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LEPTIN IS ASSOCIATED WITH ANXIETY IN WOMEN WITHIN A WIDE RANGE OF WEIGHT

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SUMMARY

Background: The effect of some peripheral hormones as leptin and ghrelin on mood and anxiety in humans is still a matter of discussion.
Aims: The aim of our study was to investigate the relationship between leptin, ghrelin levels and severity of psychopathological symptoms of anxiety, depression in female patients within a wide range of weight. Study design: Cross-sectional study.
Methods: A group of 60 female patients across the weight spectrum and 20 healthy age-matched controls were clinically examined. Bioimpedance analysis, Hamilton Rating scales for Anxiety and Depression, hormonal measurements of leptin, desacyl ghrelin, 24 hour urine cortisol and statistical analysis were conducted.
Results: In the patient group, subgroup of 22 females had lost weight (BMI kg/m^2 16.94±3.4). Subgroup of 38 females had gained weight (BMI kg/m^2 31.54±6.5) and had significantly higher anxiety (14.5±5.3), depressive (10.37±4.1) scores, leptin levels (101.06±39.7 ng/ml) and lower ghrelin (161.48± 58 pg/ml) and cortisol levels (78.63±47.6 nmol/24h) compared to the group with weight reduction and the controls. In the whole study group there was weak inverse correlation between ghrelin levels and anxiety, depressive scores ($p < 0.05$; $r \approx -0.25$), which became insignificant after controlling for fat mass. Partial correlation between HAM-A scores and leptin levels controlled for the effect of fat mass % was significant ($p < 0.05$, $r = 0.28$).
Conclusion: We found that women with higher anxiety scores had higher leptin levels, independently of body fat mass. The role of ghrelin in depression and anxiety remains to be further elucidated.
Key words: Leptin, Ghrelin, Anxiety, Depression

RÉSUMÉ

La leptine est associée à l'anxiété chez les femmes, au sein d'une population qui se répartie sur une large gamme de poids

Contexte: L'effet des hormones périphériques comme la leptine et la ghréline sur l'humeur et l'anxiété chez l'homme est encore controversé.
Propos: Le but de notre étude était d'examiner la relation entre la leptine, la ghréline et la sévérité des symptômes psychopathologiques d'anxiété et de dépression chez des patientes à large sprectre du poids corporel dont la population se répartie sur un large spectre de poids corporel. Conception des études: Etude croisée.
Méthodes: Un groupe de 60 patientes dans l'ensemble du spectre de poids corporel et 20 sujets en bonne santé de même âge et même sexe subissaient un examen clinique. Analyses de bio impédance, analyses sur l'échelle d'anxiété et de dépression de Hamilton, mesures hormonales de leptine et ghréline, cortisol urinaire sur 24 heures et évaluations statistiques ont été menées.
Résultats: Dans le groupe des patientes, un sous-groupe de 22 femmes a perdu du poids (IMC kg/m^2 16,94±3,4). Un sous-groupe de 38 femmes a pris du poids (IMC kg/m^2 31,54±6,5). Ces dernières avaient des scores d'anxiété (14,5±5,3), de dépression (10,37±4,1), un niveau de leptine (101,06 ±39,7 ng/ml) considérablement plus élevé (que la moyenne) et un niveau de ghréline (161,48±58 pg/ml) et de cortisol (78,63±47,6 nmol/24h) plus bas que le groupe des patientes avec la perte de poids et le groupe témoin. Dans l'ensemble du groupe, il y avait une faible corrélation négative entre la ghréline et les scores d'anxiété et de dépression ($p < 0,05$; $r \approx -0,25$). La ghréline est devenue insignifiante après correction pour la masse grasse. La corrélation partielle entre la leptine et les scores d'anxiété, contrôlée pour la masse grasse %, était statistiquement significative ($p < 0,05$, $r = 0,28$).

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Conclusion: **Nous avons découvert que les femmes avec des indices d'anxiété plus élevée avaient un niveau de leptine plus élevé, indépendamment de la masse grasse. Le rôle de la ghréline dans la dépression et l'anxiété doit être encore élucidé.**
Mots clés: **Leptine, Ghréline, Anxiété, Dépression**

INTRODUCTION

In modern society, we are faced with excessive psychological stress which may be a risk factor for excessive anxiety and depressive symptoms [1]. Neural circuits involved in the regulation of stress overlap largely with those regulating mood and anxiety and consequently activation of these neural pathways induces changes in mood, behavior and metabolism by complex neuroendocrine mechanisms [2]. On the other hand it's been suggested that certain circulating hormones from the periphery may act centrally on critical neuroanatomical circuits and regulate our psychological state [3]. The potent role of ghrelin and leptin as such mediators and modulators is discussed [3,4].

Leptin is mainly an adipocyto-derived hormone and except his action on food intake and energy expenditure has numerous neuroendocrine functions [5,6]. Total body fat mass, fat mass in % and BMI are the best predictors for the levels of leptin [6].

Ghrelin is a peptide hormone and the majority of circulating forms is produced by enteroendocrine cells of the gastric fundus. Ghrelin has two main forms - acylated and unacylated. It's known that expression and secretion of ghrelin are increased by fasting and reduced by feeding [7]. It was initially presumed that acylated form is the only active form but recent studies show that des-acyl ghrelin also have endocrine activity [8].

Recent studies suggest a novel role for leptin and ghrelin in the regulation of mood and anxiety. Low levels of leptin and ghrelin have been found to be associated with depressive and anxious behavior in rodents and humans [9,10] while other studies support the opposite idea – that high levels don't have anxiolytic and antidepressant-like properties [11-13]. So the available information about their role in depression and anxiety in humans is limited and controversial.

The aim of our study was to investigate the relationship between leptin, ghrelin levels and severity of symptoms of anxiety, depression in female patients within a wide range of weight.

MATERIALS AND METHODS

Subjects and study design

This was a cross-sectional study performed in a single center. The study population was of 80 women – 60 female patients recruited during hospitalization with a diagnosis of obesity, metabolic syndrome and malnutrition and 20 healthy female controls. The patients included in the study were aged 18-55 years, with body mass index (BMI) from under 18,5 kg/m^2 to over 30 kg/m^2, with symptoms of anxiety and depression. All of them reported that they had experienced stressful life event or were feeling permanently stressed and as a result had changed their body weight in the period before hospitalization. Since it's been well established that emotional state could affect food intake and consequently lead to change in body weight, we decided to divide the patient group into two subgroups: group 1 consisted of women with weight reduction and group 2 of women with weight gain. As a whole the selected patients were in good general health without a significant chronic medical illness except the aforementioned. Fourteen of the patients were previously diagnosed with mood, anxiety or eating disorder and were on psychoactive medication (neuroleptics, SSRIs, SNRIs, TCA, anticonvulsants). As the effect of these psychoactive medicaments on the measured hormones' levels is not well known, we didn't make this an exclusion criteria. The psychometric scales were administered on the background of their therapy. The study group didn't take any other concomitant treatment. The healthy controls were with normal BMI – 18,5-24,9 kg/m^2, without anxiety, depression or chronic disease, age-matched with the patient group. The study group was clinically examined, anthropometric and hormonal measurements were conducted, psychometric scales were administered. All subjects were with TSH in the reference range. Informed consent was obtained from all participants included in the study. The study was approved by the local Ethics Committee.

Psychometric scales

Patients were interviewed and Hamilton Rating Scale for Anxiety (HAM-A) and Depression (HAM-D) were administered. When HAM-A scores are under 17 – the patients are with mild anxiety, scores between 18-24 indicate mild to moderate anxiety, between 25-30 - moderate to severe. Scores $\leq$ 7 were considered to represent no/minimal anxiety. For HAM-D scale - scores between 8-13 indicate mild depression, between 14-18 – moderate, 19-22 severe and above 23 – very severe.

Hormonal measurements

Venous blood samples were collected from the patients and controls between 8.00 and 9.00 a.m after an overnight fast. Blood was drawn in EDTA plasma tubes and then centrifugated for 10 min at 4500 rpm to separate plasma. The samples were stored in -80 °C till the day of the analysis. Plasma desacyl ghrelin levels were measured by EIA technique. Analytic sensitivity of the method is 0,2 pg/ml

and 0,6 pg/ml for short and long immunological reaction. Intra and intermethod variability is respectively 6,3 % (20h at+4°C); 6.93%(3h at RT) and 7,0 %(20h at +4°C); 7.23 % (3h at RT). Leptin levels were measured by ELISA technic. Analytic sensitivity of the method is 0,2 ng/ml. Intra – and intermethod variability are 5,9 % and 5,6 % respectively. 24 hour urine samples were collected for measuring free urine cortisol. The samples were stored in -80 °C till the day of the analysis. Cortisol RIA KIT was used for analyzing cortisol levels. Analytical sensitivity of the method is 5 nM. Intra and inter-assay variation is 8,9% and 13,3% respectively with measurement range from 5 to approximately 2,000 nM.

Anthropometric measurements

Height and weight were measured. Body composition was determined by bioelectrical impedance analyzer (BIA) - TANITA TBF – 401A.

Statistical analysis

The statistical analysis was conducted by SPSS version 17.0. Quantitative variables were expressed as means ± SD and categorical ones as percentages. Correlation coefficients were calculated to determine associations - Pearson coefficient was used for continuous variables and Spearman coefficient for categorical ones. Independent sample t-test and one-way dispersion analysis (ANOVA) were used to assess differences between groups. Stepwise regression analysis was applied for identifying predictors of leptin levels. Value of $p < 0.05$ and $p < 0.01$ were considered statistically significant.

Results

Subject characteristics

The females in the patient group ranged in BMI from 12,5 to 45 kg/m^2 and in age from 18 to 55 years. Subject characteristics are presented in Table 1.

Group 1 consisted of 22 females, who had lost average 4,9 kilograms for 3 months, had mean BMI < 18,5 kg/m^2, classified in the category of underweight. Group 2 consisted of 38 women who had gained average 14,6 kilograms for 1,2 year, had mean BMI > 30 kg/m^2, classified in the category of obesity Group 2 had significantly higher anxiety scores, leptin levels and lower ghrelin, cortisol levels compared to group 1 and the controls. Although cortisol levels were lower in group 2, they were still in the reference range. As HAM-D scale has a question only estimating the reduction of weight and one part of our patients had gained weight, we decided to exclude that question from the statistical analysis. After the exclusion group 2 had statistically higher depressive scores compared to group one (Table 1). Before the exclusion there wasn't statistically significant difference in the mean depressive scores between group 1 (HAM-D scores – 9,45±5,4) and group 2 (HAM-D scores - 10,37±4,1). HAM-D scores were abnormal in 54,5 % of patients in group 1 and in 76,3 % of patients in group 2 . In group 1 72,7 % had abnormal HAM-A scores and in group 2 - 94,7 % .

Associations between measured hormones and psychometric scales' scores

In relation to psychometric scales and measured hormone levels we didn't find significant association between cortisol and psychometric scales' scores. Association between leptin, desacyl ghrelin levels and psychopathological scales' scores are presented in Table 2.

The weak positive association between leptin levels and depressive scores and weak inverse correlation between desacyl ghrelin levels and depressive scores became apparent only after the aforementioned correction made in the HAM-D scale scores. However these associations were no more significant after adjustment for fat mass. Desacyl ghrelin levels were inversely correlated with anxiety scores but the relationship became statistically insignificant after controlling for fat mass. Only the positive correlation between leptin levels and HAM-A scores remained significant after adjustment for fat mass (FM%) (Table 2) (Fig. 1).

We have used fat mass%, anxiety, ghrelin and age as independent variables into a stepwise regression model. We found that in addition to fat mass% anxiety also had significant effect on plasma leptin levels ($p = 0,022$).

Table 1 - Mean values of age, BIA measurements, psychometric scales' scores, hormone levels

	Group 1 (n = 22)	Group 2 (n=38)	Controls (n=20)
Age (years)	30,4±8,1^{*2}	36,29 ±10,1^{*1}	34,4±7,9
BMI (kg/m^2)	16,94±3,4^{**2,3}	31,54±6,5^{**1,3}	21,89±2,37
FM (%)	17,85±9^{**2,3}	42,12±7,9^{**1,3}	30,08±6,29
FM (kg)	8,83±6,12^{**2,3}	36,94±13,1^{**1,3}	18,49±5,67
Anxiety scores	10,9±6,3^{*2}	14,5±5,3^{*1}	1,35±0,87^{**1,2}
Depression scores	7,95±4,9^{*2}	10,37±4,1^{*1}	0,45±0,6^{**1,2}
Leptin (ng/ml)	10,32±8,3^{**2,3}	101,06 ±39,7$^{** 1,3}$	35,64±23,64
Ghrelin (pg/ml)	264,34±219,29^{*2}	161,48±58 ^{*1,3}	262,78±157,40 (n=15)
Cortisol (nmol/24h)	132,43±99,52^{*2} (n=17)	78,63±47,6^{*1,3} (n=35)	123,78±80,9 (n=17)

Values are expressed as mean ± SD. * P < 0.05, ** P < 0.01. 1 group 1, 2 group 2, 3 controls. FM: body fat mass

Table 2 - Correlations between psychometric scales' scores and leptin, desacyl ghrelin levels in the whole study group

	Leptin			Ghrelin	
	r	p-value		r	p-value
HAM-A	0,28	0,015*	HAM-A	- 0,26	0,024
HAM-D	0,24	0,032	HAM-D	- 0,25	0,028

* P < 0.05 after adjustment for fat mass %. HAM-A: HAM-A scores, HAM-D: HAM-D scores

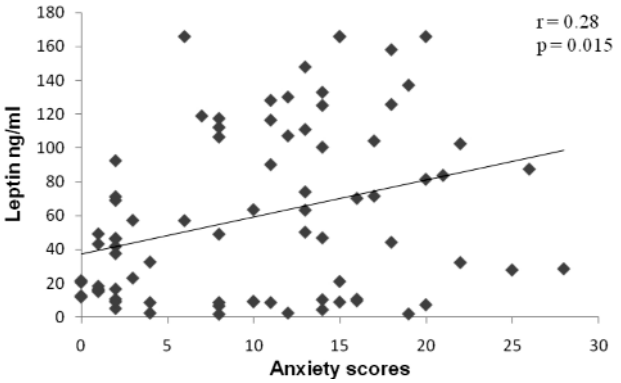

Figure 1 - Association between anxiety scores and leptin levels in the whole study group

DISCUSSION

In the present study we found correlation between anxiety and leptin in addition to the well known correlation between leptin and fat mass. Our study demonstrated that patients with higher levels of anxiety had higher leptin levels, independently of body fat mass. The results are consistent with the results of other investigators who found higher leptin levels and also significant correlation between leptin and hyperarousal symptoms in subjects who had persistent partial posttraumatic stress disorder (PTSD) compared to group that did not [14]. Another study showed that a group of 1062 Japanese male workers who estimated their daily life stress as high had higher levels of leptin and this association didn't depend on the level of obesity [13]. In contrast other reports showed inverse correlation between levels of leptin and severity of symptoms of depression, anxiety and stress [15]. Yoshida-Komiya H et al. also found lower levels of leptin in woman with mild depression and anxiety compared to healthy volunteers [16].

Several studies have reported that leptin could interact with the hypothalamic-pitiutary-adrenal (HPA) axis and exert negative feed-back control both at hypothalamic and pituitary level [17,18]. It has been found that glucocorticoids also could influence the synthesis and secretion of leptin [19]. Furthermore HPA axis abnormalities have been implicated in the pathogenesis of anxiety disorders [20]. In the light of the aforementioned interrelations we may suppose that in a state of chronic state and anxiety dysfunction of the HPA axis and changes in the glucocorticoids levels may lead to higher leptin levels. Overactivity of the HPA axis and raised glucocorticoid concentrations could also induce leptin resistance [21]. Reduced leptin sensitivity could affect neural pathways involved in regulation of mood, anxiety and HPA-axis activity [22]. This could be one explanation why we observe higher anxiety scores in patients with higher leptin levels, despite leptin anxiolytic properties. On the other hand there are also evidences of leptin to stimulate the sympathoadrenal axis and enchance the catecholamines release [23]. In our research we didn't find abnormalities in basal HPA-axis activity or association between free urinay cortisol levels and anxiety scores. In contrast, researches on cortisol levels in stress-related disorders and trauma-exposed individuals revealed lower levels in patients with PTSD [24], blunted salivary cortisol response to awakening and increased cortisol suppression after dexamethasone in trauma-exposed individuals even in the absence of psychiatric morbidity [25]. However other investigators found normal serum cortisol levels in patients with persistent partial PTSD [14]. Factors such as the time between onset of the symptoms and collection of the samples, still functioning in stressful environment, personality traits, lifestyle could bias the results.

The scientific data about the role of leptin in depression are inconsistent. Our results didn't show significant correlation between levels of leptin and HAM-D scores independently of body fat mass while decreased leptin levels were found in group of 62 patients with major depression compared to BMI-matched healthy controls [26]. Another study didn't find difference in leptin plasma concentration between 23 patients with major depression and a healthy control group [27], whereas in longitudinal epidemiological investigation 83 women with lifetime history of depression had higher levels of leptin compared to women without lifetime history of depression, independently of BMI [12]. The conflicting evidence regarding the relationship between leptin and depression may be partly explained by the influence of certain factors such as age, sex, sample size on leptin levels. Difference in clinical manifestation of depression between the investigated groups could be one more factor explaining the controversial results – our patient group had only mild depressive symptoms.

We found in our investigation that higher anxiety and depressive scores correlate with lower levels of desacyl ghrelin but in the unadjusted model only, which suggests that this association was influenced by the covariate fat mass. Our results are consistent with the results of other studies that didn't find significant correlation between ghrelin levels and stress, depression, anxiety scales' scores [15]. Other researchers found lower levels of both forms of ghrelin in 25 patients with depression than in the control group [28]. Polish study found no difference in plasma ghrelin levels in group of 43 women with depression compared to those without depression [29]. Data for the role of ghrelin in depression and anxiety in humans are limited and controversial. Some of these discrepancies may be explained by the heterogeneous methodology and study design.

Our findings of higher anxiety and depressive scores in the group with weight gain and obesity were expected. It was demonstrated in clinical and epidemiological studies that people with excess adiposity are more prone to anxiety and depression [30]. The link between different metabolic signals and anxiety, depressive-like behavior is discussed as potential underlying mechanism [22].

We acknowledge several caveats in our investigation. It was a cross-sectional study so we couldn't exclude some transient correlations. Our study group was small and to minimize heterogeneity only female subjects were included. Our results could be biased by unrecognized confounders as other unmeasured biologically active molecules, factors involved in vulnerability to development of psychopathology, other lifestyle factors. We have to notice that we have tested basal HPA-axis activity through single 24 hour urine sample and stimulation tests weren't conducted. We didn't control for the psychoactive medication, but this in our view couldn't substantially bias and explain our results.

Conclusion

In summary we found that females with higher anxiety scores had higher leptin levels, independently of body fat mass. Further investigations with longitudinal design and larger study groups would be necessary to elucidate the role of both leptin and ghrelin in depression and anxiety as well as their possible implication as neuroendocrinological markers or therapeutic agents.

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