Effect of vitamin E supplementation on cardiometabolic risk factors, inflammatory and oxidative markers and hormonal functions in PCOS (polycystic ovary syndrome): a systematic review and meta-analysis

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Polycystic ovary syndrome (PCOS) is a common endocrinopathy among reproductive-age women. Various therapeutical approaches are currently used to manage or control symptoms associated with PCOS. This systematic review intended to assess the effects of Vit E supplementation on cardiometabolic risk factors, inflammatory and oxidative markers, and hormonal functions in PCOS women based on the clinical trial's results. The databases including PubMed, Scopus, Cochrane, Web of Science, and Embase were used to find all relevant studies. The authors reviewed all relevant clinical trials via systematic evaluation of abstracts and titles. Searches were conducted on August 1, 2020. After the initial search and reading of the article's title and abstract, 353 articles were reviewed; finally, 12 articles met the inclusion criteria. Vitamin E supplementation improves lipid profile, decreases insulin and HOMA-IR levels. Furthermore, while Vitamin E supplementation decreases LH and testosterone concentrations, it increases FSH and progestrone concentrations. The following meta-analysis showed that vitamin E supplementation made statistically significant improvements in triglyceride (TG) and low-density lipoproteins (LDL) levels, meanwhile, pooled mean difference for

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waist circumference (WC) and HOMA-IR were also statistically significant. Supplementary regimens containing vitamin E can positively affect metabolic and hormonal parameters in women with PCOS.

Polycystic ovary syndrome (PCOS) is a common endocrinopathy among women in reproductive age with a variable prevalence between 4 and 8%, as defined by the NIH/NICHD criteria\(^1\). PCOS is a heterogeneous syndrome characterized by symptoms of hyperandrogenism (e.g. acne, hirsutism, and alopecia), anovulation (e.g. irregular menstrual cycles, oligomenorrhea, and amenorrhea), and polycystic ovarian morphology\(^2\). PCOS is associated with a variety of metabolic conditions, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular disease (CVD), and atherosclerosis\(^3-5\). Insulin resistance and hyperinsulinemia are common findings in PCOS as 44–70% of patients suffer from them\(^6,7\). Meanwhile, Dyslipidemia which can significantly decrease high-density lipoprotein (HDL), and increase triglyceride (TG) concentrations are certainly the most prevalent and persistent cardiovascular risk factors encountered in women with PCOS\(^8\).

The pathophysiology of PCOS is not clearly elaborated yet, but it might be associated with genetic factors, lifestyle, and deficiency of essential micronutrients in patients with insulin resistance and oxidative stress\(^9,10\). The first-line treatments of PCOS are mostly lifestyle modifications including exercise and diet alterations\(^11\), as imbalanced element status is an essential foundation for insulin resistance in PCOS\(^12\). There is growing interest in using different combinations of dietary supplements such as magnesium and vitamin E, as their synergistic impact might help improve metabolic profiles in several diseases with metabolic abnormalities\(^13-15\). Magnesium and vitamin E co-supplementation for 12 weeks could have beneficial effects on insulin metabolic parameters along with markers of cardio-metabolic risk in women with PCOS\(^16\). Furthermore, Omega-3 fatty acids (FA) and vitamin E co-supplementations for 12 weeks in PCOS women are stated to have significantly improved insulin resistance indices and both total and free testosterone. Moreover, the beneficial effects on gene expression and oxidative stress biomarkers in this regimen have been reported\(^17\). For instance, another study showed that it could significantly improve lipoprotein gene expression (a) and oxidized low-density lipoprotein, lipid profiles, and biomarkers of oxidative stress in patients with PCOS\(^18\).

According to our search in the literature, there has not been a systematic review that has evaluated the role of vitamin E supplementation in PCOS treatment, this study aimed to assess the effects of vitamin E supplementation on cardiometabolic risk factors, inflammatory and oxidative markers, and hormonal functions in PCOS women based on the clinical trials’ results.

**Methods**

This study is reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline\(^19\).

**Search strategy and data collection.** All studies evaluating the effects of supplementary vitamin E regimens on cardiometabolic risk factors, inflammatory and oxidative markers, and hormonal functions in comparison to control group (placebo/no treatment) in PCOS patients have been searched and reviewed. The databases, including PubMed, Scopus, Web of Science, and Embase, were used to find all relevant studies. Also, the references of the relevant articles were explored to find other relevant articles. The search was not restricted to any specific time frame or language. Three emails with acceptable intervals (about two weeks) were sent to the corresponding authors of restricted access articles’ for full texts. Searches were conducted on August 1, 2020, and reported the search strategy in Table 1 supplementary.

**Inclusion criteria.** Types of studies:

All relevant clinical trials (including double and single-blind and data from a parallel and cross-over group designed) evaluating the effects of vitamin E supplementary regimens in PCOS patients were gathered, and single-arm studies were not included in the study. Two authors (MM and GhT) independently screened all of the retrieved clinical trials using their titles and abstracts. Full-text of relevant articles were collected to assess their relevance according to the inclusion/exclusion criteria.

**Types of participants:**

The studies that evaluated the effects of vitamin E supplementation outcomes in the PCO adult population (≥ 18 years) were included in this study. In this regard, the subjects of the study contained patients with the PCOS receiving vitamin E supplementary regimens and control groups of PCOS patients receiving placebo or no treatment; we exclude those studies that have populations restricted to specific diseases or conditions.

**Types of interventions:**

This systematic review study included all studies evaluating vitamin E supplementation (alone or as a part of combination therapy) in PCOS patients.

**Types of outcomes:**

The effects of vitamin E on the following outcomes were evaluated in PCOS patients:
| No | Author, year | Country | Type of Study | Study Subject | Sample Size | Dose /duration of supplementation | Intervention type | Control Group | Mean Age | Outcome | Follow up duration | Measurement interval |
|----|--------------|---------|---------------|---------------|-------------|----------------------------------|------------------|---------------|----------|---------|-------------------|---------------------|
| 1  | Chen22       | China   | RCT           | PCOS          | I = 105     | 100 mg/day oral vitamin E /for 25 days | MT               | Placebo: CC: (100 mg/day for 5 days starting on day 3 of a spontaneous menstrual cycle or withdrawal bleeding) and HMG (75 IU every second day starting from day 8) | 26.88 ± 2.84 | Estradiol Testosterone LH FSH PRL | Until miscarriage or delivery | _ |
| 2  | Hager24      | Austria | RCT           | PCOS          | I = 30      | 30 mg vitamin E + 500 mg Omega-3 fatty acids + 800 μg folate acid + 70 μg selenium, 4 mg catechin, 12 mg glycyrrhiza, 30 μg Co-Q10 / 12 Weeks | CT               | Placebo (200 μg folic acid) | 27.7 ± 5.7 | Testosterone SHBG FSH LH Estradiol BMI HOMA-IR | 12 Weeks | Baseline and after 3 months |
| 3  | Jamilian16   | Iran    | RCT           | PCOS          | I = 30      | 400 mg/ day Vitamin E + 250 mg/ day Magnesium/12 Weeks | CT               | Placebo (Barir Essence Pharmaceuticals, Kashan, Iran) | 29.2 ± 7.2 | Weight BMI FBS Ins HOMA-IR TC TG LDL HDL | 12 Weeks | Baseline and after 3 months |
| 4  | Sadeghi29    | Iran    | RCT           | PCOS          | I = 32      | 400 IU vitamin E + 2 omega-3 pills daily each containing: 180 mg of Eicosapentanoic acid (EPA) and 120 mg of Docosahexaenoic acid (DHA) / 8 Weeks | CT               | Placebo (oral paraffin) | 26.67 ± 3.35 | TAC CAT GSH MDA | 8 Weeks | Baseline and after 2 months |
| 5  | Izad26       | Iran    | RCT           | PCOS          | I = 21      | 400 IU vitamin E + 200 mg (daily CoQ10) /8 Weeks | CT               | Placebo (CoQ10 placebo + vitamin E placebo) | 28.33 ± 5.52 | BMI WC TG TC LDL HDL Non-HDL | 8 Weeks | Baseline and after 2 months |
| 6  | Shokrpou30   | Iran    | RCT           | PCOS          | I = 30      | 400 mg/day Vitamin E + 250 mg/ day Magnesium/12 Weeks | CT               | Placebo (Barir Essence Pharmaceuticals, Kashan, Iran) | 27.2 ± 7.1 | Weight BMI CRP MDA GSH TAC NO Testosterone SHBG | 12 Weeks | Baseline and after 3 months |
| 7  | Jamilian27   | Iran    | RCT           | PCOS          | I = 20      | 400 IU vitamin E + 1000 mg Omega-3 fatty acids/12 Weeks | CT               | Placebo (paraffin) | 22.3 ± 4.7 | Weight BMI WC | 12 Weeks | Baseline and after 3 months |
| 8  | Izadi25      | Iran    | RCT           | PCOS          | I = 21      | 400 IU Vitamin E + 200 mg (daily CoQ10) /8 Weeks | CT               | Placebo (CoQ10 placebo + vitamin E placebo) | 28.33 ± 5.52 | Weight BMI FBS Ins HOMA-IR Testosterone SHBG FSH LH Progesterone | 8 Weeks | Baseline and after 2 months |

Continued
1. Cardiometabolic risk factors including lipid profile (Total Cholesterol (TC), HDL, Low-Density Lipoprotein (LDL), TG), glycemic indices (Fasting Blood Sugar (FBS), hemoglobin A1c (HbA1c), Insulin (ins), Insulin Resistance (HOMA-IR)), and anthropometric measures (weight, body mass index (BMI), waist circumference (WC))

2. Biomarkers of inflammation and oxidative stress including C-reactive protein (CRP), plasma nitric oxide (NO), total antioxidant capacity (TAC), glutathione (GSH), malondialdehyde (MDA)

3. Sex hormones including free testosterone, total testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone (DHEAS), follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, estradiol

Data extraction and quality assessment. Data were extracted independently from included trials by two authors according to a predefined data extraction sheet. The extracted data included (a) bibliographic and general information (author, title, publication year, type of study, randomization, and location), (b) participants (sample size and mean age), (c) intervention (type of intervention (single/combination therapy), dose of sup-

Table 1. Descriptions of the studies included in the systematic review and meta-analysis of the association between PCO and vitamin E supplementation. RCT randomized controlled trial, PCOS polycystic ovarian syndrome, I intervention, C control, MT mono therapy, CT combination therapy, CC clomiphene citrate, HMG human menopausal gonadotropin, IU international unit, LH luteinizing hormone, FSH follicular stimulating hormone, PRL prolactin, CoQ10 co-enzyme Q10, SHBG sex hormone binding globulin, HOMA-IR homeostatic model assessment of insulin resistance, TC total cholesterol, TG triglyceride, LDL low density lipoprotein, HDL high density lipoprotein, TAC total antioxidant capacity, CAT catalase, GSH glutathione, MDA malondialdehyde, WC weight circumference, FBS fasting blood sugar, Ins insulin, HOMA-B homeostatic model assessment of beta cell function, DHEAS dehydroepiandrosterone sulfate. *In this study intervention group consists of groups B and C with Vitamin E treatment during follicular and luteal phase, respectively.*
Implementation and duration), (d) control group (no treatment, placebo therapy), and (e) outcomes (reported outcomes, and follow-up time).

Two authors independently assessed the quality of included studies using the Cochrane Risk of Bias tool20,21.

Statistical analysis and data synthesis. The effects of vitamin E supplementation on cardiometabolic risk factors, inflammatory and oxidative markers, and hormonal functions in PCOS women were assessed using the standardized mean difference (SMD). The meta-analysis of SMD was performed and the outcome was demonstrated as pooled standardized mean difference with 95% confidence interval. The fixed and random effect models were considered for analysis based on homogeneity of data (I² < 50% considered as fix effect and I² ≥ 50% considered as a random effect). The publication bias was assessed using Egger test and was presented schematically using the funnel plot. Because of the scarcity of data subgroup analysis was not carried out on the extracted data.

Ethical considerations. In this study, ethical approval is not essential because used data are not subjects, and the results are discussed through peer-reviewed publications.

Results

Description of included studies. The flow chart of the search process and study selection is depicted in Fig. 1. Following a search on PubMed (n = 33), Scopus (n = 174), Web of Science (n = 54), and the Embase (n = 17) databases, 278 relevant articles were identified. After the initial search and reading of the article’s title and abstract, 353 articles were reviewed; finally, 12 articles met the inclusion criteria16,18,22–31. The characteristics of included clinical trials were summarized in Table 1. Most of the studies about vitamin E and PCO treatment were conducted in Iran. Eleven studies16,18,22–31 evaluated the effects of vitamin E co-supplementation with other supplements such as omega 3 fatty acids and magnesium in PCOS women. Table 1 shows details different regimens used in each study.

Quality of included studies. Five studies15,17,23,27,34 did not describe the method used for allocation concealment clearly. Two studies15,38 were single-blind and four others16,17,22,27 did not describe the blinding process in detail. Detection bias was considered high for three studies15,23,27 and was unclear for nearly all other
studies did not report some outcomes after the intervention. One study had a high risk of selective reporting bias as they did not report hormonal changes. The complete risk of bias evaluation is presented in Fig. 2. The GRADE framework rated the strength of the evidence for all outcomes as moderate, except for BMI and weight, which were rated as high; progesterone, LH, FSH, CAT, and PRL, which were rated as low; and CAT, which was rated as very low strength.

| Studies     | Random seq. | Allocation | Blinding | Outcome assessment | Performance | Reporting | Other |
|-------------|-------------|------------|----------|--------------------|-------------|-----------|-------|
| Chen 2020   | ✔           | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Hager 2019  | ✔           | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Jamilian 2019 | ✔        | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Sadeghi 2019 | ✔         | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Izadi 2019  | ✔           | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Shokrpour 2019 | ✔     | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Jamilian 2018 | ✔       | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Izadi 2018  | ✔           | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Talari 2018  | ✔           | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Panti 2018  | ✔           | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Ebrahimii 2017 | ✔      | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |
| Rahmani 2016 | ✔         | ✔          | ✔        | ✔                  | ✔           | ✔         | ☑     |

Figure 2. Assessment of the risk of bias in the included studies. Green circle (+): Low risk, Red circle (−): High risk, ?: Unclear.

Outcomes

Effect of vitamin E supplementation on sex hormones. Four studies evaluated testosterone levels pre and post Vitamin E co-supplementation (with magnesium, omega-3 FAs, and CoQ10). Table 2 shows all studies that showed a significant decrease in this regard in both intervention and control groups following vitamin E supplementation. In contrast, another study reported no significant differences in estradiol levels following vitamin E + omega3 FAs supplementation. As shown on Table 2, only one study reported a small increase in estradiol levels with Vitamin E + CoQ10 supplement group (d = -0.33) in comparison with the slight decrease that was observed in their control group (d = 0.21). Three studies evaluated Vitamin E’s effect on...
|    | Outcome | Intervention (mean ± SD) | Control (mean ± SD) | Between Groups |
|---|---------|--------------------------|--------------------|----------------|
|   |         |                             |                    |                |
|   |         | Mean (SD)                 | Mean (SD)          | Mean (SD)      |
| BMI | 29.28 ± 3.23 | 28.70 ± 3.13 | −0.59 ± 2.84 | 0.18 |
| Weight | 66.7 ± 9.5 | 66.6 ± 9.5 | −0.1 ± 0.3 | 0.01 |
| Estradiol | 44.87 ± 30.52 | 336.51 ± 155.62 | 291.64 ± 139.46 | −2.60 |
| BMI | 28.8 ± 5.1 | 28.5 ± 5.1 | −0.3 ± 0.6 | 0.05 |
| Weight | 66.7 ± 9.5 | 66.6 ± 9.5 | −0.1 ± 0.3 | 0.01 |
| Estradiol | 44.87 ± 30.52 | 336.51 ± 155.62 | 291.64 ± 139.46 | −2.60 |
| BMI | 27.1 ± 4.2 | 27.0 ± 4.1 | −0.1 ± 0.1 | 0.02 |
| Weight | 66.7 ± 9.5 | 66.6 ± 9.5 | −0.1 ± 0.3 | 0.01 |
| Estradiol | 44.87 ± 30.52 | 336.51 ± 155.62 | 291.64 ± 139.46 | −2.60 |
| BMI | 26.7 ± 4.1 | 26.5 ± 4.1 | −0.2 ± 0.1 | 0.02 |
| Weight | 66.7 ± 9.5 | 66.6 ± 9.5 | −0.1 ± 0.3 | 0.01 |
| Estradiol | 44.87 ± 30.52 | 336.51 ± 155.62 | 291.64 ± 139.46 | −2.60 |
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| Weight | 66.7 ± 9.5 | 66.6 ± 9.5 | −0.1 ± 0.3 | 0.01 |
| Estradiol | 44.87 ± 30.52 | 336.51 ± 155.62 | 291.64 ± 139.46 | −2.60 |

Note: The table above represents the mean ± standard deviation (SD) for various outcomes, including BMI, weight, estradiol, and other medical parameters, between the intervention and control groups. The changes and their significance levels are also indicated, along with effect sizes.
Table 2. The effect of vitamin E supplementation on cardiometabolic risk factors, inflammatory and oxidative markers, and hormonal functions in PCOS women. *In this study intervention group consists of groups B and C with Vitamin E treatment during follicular and luteal phase, respectively. SD standard deviation, d Cohens's d, LH luteinizing hormone, FSH follicular stimulating hormone, PRL prolactin, SHBG sex hormone binding globulin, HOMA-IR homeostatic model assessment of insulin resistance, FBS fasting blood sugar, Ins insulin, TC total cholesterol, TG triglyceride, LDL low density lipoprotein, HDL high density lipoprotein, TAC total antioxidant capacity, CAT catalase, GSH glutathione, MDA malondialdehyde, WC weight circumference, HOMA-B homeostatic model assessment of beta cell function, DHEAS dehydroepiandrosterone sulfate.

| Authors, year | Outcome | Intervention (mean ± SD) | Control (mean ± SD) | Between Groups | Significance | Effect size |
|---------------|---------|--------------------------|---------------------|----------------|-------------|------------|
| Izadi et al. | Weight | 74.1 ± 10.7 | 73.8 ± 10.8 | −0.3 ± 1.1 | 0.02 | 77.6 ± 18.2 | 77.4 ± 18.3 | −0.2 ± 1.1 | 0.01 | 0.10 ± 1.51 | NR | NR |
| Talari et al. | Estradiol | 85.45 ± 17.79 | 99.66 ± 23.01 | 14.21 ± 5.22 | 18.83 | 74.43 ± 17.95 | 71.09 ± 12.29 | −3.34 ± 14.4 | 0.21 | −17.55 ± 15.04 | NR | NR |
| Rahmani et al. | BMI | 28.4 ± 4.4 | 28.2 ± 4.6 | −0.1 ± 0.4 | 0.04 | 29.0 ± 6.5 | 29.0 ± 6.5 | −0.1 ± 0.4 | 0.0 | 0.00 ± 0.52 | NR | NR |
| | TC | 181.8 ± 28.0 | 161.5 ± 31.4 | −20.3 ± 16.6 | 0.68 | 166.4 ± 29.2 | 178.6 ± 29.9 | 12.2 ± 26.1 | −0.41 | 32.50 ± 30.89 | NR | NR |
| | HOMA-IR | 2.8 ± 1.17 | 2.35 ± 1.01 | −0.45 ± 0.16 | 0.985 | 2.73 ± 2.12 | 2.55 ± 1.7 | −0.18 ± 1.74 | 0.09 | 0.27 ± 1.70 | NR | NR |
| | TG | 122.7 ± 61.7 | 100.6 ± 54.0 | −22.1 ± 22.3 | 0.38 | 120.6 ± 59.4 | 128.3 ± 72.6 | 7.7 ± 23.6 | −0.11 | 29.80 ± 32.41 | NR | NR |
| | Ins | 10.8 ± 4.8 | 9.8 ± 4.9 | −1.0 ± 3.5 | 0.20 | 9.8 ± 5.7 | 12.5 ± 6.6 | 2.7 ± 6.6 | −0.43 | 3.70 ± 7.46 | NR | NR |
| | LDL | 111.1 ± 26.5 | 94.4 ± 29.8 | −16.7 ± 15.3 | 0.59 | 92.9 ± 25.5 | 104.8 ± 26.3 | 11.9 ± 26.1 | −0.45 | 28.60 ± 30.19 | NR | NR |
| | HOMA-B | 39.7 ± 18.6 | 35.4 ± 19.1 | −4.3 ± 14.3 | 0.22 | 33.7 ± 21.4 | 44.1 ± 25.4 | 10.5 ± 24.5 | −0.44 | 14.80 ± 28.35 | NR | NR |
| | MDA | 2.9 ± 0.6 | 2.5 ± 0.6 | −0.3 ± 0.4 | 0.66 | 2.2 ± 0.5 | 2.2 ± 0.5 | −0.008 ± 0.6 | 0 | 0.29 ± 0.69 | NR | NR |
| | TAC | 860.5 ± 101.0 | 949.9 ± 119.3 | 89.4 ± 108.9 | −0.80 | 969.5 ± 85.3 | 975.4 ± 98.0 | 5.9 ± 116.2 | −0.06 | −83.50 ± 159.21 | NR | NR |
| | FSH | 7.3 ± 2.5 | 7.2 ± 2.5 | −0.1 ± 3.5 | 0.03 | 7.9 ± 2.8 | 8.1 ± 3.2 | 0.2 ± 3.0 | −0.06 | 0.30 ± 3.49 | NR | NR |
| | SHBG | 37.5 ± 15.9 | 44.1 ± 21.3 | 6.6 ± 14.5 | −0.35 | 39.1 ± 15.0 | 44.9 ± 16.9 | 5.8 ± 13.7 | −0.36 | −0.80 ± 19.93 | NR | NR |
| | LH | 11.0 ± 8.0 | 10.5 ± 8.9 | −0.5 ± 10.1 | 0.05 | 13.5 ± 13.3 | 11.4 ± 7.7 | −2.1 ± 13.3 | 0.19 | −1.60 ± 16.67 | NR | NR |

Effect of vitamin E supplementation on BMI, weight. Seven studies evaluated BMI changes, but only two studies have shown significant albeit small decrease in BMI following vitamin E + CoQ10 supplementation. A study conducted in 2019 also reported a small significant decrease in waist circumference (d = 0.3). Changes in weight were not significant in either one of the studies that evaluated this concept.

Effect of vitamin E supplementation on Insulin resistance parameters. It has been hypothesized that Vitamin E supplementation could affect insulin resistance parameters among patients with PCOS. All three studies have evaluated HOMA score and insulin level changes following dietary supplementation and have shown promising results (Table 2). one of these studies showed a significant small decrease in HOMA score and insulin level (d = 0.15 and 0.2 respectively) in their vitamin E + magnesium supplemented study group25. Meanwhile, another study reported a significant small decrease in HOMA-IR, HOMA-B and insulin levels (d = 0.16 and 0.22 and 0.2 respectively) following vitamin E + Omega 3 fatty acid supplementation. one of the
The purpose of the current systematic review was to investigate the effects of vitamin E on cardiometabolic risk factors, inflammatory and oxidative markers, and hormonal function in PCOS patients. To our knowledge, this study is the first systematic review to assess the supplementary regimen role in PCOS treatment.

Vitamin E supplementation decreases testosterone and LH levels whereas it increases progesterone and FSH levels. So far, Studies have been unable to demonstrate a significant change in estradiol and DHEAS levels following vitamin E co-supplementation. A study by A Ciji et al. reported the effects of vitamin E supplementation...
to reverse oxidant agents’ impact on steroid hormones such as testosterone and estradiol. To the best of our knowledge, no other review study has evaluated the effects of supplementary vitamin E regimens on steroidal hormones. No study showed a significant change in weight following vitamin E supplementation except for one which showed a small significant decrease in BMI following vitamin E + CoQ10 supplementation. Furthermore, Insulin resistance is known to play a critical role in many PCOS comorbidities. A study conducted by Cussons AJ et al. reported that insulin resistance and obesity could lead to ventricular and endothelial dysfunction and atherosclerosis. All three studies evaluating the impact of vitamin E supplementation on insulin resistance showed decreased HOMA score and insulin levels.

A study by Renjing Xu et al. reported the beneficial effect of vitamin E on glycemic control parameters because of its antioxidant effect. And as oxidative stress might increase hemoglobin glycation, and as the detrimental effects of high blood glucose levels on pancreatic islet cells have been linked to oxidative stress. Antioxidant supplementation could manage oxidative stress.

In regards to insulin resistance and dyslipidemia, Diamanti-Kandarakis suggested that insulin resistance can increase TG and LDL levels and decrease HDL levels in PCOS patients. Moreover, they proposed that
Figure 4. (A) Vitamin E and total cholesterol, (B) Vitamin E and LDL, (C) Vitamin E and HDL, (D) Vitamin E and triglyceride.
hyperandrogenism among PCOS patients may also play a role in increasing HDL levels. Vitamin E co-supplementation decreased cholesterol, LDL, and TG levels in all three studies that evaluated the effects of vitamin E supplementary regimens on lipid profile in PCOS. Sepidarkish M et al.'s study showed that vitamin E and fatty acid supplementation could only decrease VLDL levels and do not change other lipid profiles' parameters. A review and meta-analysis on the effects of omega-3 and vitamin E co-supplementation in patients with metabolic syndrome showed that this supplementary regimen could reduce both LDL and TG levels in these patients.

There is a proposed mechanism for vitamin E's beneficial effects on lipid profile improvement, lipid peroxidation, and protection of LDL from oxidation. Niki E et al. have stated that Vitamin E's anti-oxidative feature is due to its beneficial effects on oxidative stress parameters.

The RCTs reviewed in this study showed a significant increase in TAC, NO, catalase, glutathione, GSH levels. They have also reported a substantial decrease in malondialdehyde, CRP, and MDA levels following supplementary regimen administration in PCOS patients. A study by Sepidarkish et al. showed vitamin E, and omega-3 fatty acid co-supplementation to have increased NO levels and TAC while decreasing MDA levels.

Strengths and limitations. This study is the first systematic review assessing the role of vitamin E supplementation in PCOS. In this systematic review, eligible studies couldn’t control confining residual variables. All of the Studies were adjusted for age and PCOS, but some of the reviews didn’t consider well-defined risk factors for changing hormone levels.

This systematic review was unable to show inherent differences in vitamin E supplementation effects on PCOS between different populations and races. More studies evaluating the impact of supplementary regimens in various races and societies are needed. Moreover, due to the limited number of available studies, we could not compare supplementary regimens’ effects between different age groups. The reviewed studies have not pointed out

Figure 5. (A) Vitamin E and estradiol. (B) Vitamin E and testosterone. (C) Vitamin E and SHBG.
as to whether their study populations had vitamin E deficiencies or not. Some studies have proposed that some of the beneficial effects of vitamin E supplementation might be limited to vitamin-E deficient people.

Another limitation is that due to the focus of PROSPERO (International prospective register of systematic reviews) on COVID-19 registrations during the 2020 pandemic, The PROSPERO team has not checked the eligibility of our review.

**Conclusions and implications for future research.** We found that supplementary regimens containing vitamin E can positively affect the patients who are diagnosed with PCOS in regards to metabolic and hormonal parameters. It can improve their hormonal profile by decreasing testosterone and LH levels and by increasing progesterone and FSH levels. It can also reduce insulin resistance, cholesterol, LDL, and TG levels among these patients, it can also improve their cardio-metabolic profile. We also found that vitamin E supplementation can decrease oxidative stress in PCOS.

More studies are needed in order to evaluate the effects of vitamin E supplementation in different ethnicities and age groups. Other studies that assess the effects of vitamin E supplementation in both vitamin E sufficient and deficient populations will add to current knowledge about the role of vitamin E supplementary regimens in PCOS.

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**Figure 6.** (A) Vitamin E and GSH. (B) Vitamin E and TAC. (C) Vitamin E and MDA.
Figure 7. (A) Vitamin E and insulin. (B) Vitamin E and HOMA-IR. (C) Vitamin E and FBS.

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Author contributions

M.P., M.Q., and M.E. participated in the study design, drafting of the paper, and had significant role in development of the selection criteria and data extraction criteria. G.H.T., Y.S.H., F.P., Z.H.S.H., and E.M.V. contributed to the development of the selection criteria, data extraction criteria, and drafting of the paper. N.R. and F.S.H. developed the search strategy and performed statistical analysis. B.L. participated in critical review. M.S.E.S.H. and E.M.V. assessed the quality of studies using the Cochrane Risk of Bias tool. All authors read, provided feedback, and approved the final paper.

Competing interests

The authors declare no competing interests.

Additional information

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