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ADIPONECTIN AND GLYCEMIC PROFILES IN TYPE 2 DIABETES PATIENTS ON EICOSAPENTAENOIC ACID WITH OR WITHOUT VITAMIN E

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Abstract

Background. Secreting different adipocytokines, adipose tissue plays an important role in health and disease. Upon omega-3 consumption, changes in the secretion of adipose tissue and its effects on glycemic profile are a controversial subject at the present time.

Objectives. We evaluated the effects of eicosapentaenoic acid (EPA) alone and in combination with vitamin E on adiponectin and serum glycemic indices in type II Diabetes patients.

Design. This double-blind clinical trial divided all patients randomly into four balanced permuted blocks of EPA, Vitamin E, EPA and vitamin E and placebo (Corn oil).

Subjects and Methods. 127 patients with type II diabetes living in Kashan in 2008, 35-50 years old, and 25≤BMI ≤30 were enrolled. ELISA, Glucose Oxidase, spectrophotometry, and Radioimmunoassay methods were used for measurement of serum adiponectin, Fasting Blood Glucose (FBG), HbA1C, and Insulin, respectively.

Results. Serum adiponectin increased significantly after EPA consumption in EPA and EPA+E groups. Moreover, FBG, HbA1c, serum insulin and Homeostasis Model HOMA-IR decreased significantly after EPA consumption in the two previously mentioned groups.

Conclusions. This study showed that EPA supplementation affects the secretion of adipose tissue, improves the FBS as well as HbA1c values and significantly decreases fasting serum insulin and insulin resistance.

Key words: Adiponectin, vitamin E, Diabetes, Eicosapentaenoic Acid.

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INTRODUCTION

White adipose tissue (WAT) consists of vascular, nervous and adipose tissues with scattered macrophages, fibroblasts and series of cells that secret a number of adipocytokines such as leptin, adiponectin, resistin, tumor necrosis factor-alpha (TNF-α) and interleukin - 6 (IL-6) (1, 2). Overall, these adipocytokines affect health and play important roles in energy homeostasis, progression of insulin resistance, type II diabetes and hyperlipidemia (3-5). At present, studies point to the relationship between white mature adipose tissue as an important endocrine organ that secretes adiponectin (6, 7) and type 2 diabetes (4, 8-11). As white adipose tissue has a role in regulating the metabolism of lipids and carbohydrates (4, 12), changes in the expression of genes (13) that have a role in the secretion of cytokines will result in changes in weight, lipid and carbohydrate metabolism and the related diseases (14). However, changes in the secretion of adipose tissues after Omega-3 consumption and its effects on glycemic profile are of interest among researchers carrying out clinical trials on type II diabetes (15-18). Therefore, this research was done to evaluate the effects of Eicosapentaenoic Acid (EPA), as an Omega-3 fatty acid, with and without vitamin E on adiponectin and serum glycemic profiles in patients with type II diabetes mellitus.

MATERIALS AND METHODS

The study population consisted of 136 patients with type II diabetes mellitus recruited from the Diabetes Clinic affiliated to Kashan University of Medical Sciences in the first quarter of 2008. Being identified as a patient with diabetes one had to be treated by oral hypoglycemic agents or have a fasting plasma glucose concentration > 7.0 mmol/L.

The inclusion criteria included being 35-50 years old, male or female, with a BMI = 25-30 kg/m^2, having been diagnosed with diabetes for a duration of 2-15 years, having no recent (past year) digestive, renal, microalbuminuria (19), hepatic, cardiovascular, thyroid or respiratory diseases, or a diagnosis of cancer. Additionally, being non-alcoholic, non-smoker, and having no history of drug abuse, ongoing pregnancy or breast-feeding were the other criteria for inclusion in the study.

At the beginning of the study, we recruited 136 patients, but 127 patients completed the study successfully. Two subjects withdrew because of digestive intolerance to the supplements, two for unplanned journeys, two for incompliance to the program, one for appendicectomy, one for immigration and one subject could not attend the center for blood measurement in the final stage.

Study design

In this placebo-controlled, double blind study with parallel designs, subjects were randomly (balanced permuted blocks) assigned to one of four groups after signing an informed consent form. The individuals filled a demographic questionnaire and reported a 24-hour dietary recall. They reported

the dietary recall two more times during the study. Three 24-hour food recalls (on Sundays, Wednesdays and Fridays) were collected before and after the study.

The four groups included:

For every placebo group we prepared a Corn oil pearl in similar shape and dose. Therefore, when we were providing 2 grams of EPA, we provided a 2-gram Corn oil placebo pearl or when we were providing 400 units of vitamin E we provided 0.4 gram of Corn oil placebo pearl. Therefore, we had four groups consisting of:

(P) group = Receiving placebo or 2.4 grams of corn oil (2 grams of corn oil + 0.4 gram of corn oil);

(EPA) group = The EPA group receiving two grams of EPA supplement + placebo (0.4 g);

(Vit E) group = The vitamin E group receiving 400 IU of vitamin E supplement + placebo (2 g);

(EPA+Vit E) group = The EPA plus vitamin E group receiving two grams of EPA supplement + 400 IU of vitamin E.

The individuals were told to take the supplements postprandially (after lunch and dinner) without immediately drinking hot fluids. The regimen continued for 12 weeks, while the patients took their antidiabetic agents as before. The subjects were also recommended not to change their diet or their physical activity until the end of the study. The subjects' weight, BMI and blood pressure were measured and they were referred to laboratory at the beginning and at end of the 12th week. All the subjects were closely followed up every two weeks for weight, BP and BMI measurements and the way they were taking the supplements and continuing their routine diet and physical activity. They were also called/phoned/contacted for making sure they were following the recommendations throughout the study period. The patients' weight and height were measured by a Seca height and weight measuring scale (Germany, Seca GmbH & Co. KG) and BMI was calculated using weight/height m^2 formula. Tehran University of Medical Sciences supported the study and the respective Ethics Committee approved the study proposal.

Supplement characteristics

Plus EPA (500 mg) pearls containing pure EPA (99%) were obtained from Minami Nutrition, Belgium and Vitamin E pearls containing 400 IU of α-Tocopherol acetate (natural; d) from Dana Pharmaceutical Company in Tabriz, Iran. The placebo content (corn oil) was very similar to that of the participants' dietary regimen. All the supplements were conforming to ethical points of view in taking such substances.

Blood collection

From each participant, five milliliters of venous blood were drawn into empty and EDTA vacuum tubes after an overnight fast. Serum and plasma samples were stored at -70°C until assayed. Samples were protected from the natural light. To measure serum adiponectin concentration, ELISA kits (Ani biotech OY-ADIP025-Orgenium Laboratories Division-FINLAND) were used. FBS was measured by Glucose

Oxidase using Pars Azmoon Kit (Tehran-Iran). HbA1c concentration was assessed by kit (NYCOCARD - 1042184 - Rapid Diagnostic PVT.LTD - INDIA) and evaluated by a spectrophotometer. Insulin was measured by a Radioimmunoassay kit (Immunotech - Insulin (e) IRMA KIT IM3210-FRANCE). Insulin Sensitivity Index or Quicki was calculated by the following formula (20):

1/[log insulin (μIU/mL) + log glucose(ml/dL)]=InsulinSensitivityIndex

HOMA-IR was calculated by the following formula (21):

InsulinResistance=[FastingInsulin(μIU/ml) × Fasting Glucose (mmol/L)] / 22.5

Statistical analysis

The data were analyzed using SPSS (version 16.0 for Windows, Polar Engineering and Consulting, USA) by general linear models to assess the effects of EPA, E, or EPA+E relative to the placebo. All variables were tested for normality by using histograms and Kolmogorov-Smirnov statistics. If the data distribution was not normal, either before or after the intervention, they were log transformed for statistical analysis. We used paired t-test to evaluate any differences before and after treatment within groups. By the analysis of covariance (ANCOVA) was used to identify any differences in biochemical parameters between groups after intervention, adjusting for baseline measurements and covariates. We later used the Bonferroni test to evaluate the amounts of change in different layers of the variables to determine the mean amounts of change in the main group. Significance levels were adjusted for multiple comparisons by using Bonferroni method. Differences between the four groups were considered significant when $P<0.05$. All values were reported as means ± SEMs except for the demographic data of the patients at baseline, which are reported as means ± SDs or as percentage (%).

RESULTS

Study population

One hundred and twenty seven patients completed the study successfully without any changes in their diet or fluctuations in taking the

Table 1. Characteristics of participants in the four groups at baseline

Treatment group	EPA+E (n=34)	EPA (n=34)	E (n=32)	P (n=36)
Age (Y)	45 ± 4.3	44 ± 5.0	44 ± 4.4	45 ± 4.1
Gender (M/F) (%)	67/32	58/41	53/46	63/36
Weight (kg)	72.2 ± 7.8	74.4 ± 9.2	72.4 ± 9.6	70.5 ± 8.3
BMI (kg/m²)	28.0 ± 2.4	27.9 ± 1.7	27.7 ± 1.6	27.8 ± 1.6
Duration of diagnosed diabetes (y)	7.5 ± 4.2	7.4 ± 3.9	7.1 ± 3.5	8.3 ± 3.9
Mean Blood Pressure (mmHg)	90 ± 6.1	89 ± 6.3	86 ± 6.2	90 ± 7.1
Pulse pressure (mmHg)	41 ± 10	41 ± 7	42 ± 10	42 ± 12

$\bar{x}$ ± SD or %. There were no significant differences between the four groups at baseline (by UNIANOVA).
Chi- square test was used to detect differences in gender profile between the groups. [EPA = Eicosapentaenoic acid; E = Vitamin E].

supplements. Baseline characteristics of the four groups confirmed that they had been well-matched for the entry criteria shown in Tables 1 and 2.

There were no significant differences between the groups in either the type or number of oral hypoglycemic medications (for the type of oral hypoglycemic medications we used Chi-squared distribution; for the number of oral hypoglycemic medications we used ANOVA test). The subjects also took oral hypoglycemic agents in the form of biguanides with (and) sulfonylureas (76%), sulfonylureas (16%) or biguanides agents (8%). Antidiabetic agents were taken unchanged during the intervention in all groups.

Table 2. Total energy and macro and micronutrient intakes at baseline and post intervention after 3 months in the four groups

Treatment group		EPA+E (n=34)	EPA (n=34)	E (n=32)	P (n=36)
Total energy intake (kcal/d)	Baseline	1656 ± 372	1616 ± 336	1764 ± 403	1793 ± 395
	Post intervention	1635 ± 292	1653 ± 373	1742 ± 428	1838 ± 409
Total fat (g/d)	Baseline	64 ± 15	63 ± 19	70 ± 18	70 ± 18
	Post intervention	68 ± 20	62 ± 18	70 ± 21	68 ± 21
Saturated fat (g/d)	Baseline	21 ± 7	20 ± 7	22 ± 9	22± 9
	Post intervention	21 ± 6	21 ± 6	23 ± 8	22± 7
Monounsaturated fat (g/d)	Baseline	19 ± 5	18 ± 6	21 ± 5	21± 5
	Post intervention	20 ± 6	18 ± 5	21 ± 7	21± 7
Polyunsaturated fat (g/d)	Baseline	19 ± 5	19 ± 8	23 ± 8	23 ± 8
	Post intervention	21 ± 9	19 ± 9	21 ± 7	20 ± 8
Cholesterol (mg/d)	Baseline	206 ± 106	195 ± 113	216 ± 123	200 ± 112
	Post intervention	232 ± 111	184 ± 78	213 ± 124	192 ± 105
Protein (g/d)	Baseline	60 ± 15	56 ± 13	60 ± 18	62 ± 18
	Post intervention	64 ± 13	56 ± 11	66 ± 19	64 ± 17
Carbohydrate (g/d)	Baseline	220 ± 66	215 ± 47	241 ± 73	239 ± 67
	Post intervention	229 ± 55	218 ± 50	239 ± 64	243 ± 60
Fiber (g/d)	Baseline	15 ± 5	16 ± 6	17 ± 6	17 ± 6
	Post intervention	17 ± 6	15 ± 5	17 ± 7	18 ± 6
Vit A (mcg/d)	Baseline	1073 ± 1365	844 ± 587	1165 ± 1364	890 ± 637
	Post intervention	981 ± 652	809 ± 545	1100 ± 679	974 ± 624
Vit E (mg/d)	Baseline	13 ± 5	14 ± 6	17 ± 9	17 ± 9
	Post intervention	15 ± 8	14 ± 9	17 ± 8	16 ± 9
Vit C (mg/d)	Baseline	99 ± 58	58 ± 38	86 ± 66	82 ± 57
	Post intervention	97 ± 53	68 ± 51	84 ± 68	83 ± 64
Selenium (mcg/d)	Baseline	121 ± 43	120 ± 41	128 ± 46	131 ± 42
	Post intervention	132 ± 34	114 ± 43	125 ± 40	123 ± 34
Fe (mg/d)	Baseline	11 ± 2	10 ± 2	11 ± 2	12 ± 3
	Post intervention	11 ± 2	10 ± 2	10 ± 2	11 ± 3
Zinc (mg/d)	Baseline	8 ± 3	8 ± 2	8 ± 2	8 ± 2
	Post intervention	9 ± 2	8 ± 2	9 ± 2	8 ± 2

Mean ± SD. Baseline and Post intervention measures were compared by paired t-test (within groups) and between groups by UNIANOVA. There were no significant differences between the groups in any of the dietary nutrients at baseline and no significant changes during the intervention. [EPA = Eicosapentaenoic acid; E = Vitamin E].

Energy and macronutrient intakes

Evidence of adherence to the diets was confirmed by analyzing the diet recall records and supplement counts.

Analysis of diet records indicated that total energy and major macronutrient and micronutrient intakes were not significantly different between the groups at baseline (Table 2) and did not change significantly in any of the groups during the intervention.

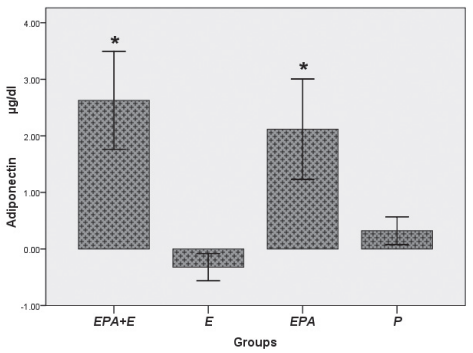

Figure 1. Effects of Eicosapentaenoic Acid supplementation with or without Vitamin E on serum Adiponectin concentration in Patients with Diabetes Type II before and after three months. P<0.01*.

Serum Adiponectin and glycemic indexes measurements

There were no significant differences either among the mean concentration of adiponectin, FBS, HbA1c, insulin, Quicki index and HOMA-IR or in the duration of diabetes diagnosis at the beginning of the study.

In comparison with baseline concentrations, serum adiponectin had a significant increase of 23.6% and 18.1% after intervention in both groups of EPA+E and EPA groups respectively (Table 3, Fig. 1).

A meaningful difference in serum adiponectin concentration was noted among the study groups after omitting the variables BMI (baseline and after intervention), PUFA intake, fasting insulin, leptin and the baseline ADP level after 3 months. The difference in EPA+E and EPA group, respectively,

Table 3. Fasting serums Adiponectin, FBG, HbA1c, Fasting Insulin, Quicki Index and HOMA-IR at baseline and post intervention in the four groups

Treatment group		EPA+E (n=34)	EPA (n=34)	E (n=32)	P (n=36)
Adiponectin(µg/dL)	Baseline	11.0±3.4	12.1±4.1	11.3±3.8	10. 2±4.4
	Post intervention	13.7±4.0*	14.4±3.7*	11.1±3.8	10.5±3.9
FBG(mg/dL)	Baseline	165.0±52.6	146.5±38.7	140.9±35.1	187.0±58.1
	Post intervention	154.9±45.9	127.0±31.9*	177.0±61.7*	191.7±41.6
HbA1c (%)	Baseline	9.0±1.3	8.9±1.3	9.0±1.3	8.9±1.8
	Post intervention	8.4±0.7*	8.1±1.2*	9.2±1.4	9.1±1.7
Insulin(µUI/mL)	Baseline	7.0±4.0	7.3±6.0	5.5±3.9	5.3±3.1
	Post intervention	5.4±3.7*	6.7±5.3	5.8±4.0	6.8±4.6*
Quicki index	Baseline	4.0±2.2	3.5±2.1	4.2±3.5	4.1±1.7
	Post intervention	3.6±6.6	3.5±3.1	4.2±4.5	3.8±2.9
HOMA-IR	Baseline	2.8±1.5	2.7±2.1	1.9±1.5	2.4±1.7
	Post intervention	2.1±1.8*	2.1±1.7*	2.4±1.7*	3.1±1.9*

Mean ± SD. There were no significant differences between the 4 groups at baseline (by UNIANOVA).
*Significantly different from before and after treatment (by paired t-test) within groups: P < 0.01. [EPA = Eicosapentaenoic acid; E = Vitamin E; FBG = *Fasting Blood Glucose.*

included an increase of 30.4% and 37% in comparison with Placebo group and 23.4% and 29.7% in comparison with E group (Table 3).

Serum FBS concentration decreased 13.3% in EPA group in comparison with its baseline after 3 months of intervention. A meaningful difference was also noted among the study groups in serum FBS serum concentration after omitting the effects of variables BMI, energy, carbohydrate, fiber and PUFA intake, in comparison with baseline FBS after the months of intervention. The difference in EPA group included a decrease of 33.7% in comparison with the Placebo and 28.2% in comparison with E groups (Table 3).

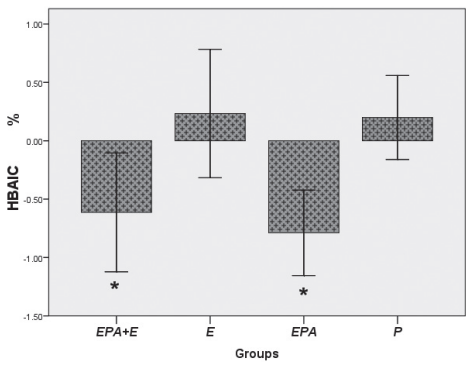

Figure 2. Effects of Eicosapentaenoic Acid supplementation with or without Vitamin E on serum HbA1c concentration in Patients with Diabetes Type II before and after three months. P<0.01*.

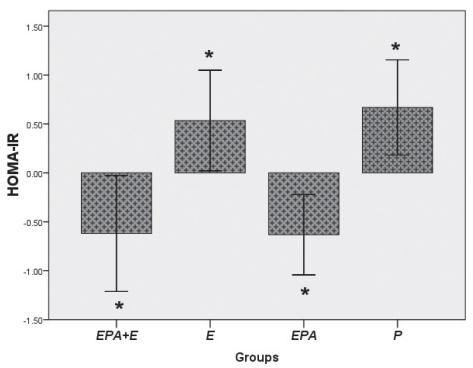

Figure 3. Effects of Eicosapentaenoic Acid supplementation with or without Vitamin E on HOMA-IR index in Patients with Diabetes Type II before and after three months. P<0.01*.

HbA1c decreased 6.6% and 7.8% in EPA+E and EPA groups, respectively, in comparison with the baseline values after three months (Fig. 2). A meaningful difference was seen in HbA1c concentration after omitting the baseline level at the end of the study. The difference in EPA+E and EPA groups included, respectively, a decrease of 83.6% and 11.6% in comparison with E group (Table 3).

Serum fasting insulin concentration decreased 22.8% in EPA+E group in comparison with its baseline levels after three months of intervention. A meaningful difference was seen in serum fasting insulin concentration after omitting the effects of BMI, waist hip ratio (WHR), and the baseline fasting insulin levels after the study period. The difference in EPA+E and EPA groups included a decrease of 20.5% and 1.4%, respectively, in comparison with the Placebo group (Table 3).

A meaningful difference was seen in Quicki index after omitting the effects of variables BMI, WHR, ADP, and the baseline Quicki index after three months of intervention. The difference in EPA+E and EPA groups included an increase of 7.8% and 5.2%, respectively, in comparison with the Placebo group (Table 3).

HOMA-IR index had a decrease of 21.4% and 22.2% in EPA+E and

EPA groups and an increase of 25 % and 21.4% in E and Placebo groups, respectively, in comparison with their baseline concentrations after the study (Fig. 3). A meaningful difference was noted in HOMA-IR index after omitting BMI, WHR, ADP, and the baseline HOMA-IR index after the study. The difference included a decrease of 32% in EPA+E and EPA groups in comparison with the Placebo group (Table 3).

We also measured changes in BMI, Waist Hip Ratio (WHR) and the participants' weight and found that in groups on EPA supplementation, weight and BMI had decreased, respectively, 1.9% (P<0.001) and 0.9% (P=0.05) but WHR did not undergo significant changes.

DISCUSSION

As we aimed to evaluate the effects of omega 3 fatty acid on the secretion of adipose tissue and also its effect on metabolism of sugars and lipids in patients with diabetes and some studies had shown the unpredictable effects of compounds containing omega 3 in predisposing the subjects to lipid peroxidation in aerobic conditions. This has been reported to happen in the absence of antioxidants. On the other hand, some studies have pointed out that the PUFAs themselves could act as antioxidants under *in vivo* conditions if they are taken with sufficient amounts of vitamin E; therefore, under this condition, the first reactive oxygen species scavenging system operates (22-24). On these grounds, while we were administering vitamin E, we evaluated this effect in some of the groups and in addition to measuring vitamin E, we also measured the total serum antioxidants and antioxidants such as glutathione peroxidase, glutathione oxidase, catalase, superoxide dismutase and also malondialdehyde and protein carbonyl levels as biomarkers for oxidative stress (25).

After three months of intervention, significant increases in serum adiponectin (ADP) concentration in EPA supplemented groups were similar to those observed by Fernández R. *et al*. (26) and reported by Havel *et al*. (27) by consumption of fish oil. Flachs *et al*. showed that ADP gene expression was stimulated by dietary EPA; hence, the serum concentrations of the substance increased (28).

Although Perez *et al.* believed that serum leptin concentration was related to intake of EPA containing foods and it had no effects on serum ADP serum concentration. Nevertheless, if the same amount of EPA intake (2 grams) is adjusted for adiposity (adiponectin concentration per content of white adipose tissue in grams), we will notice a remarkable rise in serum adiponectin concentration following daily consumption of 2 grams of EPA (P=0.05) (29). However, a different study on patients with nonalcoholic steatohepatitis (NASH) showed no difference in serum level of ADP using 2.7 g EPA for a year (30). In our study, the increase in serum ADP serum concentration could be due to administration of 2 g of EPA for three months.

Researches showing positive

results regarding control of glycaemia by the use of EPA are increasing in the literature. Mori *et al*., showed that a dietary intake of fish improves the metabolism of glucose and insulin (31). Hide Fumi *et al*. observed a decrease in FBS concentration as well as an improvement against insulin resistance following intake of EPA in diabetic rats (32). Even the results of a meta-analysis showed a negative meaningful relation between fish consumption and the incidence of diabetes type II (33). Tanaka *et al*. observed improvement in insulin sensitivity without any changes in glucose concentration or insulin resistance in patients with NASH on EPA(30); in another study no difference in FBS concentration of obese women on omega-3 supplement was observed (34). A research by Dunstan showed that daily intake of fish for two months led to the disorders in controlling glucose but if concurrent exercise could control it (35). In another study, Trevor *et al*. observed that taking 4 g EPA increased FBS significantly in patients with diabetes type II and hypertension (36). The initial reports showed that the increase in serum glucose and HbA1c concentrations were accompanied by high intakes of fish oil (10 g or more daily) which is consistent with other studies with various amounts (3.3g, 5.5g, and 10g) of EPA and docosahexaenoic acid (DHA) intake in different societies following worries about omega-3 in increasing the glycemic profiles (37-41). While most of those studies were based on 1-2 g doses, not only the intervention showed no undesirable effect on glycemic profile but it also improved it (42). In the present study in which 2 g of pure EPA was used, glycemic profile improved in the patients, which is in consistency with other studies (42). EPA also decreases the deposition of fatty acids in skeletal muscles and β cells of the pancreas; therefore, it decreases the insulin resistance and finally leads to the control of serum glucose concentration (32). As the placebo group did not have any intervention compared to their pre-study period and this could be the reason why patients with diabetes should not only be cared for their diet, but also for supplements, or even EPA supplement for the better control of their blood sugar. Mori *et al*. indicate that a combination of food regimen containing fish and dieting could improve glucose and insulin metabolism (31). Administering EPA, Morishita found that reduction of plasma insulin and blood sugar and increased sensitivity to insulin were so prominent that he suggested in conjunction with medications, diet and physical activity in patients with type 2 diabetes (43). As the placebo group in his study had had an omega-3 deficient and they were instead supplemented with omega-6, the glucose metabolism indicators not only have not improved, but also they have increased instead. Moreover, research on mice indicates that consumption of corn oil results in increases in weight, total body fat, total abdominal fat and cytokines such as Interleukin 6 and TNF-α, which both are among the substances to increase blood sugar and enhance insulin resistance (33). As Shab-Bidar *et al.* and Ford ES have previously stated there is some discrepancy among the results of association studies, which

have reported mixed findings regarding blood concentrations of vitamin E and the incidence of diabetes (44, 45). Similarly, there is no consistency between clinical trials, with some reporting possible beneficial effects of vitamin E supplementation in diabetic patients and others not (45, 46). The findings of previous studies suggest that vitamin E has a beneficial effect only among people who do not use dietary supplements regularly and obtain their vitamins from the nutritional intake of food (47), as well as in those who suffer from particularly high levels of oxidative stress and/ or have poor vitamin E status (47). As Shab-Bidar *et al*. have previously stated it seems that the use of pharmacological doses of vitamin E does not confer additional benefits and has little clinical significance (44).

In conclusion, EPA is a food supplement that could be taken safely with blood glucose lowering drugs in patients with diabetes type II. It provides the kind of fatty acid whose absence plays an etiologic role in diabetes and related diseases.

Conflict of interest

We declare that there is no conflict of interest.

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