Depression and adipose polyunsaturated fatty acids in an adolescent group

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Abstract

The purpose of the present study was to investigate the relation between adipose tissue polyunsaturated fatty acids, an index of long-term or habitual fatty acid dietary intake and depression. The sample consisted of 90 adolescents from the island of Crete. There were 54 girls and 36 boys, aged 13–18. 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). Unlike other studies, there were no significant relations between adipose tissue n-3 or n-6 polyunsaturated fatty acids and depression. BDI correlated positively with adipose tissue C20:3n-6/C18:3n-6 ratio, while CES-D correlated positively with adipose tissue (C20:3n-6 + C22:5n-3)/(C18:3n-6 + C20:5n-3) ratio. Depressed subjects (BDI > 16, CES-D > 16) had significantly elevated adipose tissue C20:3n-6/C18:3n-6 and (C20:3n-6 + C22:5n-3)/(C18:3n-6 + C20:5n-3) ratios, than non-depressed subjects. The observed positive relation between depression and the particular fatty acid ratios, in the present study, appears to indicate increasing activity of elongases, the enzymes responsible for elongating polyunsaturated fatty acids into their longer-chain derivatives, with increasing depression. This is the first literature report of a possible relation between elongases and depression. The observed relation may stem from a possible over-expression of the HELO1 (ELOVL5) gene, the gene encoding a protein responsible for elongating long-chain polyunsaturated fatty acids, in the adipose tissue of depressed adolescents.

1. Introduction

Depression has been one of the major health problems of the last century [1,2]. It appears that decreases in depression prevalence are associated with increased consumption of fish [3,4]. There are indications, that depletions in docosahexaenoic acid (C22:6n-3) (DHA), one of the long-chain polyunsaturated fatty acids (PUFA) in fish-oil [5], as well as other long-chain n-3 PUFA may be associated with depression. Significant depletions in red blood cell membrane phospholipid DHA and other n-3 long-chain PUFA, have been reported in depressed patients as opposed to healthy controls [6,7]. Furthermore, dietary intake of n-3 PUFA as well as red blood cell membrane PUFA levels have been reported to correlate negatively with depression severity [7]. As indicated by another study, erythrocyte phospholipid eicosapentaenoic acid (C20:5n-3) (EPA) levels correlated negatively with depression severity, in a group of depressed patients [8].

Besides polyunsaturated fatty acids of the n-3 series, PUFA of the n-6 family, also have been reported to relate to depression. Specifically, positive correlations have been reported between the ratio of n-6 polyunsaturated arachidonic acid (c20:4n-6) (AA) to EPA, as well as the ratio of total n-6/n-3 PUFA in erythrocytes, and depression severity [8]. In another study, major depressed patients had significantly elevated phospholipid and cholesteryl ester AA/EPA ratios and cholesteryl ester n-6/n-3 fatty acid ratios, than minor depressed patients or healthy controls. Major depressed patients had significantly decreased serum cholesteryl ester n-3 PUFA and cholesteryl ester and phospholipid EPA, than minor depressed patients or healthy controls [9]. Finally, significantly increased AA/EPA ratios and significantly decreased n-3 PUFA have been reported...
However, not all studies have shown decreased n-3 PUFA in depressed patients as opposed to healthy subjects. Specifically, two studies have shown significant increases rather than decreases in plasma choline phosphoglyceride and erythrocyte EPA and DHA levels in depressed patients as opposed to healthy control subjects [11,12]. Nevertheless, since plasma phospholipids and cholesteryl esters are markers of fatty acid intake of the preceding few weeks [13,14], the decreased n-3 PUFA in depression reported by most studies, appears to reflect, in part, a corresponding reduced intake in the particular fatty acids.

Some other reason for the reported reductions of n-3 PUFA in depression, may relate to some pathophysiological features of this disease, namely inflammation and lipid peroxidation, and low zinc concentrations [15,16]. It is known that inflammatory response system activation is associated with lipid peroxidation and reduced levels of n-3 PUFA [16,17]. Similarly, reduced levels of zinc, an inflammation marker, an antioxidant and a cofactor to the formation of desaturated and elongated products of alpha linolenic (C18:3 n-3) acid [15], are associated with reductions in n-3 PUFA [15]. It is possible, therefore, that the reported reductions in n-3 PUFA in depression, may relate to the particular pathophysiological features of the disease.

It is worth noting that only two studies used adipose tissue fatty acid measures, a biomarker of long-term (1–year) or habitual dietary fat intake [18,19]. One of these studies indicated that adipose tissue DHA related negatively to depression in an adult group [20]. The other study indicated an inverse relation between adipose tissue alpha-linolenic (C18:3 n-3) and depression, in an elderly group [21]. However, no study has as yet been conducted on the relation between adipose tissue fatty acids and depression in adolescents. The aim of the present study was to examine the relation between depression and adipose tissue PUFA of the n-3 and n-6 families in a group of adolescents.

2. Subjects and methods

2.1. Subjects

The study sample consisted of 90 adolescents from the island of Crete. There were 54 girls and 36 boys, aged 13–18. Most of the subjects (81%) were between 13 and 16.5 years of age. The mean age was 15.2 years. All subjects were informed about the nature and the purpose of this study and signed a consent form. 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.

2.2. Depression assessment

Depression level was assessed through the use of a Greek translation of the Beck Depression Inventory (BDI) and the Center for Epidemiologic Studies Depression Scale (CES-D). (BDI), a 21-itemscale, has been reported to constitute a valid and reliable depression measure in adolescents [22–24]. CES-D, a 20-item scale, is a valid and reliable measure of depression in adolescents [25,26]. Furthermore, CES-D has been standardized in Greeks [27].

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 (m²).

2.4. Adipose tissue measures

Buttock subcutaneous tissue samples were collected by aspiration, using the method described by Beynen and Katan [28]. The particular method has been reported to be rapid and safe, and to cause no more discomfort than a routine venipuncture [28]. Buttock adipose tissue samples can be safely stored for up to 1.5 year without changes in the component fatty acids [28]. Samples were taken from the left upper outer quadrant of the gluteal area, through the use of a 10 ml vacutaneous tube. Prior to aspiration, aspiration sites were sprayed with local anesthetic (ethyl chloride). Adipose tissue samples were stored in −80°C. Prior to analysis samples were thawed and the fat was transferred to 10 ml screw-capped tubes with the aid of Pasteur pipettes and several drops (~ 0.5 ml) of chloroform: methanol (2:1,v/v). Methyl esters of the fat component fatty acids were prepared in the screw-capped vials according to the method described by Metcalfe et al. [29]. Briefly, 20–30 mg of fat sample were saponified with 1.0 ml NaOH in methanol and the FAME were prepared with 14% boron trifluoride in methanol followed by extraction with hexane after washing with saturated NaCl. The hexane (upper layer) containing the FAME was transferred to GC vials and stored at −20°C until analysis. The FAME were separated on a 100 × 0.25 mm Id.SP-2560 fused silica capillary column, coated with a 0.25 μm of cyanopropyl silicone provided by SUPELCO, using a SHIMADZU
TABLE 1
Means and SD of depression, anthropometric, and adipose tissue fatty acid measures in the two genders

<table>
<thead>
<tr>
<th></th>
<th>Girls</th>
<th></th>
<th></th>
<th>Boys</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td>15.5</td>
<td>1.6</td>
<td>54</td>
<td>14.8</td>
<td>1.4</td>
<td>36</td>
</tr>
<tr>
<td>BMI</td>
<td>22.06</td>
<td>4.20</td>
<td>54</td>
<td>24.21</td>
<td>4.59</td>
<td>36</td>
</tr>
<tr>
<td>BDI</td>
<td>10.51</td>
<td>7.24</td>
<td>54</td>
<td>7.13</td>
<td>5.23</td>
<td>36</td>
</tr>
<tr>
<td>CES-D</td>
<td>17.27</td>
<td>11.32</td>
<td>54</td>
<td>11.30</td>
<td>7.67</td>
<td>36</td>
</tr>
<tr>
<td>C18:2n-6</td>
<td>13.00</td>
<td>1.70</td>
<td>54</td>
<td>13.30</td>
<td>2.31</td>
<td>36</td>
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<tr>
<td>C18:3n-6</td>
<td>0.07</td>
<td>0.01</td>
<td>54</td>
<td>0.06</td>
<td>0.02</td>
<td>36</td>
</tr>
<tr>
<td>C20:2n-6</td>
<td>0.17</td>
<td>0.02</td>
<td>54</td>
<td>0.18</td>
<td>0.04</td>
<td>36</td>
</tr>
<tr>
<td>C20:3n-6</td>
<td>0.20</td>
<td>0.05</td>
<td>54</td>
<td>0.21</td>
<td>0.05</td>
<td>36</td>
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<tr>
<td>C20:4n-6</td>
<td>0.35</td>
<td>0.07</td>
<td>54</td>
<td>0.36</td>
<td>0.11</td>
<td>36</td>
</tr>
<tr>
<td>C18:3n-3</td>
<td>0.51</td>
<td>0.05</td>
<td>54</td>
<td>0.53</td>
<td>0.07</td>
<td>36</td>
</tr>
<tr>
<td>C20:3n-3</td>
<td>0.03</td>
<td>0.01</td>
<td>54</td>
<td>0.03</td>
<td>0.01</td>
<td>36</td>
</tr>
<tr>
<td>C20:5n-3</td>
<td>0.02</td>
<td>0.01</td>
<td>54</td>
<td>0.03</td>
<td>0.01</td>
<td>36</td>
</tr>
<tr>
<td>C22:3n-3</td>
<td>0.11</td>
<td>0.03</td>
<td>54</td>
<td>0.12</td>
<td>0.03</td>
<td>36</td>
</tr>
<tr>
<td>C22:5n-3</td>
<td>0.09</td>
<td>0.03</td>
<td>54</td>
<td>0.10</td>
<td>0.03</td>
<td>36</td>
</tr>
<tr>
<td>C22:6n-3</td>
<td>0.09</td>
<td>0.03</td>
<td>54</td>
<td>0.10</td>
<td>0.04</td>
<td>36</td>
</tr>
<tr>
<td>Sum n-3 fatty acids</td>
<td>0.86</td>
<td>0.11</td>
<td>54</td>
<td>0.92</td>
<td>0.10</td>
<td>36</td>
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<tr>
<td>Sum n-6 fatty acids</td>
<td>14.08</td>
<td>1.70</td>
<td>54</td>
<td>14.36</td>
<td>2.35</td>
<td>36</td>
</tr>
<tr>
<td>n-6/n-3 ratio</td>
<td>16.65</td>
<td>3.11</td>
<td>54</td>
<td>15.85</td>
<td>3.19</td>
<td>36</td>
</tr>
</tbody>
</table>

4. Discussion

The results of the present study failed to confirm the negative relation between depression and adipose n-3 polyunsaturated fatty acids reported in adults and the elderly [20,21]. It appears that in this adolescent group, adipose tissue PUFA, an index of relatively long-term PUFA intake [18,19], is not associated with depression. The reasons for this are not clear and deserve further examination. Previous studies with adult and elderly subjects have indicated inverse relations between depression and adipose tissue docosahexaenoic (C22:6n-3) and alpha-linolenic (C18:3n-3) acids, respectively [20,21]. One reason for the failure to observe significant relations between the particular fatty acids and depression in the present study, may be the pronounced differences in the levels of these fatty acids between the adolescent and the previous two groups. Compared to the elderly group, the adolescent group had approximately 44% higher mean C18:3n-3 levels [21]. Compared to the adult group, the adolescent group had approximately 64% lower mean C22:6n-3 levels [20]. It is possible that the inverse relation of depression with
The particular fatty acids in the adult and elderly groups may have derived or have been contingent upon the specific C18:3n-3 and C22:6n-3 level ranges observed in these groups. The pronounced discrepancies of the adolescent group from the rest two groups in mean C18:3n-3 and C22:6n-3 levels, therefore, may underlie the failure to obtain a significant relation between these two fatty acids and depression in the former group. Clearly, more studies are needed on the relation between adipose polyunsaturated fatty acids and depression in adolescents.

This study indicated that the degree of depression in adolescents correlated positively with adipose tissue C20:3n-6/C18:3n-6 and (C20:3n-6+C22:5n-3)/(C18:3n-6+C20:5n-3) ratios (Table 3). Furthermore, similar results were obtained when the group was subdivided into depressed vs. non-depressed sub-samples. Specifically, depressed adolescents (BDI > 16) had higher adipose tissue C20:3n-6/C18:3n-6 and (C20:3n-6+C22:5n-3)/(C18:3n-6+C20:5n-3) ratios than non-depressed ones. Also, depressed adolescents (CES-D > 16) had higher adipose C22:5n-3/C20:5n-3 and (C20:3n-6+C22:5n-3)/(C18:3n-6+C20:5n-3) ratios than their non-depressed counterpart (Table 2). The particular ratios of polyunsaturated fatty acids probably reflect the activity of elongases, the enzymes responsible for elongating polyunsaturated fatty acids into their longer-chain derivatives [31]. C20:3n-6 and C22:5n-3 are products of chain elongation of C18:3n-6 and C20:5n-3, respectively [31]. The results of this study, therefore, appear to indicate that depression in adolescents is associated with increased chain elongation of adipose tissue C18:3n-6 and C20:5n-3, into C20:3n-6 and C22:5n-3 respectively. This is the first literature report of a possible relation between elongases and depression.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Means and SD of anthropometric, and adipose tissue fatty acid measures in depressed (BDI &gt; 16, CES-D &gt; 16) vs. non-depressed adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>Non-depressed</td>
</tr>
<tr>
<td>AGE</td>
<td>Mean</td>
</tr>
<tr>
<td>BMI</td>
<td>15.3</td>
</tr>
<tr>
<td>C18:2n-6</td>
<td>13.10</td>
</tr>
<tr>
<td>C20:2n-6</td>
<td>0.18</td>
</tr>
<tr>
<td>C20:3n-6</td>
<td>0.35</td>
</tr>
<tr>
<td>C18:3n-3</td>
<td>0.52</td>
</tr>
<tr>
<td>C20:3n-3</td>
<td>0.03</td>
</tr>
<tr>
<td>C20:5n-3</td>
<td>0.11</td>
</tr>
<tr>
<td>C22:6n-3</td>
<td>0.09</td>
</tr>
<tr>
<td>Sum n-3 fatty acids</td>
<td>14.17</td>
</tr>
<tr>
<td>Sum n-6 fatty acids</td>
<td>16.33</td>
</tr>
<tr>
<td>n-6/n-3 ratio</td>
<td>3.08</td>
</tr>
<tr>
<td>C20:3n-6/C18:3n-6</td>
<td>4.06</td>
</tr>
<tr>
<td>C22:5n-3/C20:5n-3</td>
<td>3.29</td>
</tr>
</tbody>
</table>

Comparisons are made against the non-depressed category (one-way ANOVA).

* *P < 0.05,
** P < 0.01.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Pearson correlations between depression and adipose tissue fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>Non-depressed</td>
</tr>
<tr>
<td>C18:2n-6</td>
<td>-0.007</td>
</tr>
<tr>
<td>C18:3n-3</td>
<td>-0.054</td>
</tr>
<tr>
<td>C22:6n-3</td>
<td>-0.011</td>
</tr>
<tr>
<td>Sum n-6 fatty acids</td>
<td>-0.047</td>
</tr>
<tr>
<td>Sum n-3 fatty acids</td>
<td>-0.054</td>
</tr>
<tr>
<td>n-6/n-3 ratio</td>
<td>-0.003</td>
</tr>
<tr>
<td>C20:3n-6+C22:5n-3/C20:5n-3</td>
<td>0.232</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level (2-tailed).
Recently, HELO1 (alternatively ELOVL5), a gene encoding a protein involved in the elongation of PUFA, was identified in humans [32,33]. The particular gene is located on the short arm of chromosome 6p21.1-p12.1 [32]. The highest levels of HELO1 mRNA are in testis and adrenal gland, while substantial amounts of HELO1 mRNA are found also in prostate, lung and brain tissue [32]. Chromosome 6, the largest chromosome sequenced, constitutes approximately 6% of the human genome [34]. Chromosome 6 harbors genes directly implicated, or suspected to be implicated in depression such as the heat shock protein 70 (HSP70-1) gene [35], the prolyl oligopeptidase (PREP) gene [36], the serotonin 1B (HTR1B) [37] and 1E (HTR1E) [38] receptor genes, and genes in the HLA region of the major histocompatibility complex [39]. It may be noteworthy that HELO1 is on the same domain (6p21.1-p12.1) of the cytogenetic band, albeit at an approximate distance of 11 Mb, as transcriptional regulating protein-132 (TReP-132), a protein implicated in steroid synthesis [40]. Depression has been reported to be characterized by elevated corticosteroidal activity and HPA-axis activation [41,42]. Both HELO1 and TReP-132 are highly expressed in adrenals and testis [32,40]. Cloning of the mouse orthologue of human TReP-132, indicated that expression of the gene was highest in thymus, testis and brain structures such as the hypothalamus, basal ganglia, hippocampus, and piriform and cerebral cortex. The authors concluded that although steroidogenesis pathways have not as yet been firmly established in the brain, expression of TReP-132 in the brain is an anatomical evidence that this gene may be implicated in the de novo steroid synthesis within brain regions involved in behavior and psychiatric disorders [43]. Nevertheless, although proximal genes that share related functions have been identified on the human genome, physical proximity per se does not necessitate functional association among genes [44].

Should the results of this study be replicated by other adolescent studies, this might instigate a need for investigating the possibility of an over-expression of the HELO1/ELOVL5 gene in the adipose tissue of depressed adolescents.

In conclusion, the results of the present study indicated that in this adolescent group there was no association between adipose polyunsaturated fatty acids and depression. Instead, there was a significant positive relation between depression and adipose tissue C20:3n-6/C18:3n-6, C22:5n-3/C20:5n-3, and (C20:3n-6 + C22:5n-3)/(C18:3n-6 + C20:5n-3) ratios. The observed positive relation between depression and the particular fatty acid ratios, appears to indicate increasing activity of elongases, the enzymes responsible for elongating polyunsaturated fatty acids into their longer-chain derivatives, with increasing depression. The observed relation may stem from a possible over-expression of the HELO1 (ELOVL5) gene, in the adipose tissue of depressed adolescents.

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References
