

Effects of Omega-3 Supplementation on Blood Pressure in Patients with Type 2 Diabetes: A Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Objective: Type 2 diabetes mellitus (DM-2) is a chronic and progressive metabolic disorder known as a serious threatening condition in the individual and society. Type 2 diabetes mellitus is known as the major cause of cardiovascular diseases (CVD). Contradictory evidences about the effect of omega-3 fatty acids on CVD risk factors, particularly hypertension. The aim of this study was to determine the effect of omega-3 fatty acids supplementation on blood pressure in DM-2 patients.

Materials and Methods: This is a double-blind, placebo-controlled clinical trial on patients referred to Yazd Diabetes Research Center. Seventy DM-2 patients were randomly assigned to receive either 2 g/day omega-3 soft gels (OG) or 2 g/day placebo (PG) for 6 weeks. At the beginning and end of the study, blood pressure was measured and compared

Results: Fifty nine percents of patients in OG and 41% in PG had hypertension. Initially, there was no significant difference in the mean of age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and duration of diabetes between two groups. At the end of the study, the mean of SBP, DBP and differences between groups were not significant.

Conclusion: Consumption of 2 g/day omega-3 supplement for 6 weeks has no significant effect on systolic and diastolic blood pressure in DM-2 patients.

Keywords: Type 2 diabetes, Hypertension, Omega-3 fatty acids, Docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA).

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and progressive metabolic disorder introduced as the 21st century epidemic (1-3). The main concern about DM-2 is its worldwide rapid spread. In 2010, 285 million adults 20-79 years old affected and it is expected this number will reach over 400 million people by 2030. Between 2010-2030,

there will be 69% increase in the number of diabetic adults in developing countries and 20% in developed countries (4).

Among diabetes side-effects, CVD and renal vascular disease are the most important human sufferings (5) and in diabetic patients, the prevalence of CVD is 3 to 7 times higher than non-diabetics (6).

Hypertension is a major cause of CVD. In diabetic patients, it is approximately two times more prevalent (5). Approximately 600 million people in the world suffer from hypertension. About 5.7 million deaths occur due to hypertension or its complications in a year (7). According to American Diabetes Association (ADA), about 20-60% of diabetic patients have high blood pressure (8). A positive correlation between hypertension and CVD, stroke, heart failure, and kidney-failure exists (9). DM-2, known as multiple metabolic abnormalities, is associated with hypertension and thereby a two to four times increased risk of CVD (10-11).

There are considerable evidences about protective effects of dietary omega-3 fatty acids on CVD. Omega-3 fatty acid supplementation in non-diabetic patient is potentially effective on cardiovascular system (11-12). In previous studies an inverse relation between Polyunsaturated Fatty Acids (PUFAs) and blood pressure was found (13). In recent years, several researches concerning the effects of omega-3 PUFAs supplementation, especially docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) on blood pressure, in healthy individuals (14-15), diabetics (16) or other diseases (17-20) was performed and some others measured the effect of dietary omega-3 intake on blood pressure (12,15,21); But none of them identified the precise effects of PUFAs due to the limitations such as short duration, different doses of supplements and Differences in studied groups and other restrictions. This study aimed to investigate the effect of omega-3 PUFAs supplements on blood pressure in patients with DM-2.

Materials and Methods

Study Design and Participants

This study is a double-blind, controlled clinical trial, involved 70 DM-2 patients admitted to Yazd Diabetes Research Center. Inclusion criteria included age ≤ 60 years, diagnosed DM-2 at least four years, without

any kidney, liver, heart, thyroid or bleeding disorders, and malignancies, not taking omega-3 supplementation during recent month and without insulin therapy.

Although according previous studies, supplement dosage were between 200 mg/day to 6 g/day(22), considering the effective dosage, we intended 2 g/day in this study. Thereby Subjects were randomly assigned in to 2 groups: receiving either 2 g/day omega-3 soft gels (240 mg of DHA, 360 mg EPA, 100 IU vitamin E, 500 IU of vitamin A in per capsule) and 2g/day placebo (polyethylene glycol, PG). Time requires for the chemical effects of omega-3 supplementation is about 4 to 12 weeks (6), so our Intervention period was 6 weeks. Participants were asked not to change their physical activity, diet, routine medicine and lifestyle during intervention.

Measurements

General Information checklist included age, height, weight, occupation, duration of disease, type and dose of medicines were completed. The anthropometric measurements: weight was measured, by digital scale with accuracy of 100 g and the least coating and height by the stadiometer with accuracy of 0.5 cm was measured without shoes.

Calories and macronutrients intake and participants' dietary habits changes were estimated at the beginning and end of the study by 24-hours dietary recall questionnaire. Dietary data were analyzed by Nutritionist IV. Blood pressure was measured by a mercury sphygmomanometer in the right arm sitting position and after 5 minutes of rest. High blood pressure is defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or taking antihypertensive medication (23).

Those who consumed less than 80% of the capsules or changed their medications were excluded. Assessment of the rate of patients' compliance to the intake of capsules was performed by determining the number of capsules left at the end of the study.

Ethical Considerations

This project is approved by the University Research Ethics Committee (Trial Registration Number: IRCT2013011312122N1). Entering and leaving of the study was completely voluntary and written consent was obtained. All experiments were performed free of charge.

Statistical Analysis

Data were analyzed using SPSS software v.16. To assess the normality of data distribution, Kolmogorov-Smirnov test was used first. Then, Student t-test was used to compare mean of variables between the groups and paired t-test was used for within group comparison. P-value <0.05 was considered to be statistically significant.

Results

Sixty five out of 70 participants completed the study and 5 patients were excluded (Figure 1). Age, body mass index, SBP, DBP and duration of diabetes at the beginning of the study in both groups are shown in Table 1. According to independent t-test, no significant difference was observed in baseline variables. Daily intake of energy and macronutrients were estimated at the beginning and end of the study. No significant changes were observed

during the intervention. All patients consumed less than 2 serving of fish per day.

Fifty nine percent of the intervention group and 41% in the placebo group were diagnosed with hypertension. Mean of systolic and diastolic blood pressure at the beginning and end of study in intervention and placebo groups are separately shown in Table 2. According to Table 2, based on paired t-test, systolic and diastolic blood pressure in both groups, were not statistically significant before and after the intervention. Moreover if we classify patients based on blood pressure mean of systolic and diastolic blood pressure in intervention and placebo groups were not significant (Table 3).

Discussion

Results obtained from this study suggest that daily intake of 2 gr omega-3 capsules had not significant effects on systolic and diastolic blood pressure. The results of this study are confirmed by previous studies (16,24,25), but a number of studies have reported different results (15,20).

Woodman et al. conducted a double-blind crossover study on 510 diabetic patients with treated hypertension. 24-hours ambulatory blood pressure was measured.

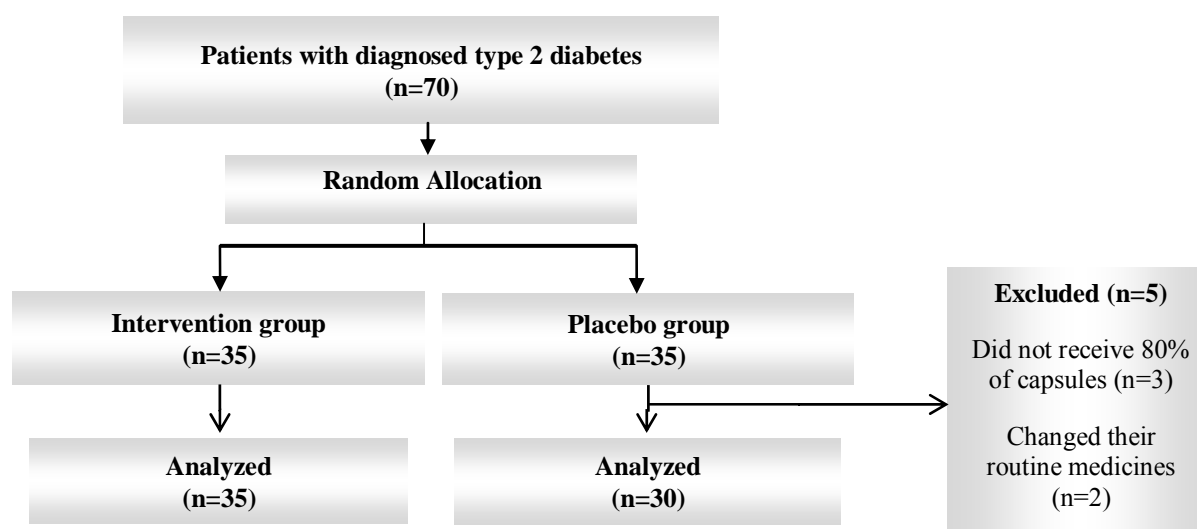


Figure 1. Study Flowchart, process of screening of selected patients

Table 1. Baseline characteristics of patients in test and placebo groups

Variable	Omega-3 group (n =35)	Placebo group (n =30)	P-value
	mean± SD	mean± SD	
Age(year)	48.51 ± 6.8	50.66 ± 6.62	0.17
BMI (kg/m ²)	28.16 ± 4.96	27.50 ± 4.63	0.62
Systolic blood pressure (mm Hg)	125.8 ± 15.75	128 ± 16.56	0.58
Diastolic blood pressure (mm Hg)	76.4 ± 9.76	77.9 ± 8.86	0.53
Diabetes duration (year)	6.48 ± 5.4	6.68 ± 5.31	0.8

Individuals were randomly assigned in to three groups, receiving one capsule, containing 4 g EPA, DHA, or olive oil (as placebo), once a day. After 6 weeks, no significant changes in 24-hour systolic and diastolic blood pressure between the intervention and placebo groups were observed and no significant differences between the groups in SBP or DBP during waking hours or during sleep (16).

Mori et al. designed a same randomized clinical trial on 56 men with moderate hyperlipidemia. 4 gr EPA or DHA (treatment group) or olive oil (placebo group) was consumed for 6 weeks. Results showed DHA decreased 24-hour blood pressure in awake time ($P < 0.05$), whereas EPA did not change in blood pressure (20).

In the prospective cohort study on 28,100 healthy U.S. women under 39 years old, during 9.12 years, was performed. After adjustment for demographic and dietary factors, there was no positive association between hypertension and dietary intake of omega-3 and omega-6 (24).

In another study (15) the relation between plasma levels of omega-3 fatty acids (DHA and EPA) and blood pressure was examined. Two hundred sixty five participants without

diabetes, cardiovascular, liver and kidney disease were participated. The main criteria for this study were untreated blood pressure below 180/110 mmHg. At the beginning and end of the study, systolic, diastolic and 24-hour ambulatory blood pressures were measured. Results indicated a modest inverse association between dietary intake of DHA, clinic and 24-hours ambulatory diastolic blood pressure.

Stirban et al. designed a randomized double-blind crossover manner. Thirty four patients with DM-2 consumed 2 gr/day purified EPA. DHA for 6 weeks. The results showed omega-3 supplementation reduced the postprandial macrovascular functions and improved postprandial microvascular functions. There was no effect on systolic and diastolic blood pressure (25).

In the most previous studies, high doses of purified omega-3 DHA and EPA were used (14,17,20); whereas foods and most of common supplements have less than this amount of DHA and EPA. Moreover, most studies were used olive, corn or sunflower oil as placebo which may be source of bias in results due to mono-unsaturated or polyunsaturated fatty acids and their beneficial effects.

Table2. Systolic and Diastolic blood pressure at baseline and after 6 weeks

Variable	Omega-3 group (n =35)	Placebo group (n =30)	P-value
	Mean ± SD	Mean ± SD	
Systolic blood pressure (mm Hg)			
Before intervention	128 ± 16.55	125.8 ± 15.66	0.58
After intervention	126.67 ± 14.0.77	124.84 ± 14.51	0.62
P-value	0.61	0.92	
Diastolic blood pressure (mm Hg)			
Before intervention	77.9 ± 8.86	76.43 ± 9.58	0.53
After intervention	73.87 ± 10.75	75.5 ± 10.59	0.62
P-value	0.77	0.22	

Table 3. Mean of systolic and diastolic blood pressure before and after the study, separately in patients with/without hypertension

variables	Number	Omega-3 group	Placebo group	P-value
SBP (mmHg)				
Before				
With	12	139.3 ± 8.49	137.9 ± 17.56	0.80
Without	23	118.7 ± 13.97	119.3 ± 9.49	0.88
After				
With	10	137.50 ± 14.19	133.43 ± 17.17	0.54
Without	22	119.09 ± 10.65	120.75 ± 9.27	0.62
DBP (mmHg)				
Before				
With	12	83.33 ± 8.33	82.78 ± 8.96	0.87
Without	23	72.82 ± 8.54	73.62 ± 6.36	0.88
After				
With	10	81.20 ± 10.21	80.57 ± 12.87	0.62
Without	22	72.90 ± 9.92	74.18 ± 7.59	0.66

In present study in order to eliminate the possibility confounding factors, an ineffective material—(polyethylene glycol- as placebo) was used.

Totally previous studies findings are parallel with our result. Effects of omega-3 fatty acids on blood pressure seems to be negligible, although it plays a preventive role in reducing the risk of Coronary heart disease.

Omega-3 polyunsaturated fatty acids effect on cardiovascular system through complex mechanisms such as: anti-inflammatory mechanisms, production of lipid mediators like prostaglandins and Lipoxin, cardiac ion channels modulation, triglycerides reduction and anti-thrombotic signaling pathways (12,13).

In some new studies, the results suggest a negative effect of omega-3 fatty acids specially high-doses (≥ 0.20 g omega-3/d or ≥ 2 servings of fish/d) in DM-2 (26). Therefore, to

determine the effectiveness of these fatty acids in diabetic patients, future studies are required. Also, the end products of lipid peroxidation such as MDA (Malondialdehyde) and TBARS (Thiobarbituric acid reactive substances) should be considered, because polyunsaturated fatty acids may cause accelerated lipid oxidation (27-28).

The main limitations of our study were short duration of intervention and low purified dose of omega-3 soft gels. To determine the pure effect and mechanisms of omega-3 fatty acids in DM-2, future studies with longer periods are needed.

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