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OMEGA-3 FATTY ACIDS SUPPLEMENTATION IN HEALTHY INDIVIDUALS

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ABSTRACT

Introduction: Omega-3 fatty acids are dietary fats with a variety of health benefits. A growing body of research on omega-3 supplementation has shown that these fatty acids influence neurotrophins related to cognitive function; decreasing lipid peroxidation; attenuating activities on inflammatory eicosanoids, presumably have antioxidant effects, anti-inflammatory benefits, and immunomodulatory effects; can prevent atherosclerosis in both human and animal models. **Aim:** This study aimed to evaluate the effect of omega-3 fatty acids supplementation on serum BDNF & cognitive function, Oxidative Stress Index (OSI), serum inflammatory markers as well as lipid profile of healthy adults. **Methods:** A total of 35 young, healthy adults participated in this pre- and post-interventional study. Each participant received one fish oil supplement comprising 1000 mg twice daily for 12 weeks. Before and after the intervention, their fasting blood samples were analyzed for serum levels of BDNF, total oxidative stress (TOS), total antioxidant stress (TAS), TNF-α, IL-6, lipid profile, and cholesterol ester transfer protein (CETP) by ELISA method. Calculation of OSI and cognitive function tests (revised Hasegawa's dementia scale; HDS-R) were also done. **Results:** After 12 weeks of supplementation, mean serum BDNF and CETP levels were significantly increased, with a substantial decrease in mean serum levels of TNF-α, IL-6, TG, and VLDL as well as OSI. Mean HDS-R was likely to increase after supplementation although it was not statistically significant. **Conclusion:** Therefore, daily omega-3 fatty acids supplementation for 12 weeks has shown beneficial outcomes on health with positive neurocognitive function, anti-oxidant improvement, anti-inflammatory action, and lipid-lowering effects even in healthy individuals.

KEYWORDS: Omega-3 fatty acids, BDNF, HDS-R, Inflammatory markers, OSI, Lipid profiles.

INTRODUCTION

The long-chain omega-3 fatty acids, in particular, eicosapentaenoic acid (EPA, C_{20}: 5_{n-3}) and docosahexaenoic acid (DHA, C_{22}: 6_{n-3}), are a family of nutrients of importance. Alpha-linolenic acid (ALA, C_{18}: 3_{n-3}) is the building block for the body's limited capacity to generate EPA and DHA, therefore these fatty acids must be either in the food or taken as supplements. Numerous advantages of polyunsaturated omega-3 fatty acids are thought to include improvements in blood pressure, cardiac function, lipid metabolism, a decrease in leucocyte-derived cytokines, anti-inflammation, anti-resolving properties, and antioxidant activity.[1] In early life, BDNF is crucial for neuronal growth and function, but in adulthood, it is engaged in synaptic plasticity and transmission mechanisms that support cognitive function.[2] Indeed, many researchers have demonstrated that lower BDNF concentrations are linked to cognitive dysfunction and greater BDNF concentrations are linked to enhanced cognitive function.[3]

Although the literature on omega-3 supplementation and brain performance is vast, most studies have concentrated on the effects on either children's cognitive and visual development or age-related decline in clinical populations.[4] However, only a small number of studies have focused on the neurocognitive effects of omega-3 supplementation in healthy young adults.[5] In addition, omega-3 fatty acids supplements reduce the production of inflammatory cytokines such as interleukin-6 (IL-6) and TNF-alpha (TNF-α). Several studies providing fish oil supplements to healthy human volunteers have reported decreased production of IL-6 and TNF-α by endotoxin-stimulated mononuclear cells, although not all studies confirm this effect. Some of the studies that fail to show the effect of omega-3 fatty acids on cytokine production have provided < 2 g of omega-3 fatty acids

(EPA + DHA) per day, which may be an insufficient dose.[6]

Moreover, fish oil-derived (n-3) long-chain polyunsaturated fatty acids reduce blood pressure, improve lipid profiles, and may reduce mortality from cardiovascular disease in adults. Early supplementation of omega-3 appears to have long-lasting impacts on metabolism and the risk of cardiovascular disease, according to animal and epidemiologic research. As a result, numerous studies have shown that omega-3 can enhance cardiovascular health by modifying a variety of pathways related to blood pressure regulation, glycaemic metabolism, increased expression and synthesis of lipoprotein lipase, and as a result, decreased triglyceride levels, enhanced lipid metabolism, a reduction in low-density lipoprotein cholesterol (LDL-C) and an increase in HDL, as well as a reduction in VLDL.[7] On the other hand, a 2012 systematic review and meta-analysis reported that there is no evidence of a beneficial effect of omega-3 on CVD mortality.[8] And another research in a 2018 study found that omega-3 in the diet and supplements were not linked to all-cause mortality.[9]

While the cardiovascular, anti-inflammatory, and mood benefits of omega-3 supplementation containing DHA and EPA are manifest, direct evidence of their effects on cognitive performance and neural activity is still limited. In this way, it is an interesting point to the effect of omega-3 fatty acids supplementation on various parameters related to the health conditions of healthy young adults. This study aimed to evaluate the effect of omega-3 fatty acids supplementation on serum BDNF, cognitive function, Oxidative Stress Index (OSI), inflammatory markers (TNF-α, IL-6) as well as Cholesterol Ester Transport Protein (CETP), and lipid profile of healthy young adults.

MATERIALS AND METHOD

This pre- and post-interventional study was conducted at Defence Services Medical Academy (DSMA), Yangon, and laboratory analysis was performed at the Common Research Laboratory of DSMA throughout the whole study period from January 2022 to June 2022. The total 35 participants were Year-1 medical students from DSMA. The study was approved by Institutional Ethical Review Committee according to the CIOMS Guidelines. Cognitive assessment by Revised Hasegawa's dementia scale (HDS-R) and their fasting blood sample collection for biochemical parameters was done before and after the omega-3 fatty acids supplementation. On the omega-3 fatty acids supplementation, each participant was given 2 oral capsules containing 1000 mg of fish oil (total of 320 mg EPA+200 mg DHA) daily for 12 weeks.

Human ELISA kits (MyBioSource) were used for serum BDNF, blood total oxidative stress (TOS) & total anti-oxidant system (TAS), TNF-α, IL-6, plasma CETP levels, and serum lipid profile (total cholesterol, triglyceride, HDL) determination. These ELISA assays were done according to the manufacturer's protocols. The oxidative stress index (OSI) can be calculated as the ratio of the TOS level to the TAS level. Specifically, OSI (Arbitrary unit) = TOS (U/L)/TAS (U/L).[10] LDL and VLDL were obtained by calculation with the Friedewald formula.[11] Their biochemical parameters and cognitive function test were noted in their proforma, and statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) software version v.25.0. Results were expressed as means ± SD (standard deviation) & student *t*-test and percent changes were applied to calculate the significance of the difference between the means on 95% confidence interval of results.

RESULTS

In this study, age and physical characteristics (Height, Weight, and BMI) were within the normal range for healthy individuals (Table. 1). Supplementation effect can be seen in serum BDNF levels in significant improvement ($p < 0.05$) with nearly 54%; however, there was no significant effect in HDS-R for cognitive assessment ($p = 0.11$). The mean serum TOS level was not significantly decreased after supplementation. An increase in mean TAS level and a decrease in mean OSI were seen significantly after supplementation of approximately 50%. Mean serum TNF-α and IL-6 levels were significantly decreased after supplementation with around 40% and 35% respectively. In the CETP and lipid profile analysis, only the mean CETP level significantly increased by nearly 270%, and mean TG and VLDL levels were significantly decreased ($p < 0.05$) by about 5% each after supplementation (Table. 2).

Table 1: General characteristics of the study population.

Variables	Study population (n = 35)		
	Mean ± SD	Minimum	Maximum
Age (years)	17.91 ± 0.45	17	19
Height (m)	1.69 ± 0.05	1.57	1.78
Weigh (kg)	57.11 ± 4.72	47.63	65.32
BMI (kg/m^2)	20.00 ± 1.48	16.4	23.2

Table 2: Comparison of biochemical parameters and Hasegawa's Dementia Scale before and after supplementation of omega-3 fatty acids.

Variables	Before consumption (Mean ± SD)	After consumption (Mean ± SD)	Statistics	
			Paired "*t*"	*p*
BDNF (ng/mL)	127.19 ± 86.48	195.30 ± 91.20	-2.84	0.008*
HDS-R	29.08 ± 1.31	29.51 ± 0.88	-1.67	0.105
TOS (U/mL)	8.56 ± 5.30	8.38 ± 4.37	0.39	0.703
TAS (U/mL)	19.55 ± 9.52	29.79 ± 4.98	-6.62	0.000*

OSI (Arbitrary unit)	0.61± 0.59	0.30 ± 0.17	3.77	0.001*
TNF-α (pg/mL)	29.10 ± 13.80	17.06 ± 12.09	3.23	0.003*
IL-6 (pg/mL)	8.99 ± 6.06	5.97 ± 3.93	2.26	0.030*
CETP (µg/mL)	0.45 ± 0.20	1.66 ± 0.55	-16.87	0.000*
Total Cholesterol (mg/dL)	135.35 ± 14.93	131.31 ± 10.59	1.89	0.067
Triglyceride (mg/dL)	100.50 ± 9.80	95.42 ± 6.70	4.58	0.000*
HDL (mg/dL)	61.05 ± 6.06	59.74 ± 4.54	1.24	0.224
LDL (mg/dL)	54.02 ± 10.01	52.48 ± 8.92	0.86	0.397
VLDL (mg/dL)	20.10 ± 2.00	19.08 ± 1.34	4.53	0.000*

HDS-R = Revised Hasegawa's dementia scale, *Significant

Table 3: Percent changes of biochemical parameters and Hasegawa's Dementia Scale after supplementation of omega-3 fatty acids.

Variables	Before consumption (Mean ± SD)	After consumption (Mean ± SD)	Statistics	
			Percent changes (%)	Increase/ decrease
BDNF (ng/mL)	127.19 ± 86.48	195.30 ± 91.20	53.55	Increase
HDS-R	29.08 ± 1.31	29.51 ± 0.88	1.48	Increase
TOS (U/mL)	8.56 ± 5.30	8.38 ± 4.37	2.10	decrease
TAS (U/mL)	19.55 ± 9.52	29.79 ± 4.98	52.38	Increase
OSI (Arbitrary unit)	0.61± 0.59	0.30 ± 0.17	50.82	decrease
TNF-α (pg/mL)	29.10 ± 13.80	17.06 ± 12.09	41.37	decrease
IL-6 (pg/mL)	8.99 ± 6.06	5.97 ± 3.93	33.59	decrease
CETP (µg/mL)	0.45 ± 0.20	1.66 ± 0.55	268.89	Increase
Total Cholesterol (mg/dL)	135.35 ± 14.93	131.31 ± 10.59	2.98	decrease
Triglyceride (mg/dL)	100.50 ± 9.80	95.42 ± 6.70	5.05	decrease
HDL (mg/dL)	61.05 ± 6.06	59.74 ± 4.54	2.15	decrease
LDL (mg/dL)	54.02 ± 10.01	52.48 ± 8.92	2.85	decrease
VLDL (mg/dL)	20.10 ± 2.00	19.08 ± 1.34	5.07	decrease

DISCUSSION

The present study evaluated changes in serum BDNF concentration following omega-3 fatty acids supplementation for 12 weeks. It has been shown that supplementation caused a considerable increase in BDNF levels of over 50%. Consistent with this observation, a study on omega-3 fatty acids supplementation in coronary artery disease patients by Agh and researchers showed that omega-3 fatty acids intake was positively associated with serum BDNF levels.[12] The possible mechanisms underlying this linkage were explored in the mice model by Balogun & Cheema[13] and Sona and colleagues.[14] In their investigation, DHA increases the expression of BDNF in the brain possibly through the activation of tropomyosin receptor kinase B (TrKB) receptor[13] or G-protein-coupled receptor 40 (GPR40)[14] and stimulation of downstream signalling cascades vital to the activities of BDNF. Many of the beneficial effects of DHA may be through the expression of BDNF.

Although BDNF protein is involved in cognitive function, it was not shown to be significantly different in HDS-R for cognitive function assessment following the supplementation of omega-3 fatty acids in the present study. A similar result was described by Hashimoto and colleagues who proved no significant relationship between omega-3 fatty acids and HDS-R in healthy elderly Japanese.[15] The findings of the present study were also in accordance with a systematic review by Issa et al (2006). They reached the conclusion that the evidence from their comprehensive review was insufficient to draw any conclusions on how omega-3 fatty acids improve cognitive function in healthy aging.[16] One potential explanation for the lack of a discernible impact of omega-3 fatty acid intake on cognitive function was early learning or education. By increasing the number of synapses and connections as well as blood flow or vascularization in the brain, this early learning may have an impact on brain structure and development. This could improve cognitive function.[17] Continuous mental stimulation through learning or education may increase favourable structural or neurochemical alterations in the brain, which in turn improve cognitive function.[18] The baseline memory function of the participants in the present study was already in a normal situation because the participants were well-educated medical students and healthy young adults.

In the role of anti-oxidant properties of omega-3 fatty acids, the present study showed that omega-3 fatty acids supplementation may significantly increase TAS and decrease OSI in the present study and these changes were nearly 50%. The possible mechanism of the effect of omega-3 fatty acids on an increase of TAS may be due to decreased production of reactive oxygen species (ROSs).[19] The dietary supplementation with omega-3

fatty acids significantly increases superoxide dismutase (SOD) activity, nitric oxide (NO) levels, and decreased thiobarbituric acid reactive substances (TBARS) levels and elevates resistance to ROS damage, decreases lipid peroxidation.[20] These mechanisms were revealed by Mustafa Iraz et al[19] and Hasan Erdogan et al[20] in rat models. These explanations were provided evidence by a pilot study of Iran's population (2020). In their study, oxidative status markers were decreased and antioxidant parameters were improved after 12-week supplementation of omega-3 fatty acids in sedentary subjects and trained athletes.[21]

In revealing the anti-inflammatory aspect of omega-3 fatty acids, the present study cannot presume that omega-3 fatty acid supplementation has a positive impact on inflammatory markers in healthy groups because inflammatory markers in healthy groups are within reference ranges. The mean serum TNF-α and IL-6 levels were dramatically reduced by around 35% after supplementation in the present study, albeit within reference values. However, the supplementation may benefit diabetes and cardiovascular diseases as stated by the previous studies. In the study of Eftekhari and researchers (2013), IL-6 was significantly reduced in atherosclerotic patients after omega-3 fatty acids supplementation.[22] And also, the meta-analysis study by Zuhair and co-workers stated that omega-3 fatty acids may be associated with lower inflammatory biomarkers among diabetic and cardiovascular patients.[23] The effect of omega-3 fatty acids on inflammatory markers was proposed to be due to several pathways. Increases the production of some metabolites including the 3 and 5 series of eicosanoids[24], and inflammation-resolving lipid mediators, and acts as a suppressor for acute phase reactants.[25] Thus, omega-3 fatty acids can reduce TNF-α, IL-6, and C-reactive protein (CRP) and upregulate the production of lipoxins, resolvins, and protectins in addition to 3 and 5 eicosanoids. Consequently, these actions lead to the inhibition of inflammatory responses.[26] Recent studies have identified potent anti-inflammatory mediators derived from omega-3 fatty acids and explained the mechanisms of their action. Omega-3 fatty acids supplements for the human diet have been shown to result in decreased production of prostaglandin E2 (PGE2) and other eicosanoids by inflammatory cells.[27] EPA and DHA induce anti-inflammatory effects via the alteration of cyclooxygenase2 (COX2) and lipoxygenase 5 pathways.[28] These two fatty acids, especially EPA, suppress the production of arachidonic acid (AA), derived 2-series PGs, and 4-series leukotrienes (LTs) that modulate the production of proinflammatory and immunoregulatory cytokines.

According to previous studies, omega-3 fatty acids have a lipid-lowering effect on patients with atherosclerosis in addition to having an anti-inflammatory effect. In the evaluation of the cardioprotective role of omega-3 fatty acids via lipid profile, the present study demonstrated that CETP was significantly increased by around 250%, and TG and VLDL levels were significantly decreased by 5% after supplementation. These findings were compatible with the reports of Oscarsson and researchers' study in Sweden (2017). In their review, the main effects of both EPA and DHA were decreased fasting and postprandial serum TG levels, through reduction of hepatic VLDL-TG production.[29] They explained the possible mechanism of their findings. In their description, omega-3 fatty acids consumption reduces VLDL production via reduced substrate availability, by increasing fatty acid oxidation, which would reduce liver TG content and substrate availability for VLDL production. The major mechanism explaining reduced fasting serum triglyceride associated with omega-3 fatty acids supplementation is reduced VLDL production, including a reduced number and size of VLDL particles. VLDL particle conversion to IDL and LDL occurred more rapidly when VLDL secretion is reduced. Moreover, omega-3 fatty acids increase lipoprotein lipase (LPL) activity, likely by increased expression of the gene and reflected as increased pre-heparin LPL activity. Increased LPL activity can explain the higher clearance rate of TG-rich lipoproteins postprandially, but normally not in the fasted state because LPL activity is not rate-limiting when TG levels are not high.[29]

CONCLUSION

Although the present study showed no sufficient effect on cognitive function and some parameters, daily omega-3 fatty acids supplementation for 12 weeks had beneficial outcomes on health by positive neurocognitive parameters, anti-oxidant improvement, anti-inflammatory action, and lipid-lowering effects even in healthy individuals.

Conflict of Interest

All the authors of the present study have no conflict of interest to declare.

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