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Depression and serum adiponectin and adipose omega-3 and omega-6 fatty acids in adolescents

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Abstract

The purpose of the present study was to investigate for a possible relationship between depression and serum adiponectin and adipose tissue omega-3 and omega-6 PUFA. The sample consisted of 90 healthy adolescent volunteers from the island of Crete. There were 54 girls and 36 boys, aged 13 to 18. The mean age was 15.2 years. Subjects were examined by the Preventive Medicine and Nutrition Clinic of the University of Crete. Depression was assessed through the use of the Beck Depression Inventory (BDI) and the Center for Epidemiologic Studies Depression Scale (CES-D). Fatty acids were determined by gas chromatography in adipose tissue. CES-D correlated with dihomo-gamma linolenic acid (DGLA). Multiple linear regression analyses showed that BDI was negatively associated with eicosapentaenoic acid (EPA), while CES-D was positively associated with DGLA in adipose tissue. Serum adiponectin was not significantly associated with depression. The negative relationship between adipose EPA and depression in adolescents, is in line with findings of previous studies involving adult and elderly subjects, demonstrating negative relations between depression and adipose omega-3 PUFA. This is the first literature report of a relationship between depression and an individual omega-3 fatty acid in adolescents. The inverse relationship between adipose EPA and depression indicates that a low long-term dietary intake of EPA is associated with an increased risk for depression in adolescents.

Keywords: Psychological; Depression; Human; Adipose tissue; Omega-3 fatty acids; Fish oil; Adiponectin

1. Introduction

Depression is characterized by an immune-inflammatory response or immune-inflammation markers such as increased number of activated T-cells and peripheral blood cells (i.e. B lymphocytes, CD+ T-cells, leukocytes, neutrophils and monocytes) and increased pro-inflammatory cytokines such as interleukin-1 (IL-1) (Maes et al., 1991, 1993b,c; Maes, 1995; Owen et al., 2001), interleukin-2 (IL-2) (Maes et al., 1993c), interleukin-6 (IL-6) (Maes et al., 1993a,b, 1995a; Frommberger et al., 1997; Musselman et al., 2001), interferon-γ (INF-γ) (Maes et al., 1994), tumor necrosis factor-alpha (TNF-α) (Hestad et al., 2003), and increased number of soluble IL-2 (sIL-2R) (Maes et al., 1991, 1995a,b) and IL-6 (sIL-6R) receptors (Maes et al., 1995a, 1999b).

Aside from pro-inflammatory cytokines, depression has been reported to relate also to anti-inflammatory cytokines. A study indicated that depressed chronic heart failure patients had lower circulating IL-10 levels, an anti-inflammatory cytokine, than non-depressed patients (Parissis et al., 2004). It has been suggested that the therapeutic efficacy of antidepressants is, among other things, due to anti-inflammatory actions or shifting the pro-/anti-inflammatory cytokine balance towards decreased expression of pro-inflammatory cytokines and increased expression of anti-inflammatory ones (Kubera et al., 2001; Capuron et al., 2002; O'Brien et al., 2004).

Adiponectin (also known as AdipoQ, Acrp 30, GBP28 or apM1), a novel adipocytokine, is secreted exclusively from adipose tissue (Stefan and Stumvoll, 2002; Lebas et al., 2003;

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Table 1
Means and S.D. of depression, serum adiponectin and adipose tissue fatty acids in the study subjects

	Girls			Boys			Total		
	Mean	(±S.D.)	*N*	Mean	(±S.D.)	*N*	Mean	(±S.D.)	*N*
BDI	10.51	(±7.24)	54	7.13	(±5.23)	36	9.1	(±6.7)	90
CES-D	17.27	(±11.32)	54	11.30	(±7.67)	36	14.9	(±10.4)	90
Adiponectin	11.9	(±2.6)	54	10.3	(±2.5)	36	11.4	(±2.7)	90
C18:2n-6	13.0	(±1.70)	54	13.30	(±2.31)	36	13.1	(±1.9)	90
C18:3n-6	0.07	(±0.01)	54	0.06	(±0.02)	36	0.07	(±0.01)	90
C20:2n-6	0.17	(±0.02)	54	0.18	(±0.04)	36	0.18	(±0.03)	90
DGLA†	0.20	(±0.05)	54	0.21	(±0.05)	36	0.20	(±0.05)	90
C20:4n-6	0.35	(±0.07)	54	0.36	(±0.11)	36	0.35	(±0.09)	90
C18:3n-3	0.51	(±0.05)	54	0.53	(±0.07)	36	0.52	(±0.06)	90
C20:3n-3	0.03	(±0.008)	54	0.03	(±0.009)	36	0.03	(±0.008)	90
EPA†	0.02	(±0.006)	54	0.03	(±0.007)	36	0.02	(±0.007)	90
C22:5n-3	0.09	(±0.03)	54	0.10	(±0.03)	36	0.1	(±0.03)	90
DHA†	0.09	(±0.03)	54	0.10	(±0.04)	36	0.09	(±0.03)	90

† Dihomo-gamma linolenic acid C20:3n-6 (DGLA).
† Eicosapentaenoic acid C20:5n-3 (EPA).
† Docosahexaenoic acid C22:6n-3 (DHA).

Xiao and Lu, 2003; Ouchi et al., 2003). The levels of this cytokine in human plasma by far exceed those of any other hormone (Stefan and Stumvoll, 2002). Adiponectin, anti-inflammatory cytokine, is inversely related to pro-inflammatory cytokines such as IL-6 and TNF-α, that are reportedly elevated in depression (Frommberger et al., 1997; Engeli et al., 2003; Krakoff et al., 2003; Kern et al., 2003; Ouchi et al., 2003; Hestad et al., 2003). Also, there are indications that adiponectin may increase the levels of IL-10, an anti-inflammatory cytokine that has been reported to be decreased in depression (Kumada et al., 2004; Parissis et al., 2004). No studies have as yet examined whether adiponectin relates to depression.

On the other hand, lower proportions of omega-3 PUFA have been reported in the plasma, red blood cell membranes, serum phospholipids and cholesteryl esters and adipose tissue of depressed patients as opposed to healthy controls (Adams et al., 1996; Maes et al., 1996; Peet et al., 1998; Edwards et al., 1998; Maes et al., 1999a; Mamalakis et al., 2002, 2004a). In addition, there are indications that adiponectin may relate to fatty acids (Bernstein et al., 2004; Fernandez-Real et al., 2005), including polyunsaturated fatty acids (PUFA) of the omega-3 family (Fernandez-Real et al., 2005). A previous study did not find a significant relationship between depression and adipose tissue omega-3 PUFA in adolescents (Mamalakis et al., 2004b). However, adiponectin had not been included as a covariate in the statistical analysis.

The aim of the present study is to examine whether serum adiponectin and adipose PUFA relate to depression in adolescents.

2. Methods

2.1. Subjects

Study subjects were 90 healthy adolescent volunteers from the island of Crete. They were enrolled in a secondary school at a low income area of west-side Iraklion. There were 54 girls and 36 boys, aged 13 to 18. The average age was 15.2 years. Subjects and their parents were informed about the nature and the purpose of this study, and a consent form was signed by parents. Children were free to refuse to participate even when there was a signed consent by the parent/legal guardian. The ethical committee at the University of Crete had previously approved the protocol of this research. Subjects were examined by the Preventive Medicine and Nutrition Clinic of the University of Crete. This is the second study on depression and polyunsaturated fatty acids in the particular adolescent group (Mamalakis et al., 2004b). The difference between this study from the previous one is that serum adiponectin measures had not been included in the statistical analysis in the previous study.

2.2. Depression assessment

Depression level was assessed through the use of the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). BDI and CES-D have been reported to be valid and reliable depression assessment tools in adolescents (Barrera and Garrison-Jones, 1988; Chabrol et al., 2002). Furthermore, CES-D has been standardized in Greeks (Fountoulakis et al., 2001).

2.3. Anthropometric measures

Body weight was assayed by a digital scale (Seca) with an accuracy of ±100 g. Subjects were weighed without shoes, in their underwear. Standing height was measured without shoes to the nearest 0.5 cm with the use of a commercial stadiometer with the shoulders in relaxed position and arms hanging freely. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2).

2.4. Adiponectin measures

All coded samples were centrifuged and frozen (−70 °C) sera were sent in dry ice initially to the coordinating center where

Table 2
Spearman correlations between depression and serum adiponectin and adipose tissue PUFA

	BDI	CES-D
Serum adiponectin	0.04	0.06
C18:2n-6	−0.03	0.009
C18:3n-6	−0.07	−0.09
C20:2n-6	−0.02	0.04
DGLA†	0.10	0.24*
C20:4n-6	0.003	0.15
C18:3n-3	−0.09	−0.04
C20:3n-3	−0.11	−0.02
EPA†	−0.21	−0.18
C22:5n-3	−0.08	0.12
DHA†	−0.03	−0.08

* Correlation is significant at the 0.05 level (2-tailed).
† Dihomo-gamma linolenic acid C20:3n-6 (DGLA).
† Eicosapentaenoic acid C20:5n-3 (EPA).
† Docosahexaenoic acid C22:6n-3 (DHA).

they were stored (−70 °C) prior to being shipped in one batch to the Beth Israel Deaconess Medical Center, in Boston, USA. Blinded adiponectin measurements were performed by RIA with a sensitivity of 2 ng/ml, and intra-assay coefficient of variation of <10% as previously described (Gavrila et al., 2003).

2.5. Adipose tissue measures

Buttock subcutaneous tissue samples were collected by aspiration, using the method described by Beynen and Katan (1985). The particular method has been reported to be rapid and safe, and to cause no more discomfort than a routine venipuncture (Beynen and Katan, 1985). Buttock adipose tissue samples can be safely stored for up to 1.5 years without changes in the component fatty acids (Beynen and Katan, 1985). Samples were taken from the left upper outer quadrant of the gluteal area, through the use of a 10 ml vaccutaneous tube. Prior to aspiration, aspiration sites were sprayed with local anesthetic (ethyl chloride). Adipose tissue samples were stored in −80 °C. Fatty acids analysis was carried out as previously described (Mamalakis et al., 2004b). The different adipose tissue n-3 and n-6 fatty acids assessed were C18:2n-6, C18:3n-6, C20:2n-6, dihomo-gamma linolenic acid C20:3n-6 (DGLA), C20:4n-6, C18:3n-3, C20:3n-3, eicosapentaenoic acid C20:5n-3 (EPA), C22:5n-3, and docosahexaenoic acid C22:6n-3 (DHA).

2.6. Data analysis

Data were analyzed through the use of the SPSS statistical package. The statistical methods used were Spearman correlations, partial correlations and linear multiple stepwise regression analysis. Because BDI and CES-D were not normally distributed, logarithmic (Natural log) transformation of the particular measures was applied.

3. Results

Table 1 depicts means and standard deviations of depression, adiponectin and adipose tissue PUFA in the two genders and the entire group, while Table 2 depicts Spearman correlations between CES-D and BDI and serum adiponectin and adipose PUFA. CES-D correlated with C20:3n-6 (DGLA) ($r=0.24$, $p<0.05$). Serum adiponectin correlated with BMI ($r=-0.27$, $p<0.004$), sex ($r=-0.31$, $p<0.001$), C20:2n-6 ($r=-0.28$, $p<0.02$), DGLA ($r=-0.33$, $p<0.003$), C20:4n-6 ($r=-0.29$, $p<0.009$) and C22:5n-3 ($r=-0.25$, $p<0.03$).

Multiple linear regression analysis indicated that 8% of the variability in the log transformed BDI scores was accounted for by age and adipose tissue C20:5n-3 (EPA) ($F=4.2$, $p<0.02$). Beta coefficients show that the log transformed BDI depression scores are related negatively to age ($B=-0.23$, $t=-2.09$, $p<0.04$) and adipose tissue EPA ($B=-0.23$, $t=-2.09$, $p<0.05$). Age and adipose EPA bear equal weights in predicting the dependent measure (Table 3).

Multiple linear regression analysis indicated that 8% of the variability in the log transformed CES-D depression scale was accounted for by sex and adipose tissue DGLA ($F=4.1$, $p<0.02$). Beta coefficients show that the log transformed CES-D scores are related negatively to sex and positively to adipose tissue DGLA. The major predictor of the log transformed CES-D scale is sex (B=−0.25, t=−2.2, $p<0.04$) followed by DGLA (B=0.24, t=2.1, $p<0.04$) (Table 4).

Partial correlations confirmed the results of linear regressions. Specifically, BDI correlated with EPA ($r=-0.23$, $p<0.05$) and CES-D correlated with DGLA ($r=0.26$, $p<0.03$), after controlling for serum adiponectin.

Table 3
Multiple linear regression analysis

Dependent variable	Predictor	Beta (standardized coefficients)	t	P
Log transformed (BDI) depression	EPA	−0.23	−2.09	<0.05
	Age	−0.23	−2.09	<0.04

Log transformed Beck Depression (BDI) in relation to adipose tissue eicosapentaenoic acid C20:5n-3 (EPA), controlling for age, body mass index (BMI), serum adiponectin, adipose tissue C18:2n-6, C18:3n-6, C20:2n-6, dihomo-gamma linolenic acid C20:3n-6 (DGLA), C20:4n-6, C18:3n-3, C20:3n-3, C22:5n-3 and docosahexaenoic acid C22:6n-3 (DHA) as continuous variables, and gender as a dummy variable (females=0, males=1).

Table 4
Multiple linear regression analysis

Dependent variable	Predictor	Beta (standardized coefficients)	t	P
Log transformed (CES-D) depression	Sex	−0.25	−2.2	<0.04
	DGLA	0.24	2.1	<0.04

Log transformed Centers for Epidemiologic Studies Depression Scale (CES-D) in relation to adipose tissue dihomo-gamma linolenic acid C20:3n-6 (DGLA), controlling for age, body mass index (BMI), serum adiponectin, adipose tissue C18:2n-6, C18:3n-6, C20:2n-6, C20:4n-6, C18:3n-3, C20:3n-3, eicosapentaenoic acid C20:5n-3 (EPA), C22:5n-3 and docosahexaenoic acid C22:6n-3 (DHA) as continuous variables, and gender as a dummy variable (females=0, males=1).

4. Discussion

The results of the present study indicate that serum adiponectin does not relate to depression in adolescents. Our results do not parallel those of another study that reported a significant relation between depression and IL-10, another anti-inflammatory cytokine (Parissis et al., 2004). Some reason for the failure to observe a significant relationship between serum adiponectin and depression may relate to the protein encoded by the adiponectin gene. The particular protein shares significant similarities to collagen X and collagen VIII, and complement protein C1q (Okamoto et al., 2000). With the exception of C1q, that appears to be implicated in Alzheimer's disease (Brachova et al., 1993; Luo et al., 2003), collagens X and VIII have not been reported to be directly implicated in any CNS or brain-related pathologies or psychiatric disorders. Moreover, none of the two adiponectin receptors (i.e. adipor1, adipor2) is highly expressed in the brain. Northern blot analysis of adipor1 and adipor2 mRNA in human tissues has shown that adipor1 is highly expressed in the skeletal muscle but moderately expressed in the brain, whereas adipor2 is highly expressed in the skeletal muscle, liver and placenta, and weakly in brain (Yamauchi et al., 2003). Finally, it is possible that the failure to observe a significant relationship between serum adiponectin and depression may relate to the particular age-group studied. More studies on serum adiponectin and depression in adolescents as well as other age-groups are, therefore, needed. This is particularly important in light of the fact that adiponectin is associated with cytokines that are implicated in depression. For example, adiponectin is inversely related to pro-inflammatory cytokines such as IL-6 and TNF-α, that are elevated in depression (Frommberger et al., 1997; Engeli et al., 2003; Krakoff et al., 2003; Kern et al., 2003; Ouchi et al., 2003; Hestad et al., 2003). In addition, adiponectin may increase the levels of IL-10, an anti-inflammatory cytokine that has been reported to be reduced in depression (Kumada et al., 2004; Parissis et al., 2004).

Although serum adiponectin did not relate to depression, adipose tissue EPA and DGLA did (Tables 3 and 4). A previous study involving the particular adolescent group had not yielded a significant relation between these two adipose tissue fatty acids and depression (Mamalakis et al., 2004b). However, serum adiponectin had not been included as a predictor variable in the particular study. Most probably, serum adiponectin must have served as a confounder variable in the present study, in that its presence as a covariate in the regression model has helped unveil an existing relationship between depression and the particular two adipose fatty acids (Edwards, 1984). Specifically, it has been reported that adiponectin correlates negatively with insulin resistance (Vasseur, 2006; Gannage-Yared et al., 2006). Given that insulin resistance has not been measured in the present study, it is possible that serum adiponectin, may have served as an indicator of insulin resistance in our adolescents. On the other hand, insulin resistance or impaired insulin sensitivity has been reported to correlate positively to depression (Timonen et al., 2005; Okamura et al., 2000). In addition, insulin resistance has been reported to relate inversely to EPA (Lombardo and Chicco, 2006; Delarue et al., 2004) and positively to DGLA (Vessby, 2000; Lewis-Barned et al., 2000; Vessby et al., 1994). It is possible therefore, that serum adiponectin may have unmasked a relationship between depression and EPA and DGLA, via its correlating with insulin resistance, a known risk factor of depression and a correlate of EPA and DGLA. However, in the absence of insulin sensitivity measures in the present study, this hypothesis cannot be tested.

Given that adipose tissue fatty acid composition is a biomarker of long-term (1 to 3 years) or habitual dietary fat intake (Dayton et al., 1966; Beynen et al., 1980), the observed inverse relationship between adipose tissue EPA and BDI depression, in the present study, indicates that lower long-term dietary EPA intakes are related to a higher depression risk in adolescents. This is the first literature report of a relationship between depression and an individual omega-3 fatty acid in adolescents. This finding parallels results of previous studies involving different age groups. Negative relationships were reported between depression and adipose tissue docosahexaenoic acid (DHA) levels in an adult sample (Mamalakis et al., 2002), and between depression and adipose tissue alpha-linolenic acid (ALA) in an elderly group (Mamalakis et al., 2004a). The results of the present study and those of previous ones indicate that lower long-term omega-3 fatty acid intake may be related to a higher depression risk in adolescents, the adults and the elderly.

In addition, the inverse relationship between adipose tissue EPA and depression, in the present study, agrees with results of other studies that have shown inverse relationships between consumption of fish and depression (Nakane et al., 1988; Hibbeln, 1998; Tanskanen et al., 2001). Furthermore, the inverse relationship between EPA and depression, is in line with findings of other studies that observed decreased levels of omega-3 fatty acids in plasma, red blood cell membranes and serum cholesteryl esters and phospholipids of depressed patients relative to healthy controls (Adams et al., 1996; Maes et al., 1996; Peet et al., 1998; Edwards et al., 1998; Maes et al., 1999a). Finally, this finding is in congruence with findings of controlled clinical studies that have shown beneficial effects of omega-3 PUFA administration on depression (Nemets et al., 2002; Peet and Horrobin, 2002; Su et al., 2003).

It has been reported that n-3 PUFA can suppress some of the pathophysiological features of depression, namely inflammation and immune reactivity markers. Specifically, in vitro studies have shown that EPA and DHA suppress IL-6 production by human endothelial cells (De Caterina et al., 1994; Khalfoun et al., 1997), and the production of IL-1, IL-2, IL-6, TNF-α and INF-γ by human lymphocytes (Purasiri et al., 1997). As shown by human studies, dietary supplementation with EPA and DHA results in suppressing IL-1, IL-2, IL-6 and TNF-α production by monocytes (Meydani et al., 1991, 1993; Calder, 1997; Kelley et al., 1999). Given the reported positive relation of depression with cytokines such as IL-1, IL-2, IL-6 and TNF-α (Maes et al., 1991, 1993a,b,c; Maes, 1995; Maes et al., 1995a; Frommberger et al., 1997; Owen et al., 2001; Musselman et al., 2001; Hestad et al., 2003), the observed inverse relationship between adipose tissue EPA and depression, in the present study, may be due to an inhibiting effect of EPA on the production of the particular cytokines.

The observed positive relation between adipose DGLA and CES-D depression, in the present study, is in line with studies that have indicated positive relations between depression and PUFA of the omega-6 family (Adams et al., 1996; Maes et al., 1996, 1999a).

Due to the cross-sectional nature of the present study, no conclusions can be drawn concerning a possible cause–effect relationship between EPA and depression. Whether the inverse relationship between adipose EPA levels and depression in the present study reflects a protective effect of long-term EPA intake on depression or is only an epiphenomenon of depression is not known. However, indications for a possible causal link between omega-3 fatty acids, including EPA, and depression have been provided by double-blind, placebo-controlled clinical trails of omega-3 fatty acids administration in major depression and bipolar disorder (Stoll et al., 1999; Nemets et al., 2002; Peet and Horrobin, 2002; Su et al., 2003), indicating that these fatty acids may affect, directly or indirectly, on the biochemical substrate of depression.

2In conclusion, the results of the present study indicated an absence of a significant association between serum adiponectin and depression. However, after controlling for adiponectin, significant relationships emerged between adipose tissue DGLA and EPA and depression. This is the first literature report of a relationship between depression and an individual omega-3 fatty acid in adolescents. The observed inverse relationship between adipose EPA and depression in adolescents parallels findings of studies involving different age-groups and may be mediated by cytokine release. Thus, a low long-term dietary intake of EPA is associated with an increased risk for depression in adolescents.

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