

## Regular Article

# Serum leptin levels in obsessive-compulsive disorder

MURAD ATMACA, MD,<sup>1</sup> ERTAN TEZCAN, MD,<sup>1</sup> MURAT KULOGLU, MD<sup>1</sup> AND BILAL USTUNDAG, MD<sup>2</sup>

*Departments of <sup>1</sup>Psychiatry and <sup>2</sup>Clinical Biochemistry, School of Medicine, Firat University, Elazig, Turkey*

### Abstract

The aim of the present study was to evaluate serum leptin levels to demonstrate whether or not its eventual alterations might have an etiopathogenetic significance in patients with obsessive-compulsive disorder (OCD). Thus, it was planned to examine whether serum leptin levels were affected by pure OCD (OCD–D), pure depression (D) or the comorbidity of OCD and depression (OCD+D). Forty-four patients with OCD (27 with OCD–D and 17 with OCD+D), 38 depressed patients and 30 control subjects were enrolled and serum leptin and cortisol levels were measured. According to the mean leptin levels, no significant difference was found between the OCD–D and control groups and between the OCD+D and D groups, while statistically significantly lower levels were found in the OCD+D and D groups than in control group. Significant difference in the mean leptin levels was found among groups even after controlling for body mass index or sex. The present study confirms the strong relationship between serum leptin and cortisol values and suggests that reduced leptin levels, rather than having an etiopathogenetic significance in patients with OCD, seem to be associated with patients with OCD and depression but not with pure OCD patients, and that OCD may be a heterogeneous subtype containing some biological indications of anxiety and affective disorders.

**Key words** cortisol, depression, leptin, OCD.

## INTRODUCTION

Leptin is a fat-cell-derived hormone involved in weight regulation. The main role of leptin in metabolic homeostasis is regulating food intake and energy expenditure, providing the hypothalamus with information on the amount of body fat.<sup>1</sup> Recently, a large body of studies has focused on the leptin levels in psychiatric disorders and psychotropic drug use.<sup>2–7</sup> An interaction between leptinergic and serotonergic systems in the central nervous system has been reported.<sup>8</sup> Obsessive-compulsive disorder (OCD) has some clinical and biological characteristics in common with depressive disorder that support the opinion that OCD is related to this disorder. Obsessive-compulsive disorder frequently has depressive symptoms and comorbid

depressive disorder.<sup>9,10</sup> While the patients with OCD have approximately 80% rate of secondary depression, 30% of the patients with depressive disorder have obsessive-compulsive symptoms (OCS).<sup>11</sup> Recently, a relationship between depressive disorders and leptin was found.<sup>2</sup> A limited number of studies have focused on the leptin levels in depressive disorders and reported controversial results.<sup>2,12</sup> In addition to a high proportion of comorbidity between OCD and depressive disorders, both conditions respond favorably to selective serotonin re-uptake inhibitors, suggesting that they may share a similar neurobiological pathophysiology. In addition, to the best of our knowledge, there is no study regarding leptin levels in OCD. Therefore, we chose to specifically measure serum leptin levels and cortisol levels, a hormone related to both depression and leptin levels, to demonstrate whether or not its eventual alterations might have an etiopathogenetic significance in patients with OCD. Thus, we planned to evaluate whether serum leptin and cortisol levels were affected by pure OCD, pure depression and the comorbidity of OCD and depression.

Correspondence address: Dr Murad Atmaca, Firat (Euphrates) Universitesi, Firat Tip Merkezi, Psikiyatri Anabilim Dalı, 23119 Elazig, Turkey. Email: matmaca\_p@yahoo.com

Received 8 July 2004; revised 14 September 2004; accepted 10 October 2004.

## METHODS

### Subjects

The study group consisted of a total of 44 patients (27 women, 17 men) and 38 major depressed patients (24 women and 14 men) who applied to the Firat University School of Medicine Department of Psychiatry and had been diagnosed with OCD according to *Diagnostic and Statistical Manual of Mental Disorders* (4th edn; DSM-IV). A semi-structured interview was carried out in order to establish DSM-IV diagnoses. Of the OCD patients, 17 (nine women, eight men) had comorbid depressive disorder (major depressive disorder in 15 patients and dysthymic disorder in two patients) according to DSM-IV, and the rest had pure OCD (18 women, nine men). No patient had a lifetime history of eating disorders. After a period of 2 weeks free from medication, all patients underwent physical examination, total biochemical evaluation, chest X-ray, urinalysis and electrocardiogram. Exclusion criteria for the patients and controls were as follows: presence of a severe physical illness, history of any endocrinological condition, gestation, obesity, history of alcohol and substance abuse or dependence, previous history of lipid-lowering treatment, and presence of comorbid axis I disorder other than depressive disorders. All participants were carefully screened to exclude autoimmune, pulmonary, endocrinological and infectious diseases, and neoplasms. Written informed consent was obtained from the subjects, after full explanation of the entire procedure. The study protocol was approved by the Local Ethics Committee of the Firat University School of Medicine.

Thirty age- and sex-matched healthy staff members (21 women, nine men) were included in the control group. They were all free of psychotropic medication and had no history of psychiatric disorder.

The patients were evaluated by the Hamilton Depression Rating Scale (HDRS) and Yale–Brown Obsession Compulsion Scale (Y-BOCS).<sup>13,14</sup>

### Determination of serum leptin and cortisol levels

The blood samples were taken from all subjects at 08.00 h after fasting and abstaining from alcohol, coffee and smoking for 12 h before drawing blood. After a 1-h resting period, samples were obtained in controlled tension. A cannula was inserted into a forearm vein and blood was drawn 45 min after inserting the cannula. Sera were stored at  $-20^{\circ}\text{C}$  until thawed for leptin and cortisol assays. Serum cortisol level was measured using a commercially available kit (Immulite 2000 cortisol, Diagnostic Products, Los Angeles, CA, USA) utilizing chemiluminoassay method. The leptin

levels were measured using the DRG Diagnostics kit (DRG Instruments, Germany) by enzyme-linked immunoassay (ELISA) method.

### Statistical analysis

Obtained data were evaluated by SPSS for Windows 9.0 (SPSS, Chicago, IL, USA). The  $\chi^2$  test was used to compare categorical variables. Group mean differences were examined by means of *t*-test or analysis of variance (ANOVA) with correcting according to the Bonferroni procedure for all post-hoc comparisons. The SPSS general linear model function was used when controlling for covariates. Correlation analysis was performed by Pearson's and Spearman rank correlations test, whenever appropriate.  $P < 0.05$  was considered to be significant.

## RESULTS

A total of 44 OCD patients (27 women, 17 men), 38 major depressed patients (24 women, 14 men; D group) and 30 controls (18 women, 12 men) took part into the study. The mean age was  $28.2 \pm 4.9$  years (range, 18–49 years) for total OCD group,  $31.4 \pm 5.8$  years for the OCD+D group (range, 22–47 years) and  $26.50 \pm 6.58$  years for the controls (range, 19–47 years), respectively ( $P > 0.05$ ).

There were no statistically significant differences between the groups with respect to weight ( $61.6 \pm 5.7$  kg, OCD+D;  $63.1 \pm 6.4$  kg, OCD–D;  $58.9 \pm 4.8$  kg, D;  $63.8 \pm 6.6$  kg, controls), body mass index (BMI;  $22.2 \pm 2.5$ , OCD+D;  $23.6 \pm 3.5$ , OCD–D;  $20.9 \pm 2.4$ , D;  $24.1 \pm 4.2$ , controls), or sex distribution ( $P > 0.05$ ).

Of OCD patients, five patients (11.4%) with mild OCD, 13 (29.5%) with moderate OCD, 19 (43.2%) with severe and seven patients (15.9%) with significant severe OCD were categorized using Y-BOCS. According to HDRS, there were seven patients (15.9%) with moderate depression and 10 patients (22.7%) with severe depression. The OCD patients were divided into two subgroups according to comorbid depression: an OCD+D group (OCD and comorbid depressed patients) and an OCD–D group (pure OCD patients). The mean HDRS scores were  $20.3 \pm 6.7$  for the D group,  $14.2 \pm 0.4.7$  for the OCD+D group,  $7.2 \pm 2.2$  for the OCD–D group, and  $5.9 \pm 2.6$  for the healthy controls ( $P < 0.01$ ). In contrast, the mean Y-BOCS scores were  $10.0 \pm 2.2$  for the D group,  $24.1 \pm 4.3$  for the OCD+D group,  $21.1 \pm 3.9$  for the OCD–D group, and  $8.7 \pm 2.5$  for the healthy controls ( $P < 0.01$ ).

The mean cortisol levels were  $14.8 \pm 4.9$   $\mu\text{g/dL}$  in the D group,  $12.5 \pm 3.8$   $\mu\text{g/dL}$  in the OCD+D group,

8.8 ± 2.7 µg/dL in the OCD–D group and 9.4 ± 3.3 in the controls, respectively ( $P < 0.01$ ). The mean leptin levels were 7.7 ± 3.6 ng/mL for the D group, 8.6 ± 3.3 ng/mL for the OCD+D group, 12.4 ± 4.2 ng/mL for the OCD–D group, and 12.9 ± 4.7 ng/mL for the control group ( $P < 0.01$ ). According to the mean leptin levels, no significant difference was found between the OCD–D and control groups, and between the OCD+D and D groups ( $P > 0.05$ ) while we found statistically significantly lower levels in the OCD+D ( $P < 0.001$ ) and D groups than in the control group ( $P < 0.001$ ). Significant difference in the mean leptin levels was found among groups even after controlling for BMI or sex ( $F = 5.34$ ,  $P < 0.05$  adjusted for BMI;  $F = 4.23$ ,  $P < 0.05$  adjusted for sex). In addition, when comparing the mean leptin level between sexes within each group, statistically significant difference was found in the OCD+D (9.4 ± 3.5 ng/mL, women; 7.5 ± 2.9 ng/mL, men;  $P < 0.05$ ) and OCD–D groups (14.1 ± 4.9 ng/mL, women; 9.0 ± 3.6 ng/mL, men;  $P < 0.01$ ) but not in the control group ( $P > 0.05$ ; Table 1).

Serum leptin levels were significantly and inversely related to cortisol levels in all groups (D group,  $r = -0.64$ ,  $P < 0.05$ ; OCD+D,  $r = -0.56$ ,  $P < 0.05$ ; OCD–D,  $r = -0.51$ ,  $P < 0.05$ ; control,  $r = -0.58$ ,  $P < 0.05$ ). A statistically significant correlation was found between leptin levels and age or HDRS in the OCD+D group ( $r = 0.58$ ,  $P < 0.05$  and  $r = -0.54$ ,  $P < 0.05$ , respectively) and in the D group ( $r = 0.49$ ,  $P < 0.05$  and  $r = -0.66$ ,  $P < 0.05$ , respectively), and between leptin level and age ( $r = 0.50$ ,  $P < 0.05$ ) in the OCD–D group. In contrast, bodyweight had a tendency toward significance with increased age ( $P = 0.05$ ). The Y-BOCS was not correlated with leptin levels in either the OCD+D or the OCD–D group (OCD+D,  $r = 0.21$ ,  $P > 0.05$ ; OCD–D,  $r = 0.07$ ).

## DISCUSSION

The preliminary data demonstrate that patients with pure OCD have comparable leptin and cortisol levels when compared with control subjects, whereas those with major depressive disorder and with OCD and comorbid depression have significantly lower leptin and higher cortisol levels than both the patients with pure OCD and healthy controls.

The finding of inverse correlation between the cortisol and leptin levels in all groups is in accordance with the fact that leptin is inversely related to pituitary–adrenal function.<sup>15</sup> Several studies have demonstrated that patients with depressive disorder had a deregulated hypothalamo-pituitary–adrenal (HPA) axis with high cortisol levels in plasma and cerebrospinal fluid (CSF).<sup>16,17</sup> This would imply elevated leptin levels because glucocorticoids stimulate leptin secretion.<sup>18</sup> In contrast with the studies showing high cortisol in depressed patients, another study showed decreased CSF-corticotropin-releasing hormone (CRH) in suicide attempters with major depressive disorder (MDD) as compared to those with other diagnoses.<sup>19</sup> Yet another study demonstrated unaltered CSF-CRH in patients with MDD as compared to healthy controls.<sup>20</sup> Westling *et al.* found that in spite of having similar BMI, women in the MDD group had lower CSF leptin than those in the non-MDD group.<sup>21</sup> These findings indicate that the secretion of CRH is inhibited, probably as a result of chronic stress, which might explain the low leptin levels. It is unclear which mechanisms underlie the decreased serum leptin levels found in OCD+D patients but not in OCD–D patients. Several explanations for these findings may be suggested. First, it is possible that the combination of OCD with depressive disorder is required to change serum leptin levels, given that pure OCD failed to demonstrate any alteration in the leptin production. Given that hyperactivity of the HPA axis causes inhibition of leptin levels, and because in depression<sup>22</sup> but not in pure OCD,<sup>23</sup> the overproduction of HPA hormones has been frequently found, this might be the reason for the lower leptin and higher cortisol levels in the OCD+D group but not in the OCD–D group. Therefore, we should note that it appears to be worthwhile in future investigations to examine leptin levels and HPA functions in parallel. It should also be taken into consideration that numerous factors rather than psychiatric diagnoses may lead to a decrease in leptin levels, for example, admission to a psychiatry department may even decrease leptin levels via elevated release of catecholamines.<sup>24</sup> A limited number of studies have investigated leptin levels in patients with depressive disorder. Deuschle *et al.*

**Table 1.** Serum cortisol and leptin levels in all groups

Groups	Cortisol (µg/dL)	Leptin (ng/mL)
OCD+D group ( $n = 17$ )	12.5 ± 3.8	8.6 ± 3.3
OCD–D group ( $n = 27$ )	8.8 ± 2.7	12.4 ± 4.2
Control group ( $n = 30$ )	9.4 ± 3.3	12.9 ± 4.7
I-II-III <sup>†</sup>	$P < 0.01$	$P < 0.01$
I-II <sup>‡</sup>	$P < 0.01$	$P < 0.01$
I-III <sup>‡</sup>	$P < 0.01$	$P < 0.01$
II-III <sup>‡</sup>	$P > 0.05$	$P > 0.05$

OCD, obsessive-compulsive disorder; D, depression.

<sup>†</sup>ANOVA; <sup>‡</sup>Student's *t*-test.

reported that there were no significant differences between depressive patients and healthy controls with respect to the leptin levels.<sup>12</sup> Kraus *et al.* found low leptin levels in both schizophrenic and depressive patients compared to control subjects.<sup>2</sup> Second, appetite and food intake, frequently altered in depressive disorders rather than in OCD, are considerably associated with serum leptin levels.<sup>1</sup> We also found a statistically significant correlation between leptin levels and age in both the OCD+D and OCD-D groups. This was also supported by the findings of Al-Harithy.<sup>25</sup> This may be associated with the fact that age is related to increased bodyweight.

The data presented here should be interpreted with caution owing to important limitations. First, a relatively small sample size might not be representative of the patients with OCD. Furthermore, poor economic status and other psychosocial factors, which might be related to serum leptin levels, could not be controlled.<sup>26</sup> In summary, the present study confirms the strong relationship between serum leptin and cortisol values and suggests that reduced leptin levels rather than having an etiopathogenetic significance in patients with OCD, seem to be associated with patients with OCD and depression but not with pure OCD patients, and that OCD may be a heterogeneous subtype containing some biological indications of anxiety and affective disorders. However, more comprehensive and detailed studies are needed to determine the exact role of leptin in OCD.

## REFERENCES

1. Prolo P, Wong ML, Licinio J. Leptin. *Int. J. Biochem. Cell Biol.* 1998; **30**: 1285–1290.
2. Kraus T, Haack M, Schuld A, Hinze-Selch D, Pollmacher T. Low leptin levels but normal body mass indices in patients with depression and schizophrenia. *Neuroendocrinology* 2001; **73**: 243–247.
3. Atmaca M, Kuloglu M, Tezcan E, Gecici O, Ustundag B. Serum cholesterol and leptin levels in patients with borderline personality disorder. *Neuropsychobiology* 2002a; **45**: 167–171.
4. Atmaca M, Kuloglu M, Tezcan E, Semercioz A, Ustundag B, Ayar A. Serum leptin levels in the patients with premature ejaculation. *Arch. Androl.* 2002b; **48**: 345–350.
5. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Gecici O, Firidin B. Serum leptin and cholesterol values in the suicide attempters. *Neuropsychobiology* 2002; **45**: 124–127.
6. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Gecici O. Weight gain, serum leptin and triglyceride levels in the patients with schizophrenia on antipsychotic treatment with quetiapine, olanzapine and haloperidol. *Schizophr. Res.* 2002d; **60**: 99–100.
7. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Weight gain and serum leptin levels in patients on lithium treatment. *Neuropsychobiology* 2002; **46**: 67–69.
8. Liebowitz SF, Alexander JT. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. *Biol. Psychiatry* 1998; **44**: 851–864.
9. Jenike MA. Obsessive compulsive disorder. *Compr. Psychiatry* 1983; **24**: 99–115.
10. Marks IM. Are there anticompulsive or antiphobic drugs? Review of the evidence. *Br. J. Psychiatry* 1983; **143**: 338–347.
11. Nemiah JC, Uhde TW. Obsessive-compulsive disorder. In: Kaplan HI, Sadock BJ (eds). *Comprehensive Textbook of Psychiatry*, 5th edn. Williams & Wilkins, Baltimore, 1989; 984–1000.
12. Deuschle M, Blum WF, Englaro P *et al.* Plasma leptin in depressed patients and healthy controls. *Horm. Metab. Res.* 1996; **28**: 714–717.
13. Hamilton M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 1960; **23**: 56–62.
14. Goodman WK, Price LH, Rasmussen SA. The Yale-Brown Obsessive Compulsive Scale. *Arch. Gen. Psychiatry*. 1989; **46**: 1006–1016.
15. Licinio J, Mantzoros C, Negrao AB *et al.* Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. *Nat. Med.* 1997; **3**: 575–579.
16. Traskman L, Tybring G, Asberg M, Bertilsson L, Lantto O, Schalling D. Cortisol in the CSF of depressed and suicidal patients. *Arch. Gen. Psychiatry* 1980; **37**: 761–767.
17. Westrin A, Ekman R, Traskman-Bendz L. Alterations of corticotropin releasing hormone (CRH) and neuropeptide Y (NPY) plasma levels in mood disorder patients with a recent suicide attempt. *Eur. Neuropsychopharmacol.* 1999; **9**: 205–211.
18. Newcomer JW, Selke G, Melson AK, Gross J, Vogler GP, Dagogo-Jack S. Dose-dependent cortisol-induced increases in plasma leptin concentration in healthy humans. *Arch. Gen. Psychiatry* 1998; **55**: 995–1000.
19. Traskman-Bendz L, Ekman R, Regnell G, Ohman R. HPA-related CSF neuropeptides in suicide attempters. *Eur. Neuropsychopharmacol.* 1992; **2**: 99–106.
20. Roy A, Pickar D, Paul S, Doran A, Chrousos GP, Gold PW. CSF corticotropin-releasing hormone in depressed patients and normal control subjects. *Am. J. Psychiatry* 1987; **144**: 641–645.
21. Westling S, Ahren B, Traskman-Bendz L, Westrin A. Low CSF leptin in female suicide attempters with major depression. *J. Affect. Disord.* 2004; **81**: 41–48.
22. Holsboer F. The rationale for corticotropin-releasing hormone receptor (CRH-H) antagonists to treat depression and anxiety. *J. Psychiatr. Res.* 1999; **33**: 181–204.
23. Kuloglu M, Atmaca M, Onal S, Gecici O, Bulut V, Tezcan E. Neopterin levels and dexamethasone suppression test in obsessive compulsive disorder. *Psychiatr. Res.* (in press).
24. Carulli L, Ferrari S, Bertolini M, Tagliafico E, Del Rio G. Regulation of ob gene expression: evidence for epineph-

- rine-induced suppression in human obesity. *J. Clin. Endocrinol. Metab.* 1999; **84**: 3309–3312.
25. Al-Harithy RN. Relationship of leptin concentration to gender, body mass index and age in Saudi adults. *Saudi Med. J.* 2004; **25**: 1086–1090.
26. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes. Rev.* 2001; **2**: 73–86.