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ORIGINAL ARTICLE

Fasting serum leptin levels in elderly women with major depressive disorder: a case-control study

Ewa Szczepocka[1], Anna Łucka[1], Adam Wysokiński [1]

1 Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Lodz, Poland

Correspondence to: Adam Wysokiński M.D., Ph.D.
Department of Old Age Psychiatry and Psychotic Disorders
Medical University of Lodz
Czechosłowacka 8/10, 92-216 Łódź, Poland
TEL.: +48 42 675 73 72; FAX: +48 42 675 77 29;
E-MAIL: adam.wysokinski@umed.lodz.pl

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Abstract

OBJECTIVE: Leptin is produced in the adipose tissue. It controls energy homeostasis by reducing food intake and increasing energy expenditure. According to the "leptin hypothesis of depression", chronic stress leads to reduced leptin concentration and leptin insufficiency may underlie depressive symptoms. However, it is also hypothesized that observed in depressed patients differences in leptin levels may be secondary to differences in adiposity. The aim of this case-control study is to evaluate fasting serum leptin levels in elderly women with major depression disorder and to compare them with non-depressed elderly women.

METHODS: We measured fasting serum leptins levels and body composition in 32 elderly (age ≥60 years) European Caucasian women with major depression disorder and in 49 non-depressed elderly (age ≥ 60 years) European Caucasian women.

RESULTS: There was no statistically significant difference (p=0.14) in fasting serum leptin level between patients with depression (3.04±1.79 ng/mL) and control subjects (2.46±1.70 ng/mL).

CONCLUSIONS: In two groups of subjects with comparable adiposity parameters we did not confirm that leptin level is changed in patients with depression. We assume that changes in leptin level in patients with depression may be mediated by adiposity.

INTRODUCTION

By 2020 major depressive disorder (MDD) will become the second most important cause of disability worldwide. (Murray & Lopez 1997) Depression is particularly common in the elderly (where its prevalence varies from 4.6% to 9.3%), while depressive symptoms are present in up to 40% elderly individuals. (Luppa *et al.* 2012) Depression may significantly affect the quality of life and directly increase mortality, but also depression has been associated secondary comorbidity and mortality due to diabetes and cardiovascular disease (CVD). (Knol *et al.* 2006)

Leptin, an anti-obesity hormone, is produced in the white adipose tissue. It controls energy homeostasis (Tilg & Moschen 2006), its level is directly proportional to the size of body fat. (Benoit *et al.* 2004) Leptin is synthesized primarily by adipocytes, mostly in the subcutaneous fat tissue than visceral fat tissue. (Baumgartner *et al.* 1999) Leptin suppresses energy consumption and

reduces food intake (Weigle *et al.* 1995) and increases energy expenditure. In obese people, sensitivity of neurons to leptin is reduced. This is accompanied by increased blood level of leptin and impaired leptin transport through the blood-brain barrier (due to saturation of leptin transporter with high concentration of peripheral leptin). We can therefore speak of leptin resistance. (Cusin *et al.* 1996)

According to the "leptin hypothesis of depression" leptin may modulate mood regulation. (Lu 2007) According to this hypothesis, chronic stress leads to reduced leptin concentration and leptin insufficiency may underlie depressive symptoms. Leptin may regulate mood via: interactions with monoamines, hypothalamic-pituitary-adrenal axis and its neurotrophic activity. (Taylor & Macqueen 2010) However, available results regarding the hypothesis are controversial: some studies showing reduced (Jow *et al.* 2006) and other increased (Rubin *et al.* 2002) or comparable (Deuschle *et al.* 1996) leptin concentration in depression. A recent meta-analysis has shown that leptin levels were significantly higher in individuals with mild/moderate depression versus controls and did not change after antidepressant treatment. (Carvalho *et al.* 2014) Animal studies suggest that reduced leptin level is associated with depression-like behavior. (Haleem 2014) It is however probable that observed difference may result not from depression, but are influenced by age, sex, body mass and the amount of adipose tissue. (Morris *et al.* 2012)

Aging is associated with increased risk of MDD, especially in women. (Djernes 2006) With aging body composition is also changing. Studies have shown that in Caucasian subjects aged >65 years body weight and lean (fat-free) body mass (LBM) is decreasing with age, while total body fat (TBF) is increasing in men and does not change or is decreasing in women. (Kyle *et al.* 2001) Since leptin production depends upon the amount of body fat and reduced leptin concentration was postulated to be involved in the pathogenesis of depression, aging-related changes in TBF (Kyle *et al.* 2001) and secondary changes in leptin levels might be responsible for increased risk of depression in elderly subjects (Milaneschi *et al.* 2014). Therefore, the aim of this study was to evaluate fasting serum leptin levels in elderly women with unipolar depression and to compare them with non-depressed elderly women, matched for various adiposity parameters (anthropometric parameters and body composition), to exclude the effect of these variables.

METHODS

Subjects

Thirty two elderly (age ≥60 years) European Caucasian women with unipolar depression (F32 and F33 according to ICD-10) were included into the study (MDD group). All patients were under ambulatory care for depression. Diagnosis was established by an attending psychiatrist, using ICD-10 criteria. Inclusion criteria were: diagnosis of unipolar depression and stable condition, defined as no changes in antidepressive treatment for at least 2 months prior the study. Forty nine non-depressed elderly (age ≥60 years) European Caucasian women were selected as control group (matched for: age, body mass index, fat mass index, total body fat, and visceral adipose tissue mass). The healthy volunteers had neither self-reported personal or familial psychiatric history nor medication history from semi-structured interview and had normal laboratory findings. All women were post menopause. Only non-demented subjects, screened using Mini-Mental State Examination (MMSE) with score ≥24, were included into the analysis. All subjects had a normal results for blood profile, ALT, AST, urea, creatinine, bilirubin, and electrolytes. Subjects with acute and chronic inflammatory conditions (e.g. pneumonia, rheumatoid arthritis), immunological disorders (e.g. AIDS, allergy), and cancer were excluded from the study. All study subjects have been informed about aims and methods of the study and expressed written informed consent. The study protocol was approved by the local bioethics committee. There was no financial involvement from the industry.

Leptin

Blood samples were collected between 7 am and 8 am, after at least 8 h of fasting. The samples were immediately transferred to the laboratory. Blood samples were centrifuged (3500 rpm, 4°C, 10 minutes) and analyzed (triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol and plasma glucose levels) using automatic analyzer Dirui CS-400 (Dirui, China). Leptin level was measured in blood serum using ELISA (enzyme-linked immunosorbent assay) method, serum samples were stored at -80°C for up to 12 months. ELISA assays were performed using commercial kits (Intra-Assay CV<10%) manufactured by Elabscience (China), according to protocol provided by its manufacturer (samples were not diluted).

Anthropometry

Height was measured with a wall-mounted height measure to the nearest 0.5 cm. Weight was measured with a seca 955 (seca, UK) digital chair scale, with subjects undressed. Waist and hip circumferences were measured using a non-stretchable fiber measuring tape. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated respectively as body weight in kilograms divided by height in meters squared (kg/m^2) and waist circumference divided by hip circumference.

Body composition

Body composition was measured using bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). For BIA we used Maltron BIOSCAN 920-2-S

Body Fat Analyzer (Maltron, UK) analyzer. For DXA we used Lunar iDXA scanner (GE Healthcare, UK) with enCORE 15 SP2 software. Standard operating conditions were observed by a trained operator. The measurements were taken immediately prior to anthropometry measurements with participants lying supine, resting. BIA determines the electrical impedance to calculate total body water, which can be used to estimate fat-free body mass and body fat. In DXA two X-ray beams, with different energy levels, are aimed at the patient's body and different tissue types (bone, muscle, fat) can be determined from the absorption of each beam by tissues. The following body composition parameters were measured using DXA: TBF, LBM, visceral adipose tissue (VAT) mass (expressed in kg), VAT volume (expressed in cm^3). TBF and LBM are expressed both in kilograms and as percentage of total body mass. Subcutaneous adipose tissue (SAT) and VAT area (expressed in cm^2) was measured at the level of the umbilicus, using data collected using the Maltron BIA. These two measurements can only be done using BIA. Fat mass index (FMI) was calculated as total body fat in kilograms (measured using DXA method) divided by the height in meter squared (kg/m^2).

Other measurements

We have assessed depression severity using 15-item Geriatric Depression Scale (GDS-15) (scores of 0–4: normal; 5–8: mild depression; 9–11: moderate depression; and 12–15: severe depression). (Marc *et al.* 2008) Type of diet, smoking and alcohol consumption were assessed using questionnaires prepared for the study protocol. Appetite, thirst, sedation, level of physical activity were assessed subjectively, using a standard 10-point visual analogue scale (with score 1 interpreted as extremely low and score 10 interpreted as extremely high). Appetite was additionally assessed using the Short Nutritional Assessment Questionnaire (SNAQ), with score<14 indicting loss of appetite (Hanisah *et al.* 2012). We did not assessed detailed dietary patterns. Behavioral factors were assessed because they may also affect body composition and leptin levels. (Baumgartner *et al.* 1995)

Statistical analysis

Statistical procedures were performed with STATA 14.2 (StataCorp, USA). Means and standard deviations were generated for all continuous variables. For discrete variables absolute numbers and percentages are given. Normality of distribution was tested with Shapiro-Wilk

Tab. 1. Demographic and clinical characteristics

	Depression (n = 32)	Control (n = 49)	*p*
Age [years]	69.8±4.6	68.2±5.7	0.19
Smokers	5 (15.6%)	8 (16.3%)	0.93
Alcohol consumption			
None	14 (43.8%)	9 (18.4%)	0.04
≥1 standard units/week	18 (56.2%)	40 (81.6%)	
Physical activity			
None	16 (50.0%)	19 (38.8%)	0.51
Mild	13 (40.6%)	22 (44.9%)	
Moderate	3 (9.4%)	8 (16.3%)	
VAS: physical activity	4.7±2.2	5.7±2.5	0.06
VAS: sedation	4.01±3.09	2.76±2.11	0.03
VAS: appetite	5.0±2.5	5.6±1.9	0.22
VAS: thirst	4.9±3.0	5.3±2.1	0.63
SNAQ	14.9±2.5	16.1±1.8	0.02
Antihypertensive treatment	18 (56.2%)	20 (40.8%)	0.17
Lipid-lowering treatment	11 (34.4%)	22 (44.9%)	0.35
Antidiabetic treatment	2 (6.2%)	5 (10.2%)	0.54
Triglycerides [mg/dL]	142.5±62.5	126.1±58.3	0.25
Total cholesterol [mg/dL]	228.2±69.3	208.3±46.4	0.31
HDL cholesterol [mg/dL]	45.1±10.7	46.3±11.8	0.65
LDL cholesterol [mg/dL]	154.7±65.9	137.1±41.2	0.35
Fasting plasma glucose [mg/dL]	94.7±32.1	94.8±13.6	0.39

Data given as mean±standard deviation or n(%).
VAS = visual analogue scale; SNAQ = Short Nutritional Assessment Questionnaire.

Tab. 2. Anthropometric parameters and body composition

	Depression (n = 32)	Control (n = 49)	*p*
Weight [kg]	74.8±14.2	70.0±12.2	0.11
BMI [kg/m^2]	29.8±5.7	27.9±4.2	0.08
FMI [kg/m^2]	12.9±4.1	12.7±4.7	0.32
Waist circumference [cm]	100.4±14.6	93.3±11.4	0.01
Hip circumference [cm]	108.9±10.8	104.6±9.9	0.06
WHR	0.92±0.07	0.89±0.06	0.05
Total body fat [kg]	32.2±9.9	31.8±12.1	0.35
Total body fat [% of total body weight]	42.2±7.7	43.5±14.5	0.31
Lean body mass [kg]	42.0±9.8	41.4±7.8	0.99
Lean body mass [% of total body weight]	57.1±12.9	58.0±10.8	0.18
VAT area [cm^2]	161.6±86.8	125.5±71.8	0.03
SAT area [cm^2]	143.5±52.0	130.2±45.2	0.23
VAT mass [kg]	1.36±0.66	1.14±0.58	0.11
VAT volume [cm^3]	1444.5±703.5	1207.4±614.8	0.11
HDL cholesterol [mg/dL]	45.1±10.7	46.3±11.8	0.65
LDL cholesterol [mg/dL]	154.7±65.9	137.1±41.2	0.35
Fasting plasma glucose [mg/dL]	94.7±32.1	94.8±13.6	0.39

Data given as mean±standard deviation or n(%).
BMI = body mass index; FMI = fat mass index; WHR = waist to hip ratio; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue.

test. Leptin level was transformed for normality using square root transformation and analyzed using parametric tests (Student's t-test, one-way analysis of variance, Pearson's correlation). Linear regressions were performed to examine the relationship between serum leptin and anthropometric parameters or body composition. Regression models were adjusted for age, smoking and alcohol consumption (as they may influence body composition and leptin expression). Adjusted effect sizes, P values, F values and R2 were computed for the linear regression models. The level of significance was set at $p<0.05$ (two sided).

RESULTS

Demographic and clinical characteristics are shown in Table 1. Apart from alcohol consumption, SNAQ score and level of sedation, there were no differences between both groups. The majority of patients (84.4% in MDD group and 75.5% in the control group) were not on any special diet. We found that SNAQ score was strongly positively associated with level of appetite assessed using visual analogue scale (r = 0.73, $p<0.001$). There were more subjects with SNAQ<14 in MDD group (9, 28.1%) compared with the control group (4, 8.2%), $p=0.02$. This may indicate that more depressed subjects might have increased risk of malnutrition due to reduced appetite. With the exception of WHR and VAT area, analysis of cardio-metabolic anthropometric and body composition parameters (Table 2) revealed no inter-group differences and we did not find differences for body composition parameters.

In MDD group treatment duration was 149.0±83.4 months, number of hospitalizations 1.3±1.4. All MDD patients were taking antidepressants (mainly selective serotonin reuptake inhibitors or selective serotonin and norepinephrine reuptake inhibitors), mostly (19, 61.3%) in monotherapy. Daily dose of antidepressants (expressed in defined daily dose units) was 1.1±0.5, which indicates regular doses of antidepressants. Detailed information on the treatment in shown in Appendix 1. Depressed subjects had higher GDS-15 score (18.0±4.0 vs. 5.4±2.9, $p=0.002$).

There was no statistically significant difference ($p=0.13$) in fasting serum leptin level between MDD (3.04±1.79 ng/mL) and control (2.46±1.70 ng/mL) groups, see Figure 1. The difference remained non-significant after adjusting for waist circumference and VAT area ($p=0.42$). Leptin level did not correlate with age ($p=0.73$). Also, there was no difference for leptin level in smokers ($p=0.16$) or subjects drinking alcohol ($p=0.33$). In MDD group leptin was not correlated with depression duration ($p=0.91$) or severity ($p=0.68$) and total dose of antidepressants ($p=0.72$). There were few healthy subjects with GDS score > 4 (a cut off point for depression), we found no difference in leptin level between subjects with GDS<5 and with GDS≥5 (2.68±1.78 vs. 2.72±1.59 ng/mL, $p=0.95$).

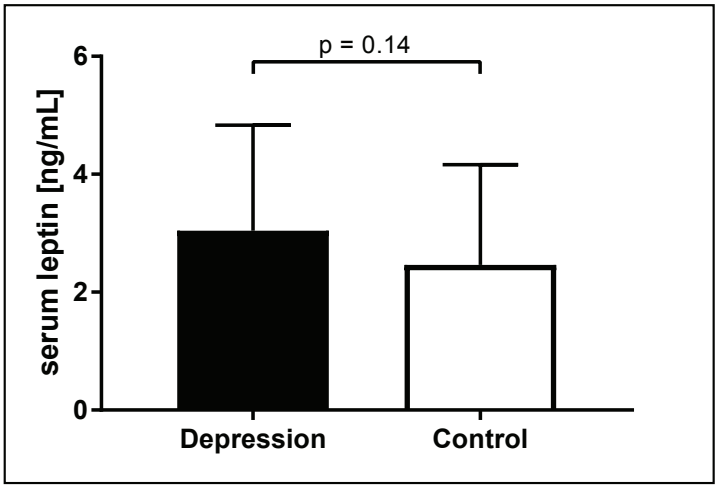

Fig. 1. Fasting serum leptin concentration in the study groups.
Vertical bars represent standard deviation.

Fasting serum leptin level was correlated with body weight (r = 0.29, *p*=0.009), BMI (r = 0.26, *p*=0.02), waist circumference (r = 0.29, *p*=0.008), WHR (r = 0.32, *p*=0.003), LBM (r = –0.26, *p*=0.02), SAT area (r = 0.37, *p*<0.001), VAT mass (r = 0.29, *p*=0.009) and VAT volume (r = 0.29, *p*=0.009). Leptin level was not correlated with appetite (*p*=0.65 for SNAQ, *p*=0.69 for VAS). In order to analyze these associations we used linear regression models, with all models adjusted for age, smoking and alcohol consumption. This analysis confirmed associations between leptin levels and BMI or markers of abdominal obesity (WHR, visceral and subcutaneous abdominal tissue) – detailed results are shown in Table 3.

DISCUSSION

The main objective of the study was to compare fasting serum leptin levels between depressed and non-depressed elderly women. We failed to find differences in this regard and did not confirm previous observations that leptin level is reduced in depression. (Jow *et al.* 2006) This may result from the fact that in previous studies only a very crude estimator of body composition was used. Since leptin production is directly regulated by the adipose tissue, any differences in the amount of this tissue may affect leptin concentrations and consequently – differences between depressed and non-

Tab. 3. Linear regression analysis (adjusted for age, smoking and alcohol consumption) of fasting serum leptin and anthropometric parameters and body composition

	Depression (n = 32)			**Control (n = 49)**			**Whole study sample (n = 81)**		
	Beta	***p***	**R^2**	**Beta**	***p***	**R^2**	**Beta**	***p***	**R^2**
Weight [kg]	0,01	0,51	0,18	**0,04**	**0,04**	**0,12**	**0.04**	**0.02**	**0,11**
BMI [kg/m^2]	0,05	0,42	0,19	0,11	0,06	0,10	**0,09**	**0,03**	**0,10**
FMI [kg/m^2]	0,07	0,42	0,19	0,03	0,56	0,04	0,04	0,36	0,05
Waist circumference [cm]	0,01	0,54	0,18	**0,05**	**0,02**	**0,14**	**0,03**	**0,01**	**0,12**
Hip circumference [cm]	0,01	0,74	0,17	0,03	0,23	0,06	0,03	0,12	0,07
WHR	4,04	0,42	0,19	**12,93**	**0,004**	**0,20**	**9,25**	**0,003**	**0,15**
Total body fat [kg]	0,03	0,43	0,19	0,02	0,45	0,04	0,02	0,26	0,06
Total body fat [% of total body weight]	0,05	0,31	0,20	0,01	0,75	0,03	0,01	0,41	0,05
Lean body mass [kg]	0,01	0,90	0,17	0,01	0,91	0,03	-0,01	0,89	0,04
Lean body mass [% of total body weight]	-0,06	0,21	0,21	-0,03	0,21	0,07	-0,03	0,08	0,08
VAT area [cm^2]	0,01	0,93	0,17	0,01	0,12	0,08	0,01	0,19	0,07
SAT area [cm^2]	**0,01**	**0,039**	**0,29**	**0,01**	**0,047**	**0,27**	**0,01**	**0,004**	**0,15**
VAT mass [g]	0,14	0,77	0,17	**1,10**	**0,01**	**0,17**	**0,78**	**0,013**	**0,11**
VAT volume [cm^3]	0,01	0,77	0,17	**0,01**	**0,01**	**0,17**	0,01	0,013	0,11

BMI = body mass index; FMI = fat mass index; WHR = waist to hip ratio; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue.

depressed subjects. Hence, we matched our patients with non-depressed subjects for anthropometric parameters and body composition. By analyzing a subgroup of elderly women we have eliminated the effect of age and sex, which may affect leptin concentration.

The leptin hypothesis of depression is supported by several studies. While there are some studies showing that the association between leptin and depression is independent from adiposity (Lawson *et al.* 2012), the majority of studies emphasizes the role of adiposity as a mediator between leptin and depression. In National Health and Nutrition Examination Survey (NHANES), a large observational study (1046 men and 1359 women aged 20–39 years), it was confirmed that the relationship between leptin and depression was significantly moderated by adiposity. (Ubani & Zhang, 2015) Another study confirmed that in older patients with depression (n = 851) the association between leptin and depressive symptoms is modulated by abdominal adiposity.(Milaneschi *et al.* 2014) The role of low leptin signaling rather than low leptin concentration as a risk factor for depression was emphasized. These observations reflect our results and support a hypothesis presented by Shelton *et al.*: changes of certain biomarkers of depression (e.g. pro-inflammatory cytokines, e.g. IL-6 or CRP) may be explained, at least partly, by obesity and not depression itself. (Shelton *et al.* 2015) Obesity may be a depression risk factor (Hamer *et al.* 2012) and treatment with antidepressants may trigger weight gain. (Arterburn *et al.* 2016) Considering that leptin secretion is regulated by the adipose tissue and that our study groups have similar amounts of total body fat, visceral and subcutaneous adipose tissues, we assume that changes in leptin level in depressed patients are secondary to body composition and its depression- or treatment-associated changes.

In this study we have compared two groups of elderly women (depressed and non-depressed) of comparable anthropometric parameters and body composition. Many lifestyle factors, such as smoking, exercise, diet and alcohol intake, are well known to influence body fat distribution. We may assume that both study groups were comparable in terms of the majority of analyzed demographic and clinical properties. Alcohol consumption may also contribute to production of leptin. It was found that women consuming moderate amounts of alcohol had higher serum leptin level. (Roth *et al.* 2003) We have found that consumption of alcohol was higher in the control group and this could have affected lack of observed difference in leptin level. However, according to Roth *et al.* the difference in leptin level was significantly associated with alcohol consumption only in pre-menopausal women, while in subjects aged ≥55 this association was no more significant.

Further studies on the leptin hypothesis of depression must include evaluation of body composition, as changes of leptin in depression may be mediated by changes in the amount of body fat. There are certain important limitations of the study, which must be taken into consideration when analyzing our result: small study groups, heterogeneous treatment and cross-sectional design, which limits its ability to establish a causal relationship. On the other hand, we studied groups that are very comparable in terms of many confounding factors, thus limiting their impact.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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