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The effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in patients with Parkinson's disease: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Objective: This study was conducted to evaluate the effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in subjects with Parkinson's disease (PD).

Patients and methods: This randomized, double-blind, placebo-controlled clinical trial was performed in 40 subjects with PD. Participants were randomly allocated into two groups to take either 1000 mg/day of omega-3 fatty acids from flaxseed oil plus 400 IU/day of vitamin E supplements or placebo (n = 20 each group) for 12 weeks. Gene expression related to inflammation, insulin and lipid were quantified in peripheral blood mononuclear cells (PBMC) of PD patients with RT-PCR method.

Results: After the 12-week intervention, compared with the placebo, omega-3 fatty acids and vitamin E co-supplementation downregulated gene expression of tumor necrosis factor alpha (TNF-α) (P = 0.002) in PBMC of subjects with PD. In addition, omega-3 fatty acids and vitamin E co-supplementation upregulated peroxisome proliferator-activated receptor gamma (PPAR-γ) (P = 0.03), and downregulated oxidized low-density lipoprotein receptor (LDLR) (P = 0.002) in PBMC of subjects with PD compared with the placebo. We did not observe any significant effect of omega-3 fatty acids and vitamin E co-supplementation on gene expression of interleukin-1 (IL-1) and IL-8 in PBMC of patients with PD.

Conclusions: Overall, omega-3 fatty acids and vitamin E co-supplementation for 12 weeks in PD patients significantly improved gene expression of TNF-α, PPAR-γ and LDLR, but did not affect IL-1 and IL-8.

1. Introduction

Parkinson's disease (PD) is a progressive disorder which related to motor symptoms such as bradykinesia, rigidity and tremor, and non-motor symptoms such as depression and cognitive disorder [1]. Previous studies have indicated that elevated levels of inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interluekin-1 (IL-1) in patients with PD play a pivotal role in the pathogenesis of PD [2,3]. In addition, modulation of peroxisomalprolifera tor-activated receptor gamma (PPAR-γ) activity leads to neuroprotective effects on oxidative stress, apoptosis and neuroinflammation in PD [4].

We have previously shown that omega-3 fatty acids and vitamin E co-supplementation intake for 12 weeks among patients with PD had benefit effects on Unified Parkinson's disease rating stage, insulin metabolism, high-sensitivity C-reactive protein, glutathione and total antioxidant capacity [5]. Few studies have reported the effects of omega-3 fatty acids and vitamin E supplementation on gene expression related to metabolic profiles in patients without PD. For example, in a study by Chen et al. [6], it was observed that the administration of omega-3 fatty acids significantly decreased TNF-α and IL-1β expression in experimental traumatic brain injury. In another study by Monteiro et al. [7], it was reported that vitamin E supplementation to rats with alcoholic chronic pancreatitis resulted in a significant decrease in gene expression of TNF-α. In addition, our previous study have supported that omega-3 fatty acids and vitamin E co-supplementation for 12 weeks among patients with polycystic ovary syndrome (PCOS) decreased gene

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expression of lipoprotein(a) [LP(a)] and low-density lipoprotein receptor (LDLR) [8]. However, no significant change in TNF-α expression was observed following the supplementation of omega-3 fatty acids for 12 weeks among subjects with insulin resistance [9].

Theses evidence suggests the importance of co-supplementation of omega-3 fatty acids and vitamin E in patients with PD. In addition, co-supplementation of omega-3 fatty acids and vitamin E might have a strong synergistic effect on gene expression related to inflammation, insulin and lipid. To our knowledge, there was no study on the effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in patients with PD. The aim of the current study was to evaluate the effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in patients with PD.

2. Patients and methods

2.1. Participants

This monocentric randomized, double-blind, placebo-controlled clinical trial, registered in the Iranian website for registration of clinical trials (http://www.irct.ir: IRCT2017061234497N1), was conducted among population with PD, aged 50–80 years old diagnosed according to clinical diagnostic criteria of the UK PD Society Brain Bank [10] referred to the Shahid Beheshti Clinic in Kashan, Iran, between April 2017 and August 2017. This study was performed according to Good Clinical Practice guidelines and the study protocol was approved by the research ethics committee of Kashan University of Medical Sciences (KAUMS), Kashan, and Iran. Written informed consent was obtained from all subjects before the study. Exclusion criteria were subjects who were already taking omega-3 and/or vitamin E, taking DDP4 inhibitors, statins and anti-inflammatory drugs, had depression and had severe psychosis.

2.2. Study design

Subjects were randomly allocated into two groups to take either 1000 mg of omega-3 fatty acids from flaxseed oil plus 400 IU of vitamin E supplements or placebo (n = 20 each group) for 12 weeks. Subjects were requested to consume supplements or placebo after lunch. Omega-3, vitamin E supplements and placebos were manufactured by Barij Essence Pharmaceutical Company (Kashan, Iran). The placebo (paraffin) was identical in color, shape, size and package to the omega-3 fatty acids plus vitamin E capsules. Subjects were requested not to change their ordinary physical activity during the 12-week trial. Randomization was conducted by a computer-generated and centrally administered procedure. Patients, investigators, clinical site staff and laboratory staff were all masked to treatment assignment throughout the study.

2.3. Treatment adherence

The consumption of supplements and placebos during the study was checked by asking people to return the medication containers and receiving brief daily cell phone reminders to take the supplements by participants.

2.4. Assessment of outcomes

The primary outcomes were gene expression related to inflammatory cytokines. The secondary outcomes were gene expression related to insulin and lipid.

2.5. Clinical evaluation at entry

To evaluate clinical signs, UPDRS total score as well as 4 subscores were used [11].

2.6. Isolation of lymphocyte, RNA extraction and cDNA synthesis

Twenty milliliters overnight fasting blood samples were collected at baseline and end-of-trial between 6.5 and 7 a.m at central reference laboratory of Kashan, and Iran. Lymphocytes were isolated using 50% percoll solution (Sigma-Aldrich, Dorset, UK) gradient by centrifugation for 20 min and 3000 rpm at 4 °C [12]. Total RNA was extracted based on acid guanidinium-phenol-chloroform procedure using RNX™-plus reagent (Cinnacolon, Tehran, Iran) according to the manufacturer's instructions. RNAs was treated with DNAase I (Fermentas, Lithuania) for the elimination of any genomic DNA contamination. Concentration, integration and purity of RNA samples were determined by spectrometry and gel electrophoresis. 3 µg of total RNA was used for cDNA synthesis with random hexamer and oligo (dT) 18 primers through RevertAid™ Reverse Transcriptase (Fermantase, Canada) in total 20 µl reaction mixture [12].

2.7. Real-time PCR analysis

Appropriate primers for IL-1, IL-8, TNF-α, PPAR-γ and LDLR, and glyceraldehyde-3 phosphate dehydrogenase-as an internal control-were designed (Table 1). Quantitative Real-time PCR was performed by the LightCycler® 96 sequence detection systems (Roche Diagnostics, Rotkreuz, Switzerland) using 4 µl of 5 × EVA GREEN I master mix (Salise Biodyne, Japan), 10 ng cDNA, 200 nM of each forward and reverse primers in final volume of 20 µl. The PCR was performed through the following instruction: an initial denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 10 s, annealing at 54–62.1 °C for 15 s and extension at 72 °C for 30 s. The specificity of PCR products was evaluated by 1.5% agarose gel electrophoresis and melting curve analysis. All experiments were performed at least in triplicate.

2.8. Sample size

To determine the sample size, we used a randomized clinical trial sample size formula where type one (α) error was considered as 5% and the study power as 80%. We considered TNF-α as the main outcome of the study; therefore, we needed 16 subjects in each group. Assuming a dropout of 4 participants per group, the final sample size was determined to be 20 participants per group.

Table 1
Specific primers used for real-time quantitative PCR.

Gene	Primer	Product size (bp)	Annealing temperature (C)
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG R: TCTTCCTCTTGTGCTCTTGCTGG	126	61.3
IL-1	F: GCTTCTCTCTGGTCCTTGG R: AGGGCAGGGTAGAGAAGAG	174	56
IL-8	F: GCAGAGGGTTGTGGAGAAGT R: ACCCTACAACAGACCCACAC	150	56
TNF-α	F: GTCAACCTCCTCTCTGCCAT R: CCAAAGTAGACCTGCCCAGA	188	52
PPAR-γ	F: ATGACAGACCTCAGACAGATTG R: AATGTTGGCAGTGGCTCAG	210	54
LDLR	F: ACTTACGGACAGACAGACAG R: GGCCACACATCCCATGATTC	223	57

GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; IL-1, interleukin-1; IL-8, interleukin-8; LDLR, oxidized low-density lipoprotein receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma; TNF-α, tumor necrosis factor alpha.

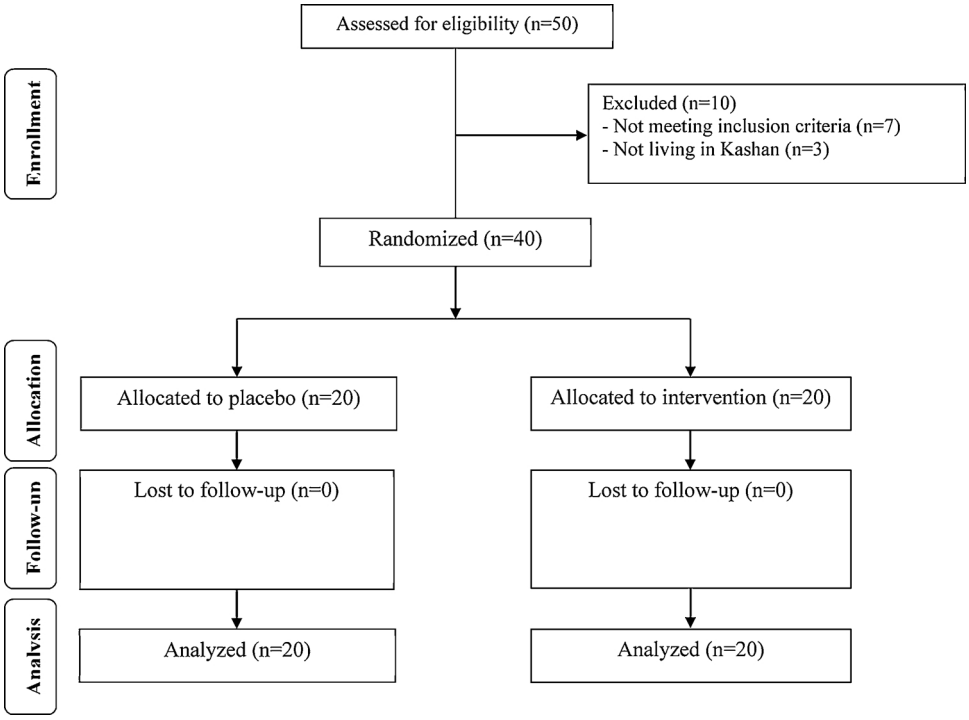

Fig. 1. Summary of patient flow diagram.

2.9. Statistical methods

To determine whether the study variables were normally distributed or not, we used the Kolmogorov-Smirnov test. To detect differences in anthropometric measures, and macro- and micro-nutrient intakes, we used Student's *t*-test to independent samples. Multiple linear regression models were used to evaluate treatment impacts on study outcomes after adjusting for confounding parameters including; age and duration of disease. The P-value < 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

Forty subjects [omega-3 and vitamin E (n = 20) and placebo (n = 20)] completed the trial (Fig. 1).

Mean age, height, weight and BMI at week 0 and week 12 of the intervention were not different between the two groups (Table 2). After 12 weeks' intervention, compared with the placebo, omega-3 and vitamin E co-supplementation led to a significant improvement in UPDRS (-3.4 ± 8.1 vs. + 7.1 ± 14.6, P = 0.008). Omega-3 and vitamin E co-supplementation significantly improved UPDRS-part I (−0.1 ± 1.0 vs. + 1.8 ± 1.4, P = 0.01) compared with the placebo, but did not affect other parts of UPDRS score.

We found no significant difference in mean macro- and micro-nutrient intakes between the two groups (Data not shown).

After the 12-week intervention, compared with the placebo, omega-3 fatty acids and vitamin E co-supplementation downregulated gene expression of TNF-α (P = 0.002) in PBMC of subjects with PD (Fig. 2). We did not observe any significant effect of omega-3 fatty acids and vitamin E co-supplementation on gene expression of interleukin-1 (IL-1) and IL-8 in PBMC of patients with PD.

Omega-3 fatty acids and vitamin E co-supplementation upregulated PPAR-γ (P = 0.03), and downregulated LDLR (P = 0.002) in PBMC of subjects with PD compared with the placebo (Fig. 3).

Table 2
General characteristics of study participants.

	Placebo group (n = 20)	Omega-3 and vitamin E group (n = 20)	P[a]
Age (y)	67.5 ± 9.8	65.5 ± 8.3	0.46
Height (cm)	166.2 ± 6.0	165.4 ± 7.1	0.72
Weight at study baseline (kg)	68.7 ± 6.3	70.1 ± 13.3	0.69
Weight at end-of-trial (kg)	68.5 ± 5.9	70.2 ± 12.9	0.60
Weight change (kg)	−0.2 ± 1.1	0.1 ± 0.8	0.26
BMI at study baseline (kg/m^2)	24.9 ± 2.3	25.7 ± 5.2	0.53
BMI at end-of-trial (kg/m^2)	24.8 ± 2.1	25.8 ± 5.1	0.46
BMI change (kg/m^2)	−0.1 ± 0.4	0.1 ± 0.3	0.26
Disease duration (y)	7.5 ± 4.6	6.3 ± 2.9	0.35
Levodopa dose equivalency (mg/d)	810 ± 360	815 ± 393	0.90
UPDRS total			
Baseline	42.9 ± 15.8	44.3 ± 18.1	0.80
End-of-trial	50.0 ± 16.1	40.8 ± 16.3	0.08
Change	7.1 ± 14.6	−3.4 ± 8.1	0.008
UPDRS part I			
Baseline	4.3 ± 2	3.3 ± 2.3	0.10
End-of-trial	6.1 ± 2.3	3.1 ± 2.1	0.01
Change	1.8 ± 1.4	−0.1 ± 1	0.01
UPDRS part II			
Baseline	12.9 ± 4.9	12.7 ± 6.3	0.90
End-of-trial	13.9 ± 6.1	11.9 ± 5.1	0.20
Change	1.0 ± 3.4	−0.8 ± 2.4	0.05
UPDRS part III			
Baseline	21.6 ± 9.4	23.7 ± 11.1	0.50
End-of-trial	24.7 ± 9.3	21.8 ± 9.7	0.31
Change	3.1 ± 9.8	−1.9 ± 5.5	0.05
UPDRS part IV			
Baseline	4.1 ± 2.9	3.5 ± 2.5	0.52
End-of-trial	5.2 ± 3.6	3.1 ± 2.2	0.02
Change	1.1 ± 4.3	−0.5 ± 2.7	0.11

Data are means ± SDs.
[a] Obtained from independent *t*-test.

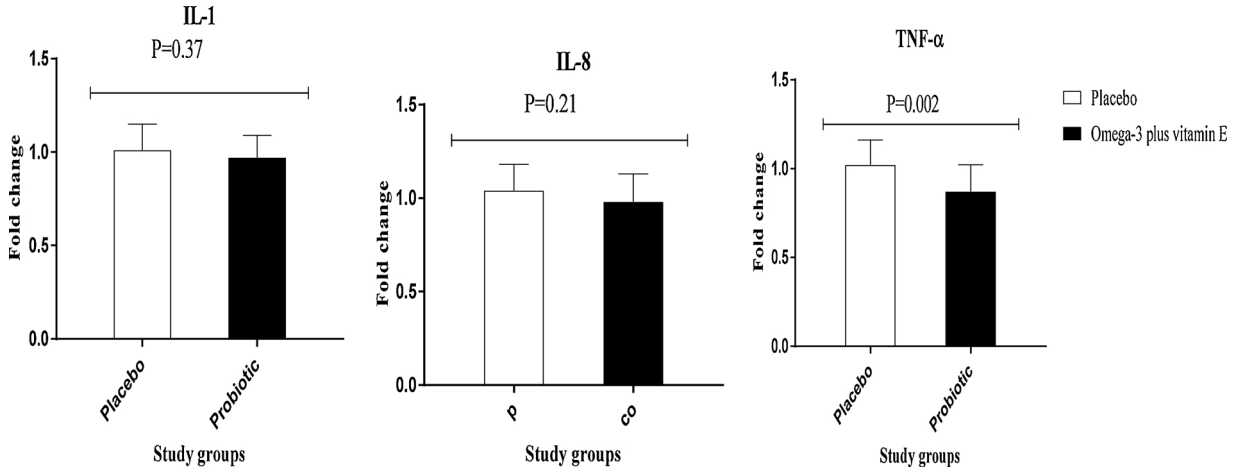

Fig. 2. Effect of a 12-week supplementation with combined omega-3 and vitamin E or placebo on gene expression of IL-1, IL-8 and TNF-α in blood mononuclear cells of patients with Parkinson's disease.
P-value obtained from multiple linear regression models adjusted based on age and duration of disease.

4. Discussion

In the current study, we evaluated the effects of omega-3 and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in populations with PD. We found that omega-3 fatty acids and vitamin E co-supplementation for 12 weeks in PD patients significantly improved gene expression of TNF-α, PPAR-γ and LDLR, but did not affect IL-1 and IL-8. To our knowledge, this study is the first report of the effects of omega-3 and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in populations with PD.

In the current study, we found that omega-3 and vitamin E co-supplementation to subjects with PD for 12 weeks significantly decreased UPDRS part I compared with the placebo, but did not affect other parts of UPDRS. Some studies have evaluated the effects of omega-3 or vitamin E supplementation on dementia and psychosis in patients without PD. In a study by Freund-Levi et al. [13], omega-3 fatty acid treatment [1.7 g of docosahexaenoic acid (DHA) and 0.6 g of eicosapentaenoic acid (EPA)] for 6 months in patients with mild Alzheimer's disease (AD) significantly improved cognitive function. In addition, omega-3 fatty acid supplementation at a dosage of 1.8 g/day for 24 weeks to subjects with mild cognitive impairment had favorable effects on cognition [14]. Also, administration of 2000 IU/day vitamin E to patients with AD led to slower functional decline [15]. In another study, taking omega-3 fatty acid supplements at a dosage of 1.2 g/day for 12 weeks by people with borderline personality disorder significantly improved psychotic disorders [16]. Furthermore, co-administration of omega-3 fatty acid (1000 mg/day) and vitamin E (400 IU/day) for 12 weeks to subjects with PCOS improved psychotic parameters [17]. Supplementation with a combination of omega-3 plus vitamins E and C also improved psychotic symptoms in patients with schizophrenia [18]. Omega-3 fatty acid intake may improve dementia and psychosis symptoms through facilitating membrane translocation/activation of Akt and a downstream effector in the phosphoinositide 3-kinase pathway [19]. In addition, vitamin E intake may improve cognitive function due to protective effect on dopamine-induced cell death and reactive oxygen species production [20].

Our study supported that omega-3 and vitamin E co-supplementation to subjects with PD for 12 weeks significantly decreased gene expression of TNF-α compared with the placebo, but did not affect IL-1 and IL-8. However, data on the effects of omega-3 and vitamin E co-supplementation on gene expression related to inflammation in subjects with PD are scarce. In a study by Abdolahi et al. [21], it was observed that omega-3 fatty acids and nano-curcumin co-supplementation for 2 months to migraine patients downregulated gene expression of TNF-α, and decreased circulating levels of TNF-α in a synergistic manner. In addition, anti-inflammatory effect of omega-3 has been reported by other researchers, when omega-3 antagonize the nuclear factor kappa B signaling pathway, and suppress the expression of inflammatory genes downstream of NF-κB [22,23]. We also previously have showed that flaxseed oil supplementation at a dosage of 2 g/day for 12 weeks to overweight diabetic patients with coronary heart disease significantly improved gene expression of IL-1 and TNF-α, but did not affect gene expression of IL-8 and transforming growth factor beta [24]. Furthermore, vitamin E supplementation at a dosage of 400 IU/day for 12 weeks to subjects with implantation failure had favorable effects on

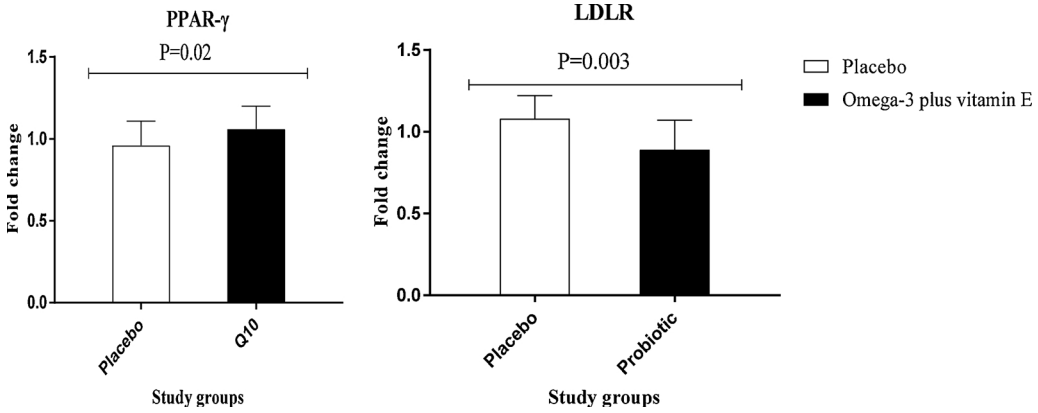

Fig. 3. Effect of a 12-week supplementation with combined omega-3 and vitamin E or placebo on gene expression of PPAR-γ and LDLR in blood mononuclear cells of patients with Parkinson's disease.
P-value obtained from multiple linear regression models adjusted based on age and duration of disease.
IL-1, interleukin-1; IL-8, interleukin-8; LDLR, oxidized low-density lipoprotein; PPAR-γ, peroxisome proliferator-activated receptor gamma; TNF-α, tumor necrosis factor alpha.

gene expression of IL-1, and TNF-α [25]. In another study, vitamin E administration had anti-inflammatory and beneficial effects on the pancreatic gene expression of some inflammatory factors in rats with alcoholic chronic pancreatitis [26]. However, there were no additive effects of omega-3 and vitamin E co-supplementation on serum levels of pro-inflammatory cytokines in immune system-stimulated growing-finishing pigs [27]. Increased inflammation both peripheral and neuroinflammation may result in immune responses in the brain [28]. Furthermore, a significant elevation in the density of glial cells expressing TNF-α and IL-1 was observed in substantia nigra of PD subjects [29], which in turn freely diffuse past the blood brain barrier into the peripheral blood supply [30]. Therefore, omega-3 fatty acids and vitamin E co-supplementation due to their beneficial effects on inflammatory markers may be useful to control neurological symptoms in population with PD.

The current study demonstrated that taking omega-3 and vitamin E co-supplements by subjects with PD for 12 weeks significantly increased gene expression of PPAR-γ, and significantly decreased LDLR compared with the placebo. We have previously showed that taking omega-3 from flaxseed oil at a dosage of 1000 mg twice a day for 12 weeks by patients with PCOS significantly improved gene expression of PPAR-γ and LDLR [31]. In addition, supplementation with 3.4 g/day of EPA and DHA for 2–3 weeks upregulated gene expression levels of PPAR-γ [32]. Similarly, vitamin E supplementation to a rabbit model resulted in increasing gene expression of PPAR-γ [33]. Omega-3 (1000 mg/day) and vitamin E (400 IU/day) co-supplementation for 12 weeks in PCOS women also improved gene expression of LDLR [8]. However, gene expression levels of PPAR-γ did not influence following supplementation with 2400 mg/day of fish oil containing 1450 mg of DHA and 400 mg of EPA to subjects with type 2 diabetes mellitus for 8 weeks [34]. Furthermore, vitamin E supplementation for 6, 14 and 22 weeks in Apolipoprotein E knockout mice significantly downregulated gene expression of PPAR-γ [35]. PPAR-γ and its ligands have been demonstrated as potential therapeutic targets for the treatment of several pathological conditions linked to neuroinflammation within the central nervous system [36]. In addition, PPAR-γ involve in differentiation, energetic metabolism, diabetes, carcinogenesis, atherosclerosis, inflammation, and neurodegeneration [37]. On the other hand, increased gene expression of PPAR-γ improves insulin sensitivity, owing to changes in the transcription and expression of genes influencing carbohydrate and lipid metabolism [38]. Furthermore, increased PPAR-γ activation can have additional effects upon cellular physiology, including anti-proliferative and anti-inflammatory [38].

Our study had few limitations. Firstly, due to budget limitations, we did not evaluate measurements of fatty acids fractions at baseline and after the 12-week intervention. In addition, we did not evaluate gene expression related to oxidative stress.

Overall, omega-3 fatty acids and vitamin E co-supplementation for 12 weeks in PD patients significantly improved gene expression of TNF-α, PPAR-γ and LDLR, but did not affect IL-1 and IL-8.

Conflicts of interest

None.

Author contributions

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

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