Assessing the effect of omega-3 fatty acids supplementation on serum BDNF (Brain derived Neurotrophic factor) in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study

Samaneh Ansari¹, Mahmoud Djalali², Niyaz Mohammadzadeh Honarvar², Maryam Mazaherioun³, Mahnaz Zarei², Zahra Gholampour⁴, Mohammad Hassan Javanbakht²*

1. MSc student of Public Health Nutrition, Faculty of nutritional sciences and dietetics, Tehran University of Medical Sciences, Tehran, Iran
2. PhD. Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.
3. PHD student of Nutrition, Faculty of nutritional sciences and dietetics, Tehran University of Medical Sciences, Tehran, Iran
4. MSc of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

*Corresponding Author email: mhjavan2001@yahoo.com

ABSTRACT: Objective: Diabetes Mellitus consist a group of metabolic diseases that are detected by high blood glucose level. It is due to either insufficient production of insulin by the pancreas or lack of proper response to insulin by the body cells. BDNF is a kind of myokine with various metabolic effects such as regulating glucose metabolism. One of the effects of omega 3 fatty acid, especially DHA is reducing stress and inflammation and as a result they can increase BDNF serum level. The aim of this study was to determination of the effect of omega 3 fatty acids supplement on BDNF serum level in diabetic patients. Methods: This study was a double-blind clinical trial which was taken on 42 person with type 2 diabetes. Participants were divided into 2 groups of omega 3 supplement and placebo, randomly. The intervention lasted 10 weeks and patients consumed omega 3 supplement with the dose of 3750 mg per day or as the same amount of placebo (edible paraffin). Anthropometric indices such as weight, WC and WHR, blood pressure and blood samples were measured twice, before and after intervention. Also BDNF serum levels in both groups were assessed by ELIZA method twice. Data was analyzed by using SPSS version 21.0 and statistical significance was considered as p value<0.05. Results: Omega-3 supplementation caused an increase in BDNF serum level in diabetic patients (P=0.03). However no significant difference was seen between two visits in terms of weight, BMI, waist circumference, hip circumference and waist to hip ratio (WHR). Conclusion: Supplementation with omega-3 fatty acids could increase BDNF serum level in type2 diabetes patients but more researches is needed. Keywords: Omega-3 Fatty acids, type 2 diabetes, brain-derived neurotrophic factor (BDNF)

INTRODUCTION

Diabetes Mellitus is a metabolic disease which is characterized by high blood glucose levels and caused by any defects in insulin secretion, action or both (1). There is a worldwide type 2 diabetes epidemic and 90 to 95 percent of the population in developed and developing countries suffer from this disease. According to WHO and IDF statistics in 2010, a total of 7 million and 412 people in the range of 20 to 79 years old had been suffering from diabetes or impaired glucose tolerance. It's estimated that by 2030 Iran one of the most prevalent regions of the world in terms of diabetes (2-4). Several studies have found that omega-3 fatty acids improve diabetes but still their effective dose is unknown in diabetic patients. Among the effects of these fatty acids, we can point to insulin synthesis via increased secretion and production of adipocytokines (adiponectin and leptin) and also preventing insulin resistance via anti-inflammatory effect (5, 6).
Muscles also secrete substances such as cytokines and growth factors (they are called mayokine overall) which play a role in the regulation of inflammatory and metabolic processes through autocrine, paracrine and endocrine routes. Myokines affect the signaling mechanisms involved in fat oxidation through paracrine and also prevent insulin resistance by having anti-inflammatory effect, resulting in glucose uptake by blood (7, 8).

BDNF is a kind of myokine which exists in Central and peripheral nervous system, endocrine system, lymphocytes, muscles, liver, heart and endothelial system (9, 10).

BDNF has metabolic properties and regulates glucose metabolism. Skeletal muscle improves fat oxidation by increasing AMPK phosphorylation and Acetyl-CoA carboxylase and as a result leads to insulin resistance (7, 10, 11).

The findings suggest that BDNF level will reduce considerably in glucose disorders, type 2 diabetes, hyperglycemia, obesity and insulin resistance (7, 12-14).

The results also suggest that omega-3 fatty acids and particularly DHA, increase BDNF level. DHA alters to NDP1 (neuroprotectin D1) in body which has anti inflammatory effect and can increase BDNF level (15, 16).

The aim of current study was evaluating the effects of supplementation with omega-3 polyunsaturated fatty acids on serum BDNF level in diabetic patients.

MATERIALS & METHODS

The current study was done on 42 subjects with type 2 diabetes as a double blind clinical randomized trial. Qualified individuals assigned to two groups of omega-3 supplementation or placebo randomly. Permuted block randomization or four blocks were used for random acts. Participants in the supplement group, received 3750 mg of omega-3 fatty acids daily which was belonged to Zahravi pharmaceutical company (each capsule contained 1250 mg omega-3 fatty acids with 600 mg EPA and 300 mg DHA). Another group received 3 placebo capsules which contained paraffin daily. Their appearance was quite similar to omega-3 capsules. Both groups were recommended to intake 3 capsules by their main meals for 10 weeks. A written consent was taken from each participant at the beginning of the study and the study was approved by Tehran University of Medical Sciences, Tehran, Iran. Subjects were collected from Tehran diabetes medical centers and necessary interventions were applied on them. At baseline fasting blood samples at a rate of 10 cc was performed.

Weight was measured with light clothes, without shoes and by a digital Seca scale to the nearest 0.1 kg and height was measured without shoes by a wall-mounted stadiometer to the nearest 0.5 cm. Waist circumference was measured as the midpoint between the last rib and iliac crest and Hip circumference was measured as the biggest circumference with a non-elastic tape to the nearest 0.5 cm.

Patient’s Blood pressure was assessed by a digital barometer. Also data related to diet were collected by a 3 day, 24 h food recall and then the information were analyzed by Nutritionist fourth version. Physical activity of subjects were controlled and assessed by a summarized international physical activity questionnaire (IPAQ). At the end of 10 weeks of supplementation participants were invited to laboratory again and 10 cc of fasting venous blood was taken. Anthropometric, blood pressure, physical activity and food recall measurements were done again.

BDNF serum level in both groups was assessed by ELIZA GmbH kit (Germany) once at the beginning of study and the other after 10 weeks of supplementation.

Statistical analysis was done by descriptive analysis, with numerical variables expressed as the mean and standard deviation (SD) or median and interquartile range. The Kolmogorov-Smirnov test was used to examine the normality of the sample distribution. The Student t test also was used in cases with a normal distribution to compare means between the two groups and the Wilcoxon test was used in cases with a non-normal distribution. Also Chi-square test was applied for comparing qualitative factors between 2 groups. Data were analyzed using SPSS for Windows (version 21.0; SPSS Inc., Chicago, IL, USA) and statistical significance was considered as p value<0.05.

RESULTS

Patients were randomly divided into two groups: 21 patients received placebo and 23 patients received omega-3 supplements. The mean age of patients in the placebo and omega-3 group was 51.34±6.5 and 48.44±7.10 years respectively. There was no significant difference between two groups in terms of age (p=0.14).

At the beginning of the intervention, the mean serum BDNF was 1.51±0.70 ng/ml in placebo group and 1.46±0.48 ng/ml in supplement group. Also at the end of the intervention, it was obtained 1.39±0.54 and 1.90±0.94 ng/ml in placebo and supplement group, respectively. Despite the decline in serum BDNF in the placebo group, no significant difference was observed (p=0.75). However it was increased significantly in supplement group (p=0.03).
A significant difference was seen in the rate of changes during intervention (p=0.001) and the mean was estimated -0.11±0.27 in placebo group and 0.44±0.69 in supplement group.

A significant difference was observed in the duration of disease in both groups as well (p=0.03) but its effect was removed.

Eventually no significant difference was seen between two visits in terms of weight, BMI, waist circumference, hip circumference and waist to hip ratio (WHR).

**Conflict of Interest**

The authors declare they have no conflict of interest.

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<tr>
<th>Table1. Anthropometric indices at baseline (before intervention) and after intervention</th>
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<td><strong>Placebo Group</strong> N=21</td>
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<tr>
<td>Weight (kg)</td>
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<td>BMI (kg/m²)</td>
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<td>WC (cm)</td>
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<td>WHR</td>
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<td>After Intervention</td>
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<td>*The results are described as mean ± Standard Error (SE), # Independent sample t-test, BMI:Body Mass Index; WC: Waist Circumference; HC: Hip Circumference; WHR: Waist-to-Hip Ratio.</td>
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<th>Table2. Serum BDNF level at baseline (before intervention) and after intervention and BDNFdiff*</th>
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<tr>
<td><strong>Placebo Group</strong> N=21</td>
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<td>Serum BDNF (ng/ml)</td>
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<td>BDNFdiff</td>
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*The results are described as mean ± Standard Error (SE), # Independent sample t-test

**DISCUSSION**

This is the first clinical trial assessed the effect of supplementation with omega-3 fatty acids on serum BDNF in diabetic patients. The current study indicated omega-3 supplementation (with the dose of 1250 mg three times per day), can increase BDNF level in patients with type2 diabetes. However no significant difference was observed in the point of weight, BMI, waist circumference, hip circumference, WHR and blood pressure between two visits. BDNF is a kind of mayokine in peripheral and central nervous system, heart, endothelial cells, lymphocytes, liver and skeletal muscle (9). Several studies have found that low serum BDNF, is one of the factors involved in the pathogenesis of type 2 diabetes, glucose metabolism disorders, hyperglycemia, Insulin resistance and obesity (7, 12-14).

Sedi and his colleagues conducted a test on 21 rat and evaluated the effects of high-fat diet and supplementation with omega-3 fatty acids on the BDNF level in their hippocampus. Rats were randomly divided into three groups of receiving high fat diet, omega-3 supplement and control group and intervention were done as long as 8 weeks. They found that BDNF level in hippocampus had a significance increase just in omega-3 group (17).

Another study which was done by Karczewska-Kupczewska et al. 64 healthy, non-obese young women were divided into two groups of high and low sensitivity to insulin. Finally they observed a reduction in BDNF level in non-obese women who had low sensitivity to insulin. So there was a significant relation between BDNF serum level by insulin sensitivity (18).

Te Lee et al. studied 34 non-diabetic men with metabolic syndrome and 24 healthy men and observed a significant difference between BDNF and VCAM-1 serum levels in the men with metabolic syndrome (19).
In Ferreira et al. study the relation between omega-3 and serum levels of BDNF on 137 worried teens was assessed and they found a meaningful correlation between them (20).

Of the study limitations we can mention that only serum BDNF was measured and it was better to measure the extractive gene too. Nevertheless this was the first study which was applied on diabetic patients and assessed omega-3 effect on BDNF level. Also the study was taken on humans by randomized and double blind sampling.

ACKNOWLEDGEMENT

This study was funded with the grant number 28679 by Tehran University of Medical Sciences.

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