Eur J Nutr (2007) 46:315–320
DOI 10.1007/s00394-007-0668-5

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# Effects of flaxseed oil supplementation on plasma adiponectin levels in dyslipidemic men

Received: 3 January 2007
Accepted: 5 June 2007
Published online: 11 July 2007

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**Abstract** *Background* Dietary alpha-linolenic acid (ALA) has been associated with reduced risk of development of atherosclerosis. Adiponectin is a hormone specifically secreted by adipocytes and considered to have anti-atherogenic properties. *Aim of the study* We examined the effect of increased dietary intake of ALA on plasma concentration of adiponectin. *Methods* Thirty-five non-diabetic, dyslipidemic men, 38–71 years old, were randomly allocated to take either 15 ml of flaxseed oil rich in ALA (8.1 g/day; $n = 18$), or 15 ml of safflower oil per day, containing the equivalent n-6 fatty acid (11.2 g/day linoleic acid, LA; $n = 17$) (control group). The intervention period lasted for 12 weeks. *Results* Plasma levels of adiponectin did not change after the increase in dietary intake of ALA in the flaxseed oil supplementation group, compared to the control group. No changes in body mass index, serum lipid concentrations, LDL density, or plasma TNF-α were found in the flaxseed oil versus the control group. *Conclusions* Dietary ALA has no effect on plasma adiponectin concentration in dyslipidemic men

**Key words** alpha-linolenic acid – plasma adiponectin – flaxseed oil – dyslipidemia

## Introduction

Adiponectin, a hormone specifically secreted by adipocytes, represents the highest concentration of all hormone-like peptides secreted by adipose tissue [1]. Adiponectin suppresses the proliferation and migration of human aortic smooth muscle cells in atherosclerotic lesions [2]. In humans, high plasma adiponectin concentration has been associated with reduced risk of incident myocardial infarction in men [3, 4]. Recent evidence from men undergoing coronary angiography revealed that adiponectin concentrations less than 4.0 μg/ml were associated with early onset of coronary heart disease (CHD) and multiple atherosclerotic lesions in coronary arteries [5]. These findings indicate that adiponectin may be anti-atherogenic.

Alpha-linolenic acid (18:3n-3), hereafter ALA, is an n-3 polyunsaturated fatty acid of plant origin and metabolic precursor of long-chain n-3 fatty acids eicosapentaenoic and docosahexaenoic. Dietary ALA has been linked with low incidence of CHD events in both primary and secondary prevention studies [6, 7]. Intervention trials investigating relationships between

EJN 668

dietary ALA and atherosclerosis risk factors mainly have focused on the effect of ALA on serum lipid profile [8]. Epidemiological evidence also has suggested an inverse relationship between dietary ALA intake and plasma triglyceride levels [9]. Metabolic studies have observed a decrease in triglyceride levels after ingestion of high amounts of ALA by volunteers [10]. However, there is the suggestion that dietary ALA may exert its effect on atherogenesis through a number of other mechanisms [11]. Given the strong negative association between plasma adiponectin and triglycerides [12, 13], we suggest that dietary ALA may increase circulating adiponectin, as an additional mechanism to protect against atherosclerosis. The purpose of the present study, therefore, is to examine the effects of a 12-week dietary supplementation with flaxseed oil, the richest dietary source of ALA, on circulating levels of adiponectin under controlled conditions.

## Material and methods

### Subjects

Subjects were recruited from the Treadmill Test Unit of the Department of Cardiology, Laiko Hospital, Athens, Greece. Potential participants were screened by medical history, physical examination, electrocardiograph, and laboratory analysis. Forty male volunteers ages 38–71 years, first diagnosed for dyslipidaemia but without evidence of CHD, were recruited. The decision on recruitment of dyslipidemic subjects was based on the low plasma concentrations of adiponectin they presented and the high risk of this group in developing atherosclerosis [13]. Inclusion criteria were total cholesterol concentration higher than 200 mg/dl, and/or an HDL-cholesterol concentration lower than 40 mg/dl. Subjects with evidence of infection or coexistent diabetes mellitus, hypertension, renal, liver or inflammatory disease were excluded. In addition, subjects taking lipid-lowering drugs, habitually consuming more than thirty units of alcohol per week, smoking, or habitually exercising vigorously at the level of 6 h/week were excluded. Of the forty men enrolled, one withdrew before completion of the study because of gastrointestinal discomfort. An additional four subjects either withdrew or were excluded for non-compliance during the 12-week intervention. Thirty-five subjects completed the study.

### Study design

The study was a single-blind, parallel design human intervention trial. Informed consent was obtained from all participants before entering the study, which was approved by the ethical committee of Harokopio University. Volunteers randomly were allocated to one of two oil supplements: (a) 15 ml of flaxseed oil containing 8.1 g of ALA (ALA group, $n = 18$), and (b) 15 ml of safflower oil containing 11.2 g of linoleic acid (LA) (LA group, $n = 17$). Fatty acid composition of the two oils is given in Table 1. The supplementation period lasted 12 weeks. Study participants were asked to maintain their usual lifestyle and were instructed to avoid intake of anti-inflammatory drugs, vitamins or other dietary supplements throughout the intervention period. Subjects were supervised with respect to their dietary habits, compliance to the oil supplements intake, alcohol consumption, and physical activity behavior by phone calls once a week, and by visits to the hospital once a month. Study participants were asked to return the oil bottles after each month of the intervention period. At the time of their monthly visits, subjects were weighed, they returned oil bottles used, and were provided with oil supplements for the following month. Compliance in the oil supplements intake was assessed by measuring the volume remaining in the bottles returned. All participants consumed >98% of the assigned oil quantity. Dietary compliance was assessed by collecting one 3-day dietary record during each patient's monthly visit (total of 3 dietary records over the 12-week intervention period).

**Table 1** Composition of the oil supplements per 100 g

| | Safflower oil | Flaxseed oil |
|---|---|---|
| Palmitic acid (g) | 5.7 | 5.9 |
| Stearic acid (g) | 2.4 | 3.6 |
| Arachidonic acid (g) | – | – |
| Oleic acid (g) | 11.5 | 18.2 |
| Eicosapentaenoic acid (g) | – | – |
| Linoleic acid (g) | 74.4 | 13.9 |
| alpha-Linolenic acid (g) | 0.5 | 54.2 |
| Total sterols (g) | 0.4 | 0.4 |
| Total tocopherols (mg) | 48.21 | 54.27 |

### Measurement of biochemical variables

Fasting blood samples were collected at 08.00 h and kept on ice until centrifuged at 3,000 rpm for 10 min at 4°C within 2 h of blood collection. Blood samples were taken at the onset and conclusion of the experimental period. Plasma and serum samples were stored at −80°C for further analysis. Serum total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol concentration were determined using enzymatic colorimetric assays on an ACE analyzer (Sciapparelli Biosystems Inc., USA). LDL subclasses were separated by density-gradient

ultracentrifugation and LDL density was calculated, as described by Griffin et al. [14]. Plasma adiponectin was assessed by enzyme-linked immunosorbent assay (ELISA) (B-Bridge International, Inc, Sunnyvale, CA). TNF-α concentration in plasma was also assayed by ELISA (R&D Systems Europe Ltd, Abingdon, UK). Intra-assay variation for adiponectin and TNF-α was <10% and <11%, respectively. The inter-assay variation was 5.2% and 4.6% for adiponectin and TNF-α, respectively. All samples were assayed twice by a single operator blinded to the timing of sampling and type of oil supplement. To minimize variability, samples before and after the experimental period for each subject were analyzed in one assay.

### Statistical analysis

Data were checked for normality using the Shapiro-Wilk test and values for triglycerides, TNF-α and adiponectin were log transformed to correct for skewed distribution. Values for triglycerides and adiponectin were not distributed normally even after log transformation. Normally-distributed variables are presented as mean +/− SD, while skewed variables are presented as median and quartiles. Baseline values from two different groups were compared by unpaired Student's *t* test or Mann-Whitney test, as appropriate. BMI, serum lipid concentrations, and plasma TNF-α levels before and after intervention were compared within each group by paired Student's *t* test. The same comparison was made using Wilcoxon signed ranks test for plasma triglycerides and adiponectin levels. The effect of dietary supplementation with flaxseed oil on body mass index (BMI), total cholesterol, HDL cholesterol, LDL density and TNF-α was tested using analysis of variance for repeated measures (RMANOVA). For triglycerides and adiponectin the Friedman test for repeated measures was used. Spearman correlation coefficient was used to test the relationships between plasma adiponectin and clinical features, serum lipids and plasma TNF-α. All hypotheses were two-sided and $P < 0.05$ was considered as statistically significant. Analysis was carried out with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

Age, height, weight, BMI, and systolic and diastolic blood pressure, were comparable at baseline between the subjects in the two intervention groups. Subjects in the two groups were not significantly different for serum total cholesterol, HDL-cholesterol, triglycerides and plasma adiponectin, TNF-α concentration or LDL density at baseline (Table 2). There were no significant differences regarding dietary intakes of macronutrients, fatty acids and alcohol consumption between the two study groups at baseline (Table 3). There were no significant changes during the experimental period in body weight, dietary intake of macronutrients, and alcohol consumption in the two groups (Table 3). Within-group analysis revealed a decrease in plasma adiponectin by 16.1% ($P = 0.003$), an increase in plasma TNF-α (22.1%, $P = 0.002$), and a small but significant decrease in serum HDL-cholesterol (4.3%, $P = 0.03$) in the ALA group and a decrease in serum total cholesterol (13.6%, $P = 0.018$) in the LA group.

Between-group analysis revealed that ALA supplementation had no effect on plasma adiponectin, TNF-α, BMI or serum lipid concentrations, compared to the LA supplementation (Table 4). Plasma adiponectin after intervention was positively correlated with end-point HDL-cholesterol levels ($r = 0.351$, $P = 0.039$) and negatively correlated with BMI ($r = -0.356$, $P = 0.036$), triglyceride ($r = -0.448$, $P = 0.007$), LDL density ($r = -0.405$, $P = 0.021$) and TNF-α ($r = -0.346$, $P = 0.042$) levels at end-point. The same correlations were not statistically significant at baseline with the exception of the positive correlation between adiponectin and HDL-cholesterol levels ($r = 0.394$, $P = 0.019$).

**Table 2** Descriptive characteristics at baseline for dyslipidemic patients in the alpha-linolenic (ALA) and linoleic (LA) acid groups

| | ALA group | LA group | *P* value |
|---|---|---|---|
| *n* | 18 | 17 | |
| Age (y) | 49 + 7 | 54 ± 10 | 0.104 |
| Height (m) | 1.75 ± 0.06 | 1.77 ± 0.06 | 0.254 |
| Weight (kg) | 86 ± 11 | 88 ± 15 | 0.638 |
| BMI | 28 ± 3 | 28 ± 4 | 0.972 |
| SBP (mmHg) | 125 ± 14 | 126 ± 14 | 0.987 |
| DBP (mmHg) | 79 ± 10 | 82 ± 10 | 0.684 |
| Total cholesterol (mg/dl) | 238 ± 35 | 242 ± 51 | 0.987 |
| Triglycerides (mg/dl) | 163 (87–202) | 153 (97–215) | 0.391 |
| HDL cholesterol (mg/dl) | 40.7 ± 9.3 | 37.5 ± 9.1 | 0.301 |
| LDL density (g/ml) | 1.029 ± 0.004 | 1.029 ± 0.006 | 0.937 |
| Adiponectin (μg/ml) | 5.97 (4.62–7.82) | 5.98 (3.87–8.04) | 0.424 |
| TNF-α (pg/ml) | 1.90 ± 0.80 | 2.06 ± 0.73 | 0.439 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure Values are means ± SD. Adiponectin and triglycerides values are medians (1–3 quartiles)

## Discussion

In the present study flaxseed oil supplementation decreased plasma adiponectin levels within the intervention group, but there were no significant

**Table 3** Nutrient composition of the diets in the alpha-linolenic (ALA) and linoleic (LA) acid groups before and after the intervention period

| | ALA group ($n$ = 18) | | | LA group ($n$ = 17) | | | ALA versus LA |
|---|---|---|---|---|---|---|---|
| | Before | After | $P$ value | Before | After | $P$ value | $P$ value |
| Energy (K cal) | 2,205 ± 257 | 2,189 ± 265 | 0.315 | 2,234 ± 248 | 2,208 ± 262 | 0.403 | 0.518 |
| Proteins % | 15.5 ± 4.2 | 15.3 ± 4.4 | 0.189 | 15.2 ± 4.6 | 15.2 ± 4.3 | 0.344 | 0.103 |
| Carbohydrates % | 47.9 ± 7.2 | 47.7 ± 7.3 | 0.324 | 47.8 ± 8.5 | 48 ± 8.1 | 0.229 | 0.288 |
| Fat % | 36.7 ± 5.5 | 37.1 ± 5.8 | 0.651 | 37 ± 6.9 | 36.8 ± 6.4 | 0.170 | 0.442 |
| Saturated fatty acids (g) | 32.9 ± 3.8 | 32.7 ± 3.9 | 0.498 | 31.6 ± 3.7 | 30.8 ± 3.6 | 0.414 | 0.709 |
| Monounsaturated fatty acids (g) | 40.5 ± 5.5 | 40.7 ± 5.6 | 0.321 | 41.4 ± 6.3 | 41.2 ± 6.0 | 0.156 | 0.655 |
| Polyunsaturated fatty acids (g) | 12.6 ± 2.3 | 12.4 ± 2.1 | 0.583 | 13.1 ± 3.0 | 13.7 ± 2.9 | 0.532 | 0.154 |
| Alcohol % | 1.3 ± 0.4 | 1.3 ± 0.5 | 0.511 | 1.4 ± 0.6 | 1.2 ± 0.5 | 0.216 | 0.363 |

Values are means ± SD. Comparisons between ALA and LA groups were made by analysis of variance for repeated measures (RMANOVA)

**Table 4** BMI, serum lipids, plasma adiponectin and TNF-α before and after the intervention in the alpha-linolenic (ALA) and linoleic (LA) acid groups

| | ALA group ($n$ = 18) | | | LA group ($n$ = 17) | | | ALA versus LA |
|---|---|---|---|---|---|---|---|
| | Before | After | % change | Before | After | % change | $P$ value[a] |
| BMI (kg/m$^2$) | 28.0 (2.7) | 28.2 (2.7) | 0.5 | 28.0 (4.4) | 27.9 (4.1) | 0.01 | 0.909 |
| Total cholesterol (mg/dl) | 238 (35) | 238 (33) | 1.6 | 242 (51) | 202 (41)* | −13.6 | 0.088 |
| Triglycerides (mg/dl) | 163 (87–202) | 167 (100–223) | 16.1 | 153 (97–215) | 146 (85–177) | −11.6 | 0.759 |
| HDL cholesterol (mg/dl) | 40.7 (9.3) | 38.6 (7.5)* | −4.3 | 37.5 (9.1) | 34.9 (6.1) | −4.4 | 0.187 |
| LDL density (g/ml) | 1.029 (0.004) | 1.029 (0.004) | −0.4 | 1.029 (0.006) | 1.028 (0.004) | −0.6 | 0.765 |
| Adiponectin (μg/ml) | 5.97 (4.62–7.82) | 4.49 (2.86–6.16)* | −16.1 | 5.98 (3.87–8.04) | 5.93 (3.79–7.34) | 1.8 | 0.844 |
| TNF-α (pg/ml) | 1.90 (0.80) | 2.25 (0.93)* | 22.1 | 2.06 (0.73) | 2.11 (0.97) | 3.0 | 0.989 |

BMI, body mass index
Values are means ± SD. Adiponectin and triglycerides values are presented as medians (1–3 quartiles) since they were not normally distributed
* Value significantly different from corresponding value before dietary intervention ($P < 0.05$, by paired Student's $t$ test for total cholesterol, HDL cholesterol, TNF-α and by Wilcoxon signed ranks test for adiponectin)
[a] Comparison of the changes during the intervention in the ALA versus the LA group using analysis of variance for repeated measures (RMANOVA). For triglycerides and adiponectin the Friedman test for repeated measures was used

differences between the intervention and the control groups. To our knowledge the present intervention study is the first to examine the effect of dietary fatty acids on plasma adiponectin levels. Previously, in a cross-sectional study that measured plasma fatty acid composition as an index of dietary intake of fatty acids, there was a negative association of saturated fatty acids in plasma with circulating adiponectin concentration [15]. The same study, however, showed no association between the plasma levels of ALA or any other n-3 polyunsaturated fatty acid and the plasma levels of adiponectin, a finding in agreement with the results presented here. Unfortunatley, we do not have data to confirm a lack of association between plasma levels of ALA and plasma adiponectin levels.

ALA, the main fatty acid in flaxseed oil, is a ligand for PPAR-γ [16]. PPAR-γ is responsible for the synthesis of adiponectin [17] and PPAR-γ activators are found to increase expression and plasma concentrations of adiponectin [18]. These findings support the hypothesis that dietary flaxseed oil has an effect on plasma adiponectin levels. Recent evidence from in vitro studies on adipose cells, however, suggests that although ALA is a ligand, it is rather poor activator of PPAR-γ in human adipocytes (Granlund L., unpublished data). This suggestion is supported in that the structural analysis of PPAR-γ reveals that fatty acids bind PPAR-γ in multiple configurations which enable them either to activate or to repress PPAR-γ [19]. We speculate, therefore, that the reason dietary flaxseed oil had no effect on plasma adiponectin levels, was because ALA is possibly an inactive ligand for PPAR-γ in adipocytes.

A second possible explanation for the lack of effect of flaxseed oil on plasma adiponectin levels may be due to the regulation of circulating adiponectin levels. Body weight and TNF-α synthesis by adipose tissue both have been shown to reduce plasma adiponectin levels since plasma adiponectin levels are low in obese men [20]. Moreover, plasma levels of adiponectin increase following weight loss [21]. A strong negative correlation between BMI and plasma adiponectin levels is evident in different human populations [13]. On the other hand, TNF-α and adiponectin inhibit production of the other from adipose tissue in vitro [22, 23]. This observation is corroborated by animal

studies since adiponectin-knockout mice showed elevated levels of TNF-α in adipose tissue and plasma [24]. Furthermore, adenovirus-mediated adiponectin expression in adiponectin-knockout mice reversed the increase of TNF-α [24].

The present study showed a strong negative correlation of plasma adiponectin levels with both BMI and plasma TNF-α levels. The regulation of circulating adiponectin levels is yet unclear but previous findings suggest that body weight and TNF-α synthesis in adipose tissue determine to a large extent plasma adiponectin levels. If correct, our finding that both body weight and plasma TNF-α levels did not change during the intervention might explain why there was no change in plasma adiponectin levels. Still, within ALA group our analysis revealed a statistically significant decrease in adiponectin levels and a corresponding increase in TNF-α levels. This could be an adverse effect of a high dietary intake of ALA. These changes, however, are not statistically significant when ALA group was compared to the control group which decreases the impact of this finding. HDL-cholesterol levels were also decreased following ALA supplementation after within group analysis. The degree of the decrease was not significant clinically since baseline HDL-cholesterol levels already were low in our subjects. As with adiponectin and TNF-α levels, no differences were observed between the two groups.

ALA supplementation had no effect on cholesterol levels but a trend was observed where cholesterol levels were lower following LA supplementation when compared to ALA supplementation. In addition, there was a significant reduction of cholesterol levels within the LA supplementation group. The lowering effect of LA on cholesterol levels is now well documented and known to be due to an increased synthesis of LDL receptors.

The levels of plasma adiponectin concentration we report for the study group are significantly lower compared to levels reported for men of similar age within the general Greek population [25]. The finding was expected since the study population consisted of slightly overweight, dyslipidemic men. Previous reports showed that dyslipidemic subjects had low plasma concentration of adiponectin [13]. More specifically, plasma adiponectin correlated negatively with serum triglycerides and plasma LDL density and positively with serum HDL-cholesterol [13, 26]. All these above correlations were evident for our study population characterized by high serum triglycerides, LDL density and low plasma levels of HDL-cholesterol.

In conclusion, the present study showed no effect of flaxseed oil supplementation on plasma adiponectin levels of dyslipidemic men. One limitation to the present study was that we used an enzyme-linked immunosorbent assay with an antibody specific for adiponectin to measure concentrations of total adiponectin in plasma. A recent publication [27] has shown that the high-molecular weight form of adiponectin is a better predictor of the existence of insulin resistance and metabolic syndrome. In this way, the high-molecular weight form of adiponectin may correlate better than total adiponectin with the relative risk of development of atherosclerosis. The findings presented here, however, cannot exclude the possibility that dietary ALA may change the high-molecular weight form of adiponectin that circulates in plasma.

**Acknowledgements** This project was supported by the Greek Ministry of Development, General Secretariat for Research and Technology (grant 97EL-55) and Becel Institute/Unilever Bestfoods Greece.

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