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Original Article

Effect of omega-3 fatty acids supplementation on testosterone levels in women with polycystic ovary syndrome: Meta-analysis of randomized controlled trials

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Background: Scientific literature has shown evidence that omega-3 polyunsaturated fatty acids (PUFA) have anti-androgenic action, and for this reason could be useful as an adjuvant in hyperandrogenism conditions including polycystic ovarian syndrome (PCOS). However, the possible effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation on testosterone concentration still remains undetermined. Therefore, we performed a meta-analysis to investigate effects of EPA/DHA supplements on testosterone hormone in PCOS women.

Methods: Randomized controlled trials (RCTs) published until end May 2015 were searched through a comprehensive search of the PubMed and Scopus electronic databases. Included RCTs evaluated omega-3 fatty acids supplements compared with control in patients with PCOS and reported circulatory androgens. The meta-analysis quality assessment was conducted by the Jadad scoring criteria.

Results: Four RCTs were analyzed in this meta-analysis. The dose range for EPA and DHA was 0.9-3.6. Follow-up ranged from 6 to 8 weeks. Meta-analysis on testosterone levels revealed a significant lowering effect (weighted mean difference - 0.264; 95% confidence interval = −0.39, 0.14; $p < 0.001$) of omega-3 fatty acids for PCOS subjects.

Conclusion: The results of our study revealed benefits on total testosterone with the use of omega-3 PUFA supplements on PCOS patients. Further, high-quality RCTs are required to definitively draw a causal interpretation of our finding.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women in reproductive age. The etiology of the disease remains unknown. The syndrome is characterized by chronic anovulation,

clinical and biochemical hyperandrogenism and irregular menstruation [1]. The prevalence estimates based on diagnostic criteria are different. According to the ESHRE/ASRM diagnostic criteria, the prevalence is estimated to be 15-20% [2].

Some metabolic complications of PCOS are insulin resistance, hyperinsulinemia, obesity and metabolic syndrome [3]. Hyperinsulinemia and insulin resistance in these patients cause stimulation of ovarian androgen production, decreasing sex hormone binding globuling and increasing free testosterone in circulation [4, 5]. Hyperandrogenism apart from infertility (due to lack of ovulation) and beauty consequences (such as acne, alopecia, and hirsutism) increases abdominal obesity which plays a role in the exacerbation of insulin resistance [6].

Non-pharmacologic treatments including lifestyle and dietary changes and weight loss [7, 8] are discussed as first-line treatment of PCOS [9]. Recommended diet changes for example foods with anti-inflammatory properties improve the androgenic profile of these women [8]. Among dietary factors, polyunsaturated fatty acids (PUFA) particularly the type of omega-3 with important bioactive properties act as potent metabolic regulators [10]. In a large body of research, long-chain n-3 fatty acids have been founded to improve several disorders such as insulin resistance, lipid profile, glucose, liver fat content and blood pressure in women with PCOS [11-13]. Moreover, the cost, monitoring and side effects of omega-3 fatty acids are comparatively less than other medical treatments [13].

For the first time, anti-androgenic effect of n-3 PUFAs was suggested in prostate cancer studies [14, 15]. The effects of n-3 PUFAS in PCOS were reported in a cohort study [9], an animal study [16] and some clinical trials [12, 17]. All the same, the anti-androgenic effect of omega-3 fatty acids in PCOS women remains controversial. Thus, current meta-analysis intended to investigate the effect of omega-3 supplementation on total testosterone concentrations in women with PCOS.

Methods

The preferred reporting items for systematic reviews and meta-analyses statement was used for writing up this systematic review [18].

We searched PubMed and Scopus databases for clinical trials published from their inception up to May 2015 investigating the effect of omega-3 supplements on hyperandrogenemia in PCOS women using no language restriction inclusive by using medical subject headings (MeSH), titles, and abstracts. Search terms included: Omega-3 fatty acid (Title/Abstract) OR docosahexaenoic acid (DHA) Title/Abstract) OR eicosapentaenoic acid (EPA) (Title/Abstract) OR n-3 PUFA (Title/Abstract) OR n-3 PUFA (Title/Abstract) OR n-3 fatty acids (Title/Abstract) AND PCOS (Title/Abstract) OR sclerocystic ovary syndrome (Title/Abstract) OR Stein–Leventhal Syndrome (Title/Abstract) OR PCO (Title/Abstract) OR PCOS (Title/Abstract) AND hyperandrogenemia (Title/Abstract) OR androgen profile (Title/Abstract) OR hormonal status (Title/Abstract) OR circulatory androgens (Title/Abstract) OR endocrine parameters (Title/Abstract) OR testosterone (Title/Abstract) OR free androgen index (Title/Abstract) OR dehydroepiandrosterone-sulfate (Title/Abstract) OR sex hormone binding globulin (Title/Abstract) OR androstenedione (Title/Abstract) AND randomized controlled trial (RCT) (Publication Type) OR controlled clinical trial (Publication Type) OR randomized (Title/Abstract) OR placebo (Title/Abstract) OR clinical trials (MeSH Major Topic) OR randomly (Title/Abstract) OR trial (Title) NOT animals (MeSH Terms) NOT humans (MeSH Terms). The search strategy modified as needed for Scopus. References from the selected articles were hand-searched for additional relevant studies.

Studies were included if they fulfilled all of the following criteria in PICOS order: (1) Participants: PCOS women, (2) Intervention: Omega-3 supplements containing EPA and DHA, (3) Comparison intervention: Placebo, (4) Outcomes: Reported final total testosterone mean and standard deviation values for omega-3 and Placebo groups, and (5) Study design: Parallel or cross-over with washout period RCT.

Each of the selected studies full texts was explored and the following data was extracted: First author's name, year of publication, country of research, total and each group sample size,

mean age of each group, total supplement dose and duration of follow-up, the baseline, final and changes in means and standard deviations of total testosterone concentrations in intervention and placebo groups and the details and total Jadad Score. Studies which reported results in ng/ml were converted to nmol/l. For one study we estimated total testosterone concentration from the figure [9], owning to lack of the data in the text and tables.

The quality of the included studies was quantified by Jadad scoring system [19]. The parameters were explored are as follows: reports of randomization, randomization scheme, blinding and withdrawal in intervention and placebo group.

Statistical analyses were made by using STATA software (version 12.0, StataCorp, College Station, Texas, USA). Heterogeneity of studies was assessed using the I^2 statistics. A random-effects model was used if heterogeneity was more than 50%, to calculate the pooled weighted mean difference (WMD).

Results

Figure 1 shows flow diagram of the study selection process. From 26 identified reports, 3 were excluded as a result of duplication. The title and abstract of the remaining 23 reports were reviewed. 18 articles were irrelevant to our meta-analysis. The full texts of 5 remaining articles were elaborated on. Of these, one of the articles had no control arm. Therefore, this study also was excluded. Finally, 4 RCTs were included in our meta-analysis.

The characteristics of including studies are provided in table 1. All of the subjects met the Rotterdam [20] or National Institutes of Health Criteria for PCOS. Nevertheless, two studies investigated only overweight/obese PCOS women [12, 21]. Study populations ranged from 22 to 78 (median: 38). The duration of follow-up ranged from 6 to 8 weeks. The design of two trials [9, 12] was crossover with 6 and 8 weeks washout period. Thus, both of other studies had parallel design. The studies were published in recent 6 years. The EPA/DHA content of daily capsules varied from 0.9 to 3.6 g (median: 2.6). Subject compliance was monitored by capsule counting [9, 21] and assessment of plasma fatty acid composition in two studies [9]. Three studies asked participants to maintain usual dietary intake for the duration of the study [9, 12, 21]. Two studies carried out 7 days food records [17] and 24 hours dietary recalls [21] at the beginning and the end of the intervention.

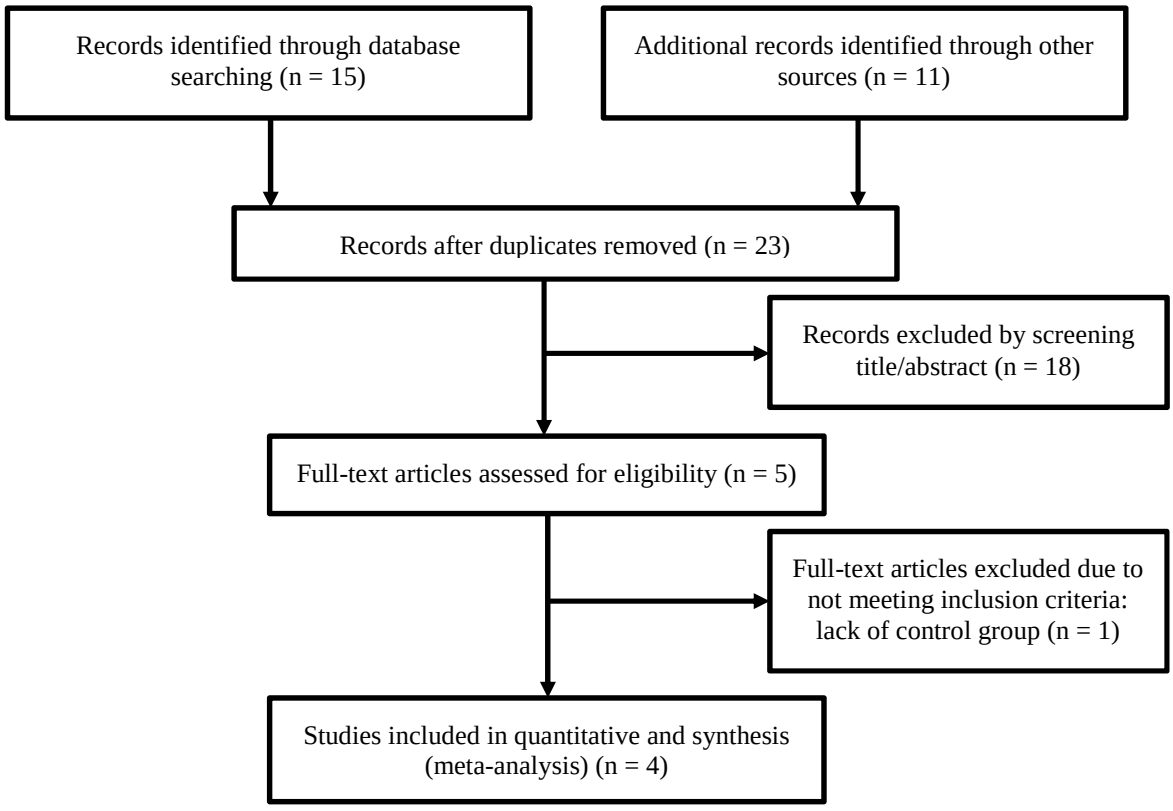

Figure 1. Flow diagram of study

Table 1. Characteristics of included studies

Study's first author	Year	Country	Study design	Participants, mean age	EPA/DHA dose	Duration (weeks)	Sample size	Jadad score
Phelan	2011	Ireland	Double-blind, crossover, randomized placebo-controlled trial	22 PCOS women, I = 29 P = 29	1.9 g	6	I = 22 P = 22	3
Vargas	2011	USA	Prospective, double-blind, placebo controlled study	34 PCOS women, I = 31.7 P = 28.9	3.6 g	6	I = 17 P = 17	3
Cussons	2009	Australia	Double-blind, randomized clinical trial	25 PCOS women I = 32.7 P = 32.7	3.32 g	8	I = 25 P = 25	2
Nadjarzadeh	2013	Iran	Double-blind, crossover, randomized controlled trial	78 obese/overweight PCOS women, I = 26.9 P = 26.9	0.9 g	8	I = 39 P = 39	4

I = Intervention; P = Placebo; EPA = Eicosapentaenoic acid; DHA = Docosahexaenoic acid; PCOS = Polycystic ovarian syndrome

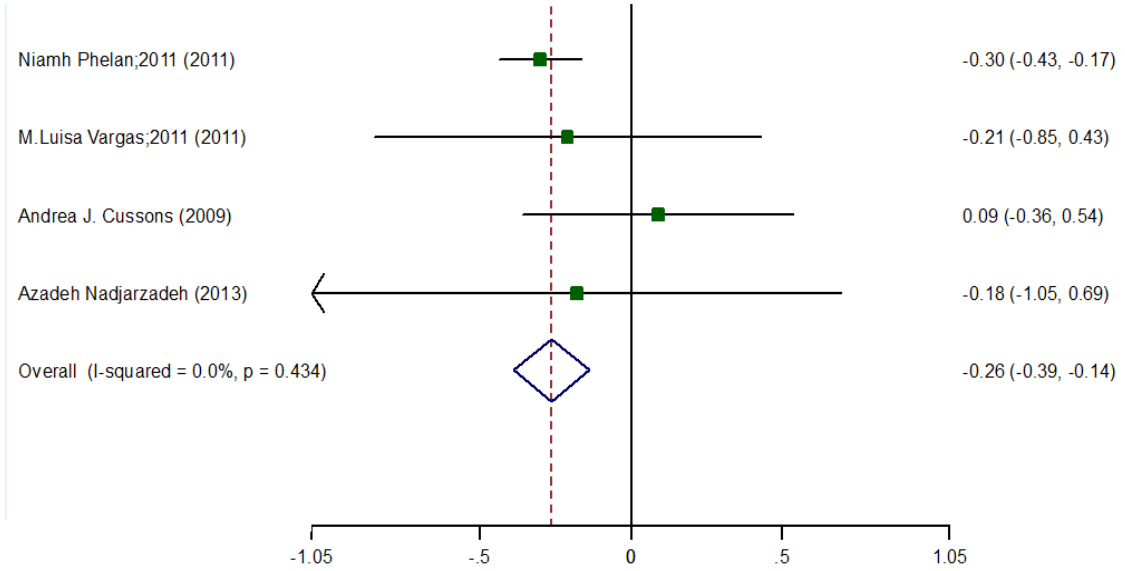

Figure 2. Effect of omega-3 fatty acid supplementation on testosterone levels in women with polycystic ovarian syndrome; meta-analysis of four clinical trials

Quality assessment of RCTs included in our meta-analysis was conducted by Jadad Scale. Although randomization was described in all the papers, only one of which was set out the randomization scheme [21]. All of the studies were double-blinded. There was a description of dropouts and withdrawals in three trials [9, 17, 21]. Only one study scored < 3 on the Jadad scale [12].

Results of changes in total testosterone levels are represented in figure 2. Results from this meta-analysis show a statistically significant improvement for lowering testosterone. The WMD of testosterone from baseline was -0.264 nmol/ml (95% confidence interval = -0.39 to -0.14, $p < 0.001$) in patients with PCOS. Tests for heterogeneity did not reveal significant differences between studies ($p = 0.434$, $Q = 2.74$, and $I^2 = 0.0\%$).

Discussion

In the present systematic review and meta-analysis, we found that omega-3 supplementation might significantly reduce testosterone concentration when compared with placebo. To the best of our knowledge, this is the first systematic review and meta-analysis trying to assess the effect of omega-3 supplementation on circulating testosterone levels.

We tried to include papers with the highest quality in the current systematic review and meta-analysis; because, we limited our analysis to randomized, placebo-controlled trials most of which were double-blinded. We also tried to include studies that used omega-3 fatty acids supplements and excluded studies in which other food or supplements were used for intervention.

EPA and DHA have been suggested to makes a contribution to antioxidant activity in studies of different circumstances [22-24] also that of PCOS [25]. On the other hand, oxidative stress plays a role in PCOS pathogenesis particularly hyperandrogenism [26, 27]. Nevertheless, a direct mechanism has been considered for lowering effect of the LC n-3 PUFAs on androgens as well. This effect was shown by prostate cancer research [14, 15]. Hyperandrogenemia gives rise to several consequences in PCOS subject. Therefore, this meta-analysis has pooled current clinical evidence on the effect of EPA/DHA supplementation on testosterone levels which is likely increased in PCOS women.

Various data from trials show conflicting results of the effect of omega-3 fatty acids supplementation on testosterone and there had been not any systematic review and meta-analysis in this issue. The pooled results from our meta-analysis of all included RCTs revealed that omega-3 fatty acids significantly reduced total testosterone level in PCOS patients. Moreover, heterogeneity testing also was not significant.

Some limitations of our meta-analysis are as follows. First, we sought to undertake the meta-analysis on all androgen parameters, but we failed to perform due to lack of all of these data in the trials. Second, it should be noted that the dosage of EPA/DHA used in included studies was considerably different. As a result, we cannot detect the most effective dose for lowering testosterone. Third, The Jadad score of one study was two. In additiona, most of the papers did not have provided an explanation for method of blinding and randomization.

Although, we included only RCTs with control group and crossover with washout period, this meta-analysis is the only one that deals with omega-3 supplementation influence on testosterone in PCOS patients. Therefore, further trials using more robust design are needed to corroborate the results of this study before the supplementation are made available to the PCOS subjects.

Conclusion

The main conclusion to be drawn from this discussion is that omega-3 supplements containing EPA and DHA generates statistically significant reductions in testosterone levels of PCOS women. Further trials with longer-term and a larger number of patients are recommended.

Acknowledgments

NF and KD designed the research and commented on the final version of the manuscript; NF and SS-b conducted in data gathering; ED analyzed the data; SS-b revised the draft and wrote the paper; NF, KD, and SS-b contributed in the conception of the work. All authors read the final manuscript and agreed for all aspects of the work.

Conflict of interest

None of the authors had any personal or financial conflicts of interest.

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