Iran J Public Health, Vol. 45, No.11, Nov 2016, pp.1465-1472

Original Article

Various Effects of Omega 3 and Omega 3 Plus Vitamin E Supplementations on Serum Glucose Level and Insulin Resistance in Patients with Coronary Artery Disease

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(Received 14 Dec 2015; accepted 17 Jul 2016)

Abstract

Background: Omega 3 and vitamin E are two critical nutrients which include beneficial effects in coronary artery disease (CAD). The aim of this study was to assess the effects of omega 3 alone supplementation or in combination with vitamin E on serum glucose and lipid levels and insulin resistance in CAD patients.

Methods: Participants of this clinical trial included 60 male patients with CAD who selected from Tehran Heart Center in Tehran, Iran in 2014. They received 4 g/day omega 3 plus 400 IU/day vitamin E (OE), 4 g/day omega 3 with vitamin E placebo (OP), or omega 3 and vitamin E placebo (PP) for two months. Serum glucose, lipids and insulin were assessed and HOMA-IR was calculated before and after the trial and effects of these nutrients on the highlighted parameters were compared within the study groups.

Results: Serum glucose level increased significantly in OP group (P=0.004), but not in OE group. OE and OP groups showed a significant decrease in fasting serum TG (P=0.020 and P=0.001, respectively). Serum insulin and HOMA-IR decreased significantly in OE group (P=0.044 and P=0.039, respectively) but did not change significantly in OP group.

Conclusion: Although, omega 3 supplementation may include adverse effects on serum glucose level, co-administration of omega 3 and vitamin E can beneficially decrease serum insulin and insulin resistance in CAD patients.

Keywords: CAD, Omega 3, Vitamin E, Glucose homeostasis, Insulin resistance

Introduction

Cardiovascular disease (CVD) is the most common disease in developing countries. Nearly 23.6 million people will die from CVDs and coronary artery disease (CAD) will become the leading cause of death by 2030 (1, 2).

Hyperinsulinemia resulted from insulin resistance is a valuable prediction factor in CAD disease (3, 4). Insulin resistance can increase blood fibrinogen (5) and is closely associated with salt-sensitive type of hypertension in obese and non-

obese patients; and therefore, can increase individual vulnerability to cardiovascular diseases (6).

Changes in lifestyle and also consumption of some dietary supplements have a critical role in managing of many chronic diseases (7). For example, diets reduced in total fat can prevent CVD (8) and high levels of monounsaturated fatty acids (MUFA) and some polyunsaturated fatty acids (PUFA) can reduce the risk of CVD (9). Relatively, Mediterranean diets rich in fish oil and other marine sources of omega 3 fatty acids can decrease the risk of CHD mortality (10).

Omega 3 supplementation can improve endothelial function and decrease serum endothelial dysfunction markers such as E-selectin, I-CAM and V-CAM (11, 12). In some studies, consumption of omega 3 fatty acids was associated to increased risk of type 2 diabetes (13, 14); however, other studies did not show such an association (15, 16). Omega 3 supplementation has resulted in a significant decrease in insulin resistance in several studies (17). This decrease seems to be linked to changes in adiponectin (18) and also activation of AMPK pathway (19).

Vitamin E is an important nutrient and can develop beneficial effects in patients with heart diseases. This vitamin is an antioxidant and can possibly decrease oxidative stress. Vitamin E also is an anti-inflammatory agent and can decrease inflammatory factors such as IL-1β and IL-6 (20, 21).

Effects of omega 3 and vitamin E co-administration on insulin resistance and glucose homeostasis have been less described in previous studies. Therefore, the current study was carried out to assess possible effects of omega 3 alone and combined omega 3 and vitamin E supplementations on serum lipid profile and glucose homeostasis in CAD patients.

Methods

Sixty-five non-smoker male patients with CAD were participated in this randomized double-blind placebo-controlled clinical trial. All participants had at least 50% stenosis in one coronary artery and were selected from the Heart Medical Center of Tehran, Tehran, Iran. Participants signed an informed consent before the study. Furthermore, this study was registered in www.clinicaltrial.org under the registry number of NCT02011906 and approved by the Ethical Committee of Tehran University of Medical Sciences (ID: 23605).

All patients had BMI ≤ 30 and none of them had history of kidney and liver disorders, diabetes and thyroid malfunction. Patients were divided randomly into three groups including OP group received 4 g/day of omega-3 fatty acids and vitamin E placebo, OE group received 4 g/day of omega-3 fatty acid soft gels and 400 IU of vitamin E, and PP group received omega-3 fatty acids and vitamin E placebos. The contents of DHA and EPA in each gram of omega 3 soft gels were respectively 120 and 180 mg. Supplementation continued for eight months. Supplements and placebos used in this study were supplied by Minoo Pharmaceutical, Cosmetic and Hygienic Company, Iran.

Anthropometric measurements were carried out before and after the intervention. Weight was measured closely to the nearest 0.1 kg with minimal clothing and no shoes. Height, hip and waist circumferences were measured to the nearest 0.1 cm. BMI was calculated as the weight in kg divided by the square of height in meter. Waist to hip ratio (WHR) was calculated by dividing the circumference of waist to the circumference of hip.

Dietary information of the patients was obtained using a 2-day food recall filled before the beginning and after finishing off the intervention. Ten milliliters of blood were collected from the patients after 12 to14 h of overnight fasting. Then, serum samples were separated and stored at -80 °C until use. Fasting serum glucose, total cholesterol, HDL-C, LDLC and triglyceride concentrations were assessed using commercial kits (Pars Azmoon, Iran). Serum insulin was assessed using ELISA method (Diametra, Italy) with the sensitivity of 0.25 mcIU/ml and HOMA-IR was calculated by fasting glucose (mg/dl) multiplied by fasting insulin (μIU/ml)/405 (22).

Dietary data were analyzed using Nutritionist IV Software and statistical analysis was carried out using SPSS Software v18. All data were shown as mean ±SE (standard error) of the parameter. Normality of the parameter distribution was checked using Kolmogorov-Smirnoff test. One-way analysis-of-variance (ANOVA) test and paired t-test were used respectively to compare the mean of variables between and within the groups before and after the intervention. Significance was considered when *P*-values ≤ 0.05.

Results

At the beginning of the study, 65 male CAD patients were participated in the clinical trial. However, three patients were hospitalized for heart surgery during the intervention and two patients consumed less than 90% of the total supplements and hence, were excluded from the study. Therefore, the study was carried out with 60 patients, as 20, 21 and 19 patients were included in OE, OP and PP groups, respectively. Patients in these groups were not statistically different from each other in mean ages and disease duration at the baseline of the study (*P*= 0.079 and *P*= 0.299, respectively).

Table 1 describes the baseline anthropometric measurements of the three groups at the beginning of intervention. No significant differences were seen between the means of weight, BMI and other anthropometric parameters of the study groups at the baseline. Dietary intakes of the three groups are shown in Table 2. Food recall analysis of the patients revealed that no significant differences existed between energy and macronutrient intakes in OP, OE and PP groups at the baseline and at the end of the intervention. Furthermore, the intakes of vitamin E and different fatty acids were not different between study groups and they were not changed their routine dietary patterns during the intervention.

Table 3 demonstrates fasting serum levels and HOMA-IR index in the study groups at the baseline and at the end of the supplementation. Serum levels of FBS increased significantly in patients receiving omega supplement (*P*=0.004). The patients were not statistically different in mean FBS at the end of the intervention. OE and OP groups showed a significant decrease in fasting serum TG (*P*=0.020 and *P*=0.001, respectively). Serum TG did not change significantly in PP group. Serum level of insulin and HOMA-IR decreased significantly in OE group (*P*=0.044 and *P*=0.039, respectively), but not in OP or PP group. Furthermore, the means of serum insulin level and HOMA-IR were significantly different between the study groups at the end of the intervention (*P*=0.032 and *P*=0.023, respectively). Post-hoc analysis (Tukey Test) showed no significant differences between the mean of serum insulin level and HOMA-IR in OE and OP groups (*P*=0.029 and *P*=0.019, respectively). Serum levels of LDL, HDL and TC did not change significantly within or between the study groups. However, differences were not significant statistically after adjusting BMI and disease duration.

Table 1: Basic anthropometric parameters of the study groups before the intervention

Variable	OE (*n* = 21)	OP (*n* = 20)	PP (*n* = 19)	*P*-value*
Height (cm)	170.32 ±1.19	169.04 ±1.36	170.92 ±1.58	0.623
Weight (kg)	78.54 ±2.17	79.95 ±2.68	78.35 ±1.87	0.864
BMI (kg/cm^2)	27.08 ±0.70	27.95 ±0.83	26.85 ±0.61	0.530
Waist circumference (cm)	95.76 ±1.58	98.72 ±2.11	96.18 ±1.88	0.479
Hip circumference (cm)	100.33 ±1.15	101.12 ±1.59	99.63 ±0.80	0.701
WHR	0.95 ±0.01	0.97 ±0.01	0.96 ±0.01	0.463

OP, omega-3 fatty acid and placebo; OE, omega-3 fatty acid and vitamin E; PP, placebo and placebo; BMI, body mass index; WHR; waist to hip ratio; *ANOVA analysis

Table 2: Dietary intakes of the study groups before and after the intervention

Treatment group		OE (*n* = 21)	OP (*n* = 20)	PP (*n* = 19)	*P*-value*
Energy (Kcal)	Baseline	1469.10 ±93.33	1450.74 ± 114.37	1528.49 ±111.25	0.867
	Post-intervention	1649.48 ±122.47	1684.55 ±131.39	1508.20 ±130.59	0.596
	difference	180.38 ±162.53	233.81 ±169.99	32.36 ±173.82	0.688
	P-value#	0.281	0.185	0.854	
Carbohydrate (g)	Baseline	228.44 ±16.93	231.47 ±22.93	246.01 ±18.52	0.800
	Post-intervention	259.51 ±21.96	271.56 ±25.45	238.00 ±21.37	0588
	difference	31.06 ±25.68	40.09 ±26.02	-8.01 ±30.04	0.426
	P-value#	0.241	0.140	0.793	
Protein (g)	Baseline	69.64 ±8.76	62.25 ±7.75	62.27 ±7.71	0.770
	Post-intervention	66.16 ±6.98	60.44 ±5.74	59.30 ±6.49	0.722
	difference	-3.48 ±11.49	-1.81 ±10.58	3.42 ±10.64	0.992
	P-value#	0.765	0.866	0.751	
Fat (g)	Baseline	33.45 ±2.96	33.05 ±2.79	35.08 ±3.82	0.895
	Post-intervention	41.80 ±4.10	42.88 ±3.75	37.01 ±3.86	0.538
	difference	8.34 ±5.28	9.82 ±4.97	1.93 ±5.53	0.538
	P-value#	0.131	0.063		
Vitamin E (mg)	Baseline	2.72 ±0.74	2.70 ±0.55	2.29 ±0.65	0.427
	Post-intervention	4.04 ±0.97	4.19 ±1.04	2.77 ±0.45	0.311
	difference	1.33 ±1.35	1.48 ±1.29	0.48 ±0.78	0.971
	P-value#	0.338	0.265	0.456	
Omega-3 fatty acids (g)	Baseline	0.13 ±0.04	0.12 ±0.03	0.11 ±0.04	0.963
	Post-intervention	0.11±0.05	0.21 ±0.10	0.10 ±0.03	0.464
	difference	-0.01±0.06	0.09 ±0.11	-0.01 ±0.05	0.570
	P-value#	0.821	0.428	0.781	
Omega 6 fatty acids (g)	Baseline	10.80 ±1.17	11.47 ±0.93	10.89 ±1.76	0.926
	Post-intervention	13.58 ±2.15	13.76 ±1.95	12.87 ±2.19	0.148
	difference	2.78 ±2.59	2.29 ±2.21	1.98 ±2.91	0.534
	P. value#	0.380	0.273	0.506	
Saturated fatty acids (g)	Baseline	9.73 ±1.05	8.17 ±6.28	10.33 ±1.19	0.333
	Post-intervention	8.98 ±0.77	9.16 ±0.80	10.11 ±1.13	0.649
	difference	-0.75 ±1.28	0.99 ±1.07	-0.22 ±1.65	0.643
	P-value#	0.566	0.367	0.897	

OE, omega-3 fatty acid and vitamin E; OP, omega-3 fatty acid and placebo; PP, placebo and placebo; *ANOVA analysis; #paired T test

Discussion

In the current study, omega 3 supplementation alone or in combination with vitamin E significantly decreased serum TG levels in OE and OP groups. Supplementation with omega 3 fatty acids can include a dose-dependent effect on serum triglycerides and reduce its concentration up to 30% (23, 24). These fatty acids seem to be able to inhibit the production of TG and apolipoprotein B by the liver (25). Furthermore, these fatty acids can increase fatty acid oxidation by mitochondria (23). Serum glucose levels have increased significantly in patients receiving omega 3 supplements alone; however, the level was in normal range. This increase was not seen in OE group.

Table 3: Serum biochemical characteristics in the study groups before and after the intervention

Treatment group		OE (*n* = 21)	OP (*n* = 20)	PP (*n* = 19)	*P*-value*
FBS (mg/dl)	Baseline	92.19 ±3.27	87.75 ±3.25	89.32 ±4.78	0.697
	Post-intervention	89.38 ±2.32	99.13 ±3.78	94.5 ±3.53	0.108
	difference	2.81 ±3.79	11.37 ±3.46	4.74 ±4.13	0.034
	P-value#	0.264	0.004	0.267	
TG (mg/dl)	Baseline	185.48 ±17.39	180.38 ±18.02	174.53 ±19.41	0.914
	Post-intervention	145.38 ±9.44	131.28 ±14.53	154.58 ±19.87	0.458
	difference	-40.10 ±15.92	-49.10 ±12.25	-19.95 ±12.25	0.325
	P-value#	0.020	0.001	0.121	
TC (mg/dl)	Baseline	186.57 ±8.71	157.95 ±7.79	170.47 ±15.85	0.190
	Post-intervention	165.00 ±12.35	154.55 ±6.16	169.76 ±10.87	0.568
	difference	-21.57 ±16.04	-3.40 ±9.09	-0.71 ±13.69	0.484
	P-value#	0.194	0.713	0.959	
LDL (mg/dl)	Baseline	109.90 ±4.38	100.10 ±3.77	105.21 ±5.26	0.302
	Post-intervention	107.14 ±6.60	95.40 ±4.05	109.21 ±5.93	0.189
	difference	-2.76 ±7.43	-4.70 ±3.94	4.00 ±3.836	0.512
	P-value#	0.311	0.248	0.714	
HDL (mg/dl)	Baseline	34.35 ±1.92	31.30 ±1.66	34.42 ±1.89	0.394
	Post-intervention	37.14 ±2.38	35.55 ±1.62	37.95 ±1.95	0.702
	difference	2.73 ±2.03	4.25 ±2.21	3.52 ±0.97	0.854
	P-value#	0.120	0.065	0.182	
Insulin (µIU/ml)	Baseline	9.96 ±0.88	13.64 ±1.79	10.74 ±1.21	0.129
	Post-intervention	9.09 ±0.71	13.83 ±1.92	10.38 ±0.90	0.032
	difference	-0.86 ±0.40	0.185 ±1.35	-0.36 ±0.86	0.729
	P-value#	0.044	0.893	0.678	
HOMA-IR	Baseline	2.28 ±0.24	2.97 ±0.39	2.48 ±0.36	0.339
	Post-intervention	2.02 ±0.20	3.45 ±0.54	2.46 ±0.27	0.023
	difference	0.48 ±0.37	-0.25 ±0.12	0.02 ±0.25	0.142
	P-value#	0.039	0212	0.931	

OE, omega-3 fatty acid and vitamin E; OP, omega-3 fatty acid and placebo; PP, placebo and placebo; hsCRP, high-sensitivity C-reactive protein; *ANOVA analysis; #paired T test

Therefore, the question was if omega 3 fatty acid supplements could include adverse effects on glucose homeostasis. Effects of omega 3 fatty acids on serum glucose level have been conflicting in various studies. While, omega 3 supplementation was previously shown to adversely influence glucose homeostasis (26, 27), these fatty acids can increase glucose uptake and improve insulin sensitivity (28, 29). An experimental study on rats has demonstrated that consumption of fish oil can prevent insulin resistance induced by high-fat feeding (30). In contrast, results of the current study revealed that serum insulin level and HOMA-IR index did not change significantly in patients receiving omega 3 supplements only. Interestingly, these parameters decreased significantly in OE group. However, the mechanism for this is not clearly explained, it is possibly associated to use of vitamin E.

Vitamin E can improve glucose homeostasis because it can influence insulin sensitivity (31, 32). Indeed, oxidative stress is a key factor in development of insulin resistance and vitamin E with its ROS scavenger ability can positively affect

insulin action and glycemic control (33). Another mechanism, which links vitamin E to insulin resistance, is the anti-inflammatory property of this vitamin. Inflammatory cytokines such as TNF-α and IL-1β have been shown to induce insulin resistance. TNF-α can increase adipocyte lipolysis and serine/threonine phosphorylation of IRS-1 and IL-1β can increase CRP level via elevating IL-6 and impair signaling of insulin in peripheral tissues which can result in reduced insulin sensitivity and impair insulin secretion (34, 35). Both α and γ-tocopherol forms of vitamin E include anti-inflammatory effects and can reduce serum level of CRP (36).

Conclusion

Supplementation with combined omega 3 fatty acids and vitamin E includes beneficial effects on serum insulin level and HOMA-IR and co-administration of these supplements can be a good strategy against development of insulin resistance seen in CAD patients.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgments

This study was supported by Health Services grants from the School of Nutritional Science and Dietetics of Tehran University of Medical Sciences (ID: 23605). The authors declare that there is no conflict of interests.

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