Effects of supplementation with omega-3 on insulin sensitivity and non-esterified free fatty acid (NEFA) in type 2 diabetic patients

Efeito da suplementação com ômega-3 sobre a sensibilidade à insulina e aos ácidos graxos livres não esterificados (AGNE) em pacientes com diabetes tipo 2

Payam Farahbakhsh Farsi[1,2], Abolghassem Djazayery[2,3], Mohammad Reza Eshraghian[4], Fariba Koohdani[1,2], Ali Akbar Saboor-Yaraghi[1,2], Hoda Derakhshanian[1,2], Mahnaz Zarei[1,2], Mohammad Hassan Javanbakht[1,2], Mahmoud Djalali[1,2]

ABSTRACT

Objective: The aim of this study was to determine the role of omega-3 supplementation on NEFA concentration, insulin sensitivity and resistance, and glucose and lipid metabolism in type 2 diabetic patients. **Subjects and methods:** Forty-four type 2 diabetic patients were randomly recruited into two groups. Group A received 4 g/day omega-3 soft gels, and group B received a placebo for 10 wks. Blood samples were collected after 12-h fast. Physical activity records, three-day food records, and anthropometric measurements were obtained from all participants at the beginning and end of the study. **Results:** Omega-3 supplementation caused a significant reduction in NEFA in the intervention group compared with the placebo group ($P = 0.009$). Additionally, the administration of omega-3 resulted in significantly greater changes (Diff) for the intervention group in various parameters, such as insulin and Quicki indices compared with the placebo group ($P < 0.05$). **Conclusions:** Omega-3 fatty acid supplementation in type 2 diabetic patients improved insulin sensitivity, probably due to the decrease in NEFA concentrations. Arq Bras Endocrinol Metab. 2014;58(4):335-40

Keywords
Non-esterified fatty acids; omega-3 fatty acids; insulin; *diabetes mellitus*

[1] Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[4] Department of Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

RESUMO

Objetivo: O objetivo deste estudo foi analisar o papel da suplementação com ácidos graxos ômega-3 sobre a concentração de ácidos graxos não esterificados (AGNE), resistência e sensibilidade à insulina e metabolismo de lipídios em pacientes com diabetes melito tipo 2. **Sujeitos e métodos:** Quarenta e quatro pacientes com diabetes tipo 2 foram recrutados aleatoriamente e alocados em um de dois grupos. O Grupo A recebeu 4 g/dia de ômega-3 na forma de cápsulas gelatinosas e o grupo B recebeu placebo durante 10 semanas. Amostras de sangue foram coletadas após 12 horas de jejum. Registros da atividade física, da dieta de três dias e medidas antropométricas foram obtidos de todos os participantes no início e no final do estudo. **Resultados:** A suplementação com ômega-3 causou uma redução significativa na AGNE em comparação com grupo placebo ($P = 0,008$). Além disso, a administração de ômega-3 resultou em alterações significativamente maiores (Dif) em vários parâmetros, tais como a insulina, HOMA-IR e QUICKI, comparando com placebo ($P < 0,05$). **Conclusões:** A suplementação com ácidos graxos ômega-3 em pacientes diabéticos tipo 2 melhorou a sensibilidade à insulina, provavelmente devido à diminuição da concentração de AGNE. Arq Bras Endocrinol Metab. 2014;58(4):335-40

Descritores
Ácidos graxos não esterificados; ácidos graxos ômega-3; insulina; diabetes melito

Correspondence to:
Mahmoud Djalali
Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Poorsina Street, Enghelab Avenue
14155-6446 – Tehran, Iran
mjalali87@yahoo.com

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INTRODUCTION

Hyperglycemia and type 2 diabetes are caused by insulin resistance and beta-cell dysfunction. Beta-cell dysfunction can be caused by genetic and environmental factors, including inflammation and stress agents, such as glucose and NEFA. Saturated NEFAs are detrimental to beta-cell function. Their effect is exacerbated in the presence of high levels of glucose and may cause a condition called glucolipotoxicity (1). As fatty acids can stimulate insulin secretion, they have an important role in the mechanism of beta-cell compensation to insulin resistance (2). In diabetics with a positive family history, an increase in lipid turnover rate can prevent diabetes (2,3). Increased NEFA stimulates insulin secretion, although omega-3 cannot stimulate insulin secretion (4,5). NEFA concentrations as co-modulators of plasma glucose levels and insulin secretion have been used in mathematical models (6,7). Studies on rodents have shown that fish oil may improve insulin sensitivity or reduce glucose levels (8). The effects of fish oil on insulin sensitivity and resistance in type 2 diabetic patients are not fully understood. NEFA interferes with pancreatic beta-cells contributing to hyperinsulinemia, hyperglycemia, and diabetes. In addition, it leads to insulin resistance in muscles and the liver. Therefore the aim of this study was to determine the role of omega-3 supplementation on NEFA concentration, insulin sensitivity and resistance, and glucose and lipid metabolism in type 2 diabetic patients.

SUBJECTS AND METHODS

Study population

This study was a randomized controlled double-blind clinical trial. Patients were enrolled from January 2012 through May 2012. All patients came from the Iranian Diabetic Association, Tehran, Iran. The criteria for inclusion were: willingness to participate, 30-65 years of age, T2DM diagnosis, and a body mass index of 18.5 to 40 kg/m^2. Patients were required to cease consumption of dietary supplements at least 2 wks. before the beginning of the test period and throughout the intervention. Subjects who had consumed omega-3 supplements in the three months before the beginning of the study were excluded. None of the patients patient had chronic renal, hepatic, gastrointestinal, or hematological disease or a thyroid disorder. None of the patients had used orlistat, sibutramine, or any other weight-loss drugs. None was pregnant or lactating. None was receiving thiazolidinediones or insulin therapy. All participants were requested to maintain their usual exercise and dietary habits. A total of 45 patients with type 2 *diabetes mellitus* who met the inclusion criteria were randomly allocated in one of two groups. Permuted-block randomization was used for grouping, and the two groups were matched according to BMI. The intervention group received 4 soft gels of omega-3 (Maxepa Forte Capsules, Seven Seas, UK) per day, and the control group received 4 g/d placebo soft gels containing corn oil, which had the same appearance (Zahravi, Iran). The protocol was approved by the Ethics Review Board of Tehran University of Medical Sciences (TUMS), and each patient signed an informed consent form.

From the 23 patients allocated to the intervention group, one patient was excluded due to non-willingness, and all of the 22 patients in the control group completed the study. Therefore, 44 patients finished the study.

Study design

To assess baseline values, blood samples were collected for analysis after 12-h overnight fast. Thereafter, for 10 wks., the intervention group received omega-3 soft gels, while the control group received the placebo. Anti-diabetic medicine and other medications were kept stable in all patients. Patient compliance was monitored every two weeks.

Anthropometric measurements (height, weight, hip and waist circumferences), physical activity (data not shown) were measured, and laboratory tests were done at the beginning and end of the study. Venous blood samples were collected. Whole blood was centrifuged at 3,000 g for 10 min and kept in -80°C freezers until the tests were performed. Plasma glucose, total serum cholesterol, blood triglyceride, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), non-esterified free fatty acid (ZiestChem Diagnostics, Tehran, Iran), and plasma insulin (ELISA kit, Diametra, Milan, Italy) were measured. Insulin resistance was estimated using the Homeostasis Model Assessment (HOMA) calculated as [fasting insulin (μIU/mL)+log fasting glucose(mg/100mL)/22.5], and insulin sensitivity was estimated using the Quantitative Insulin Sensitivity Check Index (QUICKI) as {1/[log fasting insulin(μIU/mL)xfasting glucose(mg/100mL)]} (9).

Statistical analysis

Data were expressed as the means ± standard error of mean (SEM). Student's *t* test was used to compare the mean of the responses. If normal assumption was not applicable, non-parametric tests were applied. Analysis of covariance (ANCOVA) was also used to control the effect of baseline values of different variables in the two groups. *P* values < 0.05 were considered statistically significant. Statistical analysis was performed using The Statistical Package for Social Sciences (version 18.0; SPSS Inc., Chicago, USA).

RESULTS

Effect of omega-3 supplementation on general parameters

A total of 44 diabetic patients (17 males, 27 females) completed the study. Anthropometric measurements were done as shown in table 1. No significant differences between the groups were observed at the beginning of the intervention. Comparisons of weight between the groups showed no difference before ($P = 0.15$) or after ($P = 0.19$) 10 wks. Waist and hip circumferences between the groups were not statistically different before ($P = 0.38$ and 0.32) or after the intervention ($P = 0.37$ and 0.68). BMI did not change significantly before ($P = 0.83$) or after ($P = 0.91$) the study.

Effects of omega-3 supplementation on NEFA

NEFA values had normal distribution. To control the confounding effect of baseline NEFA values, ANCOVA was used ($P = 0.57$). At baseline, there were no differences in NEFA levels between the groups ($P = 0.955$).

After 10 wks., a significant decrease in NEFA was observed for the omega-3 group ($P = 0.009$). However, no change occurred in the placebo group ($P = 0.99$). Comparisons of the groups at the end of the study showed a significant change in NEFA levels in the intervention group compared with that of the control ($P = 0.008$). The mean difference between the two groups was not significant ($P = 0.11$).

Effects of omega-3 supplementation on plasma lipid levels

Concentrations of lipid markers (total cholesterol, TG, LDL-C, and HDL-C) had normal distribution. After 10 wks., total cholesterol, HDL-C, LDL-C, and TG decreased slightly, but not significantly, for the intervention group. The mean difference between the two groups for HDL-C was significant (P = 0.03), and was marginally significant (P = 0.05) for TG.

Effects of omega-3 supplementation on insulin

After 10 wks. of intervention, insulin levels decreased in the omega-3 group compared with baseline values ($P = 0.02$). Although the difference between groups at the end of the study was not statistically significant, the mean difference between the two groups for insulin was significant ($P = 0.03$).

Effects of omega-3 supplementation on HOMA-IR and QUICKI

In contrast to QUICKI, HOMA-IR did not have normal distribution. Accordingly, we log-transformed the data to obtain a normal distribution. After 10 wks. of supplementation, within-group analysis showed a significant decrease in HOMA-IR for the intervention group ($P = 0.011$), and the QUICKI significantly increased ($P = 0.002$).

Table 1. General characteristic of participants at the baseline (week 0) and at the end of the study (week 10)

	Omega-3 group		Placebo group	
	Before	After	Before	After
Age (years)	54.23 ± 1.64	-	53.32 ± 1.45	-
Weight (kg)	69.21 ± 2.84	68.96 ± 2.91	63.57 ± 2.65	63.60 ± 2.78
Height (cm)	162 ± 2.11	-	156 ± 1.37	-
Waist circumference (cm)	86.41 ± 2.33	86.15 ± 2.44	83.66 ± 2.10	83.16 ± 2.24
Hip circumference (cm)	102.54 ± 1.62	101.83 ± 1.66	97.25 ± 1.74	97.22 ± 1.81
BMI (kg/m^2)	26.19 ± 0.78	26.11 ± 0.84	25.93 ± 0.92	25.95 ± 0.98

Data are presented as mean ± SEM. There were no significant differences between the two groups at baseline and at the end of the study (Independent t-test). Chi-square test was used to detect differences in gender profile between the groups.

Table 2. Comparison of various parameters within and between groups

	Omega-3 group			Placebo group			*P*-value between groups Before	*P*-value between groups After
	Before	After	*P*-value	Before	After	*P*-value		
Insulin (µIU/mL)	10.68 ± 0.86	8.51 ± 0.59	**0.028**	7.6 ± 0.59	7.51 ± 0.56	0.695	**0.005**	0.228
NEFA (ng/mL)	1936.73 ± 90.91	1737.72 ± 51.01	0.09	1929.64 ± 87.43	1997 ± 77.17	0.58	0.955	**0.008**
TG (mg/100 mL)	156.55 ± 15.25	131.59 ± 12.92	0.076	136.77 ± 21.34	145.86 ± 17.24	0.39	0.455	0.511
Cholesterol (mg/dL)	228.64 ± 12.75	204.36 ± 8.27	0.055	222.50 ± 9.97	215.27 ± 10.72	0.365	0.707	0.425
LDL-C (mg/dL)	107.74 ± 6.81	104.50 ± 5.00	0.634	92.05 ± 5.99	98.00 ± 4.89	0.229	0.098	0.358
HDL-C (mg/dL)	45.45 ± 2.34	43.14 ± 2.31	0.068	45.77 ± 2.04	47.18 ± 2.35	0.260	0.919	0.227
HOMA-IR	4.15 ± 0.47	3.07 ± 0.35	**0.011**	3.15 ± 0.43	3.02 ± 0.33	0.553	0.125	0.922
QUICKI	0.31 ± 0.007	0.32 ± 0.005	**0.002**	0.32 ± 0.004	0.32 ± 0.005	0.982	0.083	0.867

Data are presented as mean ± SEM. Baseline and final values were compared with paired t-test. The differences between groups were assessed by Independent t-test. $P < 0.05$ was considered as significant. NEFA: non-esterified free fatty acid; TG; triglyceride; HOMA-IR: homeostatic model assessment for insulin resistance; QUICKI: quantitative insulin sensitivity check Index.

Table 3. Comparison of changes in various parameters (Diff) between groups

	Change in omega-3 group	Change in placebo group	*P*-value
Insulin (µIU/mL)	-2.17 ± 0.92	-0.09 ± 0.24	**0.035**
NEFA (ng/mL)	199.0 ± 113.94	-67.36 ± 122.14	0.11
TG (mg/100 mL)	-24.95 ± 13.39	9.09 ± 10.35	0.051
Total cholesterol (mg/dL)	-24.27 ± 11.92	-7.22 ± 7.80	0.238
LDL-C (mg/dL)	-2.90 ± 6.01	5.95 ± 4.80	0.256
HDL-C (mg/dL)	-2.31 ± 1.20	1.40 ± 1.21	**0.035**
HOMA-IR	-1.08 ± 0.42	-0.1306 ± 0.21	0.054
QUICKI	0.0143 ± 0.004	-0.000 ± 0.003	**0.009**

Data are presented as mean ± SEM. The differences between groups were assessed by Independent t-test. $P < 0.05$ was considered as significant. NEFA: non-esterified free fatty acid; TG; triglyceride; HOMA-IR: homeostatic model assessment for insulin resistance; QUICKI: quantitative insulin sensitivity check Index.

After 10 wks., there were no significant changes in HOMA-IR and QUICKI between the groups ($P = 0.92$, and $P = 0.86$, respectively). The mean difference between the two groups for HOMA-IR ($P = 0.054$) was marginally significant, and was significant for QUICKI ($P = 0.009$).

DISCUSSION

To our knowledge, this study represents the first analysis of the effect of omega-3 supplementation on NEFA in diabetic patients. The present study showed a detrimental effect of omega-3 on NEFA reduction. Previous studies explained that long time exposure to NEFA led to impaired insulin secretion and contributed to beta-cell dysfunction and death (10). Plasma NEFA found in obese individuals was increased compared with normal-weight individuals (11). Lipolysis led to an increment in plasma NEFA concentration, which caused insulin resistance in other tissues. Furthermore, even in healthy people, increased levels of plasma NEFA contributed to insulin resistance in the liver and skeletal muscles (12-15). Previous studies have shown that acute exposure to elevated plasma NEFA enhances glucose and non-glucose stimulated insulin secretion (16).

Acute elevations in plasma levels of long-chain fatty acids enhance plasma insulin levels by stimulating insulin secretion or by decreasing insulin clearance. In normal individuals, long-term increases of fatty acids also stimulate insulin secretion. Inversely, pre-diabetic subjects cannot properly compensate for the free fatty acids that induce insulin resistance (4). Our results are in line with those of Boden and cols., who showed that omega-3 supplementation in diabetic patients cannot induce insulin secretion. It seems that a longer period of supplementation may contribute to decreasing insulin clearance.

Bariatric surgery decreases NEFA levels in morbidly obese patients (17-19). Approximately two years after bariatric surgery in type 2 diabetic patients, beta-cell glucose sensitivity returned (20), and peripheral insulin sensitivity and beta-cell glucose sensitivity improved even before weight loss (21). Some studies showed glucose and lipid metabolism interactions (2,22). It seems that bariatric surgery causes improvement in beta-cell function and their glucose sensitivity by decreasing plasma NEFA levels (21). Omega-3 supplementation, in line with bariatric surgery, decreases NEFA levels in the omega-3 group. Although the present study did not show a correlation between NEFA modification

and glucose sensitivity, their changes were in the same direction.

We observed that insulin sensitivity increased significantly. It was formerly shown that, in early-onset of diabetes in rats, fasting plasma triglyceride decreases, fasting plasma NEFA increases, and fish oil or EPA administration diminish plasma NEFA concentration in type 2 diabetic rats (8). Exposure to high NEFA concentrations causes dysfunction in glucose-stimulated insulin secretion (23). *In vivo* studies have shown that insulin gene expression and insulin content decreased following an infusion of NEFA and glucose in rats (24). Hemodialysis patients with very low levels of NEFA at baseline showed no decrease in NEFA after receiving omega-3 (25). It seems that baseline levels of NEFA are the cause of differences between hemodialysis patients and diabetic subjects.

In previous studies, in subjects with normal triglyceride levels, NEFA decreased about 25% with fish oil supplementation (26). Subjects of the present study had normal TG and showed an 11% reduction in NEFA.

Moreover, in a previous study, 30 g/day fish oil reduced NEFA levels and TG while subjects had normal triglycerides at baseline (27). It is important to note that the subjects were healthy, and the omega-3 dosage was higher than that of our study.

Fish oil administration to high triglyceride, insulin-resistant, or obese patients showed different and inconclusive changes in TG and NEFA, depending on the study population (28,29). So far, studies have not approved the effect of omega-3 on NEFA, but the reduction in TG levels has been explained (30). Koh and cols. showed that consumption of 2g/d omega-3 fatty acids did not significantly change insulin and insulin sensitivity (determined by QUICKI) in hypertriglyceridemia patients (31). It is necessary to recall that QUICKI is influenced by glucose and insulin, which may not rise in hypertriglyceridemia patients.

In conclusion, our data suggested that omega-3 fatty acid supplementation decreases HOMA-IR and increases QUICKI, while NEFA decreases only insignificantly when compared with the placebo group.

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