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Gluteal adipose-tissue polyunsaturated fatty-acids profiles and depressive symptoms in obese adults with Obstructive Sleep Apnea Hypopnea syndrome: A cross-sectional study

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ABSTRACT

Biomarkers of Polyunsaturated Fatty Acids (PUFAs) have been related to depressive symptoms in healthy adults. It is also known that depression is high prevalent in Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) and obesity. The aim of our study was to examine a possible association between PUFAs of the n-6 and n-3 families and depressive symptoms in obese OSAHS patients. Sixty three patients with OSAHS based on overnight attended polysomnography were included. Gluteal adipose tissue biopsies were performed in all participants. Fatty acids were analyzed by gas chromatography. Depressive symptoms were assessed by the Zung Self-rating Depression Scale. The majority of participants had grade II obesity (BMI: 36.2 ± 4.3 kg/m^2) and moderate to severe OSAHS. Mild depressive symptoms were found to affect 27.8% of the studied patients. No link between symptoms of depression and individual n-6 and/or n-3 PUFAs of gluteal adipose tissue was detected. However, multiple linear regression analysis showed a positive correlation between depressive symptoms and 20:3n-6/18:3n-6 ratio, and a negative association with age and n-6/n-3 ratio. The possible influence of OSAHS and obesity in depression development and the quiescent nature of gluteal adipose tissue may account for the absence of any significant relations between n-6 and/or n-3 PUFAs and depressive symptoms in our sample. The positive relationship between symptoms of depression and the particular fatty acid ratio probably indicates an increase in prostaglandins family although this needs further research.

1. Introduction

Depression constitutes a public-health concern in modern societies, recognized as the most prevalent mental illness in adults (Zheng et al., 1997). Several risk factors have been reported to mediate the development of depression (Department of Health and Human Services, 1999). Depression is often diagnosed in patients with Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) with a prevalence ranging from 24% to 45% (Banno and Kryger, 2007). The reason remains unclear, however OSAHS results in excessive daytime sleepiness and fatigue, symptoms that are also the characteristics of depression (Pillar and Lavie, 1998). In addition, the hypoxic events during sleep, a main feature of OSAHS, can affect mood by inducing cerebral metabolic impairment (Schröder and O'Hara, 2005). On the neurotransmitter level, the serotoninergic system is involved in the pathophysiology of both depression and OSAHS (Adrien, 2002).

Obstructive Sleep Apnea Hypopnea Syndrome is frequent in obese patients and there is evidence that obesity is present in 70% of adults with OSAHS (Malhotra and White, 2002). Obesity can result, in turn, to the development of depressive symptoms by inducing body image dissatisfaction, low self-esteem, and social discrimination (Roberts et al., 2003).

Previous studies using biomarkers of short (plasma cholesteryl esters and phospholipids) (Glatzz et al., 1989; Katan et al., 1997) and/or long term (gluteal adipose tissue) (Beynen et al., 1980; Dayton et al., 1966) dietary fat intake showed a correlation between n-3 and n-6 Polyunsaturated Fatty Acids (PUFAs) and mood disorders. Specifically, PUFAs of the n-3 family have been inversely associated with depressive symptoms (Hibbeln, 1998; Mamalakis et al., 2006), whereas n-6

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polyunsaturates and the ratio of n-6/n-3 have been reported to correlate positively (Hallahan and Garland, 2005; Maes et al., 1996). Biomarkers can provide a more accurate measure of long-term dietary intake than can dietary questionnaires (Baylin et al., 2002), and especially gluteal adipose tissue since it changes much slower in response to diet in comparison to adipose tissue in other sites (Bagga et al., 1997). The proposed mechanisms by which PUFAs are connected with depression may be through their role in the membrane fluidity; by influencing processes as neurotransmission and ion channel flow and/or the formation of pro-inflammatory eicosanoids effecting neurotransmission (Pawels and Volterrani, 2008).

The possible PUFAs-mediated depression-mechanisms may also be present in patients with OSAHS and obesity although this issue is not studied. To the best of our knowledge, the present study is a first attempt to compare the gluteal adipose tissue n-3 and n-6 PUFAs profile in OSAHS patients with and without symptoms of depression, and to investigate possible correlations.

2. Methods

2.1. Subjects

Consecutive patients diagnosed with OSAHS by overnight attended polysomnography (PSG) in our Sleep Disorders Clinic during a one year period (1/11/2008 to 1/11/2009), were included. Exclusion criteria were: a) diseases such as cardiac ischemic disease, diabetes mellitus, thyroid disorders, and malignancies, b) upper airway surgery, c) gestation, d) alcoholism, e) therapy with sleeping pills, f) use of anti-depressive medication, and g) ages $\leq$18 and >65 years. This study was approved by the ethical committee of the University of Crete.

2.2. Anthropometric measurements

An expert carried out body weight and height measurements. Weight was assayed using a digital scale instrument with accuracy of $\pm$0.1 kg. The subject was standing without shoes and wearing light clothes. Height was measured on bare-foot to the nearest 0.5 cm using a stadiometer with the shoulders in relaxed position and arms hanging freely. BMI was calculated dividing weight in kilograms by the square of the height in meters. Based on the classification of the World Health Organization (WHO, 2000) a subject was defined as obese when BMI was $\geq$30.0 kg/m^2. Participants were also subjected to questions regarding their educational level and smoking status. Smoking was a dichotomous variable (no smoking = 0, occasional or regular smoking = 1). Educational level was categorized in four levels (primary school = 0, secondary school = 1, post-high school education = 2, higher education = 3).

2.3. Depressive symptoms and sleepiness assessment

Depressive symptoms level was assessed through the use of Zung Self-rating Depression Scale (ZSRDS) (Zung, 1965). ZSRDS comprises a 20-item scale, which has been recognized for its validity and reliability for depressive symptoms assessment (Biggs et al., 1978) and translated/tested in Greek (Fountoulakis et al., 2001). The SDS scores reported here were obtained, as outlined by Zung (1973), by multiplying the raw scores by 1.25. The scores are able to vary between 25 and 100 (raw scores, 20 to 80). Patients with scores below 50 are considered as normal, while with scores 50–59 having mild depressive symptoms, 60–69 moderate depressive symptoms and scores 70 and above severe depressive symptoms (Zung, 1965). The Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness among the study subjects (Johns, 1991).

2.4. Polysomnography

Overnight attended polysomnography (PSG) (Alice 5, Respironics) was performed in the Sleep Disorders Unit University of Crete. Patients underwent a full diagnostic PSG study, according to standard techniques, with monitoring of the electroencephalogram (EEG) using frontal, central and occipital leads, electro-oculogram (EOG), electromyogram (EMG), flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort by uncalibrated impedance plethysmography belts, oximetry, and body position. Snoring was recorded by a microphone placed on the anterior neck. A single modified type II EKG lead was used for cardiac monitoring.

Polysomnographic recordings were manually interpreted over 30-second periods, in accordance with the guidelines of Rechtschaffen and Kales and the new American Academy of Sleep Medicine (AASM) guidelines (Rechtschaffen and Kales, 1968; Iber et al., 2007), and the scorer was blinded to the PSG findings of the initial clinical assessment. The determination of sleep stages and arousals was performed according to the AASM 2007 criteria and by using EEG montages including frontal, central and occipital leads (Iber et al., 2007).

2.5. Adipose tissue measures

All the participants included in this study were subjected to adipose tissue fatty acids analysis. Buttock subcutaneous tissue samples were collected by aspiration, using the method described by Beynen and Katan (1985). Samples were taken from the left upper outer quadrant of the gluteal area by using a 10-ml vacutainer tube. Prior to aspiration, sites were sprayed with local anesthetic (ethyl chloride). Adipose tissue samples were stored under nitrogen at $-$80 °C. Fatty acid analysis was performed as previously described (Mamalakis et al., 2009) using the FAME method on a gas chromatographer GC-17A (Shimadzu) with FID detector. The fatty acids were logged as percentage of the total fatty acids present in the chromatogram.

2.6. Statistical analysis

Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 17.0. Multiple linear regression with backward selection was performed with ZSRDS score as the dependent variable and age, gender, BMI, educational level, smoking, ESS, arousal index, oxygen desaturations, adipose tissue fatty acids as the initial independent variables set. Independent samples *t*-test was used to examine differences in adipose tissue fatty acid content between patients with and without symptoms of depression.

3. Results

Sixty-three patients (54 males and 9 females) who fulfilled the study criteria were included. During the selection of the study population, 837 patients were excluded based on the above-mentioned exclusion criteria (109 patients had cardiac ischemic disease, 78 patients had diabetes mellitus, 126 patients had thyroid disorders, 21 patients were suffered from malignancies, 28 had undertaken upper airway surgery, 3 were alcoholic, 11 were following therapy with sleeping pills, 43 were receiving anti-depressive medication, 203 had a BMI <30.0 kg/m^2, 70 were <18 years old and 145 were >65).

Demographic and polysomnographic characteristics of the studied subjects are presented in Table 1. In general, the studied patients were middle-aged (48.3 $\pm$ 11.7 years), in the majority men (85.7%) with moderate to severe OSAHS and class 2 obesity (BMI: 36.2 $\pm$ 4.3). Based on the Epworth Sleepiness Scale scores (ESS: 10.8 $\pm$ 5.5) patients had mild to moderate sleepiness. 17 patients (27.8%) were identified as

Table 1
Demographic and clinical characteristics of the subjects (n = 63).

	Mean ± S.D.	Min/Max
Age (years)	48.3 ± 11.7	21/64
BMI (kg/m^2)	36.2 ± 4.3	30/46.2
ZRSDS	42.1 ± 11.5	30/68.7
ESS	10.8 ± 5.5	0/22
Arousal index (events/h)	53.1 ± 19.1	18/97
O2 Desaturation (events/h)	49.5 ± 29.4	7/131
AHI (events/h)	51.5 ± 31.2	9/134

having mild symptoms of depression, 2 (3.3%) moderate while the remaining… were normal according to the ZSRDS scores.

The percentages of adipose tissue fatty acids from the n-6 and n-3 groups are shown in Table 2. No statistically significant differences were observed in adipose tissue n-3 and/or n-6 fatty acids content between OSAHS patients with and without symptoms of depression (Table 3).

The multiple linear regression analysis coefficients (Beta) with 95% confidence intervals are presented in Table 4. This multivariate model revealed significant associations between depressive symptoms and variables included in this model. Gender (p:<0.001, 95%CI: 11.05–23.53, Beta = 0.67), smoking (p: 0.007, 95%CI: 0.95–5.7, Beta = 0.32), ESS (p: 0.005, 95%CI: 0.15–0.83, Beta = 0.31) and 20:3n-6/18:3n-6 ratio (p: 0.012, 95%CI: 0.15–1.15, Beta = 0.34) were related positively, whereas age (p: 0.003, 95%CI: −0.52 to −0.11, Beta = −0.44) and the n-6/n-3 ratio (p: 0.012, 95%CI: −1.13 to −0.13, Beta = −0.36) negatively. Finally, a negative trend was indicated between symptoms of depression and educational level (p: 0.069).

4. Discussion

To the best of our knowledge this is the first study investigating possible links between depressive symptoms and Polyunsaturated Fatty Acids (PUFAs) in obese patients with Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS). Based on our results there is a positive correlation between adipose tissue 20:3n-6/18:3n-6 ratio and depressive symptoms in this population. On the other hand we found no notable differences in gluteal adipose tissue PUFAs between the studied patients with and without symptoms of depression. Obesity and OSAHS may mediate mechanisms of depression overlapping with other risk factors. Taking into account the grade of depression symptoms severity, a reason can be that our sample consisted of patients with mild and not severe depressive symptoms probably affecting the possibility to find any significant difference in fatty acid content when they were compared with patients without symptoms.

The correlation between depressive symptoms and Polyunsaturated Fatty Acids (PUFAs) remains controversial. Most of the already published studies showed no associations (Hakkarainen et al., 2004; Appleton et al., 2008; Mamalakis et al., 2008). On the other hand other studies have reported significant correlations between symptoms of depression and PUFAs from gluteal adipose tissue (Mamalakis et al., 2002; Mamalakis et al., 2006). A possible reason explaining the different results might be related to the fact that the latter studies focused on lean individuals while our patients were obese. Taking into account the low metabolic function of gluteal adipose tissue generally and especially under conditions where other fat stores are full (abdominal region) (Tan et al., 2004) the lack of any measurable relationship between adipose tissue PUFAs of the n-6 and n-3 families in our study, may be explained in part from the inactive nature of the site, where the adipose tissue biopsy was undertaken.

One unexpected finding of this study was the negative association between the ratio of n-6 to n-3 fatty acids and depressive symptoms. However recent studies have shown, that the above ratio may not be a useful marker in specific pathological situations like atherosclerosis (Willet, 2007) and it would be better when the n-6 and n-3 fatty acids are considered individually. The multifactor etiology of depression especially in specific population like OSAHS patients might be the reason of the above mentioned unexpected association. The n-6/n-3 ratio in the depression profile in our population might be of limited importance compared to other, still unresolved, factors.

The 18:3n-6 obtained by Δ6 desaturation can be immediately converted into 20:3n-6 (Oulhaj et al., 1992) or can be incorporated into cells (Hasler et al., 1991). The 20:3n-6/18:3n-6 ratio (Oulhaj et al., 1992) indicates the elongase activity that turns 18:3n-6 to 20:3n-6, versus 18:3n-6 availability and actual incorporation into cells. Dihomo-gamma-linolenic acid (DGLA, 20:3n-6) (Robertson, 1987) is present in adipose tissue and as precursor for prostaglandin E1 (PGE1) may exercises as inhibiting effect in the release of stress-related hormones (epinephrine, norepinephrine, dopamine, histamine, serotonin, and gastrin) (Mamalakis et al., 1998). On the other hand, the 20:3n-6 fatty acid is the immediate precursor of arachidonic acid that is converted to the prostaglandins family. Whether the increase of the 20:3n-6/18:3n-6 ratio that we found, is correlated with the PGD2, PGF2 and PEF2a prostaglandins increase reported in the saliva of major depressive patients (Ohishi et al., 1988) requires further research.

The positive association between gender and symptoms of depression shown in our study is in agreement with numerous previous studies reporting a high predominance of women with depression (Nolen-

Table 2
Adipose tissue fatty acid measures (mean ± standard deviation) in the subjects (n = 63).

Fatty acid	Mean	S.D.	Fatty acid	Mean	S.D.
Sum n-6	12.09	±2.32	Sum n-3	0.82	±0.17
18:2n-6	10.98	±2.34	18:3n-3	0.21	±0.06
18:3n-6	0.02	±0.01	20:3n-3	0.05	±0.03
20:2n-6	0.17	±0.05	20:5n-3	0.03	±0.05
20:3n-6	0.27	±0.08	22:3n-3	0.20	±0.05
20:4n-6	0.51	±0.11	22:5n-3	0.17	±0.05
			22:6n-3	0.15	±0.08

Table 3
Adipose tissue fatty acid measures in subjects with mild symptoms of depression v/s subjects without symptoms of depression.

Fatty acid	Without symptoms of depression (n = 42)	With mild symptoms of depression (n = 17)	*P*-value
	Mean ± S.D.	Mean ± S.D.	
Sum n-6	11.96 ± 2.47	12.42 ± 1.87	0.425
18:2n-6	10.98 ± 2.34	11.42 ± 1.78	0.420
18:3n-6	0.02 ± 0.01	0.02 ± 0.00	0.133
20:2n-6	0.17 ± 0.05	0.17 ± 0.03	0.146
20:3n-6	0.27 ± 0.08	0.31 ± 0.11	0.134
20:4n-6	0.51 ± 0.11	0.50 ± 0.13	0.711
Sum n-3	0.81 ± 0.16	0.85 ± 0.19	0.173
18:3n-3	0.21 ± 0.06	0.21 ± 0.07	0.786
20:3n-3	0.05 ± 0.03	0.04 ± 0.02	0.632
20:5n-3	0.03 ± 0.05	0.03 ± 0.05	0.464
22:3n-3	0.20 ± 0.05	0.22 ± 0.08	0.090
22:5n-3	0.17 ± 0.05	0.19 ± 0.06	0.185
22:6n-3	0.15 ± 0.08	0.17 ± 0.07	0.626

Table 4
Multiple linear regression predictors of depressive symptoms measured by ZSRDS scale.

Predictor	Beta	95% Lower CI	95% Upper CI	*P*-value
Age	−0.44	−0.52	−0.11	0.003
Gender	0.67	11.05	23.53	<0.001
Smoking	0.32	0.95	5.7	0.007
Educational level	−0.19	−3.18	0.12	0.069
ESS	0.31	0.15	0.83	0.005
n-6/n-3	−0.36	−1.13	−0.13	0.015
20:3n-6/18:3n-6	0.34	0.15	1.15	0.012

Hoeksema, 1987). Moreover, the association between smoking and depressive symptoms can be explained through nicotine's neurobiologic impact on the brain (Paperwalla et al., 2004). Subjective daytime sleepiness, a consequence of OSAHS (Zamarron et al., 2008), has been linked to depression and this relation was confirmed in our study, probably through its relation with the somatic symptoms of depression (Kjelsberg et al., 2005). The negative trend found between schooling and symptoms of depression is in congruence with others (Gallo et al., 1993), while the negative association indicated between depressive symptoms and age is rational as the possibility of experiencing depressive episodes by young adults is higher (Kuwabara et al., 2007).

One methodological issue that can be considered in our study is the lack of a control group comprised by obese adults without OSAHS; an issue for future research.

In conclusion, the present study showed a positive correlation between adipose tissue 20:3n-6/18:3n-6 ratio and depressive symptoms in obese adults suffering from OSAHS. Although it is difficult to translate pathophysiologically pathways into clinical decision statements, this finding merit further investigation to see its clinical relevance. In contrast to other studies including non-obese healthy patients, no differences in adipose tissue PUFAs profiles of patients with symptoms of depression compared to patients without symptoms as well as any associations between n-6 and/or n-3 PUFAs profile and depressive symptoms were revealed. The possible role of OSAHS and obesity in depression development and the metabolic nature of gluteal adipose tissue could account for this absence. Long term dietary n-6 and n-3 PUFAs intake as assessed in gluteal adipose tissue is probably not useful when evaluating depressive symptoms among obese OSAHS patients. However, further research is necessary in order to confirm this hypothesis.

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