

Inverse relationship between leptin increase and improvement in depressive symptoms in anorexia nervosa

Filip RYBAKOWSKI^{1,2}, Agnieszka SLOPIEN³, Marta TYSZKIEWICZ-NWAFOR³

¹ Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Neurology, Warsaw, Poland

² Chair of Clinical Psychology, University of Social Sciences and Humanities, Poznan, Poland

³ Department of Child and Adolescent Psychiatry, Poznan University of Medical Sciences, Poland

Correspondence to: Filip Rybakowski
Department of Child and Adolescent Psychiatry,
Institute of Psychiatry and Neurology,
Sobieskiego 9, 02-957 Warsaw, Poland.
TEL: +48 22 45 82 631; FAX: +48 22 642 12 73; E-MAIL: filrybak@yahoo.com

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Abstract

OBJECTIVES: Anorexia nervosa (AN) often presents with comorbid depressive symptoms and is characterized by low levels of neuroimmunomodulatory hormone – leptin. Treatment-induced weight gain tends to normalize those variables. The aim of the study was the longitudinal assessment of the relationship between leptin levels and depressive symptoms in patients with AN, since previous cross-sectional studies in different populations brought conflicting results.

METHODS: Thirty AN inpatients were assessed twice – at admission and after mean body mass index (BMI) increase of 3.2 kg/m². Physical parameters were measured, blood samples for leptin levels drawn and depression evaluated with both clinician – (Hamilton Depression Rating Scale – HDRS) and self – (Beck Depression Inventory – BDI) rated scales at the same morning. Correlation coefficients between changes in assessed variables, and linear regression for changes in depression scores were calculated.

RESULTS: BMI and leptin levels showed significant increase after treatment, respectively 14.45±0.90 vs. 17.61±0.87 and 1.87±1.14 vs. 7.47±4.65, whereas severity of depressive symptoms measured with BDI and HDRS was significantly reduced: 18.69±12.65 vs. 11.62±11.59; 12.76±6.90 vs. 5.66±4.91, respectively. In linear regression analysis decrease of the clinician-rated depression score (HDRS) was directly associated with decrease in the self-assessed depressive symptoms (BDI) (standardized Beta=0.45; t=2.60; p<0.05) and inversely related to the increase in leptin level (standardized Beta=-0.33; t=-2.08; p<0.05).

CONCLUSIONS: These results may suggest, that increase in leptin levels during weight recovery in patients with AN is associated with objectively measured depressive symptoms. Longitudinal studies in other populations are warranted to establish whether this relationship is valid across the weight spectrum.

INTRODUCTION

Anorexia nervosa (AN) is a severe psychiatric disorder, predominantly of young females, often presenting with comorbid depressive symptoms. Whereas “the clinical assumption” is that depressed mood in AN results from malnutrition, systematic review and cross-sectional study showed no clear relationship between the two aspects of the disorder (Mattar *et al.* 2011). Severe emaciation in acute AN is associated with low levels of leptin – neuroimmunomodulatory hormone, produced mainly by adipose tissue. During the treatment-induced weight gain in AN, both severity of depressive symptoms and leptin levels tend to normalize (Hebebrand *et al.* 1997). A role of this adipokine in the pathogenesis and treatment of depressive symptoms in normal-weight and obese subjects has been recently proposed (Lu 2007), however cross-sectional correlative studies of leptin levels and depressive symptoms show conflicting results. In females across weight spectrum, independent of body weight, leptin is correlated inversely with depressive symptoms (Lawson *et al.* 2012). On the contrary, leptin levels are also directly correlated with depressive symptoms in general population, with possible mediation of adiposity (Morris *et al.* 2012), and with somatic depressive symptoms in patients with metabolic syndrome (Chirinos *et al.* 2013). The main limitation of those studies is their cross-sectional design, and as far as we know, previous longitudinal studies in AN patients are not specifically aimed at the assessment of the relationship between depressive symptoms and leptin levels.

The action of leptin on homeostatic regulation of feeding in hypothalamus has been repeatedly shown, however its effect on ventral striatum circuits mediating reward system, and non-homeostatic feeding behavior is a subject of more recent reports (Monteleone & Maj 2013). Dysfunction of reward system was suggested as an element of depression pathogenesis (Martin-Soelch 2009) and as a core feature of anorexic behavior (Kaye *et al.* 2013). Consequently, the aim of the study was to assess leptin levels during the treatment-induced weight gain in anorexia nervosa, and analyze its association with simultaneous measurements of self-rated and clinician-rated symptoms of depression.

METHODS

Seventy adolescent patients with AN – restrictive type, diagnosed according to the DSM-IV-TR criteria (American Psychiatric Association and American Psychiatric Association. Task Force on DSM-IV, 1994), hospitalized in the Department of Child and Adolescent Psychiatry, Poznan University of Medical Sciences were recruited. All subjects and their caregivers signed the informed consent for the study, and its protocol was accepted by local Institutional Review Board. Exclusion criteria comprised psychiatric disorders outside the affective-

anxiety spectrum, serious neurological and somatic illnesses (other than consequences of emaciation) and psychoactive substance abuse. The behavioral treatment program included gradual increase in caloric value of meals, psychoeducation, and occasional cognitive and pharmacotherapeutic intervention. Thirty patients (mean age 15.6 ± 2.3 years) completed the treatment schedule (completers), and were included in the analysis. The mean age at onset, duration of illness and age of menarche in this group were 14.0 ± 2.3 , 1.7 ± 1.5 and 12.5 ± 1.2 respectively. Despite weight gain, no patient started to menstruate immediately after the program.

Completers were assessed twice – within first 3 days of admission and after normalization of body weight – mean body mass index (BMI) increase of 3.2 ± 1.2 kg/m². After night fast, at 7 AM 15 ml of venous blood samples for the biochemical assays were drawn. The same morning weight, height of patients were measured and BMI calculated, and subsequently assessment of depressive symptoms was performed with Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI).

HDRS is administered by clinician, and includes items probing mood, cognitive, motor and somatic symptoms of depression. BDI is a self-rated tool, including 21 items assessing mood, cognitions and somatic symptoms of depression. Both psychometric tools have been used in adolescent population, showing good validity and reliability (Shain *et al.* 1990). Leptin levels were assessed with ELISA assays (R & D Systems, Minneapolis, Minnesota, USA) and Sunrise microplates (Tecan Group Ltd., Mannedorf, Switzerland); mean of two measurements for each subject was calculated. Magnitude of change in each variable after weight gain was assessed, and after checking for normality of distribution Pearson correlation coefficients between changes were calculated. Afterwards, linear regression analysis of changes in both depression scales were performed including variables, which correlated with depression scores at the level of $p < 0.1$. All statistical analyses were performed with Statistica 10 (Stat Soft, Inc.)

RESULTS

Both BMI and leptin levels showed significant increase after treatment, respectively 14.45 ± 0.90 vs. 17.61 ± 0.87 and 1.87 ± 1.14 vs. 7.47 ± 4.65 . Similarly severity of depressive symptoms measured with BDI and HDRS was significantly reduced: 18.69 ± 12.65 vs. 11.62 ± 11.59 ; 12.76 ± 6.90 vs. 5.66 ± 4.91 , respectively. As expected, we observed significant correlation of improvement in HDRS and BDI score. The increase in BMI correlated significantly with reduction of depressive symptoms measured with BDI, and at the level of statistical trend with reduction in clinician-rated depression scale (HDRS). Unexpectedly increase of leptin level showed no correlation with BMI and BDI change, however the

inverse association with improvement in HDRS – at the level of statistical trend was observed (Table 1).

In linear regression analysis decrease of the clinician-rated depression score (HDRS) was directly associated with decrease in the self-assessed depressive symptoms (BDI) (standardized Beta=0.45; t=2.60; p<0.05) and inversely related to the increase in leptin level (standardized Beta=-0.33; t=-2.08; p<0.05), but show no association with increase of BMI (standardized Beta=-0.14, p>0.1). Histogram of change in HDRS score and leptin concentrations was shown in Figure 1.

Linear regression analysis of decrease in BDI score showed the association with decrease in HDRS results.

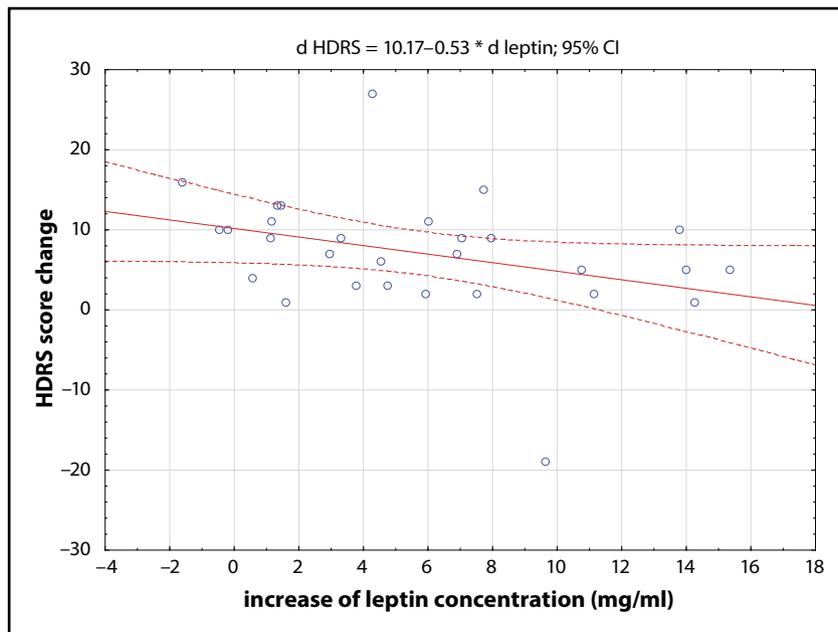


Fig. 1. Histogram of change in leptin concentration (d leptin) vs. improvement in HDRS score (d HDRS) with regression line and 95% confidence intervals.

DISCUSSION

Here we report, that improvement in the clinician-rated depression score during weight gain in patients with anorexia nervosa was inversely related to the increase of leptin levels. This result may confirm previous studies suggesting an association between leptin and depressive symptoms in general population and in patients with metabolic syndrome (Morris *et al.* 2012), (Chirinos *et al.* 2013). However it is contradictory to other study showing an association of leptin levels with decreased depressive symptomatology in females across the weight spectrum (Lawson *et al.* 2012). The tentative explanation of such discrepant results may be related to the specific action of leptin on different symptoms, and probably circuits associated with depression. The inverse relationship between leptin increase and depressive symptomatology was observed only for HDRS score, and not for BDI, which may suggest predominant relationship of leptin with the somatic and motor, and not cognitive symptoms of depression. Previous reports showed relationship between low leptin levels and hyperactivity in AN (Holtkamp *et al.* 2006). We cannot exclude, that increase of leptin may cause decrease in motor activity, which might be mirrored with increase of HDRS score. This reasoning may be partly supported by recent report showing association of leptin with inhibitory action on ventral tegmental striatum, which may explain its potential for inhibition of reward approach behavior, especially psychomotor activity (Thompson & Borgland 2013).

Leptin hypersecretion after weight gain in AN was associated higher risk of relapse (Holtkamp *et al.* 2004), and one cannot exclude, that depressive symptoms (measured with HDRS) are a mediating factor between

Tab. 1. Changes observed in patients with anorexia nervosa after treatment. Mean changes ± SD and correlation coefficients were presented for body mass index (Δ BMI), leptin concentrations (Δ leptin), Hamilton Depression Rating Scale score (Δ HDRS), and Beck Depression Inventory score (Δ BDI); *p<0.05, **p<0.1

Variable	Mean change ± SD	Δ leptin	Δ BDI	Δ HDRS
Δ BMI	3.17 ± 1.26	0.03	-0.40*	-0.30**
Δ leptin	5.74 ± 4.84		0.05	0.35**
Δ BDI	-7.07 ± 6.60			0.51*
Δ HDRS	-7.10 ± 7.48			

adipokine increase and relapsing course of the disorder. On the other hand, leptin has been proposed as potential treatment of AN, due to its action alleviating hyperactivity (Hebebrand & Albayrak 2012), whereas our results may not directly oppose this concept, they suggest careful observation for the emergence of depressive symptoms.

This study has several limitations. Merely 30 subjects completed the whole treatment protocol, and we cannot exclude, that the relationship between depression and leptin would be different, if all patients would remain in the program. Only hospitalized and female patients were recruited, and the results may not be valid for male AN patients and subjects with less severe symptoms, who do not require admission. The question whether the relationship between leptin and depression could be extrapolated into normal weight and obese populations remains open. Thus we suggest further explorations of leptin – depression relationship in subjects across weight spectrum using longitudinal design.

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