Research article

Omega-3 fatty acids' effect on leptin and adiponectin concentrations in patients with spinal cord injury: A double-blinded randomized clinical trial

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Context: Omega-3 fatty acids have been recently proposed to induce neural improvement in patients with spinal cord injury (SCI) while affecting some hormones including leptin and adiponectin.

Objectives: We tried to evaluate the effect of omega-3 fatty acids on circulatory concentrations of leptin and adiponectin among these patients.

Design: This study is a double-blinded randomized clinical trial with intervention duration of 14 months.

Setting: A tertiary rehabilitation center.

Participants: Total of 104 patients with SCI who did not meet our exclusion criteria entered the study. Those with history of diabetes, cancer, endocrinology disease, acute infection, and use of special medications were excluded. Patients were divided randomly into the treatment and control group by using permuted balanced block randomization.

Intervention: The treatment group received two MorDHA[®] capsules per day (each capsule contain 465 mg of docosahexaenoic acid (DHA) and 63 mg of eicosapentaenoic acid (EPA)) for 14 months while the control group received placebo capsules with similar color, shape, and taste.

Main outcomes measures: Leptin and adiponectin concentrations in plasma were measured at the beginning of trial and then after 6 and 14 months.

Results: Fourteen months of treatment with DHA and EPA did not influence concentrations of leptin but adiponectin level was significantly decreased ($P: 0.03$). Weight was positively correlated with leptin level at stage 0 of trial ($P: 0.008$, $r = 0.41$) while this association was attenuated through stages of trial after intervention.

Conclusion: Our data show that omega-3 fatty acids may not affect plasma concentrations of leptin but adiponectin level is decreased in patients with SCI. Moreover, this intervention influences the linear relationship between weight and leptin after 14 months administration of DHA and EPA.

Keywords: Omega-3 fatty acid, Leptin, Adiponectin, Spinal cord injury

Introduction

Some pathological changes occur after spinal cord injury (SCI) which induces neuron degeneration such as macrophage-induced inflammation¹ and

excitotoxicity.² These degenerative responses are complex and many pathological pathways have been proposed to play a role in this process. Some evidences have proposed that polyunsaturated fatty acids (PUFAs) may target some of these pathological pathways.³ Meanwhile, some hormone changes have been reported after SCI including leptin which is a fat tissue-derived hormone. The level of leptin in plasma

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is influenced by body fat composition. Moreover, the effects of leptin on bone metabolism have also been described so far.⁴⁻⁶ Previously, changes in leptin concentration after SCI was reported and most studies have illustrated higher level of leptin in these patients.⁷⁻¹¹ Besides its effects on bone mineral density, it has been shown that leptin and adiponectin may be associated with the risk of cardiovascular diseases (CVDs) because they may affect inflammatory factors. Differences in concentration of leptin among men and women and also its association with age support the probable relationship between leptin level and risk of CVD.¹² Leptin level also predicts the development of metabolic syndrome which is specially associated with glucose intolerance and insulin resistance.¹³ All these influences of leptin and adiponectin and their possible consequences on body organs including bones and cardiovascular system have made these two hormones very important and assessing their changes after SCI may give physicians some clues to target their effects in clinical practice.

Some literature have revealed the positive therapeutic effect of ω -3 PUFAs in neurological diseases because of its potential anti-inflammatory and neuroprotective effects.^{14,15} Sarsilmaz *et al.*¹⁶ showed that ω -3 PUFAs have an antioxidant effect and help to balance the oxidant/antioxidant ratio in the hippocampus. Some investigations have also shown anti-inflammatory effects of ω -3 PUFAs¹⁷ whereas others detected no significant changes of inflammatory cytokines after medical therapy with omega-3.¹⁸ However, many studies have supported the potential neuroprotective and apoptosis-inhibitory effects of ω -3 PUFAs^{19,20} which propose this medication as a treatment among patients with SCI.

The purpose of this study was to investigate the effects of interventional therapy with ω -3 PUFAs in spinal cord injured patients on changes of leptin and adiponectin levels in plasma.

Methods

Participants

This investigation was designed as a double-blind placebo-controlled clinical trial (NCT01311375: 6 March 2011). Participants were patients with SCI who were referred to Brain and Spinal Injury Research Center (BASIR). A total of 110 participants with chronic SCI were enrolled after obtaining informed consent. At the end of the study, 104 patients completed the 14-month follow-up: 54 patients in the treatment group and 50 patients treated with placebo. The most common reasons for dropout were gastrointestinal

complications and difficulty to follow routine visits schedule due to remote living location. Patients were selected to enter the study based on inclusion criteria as follows: traumatic SCI and post-injury duration longer than 1 year. Exclusion criteria were: pregnancy, lactation, amputation, and non-traumatic SCI etiology. Patients with history of diabetes, cancer, endocrinology disease, acute infection, use of special medications such as glucocorticoid, hormones, thyroid hormones, anticonvulsive drugs, heparin, aluminum-containing antacids, lithium, omega-3 fatty acids or other nutrients supplements, and smoking or alcohol consumption were also excluded. Data were collected in BASIR from November 2010 to April 2012. The protocol was approved by the ethics committee of Tehran University of Medical Sciences (Approval number: 1421 at 18 July 2010).

Anthropometric measurements

A questionnaire was used to obtain patients' demographic characteristics including age, sex, date of accident, and post-injury duration. Body weight was measured using a digital wheelchair scale, body height was obtained by measuring the supine length, and body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters) squared.

Study design

Fifty patients in the control group and 54 patients in the treatment group were randomized by using Permuted Balanced Block Randomization Method. Patients in the treatment group received two MorDHA[®] capsules (each capsule contains 465 mg of docosahexaenoic acid (DHA) and 63 mg of eicosapentaenoic acid (EPA)) per day and patients in the control group received two placebo capsules. These capsules were consumed twice daily; one with lunch and another one with dinner. The duration of treatment was 14 months. Data were collected in three stages including stage 0 (at the beginning of study before intervention), stage 1 (after 6 months), and stage 2 (after 14 months).

The assessment of pill compliance was performed by using pill count method, which is based on a confidence relationship between patient and physician and was reported every 4 weeks. No specific advices on food intake were given to patients and no diet modification was made through the study. All patients claimed to have a normal routine diet and no lifestyle, diet, or medication changes were recorded every 4 weeks by phone call or face-to-face interview.

Omega-3 capsules were provided by Minami Nutrition Co. (Aartselaar, Belgium) and placebo

capsules were supplied by Zahravi Pharmaceutical Co. (Tehran, Iran). Both capsules were similar in color, shape, and taste.

Unfortunately, there is no recommended dosage for DHA and EPA for people with SCI. The dosage of omega-3 varies for people with different medical conditions. In this study, the consumed omega-3 capsules were MorDHA[®] which contains 465 mg DHA and 63 mg EPA (with an approximate ratio of 7:1 for DHA:EPA). The World Health Organization recommends a daily EPA and DHA intake of 0.3–0.5 g. The recommended dose based on manufacturer guidelines of MorDHA[®] product is one capsule per day. However, medical literatures have illustrated that a higher dose is required to obtain a significant effect in a specific medical disorder.²¹ Based on manufacturer consumption guidelines and our own interpretation of omega-3 consumption dosage according to previous investigations in other medical conditions, and after consulting with nutrition experts, we decided to prescribe two capsules of MorDHA[®] daily (each contains 465 mg DHA and 63 mg EPA).

Laboratory measurements

Blood samples were taken under antiseptic conditions from antecubital vein. Blood samples were collected and centrifuged at 3000 rpm for 10 minutes at 4°C. Samples were sent to the Endocrinology and Metabolism Research Center laboratory for analysis and were frozen immediately. The levels of leptin and adiponectin were measured and were reported as nanogram per milliliter.

Neurological assessment

Completeness was classified as either complete (no preserved sensory or motor function) or incomplete (variable motor function preserved below the neurological level of injury).²² Level of injury was assessed with clinical examinations and para-clinical imaging aids and was confirmed by neurology experts. Patients were also classified according to American Spinal Cord Injury Association Scale (ASIA)²³ which was determined based on clinical examination. In this classification, ASIA-A indicates complete injury with no preserved motor or sensory function below the neurological level. ASIA-B describes incomplete injury in which only sensory function is preserved below the neurological level. ASIA-C illustrates preserved motor function in which more than half of key muscles below the neurological level have a muscle grade <3. ASIA-D indicates preserved motor function in which at least half of key muscles below the neurological level have a

muscle grade of 3 or more and finally, ASIA-E represents normal motor and sensory function. Only ASIA-A represents complete injury.

Statistical analyses

All statistical analyses were performed using SPSS software, Version 18.0 (SPSS Inc., Chicago, IL, USA). We reported results by expressing percentages for categorical data and mean $\pm$ standard deviation (SD) for continuous quantitative values. Proper comparison of means was performed using *t*-test. Pearson's Chi-square test was used to compare categorical data and independent *t*-test with confidence interval of 95% was used to compare quantitative value of both groups before and after intervention with each other. $P < 0.05$ was considered statistically significant. Correlation analysis with Spearman correlation coefficient was reported for comparison of the quantitative values.

Results

Total number of 104 patients (16.7% (n : 19) females and 74.6% (n : 85) males) were included in the study. Mean age was 54.12 ± 11.76 in the placebo group and 51.15 ± 13.43 in the treatment group. Patients' baseline characteristics in both the control and treatment groups are summarized in Table 1.

Mean concentrations of leptin and adiponectin at the beginning of study before applying any intervention (stage 0) was 13.72 ± 11.58 ng/ml and 5.68 ± 2.48 ng/ml, respectively, in the control group. In the treatment group, leptin and adiponectin concentrations were 16.31 ± 23.02 and 6.16 ± 3.422 ng/ml, respectively, at stage 0 (Table 2). Leptin and adiponectin levels were slightly higher at the baseline (before intervention) in the treatment group but this difference was not statistically significant (P : 0.54 and 0.49 for leptin and adiponectin, respectively). At the end of the trial after 14 months of intervention with oral capsules of MorDHA[®], no significant alterations in leptin concentration could be detected while adiponectin level was significantly decreased (P : 0.03). Table 2 shows the measures of leptin and adiponectin at the stages of 0, 1, and 2 in both the placebo and treatment groups. Adiponectin in the control group was slightly increased through time (from 5.68 ng/dl in stage 0 to 6.41 ng/dl in stage 2) while it was slightly decreased in the treatment group (from 6.16 ng/dl in stage 0 to 5.05 ng/dl in stage 2). It can be concluded that omega-3 has inhibited the raise of adiponectin when considering the mean difference between the treatment and control groups (mean difference of 0.26 in the control group and -1.11 in the treatment group (P : 0.03)). However, the

Table 1 Patients' baseline characteristics in the treatment and control groups before intervention

Patients characteristics		Placebo group (n: 50) Mean (SD)	Treatment group (n: 54) Mean (SD)	P-value*
Age		54.12 (11.76) (Range: 30–74)	51.15 (13.43) (Range: 15–74)	0.23
Sex	Male	41 (82%)	44 (81.5%)	0.57
	Female	9 (18%)	10 (18.5%)	
Body weight (kg)		68.84 (13.87) (Range: 48–106)	68.78 (15.15) (Range: 36–115)	0.98
Body height (cm)		170.32 (9.08) (Range: 145–185)	168.67 (9.19) (Range: 146–188)	0.35
BMI (kg/m ²)		23.64 (3.78) (Range: 17.36–32)	24.11 (4.89) (Range: 13.55–43.56)	0.58
Completeness of injury	Complete	40 (80%)	41 (75.9%)	0.39
	Incomplete	10 (20%)	13 (24.1%)	
Time since injury (year)		9.56 (7.2) (Range: 1–33)	8.96 (5.44) (Range: 1–31)	0.63
ASIA level	A	38 (76%)	40 (74.1%)	0.65
	B	5 (10%)	7 (13%)	
	C	3 (6%)	1 (1.9%)	
	D	4 (8%)	6 (11.1%)	
Most common level of injury		T12	C4	–
Tetraplegic/paraplegic ratio		3/47	10/44	0.07

ASIA: American Spinal Cord Injury Association Impairment Scale.

*P-values were not significant in any items which show that there was not a significant difference between the treatment and placebo group in patients' characteristics.

Categorical data are expressed as number (percentage).

level of adiponectin showed no significant difference in stage 1 (P: 0.64) and stage 2 (P: 0.63) between the treatment and control groups but it seems that increase of adiponectin can be inhibited by omega-3 consumption.

Tetraplegic and paraplegic patients did not show any different relationship in any stages of trial with concentrations of leptin and adiponectin in both groups. Completeness of injury did not also influence leptin and adiponectin levels in any stages as well. Female patients in the treatment group had a higher level of leptin in all three stages (Table 3) while no other sex-related effect could be detected. As this difference existed at the beginning of trial before applying any intervention between both groups, we could not conclude a specific sex effect on leptin level by omega-3 fatty acid treatment. Weight was positively correlated with leptin level at stage 0 of trial (P: 0.008, $r = 0.41$) while this association was vanished through stages of trial after intervention. In the placebo group, the positive relationship between weight and leptin concentration remained significant till the end of the trial (Table 3). Otherwise, weight was negatively correlated with adiponectin concentration at stage 0 (P: 0.004, $r = -0.45$) and this relationship also decreased through time in other stages of this study.

Body weight and BMI showed no significant changes after 14 months of ω -3 PUFA administration. Mean BMI in the placebo group was 23.64 ± 3.78 at the

beginning of the trial and 24.22 ± 4.20 at the end of the study. The treatment group had mean BMI of 24.11 ± 4.89 at stage 0 and 24.80 ± 4.91 at stage 2. It seems that treatment with ω -3 PUFA does not affect body weight.

Discussion

Induction of neurological recovery after SCI is a very challenging issue and can improve quality of life tremendously. Recently, the effect of omega-3 fatty acid has shown therapeutic potential in neural function by reducing inflammation.²⁴ Dietary supplements have been proposed to augment central nerve system functions not only in SCI but in many pathological circumstances such as epilepsy²⁵ and Alzheimer's disease.²⁶ It has been reported that DHA promotes neurotransmission and ion channel activities.²⁶ Some literatures have demonstrated some hormonal and prostaglandins changes²⁷ by ω -3 fatty acid intake. Leptin is a hormone which is produced in adipocytes and is a known risk factor for CVD.²⁸ On the other side, adiponectin is a cytokine that is inversely related to visceral fat tissue and increases insulin sensitivity.²⁹ Some alterations in leptin and adiponectin concentrations have been reported after intervention with omega-3 fatty acids. Mostowik *et al.*³⁰ showed increased adiponectin to leptin ratio with a 30-day administration of omega-3 fatty acids in patients with stable coronary artery

Table 2 Alterations of leptin and adiponectin concentrations by omega-3 fatty acids administration

	DHA group (n = 54)					Placebo group (n = 50)					P-value (S1 – S0)	P-value (S2 – S0)
	Mean (SD)			Mean difference		Mean (SD)			Mean difference			
	0 month	6 months	14 months	(S1 – S0)	(s2 – s0)	0 month	6 months	14 months	(S1 – S0)	(S2 – S0)		
L	16.31 (23.02)	16.03 (19.73)	18.81 (26.80)	–0.41	1.10	13.72 (11.58)	12.16 (14.6)	15.13 (13.64)	–1.49	–0.52	0.71	0.63
A	6.16 (3.42)	6.22 (3.31)	5.05 (2.89)	0.22	–1.11	5.68 (2.48)	6.59 (3.72)	6.41 (3.51)	0.89	0.26	0.14	0.03*

A, adiponectin concentration (ng/dl); L, leptin concentration (ng/dl); S0, stage 0 (at the beginning of study); S1, stage 1 (after 6 months of trial); S2, stage 2 (after 14 months of trial).
*Significance level of $P < 0.05$.

disease. However, its effect on circulatory concentrations of leptin and adiponectin was not yet evaluated in spinal cord injured patients. According to our data, adiponectin/leptin ratio was not significantly changed in both groups at the end of the trial ($P: 0.24$). However, a significant reduction in adiponectin level was observed after 14 months intervention with omega-3 fatty acids.

Itoh *et al.*³¹ also reported increased level of adiponectin with ω -3 PUFA treatment in animal models which have a controversy with our results in human models with SCI which illustrated the probability of existence of different responding mechanism between human bodies and experimental cases. Our results also show contradictory outcomes with the findings of Kratz *et al.*,³² who detected no influence of ω -3 PUFA on adiponectin in healthy overweight to moderately obese men and women. The reason for these disparate findings could be the difference in study population as the increased weight of participants in Kratz's study population may have modulated the concentrations of leptin and adiponectin and consequently could have influenced the response to ω -3 PUFA administration.

We did not detect any influence of 14-month administration of ω -3 PUFA on circulatory leptin concentration in patients with SCI, which is in line with the findings of Sneddon *et al.*³³ who investigated this association in lean and obese men. By considering previous reports^{30,31,34,35} that demonstrated increased adiponectin after ω -3 PUFA therapy and decreased leptin³⁰ concentration in patients with CVDs, this point is clarified that the effect of ω -3 PUFA is dependent on patients' background disorders.

Weight was positively related with leptin concentration at the beginning of the trial (stage 0) but this association was attenuated only in the treatment group after receiving ω -3 PUFA while it remained significant in the placebo group till the end of the trial. Because leptin is a fat-derived hormone, its correlation with weight and BMI was expected. While some literature supports the effect of ω -3 PUFA in helping weight loss,³⁶ some other found no influence.³⁷ We have observed that weight was not related to leptin concentration after ω -3 PUFA therapy even when it had a strong positive association with it at the beginning of the trial. Weight reduction leads to lower leptin levels³⁸ and while omega-3 fatty acids are assumed to help in weight loss, they may interact with leptin concentration as well. However, it seems that weight reduction is not initiated at the same time of alteration of leptin concentration because the association between weight and leptin level was attenuated through time by

Table 3 Association of demographic characteristics in patients with SCI with leptin and adiponectin levels through three stages of trial

	Treatment group						Placebo group					
	L0	L1	L2	A0	A1	A2	L0	L1	L2	A0	A1	A2
Sex	0.002*	0.0001*	0.0001*	0.152	0.156	0.067	0.23	0.26	0.012	0.54	0.50	0.49
Age	0.053	0.65	0.97	0.25	0.012 [†]	0.13	0.67	0.09	0.21	0.19	0.14	0.02 [‡]
Level of injury	0.73	0.66	0.21	0.66	0.41	0.39	0.68	0.54	0.74	0.23	0.50	0.16
Completeness of injury	0.52	0.55	0.56	0.62	0.52	0.63	0.27	0.81	0.75	0.97	0.99	0.94
Weight	0.008 [§]	0.059	0.77	0.004 [§]	0.13	0.2	0.0001 [§]	0.0001 [§]	0.002 [§]	0.12	0.052	0.49

L0, 1, and 2: leptin concentration at stages of 0, 1, and 2 of trial.

A0, 1, and 2: adiponectin concentration at stages of 0, 1, and 2 of trial.

*Female patients had higher leptin concentration at significance level of $P < 0.01$ ($r = 0.23, 0.41$, and 0.30 , respectively, for L0, L1, and L2).

[†]Correlation is significant at 0.05 level, $r = -0.38$.

[‡]Negative correlation between age and adiponectin level at stage 2 of the trial ($r = -0.20$).

[§]Correlation is significant at $P < 0.01$ level, $r = 0.41$ and -0.45 , respectively, for L0 and A0 in the treatment group and $r = 0.61, 0.66, 0.48$ for L0, L1, and L2 in the placebo group.

administration of ω -3 PUFA. However, the included mechanisms seem to be much more complicated and are applied through multiple pathways. We have observed previous reports indicating no influence of ω -3 PUFA on body weight³⁹ and therefore no influence on leptin level could be expected as well, which is in line with our findings. Our data also shows no influence of ω -3 PUFA on body weight which agrees with Bays *et al.*⁴⁰ This is the first study indicating that ω -3 PUFA may not affect body weight but that it alters the linear relationship between weight and plasma leptin concentration. Previously, it has been suggested that omega-3 may be effective in the prevention of obesity and reducing weight,⁴¹ and by considering the positive association between weight and leptin, we expected that we would observe a reduction of leptin level as well. However, this effect has only been observed in non-obese individuals.⁴² It can be concluded that omega-3 decreases leptin level and weight when BMI is within the normal range but in obese patients it may only reduce weight without affecting leptin (and therefore affects the linear relationship between leptin and weight). However, a slight increase in weight was observed in both groups in our study (from 68.84 ± 13.87 to 70.77 ± 14.35 in the placebo group and from 68.78 ± 15.15 to 71.37 ± 14.42 in the treatment group) and attenuation of linear association between leptin and weight only in the treatment group cannot be explained by weight gain in these patients. Furthermore, lower levels of leptin in patients with SCI have already been demonstrated, which is perhaps due to changes of fat distribution in these patients.¹¹ In contrary with Hariri *et al.*⁴² study, who showed that high levels of leptin (which is detected in obese individuals) is non-responsive to omega-3 administration, here we have shown that low levels of leptin which can be

detected in patients with SCI are also non-responsive to omega-3 consumption. Besides changes in fat distribution, higher injury level is also associated with higher leptin level.¹¹ As it has been mentioned, the baseline level of leptin affects changes of leptin as a response to omega-3 consumption. Although injury level showed no relationship with leptin level among the treatment and control groups in our study, it is essential to consider these factors to obtain a better understanding about the effect of omega-3 on the association between leptin and weight. So, future investigations with a more homogeneous study group (considering patients with similar injury levels) can lighten this point more conclusively. Finally, omega-3 showed no beneficiary effect in reducing weight in patients with SCI which is in line with Munro's report⁴³ in healthy individuals.

Conclusion

Our data show that omega-3 fatty acids may not affect plasma concentrations of leptin but adiponectin level is decreased by this intervention in patients with SCI. Moreover, this intervention influences the linear relationship between weight and leptin after 14 months administration of DHA and EPA in patients with SCI.

Study limitations

This study evaluates body weight and plasma concentrations of leptin and adiponectin alterations after 14 months of omega-3 fatty acid administrations but still some body adjustment changes after omega-3 fatty acid therapy may take more time in patients with SCI. Longer intervention duration may lighten new points in this field. Another noble investigation can be designed on the effect of omega-3 on the risk of CVDs. To derive the risk of CVD after omega-3

consumption, it is necessary to measure CVD risk factors such as serum lipids (total cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride), apolipoproteins (Apo A-I, Apo B, ApoB/Apo A-I ratio), lipoprotein (a), fasting plasma glucose, Hb A1c, other metabolic factors (insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-1 (IGFBP-1)), cortisol, and inflammation markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, and haptoglobin). Since the purpose of this study was not to evaluate the effect of omega-3 consumption on CVD risk, the mentioned factors were not measured through this trial.

Disclaimer statements

Contributors HS contributed in study design and critical edition of manuscript. ANJ contributed in data collection and recruiting the participants. SL contributed in statistical analysis, interpretation of data, and writing the paper. FS contributed in study design and data collection. RH contributed in study design and was responsible for laboratory analysis and reports. HER contributed in study design and obtaining the ethical approve. MRV contributed in editing the manuscript. BL contributed in study design, collecting data, and providing support.

Conflicts of interest None.

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