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The effects of omega-3 fatty acids and vitamin E co-supplementation on clinical and metabolic status in patients with Parkinson's disease: A randomized, double-blind, placebo-controlled trial

Mohsen Taghizadeh [a], Omid Reza Tamtaji [b], Ehsan Dadgostar [c], Reza Daneshvar Kakhaki [d], Fereshteh Bahmani [a], Javad Abolhassani [d], Mohammad Hossein Aarabi [a], Ebrahim Kouchaki [b, d], Mohammad Reza Memarzadeh [e], Zatollah Asemi [a, *]

[a] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran
[b] Physiology Research Center, Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran
[c] Student Research Committee, Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran
[d] Department of Neurology, School of Medicine, Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran
[e] Barij Medicinal Plants Research Center, Kashan, Islamic Republic of Iran

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ABSTRACT

The current research was performed to evaluate the effects of omega-3 fatty acids and vitamin E co-supplementation on clinical signs and metabolic status in people with Parkinson's disease (PD). This randomized double-blind placebo-controlled clinical trial was conducted in 60 patients with PD. Participants were randomly assigned into two groups to receive either 1000 mg omega-3 fatty acids from flaxseed oil plus 400 IU vitamin E supplements (n = 30) or placebo (n = 30) for 12 weeks. Unified Parkinson's disease rating stage (UPDRS) were recorded at baseline and the after 3-month intervention. After 12 weeks' intervention, compared with the placebo, omega-3 fatty acids and vitamin E co-supplementation led to a significant improve in UPDRS (−3.3 ± 10.0 vs. +4.4 ± 14.9, P = 0.02). Furthermore, co-supplementation decreased high-sensitivity C-reactive protein (hs-CRP) (−0.3 ± 0.6 vs. +0.3 ± 0.3 μg/mL, P < 0.001), and increased total antioxidant capacity (TAC) (+65.2 ± 68.7 vs. +16 ± 52.4 μmol/L, P = 0.003) and glutathione (GSH) concentrations (+41.4 ± 80.6 vs. −19.6 ± 55.9 μmol/L, P = 0.001) compared with the placebo. Additionally, co-supplementation meaningfully decreased insulin (−2.1 ± 4.9 vs. +1.4 ± 6.2 μIU/mL, P = 0.01), homeostasis model of assessment-estimated insulin resistance (−0.7 ± 1.8 vs.+0.3 ± 1.6, P = 0.02) and Beta cell function (−5.9 ± 13.9 vs. +5.7 ± 25.5, P = 0.03), and increased quantitative insulin sensitivity check index (+0.009 ± 0.02 vs. −0.006 ± 0.03, P = 0.03) compared with the placebo. Overall, our study demonstrated that omega-3 fatty acids and vitamin E co-supplementation in people with PD had favorable effects on UPDRS, hs-CRP, TAC, GSH and markers of insulin metabolism.

1. Introduction

Parkinson's disease (PD) is a progressive disorder influencing more than 3% of subjects with age over 75 years (de Lau and Breteler, 2006). Prior studies have demonstrated that the pathological marking of PD is the intraneuronal reposition of uncommon filamentous inclusions containing phosphorylated α-synuclein (phosαSYN) (Jellinger, 2003; Braak and Del Tredici, 2008). In addition, increased oxidative stress involves early events associated with dopaminergic neuronal degeneration in PD (Lv et al., 2015). Neuroendocrine abnormalities including glucose intolerance, insulin resistance and bone metabolism, and body weight changes are also common in PD (De Pablo-Fernandez et al., 2017).

Previous reports have indicated that omega-3 fatty acids deficiency can reduce the nigrostriatal system's ability to maintain homeostasis under oxidative conditions, which may increase the risk of PD (Fabelo et al., 2011; Cardoso et al., 2014). Furthermore, few researchers have exhibited that concentrations of vitamin E

* Corresponding author.
E-mail address: asemi_r@yahoo.com (Z. Asemi).

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were lower in PD patients than healthy subjects (Paraskevas et al., 2003; Fukushima et al., 2011). Our previous study among gestational diabetes (GDM) have demonstrated that co-supplementation with 1000 mg omega-3 fatty acids and 400 IU vitamin E daily for 6 weeks increased total antioxidant capacity (TAC) and nitric oxide (NO), and decreased malondialdehyde (MDA) values, but unaltered glutathione (GSH) and high-sensitivity C-reactive protein (hs-CRP) levels (Jamilian et al., 2016). However, no significant effect in indices of oxidative stress and/or inflammation was seen following supplementation with omega-3 fatty acids in healthy adults for 4 weeks (Cunnane et al., 1995) and vitamin E in hemodialysis (HD) people for 8 weeks (Ahmadi et al., 2013).

Omega-3 and vitamin E may result in improved clinical signs, indices of inflammation and oxidative stress, and metabolic status through their effects on modifications in the dopamine metabolism (Cardoso et al., 2014), decreased inflammatory markers (Zhuang et al., 2013), reducing production of reactive oxygen species (ROS) in the mitochondria (Capo et al., 2015) and improved antioxidant defense (Gupta et al., 2011). However, whether omega-3 and vitamin E co-supplementation have direct benefits on clinical signs, biomarkers of inflammation and oxidative stress, and metabolic parameters in people with PD has to date not been evaluated. This intervention was, therefore, performed to determine the effects of omega-3 and vitamin E co-supplementation on clinical signs, indices of inflammation and oxidative stress, and metabolic parameters in people with PD.

2. Materials and methods

2.1. Participants

This treatment, registered in the Iranian website for registration of clinical trials (http://www.irct.ir: IRCT201604035623N73), was a randomized, double-blind, placebo-controlled clinical trial that was done among people with PD aged 50–80 years old diagnosed according to clinical diagnostic criteria of the UK PD Society Brain Bank (Hughes et al., 1992) referred to the Shahid Beheshti Clinic in Kashan, Iran, between March 2016 and June 2016. The diagnosis of PD was confirmed by 2 neurologists. Exclusion criteria were patients who were already taking omega-3 and/or vitamin E, had depression and had severe psychosis.

2.2. Study design

Subjects were randomly divided into two groups to intake either 1000 mg omega-3 fatty acids from flaxseed oil plus 400 IU vitamin E supplements (n = 30: 21 males and 9 females) or placebo (n = 30: 21 males and 9 females) for 12 weeks. Subjects were requested not to change their ordinary physical activity during the 12-week trial. All subjects completed 3-day food records and three physical activity records at weeks 0, 3, 6, 9 and 12 of the intervention. Daily macro- and micro-nutrient intakes were analyzed by nutritionist IV software (First Databank, San Bruno, CA).

2.3. Treatment adherence

The use of supplements and placebos during the study was checked by asking participants to return the medication containers. To increase compliance, all participants received brief daily cell phone reminders to intake the supplements.

2.4. Assessment of anthropometric measures

Weight and height of subjects were determined in a fasting status using a standard scale (Seca, Hamburg, Germany) at week 0 and after the 12-week treatment. BMI was calculated as weight in kg divided by height in meters squared.

2.5. Assessment of outcomes

The primary outcomes variables were Unified Parkinson's Disease Rating Stage (UPDRS) and inflammatory markers in the current study. The secondary outcomes variables were biomarkers of oxidative stress and metabolic profiles.

2.6. Clinical evaluation at entry

To assess clinical signs, UPDRS total score as well as 4 subscores (part I: nonmotor experiences of daily living; part II: motor experiences of daily living; part III: motor examination; and part IV: motor complications) were used (Goetz et al., 2008).

2.7. Assessment of outcomes

Twelve-hour fasting blood samples were collected at baseline and after the 12-week intervention at Kashan reference laboratory. Serum hs-CRP values were assessed using commercial ELISA kit (LDN, Nordhorn, Germany) with the intra- and inter-assay coefficient variances (CVs) 3.7 and 5.6%, respectively. Plasma nitric oxide (NO) levels were determined by the Giess method (Tatsch et al., 2011). Plasma total antioxidant capacity (TAC) using the method of ferric reducing antioxidant power method developed by Benzie and Strain (Benzie and Strain, 1996), GSH by the method of Beutler et al (Beutler and Gelbart, 1985) and malondialdehyde (MDA) values using the thiobarbituric acid reactive substance method (Janero, 1990) were quantified. All inter- and intra-assay CVs for NO, TAC, GSH and MDA were lower than 5%. To assess fasting plasma glucose (FPG), serum triglycerides, VLDL-, total-, LDL- and HDL-cholesterol fractions, we used available kits (Pars Azmun, Tehran, Iran). All inter- and intra-assay CVs for FPG and lipid fractions were lower than 5%. Serum insulin values were assessed using ELISA kit (Monobind, California, USA) with the intra- and inter-assay CVs 3.2 and 5.1%, respectively. HOMA-IR, homeostatic model assessment for B-cell function (HOMA-B) and the quantitative insulin sensitivity check index (QUICKI) were calculated according to suggested formulas (Pisprasert et al., 2013).

2.8. 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 values as key variable (Asemi et al., 2016), we used 2.5 as SD and 2.1 μg/mL as the change in mean (d) of serum hs-CRP levels as main variable. Based on this, we needed 25 subjects in each group. Assuming 5 dropouts in each group, the final sample size was determined to be 30 subjects per group.

2.9. Randomization

Randomization assignment was done using computer-generated random numbers as blindness by a trained staff at the clinic.

2.10. Statistical methods

To determine whether the study variables were normally distributed or not, we applied the Kolmogrov-Smirnov test. Analyses were performed based on an intention-to-treat (ITT) principle. To detect differences in anthropometric measures as well as in

macro- and micro-nutrient intakes between the two groups, we used Student's *t*-test to independent samples. Differences in proportions were evaluated by Chi square test. To evaluate the effects of omega-3 fatty acids and vitamin E co-supplementation on UPDRS, biomarkers of inflammation and oxidative stress, and metabolic profiles, we used one-way repeated measures analysis of variance. Adjustment for changes in baseline values of biochemical variables, age and BMI at baseline 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).

3. Results

Among subjects in the supplements and placebo groups, 3 people [withdrawn (n = 3)] were excluded (Fig. 1). In the end, 54 subjects [omega-3 and vitamin E (n = 27) and placebo (n = 27)] completed the trial. However, as the analysis was based on the ITT principle, all 60 people (30 in each group) were included in the final analysis.

Distribution of gender, disease severity, mean age, height, weight and BMI as well as METs at week 0 and week 12 were not different between the two groups (Table 1).

Based on the 3-day dietary records obtained at week 0, throughout of the trial and week 12, we found no significant difference in mean macro- and micronutrient intakes between the two groups (Data not shown).

After 12 weeks' intervention, compared with the placebo, omega-3 and vitamin E co-supplementation led to a significant improvement in UPDRS (−3.3 ± 10.0 vs. +4.4 ± 14.9, P = 0.02) (Table 2). Furthermore, co-supplementation decreased high-sensitivity C-reactive protein (hs-CRP) (−0.3 ± 0.6 vs. +0.3 ± 0.3 μg/mL, P < 0.001), and increased TAC (+65.2 ± 68.7 vs. +16 ± 52.4 μmol/L, P = 0.003) and GSH concentrations (+41.4 ± 80.6 vs. −19.6 ± 55.9 μmol/L, P = 0.001) compared with the placebo. Additionally, co-supplementation meaningfully decreased insulin (−2.1 ± 4.9 vs. +1.4 ± 6.2 μIU/mL, P = 0.01), HOMA-IR (−0.7 ± 1.8 vs.+0.3 ± 1.6, P = 0.02) and HOMA-B (−5.9 ± 13.9 vs. +5.7 ± 25.5, P = 0.03), and increased QUICKI (+0.009 ± 0.02 vs. −0.006 ± 0.03, P = 0.03) compared with the placebo. We did not see any significant change on other indices of inflammation, oxidative stress, FPG and lipid profiles following intake of omega-3 plus vitamin E.

Baseline levels of plasma TAC were different between the two groups. Therefore, we controlled the analyses for the baseline values of biochemical parameters, age and baseline BMI. However, after this adjustment, QUICKI (P = 0.05) became non-significant, while plasma MDA levels (P = 0.02) became significant, and other findings did not alter (Table 3).

4. Discussion

In this research, we evaluated the effects of omega-3 and vitamin E co-supplementation on clinical signs and metabolic indices in people with PD. We found that omega-3 fatty acids and vitamin E co-supplementation for 12 weeks in patients with PD had favorable effects on UPDRS, serum hs-CRP, plasma TAC, GSH and markers of insulin metabolism, but did not affect other indices of inflammation and oxidative stress, and lipid profiles. To our knowledge, this trial is the first to have assessed the effects of omega-3 and vitamin E co-supplementation on clinical signs and metabolic indices in people with PD. It must be kept mind that biomarkers of inflammation or oxidative stress can be different in the early and late stages of PD, and biomarkers such as MDA, CRP, NO, and antioxidant resources are differentially affected (de Farias et al., 2016), therefore, all patients were matched for disease severity based on UPDRS and gender.

We found that omega-3 and vitamin E co-supplementation in people with PD for 12 weeks improved UPDRS compared with the placebo. However, data on the effects of omega-3 and vitamin E co-supplementation on UPDRS in human studies are scarce. In a study by Tanriover et al. (2010) it was observed that docosahexaenoic acid (DHA) increased glial cell-derived neurotrophic factor and

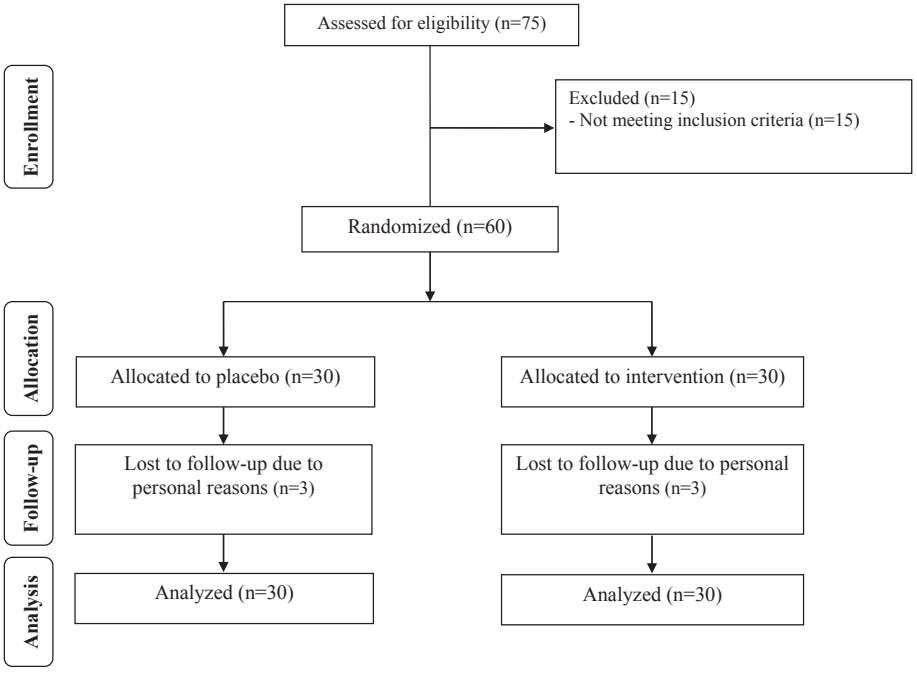

Fig. 1. Summary of patient flow.

Table 1
General characteristics of study participants.[a]

	Placebo group (n = 30)	Omega-3 plus vitamin E group (n = 30)	P[b]
Gender (%)			
Male	21 (70.0)	21 (70.0)	1.00[c]
Female	9 (30.0)	9 (30.0)	
Disease severity (%)			
Mild	6 (20.0)	5 (16.7)	0.73[c]
Moderate	24 (80.0)	25 (83.3)	
Age (y)	66.0 ± 10.4	63.9 ± 8.9	0.38
Height (cm)	163.1 ± 5.9	163.5 ± 5.4	0.78
Weight at study baseline (kg)	66.6 ± 7.6	68.3 ± 12.9	0.53
Weight at end-of-trial (kg)	66.3 ± 6.9	68.7 ± 12.5	0.34
Weight change (kg)	−0.4 ± 2.2	0.4 ± 0.9	0.08
BMI at study baseline (kg/m^2)	25.1 ± 3.1	25.6 ± 4.7	0.65
BMI at end-of-trial (kg/m^2)	25.0 ± 2.8	25.7 ± 4.6	0.44
BMI change (kg/m^2)	−0.1 ± 0.8	0.1 ± 0.3	0.07

[a] Data are means± SDs.
[b] Obtained from independent *t*-test.
[c] Obtained from Pearson Chi-square test.

Table 2
Unified Parkinson's disease rating stage, biomarkers of inflammation and oxidative stress, and metabolic profiles at baseline and after the 3-month intervention in patients with Parkinson's disease that received either omega-3 fatty acids plus vitamin E or placebo.[a]

	Placebo group (n = 30)			Omega-3 and vitamin E group (n = 30)			P[b]
	Baseline	End-of-trial	Change	Baseline	End-of-trial	Change	
UPDRS total (0–195)	46.1 ± 18.0	50.5 ± 17.1	4.4 ± 14.9	47.4 ± 16.6	44.1 ± 14.7	−3.3 ± 10.0	0.02
hs-CRP (μg/mL)	3.4 ± 1.5	3.7 ± 1.7	0.3 ± 0.3	3.7 ± 1.7	3.4 ± 1.9	−0.3 ± 0.6	<0.001
NO (μmol/L)	47.5 ± 3.0	51.3 ± 5.5	3.7 ± 5.5	48.1 ± 4.1	52.3 ± 5.1	4.2 ± 4.7	0.72
TAC (mmol/L)	735.9 ± 79.7	751.9 ± 85.9	16.0 ± 52.4	819.8 ± 26.1	885.0 ± 60.4	65.2 ± 68.7	0.003
GSH (μmol/L)	603.3 ± 77.5	583.7 ± 55.8	−19.6 ± 55.9	591.1 ± 59.6	632.5 ± 85.9	41.4 ± 80.6	0.001
MDA (μmol/L)	2.3 ± 0.4	2.3 ± 0.3	0.009 ± 0.4	2.3 ± 0.4	2.2 ± 0.2	−0.1 ± 0.4	0.18
FPG (mg/dL)	101.8 ± 40.8	100.3 ± 42.3	−1.5 ± 13.7	105.0 ± 38.1	94.0 ± 38.0	−11.0 ± 22.4	0.05
Insulin (μIU/mL)	10.1 ± 6.1	11.5 ± 5.0	1.4 ± 6.2	11.2 ± 6.0	9.1 ± 4.6	−2.1 ± 4.9	0.01
HOMA-IR	2.8 ± 3.0	3.1 ± 2.5	0.3 ± 1.6	3.0 ± 2.2	2.3 ± 1.3	−0.7 ± 1.8	0.02
HOMA-B	33.7 ± 19.2	39.4 ± 18.9	5.7 ± 25.5	37.0 ± 20.7	31.1 ± 19.8	−5.9 ± 13.9	0.03
QUICKI	0.34 ± 0.03	0.33 ± 0.03	−0.006 ± 0.03	0.33 ± 0.03	0.34 ± 0.03	0.009 ± 0.02	0.03
Triglycerides (mg/dL)	116.3 ± 45.0	118.4 ± 55.5	2.1 ± 4.9	106.3 ± 38.6	106.7 ± 37.3	0.4 ± 46.3	0.85
VLDL-cholesterol (mg/dL)	23.2 ± 9.0	23.7 ± 11.1	0.4 ± 4.9	21.3 ± 7.7	21.3 ± 7.5	0.1 ± 9.3	0.85
Total cholesterol (mg/dL)	165.5 ± 29.5	159.9 ± 32.9	−5.6 ± 31.9	163.2 ± 36.7	157.5 ± 34.1	−5.7 ± 34.6	0.99
LDL-cholesterol (mg/dL)	101.7 ± 28.1	94.4 ± 30.2	−7.3 ± 28.8	99.7 ± 32.0	94.6 ± 31.1	−5.1 ± 28.4	0.76
HDL-cholesterol (mg/dL)	40.5 ± 8.3	41.9 ± 9.0	1.4 ± 5.6	42.1 ± 7.5	41.5 ± 8.1	−0.6 ± 3.0	0.10

FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; HOMA-B, homeostasis model of assessment-estimated B cell function; hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; NO, nitric oxide; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity; UPDRS, unified Parkinson's disease rating stage.
[a] Data are means± SDs.
[b] P values represent the time × group interaction (computed by analysis of the one-way repeated measures ANOVA).

neurturin in the Substantia nigra (SN), and reduced dopaminergic cell death induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in bilateral rat model of PD. In addition, the influence of DHA on brain-derived neurotrophic factor (BDNF) levels has reported in the hippocampus, cerebral cortex (Vines et al., 2012) and spinal cord (Ying et al., 2012). In another study, using the MPTP-induced experimental PD model, vitamin E deficient mice were much more susceptible to MPTP toxicity than control mice (Odunze et al., 1990). However, α-tocopherol did not prevent the marked striatal dopamine depletions produced by MPTP (Martinovits et al., 1986). Omega-3 intake may improve neuronal survival through facilitating membrane translocation/activation of Akt and a downstream effector in the phosphoinositide 3-kinase (PI3K) pathway (Akbar et al., 2005). Vitamin E intake may have protective effect on dopamine-induced cell death and ROS production (Storch et al., 2000), which in turn would result in a control over neurological symptoms in people with PD.

This intervention demonstrated that omega-3 and vitamin E co-supplementation in subjects with PD for 12 weeks decreased serum hs-CRP, and increased plasma TAC and GSH levels, while unchanged plasma NO and MDA levels. Our previous study in GDM women was demonstrated that co-administration with 1000 mg omega-3 fatty acids and 400 IU vitamin E daily for 6 weeks elevated TAC and NO, and decreased MDA values, but did not influence plasma GSH and serum hs-CRP (Jamilian et al., 2016). In line with our results, taking omega-3 in subjects with systemic lupus erythematosus for 12 weeks decreased CRP concentrations (Borges et al., 2016). In a meta-analysis study, it was reported that vitamin E intake decreased serum CRP concentrations (Saboori et al., 2015). Unlike, supplementation with 1400 mg of EPA + DHA for 18 weeks did not reduce indices of systemic inflammation in healthy adults (Muldoon et al., 2016). In addition, no significant effect in TAC values was seen after intake of a combined dietary supplementation containing omega-3 fatty acids, vitamin E, B3 and gamma-oryzanol among dyslipidemic subjects (Accinni et al., 2006). Previous studies have shown that signs of oxidative and nitrosative stress (O&NS) were observed in the peripheral blood of PD patients, including increased lipid hydroperoxides, higher levels of by-

Table 3
Adjusted changes in unified Parkinson's disease rating stage, biomarkers of inflammation and oxidative stress, and metabolic profiles in patients with Parkinson's disease that received either omega-3 fatty acids plus vitamin E or placebo.[a]

	Placebo group (n = 30)	Omega-3 and vitamin E group (n = 30)	P[b]
UPDRS total (0–195)	4.7 ± 2.0	−3.4 ± 2.0	0.005
hs-CRP (μg/mL)	0.3 ± 0.1	−0.3 ± 0.1	<0.001
NO (μmol/L)	3.6 ± 0.9	4.3 ± 0.9	0.60
TAC (mmol/L)	6.8 ± 12.4	74.4 ± 12.5	0.001
GSH (μmol/L)	−17.4 ± 11.5	39.2 ± 11.5	0.001
MDA (μmol/L)	0.02 ± 0.04	−0.14 ± 0.04	0.02
FPG (mg/dL)	−1.9 ± 3.3	−10.6 ± 3.3	0.07
Insulin (μIU/mL)	1.1 ± 0.8	−1.8 ± 0.8	0.01
HOMA-IR	0.3 ± 0.2	−0.7 ± 0.2	0.005
HOMA-B	4.5 ± 3.2	−4.7 ± 3.2	0.04
QUICKI	−0.006 ± 0.005	0.008 ± 0.005	0.05
Triglycerides (mg/dL)	3.0 ± 6.7	−0.6 ± 6.7	0.70
VLDL-cholesterol (mg/dL)	0.6 ± 1.3	−0.1 ± 1.3	0.70
Total cholesterol (mg/dL)	−5.5 ± 5.3	−5.7 ± 5.3	0.97
LDL-cholesterol (mg/dL)	−7.2 ± 4.8	−5.2 ± 4.8	0.76
HDL-cholesterol (mg/dL)	1.2 ± 0.8	−0.4 ± 0.8	0.16

FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; HOMA-B, homeostasis model of assessment-estimated B cell function; hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; NO, nitric oxide; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity; UPDRS, unified Parkinson's disease rating stage.

[a] All values are means± SEs.

[b] Obtained from analysis of ANCOVA adjusted for baseline values + age and baseline BMI.

products of NO and changes in antioxidants (Nikam et al., 2009; de Farias et al., 2016). As MDA is a highly significant biomarker of PD per se, changes in lipid hydroperoxides are more associated with disease progression (Baillet et al., 2010). Few studies have reported that lipid peroxidation with the formation of neoepitopes like MDA is a key phenomenon of PD that further drives adaptive changes in superoxide dismutase (SOD) and catalase (CAT) activity (Cheng et al., 2016; de Farias et al., 2016). In addition, higher concentrations of plasma NO can nitrosylate proteins thereby modifying the activity of many proteins related to intracellular signaling and immune responses. This explains that NO generated by inducible nitric oxide synthase (iNOS) may result in inflammatory responses and apoptosis. In PD patients, the injury to dopaminergic neurons promotes microglial activation, upregulation of iNOS and increased NO production (Moylan et al., 2014). The absence of significant effect of omega-3 and vitamin E co-supplementation on plasma NO and MDA levels in the current study might be mediated by different study designs, the source of omega-3 and vitamin E, dosage of omega-3 and vitamin E as well as duration of the study. Neuroinflammation due to increased biomarkers of inflammation and oxidative stress is considered a major factor promoting the pathogenesis of PD (Yu et al., 2016). Inflammation both peripheral and neuroinflammation may lead to immune responses in the brain (Phani et al., 2012). Then, the immune response in the brain leads to microglial activation, elaboration of pro-inflammatory cytokines, the production of ROS (Wypijewska et al., 2010), pigment formation (Double, 2012), and secondary neuronal injury (Shi et al., 2010). Omega-3 and vitamin E directly decrease the production of inflammatory cytokines in liver (Devaraj and Jialal, 1998; Li et al., 2005). Furthermore, omega-3 fatty acids and vitamin E may decrease inflammation and oxidative stress through inhibiting activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Rossi et al., 2000; Wu et al., 2004) and activity increase of protein phosphatase 2A (Nakamura et al., 1998).

We found shown that omega-3 and vitamin E co-supplementation in subjects with PD for 12 weeks decreased serum insulin values, HOMA-IR, HOMA-B, and increased QUICKI, but it did not affect FPG and lipid fractions. We have previously shown that omega-3 plus vitamin E intake in patients with GDM for 6 weeks had beneficial effects on glucose metabolism, serum triglycerides, VLDL-cholesterol, and HDL-cholesterol values, but unaltered other lipid profiles (Taghizadeh et al., 2016). In a study conducted by Hutchins et al. (2013) it was observed that flaxseed oil intake in overweight or obese people with pre-diabetes for 3 months led to a significant reduction in insulin and a significant elevation in insulin sensitivity. In another study, a significant reduction in HOMA-IR was also observed following intake of vitamin E at a dosage of 600 mg/day in obese children with non-alcoholic fatty liver disease for 6 months (D'Adamo et al., 2013). However, taking flaxseed oil among patients with T2DM for 180 days did not affect glucose metabolism and lipid profiles (Zheng et al., 2016). In addition, high-dose vitamin E intake (1200 IU/day) in subjects with diabetic nephropathy (DN) for 12 weeks did not influence glucose metabolism (Khatami et al., 2016). Early reports previously have shown that up to 50–80% of subjects with PD have glucose intolerance (Sandyk, 1993), however data from more contemporary prospective studies suggest the relation is more modest with T2DM subjects having approximately a 40% increased risk of developing PD (Driver et al., 2008). Abnormal insulin signaling and insulin resistance in patients with PD may be linked with extracellular events of relevance to neurodegeneration and inflammation, which in turn is increasingly recognised as a main contributor to the pathogenesis of PD (Athauda and Foltynie, 2016). Therefore, joint omega-3 fatty acids and vitamin E supplements due to their useful effects on glycemic control may be useful to control neurological symptoms in patients with PD. Omega-3 fatty acids plus vitamin E intake might improve markers of insulin metabolism through stimulating AMP-activated protein kinase (AMPK) in the muscle (Yamauchi et al., 2002) and inhibiting activation of NF-kB (Altavilla et al., 2000).

This research had few limitations. Firstly, due to budget limitations, we did not evaluate measurements of fatty acids profiles and vitamin E levels at baseline and the after 12-week intervention. We did not evaluate the relative contribution of omega-3 fatty acids and vitamin E in the outcomes. One want conclude that the treatment effects observed in the current study was due to the effect of omega-3 fatty acids or vitamin E supplements. Therefore, further studies are needed with single supplements compared with co-supplements used in the current study in order to assess beneficial effects on UPDRS and metabolic profiles in PD patients. In

addition, we did not evaluate other biomarkers of inflammation and oxidative stress.

5. Conclusions

Overall, our study demonstrated that omega-3 fatty acids and vitamin E co-supplementation in people with PD had favorable effects on UPDRS, hs-CRP, TAC, GSH and markers of insulin metabolism, whereas it did not affect other biomarkers of inflammation and oxidative stress, and lipid profiles.

Conflicts of interest

No conflicts are declared.

Author contributions

ZA and MT contributed in conception, design, statistical analysis and drafting of the manuscript. O-RT, ED, RD-K, FB, JA, M-HA, EK and M-RM. contributed in conception, data collection and manuscript drafting. The final version was confirmed by all authors for submission.

Clinical registration

http://www.irct.ir: IRCT201604035623N73.

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Appendix A. Supplementary data

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