

Leptin, adiponectin, leptin to adiponectin ratio and insulin resistance in depressive women

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Abstract

BACKGROUND: Depressive disorder (DD) is associated with an increased risk of type 2 diabetes mellitus (DM2) and cardiovascular disease (CVD). It was suggested, that metabolic syndrome (MetS), cluster of metabolic and hormonal changes, such as insulin resistance (IR), abdominal obesity, dyslipidemia, arterial hypertension and elevated fasting glycaemia, could stand behind the connection. Recent findings have shown, that adipocytokines leptin and adiponectin might play a role in both depression and MetS.

AIM: The aim of this pilot study was to observe the plasma concentrations of leptin, adiponectin, leptin-to-adiponectin ratio and indices of IR in women with depressive disorder.

MATERIALS AND METHODS: The plasma leptin, adiponectin, parameters of lipid and glucose homeostasis and indices of IR were investigated in a group of 38 women with DD. The results were compared with those of 38 healthy women of the control group, matched for age.

RESULTS: Depressive women differed significantly from the controls in higher concentrations of plasma leptin ($p < 0.05$), insulin ($p < 0.01$), C-peptide ($p < 0.01$), value of HOMA-IR ($p < 0.01$), and the leptin-to-adiponectin ratio ($p < 0.05$). The QUICKI index of insulin sensitivity was lower ($p < 0.01$). HAM-D score of DD cases correlated negatively with adiponectin ($r = -0.3505$; $p < 0.05$), independently of HOMA-IR. We have not found in DD group any differences between the drug free patients and those treated either with escitalopram alone or in the combination with mirtazapine.

CONCLUSIONS: The results of the pilot study presented support the hypothesis that at least part of DD cases has increased leptin serum levels and certain features of MetS. It could be the factor connecting depression with an increased risk of either DM2 or CVD.

Abbreviations:

AMP	– adenosine monophosphate
AMPK	– AMP-activated protein kinase
CNS	– central nervous system
CRP	– C reactive protein
DD	– depressive disorder
DM2	– type 2 diabetes mellitus
GABA _A	– gamma-aminobutyric acid receptor type A
HAM-D	– Hamilton Depression Rating Scale
HDL	– high-density lipoprotein
HPA-axis	– hypothalamic-pituitary-adrenal axis
IR	– Insulin resistance
LTP	– long-term potentiation
MetS	– metabolic syndrome
NGT	– normal glucose tolerance
NMDA	– N-methyl D-aspartate
PCOS	– polycystic ovary syndrome
PTA	– phosphotungstic acid
QUICKI	– quantitative insulin-sensitivity check index
TG	– triglycerides
TNFalpha	– tumor necrosis factor alpha
WHO	– World Health Organization

INTRODUCTION

Nowadays, there is an increasing incidence of depressive disorder. In the National Comorbidity Replication Survey, based on DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for the lifetime prevalence rate of major depressive disorder (MDD) was 16.2% (Kessler *et al.* 2003). In Finland the prevalence of MDD is approximately 5% (Pirkola *et al.* 2005), and in the Netherlands Mental Health Survey and Incidence Study (Cuijpers *et al.* 2007) 7.5% respondents met the criteria for minor DSM-IV depression in the previous year. According to Czech Health Statistics Yearbook, 168 new cases of affective disorders to 100 000 inhabitants were noticed in Czech Republic in 2006, the incidence was 2 times higher in women than in men. (Czech Health Statistics Yearbook 2007, ÚZIS, Prague 2008). Depressive disorder is not only a psychiatric problem but it is associated with an increased risk of type 2 diabetes mellitus (DM2) (Musselman *et al.* 2003) and both cardiovascular and all-cause mortality (Muselman *et al.* 1998, Wulsin *et al.* 1999).

Recently it was suggested that metabolic syndrome (MetS) is one possible connection between depressive disorder and cardiovascular diseases (Chrousos, 2000, Kinder *et al.* 2004). MetS is a cluster of metabolic and hormonal changes, such as abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, arterial hypertension, elevated fasting glycaemia but also subclinical inflammation, pro-coagulation state or increased oxidative stress (Eckel *et al.* 2005). Insulin resistance and visceral fat accumulation are supposed to be key players in MetS (Eckel *et al.* 2005). Increasing attention is now being paid to functioning of adipocytokines leptin and adiponectin, which are associated with mechanisms connecting visceral obesity to complications of MetS (e.g. oxidative stress or inflammation) (Lau *et al.* 2005, Han *et al.* 2007).

The association between depressive disorder and MetS was described in the study with male twins (McCaffery 2003). In the NHANES III study (Third National Health and Nutrition Examination Survey) women with history of depressive episode were more than twice likely to have MetS compared to women with no history of depressive episode (Kinder *et al.* 2004).

Several factors take part in the pathogenesis of depressive disorder, such as dysfunction of serotonergic, noradrenergic and dopaminergic neurotransmission (Hindmarch 2002, Malhi *et al.* 2005), abnormal regulation in the hypothalamic-pituitary-adrenal axis (HPA) (Brown *et al.* 2004) or disturbance of cellular plasticity, including reduced neurogenesis (Kempermann & Kronenberg, 2003, Fišar & Raboch, 2008). The significance of action of the increased oxidative stress and chronic inflammation-induced neurodegeneration in the pathogenesis of depressive disorder are also being studied (Smith 1991). Depression is a heterogenous disorder and several subtypes with different mechanisms can be distinguished. Changes of appetite and body weight belong to the main symptoms of depression (Nelson & Charney, 1981). In the regulation of both energy intake and expenditure, adipocytokines leptin and adiponectin play a significant role (Zhang *et al.* 1994, Kubota *et al.* 2007). Leptin, the product of the Ob gene, is produced mainly by adipocytes, circulates in the plasma proportionally to the volume of body fat and acts centrally in the hypothalamus to suppress appetite and increase energy expenditure (Minokoshi *et al.* 2004). After binding to specific receptors (Ob-R) in the hypothalamus it reduces activity of the enzyme AMP-activated protein kinase (AMPK) which leads to the suppression of the neuropeptide Y (NPY) and agouti-related protein, with subsequent inhibition of appetite (Bates & Myers, Jr., 2003, Minokoshi *et al.* 2004). Recently, it was suggested that adiponectin, contrary to leptin, after binding to its receptors in the hypothalamus, activates AMPK, increases appetite and induces feeding (Yamauchi *et al.* 2001, Kubota *et al.* 2007).

Leptin has also plenty of important peripheral effects. It increases the fatty acid oxidation in skeletal muscle by activation of AMPK, decreases intramyocellular triglyceride content and increases insulin sensitivity (Havel, 2004). Leptin has angiogenic activity, causes increased oxidative stress in endothelial cells, promotes vascular smooth muscle cell migration and proliferation, decreases arterial distensibility and contributes to obesity-associated hypertension (Bouloumie *et al.* 1999, Dubey & Hesong, 2006). Leptin also causes increased oxidative stress in endothelial cells, promotes calcification of the vascular wall and facilitates thrombosis by increasing platelet aggregation (Parhami *et al.* 2001, Konstantinides *et al.* 2001). Adiponectin, similarly to leptin, decreases gluconeogenesis in liver, increases metabolism of glucose and fat in muscle. Its plasma concentrations are negatively associated with obesity and insulin resistance (Hotta *et al.* 2000, Weyer *et al.* 2001)

and low levels of adiponectin can predict the future risk of developing type 2 diabetes (Spranger *et al.* 2003). Besides its insulin-sensitizing effects, adiponectin has also anti-atherogenic and anti-inflammatory properties (Hotta *et al.* 2000, Weyer *et al.* 2001).

It was suggested that in the central nervous system (CNS) leptin functions as more than just an adiposity signal, but it is a multifaceted hormone, influencing plenty of CNS functions (Harvey, 2003). Its effects in the hippocampus are supposed to influence the processes of learning and memory (Harvey, 2007).

Not many studies have been accomplished to deal with the relationships of serum leptin and adiponectin to depressive disorder and the results were inconsistent. With regard to leptin, it was found that serum leptin concentration was decreased in DD (Kraus *et al.* 1999), increased (Gecici *et al.* 2005), or not changed (Deuschle *et al.* 1996, Kaufmann *et al.* 2005). In one study were shown plasma adiponectin concentrations decreased in major depression patients and adiponectinemia reduction was related to major depression severity (Leo *et al.* 2006) but others (Mamalakis *et al.* 2006) did not find any association of adiponectin with depression.

MATERIAL AND METHODS

Patients

We have investigated 38 women suffering from DD, age 59.2 ± 16.4 years, body mass index (BMI) 26.1 ± 4.6 kg/m², who were recruited from the consecutive outpatients of the Psychiatric Department of 1st Faculty of Medicine of Charles University in Prague (from May 2006 to May 2008). DD was diagnosed based on criteria specified in the DSM-IV (American Psychiatric Association, 1994). All patients were evaluated using Hamilton Depression Rating Scale (HAM-D). The control group consisted of 38 healthy women (medical staff of the 1st Faculty of Medicine), age 57.8 ± 17.0 years, BMI 25.2 ± 3.5 kg/m². Basic clinic and anthropometric parameters of the groups studied are shown in Table 1. The waist circumference was measured according to the WHO recommendation: midway between the upper iliac crest and the lower rib. Subjects were excluded if they had a history of diabetes mellitus (DM), cardiovascular and cerebrovascular disease, hepatic and/or renal disease, hypothyroidism, malignancies, macroalbuminuria (proteinuria higher than 300 mg/day), excessive alcohol consumption (> 30 g/day), or were being treated with antihyperlipidemic medications, or supplemented by vitamins, polyunsaturated fatty acids and/or antioxidants.

Eleven depressive women were treated with escitalopram in a daily dose 10 mg (subgroup C), the combination of escitalopram in a daily dose 10 mg plus mirtazapine 30 mg daily was used by fourteen women (subgroup CM). Two women were treated with venlafaxine 150 mg/day, one with combination of venlafaxine 150 mg/day and mirtazapine 30 mg/day, two with

Table 1: Basic clinical characteristics of the studied groups

Parameter	Depressive disorder (n = 38)	Controls (n = 38)	Statistical significance ²
Age (years)	59.2 ± 16.4 ¹	57.8 ± 17.0	NS
Weight (kg)	71.0 ± 12.9	68.7 ± 6.1	NS
BMI (kg/m ²)	26.4 ± 4.6	25.2 ± 3.5	NS
Waist circumference (cm)	86.1 ± 13.8	83.4 ± 10.4	NS
Systolic blood pressure (mmHg)	126.0 ± 16.6	129.1 ± 11.3	NS
Diastolic blood pressure (mmHg)	77.0 ± 9.3	79.2 ± 5.7	NS
Smokers (number/total)	4/38	4/38	NS ⁵

¹ Average ± SD; ² Student's t-test; ⁵ Pearson's χ^2 test

sertraline 100 mg/day plus trazodon 150 mg/day, two with sertraline 100 mg/day plus mirtazapine 30 mg/day, six depressive women were drug free in the time of the investigation (subgroup DF).

The study protocol was approved by the Joint Ethical Committee of the General Teaching Hospital and the 1st Faculty of Medicine of Charles University in Prague. Every proband gave his informed consent to participate in the study.

Laboratory procedures

Blood samples were collected after overnight fasting. Concentrations of total cholesterol (TC), triglycerides (TG), uric acid, and glucose were assessed by enzymatic-colorimetric methods, HDL-C in supernatant after precipitation of lipoproteins-B with PTA (phosphotungstic acid) /Mg²⁺. Concentrations of apolipoproteins (apo) were measured by the Laurell rocket electroimmunoassay, using standards and specific antibodies [apo B, apo A-I (Behring Werke, Marburg, Germany)]. Microalbuminuria was analyzed by the laser nephelometry method (Image MA reagent kit, Beckman Coulter, USA). Immunoreactive insulin was determined by the RIA method using double monoclonal antibodies (Insulin IRMA, Immunotech Praha, CR). Concentrations of C-peptide were determined by chemiluminescence method ECLIA (Roche Diagnostics GmbH, Mannheim, FRG). Serum adiponectin and leptin were determined using the RIA method (LINCO Res., Mo., USA). Indices of insulin resistance were calculated according to the homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews *et al.* 1985) and Quantitative Insulin Sensitivity Check Index (QUICKI) (Katz *et al.* 2000).

Table 2: Metabolic parameters of the studied groups

Parameter	Depressive disorder (n = 38)	Controls (n = 38)	Statistical significance ²
Total cholesterol (mmol/l)	5.74 ± 1.33	5.80 ± 0.80	NS
Triglycerides (mmol/l)	1.60 ± 1.06	1.19 ± 0.28	0.05
HDL-cholesterol (mmol/l)	1.54 ± 0.52	1.67 ± 0.42	NS
LDL-cholesterol (mmol/l)	3.49 ± 1.30	3.41 ± 0.92	NS
Apolipoprotein A-I (g/l)	1.45 ± 0.35	1.39 ± 0.16	NS
Apolipoprotein B (g/l)	1.10 ± 0.34	1.03 ± 0.23	NS
Uric acid (μmol/l)	274.1 ± 83.1	259.8 ± 66.2	NS
f-Glucose (mmol/l)	5.33 ± 1.11	4.70 ± 0.31	NS
f-Insulin (μU/ml)	13.38 ± 8.0	7.8 ± 3.8	0.01
C-peptide (pmol/l)	0.84 ± 0.31	0.66 ± 0.19	0.01
Leptin (μg/l)	21.80 ± 13.28	14.12 ± 6.25	0.05
Adiponectin (mg/l)	13.07 ± 6.43	14.98 ± 4.88	NS
NEFA (mmol/l)	0.66 ± 0.31	0.56 ± 0.19	NS
hsCRP (mg/l)	6.61 ± 8.30	4.56 ± 3.25	NS
Microalbuminuria (mg/l)	12.65 ± 10.18	4.49 ± 3.07	0.05
HOMA-IR	3.22 ± 3.44	1.69 ± 0.87	0.01
QUICKI	0.341 ± 0.042	0.365 ± 0.031	0.01
Leptin to adiponectin ratio	1.80 ± 1.12	1.04 ± 0.72	0.05

¹ Average ± SD; ² Student's t-test; NEFA= non-esterified fatty acids; hsCRP= highly sensitive C-reactive protein; HOMA-IR = homeostasis model assessment for insulin resistance = f-insulin (μU/ml) × f-glucose (mmol/l)/22.5; QUICKI = quantitative insulin-sensitivity check index = 1/[(log(I₀) + log(G₀))], where I₀ is the fasting plasma insulin level (microunits per ml), and G₀ is the fasting blood glucose level (milligrams per dl)

Statistical methods

All data were processed and statistical analyses performed in the statistical environment STATISTICA CZ ver 7.1 (StatSoft Inc., Tulsa, U.S.A.). Continuous data are summarized as mean and standard deviations. Student t-test and Bonferroni correction of significance levels were used to compare the mean values of nominal parameters. For small samples Kruskal-Wallis test was performed. The variables without normal distributions (adiponectin, leptin) were log-transformed. Pearson

χ²-test was employed in testing the differences of the categorical data. For the correlation analysis Pearson's correlation test was used. The statistical significance was defined as $p < 0.05$.

RESULTS

No significant differences of BMI, waist circumference or both systolic and diastolic blood pressure were observed between the DD and controls (Table 1). The concentrations of plasma lipids, apolipoproteins, glucose, uric acid, C-reactive protein, microalbuminuria, leptin, adiponectin, leptin to adiponectin ratio and indices of glucose homeostasis are shown in Table 2. Women of the DD group differed from those of the control group in higher concentrations of plasma TG, insulin, C-peptide, microalbuminuria, leptin, the ratio leptin to adiponectin and in the higher value of the HOMA-IR index. On the other hand, the QUICKI index of insulin sensitivity was decreased.

Values of parameters of glucose and lipid metabolism, as well as concentrations of leptin and adiponectin were compared between the drug free patients and the two main treated groups (escitalopram alone or in the combination with mirtazapine), and we did not find statistically significant differences (Table 3).

We only found the following significant correlations in the whole group of investigated probands (expressed as Pearson's correlation coefficients) between serum leptin, adiponectin, leptin to adiponectin ratio on the one hand and parameters relating to MetS on the other hand (Table 4): adiponectin correlated positively with HDL-C ($r = .3807$, $p < 0.01$), QUICKI ($r = .2911$, $p < 0.01$) and negatively with BMI ($r = -.2957$, $p < 0.01$), insulin ($r = -.2138$, $p < 0.05$), C-peptide ($r = -.3232$, $p < 0.01$), TG ($r = -.2127$, $p < 0.05$), HOMA-IR ($r = -.2162$, $p < 0.05$) and uric acid ($r = -.3054$, $p < 0.01$). Leptin correlated positively with BMI ($r = .3170$, $p < 0.01$), insulin ($r = .2707$, $p < 0.01$), C-peptide ($r = .3259$, $p < 0.01$), and HOMA-IR ($r = .2116$, $p < 0.05$) and negatively with QUICKI ($r = -.2891$, $p < 0.01$). The ratio leptin to adiponectin correlated positively with BMI ($r = .4829$, $p < 0.01$), insulin ($r = .3156$, $p < 0.01$), C-peptide ($r = .4193$, $p < 0.01$) and HOMA-IR ($r = .2631$, $p < 0.05$) and negatively with HDL-C ($r = -.2558$, $p < 0.05$), QUICKI ($r = -.4790$, $p < 0.01$). When we have calculated the correlations between the values provided by HAM-D and parameters relating to MetS, we have found only significant negative correlation with adiponectin ($r = -.3505$, $p < 0.05$), which still remained significant after the adjustment to HOMA-IR.

DISCUSSION

The most important finding of the study was significantly increased serum concentration of leptin and the increased ratio leptin to adiponectin in depressive women in comparison with the control group of appar-

Table 3: Basic investigated parameters according to treatment modality

Parameter	Group DF (n=6)	Group C (n=11)	Group CM (n=14)	Statistical significance ²
Age (years)	55.9 ± 11.4 ¹	60.2 ± 19.9	62.1 ± 15.8	NS
BMI (kg/m ²)	26.7 ± 5.30	26.3 ± 6.43	26.1 ± 4.61	NS
Waist (cm)	85.1 ± 12.2	87.3 ± 15.3	87.8 ± 12.4	NS
TC (mmol/l)	6.27 ± 1.84	5.63 ± 1.71	5.69 ± 0.90	NS
TG (mmol/l)	2.23 ± 2.03	1.59 ± 0.93	1.29 ± 0.58	NS
HDL-C (mmol/l)	1.65 ± 0.39	1.38 ± 0.45	1.69 ± 0.74	NS
f-Glucose (mmol/l)	4.82 ± 0.84	5.59 ± 1.46	4.85 ± 0.86	NS
f-Insulin (μU/ml)	11.94 ± 4.76	13.88 ± 10.97	12.05 ± 5.59	NS
C-peptid (pmol/l)	0.79 ± 0.39	0.97 ± 0.36	0.78 ± 0.27	NS
Leptin (μg/l)	20.15 ± 6.23	19.69 ± 11.00	23.63 ± 19.47	NS
Adiponectin (mg/l)	11.43 ± 3.36	14.59 ± 6.45	16.16 ± 8.21	NS
HOMA-IR	2.48 ± 1.15	3.54 ± 6.05	2.50 ± 1.04	NS
QUICKI	0.344 ± 0.024	0.330 ± 0.038	0.346 ± 0.027	NS
Leptin to adiponectin ratio	1.88 ± 1.03	1.59 ± 0.96	1.69 ± 1.17	NS

¹ Average ± SD; ² Kruskal-Wallis test; DF = patients drug-free in the time of examination ; C = escitalopram 10 mg daily; CM = escitalopram 10 mg daily + mirtazapine 30 mg daily; TC = total plasma cholesterol; TG = triglycerides; HOMA-IR = homeostasis model assessment for insulin resistance; QUICKI = quantitative insulin-sensitivity check index

ently healthy women. The increased values of fasting insulin, C-peptide, TG and index of insulin resistance (HOMA-IR) as well as decreased value of index of insulin sensitivity (QUICKI) in depressive women were another important findings of this study. Moreover, the adiponectin concentrations have significantly negatively correlated with severity of depression, assessed by HAM-D, independently of HOMA-IR.

Data from literature concerning serum leptin concentrations in the depressive disorder are ambiguous. Gecici *et al.* (1996) have found increased serum leptin in patients suffering from atypical depression, while no differences were observed between the leptin concentrations in persons with non-atypical depression and controls. On the other hand, Kraus *et al.* (2001) have described lower serum leptin concentrations in both men and women with depression. In another study (Deuschle *et al.* 1996) it was found that leptin plasma concentrations did not differ between depressed patients and healthy controls. However, in this study leptin was positively associated with female gender, body mass index (BMI) and fasting insulin.

The significance of the finding of increased leptin in depressive women cannot be simply explained. It was recently suggested based on the results of experimental works that leptin can act as an antidepressant and that the hippocampus might be a target site for leptin's mood-promoting action (Lu *et al.* 2006). Leptin influences hippocampal learning and memory processes by enhancing NMDA receptor function and by facilitating hippocampal long-term potentiation (LTP) and modulates function of postsynaptic Ca²⁺-activated K⁺ (BK)

Table 4: Pearson's correlation coefficients between leptin, adiponectin, leptin to adiponectin ratio and selected parameters related to MetS in the whole investigated population

Parameter	Leptin	Adiponectin	L/A ratio
BMI	0.3170 ⁺⁺	0.2957 ⁺⁺	0.4829 ⁺⁺
TG	0.0194	0.2127 ⁺	0.1290
HDL-C	-0.0726	0.3807 ⁺⁺	-0.4721 ⁺⁺
Insulin	0.2707 ⁺	0.2138 ⁺	0.3156 ⁺⁺
C-peptide	0.3259 ⁺⁺	0.3232 ⁺⁺	0.4193 ⁺⁺
HOMA-IR	0.2116 ⁺	-0.2162 ⁺	0.2631 ⁺
QUICKI	-0.2891 ⁺⁺	0.2911 ⁺⁺	-0.4721 ⁺⁺
Uric acid	0.0709	0.3054 ⁺⁺	0.0695

L/A = leptin to adiponectin ; + $p < 0.05$; ++ $p < 0.01$

channels that play a role in neuronal excitability, and also in fast inhibitory synaptic transmission modulated by GABA_A receptors (Harvey *et al.* 2007). Recently, the conception of central leptin insufficiency was suggested to explain some metabolic disturbances, connected with hyperleptinemia (Kalra *et al.* 2008). According to this conception, hyperleptinemia, accompanying for instance aging or consuming energy-rich diet, leads to the leptin resistance, attended by the decrease of leptin transport across the blood-brain barrier, decreased leptin levels in the cerebrospinal fluid and decreased functioning of leptin in the brain. It causes several metabolic consequences, such as decreased restraint of the

insulin synthesis in the pancreas and hyperinsulinemia, decreased glucose metabolism in peripheral organs and decreased energy expenditure (Kalra *et al.* 2008). It is possible that the leptin insufficiency in the brain could also take part in the processes affecting the cognitive disturbances and mood variations at least in a subpopulation of the depressive patients (Lu, 2007).

Another feasible mechanism of the leptin functioning in the pathogenesis of depression is a possible interaction between leptin and the serotonergic system as it was found that leptin treatment could regionally down-regulate serotonin transporter binding sites in the brain (Charnay *et al.* 2000).

On the other hand, increased serum leptin in depressive patients could be induced by functioning of the inflammatory cytokines, as e.g. TNF α increases leptin, and decreases adiponectin concentrations (Bastard *et al.* 2006). However, in this work CRP concentration in depressive women was slightly increased, but the difference in comparison with the control group did not reach the statistical significance.

The relation of adiponectin to depression is not yet clear. Leo *et al.* (2006) have found in the patients with the first episode of depression without any signs of the cardiovascular disease significantly decreased concentrations of adiponectin in comparison with the healthy persons. Moreover, adiponectin concentrations correlated negatively with the severity of depression, similarly as in our work. In the study of Narita *et al.* (2006), the antidepressant therapy led to improvement of adiponectin levels in patients with major depression. In another study (Pan *et al.* 2008) depressive symptoms were not associated with increased mean levels of any other inflammatory factors or adipokines in the unadjusted or adjusted analyses. Concentration of plasma adiponectin was significantly decreased in patients with bipolar disorder (Hung *et al.* 2007). Adiponectin circulates in serum as three oligomeric complexes known as the high, medium and low molecular weight form (HMW, MMW and LMW), and in the work of Narita *et al.* (2008) the ratio of HMW to total adiponectin or to LMW, not the absolute amount of plasma adiponectin, was negatively associated with depression severity in healthy elderly subjects without metabolic syndrome.

In this pilot study, we have found the significant increase of the leptin to adiponectin ratio in depressive women compared to healthy controls. To our knowledge, it is the first finding of the altered leptin to adiponectin ratio in depressive disorder. It could be another common feature of both depression and MetS. The ratio of leptin-to-adiponectin has been suggested to be an indicator of insulin resistance in subjects without hyperglycemia (Inoue *et al.* 2006) and it was also found to be powerful independent predictor of preclinical atherosclerosis in healthy subjects (Norata *et al.* 2007). In another work (Xita *et al.* 2007), the adiponectin-to-leptin ratio could serve as a biomarker of both insulin

resistance and low-grade inflammation in women with polycystic ovary syndrome (PCOS).

We have also found increased both fasting insulinemia, C-peptide levels and HOMA-IR indices in depressive women in comparison with the healthy controls. In non-diabetics, increased fasting insulinemia in persons with either normal or impaired glucose tolerance can be used as a marker of insulin resistance (Vanhalo *et al.* 1997). Insulin resistance (IR) is frequently (Winokur *et al.* 1988, Okamura *et al.* 2000, Rasgon *et al.* 2005a), though not always (Lawlor *et al.* 2003), found in patients with the depressive disorder. Recently, it was published (Hung *et al.* 2007), that in the patients with either major depressive disorder (MDD) or bipolar depression (BD) insulin sensitivity was significantly decreased in comparison with the controls and persons with the reactive depression, as well. Moreover, insulin sensitivity significantly negatively correlated with HAM-D score both in MD and BD patients and plasma adiponectin was significantly decreased in the BD group. In the last years, several studies were published, referring to possible relevance of the IR in the pathogenesis of depressive disorder. In one study depressive patients with normal glucose tolerance (NGT) were characterized by significantly higher HOMA-IR indices in comparison with healthy persons with NGT (Chiba *et al.* 2000). Rasgon *et al.* (2005b) have found increased values of HOMA-IR in majority still untreated patients suffering from the unipolar depression. In another study Okamura *et al.* (2000) have evaluated insulin sensitivity in depression by using minimal model and found that the depressive patients have both hyperinsulinemia and decreased insulin sensitivity and that these changes eased off during the treatment. Lee *et al.* (2005) have described that depressive mood was independently associated with visceral adipose tissue size, another component of metabolic syndrome. Depression, dietary disinhibition and stress have been found to be associated with accumulation of abdominal fat which may again cause disturbances in hypothalamo-pituitary-adrenal function, while antidepressant treatment might interrupt the vicious cycle (Hainer *et al.* 2006). Different antidepressants can influence insulin sensitivity of tissues by different way. Treatment with the tricyclic antidepressants can increase the IR (Gupta *et al.* 1992, Chadwick *et al.* 2007), whereas selective serotonin-reuptake inhibitors, SSRI were described to decrease IR (Okamura *et al.* 2000). In the presented work we were not able to detect any significant difference in the lipids, glucose homeostasis parameters and both leptin and adiponectin levels when comparing the group of untreated depressive women with the group treated with escitalopram alone or in combination with mirtazapine. However, this finding should be interpreted with caution due to the limited number of probands and relatively short duration of the treatment (median seven days). Mirtazapine is a novel antidepressant increasing both serotonergic and noradrenergic neurotransmissions and concurrently block-

ing 5HT₂ and 5HT₃ receptors, thus limiting undesirable effects of SSRI (serotonin syndrome symptoms). Treatment with mirtazapine can cause body weight increase, but unfavourable changes of glucose homeostasis were not noticed (Laimer *et al.* 2006). Significant influencing of the glucose metabolism and insulin sensitivity was not described during escitalopram treatment (McIntyre *et al.* 2006, Baldwin *et al.* 2007).

Functioning of IR in the pathogenesis of depression is not clear. At least in part of the depression cases the activation of sympathoadrenal system can be demonstrated accompanying with the increased glucocorticoids level in serum, which can contribute to IR, DM2 and CVD development (Rasgon *et al.* 2005a). Hypercortisolemia is toxic for hippocampus and causes its atrophy, which was in magnetic resonance imaging studies seen in DM2 (Den Heijer *et al.* 2003) or depression (Sheline *et al.* 1996), but diminished hippocampus volume was described also in not demented, non-diabetic persons with only impaired glucose tolerance (Convit *et al.* 1997).

In this study no differences in the parameters investigated were seen between the drug free depressive women or those treated with or escitalopram alone or in the combination with mirtazapine. There are only few data published about the influence of antidepressant treatment on leptin or adiponectin serum levels. In the experimental study with lean or obese Zucker rats fluoxetine decreased serum leptin levels (Dryden *et al.* 1999) while in another study (Westbroek *et al.* 2007) no changes were found. In the group of depressive women treatment with citalopram did not lead to changes in serum leptin. Similarly, in persons suffering from binge eating disorder, who were treated with escitalopram (Guerdjikova *et al.* 2008) or zonisamide (McElroy *et al.* 2006), leptin serum levels were not changed. In patients with ejaculatio praecox, where serum leptin is usually increased, the treatment with citalopram led to leptin decrease in one study (Atmaca *et al.* 2003). In the recently published study, five weeks lasting treatment of depression by paroxetine did not change the adiponectin level (Weber-Hamann *et al.* 2007).

In summary, in the pilot study presented, depressive women were characterized by increased concentrations of serum leptin and increased ratio leptin to adiponectin in comparison with controls. We have also found increased fasting insulinemia, C-peptide concentration and increased values of HOMA-IR index, while the value of QUICKI index of insulin sensitivity was significantly decreased. These results support the hypothesis that at least part of DD cases has some features of MetS and common neuroendocrine mechanisms may operate in the pathogenesis of both conditions. Dysregulation of leptin in DD could be the factor connecting depression with an increased risk of either DM2 or CVD.

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