Original Article

Effects of omega−3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome

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Objective: Polycystic ovary syndrome (PCOS) is a common female endocrine disorder associated with several risk factors of type 2 diabetes and cardiovascular diseases. The objectives of this study were to investigate the effects of omega−3 fatty acids on serum adiponectin levels and some metabolic risk factors in PCOS patients. Methods: This double-blind randomized controlled clinical trial was conducted on 64 overweight or obese PCOS patients; aged 20-35 years. Subjects in omega−3 fatty acids (n=32) and placebo (n=32) groups were given 4 omega−3 fatty acids capsules (each one contained 180 mg eicosapentaenoic acid and 120 mg docosahexanoic acid) or placebo daily for 8 weeks. Fasting blood samples, anthropometric measurements and 3-day, 24-hour dietary recalls were collected at the baseline and at the end of the trial. Results: The study was completed by 61 subjects. Omega−3 fatty acids significantly increased serum levels of adiponectin (p=0.003) and decreased glucose (p<0.001), insulin (p=0.002), homeostatic model assessment for insulin resistance (p<0.001), total cholesterol (p=0.002) and low-density lipoprotein cholesterol (p=0.003) compared with placebo. Serum levels of triglyceride significantly decreased (p=0.024) and high-density lipoprotein cholesterol increased (p=0.018) in the omega−3 fatty acids group, in comparison with baseline values. No significant changes were shown in serum high sensitive C-reactive protein (hs-CRP) levels in both groups. Conclusion: Omega−3 fatty acids had some beneficial effects on serum adiponectin levels, insulin resistance and lipid profile in PCOS patients and may contribute to the improvement of metabolic complications in these patients.

Key Words: omega−3 fatty acids, polycystic ovary syndrome, adiponectin, insulin resistance, lipid profile

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder, presents in 6–10% of women of reproductive age.[1] The disorder is characterized by irregular menstrual cycle, chronic anovulation, and hyperandrogenism. Polycystic ovary syndrome is the main cause of female infertility due to anovulation.[2] The etiology of PCOS is not completely known but it is now clear that insulin resistance has an important role in enhancing androgen production in ovaries.[1] Hyperinsulinemia and early onset of type 2 diabetes are more frequent in PCOS patients than in the general population.[2] Polycystic ovary syndrome is also associated with other risk factors of cardiovascular disease such as dyslipidemia and elevated levels of hs-CRP (high sensitive C-reactive protein), an acute-phase reactant that increases during inflammatory response.[3]

About half of PCOS women are obese.[1] Adipose tissue, especially visceral fat is considered as an active endocrine organ which produces several proteins that called adipocytokines.[4] Adiponectin is one of the most abundant adipose-derived factors that improves insulin sensitivity

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and has antiatherogenic and anti-inflammatory effect.[4]

Several studies have showed a reduction in adiponectin levels in PCOS patients.[5,6] It seems that hypo-adiponectinemia can be associated with the pathogenesis of PCOS and metabolic complications of this syndrome such as hyperinsulinemia and dyslipidemia.[6]

It was reported that specific dietary unsaturated fatty acids can be associated with improved endocrine and metabolic characteristics in women with PCOS.[7] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are n−3 long chain polyunsaturated fatty acids (n−3 LC PUFA) found primarily in fatty fish. In Current diets, n−6 fatty acids are predominant PUFA and imbalance in the n−6/n−3 PUFA ratio may be related to chronic disease.[8]

Studies have shown increasing evidence for antiatherogenic and anti-inflammatory effects of fish oil and it is conceivable that dietary PUFA might also have benefit effects on glycemic control and lipid profile.[8-11] It is suggested that positive effects of EPA and DHA on metabolic parameters can be partially due to enhancement of adiponectin production.[12]

Mehendale *et al*. reported that plasma EPA and erythrocyte DHA levels were reduced in infertile women as compared with controls and hypothesised that omega−3 fatty acids probably contribute to the management of female infertility.[13] Another study by Cussons *et al*. showed that omega−3 fatty acid supplementation had beneficial effects on some cardiometabolic risk factors in PCOS patients.[14] However, effects of n−3 LC PUFA on adiponectin levels and metabolic status in PCOS women are little known. So the objectives of this study were to determine the effects of omega−3 fatty acids on serum adiponectin levels and some metabolic risk factors including insulin resistance, serum lipids and hs-CRP levels in PCOS patients.

MATERIALS AND METHODS

Sixty-four PCOS patients aged 20-35 years old and with BMI ranging from 25 to 40 kg/m^2 were recruited in this double-blind randomized controlled clinical trial from outpatient department of obstetrics of Alzahra hospital in Tabriz, Iran in 2011. The Ethical Committee of Tabriz University of Medical Sciences approved the study protocol. The registration ID of this study in Iranian Registry of Clinical Trials was: IRCT201011083664N3. Written informed consent obtained from each subjects prior to study.

The diagnosis of PCOS was established according to 2003 Rotterdam criteria, which require at least two of three features for diagnosis: chronic anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovaries in ultrasonography.[15] Study exclusion criteria included: smoking, pregnancy, using any medications, consumption of fish oil and other dietary supplements with the past 3 months or during the study, history of diseases including diabetes, liver, kidney and cardiovascular diseases, thyroid disorders, hyperprolactinemia, cushing's syndrome. The participants were randomly allocated in two groups using a block randomization procedure with matched subjects in each block based on BMI and age. A general questionnaire was completed for each subject. Body weight was measured using a scale (Seca, Germany), without shoes and wearing light clothing. Height was measured using a mounted tape without shoes. BMI was calculated as the weight in Kilogram divided by the height in meters squared. Waist circumference (WC); and hip circumference (HiC) were taken with a soft tape in standing position, waist being defined as the narrowest circumference between the costal margin and the iliac crest and hip as the widest circumference between the waist and tight. Waist to hip ratio (WHR) was calculated as WC in centimeter divided by HiC in centimeter.

Information about daily energy and macronutrient intakes were obtained by 24-hour recall method for 3 days, including 2 week day and 1 weekend. Three day average of energy and macronutrient intakes of all subjects were analyzed by Nutritionist 4 software (First Databank Inc., Hearst Corp., San Bruno, CA). The blood sampling (5 cc) was conducted after 12 hours of fasting between 7 and 10 am. Serum was separated by centrifugation and stored at −70°C until further analysis. The omega−3 fatty acids group (n=32) was given 4 g daily of omega−3 fatty acids (4×1000-mg capsules, each capsule contained 180 mg EPA and 120 mg DHA ,Good Health Company, USA) for 8 weeks. The placebo group (n=32) was given 4 placebo capsules, contained 500 mg liquid paraffin (Zahravi Company, Tabriz, Iran) for the same period. The compliance of the volunteers with the study protocol was monitored by counting returned capsules every two weeks. Subjects were asked to maintain their usual dietary intakes and physical activity throughout the study. All anthropometric, dietary intakes and biochemical measurements were assessed again at the end of intervention period in both groups.

Serum adiponectin level was measured by ELISA method using BioVendor kit (Germany). Serum glucose was measured using the standard enzymatic methods with commercially available Pars Azmun kit (Karaj, Iran). Serum Insulin level was measured by ELISA method using DiaMetra kit (Italy) and insulin resistance was determined by Homeostasis Model Assessment (HOMA) index with formula: HOMA-IR = fasting insulin (μU/mL) ×fasting glucose (mg/dl)/405.[15] Serum total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using the standard enzymatic methods by Pars Azmun kits. Low-density lipoprotein cholesterol (LDL-C) concentration was determined by the Friedewald formula: LDL-C=TC – (HDL-C + TG/5).[15] Serum hs-CRP level was measured using immunoturbidometric methodology by Pars Azmun kit at 500 nm and 37 ^{o}C.

Statistical analysis

Data were analyzed using SPSS software (version 11.5; SPSS Inc., Chicago, IL) and the results are expressed as mean±SD. The normality of the distribution of variables was determined by the Kolmogorov-Smirnov test. The baseline measurements and dietary intakes of subjects in two groups were compared using independent samples *t*-test. ANCOVA was used to identify any differences between the two groups at the end of the study, adjusting for baseline values and covariates. The changes in anthropometric measurements, energy and nutrient intakes, serum

Table 1. Characteristics of women with PCOS at baseline and after 8 weeks of either placebo or omega-3 fatty acids intervention

variable	Measurement period	Placebo (n=31)	Omega-3 fatty acids (n=30)
Age (yr)	Baseline	27.7 ± 4.53	27.3 ± 4.27
Weight (kg)	Baseline	74.9 ± 9.95	73.7 ± 8.87
	After intervention	75.1 ± 9.88	73.4 ± 8.88
BMI (kg/m2)	Baseline	28.8 ± 2.90	28.7 ± 3.21
	After intervention	28.8 ± 2.94	28.6 ± 3.30
WC (cm)	Baseline	91.2 ± 6.38	91.1 ± 5.99
	After intervention	91.3 ± 6.48	90.9 ± 6.14
WHR	Baseline	0.82 ± 0.03	0.81 ± 0.03
	After intervention	0.82 ± 0.03	0.82 ± 0.04

BMI: body mass index, WC: waist circumference, WHR: waist to hip ratio.
Data are presented as mean ± SD

Table 2. Dietary intakes of women with PCOS at baseline and after 8 weeks of either placebo or omega-3 fatty acids intervention

variable	Measurement period	Placebo (n=31)	Omega-3 fatty acids (n=30)
Energy (kcal/day)	Baseline	1735 ± 408	1742 ± 419
	After intervention	1680 ± 368	1668 ± 415
Carbohydrate (g/day)	Baseline	215 ± 63.5	224 ± 65.9
	After intervention	216 ± 52.8	209 ± 51.5
Protein (g/day)	Baseline	62.8 ± 19.5	63.6 ± 19.2
	After intervention	62.1 ± 18.7	61.7 ± 21.9
Total Fat (g/day)	Baseline	67.0 ± 22.0	65.0 ± 21.2
	After intervention	65.8 ± 19.8	64.6 ± 20.1
SFA (g/day)	Baseline	17.7 ± 6.59	16.8 ± 6.20
	After intervention	17.3 ± 6.30	18.1 ± 6.82
MUFA (g/day)	Baseline	20.3 ± 6.20	18.3 ± 6.72
	After intervention	21.1 ± 7.11	19.7 ± 6.87
PUFA† (g/day)	Baseline	20.9 ± 8.65	20.0 ± 9.55
	After intervention	19.1 ± 7.62	17.8 ± 6.81
Cholesterol (mg/day)	Baseline	203 ± 39.4	183 ± 34.5*
	After intervention	188 ± 45.8	191 ± 38.1

SFA: Saturated fatty acids, MUFA: Monounsaturated fatty acids, PUFA: Polyunsaturated fatty acids
† Excluding the PUFA from the supplement
*Significant difference between two groups at baseline ($p<0.05$, independent sample t-test)
Data are presented as mean ± SD

levels of adiponectin, glucose, insulin, HOMA-IR, lipids and hs-CRP between the beginning and end of the study were compared by paired samples t-test. The percentage of changes in variables after intervention was determined by formula: [(after values – before values) / before values] × 100. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 3 patients were excluded from the study because of personal reasons. Sixty one patients (30 patients in omega−3 fatty acids group and 31 patients in placebo group) completed the study. Patients demonstrated good compliance with the study design. Age and anthropometric characteristics of the subjects at the beginning and end of the study are shown in Table 1. There were no significant differences between and within groups in weight, BMI, WC and WHR in the beginning of the study and after 8 weeks of intervention.

Daily dietary intakes of participants throughout the study are shown in Table 2. Intake of cholesterol was significantly different between placebo and omega−3 fatty acids group at the beginning of the study (p=0.043). No significant differences in energy and other dietary intakes were observed between two groups at baseline. Total energy and nutrient intakes also did not change significantly in any of the groups during the study.

Serum levels of adiponectin and metabolic parameters of subjects at baseline and after 8 weeks intervention are shown in Table 3. There were no significant differences between the 2 groups in terms of serum adiponectin, glucose, insulin, HOMA-IR, lipids and hs-CRP levels at baseline. Results of analysis of covariance showed statistically significant differences between two studied groups in serum adiponectin (p=0.003), glucose (p<0.001), insulin (p=0.002), HOMA-IR (p<0.001), TC (p=0.002) and LDL-C (p=0.003) levels at the end of the study, adjusted for energy, PUFA and cholesterol intakes and baseline values, but changes in serum TG, HDL-C and hs-CRP levels were not significant. Supplementation with omega−3 fatty acids increased levels of adiponectin by 19.5% and resulted in 11.4%, 8.4%, 21.8%, 8.1% and 14.9% reduction in serum levels of glucose, insulin, HOMA-IR, TC and LDL-C, respectively, compared with these variables in placebo group.

As shown in Table 3, serum levels of adiponectin and

Table 3. Serum adiponectin levels and metabolic parameters of women with PCOS at baseline and after 8 weeks of either placebo or omega-3 fatty acids intervention

variable	Measurement period	Placebo (n=31)	Omega-3 fatty acids (n=30)
Adiponectin (μg/mL)	Baseline	12.3 ± 3.62	11.8 ± 3.18
	After intervention	12.0 ± 3.10	13.5 ± 2.41 *†
Glucose (mg/dL)	Baseline	91.7 ± 12.3	95.2 ± 10.3
	After intervention	92.4 ± 9.92	85.4 ± 8.95 *†
Insulin (μIU/mL)	Baseline	16.4 ± 3.54	16.5 ± 2.96
	After intervention	16.4 ± 3.39	15.1 ± 2.68 *†
HOMA-IR	Baseline	3.79 ± 1.28	3.91 ± 1.03
	After intervention	3.80 ± 1.11	3.20 ± 0.80 *†
TC (mg/dL)	Baseline	188 ± 29.2	187 ± 32.5
	After intervention	187 ± 25.9	170 ± 32.0 *†
TG (mg/dL)	Baseline	126 ± 28.5	127 ± 29.5
	After intervention	120 ± 28.5	119 ± 26.0 *
LDL-C (mg/dL)	Baseline	117 ± 31.5	118 ± 29.4
	After intervention	117 ± 27.4	102 ± 29.6 *†
HDL-C (mg/dL)	Baseline	44.9 ± 6.11	43.1 ± 6.55
	After intervention	45.3 ± 4.49	45.9 ± 6.53 *
hs-CRP (mg/L)	Baseline	2.22 ± 0.83	2.26 ± 0.70
	After intervention	2.08 ± 0.80	2.11 ± 0.80

HOMA-IR: homeostatic model assessment for insulin resistance, TC: total cholesterol, TG: triglyceride, LDL-C: low density lipoprotein, HDL-C: high density lipoprotein, hs-CRP: high sensitive C-reactive protein
*Significant difference within groups after intervention ($p < 0.05$, paired sample *t*-test)
†Significant difference between groups after intervention ($p < 0.05$, analysis of covariance)
Data are presented as mean ± SD

HDL-C significantly increased in the omega−3 fatty acids group (by 19.8%, p=0.006 and by 7.4%, p=0.018, respectively) at the end of the study. Significant decrease in serum levels of glucose, HOMA-IR, TC and LDL-C (by 10.0 %, 16.3%, 8.2% and 12.6% respectively, p<0.001 for all), TG (by 5.0 %, p=0.024) and insulin (by 7.5%, p= 0.002) was obtained in omega−3 fatty acids group over the 8 weeks in comparison to baseline values. Levels of serum hs-CRP remained unchanged in both groups at the end of the study.

DISCUSSION

Current evidence from clinical, experimental and epidemiologic investigations indicates that omega−3 fatty acids are protective against cardiovascular disease and inflammatory disorders.[16]

According to our results, no significant changes were observed in anthropometric measurements, energy and macronutrient intakes within omega−3 fatty acids and placebo groups during the study. These results were similar to the previous studies in PCOS patients.[14,17] Cussons *et al*. reported that omega−3 supplementation by dose of 4 g/day for 8 weeks, had no significant effects on BMI and WHR of PCOS patients with nonalcoholic fatty liver disease.[14] Results of another study conducted by Vargas *et al*. in PCOS patients indicated that 6 weeks supplementation with 3.5 g/day fish oil did not change weight, BMI, and WC significantly.[17] No other published data are available about the effects of omega−3 supplementation in PCOS subjects. However, Hajianfar *et al*. reported that consumption of fish oil reduced BMI, WC and WHR in women by type 2 diabetes compared with the placebo group.[18] Findings obtained by Flachs *et al*.[19] and Nakatani et al.[20] demonstrated that PUFA of marine origin resulted in lower body weight in mice.

It has been reported that effects of omega−3 fatty acids on anthropometric measurements might be dependent on sex, age and BMI of subjects at baseline.[21,22] It was also proposed that along with different mechanisms, intake of fish oil may decrease fat mass via lowering energy intake.[22] The overall energy intakes of our studied subjects in both groups were not significantly different at the end of the study compared to baseline values, so no significant variations in anthropometric measurements of all subjects would be partially expected. As a result, anthropometric measurements would not be considered as confounding factors in the interpretation of studied biochemical variables.

Adiponectin is an adipose tissue-derived protein that exists in the human serum at range of 5-30 μg/ml.[4] Our results indicated the mean baseline levels of adiponectin in all studied subjects was near to low range and increased significantly at the end of the study in omega−3 fatty acids group. This finding was compatible with some recent studies. Kondo *et al*. demonstrated that consumption of fish oil for 8 weeks increased serum adiponectin levels in young, non-obese female subjects.[23] In studies by Itoh *et al*. in obese subjects and by Krebs *et al*. in overweight hyperinsulinaemic women, supplementation with n−3 LC PUFA increased serum adiponectin levels.[24, 25] In several animal researches, experimental diet containing fish oil was associated with higher adiponectin concentration.[26,27]

One of the main effects of EPA and DHA is the stimulation of Adipoq (adiponectin gene) in adipose tissue, probably by acting as ligands of PPAR-γ (peroxisome proliferator- activated receptor γ), the transcriptional regulator interacting with Adipoq promoter.[19] However some studies did not show significant effects of omega−3 fatty acids on serum adiponectin levels[12,28] that might be relat-

ed to metabolic status of subjects or different study designs. Vargas *et al*. also reported no significant changes in serum adiponectin levels in PCOS patients after 6 weeks supplementation by fish oil.[17]

According to results, omega−3 fatty acids caused a considerable decrease in insulin resistance. Our results were similar to the findings of other studies which reported decreased fasting serum glucose in healthy female,[29] reduction in insulin levels and HOMA-IR in young women[30] and decreased fasting insulin levels in non-diabetic, moderately hypertriglyceridaemic patients[31] and hemodialysis patients[32] after supplementation with omega−3 fatty acids. Lower plasma glucose[27] and insulin[19] concentrations were reported in studies on mice fed diets rich in EPA and DHA compared to other experimental diets.

Improvement in insulin sensitivity by omega−3 fatty acids in our patients might be resulted from elevated adiponectin level which has anti-diabetic, anti-atherosclerotic and anti-inflammatory effects.[23] Adiponectin increases glucose utilization by activation of AMPK (AMP-activated protein kinase).[27,33] Moreover, AMPK suppresses gluconeogenesis in the liver and stimulates glucose transport in muscle.[33] It has also been suggested that inhibition of the activity and expression of glucose-6-phosphatase by n−3 fatty acids, decreases hepatic glucose output.[34]

Conversely a number of other studies have failed to show improvement in insulin sensitivity by omega−3 fatty acids in PCOS patients[14,17] young healthy subjects[23] and type 2 diabetic patients.[18] It seems that the dose and fatty acid composition of the n−3 PUFA supplements, duration of intervention, health status of the study subjects, degrees of obesity and insulin resistance, the presence of other conditions that may also affect insulin sensitivity and differences in the sensitivities of the tools used to assess insulin resistance, also contribute to the inconsistencies.[35]

In our study supplementation with omega−3 fatty acids leaded to significant reduction in serum lipids. Cussons *et al*. and Vargas *et al.* also showed significant decrease in serum TG levels in PCOS patients after supplementation with fish oil but serum TC, LDL-C and HDL-C concentrations remained unchanged.[14,17] In addition, reduction in serum TG levels by fish oil was reported in several other studies.[8, 35] In a study by Nilsen *et al*, intake of omega−3 fatty acids, resulted in significant reduction in serum TG and increase in HDL-C levels in patient with acute myocardial infarction.[36] The omega−3 fatty acids are natural ligands for 4 metabolic nuclear receptors including PPARs, LXR (liver X receptor), HNF-4α (hepatocyte nuclear factor-4α) and FXR (farnesol X receptor). Activation of these receptors by EPA and DHA down-regulates genes encoding proteins that stimulate lipid synthesis and up-regulates genes that enhance fatty acid oxidation in liver and muscle.[37] In addition, some positive effects of n−3 LCPUFA on lipid profile is mediated by enhancement of AMPK, a major sensor of cellular energy status which regulates partitioning between lipid oxidation and lipogenesis.[33] It is also proposed that fish oil intake improves LDL receptor activity in the liver, reduces LDL-C synthesis and increases fractional rate of catabolism of LDL-C.[28, 38, 39]

Based on obtained results, serum levels of TG significantly decreased and HDL-C increased in the omega−3 fatty acids group only compared to their baseline values. It was shown that effect of fish oil on TG levels is dose-dependent.[8] Studies on hypertriglyceridemic patients demonstrated that high doses of fish oil had remarkable effects in reducing TG levels.[8, 40] It was possible that in our study, dose of omega−3 fatty acids or duration of intervention period were not sufficient to have considerable impact on serum TG and HDL-C levels in comparison to placebo group.

We observed that omega−3 fatty acids had no significant effect on serum hs-CRP in studied patients. This finding is in accordance with the results of previous studies in PCOS women.[14, 17] However, Tsitouras *et al*. and Rasic-Milutinovic *et al*. reported significant decrease in hs-CRP levels after diet intervention high in EPA and DHA in healthy older adults and fish oil supplementation in hemodialysis patients.[28, 32] The effect of n−3 PUFA on markers of chronic inflammation such as hs-CRP is largely unknown.[41] When the intake of n−3 PUFA is high, EPA and DHA replace arachidonic acid in the cell membranes and produce eicosanoids which have less inflammatory actions.[41] Non significant effect of omega−3 fatty acids on serum hs-CRP levels in our study might be due to low baseline serum levels of hs-CRP in the studied patients. Other studies are needed to evaluate effects of omega−3 fatty acids on serum hs-CRP in PCOS patients with higher baseline serum hs-CRP values or on other inflammatory markers.

Our study had some limitations. This research included only overweight and obese PCOS patients. In addition, effects of omega−3 fatty acids on metabolic parameters are dose-related.[35,42] Therefore, the results of our study may not be applicable to underweight or normal weight PCOS patients and also to other doses of omega−3 fatty acids supplements or different intervention period durations.

As a conclusion the present trial showed that supplementation with omega−3 fatty acids had some beneficial effects on serum adiponectin, insulin resistance and lipid profile in PCOS patients. Omega−3 fatty acids may be useful in the control and prevention of metabolic complications of PCOS patients such as type 2 diabetes and cardiovascular diseases.

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AUTHOR DISCLOSURES

The investigators did not have any conflict of interest.

REFERENCES

1. Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol. 2010;122:42-52.
2. Ovalle F, Azziz R. Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. Fertil Steril. 2002;77: 1095-105.

3. Cussons AJ, Stuckey BG, Watts GF. Cardiovascular disease in the polycystic ovary syndrome: New insights and perspectives. Atherosclerosis. 2006;185:227-39.
4. Mamaghani F, Zarghami N, Maleki MJ, Pourhassan-Moghaddam M, Hosseinpanah F. Variation of adiponectin levels in normal and obese subjects: possible correlation with lipid profiles. Int J Endocrinol Metab. 2009;3:170-8.
5. Panidis D, Kourtis A, Farmakiotis D, Mouslech T, Rousso D, Koliakos G. Serum adiponectin levels in women with polycystic ovary syndrome. Hum Reprod. 2003;18:1790-6.
6. Escobar-Morreale HF, Villuendas G, Botella-Carretero GI, Alvarez-Blasco F, Sanchon R, Luque-Ramirez M, Millan JL. Adiponectin and resistin in PCOS: a clinical, biochemical and molecular genetic study. Hum Reprod. 2006;21:2257-65.
7. Kasim-Karakas SE, Almario RU, Gregory L, Wong R, Todd H, Lasley BL. Metabolic and endocrine effects of a polyunsaturated fatty acid-rich diet in polycystic ovary syndrome. J Clin Endocrinol Metab. 2004;89:615-20.
8. Oh R. Practical applications of fish oil (Ω-3 fatty acids) in primary care. J Am Board Fam Pract. 2005;18:28-36.
9. Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives. Atherosclerosis. 2008; 197:12-24.
10. Fedor D, Kelley DS. Prevention of insulin resistance by n-3 polyunsaturated fatty acids. Curr Opin Clin Nutr Metab Care. 2009;12:138-46.
11. Ebbesson SOE, Risica RM, Ebbesson LOE, Kennish JM, Tejero ME. Omega-3 fatty acids improve glucose tolerance and components of the metabolic syndrome in Alaskan eskimos: The Alaska Siberia project. Int J Circumpolar Health. 2005;64:396-408.
12. Kratz M, Swarbrick MM, Callahan HS, Matthys CC, Havel PJ, Weigle DS. Effect of dietary n–3 polyunsaturated fatty acids on plasma total and high-molecular-weight adiponectin concentrations in overweight to moderately obese men and women. Am J Clin Nutr. 2008;87:347-53.
13. Mehendale S. Oxidative stress-mediated essential polyunsaturated fatty acid alterations in female infertility. Hum fertile. 2009;12:28-33.
14. Cussons AJ, Watts GF, Mori TA, Stuckey BGA. Omega-3 fatty acid supplementation decreases liver fat content in polycystic ovary syndrome: A randomized controlled trial employing proton magnetic resonance spectroscopy. J Clin Endocrinol Metab. 2009;94;3842-8.
15. Ozkaya M, Cakal E, Ustun Y, Engin-Ustan Y. Effect of metformin on serum visfatin levels in patients with polycystic ovary syndrome. Fertil Steril. 2010;93:880-4.
16. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr. 2002;21:495-505.
17. Vargas ML, Almario RU, Buchan W, Kim K, Karakas SE. Metabolic and endocrine effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome. Metabolism. 2011;60:1711-8.
18. Hajianfar H, Hosseinzadeh MJ, Bahonar A, Mohammad K, Askari GR, Entezari MH, Keshavarz A, Ansari N. The effect of omega-3 on the serum visfatin concentration in patients with type II diabetes. J Res Med Sci. 2011;16:490-5.
19. Flachs P, Mohamed-Ali V, Horakova O, Rossmeisl M, Hosseinzadeh-Attar MJ, Hensler M, Ruzickova J, Kopecky J. Polyunsaturated fatty acids of marine origin induce adiponectin in mice fed a high-fat diet. Diabetologia. 2006;49: 394-7.
20. Nakatani T, Kim HJ, Kaburagi Y, Yasuda K, Ezaki O. A low fish oil inhibits SREBP-1 proteolytic cascade, while a high-fish-oil feeding decreases SREBP-1 mRNA in mice liver. J Lipid Res. 2003;44:369-79.
21. Sneddon AA, Tsofliou F, Fyfe CL, Matheson I, Jackson DM, Horgan G, Winzell MS, Wahle KW, Ahren BO, Williams LM. Effects of a conjugated linoleic acid and ω-3 fatty acid mixture on body composition and adiponectin. Obesity. 2008;16:1019-24.
22. Hill AM, Buckley D, Murphy KJ, Howe PRC. Combining fish-oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors. Am J Clin Nutr. 2007;85:1267-74.
23. Kondo K, Morino K, Nishio Y, Kondo M, Fuke T, Ugi S, Iwakawa H, Kashiwaqi A, Maeqawa H. Effects of a fish-based diet on the serum adiponectin concentration in young, non-obese, healthy Japanese subjects. J Atheroscler Thromb. 2010;17:628-37.
24. Itoh M, Suqanami T, Satoh N, Tanimoto-Koyama K, Yuan X, Tanaka M et al. Increased adiponectin secretion by highly purified eicosapentaenoic acid in rodent models of obesity and human obese subjects. Atheroscler Thromb Vasc Biol. 2007;27:1918-25.
25. Krebs JD, Browning LM, McLean NK, Rothwell JL, Mishra GD, Moore CS, Jebb SA. Additive benefits of long-chain n-3 polyunsaturated fatty acids and weight-loss in the management of cardiovascular disease risk in overweight hyperinsulinaemic women. Int J Obes. 2006;30:1535-44.
26. Duda MK, O'Shea KM, Lei B, Barrows BR, Azimzadeh AM, McElfresh TE, Hoit BD, Kop WJ, Stanley WC. Dietary supplementation with ω-3 PUFA increases adiponectin and attenuates ventricular remodeling and dysfunction with pressure overload. Cardiovasc Res. 2007;76:303-10.
27. Higuchi T, Shirai N, Saito M, Suzuki H, Kagawa Y. Levels of plasma insulin, leptin and adiponectin, and activities of key enzymes in carbohydrate metabolism in skeletal muscle and liver in fasted ICR mice fed dietary n-3 polyunsaturated fatty acids J Nutr Biochem. 2008;19:577-86.
28. Tsitouras PD, Gucciardo F, Salbe AD, Heward C, Harman SM. High omega-3 fat intake improves insulin sensitivity and reduces CRP and IL6, but does not affect other endocrine axes in healthy older adults. Horm Metab Res. 2008; 40:199-205.
29. Tahvonen RL, Schwab US, Linderborg KM, Mykkanen HM, Kallio HP. Black currant seed oil and fish oil supplements differ in their effects on fatty acid profiles of plasma lipids, and concentrations of serum total and lipoprotein lipids, plasma glucose and insulin. J Nutr Biochem. 2005;16:353-9.
30. Navas-Carretero S, Perez-Granados AM, Schoppen S, Vaquero MP. An oily fish diet increases insulin sensitivity compared to a red meat diet in young iron-deficient women. Br J Nutr. 2009;102:546-53.
31. Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H, Torjesen A. Long-term effects of n-3 fatty acids on serum lipids and glycaemic control. Scand J Clin Lab Invest. 1994;54:273-80.
32. Rasic-Milutinovic Z, Perunicic G, Pljesa S, Gluvic Z, Sobajic S, Djuric I, Ristic D. Effects of n-3 PUFAs supplementation on insulin resistance and inflammatory biomarkers in hemodialysis patients. Ren Fail. 2007;29:321-9.
33. Flachs P, Rossmeisl M, Bryhn M, Kopecky J. Cellular and molecular effects of n−3 polyunsaturated fatty acids on adipose tissue biology and metabolism. Clin Sci. 2009;116:1-16.
34. Perez-Echarri N, Perez-Matute P, Marcos-Gomez B, Martinez JA, Moreno-Aliaga MJ. Effects of eicosapentaenoic acid ethyl ester on visfatin and apelin in lean and overweight (cafeteria diet-fed) rats. Br J Nutr. 2009;101:1059-67.
35. Woodman RJ, Mori TA, Burke V, Puddey IB, Watts GF, Beilin LJ. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. Am J Clin Nutr. 2002;76:1007-15.

36. Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. Am J Clin Nutr. 2001;74:50-6.
37. Davidson MH. Mechanisms for the hypotriglyceridemic effect of marine Omega-3 Fatty Acids. Am J Cardiol. 2006; 98:27i-33i.
38. Nestel PJ. Fish oil and cardiovascular disease: lipids and arterial function. Am J Clin Nutr. 2000;71:228S-31S.
39. Illingworth DR, Harris WS, Connor WE. Inhibition of low density lipoprotein synthesis by dietary omega-3 fatty acids in humans. Arterioscler Thromb Vasc Biol. 1984;4:270-5.
40. Harper CR, Jacobson TA. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. Arch Intern Med. 2001;161:2185-92.
41. Madsen T, Skou HA, Hansen VE, Fog L, Christensen JH, Toft E, Schmidt EB. C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease. Am J Cardiol. 2001;88:1139-42.
42. Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005;105:428-40.

Original Article

Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome

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Omega-3 脂肪酸的補充對於多囊性卵巢症婦女血清中脂聯素與其他代謝危險因子的影響

多囊性卵巢症是常見的女性內分泌失調疾病，且與第 2 型糖尿病及心血管疾病之某些危險因子相關。此研究的目的在探討 omega-3 脂肪酸，對於多囊性卵巢患者血清中脂聯素和數項代謝危險因子的影響。研究方法採雙盲隨機臨床試驗，研究對象為 64 位過重或肥胖，年齡介於 20-35 歲的多囊性卵巢患者。8 週試驗期內，試驗組(32 位)每天接受 4 顆各含 180 毫克的 EPA 與 120 毫克 DHA 的膠囊；而對照組(32 位)則每天給予 4 顆安慰劑。在試驗前及結束時，皆收集空腹血液樣本、體位測量及 3 天的 24 小時飲食回憶記錄。最後共 61 位參與者完成試驗。研究結果顯示，與對照組相比，omega-3 脂肪酸顯著地增加試驗組的血清脂聯素濃度(p=0.003)，並降低血糖(p<0.001)、胰島素(p=0.002)、胰島素阻抗(p<0.001)、總膽固醇(p=0.002)以及低密度脂蛋白膽固醇(p=0.003)。與試驗前的數值相比，omega-3 脂肪酸的補充顯著地減低血清中三酸甘油酯，且增加高密度脂蛋白膽固醇的濃度。兩組試驗前後的血清高敏感性 C 反應蛋白，皆不具顯著的改變。結論：omega-3 脂肪酸有助於多囊性卵巢症患者，維持較佳的血清脂聯素濃度、胰島素抗性及血脂狀態，而這可能改善患者的代謝性併發症。

關鍵字：omega-3 脂肪酸、多囊性卵巢症、脂聯素、胰島素阻抗、血脂全套指數