

## Effects of Flaxseed Oil Omega-3 Fatty Acids Supplementation on Regression and Metabolic Status in Endometrial Hyperplasia: A randomized, Double-Blind, Placebo-Controlled Trial

### Abstract

**Background:** Data on the effects of omega-3 fatty acid supplementation on clinical symptoms and metabolic profiles in patients with endometrial hyperplasia (EH) are limited. This intervention was performed to assess the effects of omega-3 fatty acid supplementation on clinical symptoms and metabolic profiles in patients with endometrial hyperplasia (EH). **Methods:** This randomized, double-blind, placebo-controlled trial was conducted among 40 women diagnosed with simple endometrial hyperplasia (EH). EH diagnosis was performed based on specific diagnostic procedures of biopsy. Participants were randomised into two groups to intake 1,000 mg omega-3 fatty acid supplements from flaxseed oil ( $n = 20$ ) or placebo ( $n = 20$ ), twice a day for 12 weeks. Fasting blood samples were taken at baseline and after the 12-week intervention to determine related markers. **Results:** Compared with the placebo, omega-3 fatty acid supplementation significantly decreased fasting plasma glucose (FPG) ( $-7.1 \pm 9.6$  vs.  $+2.0 \pm 4.9$  mg/dL,  $P = 0.001$ ), serum insulin levels ( $-1.5 \pm 4.6$  vs.  $+1.6 \pm 3.9$   $\mu$ IU/mL,  $P = 0.02$ ) and homeostasis model of assessment-insulin resistance (HOMA-IR) ( $-0.4 \pm 1.1$  vs.  $+0.4 \pm 1.0$ ,  $P = 0.02$ ). In addition, a significant increase in plasma total antioxidant capacity (TAC) ( $+102.6 \pm 69.6$  vs.  $+5.0 \pm 37.1$  mmol/L,  $P < 0.001$ ) and total glutathione (GSH) levels ( $+63.6 \pm 84.9$  vs.  $-3.0 \pm 69.4$   $\mu$ mol/L,  $P = 0.01$ ) were seen following the supplementation of omega-3 fatty acid compared with the placebo. Omega-3 fatty acid supplementation had no significant effect on regression, lipid profiles, and other biomarkers of inflammation and oxidative. **Conclusions:** In conclusion, we found that omega-3 fatty acid administration for 12 weeks to subjects with EH significantly improved FPG, insulin, HOMA-IR, TAC and GSH levels, but did not influence regression, lipid profiles, and other biomarkers of inflammatory and oxidative stress.

**Keywords:** Endometrial hyperplasia, flaxseed oil, metabolic profiles, supplementation

### Introduction

Endometrial hyperplasia (EH) represents a spectrum of irregular morphological changes, whereby unusual proliferation of the endometrial glands leads an elevation in gland-to-stroma ratio when compared to endometrium from the proliferative phase of the cycle.<sup>[1]</sup> It has reported that EH may led to endometrial cancer (EC) up to 50% of cases.<sup>[2]</sup> Several studies have suggested the relationship between insulin resistance, inflammation and oxidative stress, and the progression of EH. Luo *et al.*<sup>[3]</sup> demonstrated that, subjects who developed diabetes mellitus (DM) during the follow-up period, the association between DM and EC was significant even after adjusting for BMI. This result documented that pre-DM status is also a potential risk factor for EC.

In addition, the progress of inflammatory changes in EH may be considered as an important factor in the promotion of pathology, as well as an attributed risk factor for malignancy in EH.<sup>[4]</sup>

Epidemiological literatures on the linkage between omega-3 fatty acid and cancer incidence, such as cross-sectional and migrational studies, have demonstrated a protective effect of omega-3 fatty acid and a promoting impact of omega-6 fatty acid on the development of cancers.<sup>[5,6]</sup> Furthermore, dietary intake of high levels of omega-3 fatty acid has been showed to reduce various cancers and alleviate their complications.<sup>[7,8]</sup> Previous studies have documented that long-term high intake of diets or supplementation with

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**How to cite this article:** Jamilian M, Khademi L, Vahedpoor Z, Bahmani F, Mahmoodi S, Taghizadeh M, *et al.* Effects of flaxseed oil omega-3 fatty acids supplementation on regression and metabolic status in endometrial hyperplasia: A randomized, double-blind, placebo-controlled trial. *Int J Prev Med* 2019;10:61.

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**DOI:**  
10.4103/ijpvm.IJPVM\_73\_18

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eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were associated with lower risk of endometrial cancer.<sup>[9,10]</sup> Dietary omega-3 fatty acid significantly decreased endometrial cancer cell growth in xenograft models.<sup>[11]</sup> Hence, high circulating and tissue contents of omega-3 fatty acid may be an important function in the prevention and treatment of cancer pathogenesis.<sup>[12]</sup> On the other hand, several studies have reported the beneficial effects of omega-3 fatty acid supplementation on markers of insulin metabolism, inflammation and oxidative stress in patients without EH. For instance, overweight schoolchildren with metabolic syndrome (MetS) who received 2.4 g/day omega-3 fatty acid for 1 month displayed improved lipid profiles and reduced fasting glucose.<sup>[13]</sup> In addition, we have demonstrated that omega-3 fatty acid supplementation for 6 weeks to women with gestational diabetes mellitus (GDM) significantly decreased high-sensitivity C-reactive protein (hs-CRP) and malondialdehyde (MDA) levels, but could not influence other biomarkers of inflammation and oxidative stress.<sup>[14]</sup>

However, these evidence might suggest the importance of omega-3 fatty acid supplementation in the control of EH regression and its metabolic status. Therefore, based on existing evidence, we hypothesized that clinical signs, metabolic profiles, biomarkers of inflammation and oxidative stress of EH patients might be improved by omega-3 fatty acid supplementation. To our knowledge, data on the effects of omega-3 fatty acid supplementation on regression, glucose control, lipid concentrations, biomarkers of inflammation and oxidative stress in patients with EH are scarce. The purpose of the present study was to determine the effects of omega-3 fatty acid supplementation on regression and metabolic status of patients with EH.

## Methods

### Trial design and participants

This randomized, double-blind, placebo-controlled trial, registered in the Iranian website for registration of clinical trials (<http://www.irct.ir>: IRCT201701015623N98), was carried out among 40 subjects with simple EH without atypia and the history of vaginal bleeding during one ago year, aged 35-55 years old diagnosed with endometrial biopsy, who were referred to the Kosar Clinic in Arak, Iran, from December 2016 to April 2017. This research was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was taken from all subjects as well. Study protocol was confirmed by the research ethics committee of Arak University of Medical Sciences (no. IR.ARAKMU.REC.1395.310). Exclusion criteria were menopausal women, history of cardiovascular disease (CVD), DM, hypertension, untreated thyroid disease and taking anti-inflammatory agents.

### Study design

Firstly, to decrease potential confounding effects, all patients were randomized according to BMI (<25 and  $\geq$ 25 kg/m<sup>2</sup>) and age (<40 and  $\geq$ 40 y) strata. Participants in each stratum were randomly allocated into two treatment groups to take either 1,000 mg omega-3 fatty acid supplements from flaxseed oil or placebo (Barij Essence, Kashan, Iran) ( $n = 20$  each group) twice a day for 12 weeks. Both omega-3 fatty acid supplements and placebo capsules had similar packaging and patients and researchers were unaware of the content of the package until the end of study. Randomization assignment was carried out using computer-generated random numbers. Randomization and allocation were concealed from the researchers and subjects until the final analyses were completed. The randomized allocation sequence, enrolling patients and allocating them to interventions were conducted by a trained staff at the clinic. Patient-reported adherence with the consumption of supplements and placebos was evaluated by examining the containers as well as receiving short messages every day to remind them about taking the capsules. All patients completed 3-day food records and 3 physical activity records at baseline, weeks 3, 6, 9 and 12 of the intervention. Physical activity was described as metabolic equivalents (METs) in hours per day.<sup>[15]</sup> Daily macro- and micro-nutrient intakes were analyzed by nutritionist IV software (First Databank, San Bruno, CA).

### Assessment of anthropometric measures

Weight and height of participants were determined in an overnight fasting status using a standard scale (Seca, Hamburg, Germany) at baseline and after the 12-week treatment. BMI was calculated as weight in kg divided by height in meters squared. All anthropometric measures were carried out by a trained staff.

### Assessment of outcomes

Primary outcomes were regression and inflammatory markers. Secondary outcomes were parameters of glucose homeostasis, lipid profiles and biomarkers of oxidative stress.

### Clinical assessment

Diagnosis of EH was performed through biopsy and pathological diagnosis at baseline and after the 12-week intervention. Endometrial biopsies were conducted by the use of suction pipelles. Assessment of the pathological diagnosis was performed as blindness by a single experienced pathologist at baseline and the end of the trial. Informed consent was taken from all participants for biopsy both baseline and end-of-treatment.

### Biochemical assessment

At baseline and after the 12-week intervention, ten mL fasting blood samples were collected from the participants

at Arak reference laboratory, Arak, Iran. Serum insulin concentrations were quantified using commercial ELISA kit (DiaMetra, Milano, Italy) with intra-assay and inter-assay coefficient variances (CVs) below 5%, respectively. The homeostasis model of assessment-insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated according to the suggested formulas.<sup>[16]</sup> Enzymatic kits (Pars Azmun, Tehran, Iran) were used to determine fasting plasma glucose (FPG) and lipid profiles. Serum hs-CRP concentrations were quantified by an available ELISA kit (LDN, Nordhorn, Germany). The plasma nitric oxide (NO) concentrations using Griess method,<sup>[17]</sup> total antioxidant capacity (TAC) concentrations by the method of ferric reducing antioxidant power developed by Benzie and Strain,<sup>[18]</sup> total glutathione (GSH) using the method of Beutler *et al.*<sup>[19]</sup> and MDA concentrations by the thiobarbituric acid reactive substances spectrophotometric test<sup>[20]</sup> were evaluated. All inter-assay and intra-assay CVs for FPG, lipid fractions, NO, TAC, GSH and MDA concentrations were less than 5%.

### Sample size

On the basis of sample size formula suggested for randomized clinical trials, considering the type I error of 5% ( $\alpha = 0.05$ ) and type II error of 20% ( $\beta = 0.20$ ; Power = 80%) and serum hs-CRP levels as key variable,<sup>[14]</sup> we used 1570.5 as SD and 1600.0 ng/mL as the change in mean (d) of serum hs-CRP levels as main variable. Based on this, we needed 16 subjects in each group. However, we recruited 40 subjects in each group (totally, 40 subjects) to compensate for the probable loss to follow up.

### Statistical analysis

To ensure the normal distribution of variables, the Kolmogorov-Smirnov test was used. To detect differences in anthropometric measures as well as in macro-nutrient and micro-nutrient dietary intakes between the two groups, we applied independent *t*-test. Differences in proportions were evaluated by Fisher's exact test. To determine the effects of omega-3 fatty acid administration on laboratory values, we used one-way repeated measures analysis of variance. Adjustment for changes in baseline values of biochemical values, age and baseline BMI was performed by analysis of covariance (ANCOVA) using general linear models. The *P* value of <0.05 were considered statistically significant. All statistical analyses used the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

### Results

At baseline, we invited 48 subjects; however, 8 subjects were excluded from the study because of not living in Arak. In the current study, 40 subject with EH [omega-3 fatty acid and placebo ( $n = 20$  each group)] completed the trial [Figure 1]. On average, the rate of compliance in

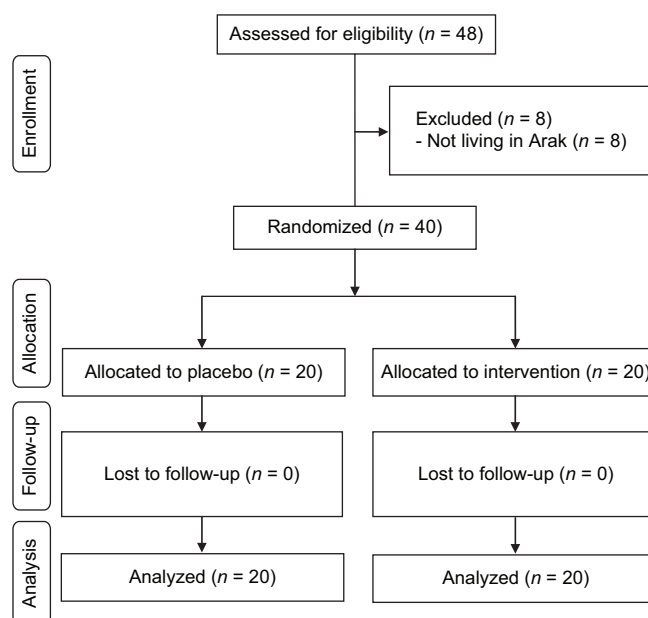


Figure 1: Summary of patient flow diagram

the present study was high, such that higher than 90% of supplements and placebos were taken throughout the study in both groups. No side effects were reported following the supplementation of omega-3 fatty acid in subject with EH throughout the study.

Mean age and height, baseline weight and BMI as well as their means before and after the 12-week treatment of subjects were not statistically different between omega-3 fatty acid and placebo groups [Table 1]. In addition, omega-3 fatty acid supplementation for 12 weeks did not affect EH regression ( $P = 0.28$ ).

Based on the 3-day dietary records obtained at baseline, weeks 3, 6, 9 and 12 of the intervention, no significant changes were observed between the two groups in macro- and micronutrients (Data not shown).

Compared with the placebo, omega-3 fatty acid supplementation significantly decreased FPG ( $-7.1 \pm 9.6$  vs.  $+2.0 \pm 4.9$  mg/dL,  $P = 0.001$ ), insulin levels ( $-1.5 \pm 4.6$  vs.  $+1.6 \pm 3.9$   $\mu$ IU/mL,  $P = 0.02$ ) and HOMA-IR ( $-0.4 \pm 1.1$  vs.  $+0.4 \pm 1.0$ ,  $P = 0.02$ ) [Table 2]. In addition, a significant increase in TAC ( $+102.6 \pm 69.6$  vs.  $+5.0 \pm 37.1$  mmol/L,  $P < 0.001$ ) and GSH levels ( $+63.6 \pm 84.9$  vs.  $-3.0 \pm 69.4$   $\mu$ mol/L,  $P = 0.01$ ) were seen following the supplementation of omega-3 fatty acid compared with the placebo. Omega-3 fatty acid supplementation had no significant effect on lipid profiles, and other biomarkers of inflammation and oxidative.

We controlled the analyses for the baseline values of biochemical parameters, age and baseline BMI. When we adjusted the analysis for baseline values of biochemical parameters, age and baseline BMI, insulin ( $P = 0.05$ ) and HOMA-IR ( $P = 0.06$ ) became non-significant, but other findings did not alter [Table 3].

**Table 1: General characteristics of study participants<sup>1</sup>**

	Placebo group (n=20)	Omega-3 group (n=20)	P <sup>2</sup>
Age (y)	44.5±3.9	47.0±6.7	0.12
Height (cm)	159.8±8.3	155.7±6.1	0.08
Weight at study baseline (kg)	78.0±12.4	74.1±8.1	0.24
Weight at end-of-trial (kg)	77.9±12.2	74.3±8.6	0.29
Weight change (kg)	-0.1±1.0	0.2±1.6	0.45
BMI at study baseline (kg/m <sup>2</sup> )	30.5±4.1	30.6±3.1	0.92
BMI at end-of-trial (kg/m <sup>2</sup> )	30.5±4.1	30.6±3.3	0.84
BMI change (kg/m <sup>2</sup> )	-0.03±0.4	0.1±0.7	0.45
EH regression (%)	13 (65.0)	16 (80.0)	0.28 <sup>†</sup>

<sup>1</sup>Data are means±SDs. EH=Endometrial hyperplasia. <sup>2</sup>Obtained from independent *t*-test. <sup>†</sup>Obtained from Fisher's exact test

**Table 2: Metabolic profiles at baseline and after the 12-week intervention in women with endometrial hyperplasia that received either omega-3 supplements or placebo<sup>1</sup>**

	Placebo group (n=20)			Omega-3 group (n=20)			P <sup>2</sup>
	Baseline	End-of-trial	Change	Baseline	End-of-trial	Change	
FPG (mg/dL)	95.5±8.5	97.5±7.5	2.0±4.9	100.5±8.9	93.4±13.1	-7.1±9.6	0.001
Insulin (μIU/mL)	10.1±4.0	11.7±4.8	1.6±3.9	10.3±5.7	8.8±4.5	-1.5±4.6	0.02
HOMA-IR	2.4±1.0	2.8±1.2	0.4±1.0	2.6±1.5	2.2±1.0	-0.4±1.1	0.02
QUICKI	0.34±0.02	0.33±0.02	-0.01±0.02	0.34±0.04	0.34±0.02	0.002±0.02	0.19
Triglycerides (mg/dL)	122.2±35.7	126.7±34.4	5.5±24.2	140.0±53.4	125.5±42.5	-14.5±40.0	0.06
VLDL-cholesterol (mg/dL)	24.4±7.1	25.5±6.9	1.1±4.8	28.0±10.6	25.1±8.5	-2.9±8.0	0.06
Total cholesterol (mg/dL)	193.0±32.1	199.2±31.4	6.2±25.6	189.1±58.8	183.3±45.9	-5.7±33.1	0.21
LDL-cholesterol (mg/dL)	123.8±33.4	128.5±33.0	4.7±23.4	115.7±54.9	113.8±42.1	-1.9±33.4	0.47
HDL-cholesterol (mg/dL)	44.8±8.6	45.2±10.6	0.5±5.1	45.3±8.2	44.4±8.2	-0.9±4.4	0.36
hs-CRP (mg/L)	5.3±4.1	5.1±3.6	-0.2±2.3	5.3±3.2	4.3±2.5	-1.0±2.9	0.32
NO (μmol/L)	41.5±4.7	42.1±5.2	0.6±3.7	39.3±3.6	38.6±3.5	-0.6±1.7	0.16
TAC (mmol/L)	796.0±54.2	801.0±61.6	5.0±37.1	831.3±57.2	933.9±68.7	102.6±69.6	<0.001
GSH (μmol/L)	544.6±67.6	541.6±60.2	-3.0±69.4	571.6±77.2	635.3±78.8	63.6±84.9	0.01
MDA (μmol/L)	2.4±0.3	2.4±0.3	-0.01±0.3	2.5±0.3	2.4±0.2	-0.1±0.3	0.13

<sup>1</sup>Data are means±SDs. <sup>2</sup>Obtained from repeated measures ANOVA test. *P*<0.05, significant effect. FPG=Fastening plasma glucose; GSH=Total glutathione; HOMA-IR=Homeostasis model of assessment-estimated insulin resistance; hs-CRP=High-sensitivity C-reactive protein; MDA=Malondialdehyde; NO=Nitric oxide; QUICKI=Quantitative insulin sensitivity check index; TAC=Total antioxidant capacity

## Discussion

To our knowledge, this study is the first report of omega-3 fatty acid administration on regression and metabolic profiles in patients with EH. We found that omega-3 fatty acid administration for 12 weeks to subjects with EH improved FPG, insulin, HOMA-IR, TAC and GSH levels, but did not influence regression and lipid profiles, and other biomarkers of inflammatory and oxidative stress.

Subjects with EH are susceptible to metabolic disorders and endometrial cancer.<sup>[2]</sup> We demonstrated that omega-3 fatty acid supplementation for 12 weeks to subjects with EH did not influence EH regression. Mounting evidence has linked dietary gain of omega-3 fatty acid to the prevention or attenuation of progression of several cancers, including colon,<sup>[21]</sup> breast,<sup>[22]</sup> and prostate cancers.<sup>[23]</sup> Several studies have also shown that mfat-1 expression, which produces omega-3 fatty acid endogenously, also inhibited the growth of colon<sup>[24]</sup> and breast cancer.<sup>[25]</sup> However, these strong phenotypic results, such as the aforementioned phenotypes

of omega-3 fatty acid on endometrial cancer have not conclusively indicated how omega-3 fatty acid achieved these anti-tumor effects. This discrepancy between our study with others might be mediated by distinct trial designs, various dosages of omega-3 fatty acid supplements and characteristics of the subjects.

Our data supported that omega-3 fatty acid supplementation for 12 weeks to subjects with EH led to a significant decrease in FPG, insulin and HOMA-IR, but did not affect lipid concentrations and QUICKI. In consistent with our study, purified EPA supplementation at a dosage of 2 g/day for 12 weeks to overweight subjects with T2DM significantly decreased FPG and insulin resistance.<sup>[26]</sup> We have previously shown that omega-3 fatty acid supplementation at a dosage of 1,000 mg twice a day for 12 weeks to subjects with diabetic foot ulcer had beneficial effects on markers of insulin metabolism, but did not affect lipid profiles.<sup>[27]</sup> A large number of nutraceuticals such as flaxseed oil have been tested in several studies, demonstrating their lipid-lowering effects.<sup>[28]</sup> However,

**Table 3: Adjusted changes in metabolic variables in women with endometrial hyperplasia that received either omega-3 supplements or placebo<sup>1</sup>**

	Placebo group (n=20)	Omega-3 group (n=20)	P <sup>2</sup>
FPG (mg/dL)	1.2±1.6	-6.3±1.6	0.003
Insulin (μIU/mL)	1.2±0.8	-1.1±0.8	0.05
HOMA-IR	0.3±0.2	-0.3±0.2	0.06
QUICKI	-0.007±0.004	0.002±0.004	0.10
Triglycerides (mg/dL)	0.6±6.4	-9.7±6.4	0.27
VLDL-cholesterol (mg/dL)	0.1±1.3	-1.9±1.3	0.27
Total cholesterol (mg/dL)	5.9±5.6	-5.5±5.6	0.16
LDL-cholesterol (mg/dL)	5.2±5.6	-2.5±5.6	0.34
HDL-cholesterol (mg/dL)	0.4±1.1	-0.9±1.1	0.42
hs-CRP (mg/L)	-0.1±0.5	-1.1±0.5	0.19
NO (μmol/L)	0.8±0.7	-0.8±0.7	0.10
TAC (mmol/L)	-0.6±12.7	108.3±12.7	<0.001
GSH (μmol/L)	-9.1±14.8	69.7±14.8	0.001
MDA (μmol/L)	-0.1±0.04	-0.1±0.04	0.75

<sup>1</sup>All values are means±SEs. <sup>2</sup>Obtained from analysis of covariance adjusted for baseline values + age and baseline BMI. FPG=Fasting plasma glucose; GSH=Total glutathione; HOMA-IR=Homeostasis model of assessment-estimated insulin resistance; hs-CRP=High-sensitivity C-reactive protein; MDA=Malondialdehyde; NO=Nitric oxide; QUICKI=Quantitative insulin sensitivity check index; TAC=Total antioxidant capacity

no significant change in triglycerides concentrations was observed following the supplementation of flaxseed oil (1 g twice a day) for 120 days to chronic hemodialysis patients.<sup>[29]</sup> Omega-3 fatty acid supplementation at a dosage of 4 g/day for 8 weeks to patients with coronary artery disease did not result in any significant changes in serum lipids except for LDL-cholesterol, and FPG and serum insulin levels.<sup>[30]</sup> In addition, taking omega-3 fatty acid for 12 weeks by patients with T2DM had no significant impact on HOMA-IR despite statistically significant alterations in correlations compared to baseline HOMA-IR.<sup>[31]</sup>

Different findings of our study with others especially about lipid profiles might be explained by different study designs, the variation in the individuals studied, the source of omega-3 fatty acid, dosage of omega-3 fatty acid used as well as duration of the study. However, exact mechanism by which omega-3 fatty acid might influence FPG and markers of insulin metabolism is unknown, improved markers of insulin metabolism by omega-3 fatty acid intake may be mediated by the inhibiting production of pro-inflammatory cytokines and gene expression levels of nuclear factor-κB (NF-κB).<sup>[32]</sup> Moreover, omega-3 fatty acid intake may reduce insulin resistance through modulating the secretion of adipocytokines, the suppression of sterol regulatory element-binding transcription factor 1 mediated lipogenesis and enhancing fatty acid β-oxidation.<sup>[33]</sup>

This study demonstrated that omega-3 fatty acid supplementation for 12 weeks to subjects with EH resulted in a significant increase in TAC and GSH levels, but did not affect

other biomarkers of inflammation and oxidative stress. In line with the current study, omega-3 fatty acid supplementation at dosage of 1.28 g/day for 12 weeks to hemodialysis patients was associated with the improvement of biomarkers of oxidative stress such as isoprostane and advanced oxidation protein product.<sup>[34]</sup> A highly significant elevation in glutathione peroxidase and superoxide dismutase levels was also seen following the supplementation of omega-3 fatty acid at a dosage of 1 g/day for 12 weeks to children undergoing hemodialysis.<sup>[35]</sup> In addition, supplementation with omega-3 fatty acids for 6 and 12 weeks could not affect CRP levels among patients with chronic periodontitis.<sup>[36]</sup> Furthermore, no significant impact in TAC values was observed following the consumption of a combined dietary supplements containing omega-3 fatty acid, vitamin E, niacin and gamma-oryzanol among dyslipidemic subjects.<sup>[37]</sup> However, we have reported that omega-3 fatty acid supplementation for 6 weeks to women with GDM was associated with decreased circulating levels of hs-CRP and MDA, but could not influence other biomarkers of inflammation and oxidative stress.<sup>[14]</sup> Omega-3 fatty acid intake directly decreases the production of inflammatory cytokines,<sup>[38]</sup> which in turn may decrease oxidative stress. Moreover, omega-3 fatty acid may decrease oxidative stress through inhibiting activation of NF-κB.<sup>[39,40]</sup>

This research had few limitations. Firstly, we did not evaluate gene expression related to insulin and oxidative stress to explore the plausible mechanism. In addition, we determined serum hs-CRP levels as a systemic inflammatory marker. Systemic markers such as CRP can be influenced by a variety of factors. Future studies with cross-over design, longer duration of the intervention, and bigger sample size are needed to confirm the validity of our findings.

## Conclusions

In conclusion, we showed that omega-3 fatty acid administration for 12 weeks to subjects with EH significantly improved FPG, insulin, HOMA-IR, TAC and GSH levels, but did not influence regression and lipid profiles, and other biomarkers of inflammatory and oxidative stress. This suggests omega-3 fatty acid supplementation may confer advantageous therapeutic potential for patients with EH. Further studies are needed in other participants and with longer periods to explore the plausible mechanism and confirm our findings.

## Acknowledgments

The current research was supported by a grant from the Vice-chancellor for Research, AUMS, Arak, and Iran.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

**Received:** 10 Feb 18 **Accepted:** 02 Apr 19

**Published:** 17 May 19

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