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Omega-3 supplementation in the treatment of polycystic ovary syndrome (PCOS) – a review of clinical trials and cohort

Vitoria Melo [1], Thomas Silva [1], Thaissa Silva [1], Juliana Freitas [1], Joselita Sacramento [1], Mirian Vazquez [1], Edilene Araujo [1,2,3]

[1]Life Sciences Department, University of the State of Bahia (UNEB), Bahia, Brazil; [2]Life Sciences Departmen, Nucleus of Research and Extension in Nutritional Genomics and Metabolic Dysfunctions (GENUT), University of the State of Bahia (UNEB), Salvador, Brazil; [3]Post-graduation Program Interactive Process of Organs and Systems, Health Sciences Institute/UFBA, Salvador, Brazil
E-mail: emaraujo@uneb.br

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women associated with cardiovascular disease and obesity. The possible benefits of omega-3 supplementation in this syndrome have been discussed much. This study is aimed to verify, based on the scientific data published, if there are any benefits in the omega-3 supplementation in the treatment of PCOS and to indicate its possible dosages for the treatment of polycystic ovary. The work consists of a systematic review of clinical trials and cohort of the MEDLINE/PubMed database from 2009 to October 2019. All studies that analyzed the omega-3 supplementation in women with PCOS were included. Cross-sectional studies, review articles, systematic reviews, meta-analysis, duplicates, studies in animals or cell culture, studies with omega-3 supplementation via food or associated with other supplementations were not included, except those involving vitamin E. In total, 21 articles were selected. Despite the heterogeneity of the studies selected, indirect benefits were observed mainly regarding the glycemic profile, such as insulin resistance reduction, lipid profile modulation (i.e. decrease in total cholesterol, triglycerides, and elevation of high-density lipoprotein), and the regulation of the androgenic profile. As for the anthropometric profile, the studies were scarce and most of them had no significant meaning. Regarding the antioxidant profile and inflammatory biomarkers, the findings differ among studies, but promising results were observed with different doses over 12 weeks of use, such as C-reactive protein (CRP) reduction. Thus, omega-3 fatty acids promote indirect benefits in the treating of women with PCOS. However, to reveal well-defined standards for dosage and supplementation time, further studies are needed.

Key words: polycystic ovary syndrome, fatty acids, omega-3, fish oil, linseed oil

Polycystic ovary syndrome (PCOS) is characterized by clinical, endocrine, and metabolic disorders, including hyperandrogenism associated with the insulin resistance (de Sousa et al. 2013). It is the most common endocrine disorder in women, whereas about 6–10% of women in reproductive age has this condition (Baptiste et al. 2010). However, although such high prevalence of the syndrome has been observed, the etiology of PCOS is still not completely known. However, it is evident that insulin resistance may play an important role due to insulin stimulation to produce ovarian androgens (Silva et al. 2006; Goodarzi et al. 2011). The traditional treatment of PCOS is usually based on oral contraceptives. However, these drugs may promote several side effects, including blood clots formations, headache, weight gain, breast cancer, and depletion of different micronutrients (folic acid and vitamins B2, B6,

Corresponding author: Dr. Edilene Araujo, Universidade do Estado da Bahia, Departamento de Ciencias da Vida, predio 1. Rua Silveira Martins, 2555, Cabula, Salvador, Bahia, Brasil, 41150-000; phone: +55 71 3117-2289; e-mail: emaraujo@uneb.br.

B12, C and E) (Palmery et al. 2013; Stegeman et al. 2013; Mohammad-Alizadeh-Charandabi et al. 2015; Li et al. 2017). Given this context, it is important to understand alternative therapies to promote improvements in the health status and quality of the life. Weight loss, caloric restriction, and intake of inadequate nutrients have contributed to the significant reduction of the symptoms associated with PCOS (Moran et al. 2009; Nybacka et al. 2011) since the syndrome has inflammatory characteristics that change the glycemic and lipid metabolism (Goodarzi et al. 2011). Due to this inflammatory feature of PCOS, the consumption of the omega-3 fatty acids may be a promising nutritional strategy to treat the disease regarding to its anti-atherogenic and anti-inflammatory effects. In addition, the omega-3 fatty acids might have beneficial effects on the glycemic control and lipid profile (Becic and Studenik 2018; Thota et al. 2018). Therefore, this study is aimed to verify, based on the scientific literature data, if there are benefits in the omega-3 supplementation in the treatment of PCOS as well as indicates possible dosages for the treating of this syndrome.

Materials and methods

This work is a systematic review of selected articles, based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendation, to evaluate the possible effects of the omega-3 supplementation for PCOS cases. Scientific literature was researched to identify the relevant studies to this review by using the MEDLINE/PubMed database until October 2019. Inclusion criteria were that all articles published in the last 10 years (2009–2019) contained full text and the following characteristics: clinical trials, randomized/cohort, in which oral animal and/or vegetal omega-3 supplementation has been analyzed and applied to women with PCOS. Those studies were included, in which omega-3 supplementation was associated with vitamin E as the most common commercial association. Cross-sectional studies, review articles, duplicate publications, studies in animals or cell culture studies that analyzed omega-3 supplementation via food or associated with another supplementation, except vitamin E, were not included. In the search for publications, the logical AND operator was used to combine the term *Ovary Polycystic Syndrome* with the following terms: *omega 3*; *fish oil*; *linseed oil*; *alpha linolenic acid*; *linolenic acid*; *polyunsaturated fatty acids*; *eicosapentaenoic acid,* and *docosahexaenoic acid*. Three reviewers independently carried out the selection and analysis of articles by using the predefined eligibility criteria (Figure 1).

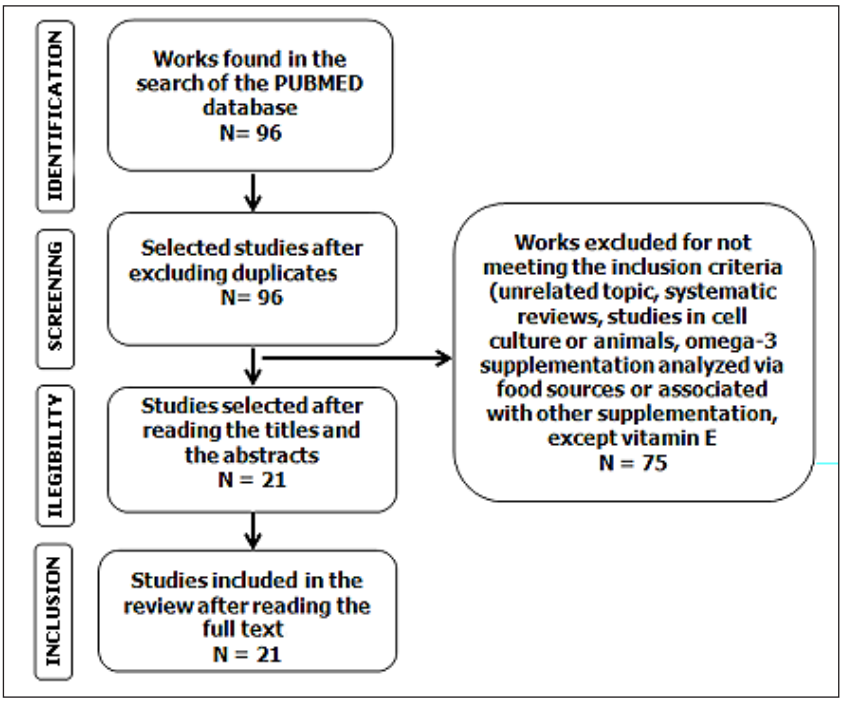

Figure 1. Flowchart of the systematic search for articles.

Results

Altogether, 96 articles were obtained without duplicates. After reading the titles and abstracts, 21 studies were selected. The main reason for excluding the articles was the non-adequacy to the proposed theme or studies done on animals or *in vitro* conditions. After the reading completing, 21 articles remained in the study, which met the criteria established (Figure 1). The average time for clinical trials in this review endured from 6 to 12 weeks (only two articles lasted 6 months) and an average of 63.7 women participated in the study. The age of these women ranged between 18 and 45 years. Out of the 21 clinical trials, 12 used fish oil as a source of omega-3 supplementation; 2 used omega-3 fat associated with vitamin E; 2 used linseed oil; 3 used linseed oil associated with vitamin E; and 2 used fish oil and linseed oil in the same study. Parameters associated with PCOS were analyzed, such as lipid, glycemic, hormonal profiles, inflammation and oxidative stress biomarkers, and anthropometric parameters. The results are described in the Table 1.

Discussion

According to the studies analyzed, supplementation with animal/vegetable origin the omega-3 fatty acids might have indirect beneficial effects on PCOS via the significant improvement of parameters of the lipid, glycemic profile, in addition to some effects on the hormonal profile and antioxidant and inflammatory biomarkers. However, controversial results were found, which might be related to different dosages, supplementation time, and the sample size. It is noteworthy that the studies included in this review simultaneously analyzed several aspects related to PCOS. For a better understanding, several aspects will be discussed below in separate topics.

Effect on lipid profile and hepatic fat. The omega-3 consumption is related to the improvement of the lipid profile and reduction of cardiovascular risk since fatty acids are natural ligands of the metabolic nuclear receptors, such as PPARs (peroxisome proliferator-activated receptors), and SREBP-1 (sterol regulating element binding protein 1). Activation of these omega-3 receptors can inhibit coding of proteins that stimulate lipid synthesis and stimulate genes that increase lipid oxidation in liver and muscle (Cussons et al. 2009; Mohammadi et al. 2012; Rafraf et al. 2012). In addition, the omega-3 supplementation seems to play an important role in the activation of AMPK (AMP-activated protein kinase), a sensor of cellular energy status that regulates the balance between lipid oxidation and lipogenesis. Ingestion of the omega-3 supplementation also increases the activity of the low-density lipoprotein (LDL) receptor in the liver, which reduces LDL-cholesterol synthesis and thus, increases the LDL-cholesterol catabolism rate (Cussons et al. 2009; Mohammadi et al. 2012; Rafraf et al. 2012). This effect has been observed in women with high omega-3 plasma levels, which resulted in a significant improvement in the lipid profile for triglycerides and triglyceride ratio: high-density lipoprotein (HDL) (Phelan et al. 2011; Vargas et al. 2011; Karakas et al. 2016).

In addition, it has been noted that the use of fish and linseed oils provides a significant reduction in serum triglycerides, without changing the total cholesterol (TC) levels, HDL or apoprotein B (Vargas et al. 2011). However, the omega-3 consumption from linseed oil associated with vitamin E significantly decreases serum triglycerides, very low-density lipoproteins (VLDL), LDL, and TC, as well as reduces the lipoprotein A (Lp [a]) and oxidized LDL (Ox-LDL) mRNA in peripheral blood mononuclear cells (Rahmani et al. 2016). Reduction of TC indices and their fractions were noted after supplementation with fish oil, in addition to a significant reduction in LDL and an increase in HDL (Mohammadi et al. 2012; Khani et al, 2017; Mejia-Montilla et al. 2018; Yang et al. 2018).

The effects of the omega-3 oils on triglyceride levels, HDL, LDL, and TC seem to be contradictory due to the heterogeneity of the studies (Arentz et al. 2017). It is noticeable that the dosages and the supplementation time were very different among studies, which makes standardization difficult. From the 12 clinical trials that analyzed lipid profile, 11 found positive results regarding the modulation of levels. The study without significant results analyzed a dosage of 800 mg of omega-3 supplementation from fish oil (Amini et al. 2018). The reduction in triglycerides was mostly found in the studies analyzed (Mohammad-Alizadeh-Charandabi et al. 2015). As for supplementation, the procedures with best results in the treatment of lipid profile women with PCOS were as follows: 1200 mg/day of omega-3 supplementation from fish oil (eicosapentaenoic acid, EPA+docosahexaenoic acid, DHA), for 8 weeks (2 studies) (Mohammadi et al. 2012; Rafraf et al. 2012) and 600 mg/day (EPA+DHA) from fish oil for 6 months (1 study) (Oner and Muderris 2013). For linseed-oil-based omega-3 supplementation, the most effective results were 800 mg alpha-linolenic acid (ALA)/day for 12 weeks (1 study) (Mirmasoumi et al. 2018) and 400 mg

Table 1
Works found in the review (clinical trials and cohort).

Year	Author(s)	Kind of study	Sample/ Intervention	Duration	Results	Conclusion
2009	Cussons et al.	Randomized, double-blind, cross-over, placebo-controlled clinical trial	25 patients. **Case group**: Omega-3 supplementation [4 capsules: DHA (560 mg) + EPA (270 mg) each]. **Control group**: placebo. There was an 8-week wash-out and then the cross-over of the groups.	8 weeks	Reduction of liver fat (p=0.022), TG (p=0.002), systolic and diastolic pressure (p=0.018; p=0.005) compared to placebo. Furthermore, in women with a high level of liver fat (>5%), there was also a reduction in fasting insulin (p=0.038) and HOMA-IR score (p=0.021) compared to placebo.	Omega-3 supplementation had a beneficial effect in reducing liver fat and other cardiovascular risk factors in women with PCOS who were overweight/obese. These benefits were more evident in patients with hepatic steatosis (>5%).
2011	Phelan et al.	Cross-sectional cohort study and Randomized, double-blind, cross-over, placebo-controlled clinical trial	**Cohort:** Blood samples from 104 women were analyzed for plasma FA composition and the relationship with plasma hormones, weight, height, BMI, WC, and QC. **Clinical trial:** 22 women. **Case group:** Omega-3 supplementation [EPA (1.9 g) + DHA daily]. **Control group:** placebo. There was a 6-week wash-out and then the cross-over of the groups.	6 weeks	**Cohort:** Women with higher omega-6 plasma levels (W6) had higher testosterone (p=0.013) and DHEAS (p=0.033). Women with higher levels of omega-3 fats (W3) had significantly better lipid profile in terms of TG and TG ratio: HDL (p<0.05). **Clinical trial:** Experimental group obtained a reduction in bioavailable testosterone concentrations (p<0.05) compared to baseline and placebo. No significant results for: total testosterone, DHEAS, androstenedione, SHBG estrogen, LH, FSH, lipid and glycemic profile.	Omega-3 FAs can improve the concentration of bioavailable testosterone in PCOS.
2011	Vargas et al.	Randomized, double-blind, placebo-controlled clinical trial	51 women. **Case group 1:** fish oil [6 capsules: EPA (358 mg) and DHA (242 mg)]. **Case group 2:** linseed oil [6 capsules: ALA (545 mg)]. **Control group:** placebo.	6 weeks	Fish oil raised glucose levels during OGTT (p=0.0355) and decreased the insulin sensitivity index (Matsuda) (p=0.0378), without significantly affecting fasting glucose, insulin or HOMA-IR. Linseed oil increased blood glucose for 30 min in OGTT, but did not change glucose homeostasis. None of the supplements affected CRP levels. Compared to baseline, fish oil and linseed, serum triglycerides decreased (p=0.0154 and p=0.0176). None of the oils altered TC, HDL or Apo B, nor testosterone, SHBG or DHEAS.	Animal and vegetable omega-3 FAs reduced serum triglycerides, and despite elevating blood glucose during OGTT they did not significantly affect glucose homeostasis.

Table 1
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Year	Author(s)	Kind of study	Sample/ Intervention	Duration	Results	Conclusion
2012	Mohammadi et. al.	Randomized, double-blind, placebo-controlled clinical trial	61 patients. **Case group:** Omega-3 supplementation (4 capsules daily with 180 mg of EPA and 120 mg of DHA). **Control group:** placebo.	8 weeks	In the test group, a significant increase in serum adiponectin (p=0.003), a reduction in glucose (p<0.001), insulin (p=0.002), HOMA-IR (p<0.001), TC (p=0.002) and levels of LDL-c (p=0.003), compared to placebo. Serum TG levels decreased significantly (p=0.024) and HDL increased (p = 0.018) compared to baseline values. No significant changes to PCR.	Omega-3 supplementation had beneficial effects on serum adiponectin, insulin resistance and lipid profile in patients with PCOS.
2012	Mohammadi and Rafraf	Randomized, double-blind, placebo-controlled clinical trial.	61 patients. **Case group:** Omega-3 supplementation (4 capsules daily with 180 mg of EPA and 120 mg of DHA) **Control group:** placebo.	8 weeks	The test obtained a significant reduction in the TC/HDL-c and LDL-c/ HDL-c ratio (p=0.009) and significantly increased the serum activity of PON1 (p=0.048) when compared to placebo. The reduction in the proportions TC/ HDL-C, LDL-C/HDL-C and TG/ HDL-C and the increase in serum PON1 activity were also significant in the group of omega-3 FAs at the end of the study when compared to the baseline values (p<0.001, p<0.001, p=0.004 and p=0.001, respectively). There were no significant differences in weight and BMI.	Omega-3 supplementation can be a useful approach to decrease cardiometabolic risks in women with PCOS, both by improving the activity of PON1 as an antioxidant marker, and by reducing some serum lipid proportions.
2012	Rafraf et al.	Randomized, double-blind, placebo-controlled clinical trial.	61 patients. **Case group:** Omega-3 supplementation (4 capsules daily with 180 mg of EPA and 120 mg of DHA). **Control group:** placebo.	8 weeks	In the experimental group, omega-3 supplementation did not promote significant effects for weight, BMI, WC and WHR. There was a reduction in glucose (in 11.4%, p <0.001), insulin (in 8.4%, p, 0.05) and HOMA-IR (in 21.8%, p, 0.001) when compared to placebo group.	Omega-3 FAs improved glucose parameters in patients with PCOS.
2013	Oner; Muderris.	Clinical trial	45 patients supplemented with 1500 mg/day of omega-3 FAs.	6 months	The mean BMI significantly decreased during the treatment period (p=0.007), in addition to: scores of hirsutism (p<0.001), insulin (p=0.009) and HOMA-IR (p=0.017). Serum levels of FSH, DHEAS. TSH, androgen and resistin levels did not change, while LH (p<0.001), total (p=0.032) and free (p=0.02) testosterone decreased significantly. The levels of SHBG (p=0.008) and TNF (p=0.03) increased after treatment.	There was a positive correlation between omega-3 supplementation and decreased insulin resistance, hirsutism, BMI and some hormonal androgenic parameters.

Table 1
Continued ...

Year	Author(s)	Kind of study	Sample/ Intervention	Duration	Results	Conclusion
2013	Nadjarzadeh et al.	Randomized, double-blind, placebo-controlled clinical trial.	78 women. **Case group:** Omega-3 supplementation (3 capsules containing 180 mg of EPA + 120 mg of EPA each). **Control group:** placebo.	8 weeks	The mean testosterone concentration decreased in the test group (p=0.04), while the FAI and SHBG did not differ significantly between groups. The Omega-3 group had their menstrual cycle regularized in relation to the placebo (p=0.049).	In addition to making the menstrual cycle more regular, 3 g omega-3 supplementation could reduce serum testosterone concentrations in overweight and obese patients with PCOS.
2015	Nadjarzadeh et al.	Randomized, double-blind, placebo-controlled clinical trial.	78 women. **Case group:** Omega-3 supplementation (3 capsules containing 180 mg of EPA + 120 mg of EPA each). **Control group:** placebo	8 weeks	There was no significant difference in relation to BMI, visfatin, FSH and prolactin in both groups. WHR decreased significantly in the test group compared to the baseline (p<0.005). Adiponectin increased significantly in the test group (p<0.001) and the mean LH decreased (p<0.005).	Omega-3 supplementation in women with PCOS may have a beneficial effect on adiponectin, LH concentration, WHR, and LH/ FSH ratio.
2016	Karakas et al.	Randomized, double-blind and placebo-controllled clinical trial.	51 women. **Case group 1:** fish oil, **Case group 2:** linseed oil. **Control group:** placebo with soybean oil.	6 weeks	Fish oil decreased the glycated hemoglobin HGBA1c (p<0.05) and Matsuda's insulin sensitivity index (p<0.05) when compared to the baseline. Triglycerides were also reduced with the use of fish oil and linseed compared to the baseline (p<0.05 for both), but did not decrease with placebo (soy oil).	Omega-3 FAs from fish oil could improve parameters related to the glycemic profile (HGBA1c and Matsuda Index) and triglyceride levels in women with PCOS. Omega-3 FAs from linseed oil also reduced triglyceride levels in women with PCOS. However, neither of them significantly interfered in other parameters of glycemic and/or lipidic profile.
2016	Rahmani et al.	Randomized, double-blind, placebo-controlled clinical trial.	68 patients. **Case group:** 1000 mg linseed oil containing 400 mg of ALA plus 400 IU of vitamin E. **Control group**: placebo	12 weeks	The experimental group obtained a reduction in the expression of Lp (a) RNAm and Ox-LDL mRNA in peripheral blood mononuclear cells (p<0.001 for both) and reduced triglycerides, VLDL, LDL and TC (p<0.001 for all). There was also a significant increase in antioxidants in plasma (p=0.003) and a decrease in MDA levels (p=0.01).	Omega-3 supplementation associated with vitamin E for 12 weeks in women with PCOS significantly improved the gene expression of Lp (a) and Ox-LDL, lipid profile parameters and oxidative stress biomarkers.

Table 1
Continued ...

Year	Author(s)	Kind of study	Sample/ Intervention	Duration	Results	Conclusion
2017	Ebrahimi et al.	Randomized, double-blind, placebo-controlled clinical trial.	68 women. **Case group:** 1000 mg omega-3 FAs from linseed oil (400 mg of ALA + 400 IU vitamin E). **Control group:** placebo.	12 weeks	Omega-3 supplementation + vitamin E reduced insulin (p=0.004), HOMA-IR (p=0.005), HOMA-B (p=0.004), and increased QUICKI (p=0.008). In addition to significant reductions in total testosterone (p=0.008) and free testosterone (p=0.04) compared to placebo. No significant effect on fasting plasma glucose and other hormonal profiles.	The omega-3 supplementation associated with vitamin E for 12 weeks in women with PCOS significantly improve indices of insulin resistance and total/free testosterone.
2017	Mirmasoumi et al.	Randomized, double-blind, placebo-controlled clinical trial.	60 women. **Case group:** omega 3 (2000 mg of linseed oil with 800 mg of ALA) twice a day. **Control group:** placebo.	12 weeks	Omega-3 supplementation reduced insulin (p=0.01), HOMA-IR (p=0.01), mF-G score (p=0.001) and increased QUICKI (p=0.01). There was also a reduction in triglycerides, VLDL (p=0.01 for both) and CRP (p=0.004). No significant changes were observed in hormonal profiles, plasma nitric oxide levels, as well as TC, LDL and HDL.	Omega-3 supplementation for 12 weeks in women with PCOS had beneficial effects on insulin metabolism, mF-G scores, serum triglycerides, VLDL and CRP levels, but did not affect hormone levels, other lipid profiles and nitric oxide plasma levels.
2017	Mejia-Montilla et al.	Randomized, double-blind, placebo-controlled clinical trial.	195 women. **Case group:** omega-3 supplementation derived from fish oil, 180 mg of EPA + 120 mg of DHA) and **Control group:** placebo.	12 weeks	In the test group there was a significant reduction in insulin, HOMA-IR, area under the insulin curve and area under the glucose curve ($p<0.05$ for all) TC, LDL-c and TG ($p<0.0001$ for all), and also significant increase in the concentrations of HDL ($p<0.0097$), Apo-B ($p<0.0001$), as well as average adiponectin ($p<0.0001$).	Omega-3 supplementation for 12 weeks can promote significant improvements in the glycemic and lipidic profile of women with PCOS, in addition to raising levels of adiponectin, which is directly linked to metabolic regulation and insulin resistance improvement.
2017	Nasri et al.	Prospective, randomized, double-blind, placebo-controlled clinical trial.	60 women. **Test group:** omega-3 supplementation (1000 mg of linseed oil containing 400 mg of ALA) twice a day. **Control group:** placebo.	12 weeks	Omega-3 supplementation increased mRNA activation of PPAR-γ (p=0.005) in peripheral blood mononuclear cells and decreased LDL-R mRNA expression (p=0.002). There was no significant effect on the expression of the GLUT-1 and Lp (a) gene.	Omega-3 supplementation for 12 weeks in women with PCOS significantly improved the gene expression of PPAR-γ and LDL-R, but did not affect the gene expression of Lp (a) and GLUT-1 in peripheral blood mononuclear cells.

Table 1
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Year	Author(s)	Kind of study	Sample/ Intervention	Duration	Results	Conclusion
2017	Jamilian et al.	Randomized, double-blind, placebo-controlled clinical trial.	40 women. **Test group:** Omega-3 supplementation (1000 mg of linseed oil with 400 mg of ALA + 400 IU of vitamin E). **Control group:** placebo.	12 weeks	The test group had a significant reduction in insulin (p=0.02) and HOMA-IR (p=0.03), expression of IL-8 (p=0.003) and TNF-α (p=0.001) and increased regulation of PPAR-γ expression (p=0.04).	Omega-3 supplementation associated with vitamin E for 12 weeks in women with PCOS resulted in significant improvements in the gene expression of PPAR-γ, IL-8 and TNF-α. This suggests that omega-3 supplementation associated with vitamin E may have beneficial therapeutic potential for patients with PCOS.
2017	Khani et al.	Randomized, double-blind, placebo-controlled clinical trial.	87 patients. **Test group:** omega-3 (2 capsules/ day each containing 180 mg of EPA and 120 mg of DHA). **Control group:** no intervention.	6 months	In the test group, there was a reduction in WC, TC, TG, and an increase in HDL (p<0.0001 for all) and the interval between menstrual periods was significantly regularized (p<0.001). There were no significant differences in weight, QC, blood glucose, number of ovarian follicles, ovary size, bleeding volume, menstrual bleeding and hirsutism score.	Omega-3 supplementation in women with PCOS beneficially modulated lipid profiles, decreased waist circumference and the interval between menstrual periods. These data suggest that omega-3 supplementation can improve metabolic parameters and make menstrual state regular.
2018	Amini et al.	Randomized, double-blind, placebo-controlled clinical trial.	60 women. **Test group:** 1000 mg of fish oil containing 240 mg of EPA and 160 mg DHA, 2 capsules/day. **Control group**: placebo.	12 weeks	In the test group there was a significant reduction in serum insulin (p=0.01), HOMA-IR (p<0.001), total testosterone (p=0.03) and hirsutism index (p=0.001) and significantly increased QUICKI (p=0.008). There was also a decrease in CRP (p<0.001) and MDA (p=0.03) and a significant increase in total plasma glutathione (p=0.02).	Omega-3 supplementation for 12 weeks for PCOS patients promoted beneficial effects on insulin metabolism, total testosterone, hirsutism, as well as some inflammatory and oxidative stress markers.
2018	Rahmani et al.	Randomized, double-blind, placebo-controlled clinical trial.	40 women. **Test group:** 1000 mg of fish oil containing 180 mg of EPA and 120 mg of DHA. **Control group:** placebo twice a day.	12 weeks	Omega-3 supplementation did not affect LDL-R, Lp (a), TNF and TGF-β gene expression. However, it significantly increased the PPAR-γ gene expression (p<0.001) and reduced the IL-1 (p=0.02) and IL-8 (p=0.01) gene expressions.	Fish oil supplementation for 12 weeks to women with PCOS promoted a significant improvement in the PPAR-γ, IL-1 and IL-8 gene expressions, but did not influence the LP (a), LDL-R, GLUT- 1, TNF and TGF-β ones.

Table 1
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Year	Author(s)	Kind of study	Sample/ Intervention	Duration	Results	Conclusion
2018	Talari et al.	Randomized, double-blind, placebo-controlled clinical trial.	60 women. **Test group:** 1000 mg omega-3 supplementation + 400 IU vitamin E. **Control group:** placebo.	12 weeks	Omega-3 supplementation reduced left ($p<0.001$) and right ($p=0.010$) carotid intima-media thickness (CIMT), and reduced CRP levels ($p=0.006$) without significantly affecting nitric oxide levels.	Co-supplementation with omega-3 and vitamin E for 12 weeks among patients with PCOS had beneficial effects on carotid thickness and serum CRP values, but without changes in nitric oxide levels.
2019	Sadeghi et al.	Randomized, double-blind, placebo-controlled clinical trial.	62 women. **Test group:** 2000 mg of omega-3 supplementation + vitamin E 400 IU. **Control group**: placebo.	8 weeks	Co-supplementation of omega-3 and vitamin E significantly increased total antioxidant capacity ($p<0.001$), catalase activity ($p<0.001$), glutathione levels ($p=0.028$) and a significant reduction in malondialdehyde levels ($p=0.008$).	Co-supplementation with omega-3 and vitamin E had a beneficial effect on the total antioxidant capacity, malondialdehyde concentrations, glutathione levels and catalase activity.

Abbreviations: ALA – alpha-linolenic acid; Apo-B – apolipoprotein B; WC – waist circumference; HC – hip circumference; DHA – docosahexaenoic acid; DHEA – dehydroepiandrosterone; EPA – eicosapentaenoic acid; FA – fatty acid; FAI – free androgen index; FSH – follicle stimulating hormone; GLUT-1 – glucose transporter 1; HDL-c – cholesterol associated with high density lipoprotein; HGBA1c – glycated hemoglobin; HOMA-B – Beta homeostasis assessment model; HOMA-IR – homeostasis assessment model related to insulin resistance; IL-1 and IL-8 – interleukin 1 and 8; BMI – body mass index; LDL-c – cholesterol associated with low-density lipoprotein; LDL-R – LDL receptor; LH – luteinizing hormone; Lp (a) – lipoprotein (a); MDA – malondialdehyde; mF-G – modified by Ferriman and Gallwey; Ox-LDL – oxidized LDL; PCR – C-reactive protein; PCR-as – highly sensitive C-reactive protein; PON1 – paraoxonase 1; PPAR-γ – peroxisome-proliferator-activated receptor; QUICKI – quantitative index of verification of insulin sensitivity; WHR – waist/hip ratio; MRNA – messenger ribonucleic acid; SHBG – sex hormone-binding globulin; TC – total cholesterol; TG – triglycerides; TGF-β – growth transformation factor-beta; TNF – tumor necrosis factor; OGTT – oral glucose tolerance test; TSH – thyroid stimulating hormone; VLDL – very low-density lipoprotein.

ALA+400 IU vitamin E/day for 12 weeks (1 study) (Rahmani et al. 2016). As for hepatic steatosis, the only data found for 3.32 g of EPA+DHA/day for 8 weeks. In this case, a reduction of >5% of hepatic fat reduction was observed ($p=0.022$) (Cussons et al. 2009).

Effect on the steroidogenic profile. Hyperandrogenism is a hallmark of PCOS related to hyperinsulinemia, as this factor in the syndrome is associated with a direct increase in the production of androgens by the ovary and a decrease in the levels of sex hormone-binding globulin (SHBG). SHBG is a protein that binds to testosterone, reducing its action potential. Therefore, after the reduction of SHBG caused by hyperinsulinemia, there is a massive increase of free testosterone. In addition, patients with PCOS have hypersecretion of the luteinizing hormone (LH), which further increases the production of androgens and causes disturbance of the menstrual cycle, infertility, hirsutism, acne, and alopecia (Hajishafiee et al. 2016; Yao et al. 2017; Amini et al. 2018).

Clinical trials have demonstrated a possible anti-androgenic function of omega-3 fatty acids in PCOS. Although the mechanisms have not been well established, insulin reduction is an important factor of these fatty acids (Oner and Muderris 2013; Ebrahimi et al. 2017; Khani et al. 2017). This relationship was well demonstrated in a study that observed the omega-6/omega-3 ratio in the blood plasma of women with PCOS and concluded that the higher the omega-6/omega-3 ratio in the plasma, the higher levels of testosterone and dehydroepiandrosterone (DHEA-S) (Phelan et al. 2011). The omega-3 supplementation of 1.9 g (EPA+DHA) for 6 weeks can reduce free testosterone levels without interfering with the total testosterone, DHEA-S, androstenedione, SHBG, estrogen, LH or follicle-stimulating hormone (FSH). However, ALA supplementation of 400 mg ALA+400 IU of vitamin E for 12 weeks promoted significant reductions not only in the free testosterone, but also in the total plasma testosterone and decreased hirsutism index when compared to the placebo group (Ebrahimi et al. 2017; Amini et al. 2018). Similarly, the omega-3 supplementation of 800 mg for 12 weeks

or 1500 mg for a period of more than 6 months significantly reduced several steroidogenic parameters, such as serum levels of the total testosterone, free testosterone, LH, androgens, and hirsutism score (Oner and Muderris 2013; Amini et al. 2018). Lower doses of EPA+DHA (600 mg/day) did not reduce the hirsutism index, but the menstrual cycle of women with PCOS became more regular (Khani et al. 2017). The same result was found in the fish oil omega-3 supplementation of 900 mg since there was a reduction in the mean testosterone concentration (Nadjarzadeh et al. 2013) and the LH levels (Nadjarzadeh et al. 2015).

In contrast to these findings, supplementation with a higher dosage of 3.6 g of EPA+DHA for 6 weeks did not induce effects on testosterone, SHBG or DHEAS (Vargas et al. 2011). The omega-3 supplementation may have an effect in reducing the total testosterone, but it does not reduce both SHBG and DHEA-S, as the results were controversial and this supplementation is suggested for longer periods (>6 weeks) to obtain the same effect (Hajishafiee et al. 2016). The effects found in the studies were widely different, as well as their doses and supplementation time. Among the 8 clinical trials analyzing steroidogenic hormonal aspects, only one did not find any benefit in this profile (Vargas et al. 2011). However, this study had the highest dosage (3.6 g of EPA+DHA) in a reduced period of time, which raises the discussion that the standard dose used (1.5 g of EPA+DHA) for long periods (>6 months) may show better benefits (Oner and Muderris 2013).

Effect on the glycemic profile. As already discussed, the PCOS pathogenesis may have a direct link to insulin resistance since hyperinsulinemia promotes hyperandrogenism by stimulating androgen synthesis via teak cells and reduces SHBG and thus, produces free testosterone increasingly (Avila et al. 2014; Sadeghi et al. 2017). Studies have shown that women with PCOS have an increased risk of type 2 diabetes mellitus (DM2) in comparison to non-PCOS women, and more than 50% of patients with PCOS are insulin resistant (Unluhizarci et al. 2012; Jamil et al. 2015). Therefore, the discussion arises about the possible relationships between the omega-3 fatty acids, insulin resistance, and PCOS. Several studies have found positive results from omega-3 supplementation on glycemic parameters and adiponectin levels (Mohammadi et al. 2012; Ebrahimi et al. 2017; Amini et al. 2018; Jamilian et al. 2018). Adiponectin is a hormone that improves sensitivity of cells to insulin and has an anti-inflammatory and anti-atherogenic effects. The possible beneficial effects of omega-3 supplementation on glucose parameters can be partially associated with this fatty acid potential to increase adiponectin production (Mohammadi et al. 2012). The significant increase of this hormone was noticed after 8 weeks of the omega-3 supplementation (900 mg of EPA+DHA) (Nadjarzadeh et al. 2015). However, in addition to significantly increasing levels of adiponectin, the use of 1200 mg of EPA+DHA for the same period favored the reduction of glucose, insulin, and HOMA-IR (Mohammadi et al. 2012; Rafraf et al. 2012).

In a longer supplementation period (6 months) with 1500 mg of EPA+DHA/day, levels of insulin and HOMA-IR were reduced without a significant reduction in blood glucose (Cussons et al. 2009; Oner and Muderris 2013). Some studies did not find significant changes in insulin, glycemia, and HOMA-IR levels even after higher omega-3 doses (1.9 g and 3.6 g for 6 weeks) (Phelan et al. 2011; Vargas et al. 2011). A meta-analysis concluded that there was no significant effect of the omega-3 supplementation, when compared to placebo, on insulin resistance, and HOMA-IR in women with PCOS (Sadeghi et al. 2017). However, recent studies have shown promising results in this regard. The omega-3 supplementation from linseed oil with vitamin E co-supplementation (400 mg ALA+400 IU vitamin E) for 12 weeks had benefits on the glycemic profile of women with PCOS, such as reduced insulin and HOMA-IR (Ebrahimi et al. 2017; Jamilian et al. 2018). Similar findings were found with the linseed oil supplementation without vitamin E (800 mg of ALA) (Mirmasoumi et al. 2018), fish oil supplementation (dosage not reported) (Mejia-Montilla et al. 2018), and fish oil supplementation (800 mg of EPA+DHA) (Amini et al. 2018) all lasting 12 weeks. The heterogeneity of the studies has revealed contradictory results in relation to the omega-3 supplementation in women with PCOS and changes in the glycemic profile. However, the beneficial effects are clearly evident (Arentz et al. 2017; Yang et al. 2018). According to the analyses, the omega-3 supplementation may have benefits in reducing insulin and HOMA-IR in women with PCOS. In 12 clinical trials that evaluated at least 1 parameter related to the glycemic profile, 10 found positive results mainly in the longer supplementation periods. From the 12 studies, 5 found reduced insulin and HOMA-IR within 12 weeks of supplementation, either with linseed oil (400 mg ALA+400 IU vitamin E/day or 800mg ALA/day without adding vitamin E) or fish oil (1200 or 1500 mg/day of EPA+DHA).

Effect on the anthropometric profile. Women with PCOS have a higher prevalence of obesity and metabolic syndrome since the correlation between

obesity, insulin resistance, and PCOS pathogenesis (Oner and Muderris 2013; Silva 2013). Therefore, diets and healthy eating patterns for weight loss have been widely discussed in the treatment of this disease. A study that proposed a diet with a healthy eating pattern for women with PCOS has shown significant weight loss in these women in addition to improvements in steroidogenic parameters and the glycemic profile related to the syndrome. Thus, weight loss is related to a positive impact of PCOS treatment (Foroozanfard et al. 2017). It has been discussed much in relation to the effects of omega-3 fatty acids on weight loss since some studies have made this association. A trial carried out with diabetic women observed a reduction in adiposity after the omega-3 supplementation (Lee et al. 2013). Although there are significant results of weight loss in rodents (Buckley and Howe 2010), studies in humans that demonstrate weight loss with the omega-3 supplementation are still scarce. There were no significant differences in body mass index (BMI) and body weight after using 1200 mg omega-3 supplementation (EPA+DHA) for 8 weeks in women with PCOS (Rafraf et al. 2012; Mohammadi and Rafraf 2012). However, a significant reduction in mean BMI has been observed in a group of women supplemented with omega-3 after 6 months of treatment, with 1500 mg of EPA+DHA (Oner and Muderris 2013). For the same period, the omega-3 supplementation of 2000 favored a reduction in waist circumference (WC) without changes in weight (Khani et al. 2017). After 8 weeks of the omega-3 supplementation of 900 mg (EPA+DHA), there was a significant decrease in the waist-to-hip ratio (WHR) compared to baseline, but BMI did not change significantly (Nadjarzadeh et al. 2015). Data suggest that there is an association between omega-3 fatty acids for long periods and reduction in body measurements, even though there is no strong evidence that the omega-3 supplementation has a significant effect on BMI (Yang et al. 2018).

Effect on the inflammation and oxidative stress biomarkers. PCOS is related to a chronic inflammatory process with elevated serum levels of pro-inflammatory markers. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin 6 (IL-6), are important factors for the insulin resistance development (Escobar-Morreale et al. 2011; Oner and Muderris 2013). Furthermore, this syndrome is also associated with oxidative stress, in which the increased production of free radicals and reactive oxygen species (ROS) are made for the decreased levels of plasma antioxidants (Gonzalez et al. 2013). Therefore, the omega-3 supplementation could be beneficial for women with PCOS as these fatty acids act in competition with arachidonic acid leading to the inhibition of the production of pro-inflammatory eicosanoids. These eicosanoids serve as an alternative substrate for cyclooxygenase (COX and COX2), which results in the formation of less potent products than pro-inflammatory ones (Barbalho et al. 2011).

There are evidences that omega-3 supplementation significantly increases the body's antioxidant capacity as well as reduces the levels of malondialdehyde (MDA) (Najafi et al. 2017; Ali and Rifaai 2019). However, no satisfactory results were found for C-reactive protein (CRP) levels reduction after administration of 1.2 g fish oil omega-3 supplementation for 8 weeks (Mohammadi et al. 2012) or 3.6 g of fish/flax oil omega-3 supplementation (3.2 g) for 6 weeks (Vargas et al. 2011). A significant reduction in CRP levels was noticed with 800 mg ALA supplementation (Mirmasoumi et al. 2018), 1000 mg of omega-3+400 UI vitamin E, both over a 12-week period (Talari et al 2018) 800 mg of EPA+DHA also decreased the levels of CRP and malondialdehyde with a significant increase in total plasma glutathione, which points out body's antioxidant efficiency (Amini et al. 2018). The increase in the serum activity of paraoxonase 1 (PON1), an antioxidant enzyme linked to HDL, has been observed after administration of 1200 mg of EPA+DHA for 8 weeks (Mohammadi and Rafraf 2012). Other findings showed a significant increase in the levels of total plasma antioxidants and a decrease in malondialdehyde levels after using 400 mg of ALA+400 IU vitamin E, for 12 weeks (Rahmani et al. 2016). Based on the same dosage and supplementation time, there was an increase in TNF, PPAR-γ, and IL-8 gene expressions, but without influencing the glucose transporter type 1 (GLUT-1), IL-6, and transforming growth factor β (TGF-β) levels (Jamilian et al. 2018) and 2000 mg of omega-3 supplementation+400 IU of vitamin E for 8 weeks significantly increased the total antioxidant capacity, catalase activity, glutathione levels, and reduced MDA levels (Sadeghi et al. 2020). The omega-3 supplementation can increase TNF levels since it reduces insulin levels, which is a hormone associated with anti-inflammatory effects. Therefore, insulin reduction could influence the TNF elevation (Oner and Muderris 2013). Fish oil supplementation for 12 weeks for women with Polycystic Ovary Syndrome also improved complementing PPAR-γ, IL-1 and IL-8 gene expression, but did not influence LP(a), LDLR, GLUT gene expression -1, TNF-α and TGF-β (Rahmani et al. 2018).

In the analyzed studies, it was observed that the results are scarce and quite controversial regarding

the effects of the omega-3 fatty acids on inflammatory biomarkers and oxidative profile in women with PCOS. In total, 12 clinical trials evaluated at least one aspect related to these profiles, whereas only 3 of them were found with a CRP reduction. They all lasted 12 weeks of supplementation with different doses as follows: 1000 mg of EPA+DHA+400 IU of vitamin E or 800 mg of ALA or 800 mg of EPA+DHA. In 3 cases, an improvement in the PPAR-γ gene expression also lasting 12 weeks and different doses as follows: 400 mg of ALA or 400 mg of ALA+400 IU vitamin E or 600 mg EPA+DHA was found.

Conclusions

Despite the fact that the selected studies did not show any direct benefits of the omega-3 supplementation in PCOS, this fatty acid clearly promotes indirect benefits by improving the metabolic profile associated with the disease. However, due to the great heterogeneity of the studies, it became difficult to standardize the dosages and the time of use. However, more efficient results could be noticed in the lipid and glycemic profiles with dosages between 1200 to 1500 mg of the fish-oil EPA+DHA/day, 800 mg of ALA/day or 400 mg of ALA+400 IU of vitamin E from oil linseed during the same time between 8 and 12 weeks. As for the androgenic profile, the dosage of 1200 to 1500 mg of EPA+DHA seems to be necessary for a longer period, i.e. 6 months of use. As for the anthropometric profile, the studies analyzed in women with PCOS are scarce and incongruous regarding the benefits from weight loss and/or body fat. For the antioxidant profile and biomarkers of the inflammatory process, positive results were observed for the reduction of CRP and regulation of PPAR-γ gene expression with different doses above 12 weeks of use. Since the results are promising, further studies should be performed with better-defined standards regarding the dosage and the supplementation time.

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