Journal of Psychiatric Research 46 (2012) 1081–1085

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Reduced serum levels of adiponectin in elderly patients with major depression

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ARTICLE INFO

Article history:
Received 11 March 2012
Received in revised form
23 April 2012
Accepted 26 April 2012

Keywords:
Late-life depression
Adiponectin
Biomarker
Elderly
Cognition
Physiopathology

ABSTRACT

Recent studies have implicated adiponectin and other adipocytokines in brain function, particularly in processes related to memory and cognition. Blood levels of adiponectin are reduced in patients with primary cognitive disorders, such as Alzheimer's disease and mild cognitive impairment, and in adult patients with major depression. The aim of the present study is to determine serum levels of adiponectin in a sample of elderly patients with major depressive disorder (MDD) as compared to healthy older adults, and to examine the correlations between adiponectin levels and parameters indicative of mood and cognitive state. We recruited fifty-one unmedicated outpatients with late-life depression (LLD) and 47 age-matched controls in this study. The diagnosis of MDD was made according to the DSM-IV criteria, and the severity of depressive episode was determined with the 21-item Hamilton Depression Scale (HDRS). Cognitive state was ascertained with the Cambridge Cognitive Test (CAMCOG) and the Mini-Mental State Examination (MMSE). Serum concentrations of adiponectin were determined using a sandwich ELISA method. Serum levels of adiponectin were significantly reduced in individuals with LLD ($F = p < 0.001$). Adiponectin level remained significantly reduced in after controlling for BMI index, scores on the CAMCOG, MMSE and HDRS and educational level ($p < 0.001$). Adiponectin levels showed a negative correlation with HDRS scores ($r = -0.59$, $p < 0.001$) and BMI index ($r = -0.42$, $p < 0.001$); and showed a positive correlation with CAMCOG ($r = 0.34$, $p < 0.01$) and MMSE scores ($r = 0.20$, $p = 0.05$). The availability of circulating adiponectin is reduced in older adults with major depression, with likely implications on cognitive and mood state. Additional studies are required to determine whether this abnormality pertains to the pathophysiology of geriatric depression *per se*, or is a consequence of the morbid state.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric diseases with high prevalence in the elderly population (Castro-Costa et al., 2007). Several studies have suggested a significant association between MDD and cardiovascular and metabolic conditions, such as diabetes, stroke, heart disease (Frasure-Smith et al., 1993, 1995). Obesity is also associated to a high frequency of negative mood symptoms (Kessler et al., 2003; Patten et al., 2006; Vasiliadis et al., 2007). Epidemiological studies have documented that people who experience major depressive or manic episodes have more chance to become obese than the general population (McIntyre et al., 2006; Simon et al., 2006). Although the mechanisms underlying the relationship between obesity and depression are not fully understood, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis as well as elevated insulin resistance have been associated with increased abdominal and visceral fat in patients with MDD (McIntyre et al., 2010; Thakore et al., 1997; Weber-Hamann et al., 2005).

Besides storing energy, the adipose tissue can also secrete adipokines, such as adiponectin and resistin, which modulate sensitivity to insulin and may be implicated in the development of insulin resistance and increased visceral fat found in obese and depressed patients (Weber-Hamann et al., 2007). Adiponectin is a polypeptide secreted exclusively by the adipose tissue and corresponds to the most abundant adipose-derived serum protein.

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doi:10.1016/j.jpsychires.2012.04.028

It circulates in the blood as oligomeric complexes, and is involved in glucose homeostasis and fatty acid catabolism. Adiponectin exerts insulin-sensitizing, anti-inflammatory and anti-atherogenic functions (Pajvani et al., 2004; Hara et al., 2006). Its expression has been inversely associated with risk factors for atherosclerotic disease, hypertension and dyslipidemia (Tilg and Moschen, 2006; Han et al., 2007). Due its relationship with HPA axis, adiponectin levels could be correlated with stress and the development of psychiatry diseases (Taylor and MacQueen, 2010). In fact, previous studies reported decreased circulating levels of adiponectin in adult depressed patients (Leo et al., 2006; Narita et al., 2006, 2008).

Despite the common association between medical conditions and late-life depression (LLD) few studies so far addressed the circulating levels of adiponectin in these individuals. A previous study reported no significant differences in adiponectin levels in elderly individuals with major depression compared to healthy elderly controls (Jeong et al., 2011). Thus, the objectives of the present work are: a) to assess changes in serum levels of adiponectin in individuals with late-life depression compared to age and gender-matched healthy elderly controls, and b) to assess whether circulating adiponectin is correlated with clinical parameters (body mass index, severity of depression, cognitive functioning) in these individuals.

2. Methods

2.1. Patient recruitment and assessment

Elderly outpatients with a current major depressive episode (first or recurrent episode), assessed in the Psychogeriatric Program Outpatient Service at the Institute of Psychiatry, Faculty of Medicine of the University of São Paulo, were recruited to this study. All participants underwent a comprehensive clinical, psychiatric and cognitive assessment. The diagnosis of major depressive disorder was made according to the DSM-IV criteria (APA, 2000) following the Structured Clinical Interview for DSM-IV disorders (SCID) (First et al., 2002). The severity of depressive episode was determined with the 21-item Hamilton Depression Scale (HAM-D) (Hamilton, 1960). The minimum HAM-D scores for study entry were 10 points. Cognitive state was ascertained with the Cambridge Cognitive Test (CAMCOG) (Nunes et al., 2008; Roth et al., 1986), and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The CAMCOG is a brief neurocognitive test that independently assesses eight cognitive domains: attention, language, short and long-term memory, calculation, abstraction, praxis and perception. All depressed patients were not under antidepressant treatment at the time of psychiatric assessment and blood sampling.

The comparison group comprised healthy volunteers recruited from an ongoing clinical cohort dedicated to the study of health and cognition in older adults (Diniz et al., 2008; Forlenza et al., 2010). They were also interviewed with the SCID protocol and their cognitive function was assessed by the CAMCOG and MMSE. The elderly subjects were included in the comparison group if they did not have any evidence of current or past major depression or other major psychiatric disorder, such as bipolar disorder, schizophrenia, alcohol and other substance abuse disorder, and no evidence of current cognitive impairment.

Depressed patients and controls were excluded if they had a history of uncontrolled medical conditions, such as chronic inflammatory diseases, cardiovascular diseases and diabetes, at the time of entry in this study. Depressed patients with evidence of treatment resistant depression were not included in this study. There was no *a priori* matching strategy for the selection of subjects in the comparison group. The local ethics committee approved all procedures related to this study and it was conducted under the tenets of the Declaration of Helsinki.

After the interview, blood samples were collected from all patients between 8 and 10 A.M. after overnight fasting. After serum separation, the samples were stored at −80 °C until adiponectin analysis. The body weight and the height were measured for the calculation of the body mass index (BMI, Kg/m^2).

2.2. Adiponectin assay

Adiponectin levels were determined by Quantikine Human Total Adiponectin Immunoassay ELISA kit (R&D Systems, Minneapolis, USA). The assay conditions were controlled, standardized and pre-optimized to ensure optimal repeatability and reproducibility of the assays according to the kit instruction manual. The analytical sensitivity was 5 pg/mL.

2.3. Statistical analysis

We carried out Kolmogorov–Smirnoff test to screen for normality distribution of continuous variables prior to all analysis. HDRS scores were not normally distributed and were log-transformed prior to all analysis. Chi-square tests were carried to assess for differences in the distribution of dichotomous variables between depressed elderly patients and controls. Independent Student *t*-test was done to assess for mean differences in the socio-demographic and clinical variables, and adiponectin serum levels between depressed elderly patients and controls. Pearson correlation analysis was done to address the correlation between adiponectin levels and depressive symptoms, cognitive performance, socio-demographic and clinical variables.

3. Results

A total of 98 elderly subjects (47 depressed patients and 51 controls) were included in this study. The mean duration of the depressive episode was 13.4 ± 5.2 months and they had a mean of 2.8 ± 2.0 lifetime depressive episodes. Depressed patients had significantly lower educational level and worse cognitive performance as compared to elderly controls (Table 1). There were no significant differences in gender distribution, age, BMI index and frequency of cardiovascular comorbidities between groups (Table 1). LLD patients and elderly controls did not have previous history of cerebrovascular disease, stroke, nor had evidence of focal neurologic signs at the clinical examination.

Serum levels of adiponectin were significantly reduced in depressed patients *versus* elderly controls ($p < 0.001$). These results remained statistically significant after controlling for the effects of

Table 1
Comparison between control and depressed groups in elderly subjects.

	Control group ($n = 51$)	LLD ($n = 47$)	p
Gender (W/M)	40/11	37/10	0.9
Age (years)[a]	68.7 ± 5.6	70.2 ± 4.7	0.18
Education (years)[a]	13.9 ± 5.1	9.8 ± 4.8	<0.001
CAMCOG (mean ± SD)[a]	98.1 ± 4.4	85.8 ± 8.1	<0.001
MEEM (mean ± SD)[a]	28.9 ± 1.4	26.6 ± 2.4	<0.001
HAM-D (mean ± SD)[a]	1.2 ± 2.0	19.4 ± 6.9	<0.001
BMI (mean ± SD)[a]	23.3 ± 3.2	24.4 ± 2.5	0.1
High blood pressure[b]	78%	85%	0.6
Dyslipidemia[b]	66%	62%	0.8
Diabetes Mellitus[b]	8%	13%	0.1
Other CVDs[b]	3%	3%	0.9

Values are expressed by mean ± SD.
BMI – body mass index; CAMGOG – Cambridge Cognitive Test; MMSE – Mini-Mental State Examination; HAM-D – Hamilton Depression Scale; LLD – late-life depression. CVD: cardiovascular disease.
[a] *T*-test.
[b] Chi-square test.