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Effects of Fish Oil on Cytokines, Glycemic Control, Blood Pressure, and Serum Lipids in Patients with Type 2 Diabetes Mellitus

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Abstract

Objective: We examined the ability of dietary fish oil to suppress markers of inflammation and consequent effect(s) on serum fasting glycemia, lipids, and blood pressure in patients with T2DM.

Design: Correlations between serum fasting interleukin-6, Interleukin-1β (IL-1β), TNF-α (TNF-α), C-reactive Protein (CRP), and sialic acid, with indices of glycemia, insulin, and lipids were determined in 26 patients with T2DM at baseline, 4 weeks and 8 weeks after supplementation with fish oil (3 g/d) to analyse possible correlations between markers of inflammation and indices of glycemia.

Results: There were no significant correlations between markers of inflammation with indices of glycemia at baseline, 4 weeks and 8 weeks after fish oils supplementation. Serum CRP concentrations were negatively correlated with fasting serum LDL, and with Cholesterol (r=-0.424, P<0.04; r=- 0.447, P<0.03, respectively). Fasting IL-1 β concentrations were positively correlated with fasting LDL, and with cholesterol at week 4 (r=0.482, P<0.02; r=0.469, P<0.02, respectively). There were no significant correlations between serum lipids with markers of inflammation at the end of intervention. There were no significant changes in serum fasting insulin, and glucose concentrations at the end of the intervention.

Conclusions: A moderate dose of fish oil did not lead to deleterious effects on glycemic control in patients with T2DM, with preserved triacyglycerol-lowering capacities.

Keywords: Eicosapentaenoic acid; Docosahexaenoic acid; Type 2 Diabete; Fish oil; Glucose; Blood pressure; Lipids; Omega-3 fatty acids; Inflammation; Cytokines

Introduction

Type 2 Diabetes Mellitus (T2DM) may represent a disease of the innate immune system responsible for an ongoing cytokine-mediated acute phase response [1]. In a prospective study two circulating markers of systemic inflammation, C-reactive Protein (CRP) and Interleukin-6 (IL-6), were determinants of risk for development of T2DM in apparently healthy middle-aged women [2]. Moreover, several studies have demonstrated elevated concentrations of IL-6 and Tumour Necrosis Factor-α (TNF-α) among individuals both with Impaired Glucose Tolerance (IGT) and with clinically overt T2DM [3,4]. TNF−α produces insulin resistance by inhibiting insulin receptor and Insulin Receptor Substrate-1 (IRS-1) tyrosin phosphorylation, leading to an impairment in phosphoinositol-3 kinase activity [5,6]. Experimental and clinical studies provide evidence of anti-inflammatory effects of Eicosapentaenoic (EPA; 22:5 omega-3) and Docosahexaenoic (DHA; 22:6 omega-3) fatty acids from fish oil [7,8]. We hypothesized that suppression of inflammatory cytokines may exert beneficial effects on serum lipids and glycemia in patients with TD2M. Fasting serum IL-6, IL-1 β, CRP, TNF-α, and sialic acid were measured and correlations with glycemia indices and serum lipids were analysed.

Subjects and Methods

A total of 26 men and postmenopausal women aged 52 ± 1.2 y who had T2DM (as defined by being treated with oral hypoglycemic medications or having a fasting glucose concentration >7.0 mmol/L or a non fasting glucose concentration >11.1 mmol/L), were recruited. The inclusion criteria were 1) known T2DM for >2 years, 2) diabetes onset >30 years of age, 3) no use of dietary supplements with fish oil, 4) no alcohol intake, 5) Body Mass Index (BMI) (in kg/m^2) <35, and 6) not receiving insulin therapy.

All patients who had suffered recent history (within one year) of heart disease, angina, or myocardial infarction or stroke; had significant liver or renal disease or regularly used nonsteroidal anti-inflammatory drugs were excluded. Cases of asthma, emphysma, rheumatoid arthritis, chronic bronchitis, periodontal disease, infectious disease and colds in recent days were excluded. Patients who were taking lipid-lowering drugs, aspirin, or antioxidant vitamins were excluded. Patients on other non-lipid lowering medications beta blockers, Angiotensin Converting Enzyme (ACE) inhibitors, calcium channel blockers, oral hypoglycaemic agents, as well as other medications were excluded. All of patients gave their informed consent to take part in the trial which was approved by the ethical committees of Shaheed Beheshti University of Medical Sciences. All patients completed the study.

Study design and interventions

Baseline measurements were collected during a 3-wk period. Fasting blood samples were collected from each patient at week 4 and at the end of week 8. We advised subjects to keep their level of physical activity and dietary habits, especially oily fish intake as well as other lifestyle factors, constant during the study. During an 8-week run-in phase, all subjects took 3 softgels containing 3000 mg fish oil (900 mg

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EPA and 600 mg DHA). The softgels, which contained 4 I.U. Vitamin E, were provided by the All Nature Pharmaceuticals, Inc, USA. There were only negligible amounts of gelatin, glycerin and purified water. Compliance was assessed by softgels counts and periodic telephone or personal contact.

Nutritional methods and lifestyle assessment

Before the baseline period, a dietician gave verbal instructions to the subjects on how to keep accurate dietary records, including how to weigh or measure foods. Six days of dietary data were collected at each interview (four 24-hour recalls at the interview and two days of food records that had been kept before the interview) and a lifestyle questionnaire including history of illness, supplements intake, medications, anthropometric measurements, demographic information and physical activity were completed at baseline, week 4 and week 8. Waist-to-hip ratio was calculated as the body circumference midway between the inferior border of the rib cage and the superior border of the iliac crest, divided by the maximal body circumference at the buttocks [9]. The Nutritionist IV (version 4; N-Squared Computing, San Bruno, CA) computer program was used to transform data and calculate EPA and DHA intake and to determine mean daily nutrient intakes**.** Weight, dietary intake, changes in physical activity and medication, and any illness were recorded each week during baseline and at weeks 4, and 8 of the intervention. Blood pressure was measured to within 2 mm Hg, with the patient semirecumbent after resting for five minutes, using a mercury sphygmomanometer.

Blood biochemistry

Serum glucose was determined according to the glucose oxidase method with an autoanalyzer (Beckman Instruments). Serum insulin concentrations were determined with ELISA (Monobind Inc, USA). Cholesterol and triacylglycerol concentrations were measured after an overnight fast by the CHOP-PAP method and GPO-PAP method respectively (both supplied by Roche Diagnostics, Lewes, UK). HDL cholesterol concentrations were measured after precipitation with phostungstic acid/Mg^{2+} (Roche Diagnostics), while LDL cholesterol was calculated as follows: LDL=TG–(HDL + TG/5) [10]. QUIKI was assessed as: 1/[log fasting insulin (m U/ml)+log fasting glucose (mg/100 ml)] [11].

Characteristic	
n	26
Sex (F/M)	10/16
Age (years)	52.7 ± 9.2
Duration of diagnosed diabetes (y)	9 ± 6.0
BMI (kg/m^2)	27.32 ± 2.9
Waist-to-hip ratio	0.88 ± 0.07
Fasting glucose (mmol/L)	9.5 ± 3.00
Blood Pressure(mmHg) Systolic Diastolic	 122 ± 14 76 ± 15
Serum lipids (mmol/L) Cholesterol LDL cholesterol HDL cholesterol Triacylglycerol	 5.26 ± 0.82 3.22 ± 0.70 1.23 ± 0.28 1.77 ± 0.93
Dietary variables Energy (kcal) Total fat* Monounsaturated fatty acids[1] Polyunsaturated fatty acids[1] Alcohol* P: S ratio† Cholesterol (mg/day)	 6570 ± 2030 28.90 ± 2.90 8 9.2 0 0.71 230 ± 150

Data are means ± SDs or n.
* % energy
† Polyunsaturated to saturated fatty acid ratio.

Table 1: Characteristics of the diabetic patients at baseline.

Analysis of acute-phase proteins and cytokines

Serum samples for cytokine concentrations were stored at -70°C until assay. Serum concentrations of TNF–α, IL-1 β, IL-6, and CRP were determined in duplicate by Instant ELISA (Bender MedSystems, Vienna, Austria and DCB-Diagnostics Biochem Canada Inc, for CRP). All instant ELISAs were established to meet the following criteria: linearity of signal for the standard curve between Optical Density (OD) 0.05 and 2.0 , difference between expected and measured signal in spiking experiments less than 10%, mean intra-assay variation below 10%, mean interassay variation below 10%, loss of signal after freezing and thawing of sera three times less than 10%. Dilution curves of serum samples were parallel those of standard. Intra-assay and interassay coefficients of variations were 5.3% and 4.2%, respectively, for TNF–α; 5.1% and 4.3%, respectively, for IL-1 β; 4.2% and 3.2%, respectively for IL-6 and 5.1% and 3.1%, respectively, for CRP.

Serum sialic acid determination was performed as previously described [12]. Samples from baseline, week 4, and at the end of the intervention were measured in a single assay to minimize interassay variation.

Statistical analysis

Data were analysed by using SPSS version 12.0 (SPSS Inc, Chicago). The normality of all variables was assessed by examining their histograms and using Kolmogorov-Smirnov test. No significant deviation from normality was observed among data either before or after the intervention. Significance levels were adjusted for multiple comparisons by using the Bonferroni method. All values are reported as means ± SEs except for the characteristics of the patients at baseline, which are reported as means ± SDs. Repeated-measures analysis of variance comparing the variables between two sexes and different time points of the intervention were performed using SYSTAT 10 (SPSS Inc, Chicago). All tests were two-tailed and P-values less than 0.05 were taken as significant. The correlations between variables were examined by Pearson correlation linear regression, by using the SYSTAT program.

Results

Study population

All subjects completed the study. The characteristics of the patients are shown in Table 1. None of the subjects was taking antihypertensive medications or oral hypoglycemic agents.

Diet, lifestyle, and blood pressure

There were no significant differences in total energy intake, EPA/DHA intake, polyunsaturated to saturated fatty acid (P:S) ratio, and macronutrient intake at baseline, week 4 and week 8 in the control and the intervention group (data not shown). Alcohol intake and physical activity remained unchanged during the study. There were no significant differences in mean BMI at baseline, week 4 and week 8. Systolic blood pressure at the end of the intervention was decreased by 8% (113 ± 4.0 vs. 122 ± 2.0 mmHg, P<0.001). Diastolic blood pressure decreased by 1.2 % (75.30 ± 2.0 vs. 76.2 ± 3.0 mmHg, NS).

Serum glucose, fasting insulin, and QUIKI

There were no significant differences between males and females

Fasting glucose (mmol/L)	
Baseline	9.56 ± 0.63
Week 4	10.02 ± 0.64
Week 8	9.28 ± 0.66
Fasting insulin (pg/ml)	
Baseline	58.75 ± 9.60
Week 4	67.55 ± 10.90
Week 8	77.90 ± 17.00
Fasting insulin/glucose*	
Baseline	6.50 ± 0.90
Week 4	7.40 ± 1.30
Week 8	10.50 ± 3.60

Data are means ± SEs (n=26), Repeated measurements ANOVA was used to compare baseline, week 4, and week 8. None of the comparisons were significant. *pg/ml to mmol/L ratios.

Table 2: Fasting glucose, and insulin concentrations, and insulin/glucose ratios at baseline, week 4 and week 8.

Cholesterol (mmol/L)	5.26 ± 0.16*
Baseline	
Week 4	5.09 ± 0.15**
Week 8	4.95 ± 0.16***
Triacylglycerols (mmol/L)	1.77 ± 0.18****
Baseline	
Week 4	1.40 ± 0.09
Week 8	1.43 ± 0.11†
LDL cholesterol (mmol/L)	3.22 ± 0.13
Baseline	
Week 4	3.14 ± 0.13
Week 8	3.11 ± 0.13
HDL cholestrol(mmol/L)	1.23 ± 0.05
Baseline	
Week 4	1.28 ± 0.04
Week 8	1.20 ± 0.03††
LDL/HDL	
Baseline	2.74 ± 0.16
Week 4	2.52 ± 0.14
Week 8	2.64 ± 0.13
Chol/HDL	4.44 ± .20†††
Baseline	
Week 4	4.05 ± .17††††
Week 8	4.20 ± 0.17‡

Data are means ± SE (n=26)
*P<0.02 (Baseline vs. wk 8)
**P<0.001 (Baseline vs. week 4)
***P<0.001 (Week 4 vs. week 8)
****P<0.01 (Baseline vs. week 4)
† P<0.009 (Baseline vs. wk 8)
†† P<0.01 (Week 4 vs. week 8)
††† P<0.001 (Baseline vs. wk 8)
†††† P<0.001 (Baseline vs. week 4)
‡ P<0.001 (Week 4 vs. week 8)

Table 3: Fasting serum lipids at baseline, week and week 8.

in fasting serum glucose, insulin concentrations and QUIKI at baseline week 4, and week 8 (data not shown). There were no significant changes in fasting serum glucose, insulin, and QUIKI at week 4 and at the end of intervention compared to baseline (Table 2).

Serum lipids

The mean values for serum lipids at baseline, week 4, and week 8 are shown in Table 3. There were no significant differences between males and females in fasting serum lipids (cholesterol, triacylglycerol, HDL-C, LDL-C, LDL-C/HDL-C, and Chol/HDL-C) at baseline, week 4 , and week 8 (data not shown). At the end of intervention, fasting cholesterol, and triacylglycerol, concentrations decreased by 6% (P<0.02), and 19% (P<0.009), respectively. LDL-C to HDL-C ratio, and Chol to HDL-C ratio decreased by 4% (NS), and 6% (P<0.001), respectively. There were no significant changes in total HDL, and LDL cholesterol concentrations, at the end of the intervention (Table 3).

Serum cytokines

There were no significant differences between males and females in serum IL-6, IL-1 β, TNF−α, CRP, and sialic acid concentrations at baseline, week 4, and week 8 (data not shown).

There were no significant changes in serum TNF−α, or IL-1 β concentrations following 8 weeks EPA/DHA supplementation, compared to baseline (Table 4). There was a no significant trend for TNF−α to be increased following EPA/DHA supplementation at week 4 and 8 compared to baseline.

Mean serum sialic acid concentrations at week 8 were significantly lower than baseline value. Serum IL-6 concentration showed a significant decrease at week 4 but showed a no significant increase at the end of intervention; mean concentrations were still lower than baseline value. At week 8, there was a 22% significant decrease in CRP concentrations comparing week 4 and baseline value but this was not significant. Serum IL-1 β showed a no significant 29% decrease at week 4 and returned to baseline value at week 8 (Table 4).

Associations between glycemia indices, lipids and inflammatory markers

For all patients combined, there was no significant correlation between glycemia indices (fasting glucose and insulin) with

TNF-α (pg/ml)	20.30 ± 4.50
Baseline	
Week 4	22.80 ± 4.40
Week 8	25.50 ± 5.20
Sialic acid(mmol/L)	2.24 ± 0.07*
Baseline	
Week 4	2.18 ± 0.06
Week 8	1.90 ± 0.09
IL-6 (pg/ml)	4.50 ± 0.70**
Baseline	
Week 4	3.40 ± 0.40
Week 8	4.10 ± 0.80
CRP (ng/ml)	80.70 ± 11.80***
Baseline	
Week 4	81.38 ± 14.00****
Week 8	63.00 ± 11.80
IL-1 β (pg/ml)	20.40 ± 3.90
Baseline	
Week 4	14.68 ± 1.30
Week 8	20.00 ± 4.80

Data are means ± SE (n=26).
* P<0.01 (Baseline vs. week 8)
** P<0.03 (Baseline vs. week 4)
*** P<0.001 (Baseline vs. week 8)
**** P<0.05 (Week 4 vs. week 8

Table 4: Fasting serum cytokines at baseline, week 4 and week 8.

Model	Unstandardised coefficients		Standardised coefficients	t	Significant
	B	S.E	Beta		
(Constant)	0.387	0.07		5.56	<0.0001
IL-6	0.005	0.002	0.57	2.54	<0.01
CRP	-1.351E-04	0.00	-0.25	-1.17	0.25
IL-1β	3.718E-05	0.00	0.02	0.11	0.90
TNF-α	1.526E-04	0.00	0.10	0.56	0.57
BMI	-0.261	0.002	-0.23	-1.16	0.25

Adjusted R Square=0.150, R Square=0.320, ANOVA F=1.884, P=0.142

Table 5: Linear regression to explain variation in QUIKI (n=26).

inflammatory markers (IL-6, IL-1 β, TNF–α, CRP, and sialic acid) at baseline.

There were no significant correlations between serum lipids and markers of inflammation at baseline.

There was no significant correlation between markers of inflammation (IL-6, IL-1 β, TNF–α, CRP, and sialic acid) with duration of diabetes at baseline. Table 5 shows the linear regression analysis controlled for age, gender and BMI, which explains 32.0 % of variation in QUIKI. Only IL-6 remained in the model during the stepwise analysis. IL-6 seemed to play a main role in influencing QUIKI, while IL-1β, CRP, and TNF-α did not play any significant role. After exclusion of IL-6 from the group of independent variables, the value of R square decreased by 25% (data not shown), which could reflect interference of IL-6 with factors increasing insulin resistance.

Discussion

In our study there were no significant changes in serum IL-6, IL-1 β, CRP or TNF–α following 3000 mg omega-3 fatty acid supplementation for 8 weeks. The data from the present study, agree with data from other study in patients with T2DM that there were no significant changes in serum IL-6 or CRP concentrations following 4 g/d EPA or DHA supplementation for 6 weeks, but there was a no significant trend for TNF–α to be decreased following EPA or DHA supplementation [13]. In our study there was a trend for TNF–α to be increased.

The data from the present study agree with data from other studies which suggest that fish oil does not exert a modulatory effect on TNF–α production [14-19]. A wide range of doses of fish oil have been used in similar studies (0.55–6.00 g omega-3 PUFAs/d). Suppressive effects of fish oil on TNF–α production have generally been shown in studies that used doses of omega-3 PUFAs that were greater than those used in the present study (18 g fish oil concentrate/d for 6 weeks [20], 6 g fish oil/d with an EPA and DHA at least 86% for 6 months [21], and 6 g/d DHA/d for 3 months [22]). However, this is not universally the case, because some studies that used higher doses showed no effect on TNF–α production [14,17,18]. Of the 3 studies that used doses similar to or lower than those used in the present study [14,17,23] only 1 [23] showed an inhibitory effect of fish oil on TNF–α production.

This study showed that treatment with a low dose of EPA/DHA (1.5 g/day) can reduce triacylglycerol, and cholesterol by 20%, and 6%, respectively; in a 2 month period. The study also confirmed that this type of treatment does not impair glycemic control. In fact, there was neither a rise of glycemia, nor changes in the other glycemic indices (fasting glucose, insulin concentrations and, insulin sensivity) in patients with T2DM. In our study EPA/DHA 1.5 g/d decreased systolic blood pressure by 8 mmHg compared with baseline, which agrees with data from other study in which subjects with T2DM took 2.5 omega-3 fatty acids /d for 6 weeks. Fish oil significantly reduced TG concentrations by about 0.50 mmol/L; and decreased upright SBP by 8 mmHg compared with safflower oil, but had no effect on fasting glucose, HDL-C, or LDL-C concentrations [24].

It has been suggested that omega-3 fatty acids impair glycemic control in patients with T2DM [25,26]. In other studies, glucose control was improved or remained unchanged [24,27]. According to Puhakainen et al. differences in the dosage of omega-3 fatty acids may provide a potential explanation for the differences in effects of fish oil on glycemia [28]. Achievement of a sustained reduction of TG, and Chol, in addition to the other favourable serum lipid, cytokine and blood pressure changes, indicates that low/moderate dose of EPA/DHA fatty acids given in the form of softgels, can provide an appropriate treatment for this common metabolic disorder with a high atherosclerosis risk.

TNF–α system might contribute to the development of insulin resistance in glucose-intolerant subjects [29]. An increase in circulating TNF–α concentration is associated with peripheral insulin resistance and increased plasma glucose and insulin concentrations prior to the onset of T2DM; but the further deterioration in peripheral insulin resistance in T2DM (compared with normal glucose tolerance and IGT) is unrelated to the increase in serum TNF–α concentration [30].

According to Leinonen et al. there were no significant correlations between markers of inflammation with duration of T2DM, which agree with data from present study [31].

We could not find supportive evidence for causal association between serum markers of inflammation and indices of glycemia. This study was unable to determine a significant change in TNF-α and IL-1β concentrations. Lack of a control group, and insufficient dose of fish oil or shortness of the intervention period may have been contributed to these results. A moderate dose of fish oil did not lead to deleterious effects on glycemic control in patients with T2DM, with preserved triacyglycerol-lowering capacities.

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