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Brain-derived neurotrophic factor is increased by omega-3 fatty acids in coronary artery disease: A randomized, double-blind, placebo-controlled

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A B S T R A C T

Background: Cardiovascular disease is the most common cause of morbidity and mortality throughout the world. Diminution of brain-derived neurotrophic factor (BDNF) plays a chief role in the pathogenesis of coronary artery disease (CAD). One of the beneficial effects of Omega-3 fatty acids is to modulate the secretion of BDNF. We aimed to evaluate the effects of Omega-3 fatty acids supplementation on serum BDNF in men with CAD.

Methods: Forty-eight CAD male patients were randomly assigned to either the Omega-3 (n=24) or placebo (n=24) group by permuted block randomization method. Forty-five subjects completed the study (Omega-3, n = 24; placebo, n = 21). In the omega-3 group each subject received 4 omega-3 soft gels per day (720 mg eicosapentaenoic acid plus 480 mg docosahexaenoic acid), while each subject in the placebo group received 4 placebo soft gels (edible paraffin) for a period of 8 weeks. Serum BDNF, high-sensitivity C-reactive protein (hs-CRP), serum LDL, anthropometric indices, food intake and physical activity were evaluated before and after intervention.

Results: Omega-3 fatty acids supplementation increased serum BDNF (p= 0.015) while decreased serum hs-CRP (p=0.018) and LDL cholesterol (p=0.031). Furthermore omega-3 fatty acids supplementation did not result in any significant changes in anthropometric measurements (p > 0.05 for all).

Conclusion: Following omega-3 fatty acids supplementation, CAD male patients may benefit of increasing BDNF and decreasing serum hs-CRP and LDL levels. (NCTO2382471).

Introduction

Coronary artery disease (CAD) is currently an important health issue and one of the most common causes of morbidity and mortality in both developed and developing countries [1]. This disease is also the major cause of morbidity, mortality in Iranian people and accounts for nearly 50 % of mortality each year [1]. One of the main factors for development of CAD is higher levels of oxidative stress and inflammation [2].

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Brain-derived neurotrophic factor (BDNF) is belonging to the neurotrophin family that exert its antioxidant function by activating the tropomyosin-related kinase B (TrkB) receptor [3, 4]. Recent studies have shown that BDNF and its receptor also are expressed in the skeletal muscle, developing heart, atherosclerotic vessel, endothelial cell and vascular smooth muscle [5, 6]. Plasma BDNF levels was shown decreased with increasing age and in male sex [7]. BDNF is known to be involved in the development of the cardiovascular system [8] and has protective roles against atherosclerotic plaque instability and cardiac dysfunction [9]. Low circulating BDNF levels has been found related to increased TG and LDL levels, decreased HDL levels, presence of diabetes mellitus and occurrences of cardiovascular events [3, 7].

Epidemiological studies have demonstrated that Omega-3 fatty acids in foods or as supplementation could reduce extend of morbidity and rates of mortality due to CAD [10, 11]. Because Omega-3 fatty acids have a protective role against inflammation related diseases such as cardiovascular disease; nowadays, there is a pervasive interest in the health beneficial effects of Omega-3 fatty acids [11]. Omega-3 fatty acids, e.g. eicosapentaenoic acid (EPA; 20:5n3) and docosahexaenoic acid (DHA; 22:6n3), present in oily fish and fish oil supplements; attenuate inflammatory reactions, increase production of anti-inflammatory and decreased production of the classic inflammatory cytokines and ameliorate symptoms of several inflammatory disease [12]. Another mechanism by which Omega-3 fatty acids may exert beneficial effects is modulation of BDNF secretion [13]. Brain BDNF levels could be modulated by diet and physical activity [14]. The diet high in saturated fat can decrease BDNF concentration, while dietary supplementation with Omega-3 fatty acids has been demonstrated to cause BDNF restoration in brain injury model, in which BDNF levels are decreased [15]. The potential mechanism by which Omega-3 fatty acids modulate BDNF secretion is not fully understood; but may partially attribute to the following:

a) It is known that DHA is converted to Neuroprotectin D_1 (NPD_1). Recent data have demonstrated that endogenous DHA-derived NPD1 has anti-inflammatory properties by which elevate BDNF [16, 17].
b) BDNF expression is decreased in the case of oxidative stress. The antioxidant characteristic of DHA could elevate BDNF through attenuation of oxidative stress [16].

Previous reports have shown that circulating BDNF concentrations were lower in men compared with women [18]. Hence it seems to be the reason which makes males more prone to CAD than females [19]. Furthermore, the status of BDNF is not clearly understood in health and disease. Therefore, the purpose of current study was to investigate the effects of Omega-3 fatty acids supplements on serum BDNF in male CAD patients.

Methods

The present study was designed as a randomized, double-blind and placebo-controlled trial study. Patients with CAD were randomized into two groups (Omega-3 or placebo) by permuted block randomization method. The Omega-3 group received daily 4 soft gels of Omega-3 (Minoo Pharmaceutical, Cosmetic and Hygienic Co., Tehran, Iran); containing 720 mg EPA and 480 mg DHA. Whereas the placebo group received 4 placebo soft gels containing edible paraffin which were identical in size and color (Minoo Pharmaceutical, Cosmetic and Hygienic Co., Tehran, Iran). All subjects were prescribed to take soft gels with meals during the 8-week intervention.

Patients were enrolled from those who referred to cardiology clinic of cardiology Tehran Heart center. Those meeting the inclusion criteria were invited to participate the project. The subjects allocated to each group were comprised of 55 male patients with CAD (aged 45 to 65 years). All patients had >50 % stenosis in at least one major coronary vessel as determined by coronary angiography. The patients with diabetes, liver diseases, renal diseases, cancer or thyroid dysfunction were excluded to remove the influence of known confounding factors. The patients who were taking medicines, such as warfarin and those currently receiving multivitamins, fish oil or Omega-3 fatty acids supplements were also excluded. The persons who affected with any kind of myopathies and smokers (at least 5 cigarettes per day during the last 6 months) were not allocated. At the beginning, written informed consent was read and signed by all participants. Patients were informed of the aim and possible disadvantage of this clinical trial and were free to leave the study at any time. The study was approved by the local ethics Committee at

Tehran University of Medical Sciences and registered according to the appropriate clinical trial registration system (NCTO2382471).

Patients were followed up by a multidisciplinary team. All patients were requested to maintain their usual physical activity and dietary habits during the intervention and all patients were asked to report any change in the treatment protocol, prescribed medication and dietary intake.

All the measurements were done at the baseline and after 8 week intervention, body weights were evaluated by digital scale (Seca Hamburg, Germany) to the nearest of 0.1 kg while the subjects were in light clothes and without shoes. Patients' heights were measured without shoes using a stadiometer (Seca) to the nearest 0.1 cm. Body mass index (BMI) was calculated using the equation BMI = weight (kg)/height^2 (m). The waist circumference (WC) was indicated at the smallest circumference between the rib cage and the iliac crest with the subject in the standing position using non-stretchable measuring tape; hip circumference was measured at the widest circumference of the hip, using non-stretchable measuring tape; measurements were recorded to the nearest 0.1 cm. The waist-to-hip ratio (WHR) was calculated. The percent of body fat was assessed by bioelectric impedance analysis (Takara BC-418, Japan).

At the start of study, each patient was requested to filling a set of questionnaires including: a general information questionnaire, 3 day 24 hours food recalls to evaluate dietary intakes. Dietary intakes were again assessed with the same method at the end of intervention. N4 nutritional software was used to determine nutrient compositions of all foods and energy intake. Physical activity was assessed by IPAQ (international physical activity questionnaire). Blood pressure was measured (Zyklusmed, Monheim, Germany) on the left arm with the patient sitting down in a resting position and reported as the average of two separate measurements.

Venous blood samples were obtained from all participants in the morning following 12-14 hour overnight fasting. All samples were centrifuged with 3500 rpm for 10 min at 4°C and separated sera stored at -70°C until analysis. The serum BDNF (CAT.NO: E1302Hu), high-sensitivity C-reactive protein (hs-CRP) concentrations (Labor Diagnostika Nord (LDN), Germany) and serum insulin (DiaMetra, Perugia Italy) were measured by ELISA kits according to the manufacturer's instructions. Serum glucose**,** triglyceride (TG), total cholesterol (TC), LDL- cholesterol (LDL-C) and HDL-cholesterol (HDL-C) levels were measured by enzymatic methods using commercial kits (Pars Azmun, Iran) and auto-analyzer system (Selectra E, Vitalab, Netherland).

Data were analyzed using SPSS 21.00. Normality of the data distribution was assessed by the Kolmogorov-Smirnov test. Data are expressed as mean ± standard error. Paired t-test was used for within-group effects from baseline. Variables with normal distribution were compared by independent t test between 2 groups. Statistical significance was accepted at $P < 0.05$ for all tests.

Results

The flow chart of the trial profiles are shown in Figure 1. Of the 55 subjects enrolled, 48 were found to be eligible and subsequently randomized into the study. Of these 48 subjects, three persons in placebo group withdrew follow up (one subject was on trip; two subject underwent open heart surgery). Finally, 45 volunteers were participated to the end of the study. The baseline and mean changes in BMI and serum biomarkers of subjects are shown in Table 1. There were no statistically significant differences in food intake, anthropometric measurements, in terms of dosage and type of lipid lowering and antihypertensive drugs and in physical activity between the groups (data not shown). The mean age of the Omega-3 group was 55.00 ± 1.29 years and that of the placebo group was 57.76 ± 1.36 years old; there was no significantly difference between the subjects' age ($p= 0.150$).

After treatment with 4 soft gels of Omega-3 fatty acids supplementation; mean serum BDNF level increased significantly from 14.64±5.07 ng/ml to 16.29±5.56 ng/ml in the Omega-3 group ($p= 0.015$), while it decreased from 8.03±3.37 ng/ml to 7.27±2.99 ng/ml in the placebo group ($p=0.068$), probably due to the disease process. After 8 weeks follow-up, patients who received Omega-3 fatty acids supplementation showed a significantly decrease in serum LDL ($p=0.031$). Moreover, hs-CRP decreased from 2.96±0.41 mg/l to 1.86±0.15 mg/l in the Omega-3 group, but not in the placebo group ($p= 0.018$). Table 2 displays the baseline and mean changes in energy and macronutrients intakes in Omega-3 and placebo

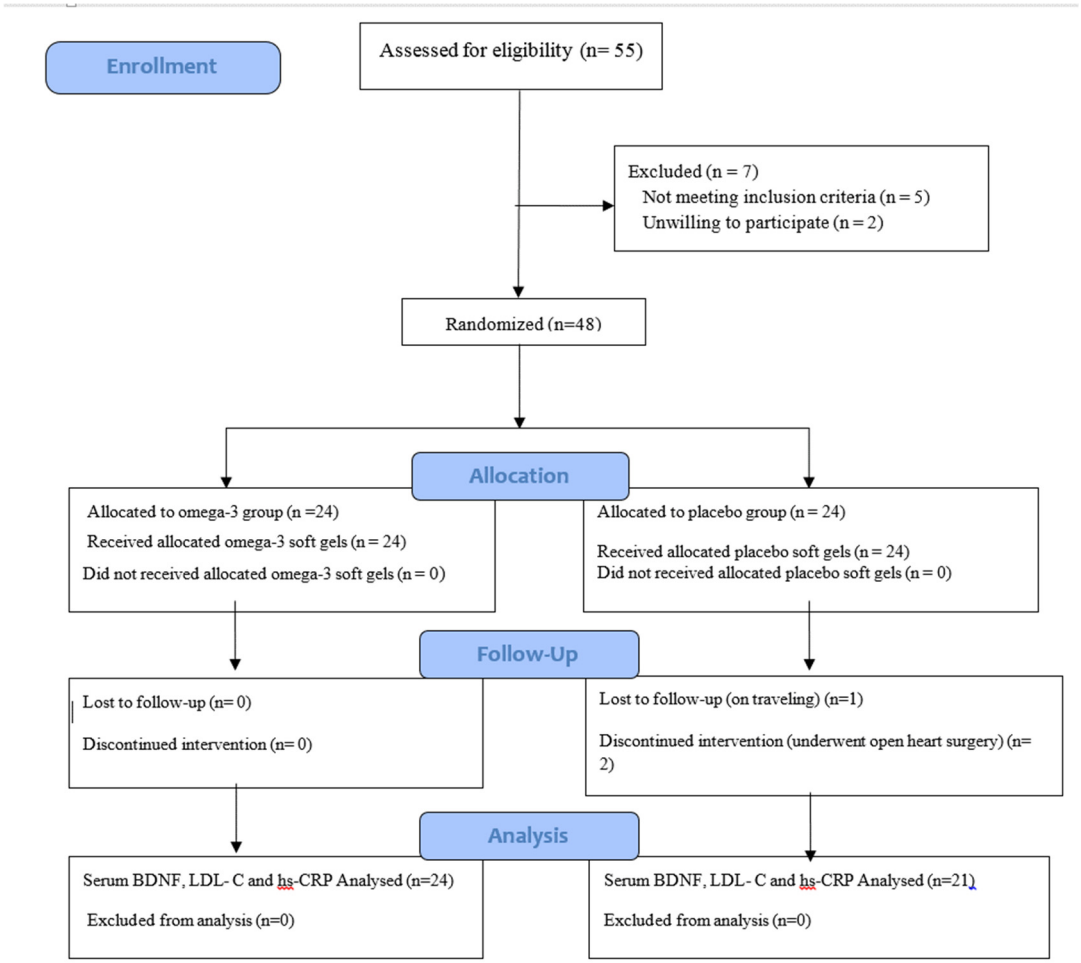

Figure 1. Flow chart of a randomized control trial

groups.

Discussion

This study evaluated changes in serum BDNF concentration following Omega-3 fatty acids supplementation during 8 weeks double-blind and randomized trial in male CAD patients. It has been demonstrated that 720 mg EPA and 480 mg DHA could significantly reduce the hs-CRP and increase serum BDNF in male patients with CAD. It was not found any statistically significant association between Omega-3 fatty acids supplementation and BMI.

In this study hs-CRP was found to be significantly and inversely associated with Omega-3 fatty acids intake. A similar result was

Table 1. Body mass index and serum biomarkers at baseline and their changes during intervention*

		Omega-3group n=24	Placebo group n=21	Pvalue #
Serum BDNF (ng/ml)	baseline	14.64±5.07	8.03±3.37	0.285
	changes	1.65±0.63	-0.76±0.39	0.002
Serum LDL- C (mg/dl)	baseline	101.96±4.29	102.81±4.976	0.897
	changes	-5.54±3.83	9.42±5.30	0.025
Serum hs-CRP (mg/l)	baseline	2.96±0.41	2.51±0.35	0.419
	changes	-1.10±0.43	0.81±0.49	0.005
BMI (kg/m^2)	baseline	28.34±0.68	27.53±0.75	0.430
	changes	-0.07±0.11	0.21±0.13	0.111

*The results are described as mean ± Standard Error (SE)

Independent sample t-test

BDNF: Brain-Derived Neurotrophic Factor, hs-CRP: High Sensitive C Reactive Protein, LDL: Low Density Lipoprotein, BMI: Body mass index

Table 2. Daily energy and macronutrients intakes at baseline and their changes during intervention*

		Omega 3group n=24	Placebo group n=21	Pvalue #
Total energy (kcal)	baseline	1557.97±128.47	1592.73±139.17	0.855
	changes	138.65±144.88	-77.73±170.37	0.336
Saturated fatty acids (g)	baseline	10.24±2.21	9.68±1.22	0.832
	changes	-0.61±2.33	0.80±1.90	0.642
Polyunsaturated fatty acids	baseline	14.27±1.80	12.44±2.16	0.517
(g)	changes	2.07±2.33	2.81±3.00	0.847
Mono-unsaturated fatty acids	baseline	9.97±1.96	8.83±1.17	0.630
(g)	changes	-0.14±2.12	0.88±1.71	0.711
Fiber(g)	baseline	13.92±1.93	11.90±1.31	0.402
	changes	1.40±2.55	-3.31±1.31	0.110
Eicosapentaenoic acid(g)	baseline	0.007±0.006	0.0007±0.0004	0.319
	changes	0.018±0.018	0.011±0.010	0.752
Docosahexaenoic acid(g)	baseline	0.029±0.017	0.005±0.003	0.177
	changes	0.042±0.050	0.029±0.025	0.832
Omega6.omega3	baseline	827.89±457.93	964.37±732.83	0.870
	changes	135.58±717.19	-1581.72±2028.52	0.410
Alpha-tocopherol(mg)	baseline	5.02±0.37	4.63±0.59	0.582
	changes	1.16±0.66	0.28±0.75	0.381

*The results are described as mean ± Standard Error (SE)
Independent sample t-test

reported by Niknam et al. who demonstrated an inverse relationship between Omega-3 fatty acids and hs‑CRP concentration in CAD male patients [1]. Omega-3 fatty acids through activation of peroxisome proliferator activated receptor (PPAR)- γ and following inhibition of the nuclear factor (NF)-kB exert anti-inflammatory properties [12]. It is not clear how Omega-3 fatty acids enhance BDNF concentration but it may be due to the anti-inflammatory effects of Omega-3 fatty acids. It can be speculated that elevation of serum BDNF is related to the decreased serum hs-CRP concentration. The reduced inflammation may account for the effect of Omega-3 supplementation on serum BDNF levels, because the previous studies have demonstrated that inflammation and administration of pro-inflammatory cytokines resulted in significant reduction of BDNF gene expression [20].

Consistent with this observation, study on dogs fed antioxidant diet showed that intake of antioxidants can lead to up-regulation of brain BDNF [14]. Likewise, in anxious adolescents, Omega-3 fatty acids intake was positively associated with serum BDNF levels [21]. Findings in animal models indicate a role of DHA in the regulation of hippocampal BDNF expression and function. Notably, short period of DHA supplementation counteracted the decrease in BDNF and increased hippocampal expression of BDNF in the brains of traumatic brain injury rats [22] . Similarly, an increase in hippocampal BDNF was observed in rats receiving DHA supplementation (1.25% DHA) with or without voluntary exercise for 12 days [16]. Results of this project indicate that DHA-enriched diet through increase of pro-BDNF and mature BDNF; enhances cognition and reduces the risk of neurological disorders [16]. The study by Erik et al. demonstrated that EPA has a stimulatory effect on BDNF production in vitro [23]. A research on experimental model of Parkinson's disease has demonstrated that Omega-3 fatty acids elevate BDNF and TrkB messenger RNA (mRNA) expressions [24]. The results of an animal survey revealed that perinatal and post weaning diets high in Omega-3 fatty acids enhance cortical BDNF and TrKB expressions [25]. Since BDNF signals via a TrKB receptor, results of aforementioned study reinforce the importance of Omega-3 fatty acids in regulation of BDNF gene expression and stimulation of downstream signaling cascades vital to the activities of BDNF [25]. Consistent with these findings, Hashimoto et al. indicated that TAK-085 administration [highly purified and concentrated Omega-3 fatty acid formulation containing EPA and DHA ethyl esters] for 13 weeks could enhance BDNF concentration in the cortical and hippocampal tissues in an animal model for metabolic syndrome [26]. Furthermore

the study revealed that TAK-085 supplementation declines the oxidative stress and elevates antioxidative defenses [26]. On the other hand; BDNF increase may be partially due to reduction of lipid peroxidation and reactive oxygen species and also due to the inhibitory effect of DHA on oxidative processes [26]. There are many confirming studies which have demonstrated that DHA could prevent the reduction of BDNF through its antioxidant properties [16]. Thus, these findings suggest that antioxidants are able to modulate the BDNF expression. Previous researches have shown that NPD1, as a metabolite of Omega-3 fatty acids, can exert anti-inflammatory effect and increase BDNF expression; consequently Omega-3 fatty acids modulate BDNF through its metabolites besides the anti-oxidative effects [16, 17, 27].

Many studies have been demonstrated the various functions of BDNF and its role in modulation of different systems in the body. Recently, the association of low BDNF levels with obesity, type 2 diabetes and acute coronary syndromes has been suggested [3, 28]. Based on the role of BDNF in metabolic disorders, our findings suggest that supplementation of Omega-3 fatty acids may provide protection against the cardiovascular events via anti-inflammatory properties. Also, the study showed that increased peripheral BDNF levels could be attributed to anti-inflammatory characteristics of Omega-3 fatty acids, since hs-CRP has been decreased in Omega-3 group .

Conclusion

Omega-3 fatty acids supplementation in CAD male patients increases BDNF and decrease the hs-CRP and LDL levels. The most likely mechanism seems to be the anti-inflammatory effects of Omega-3 fatty acids. Further research is needed to investigate the underlying mechanisms.

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Conflict of interest

None of authors have conflict of interest.

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