reactive oxygen and nitrogen species, SS can improve reproductive outcomes and reduce inflammatory biomark-

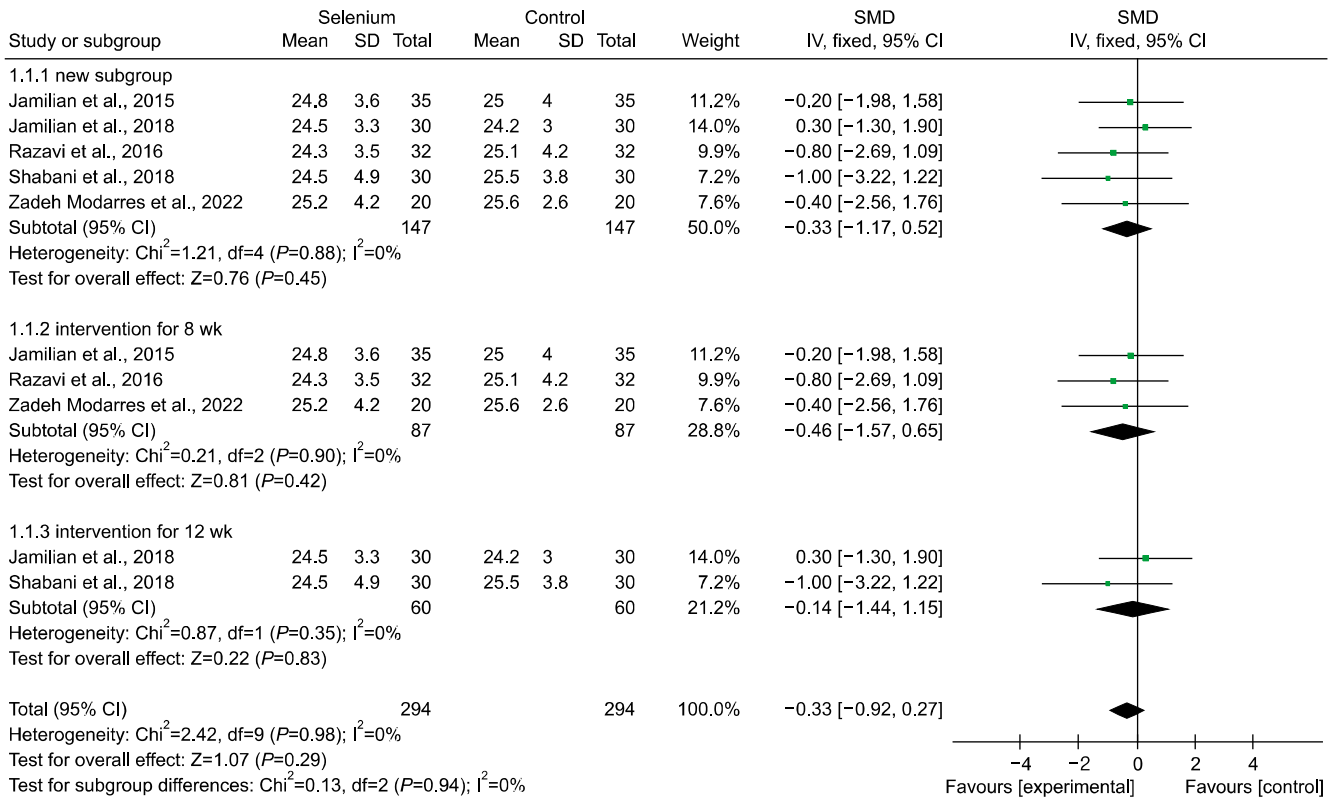

Fig. 10. Forest plot comparing body mass index between the selenium and placebo groups. SD, standard deviation; SMD, standardized mean difference; IV, interval variable; CI, confidence interval.

ers and oxidative stress (Duntas and Hubalewska-Dydejczyk, 2015).

SHBG is a protein that binds to androgens and estrogens, reduces the access of target tissues to sex steroids, and thus modulates the biological activity of steroids. In other words, it reduces free steroids in the blood circulation (Laurent et al., 2016). However, we found that SS had no effect on SHBG levels. In this regard, Mohammad Hosseinzadeh et al. (2016) reported no relationship between selenium intake and SHBG. Furthermore, Wu et al. (2022) found that SS did not affect SHBG levels in women with PCOS.

We found no improvement in testosterone levels after the intervention. This finding is consistent with a previous study, which reported that a 4-week selenium intake among athlete participants with a selenium-sufficient diet did not significantly affect their resting testosterone levels (Shafiei Neek et al., 2011). Another trial study showed that a 12-week SS did not benefit the level of serum total testosterone in patients with PCOS (Mohammad Hosseinzadeh et al., 2016). Although our study participants were not athletes, the results of these two studies support ours. Of course, few studies, if any, have examined the impact of SS on testosterone. Coskun et al. (2013) reported decreased serum selenium levels in women with PCOS and that decreased selenium was associated with elevated total testosterone levels. However, Wu et al. (2022) reported that selenium consumption reduced testosterone levels in women with PCOS. The discrepancies in results could be attributed to the use of MD in groups (before/after the intervention) in the meta-analysis.

According to our results, SS could reduce the levels of serum lipid profiles, such as triglyceride and cholesterol. Similar to our findings, two meta-analysis reported that in their trial studies, selenium intake was likely to result in reduced serum levels of total cholesterol and triglyceride, whereas it did not have any benefit for other lipid profile levels (Rad et al., 2019; Wu et al., 2022). Even though the exact mechanisms underlying the relationship between selenium and lipid metabolism are not properly identified, human lipoproteins have been found to contain small amounts of selenium element (Ducros et al., 2000). Moreover, SS has been found to boost the production of a peroxisome proliferator-activated receptor-γ (PPAR-γ) ligand called 15-deoxyprostaglandin J_2 (Vunta et al., 2007). By reducing the concentration of sterol regulatory element-binding protein-2, activation of PPAR-γ decreases cholesterol synthesis (Klopotek et al., 2006).

Despite the lack of a precise etiology for PCOS, the relationship between insulin resistance and hyperandrogenemia is well recognized. There are two main mechanisms underlying this relationship. First, insulin resistance leads to increased androgen production in the thecal cells through a synergic action with the luteinizing hormone (Poretsky et al., 1999). Second, hepatic synthesis of

SHBG is reduced by insulin resistance after subsequent hyperinsulinemia, and this reduced rate of SHBG accounts for increased levels of free androgens (Pugeat et al., 1991; Poretsky et al., 1999).

In this study, we showed a positive effect of SS on the serum biomarkers of oxidative stress, meaning that selenium could increase TAC and GSH. According to the results of a systematic review, which are consistent with our findings, the reduction of oxidative stress by SS has been attributed to increasing TAC levels and decreasing serum MDA. (Klopotek et al., 2006). Zadeh Modarres et al. (2022) showed that an 8-week SS program for infertile women with PCOS undergoing *in vitro* fertilization did not affect TAC levels. These conflicting results are probably due to differences in the severity of the illness and the study samples.

In this study, we showed a positive effect of selenium intake on serum glucose homeostasis, effectively reducing FPG, insulin, and HOMA-IR levels but increasing QUICKI levels. Similar to our findings, Jamilian et al. (2015) found a significant increase in QUICKI levels following an 8-week administration of 200 μg SS daily among women with PCOS. A meta-analysis showed that selenium intake significantly reduced insulin levels and increased QUICKI levels (Tabrizi et al., 2017). However, Raygan et al. (2018) reported no effects of SS on the QUICKI level in patients with congestive heart failure. Another study found no significant effects of SS on oxidative stress markers (Razavi et al., 2016). Additionally, a systematic review showed that SS among patients with metabolic diseases had no significant effects on glucose homeostasis parameters, such as fasting blood sugar and HOMA-IR (Tabrizi et al., 2017). These results are inconsistent with our study results, possibly due to differences in the study population. Despite the common features between metabolic syndrome and PCOS, only 43% of PCOS women have metabolic syndrome, and their causes can differ (Chen and Pang, 2021). Thus, SS may affect their biochemical pattern differently based on the causative factors.

The results of this study showed no difference between the two groups regarding BMI. In other words, selenium does not seem to induce BMI reduction in women with PCOS. However, another study that investigated the effect of selenium on body weight in obese people aged 18 to 65 showed that selenium reduced body mass and leptin levels (Cavedon et al., 2020). This difference can be due to the hypocaloric diet with selenium intake used in the study. Overall, the present study's result showed that SS could improve the lipid profile, and glucose hemostasis markers and increase the level of antioxidants in women with PCOS. Therefore, SS could be recommended for treating biochemical disorders in these women. However, due to the heterogeneity and scarcity of studies in this field, more studies are needed to elucidate the effect of selenium on the clinical and biochemical symptoms of women with PCOS.

There are several limitations to the current systematic review. First, only two studies examined the effect of selenium combined with probiotics. Thus, we could not perform subgroup analysis because the variables were different in these two papers. Second, the duration of intervention was not the same in all the selected studies. Third, publication bias could not be definitively detected due to the low number of selected studies. Fourth, all the selected studies were conducted in Iran, which reduces the generalizability of this study.

FUNDING

None.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: SFS, RK, PA, MZ. Analysis and interpretation: SFS, RK. Data collection: SFS, RK. Writing the article: SFS, FS. Critical revision of the article: PA, SFS. Final approval of the article: all authors. Statistical analysis: SFS, RK. Overall responsibility: SFS.

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