

Alzheimer's Disease Patients Display Gender Dimorphism in Circulating Anorectic Adipokines

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Key Words

TNF- α · Leptin · Inflammation · Cytokine · Dementia · Aging

Abstract

Among neurodegenerative diseases, Alzheimer's disease (AD) is a leading cause of death in elderly individuals. AD is characterized, among other clinical findings, by unexplained weight loss, cachexia and altered immune function. To explore whether any relationship between gender and circulating levels of several eating-controlling metabolites exist, we evaluated leptin, tumor necrosis factor (TNF)- α , triiodothyronine (T₃), free (F) thyroxine (T₄), TSH, PRL, insulin (INS), and cortisol in 15 AD-treated patients (age range 55–82 years): 9 postmenopausal females (without hormone replacement therapy) and 6 males. The results (mean \pm SEM) indicated that circulating leptin levels were significantly ($p < 0.05$) higher in female AD (40.34 ± 11.1 ng/ml) than in male AD (6.07 ± 1.39 ng/ml) patients. The difference found in circulating leptin levels was noticed regardless of BMI (26.75 ± 1.77 and 24.55 ± 1.93 kg/m², in females and males, respectively) and waist:hip ratios (0.91 ± 0.03 and 0.94 ± 0.02 ,

in females and males, respectively). Moreover, serum TNF- α concentrations were also significantly ($p < 0.02$) higher in AD females (12.24 ± 1.47 pg/ml) than in AD males (6.62 ± 1.44 pg/ml), regardless of TNF- α :BMI ratios (0.50 ± 0.09 and 0.28 ± 0.08 , in females and males, respectively; $p > 0.05$). Finally, no differences were observed between gender (in female and male AD patients, respectively) in circulating levels of T₃ (151.33 ± 9.91 vs. 116 ± 17.04 ng/dl), FT₄ (1.26 ± 0.08 vs. 1.24 ± 0.06 ng/dl), TSH (1.28 ± 0.16 vs. 2.46 ± 0.67 μ U/ml), PRL (10.53 ± 2.47 vs. 12.61 ± 2.37 ng/ml), INS (11.76 ± 1.95 vs. 8.59 ± 1.34 μ U/ml) and cortisol (15.71 ± 1.23 vs. 12.63 ± 1.47 μ g/dl). These results indicate that our AD group of patients, with normal corticoadrenal and thyroid functions and normoprolactinemia, displayed a gender-related characteristic in the circulating levels of two very important anorectic signals, leptin and TNF- α , being both higher in female than in male AD patients, regardless of BMI. Our study suggests that increased circulating levels of both anorexigenic adipokines may contribute to the metabolic changes observed in AD females.

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Introduction

Alzheimer's disease (AD) is a leading cause of death, around the world, in elderly people. Unexplained weight loss and cachexia are frequent clinical findings in patients with AD [1]. Dysphagia is a common feature in AD patients, namely in late stages [2], however, whether the weight loss associated with advanced AD can entirely be prevented by optimizing the management of dysphagia remains unanswered. It has been claimed that the local inflammatory processes, surrounding the amyloid plaques [3], could contribute to the progression and acceleration of AD-related neurodegeneration. Experimental and clinical evidence suggests that the brain inflammatory process, due to the increase in tumor necrosis factor (TNF)- α production followed by a subsequent rise in free radicals, is instrumental in causing the pathological changes that underlie AD [4]. In fact, it has been found that the treatment in AD patients with nonsteroidal anti-inflammatory drugs (NSAIDs) ameliorates the progression of the disease [5]. Although more deep research is needed on the relationship between various pro-inflammatory cytokines and the behavioral changes characterizing major depression and AD, the immunological hypothesis has played an important role in stimulating new concepts regarding the causes of the pathological changes involved in AD. Leptin and TNF- α share, at least, two common properties: (1) they increase during the inflammatory process [6], and (2) they bind to the class 1 cytokine receptor family [7] inducing, among others, anorectic effects [8]. Interestingly, it has been reported [9] that weight loss precedes dementia in community-dwelling older adults. However, the elucidation of the role played by these two adipokines in the development of physiopathological events associated with AD still remains unclear. Although no prevalence by gender has been estimated for AD up to now, a higher risk for AD development in females than in males is evident for, among others, the longer life span of this sex. Because it is accepted that AD is a well-characterized eating disorder, the aim of the present study was to determine whether AD patients display any gender-related characteristic in several circulating eating-controlling metabolites that further could contribute to the eating disorder observed in AD patients [9].

Subjects and Design

Subjects

Fifteen outpatients with AD were evaluated in our study: 9 postmenopausal females, without hormone replacement therapy (HRT) (age range 61–82 years), and 6 males (age range 55–80 years). All patients met the DSM-III criteria for primary degenerative dementia and diagnostic for AD, based on criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [10]. Patients presented no history of stroke or ischemic attack and any type of diabetes; no focal neurological signs or symptoms; resting blood pressure not higher than 150/90 mm Hg; ECG without evidence for ischemia, infarction or serious arrhythmia; CAT scan indicating no focal pathology; normal values on blood chemistries, complete blood count, folate/B₁₂, and VDRL. Exclusion criteria were smoking, Parkinson's disease, Huntington's disease, alcoholism/substance abuse, history of schizophrenic disorder or any other psychiatric illness, endocrine disease or any type of acute infection in the last 6 months. Patients were also excluded if they had received NSAID treatment in the last 2 months. All AD patients were on vitamin E (1,000 IU/day) and donepezil (10 mg/day). The Fernandez Hospital's Research Committee approved the study protocol.

Experimental Design and Assays

Patients had a nutritional assessment, which included measurements for the calculation of body mass index (BMI) and waist-to-hip circumferences ratio (W:H). After 11–12 h fasting, blood samples were obtained by a simple vein puncture (right arm). Plasma samples were split into aliquots and kept frozen (-20°C) until determination of several plasma hormone concentrations: (a) PRL (immunoradiometric assay, Immunotech, France), standard curve between 4.6 and 180 ng/ml, coefficients of variation (CVs) intra- and interassay of 1.6–2.8 and 6.2–8%, respectively; (b) cortisol (radioimmunoassay, Immunotech), standard curve between 0.725 and 72.5 $\mu\text{g}/\text{dl}$, CVs intra- and interassay of 3–6 and 5–9%, respectively; (c) TSH (immunoradiometric assay, Diagnostic Product Corp., USA), standard curve ranging from 0.15 to 150 $\mu\text{IU}/\text{ml}$, CVs intra- and interassay of 2–4 and 4–10%, respectively; (d) leptin (immunoradiometric assay, Diagnostic Systems Lab., Webster, Tex., USA), standard curve between 0.25 and 120 ng/ml, CVs intra- and interassay of 2.6–4.9 and 3.7–6.6, respectively; (e) triiodothyronine (T₃; radioimmunoassay, Diagnostic Product Corp.), standard curve ranging from 20 to 600 ng/dl, CVs intra- and interassay of 3–8 and 5–10%, respectively; (f) free thyroxine (FT₄; radioimmunoassay, Diagnostic Product Corp.), standard curve ranging from 0.1 to 10 ng/dl, CVs intra- and interassay of 3–5 and 7–9%, respectively; (g) insulin (INS; radioimmunoassay, Diagnostic Product Corp.), standard curve ranging from 5 to 400 $\mu\text{IU}/\text{ml}$, CVs intra- and interassay of 3–7 and 5–10%, respectively, and (h) TNF- α (enzyme immunoassay, Immunotech), standard curve between 0 and 1,000 pg/ml, CVs intra- and interassay of 1.6–9.9 and 5.4–12.8%, respectively. In addition, correlations between circulating levels of leptin and TNF- α with BMI values as well as between circulating leptin and insulin/W:H ratios were calculated.

Statistical Analysis

Results, expressed as the mean \pm SEM, were analyzed by Fisher's test for comparison of different mean values, and Spearman's correlation test when appropriate [11].

Results

Clinical Features of AD Patients

Table 1 shows individual values of several parameters evaluated in AD patients of different sex. We found no significant differences among sexes in basal circulating levels of various eating-controlling metabolites (mean \pm SEM, AD females vs. males): T₃ (151.33 \pm 9.91 vs. 116 \pm 17.04 ng/dl), FT₄ (1.26 \pm 0.08 vs. 1.24 \pm 0.06 ng/dl), TSH (1.28 \pm 0.16 vs. 2.46 \pm 0.67 μ IU/ml), PRL (10.53 \pm 2.47 vs. 12.61 \pm 2.37 ng/ml), INS (11.76 \pm 1.95 vs. 8.59 \pm 1.34 μ IU/ml) and cortisol (15.71 \pm 1.23 vs. 12.63 \pm 1.47 μ g/dl). Auto-antithyroid antibody titles were undetectable in all patients.

Gender-Related Characteristics of Circulating Anorexigenic Signals in AD Patients

Figure 1 shows the results of circulating concentrations, in basal condition, of leptin (fig. 1a) and TNF- α (fig. 1b) in AD patients of different sex. Females displayed significantly ($p < 0.05$) higher levels than male AD

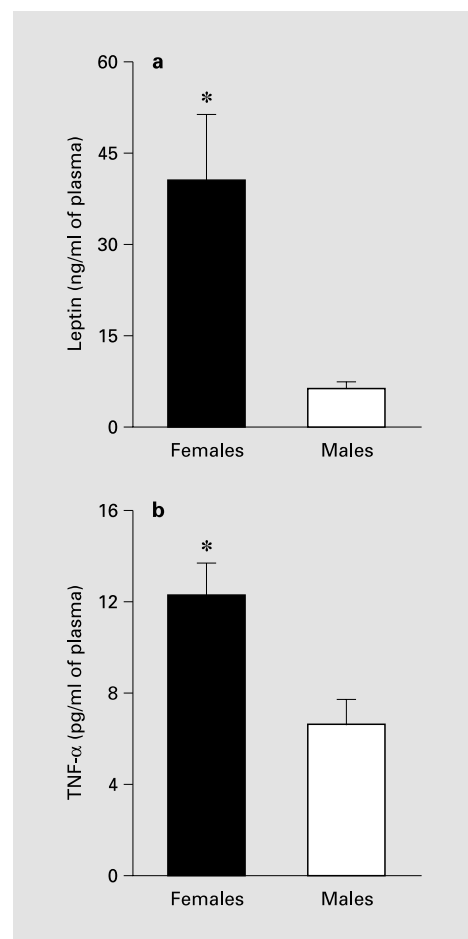


Fig. 1. Basal circulating levels of leptin (**a**) and TNF- α (**b**) in female (n = 9) and male (n = 6) AD patients. Values are the mean \pm SEM. * $p < 0.05$ vs. male values.

Table 1. Clinical features of male (M) and female (F) AD patients

Patient	Sex	Age ^a	W:H	BMI ^b	T ₃ ^c	FT ₄ ^d	TSH ^e	PRL ^f	INS ^g	Cortisol ^h
1	M	80	0.93	18.7	88	1.41	4.11	7.41	10.59	17.01
2	M	75	0.93	21.9	102	0.98	4.02	10.01	5.51	12.11
3	M	74	0.86	20.3	143	1.34	1.01	10.11	9.11	13.07
4	M	55	1.01	31.6	123	1.30	1.75	22.02	4.62	7.21
5	M	74	0.97	24.5	97	1.21	1.00	19.10	7.29	16.99
6	M	73	0.96	24.1	183	1.20	1.55	7.01	14.41	9.41
7	F	61	0.93	31.5	175	1.14	4.12	7.11	22.69	20.01
8	F	77	0.92	20.6	98	1.17	1.26	15.02	4.51	17.12
9	F	76	0.94	24.8	131	1.15	1.08	10.03	4.82	12.92
10	F	79	0.74	28.8	178	1.10	1.85	8.04	12.28	10.02
11	F	82	0.86	19.9	110	1.47	0.91	22.99	4.63	16.98
12	F	64	0.91	32.2	131	1.06	0.66	7.81	6.32	16.12
13	F	67	0.98	24.4	200	1.62	1.68	7.03	22.89	20.98
14	F	66	0.93	23.7	142	0.98	1.76	7.79	12.23	18.13
15	F	67	0.86	34.9	147	1.33	0.81	5.52	12.18	11.98

^a Years; ^b kg/m²; ^c ng/dl of plasma (NR: 80–220); ^d ng/dl of plasma (NR: 0.70–1.80); ^e μ IU/ml of plasma (NR: 0.50–4.50); ^f ng/ml of plasma (NR: 4–20); ^g μ IU/ml of plasma (NR: up to 30); ^h μ g/dl of plasma (NR: 9.4–26.1).

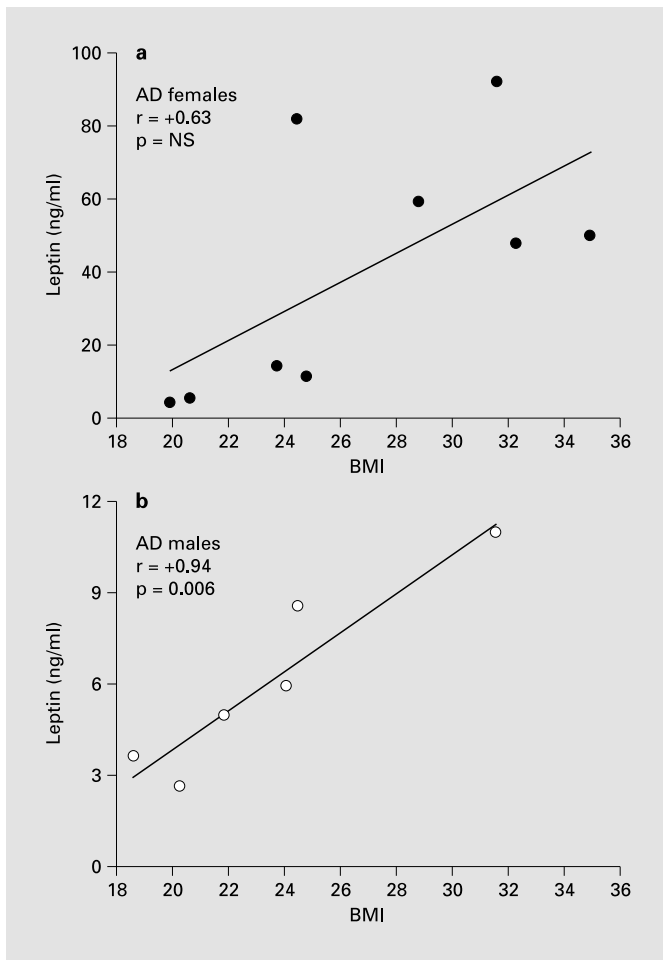


Fig. 2. Direct correlation between BMI and basal circulating concentrations of leptin in female (**a**, $n = 9$) and male (**b**, $n = 6$) AD patients. Coefficient of correlation (r) and statistical significance (p) are indicated.

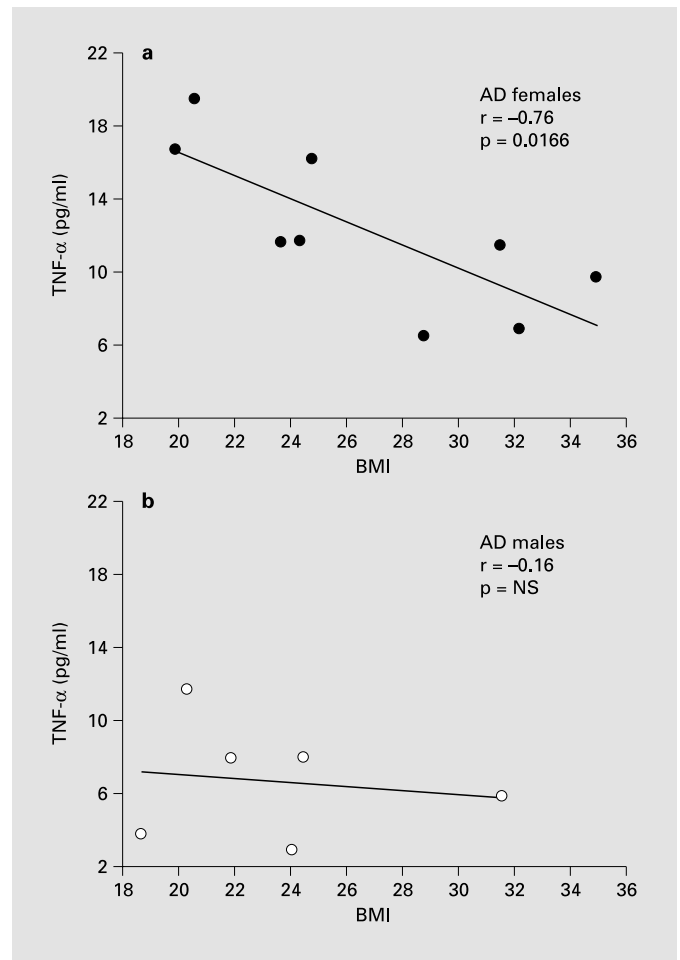


Fig. 3. Inverse correlation between BMI and basal circulating concentrations of TNF- α in female (**a**, $n = 9$) and male (**b**, $n = 6$) AD patients. Coefficient of correlation (r) and statistical significance (p) are indicated.

patients in both eating-controlling peptides. In fact, plasma leptin (fig. 1a) values were (approximately) 5-fold higher in AD female than in AD male patients and circulating TNF- α (fig. 1b) concentrations were (approximately) 2-fold higher in female than in male AD patients. It is important to remark that these two adipokines were higher in females than in males despite similar BMI.

Interestingly, plasma leptin values significantly ($p = 0.006$) correlate ($r = +0.94$) with BMI (fig. 2b) and with W:H ratio ($p = 0.0103$) ($r = +0.92$) in male AD patients; conversely, female AD patients did not display any of these correlations ($r = +0.63$, $p > 0.05$ for BMI, fig. 2a; $r = +0.02$, $p > 0.05$ for W:H ratio), thus clearly indicating that the increase in the most important peripheral anorexigenic signals in AD females is not due to increased BMI.

Interestingly, female AD patients displayed a significant ($p = 0.0166$) inverse correlation ($r = -0.76$) between circulating concentrations of TNF- α and BMI (fig. 3a), however, this correlation was not statistically significant in AD males ($r = -0.16$, $p > 0.05$) (fig. 3b).

Finally, female AD patients displayed a significantly positive correlation between serum leptin and serum insulin concentrations ($p = 0.0004$) ($r = +0.92$), as normally expected (fig. 4a); conversely, in male AD patients, serum leptin and insulin levels did not display significant correlation between these signals (fig. 4b). No other type of correlation between hormones was found in our study.

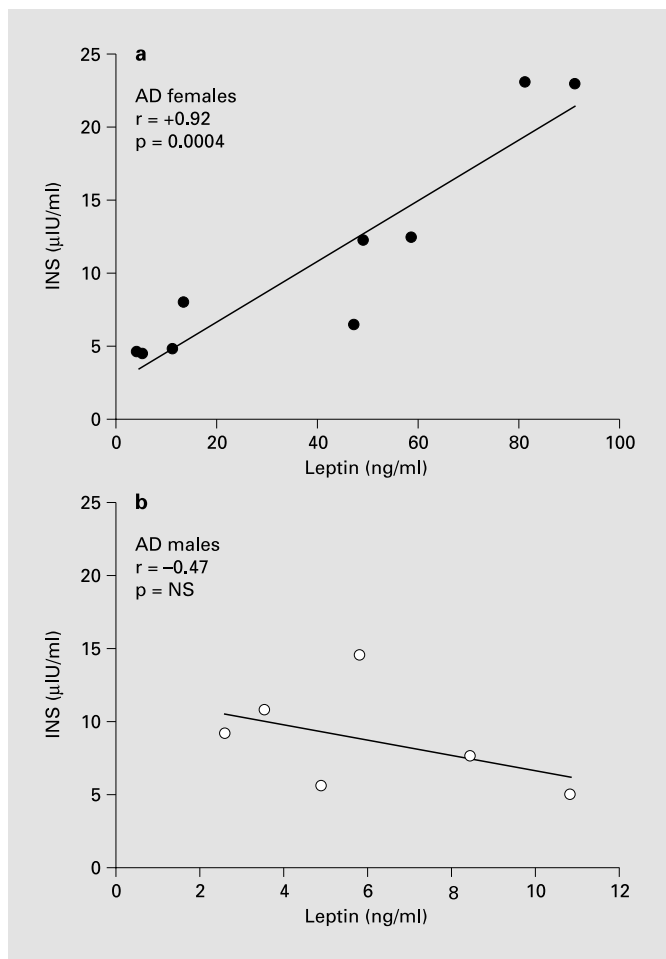


Fig. 4. Correlation between basal circulating levels of leptin and insulin in female (**a**, $n = 9$) and male (**b**, $n = 6$) AD patients. Coefficient of correlation (r) and statistical significance (p) are indicated.

Discussion

To our knowledge, this is the first study showing gender prevalence in plasma levels of leptin and $\text{TNF-}\alpha$, the most physiologically relevant circulating, anorexigenic signals in AD patients. The gender dimorphism was characterized by higher peripheral levels of adipokines in female than in male AD patients. Importantly, this characteristic was not dependent on differences in BMI, thus clearly indicating a highly probable adipocyte overfunction in AD postmenopausal women without HRT. Furthermore, other peripheral eating-controlling signals evaluated (T_3 , FT_4 , TSH, PRL, INS and glucocorticoid) in AD patients did not display any sex-related difference and were within the normal range.

AD is one of the most common neurodegenerative diseases associated with aging. Although the exact cause remains still unclear, this illness could be considered of a complex origin, with both genetic and environmental inputs [12]. Although studies on overall dementia did not find any gender prevalence, it has been described that there is a tendency of higher rate of AD incidence in females than males [13] and that the incidence of AD in females increases with age [14]. Conversely, vascular dementia seems to be more common in males than in females [15], thus indicating the complexity in the development of different types of dementia. Leptin is an important factor in the regulation of appetite and energy expenditure [16]. Previous studies have revealed increased serum leptin levels in females than males in both normal [17] and obese [18] subjects, even after the correction of leptin serum concentrations for percentage in body-fat composition [17]. We presently found that this characteristic remains in AD patients. The normal mechanisms driving gender differences in circulating leptin are not fully understood. Hellstrom et al. [19] proposed that, in normal subjects, sex-related differences in circulating leptin could be due to, at least in part, a higher proportion of adipose tissue and/or increased production rate of leptin, per mass unit of adipose tissue, in females than in males. However, it should be not excluded that subcutaneous fat expresses more leptin mRNA than intra-abdominal fat [20]. Moreover, a suppressive effect of androgens [21] and a positive action of estrogens [22] on adipokine production have also been proposed. Several studies in psychiatrically ill subjects indicate that the treatment with antipsychotic drugs could increase body weight [23] and circulating leptin [24]. However, the gender-related difference in circulating leptin found in our AD patients seems to be not due to the pharmacological therapy itself since all patients were under identical drug treatment, and for a similar period of time. Whether the sexual dimorphism in other eating-controlling signals could account for the difference in leptin signaling is an open field for research. For instance, hypothalamic NPY expression [25] and secretion [26] have been proposed to be under a sexual dimorphic control. Also, the brain is a source of leptin production [27], and it has been suggested that the proportional participation of the brain to the circulating plasma leptin pool is larger in females than in males [27]. In addition, the leptin-saturable transporter system, from the periphery into the brain [28], could be under a gender-related regulation. We found also significant direct correlation between circulating leptin and BMI, and between plasma leptin levels and W:H in AD male but not female

patients. These gender-related differences could possibly indicate a disrupted communication between adipocyte and brain functions [29], thus contributing to an increased satiety signal in female AD patients.

It has been described that increased levels of circulating TNF- α are characteristic of AD [30], however, we now show that this event is displayed, in AD patients, in a gender-related fashion and regardless of similar BMI, being higher in female than male AD patients. Although it is not clear why females have higher TNF- α levels than males, it is possible that enhanced leptin could activate cytokine secretion from both peritoneal macrophages [31] and, in a paracrine fashion [32], adipocytes. In addition, low circulating levels of estradiol, as occurs in postmenopausal females, might stimulate cytokine production. In fact, a previous study demonstrated increased cytokine (IL-1) production in postmenopausal females [33], and that estrogen replacement therapy reversed this effect [34]. Interestingly, we found a significant negative correlation between serum TNF- α levels and BMI only in AD females. This observations probably represents an increased satiety signal previously described in different states of cachexia, either related or not to cancer [35], in female patients; thus weight loss that occurred in cancer and AD could be mediated by a common pathway [36]. Conversely, we did not find any positive correlation between peripheral TNF- α and leptin levels, nor between serum TNF- α and insulin concentrations, as observed in normal subjects [37], thus probably indicating an additional disrupted communication between these eating-controlling signals.

Although the precise role of increased circulating leptin and TNF- α levels in AD females is uncertain, it could be expected that they might play a protective role within the brain against illness in this sex. Several studies indicate that leptin regulates protein expression of neuronal/glial origin [38] and neurotransmission [39]. Leptin has recently been proposed to counterregulate the inflammatory effect of IL-1 [32], a cytokine implied in the pathophysiology of AD [40]. In addition, it has been reported that TNF- α is able to promote neuron survival [41]. On the other hand, leptin and TNF- α could play a degenerative role by interfering with the insulin or insulin-like growth factor I (IGF-I) signal [42, 43], thus contributing with the impaired glucose metabolism described in AD [9] and modulating the immune response, as proposed in other types of dementia [44]. AD certainly is a pathology associated with weight loss [45], however, the exact mechanisms linking AD and weight loss are still unclear. Our finding of increased peripheral TNF- α levels in female

AD patients could indicate that these anorectic signals could be contributing to the weight loss [7]. Throughout our study, however, the precise origin of adipokines in AD females contributing to enhanced peripheral levels, cannot be fully ascertained; in fact, they could be derived from the adipocyte and other, non-adipocyte sources (e.g. brain, immune cells).

Finally, although adrenal dysfunction in AD has been described [46], our group of AD patients, as well as those reported earlier [47], displayed normocortisolemia without gender-related differences. Also, a higher frequency of prior thyroid disease in AD females than in normal female controls has been claimed [48], however, this observation remains controversial. In fact, the present study and previous results [49] indicate normal thyroid function in AD patients of both sexes. It is recognized that prolactin is implicated in the regulation of the immune function [50], however, very few studies have been focused on the relationship between PRL and AD; in our study, mean PRL levels were within the normal range and no gender-dependent differences were noticed.

In summary, to our knowledge, this is the first study describing a sexual dimorphism in the circulating levels of anorectic adipokines in AD patients. Our results suggest that increased levels of adipokines may contribute to develop metabolic changes in AD patients in a gender-related fashion and, in turn, they could interfere with the insulin receptor-signaling system characteristic of AD [51]. This study indicates that more prospective research is needed to clarify the precise role of anorexigenic adipokines on the disrupted eating behavior characterizing female AD patients.

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