Original Article

Effect of Omega-3 Supplementation on Visfatin, Adiponectin, and Anthropometric Indices in Women with Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a multifactorial, metabolic disorder. Characteristics are chronic anovulation, polycystic ovaries and hyperandrogenism. The aim of this study was to determine the effect of omega-3 supplementation on visfatin, adiponectin, and anthropometric indices in PCOS women.

Methods: The study was a randomized double blind placebo-controlled clinical trial. It was conducted on 84 women with polycystic ovary syndrome (26.92±5.05 years, BMI=31.69 Kg/m^2) who referred to the fertility and infertility research center and Shahid Sadoughi hospital in Yazd. After the examination, evaluation and paramedical assessment by obstetrician, they were recruited. They took 3 capsules of omega-3 (each one contained 180 *mg* EPA and 120 *mg* DHA) or placebo (each contained 1 *g* paraffin) daily for 8 weeks. Statistical analysis was paired T-test and student T-test, and a $p<0.05$ was considered statistically significant.

Results: After the intervention, visfatin concentration did not change in neither groups. But, at the end of the study, the mean of adiponectin concentration increased ($p<0.001$) in omega-3 group. Moreover, the mean of changes in this factor was significantly different between groups ($p<0.005$). FSH did not change in two groups of the study. However, the mean of LH decreased about 1.74 *mIU/ml* in omega-3 group ($p<0.005$). The mean of change of LH/FSH ratio between groups was significant ($p<0.05$). After the intervention, prolactin did not meaningfully change in both groups.

Conclusion: Our results showed that 8 weeks of supplementation of omega-3 may have some beneficial effects on PCOS biochemical characteristics such as LH, LH/FSH, and adiponectin.

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Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial, complex genetic, endocrine and metabolic disorder. Characteristics are chronic anovulation, polycystic ovaries and hyperandrogenism (1). According to different criteria, 4% to 8% of women exhibit PCOS in the world (2). The prevalence of PCOS in Iran was 14.6% using Rott's definition (3). PCOS has a tremendous negative impact on the physiology and metabolism of the body such as metabolic syndrome, in-

sulin resistance (IR), dyslipidemia, hypertension, hyperinsulinemia, abdominal obesity, type 2 dia betes mellitus (4), endometrial hyperplasia, cardiovascular disease (5), eating and mood disorders (6).

Omega-3 fatty acids are mainly found in plant oils and marine (7). It is beneficial for health and has protective effects on cardiovascular disease (8) and metabolic syndrome (9). In recent years, intake of omega-3 in diets is less than omega-6, and this imbalance in omega-6 to omega-3 ratio can be related to chronic diseases (10).

Symptoms of PCOS differ among women with PCOS and vary over time in each woman in the presence of particular precipitating factors, the most significant of which is an alteration in body weight (11, 12). There is evidence that obese PCOS women have more severe hyperandrogenism and a significantly higher incidence of anovulatory cycles, oligomenorrhea and/or hirsutism compared to normal weight ones (12) and weight has an effect on the levels of androgens (13), adiponectin, and visfatin (14). Belzung et al. demonstrated the highest dose of omega-3 causes the more reduction in fat mass (16). Campbell et al. showed that the impact of omega-3 on obesity is obvious (17).

Visfatin is an adipokine that mimics the effect of insulin and is secreted by visceral fat tissue (18) and it is related to insulin resistance (19). Visfatin is related to Body Mass Index (BMI) (20) and Waist to Hip Ratio (WHR) (21). Some studies showed that visfatin increased in subjects with abdominal obesity and PCOS (19, 22, 23). Visfatin similarity to insulin may stimulate the androgen synthesis and be the pathogenesis of PCOS (24). The regulatory effect of omega-3 on the level of some adipokines like leptin was evaluated (25), but its effects on visfatin levels was limited (26).

Adiponectin, as another adipokine, improves insulin sensitivity and has an anti-inflammatory effect (27). Some studies showed a decrease in adiponectin level in PCOS women (28). Some studies demonstrated that the low level of adiponectin can be related to pathogenesis of PCOS and its metabolic complications (29). Mohammadi et al. showed the effect of omega-3 on elevating the level of adiponectin in PCOS women (30).

Release of LH in PCOS women is more irregular than other women (31). Elevation in serum LH and LH:FSH ratio in PCOS women is common (32, 33). Also, prolactin level is higher in these women despite FSH level (34). Some studies showed the effect of omega-3 on treatment of PCOS (35). Others showed no effect on LH and FSH after supplementation by polyunsaturated fatty acid (PUFA) (36, 37).

There were many studies about the effect of omega-3 on metabolic statues of many diseases (38-40), but studies on PCOS patients were limited (41). Understanding the effects of omega-3 on obesity and some adipokines can be critical. The objective of this study was evaluating the effect of omega-3 supplementation on these hormone profiles, some adipokines, and some anthropometric indices in PCOS women.

Methods

The study was a randomized double blind placebo-controlled clinical trial and was executed from November 2011 to May 2012. It was approved by Shahid Sadoughi University of Medical Sciences' ethics committee (IRB no 50338), Yazd, Iran. This study was a part of the large trial registered in Iranian Registry of Clinical Trial (Registry no IRCT2012071410281N1). It was conducted on 84 women with polycystic ovary syndrome (26.92± 5.05 years, BMI=31.69 Kg/m^2), referred to the fertility and infertility research center and Shahid Sadoughi hospital in Yazd. After the examination, evaluation and para-medical assessment by obstetrician, they were recruited. Inclusion criteria were: PCOS diagnostic criteria, age between 20-40 years, and BMI of 25-40. Exclusion criteria included metabolic disease, thyroid disease, hyperprolactinemia, hypercortisolemia, congenital adrenal hyperplasia, Cushing's syndrome, pituitary disorder, neoplasm, renal and liver diseases, history about intake of any drug during the last 3 months that may affect the insulin sensitivity or hormonal profile such as: oral contraceptives, glucocorticoids, ovulation induction agents, antidiabetic and anti-obesity drugs, estrogenic, antiandrogenic or anti-hypertensive medication, being in any diet in the last 6 months, any addiction to tobacco and alcohol, taking omega-3 supplement in the last 3 months, menopause, allergy to sea foods, and the use of anti-coagulant medicine. And the participants were excluded if they needed OCP for treatment, were not willing to be in the study, did not obey the protocols of the study, or could not digest more than 20% of supplements.

The Rotterdam ESHRE/ASRM criteria for confirming the diagnosis of PCOS were: oligo-anovulation, clinical/or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound examination (11). Thorough clinical examination with special focus on clinical hyperandrogenism (*i.e.* hirsutism and or hypergonadism) was done.

After explaining the objectives of the study to the patients, they signed the consent form. The 24 *hr* recall was completed for each patient before and after the intervention to eliminate the effect of change in dietary intake. Recall's data were analyzed using Nutritionist 4 software (N-Squared Inc, San Bruno, CA, USA). Subjects were randomly divided in to two groups of A and B to reduce the bias. Researchers didn't know which groups take the omega-3 supplement or placebo until the end of the study. Both groups were given three capsules of omega-3 or placebos every day for 8 weeks (42). Each capsule of omega-3 contained 180 *mg* EPA and 120 *mg* DHA, and each placebo included 1 *g* paraffin (Zahravi, Iran). The appearance of placebo and omega-3capsules were similar. All subjects were followed weekly by phone call, and they referred to the office bi-monthly to take the supplements to reduce the drop out. All participants were asked to maintain their usual diet and lifestyle habits.

For biochemical analysis, 10 *ml* of blood were collected from all samples before and after the intervention. Serum was kept in -80°*C* until analysis. Serum levels of visfatin, adiponectin, LH, FSH, and prolactin were measured. The LH/FSH ratio was calculated. Serum levels of visfatin (Cusabio, China), adiponectin (Medignost, Germany), LH (DiaMetra, Germany), FSH (DiaMetra, Germany), and prolactin (DiaMetra, Germany) were measured by ELISA Reader (Statfax2600, USA).

Weight, height, and BMI (weight in *kg* divided by height in m^2) were measured before the intervention for checking the inclusion criteria.

Weight (*kg*) was measured twice to the nearest 0.1 *kg*, with no shoes. Height (*m*) was measured twice to the nearest 0.5 cm, with no shoes.

Statistical analysis included mean and standard deviation, percentage, ratio, chi-square, pearson correlation coefficient test, paired T-test, student T-test, ANOVA, Wilcoxon, and Mann-whitney. SPSS 12 Software was used (SPSS Inc, Chicago IL) for analyzing the data and a p-value less than 0.05 was considered statistically significant.

Results

In this study, one of the participants became pregnant and left the study. Five participants dropped out because of taking less than 20% of our capsules. The remaining 78 participants completed the study. Finally, 78 people (92.8%) among the patients, 39 patients in the group receiving omega-3 and 39 patients in the group receiving placebo, finished the eight week trial.

Mean of age was 26.9±5.9 years in omega-3 and 26.9±5.0 years in placebo groups. Mean of BMI was 31.46±5.74 Kg/m^2 in omega-3 and 31.88±3.86 Kg/m^2 in placebo group. There were not any significant differences between groups in terms of age, weight, and other characters before the study.

There were no significant differences between and within groups in energy, macronutrients, omega-3, omega-6, and omega-6/mega-3 daily intake in the beginning of the study and after the intervention (Table 1).

Table 2 shows the mean of BMI and WHR in both groups. There were no significant differences between groups before the study. BMI remained unchanged in both groups at the end of the study. Significant increase in WHR was obtained in omega-3 group over the 8 weeks in comparison to baseline values ($p<0.005$). WHR remained unchanged in placebo group after the intervention.

Before the study, there was not a meaningful difference in terms of mean of visfatin, adiponctin, FSH, LH, prolactin concentration, and LH/FSH ratio in serum between groups. After the intervention, mean of visfatin increased up to 0.07 *ng/ml* in omega-3 group but the increasing level was not significant ($p=0.34$). There was not a significant change ($p=0.61$) in placebo group, too. Also, the mean of change between groups after the study was not significant ($p=0.82$).

At the end of the study, mean of adiponectin significantly increased ($p<0.001$) in supplement group. The mean of change of this factor was significantly different between groups ($p<0.005$).

After 8 weeks of supplementation, no significant change in FSH concentration was shown in supplement and placebo groups ($p=0.83$, $p=0.87$, respectively). Also, the mean of change between groups after the study was not significant ($p=0.79$).

The mean of LH decreased ($p<0.005$) in omega-3 group, but there was not a significant change in placebo one ($p=0.87$).

Table 1. Mean and standard deviation of intake of omega-3, omega-6, omega-6/omega-3, energy, and macronutrients between both groups before and after the intervention

	Placebo group N=39		Supplement group N=39		P-value (between groups)
	SD±Mean	Median	SD±Mean	Median	
Omega-3 (*g/d*)					
Before the intervention	9.9±24.4	0.7	5.4±15.8	0.8	0.6 ***
After the intervention	14.5±33.5	0.9	9.5±28.9	0.7	0.7 ***
P-value *	0.34	--	0.6	--	--
Omega-6 (*g/d*)					
Before the intervention	32.1±36.9	19.6	25.4±22.4	19.1	0.9 ***
After the intervention	38.1±52.4	19.6	33.3±45.5	21.4	0.4 ***
P-value *	0.4	--	0.1	--	--
Omega-6/omega-3					
Before the intervention	26.0±20.4	--	22.9±11.4	--	0.4 ****
After the intervention	23.4±20.0	--	25.1±12.4	--	0.6 ****
P-value **	0.1	--	0.1	--	--
Energy (*Kcal/d*)					
Before the intervention	2020.2±262.1	--	1970±235.3	--	0.4 ****
After the intervention	1998.5±213.6	--	1960.6±223.8	--	0.5 ****
P-value **	0.3	--	0.6	--	--
Fat (*g/d*)					
Before the intervention	78.4±19.1	--	79.0±19.2	--	0.8 ****
After the intervention	76.5±20.2	--	79.4±20.2	--	0.5 ****
P-value **	0.5	--	0.5	--	--
Protein (*g/d*)					
Before the intervention	63.5±11.6	--	59.8±10.5	--	0.1 ****
After the intervention	65.1±12.8	--	59.6±9.3	--	0.3 ****
P-value **	0.3	--	0.8	--	--
Carbohydrate					
Before the intervention	268.6±58.6	--	260.2±32.3	--	0.5 ****
After the intervention	266.5±41.2	--	259.2±29.1	--	0.3 ****
P-value **	0.9	--	0.6	--	--

* Wilcoxon test, ** Paired sample t-test, *** Mann-Whitney U test, **** Student t test

The mean of prolactin did not meaningfully change in both groups (supplement group p=0.62, and placebo group p<0.05). After 8 weeks of the study, the mean of change of prolactin between groups was not significant (p=0.08) (Table 2).

The mean of LH/FSH ratio decreased (p<0.001) in supplement group, but there was not a significant change in placebo group (p=0.98). The mean of change of LH/FSH ratio between groups after the study was significant (p<0.05) (Table 2).

Discussion

The results of our study showed that omega-3 treatment was associated with significant improvement with LH, adiponectin concentration, WHR, and LH/FSH ratio in PCOS.

According to this study, no changes were seen in energy and macronutrient intakes and BMI in both groups after the intervention. These findings were similar to previous studies (30, 43). The study of Mohammadi et al. showed no changes in

Table 2. Comparison of quantitative variables between both groups before and after intervention

	Placebo group N=39		Supplement group N=39		P-value**
	SD±Mean	Median	SD±Mean	Median	
BMI (*Kg/m²*)					
Before the intervention	31.88±3.86	--	31.46±5.74	--	0.75
After the intervention	31.83±3.68	--	31.17±5.93	--	0.56
P-value*	0.70	--	0.09	--	--
Mean of change ***	-0.05±0.89	--	-0.29±1.04	--	0.28
WHR (*cm*)					
Before the intervention	102.59±10.75	--	100.55±14.36	--	0.48
After the intervention	102.27±10.20	--	98.77±14.55	--	0.22
P-value *	0.53	--	<0.005	--	
Mean of change ***	-0.32±3.17	--	-1.78±3.21	--	0.28 *****
Visfatin (*ng/ml*)					
Before the intervention	6.97±2.46	--	6.91±2.41	--	0.92
After the intervention	7.01±2.60	--	6.98±2.51	--	0.96
P-value *	0.61	--	0.34	--	--
Mean of change ***	0.04±0.52	--	0.07±0.44	--	0.82
Adiponectin (*ng/ml*)					
Before the intervention	5.16±3.93	--	4.44±1.92	--	0.31
After the intervention	4.65±3.14	--	5.62±2.68	--	0.15
P-value *	0.05	--	<0.005	--	--
Mean of change ***	-0.51±1.60	--	1.17±2.10	--	<0.01
FSH (*mIU/ml*)					
Before the intervention	5.60±2.22	--	5.75±3.07	--	0.80
After the intervention	5.64±2.25	--	5.70±3.37	--	0.93
P-value *	0.87	--	0.83	--	--
Mean of change ***	-0.04±1.73	--	-0.05±1.50	--	0.79
LH (*mIU/ml*)					
Before the intervention	6.60±3.62	--	8.18±3.87	--	0.07
After the intervention	6.49±3.71	--	6.44±3.62	--	0.96
P-value *	0.87	--	<0.01	--	--
Mean of change ***	-0.11±4.28	--	-1.74±2.76	--	0.050
Prolactin (*ng/ml*)					
Before the intervention	332.13±221.88	--	366.38±187.73	--	0.46
After the intervention	388.08±197.97	--	353.18±178.02	--	0.42
P-value *	0.05	--	0.62	--	--
Mean of change ***	55.95±175.16	--	-13.20±165.14	--	0.08
LH/FSH ratio					
Before the intervention	1.38±1.03	1.11	2.09±3.24	1.35	0.2
After the intervention	1.33±0.85	1.33	1.33±0.92	1.05	0.8
P-value ****	--	0.98	--	0.001	--
Mean of change ***	-0.05±1.13	--	-0.76±2.94	--	0.02 *****

* Paired sample t-test, ** Independent sample t-test, *** Data after the study- first data, **** Wilcoxon test, ***** Mann-Whitney U test

WHR after 8 weeks of supplementation (30). However, some studies showed a reduction in WHR, BMI after 8 weeks of omega-3 supplementation in women with type 2 diabetes (26) and reduction of weight in mice (44, 45). Obesity and its comorbidities (diabetes, cancer, and heart disease) are linked to inflammation. Omega-3 had anti-inflammatory properties and has some effects on mediating receptors (46).

Our result about adiponectin level was compatible to previous studies in human (30, 47, 48) and animals (49, 50). The stimulation of Adipoq (adiponectin gene) in adipose tissue as a ligand of PPAR-γ (peroxisome proliferator-activated receptor γ) is one of the effects of EPA and DHA (44).

Evidence about the effect of omega-3 on visfatin level is limited. According to the study of Hajianfar et al., visfatin concentration increased after 8 weeks of the omega-3 supplementation (2 capsule/day, each capsule contain EPA 360 mg, DHA 240 *mg*) (26). In an *in vitro* study, it was suggested that AMPK activation has a role in up-regulation of visfatin gene after omega-3 intervention (51). This study showed no effect of omega-3 on visfatin level. The duration of the study and dose of EPA/DHA may not be enough to detect visfatin changes.

The improvement of LH concentration and LH/FSH ratio can cause the improvement of reproductive system. This trend can be explained by the mechanism related to arachidonic acids (52). Arachidonic acid can activate a steroidogenic acute regulatory protein (StAR). StAR is the rate-limiting step in steroidogenic pathway. High arachidonic acid can make 2-series prostaglandins (PGs), thromboxanes (TXs), and 4-series leukoterienes (LTs) and they induce StAR. However, high aracchidonic acid can activate the LH-stimulated steroidogenesis. Increase of omega-3 in membrane can reduce the availability of arachidonic acid. So, StAR moves the cholesterol to the inner of mitochondrial membrane. It is the first and main step for steriodogenic pathway which results in production of androstenedione and testosterone (52).

Our data showed that omega-3 supplementation in 8 weeks has no effect on FSH concentration in PCOS women. These results are similar to the results of Kuzmanov et al.'s study. They examined 3 months of n-3 PUFA application on hormone status in 12 PCOS samples, but they did not see any changes on FSH concentration (53). Karakas et al.'s study showed similar results (36). In our study, LH concentration and LH/FSH ratio significantly decreased after the intervention. Some studies showed no changes in LH concentration (52) and LH/FSH ratio after the intervention (37) like Karakas et al.'s study in using rich-PUFA diet for 3 months (36). Karakas suggested the intervention with more participants.

The concentration of prolactin after this study did not meaningfully change. No similar study about variation of prolactin in this case was found.

The strength of the current study was the clinical trial design. The limitation of our study was a shortness of intervention period and the clinical impacts were not collected. It is suggested that more clinical trials be conducted in this field with longer duration of intervention and in women with similar pattern of ovulations.

It has been suggested to design other studies with longer intervention. So, the effect of omega-3 could be more obvious. It has been suggested to measure the concentration of fatty acid on RBC membrane to check the protocol adherence and effect of omega-3 on other adipokines.

Conclusion

Omega-3 supplementation in PCOS women can show a benefit effect on adiponectin, LH concentration, WHR, and LH/FSH ratio. This effect was not associated with BMI, visfatin, FSH, and prolactin levels.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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