Ghrelin Plasma Levels Are Not Altered in Major Depression

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Key Words
Ghrelin · Major depression · Secretion pattern

Abstract
Background: In patients with major depression, the function of most endocrine axes is altered compared to healthy subjects. The orexigenic hormone ghrelin, which shows higher plasma levels in females than males, interacts with several of these endocrine axes. In addition, ghrelin levels in depressed patients decrease with psychopathological improvement. Therefore, we hypothesized that ghrelin levels in patients with major depression would be higher than in healthy subjects. Methods: Nocturnal (20:00–07:00 h) secretion patterns of ghrelin in 20 patients with major depression [11 females, age 39.4 ± 10.2 years (mean ± standard deviation); 9 males, age 38.3 ± 10.4 years] with a total score on the Hamilton Depression Rating Scale, 21-item version, of 24.8 ± 5.2 and 20 healthy subjects [11 females, age 38.7 ± 10.8 years; 9 males, age 39.1 ± 11.2 years] were determined following an adaptation night. Results: Ghrelin plasma levels of depressed patients and matched healthy subjects did not differ at any point in time when stratified for sex. Accordingly, the area under the curve was comparable: depressed females, 423.3 ± 103.4; healthy females, 398.0 ± 94.6; depressed males, 266.3 ± 56.9, and healthy males, 228.4 ± 41.3. Conclusion: This is the first comparison of ghrelin secretion patterns in patients with major depression and healthy controls. Surprisingly, no relevant differences were ascertained between the two groups.

Introduction
Major depression is a frequent psychiatric disorder with a 12-month prevalence of more than 10% in females and more than 5% in males [1]. Core symptoms are depressed mood, markedly diminished interest or pleasure, weight loss and insomnia [2]. Major depression is associated with distinct endocrine disturbances affecting most hormone axes. The activity of the hypothalamic-pituitary-adrenal (HPA) axis is increased, as indicated, for example, by enhanced cortisol levels. In line with this finding, vasopressin, which releases ACTH synergistically with corticotropin-releasing hormone, is enhanced in depression, and oxytocin, which is regarded as a stress-attenuating hormone, is decreased [3–5]. In fact, there is good evidence that the activation of the HPA axis is causally involved in the induction of depression [3]. In terms of the hypothalamic-pituitary-gonadal axis, luteinizing hormone secretion was found to be disrupted, while the secretion of dehydroepiandrosterone, a prohormone of androgens and estrogens, was increased and the secretion of testosterone was decreased [6–8]. The sleep-related growth hormone (GH) surge is suppressed (somatotropic axis) [9, 10]. In addition, a subgroup of depressed patients has a thyroid dysfunction such as a decreased basal secretion of thyroid-stimulating hormone and an impaired nocturnal thyroid-stimulating hormone surge (hypothalamic-pituitary-thyroid axis) [11]. Findings on the anorexigenic hormone leptin are contradictory, with reports of increased [12, 13] and decreased leptin plasma levels [14, 15] in depressed patients compared to healthy controls.
Ghrelin, the endogenous ligand of the GH secretagogue receptor, is an orexigenic hormone [16]. In the brain, ghrelin is predominantly synthesized in the hypothalamus, but GH secretagogue receptors have also been detected in various other brain regions such as the hippocampus and pituitary [17, 18]. Ghrelin affects the majority of endocrine axes that are disturbed in major depression. In humans, it stimulates the secretion of GH, ACTH, prolactin and cortisol 

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There are some publications linking ghrelin to depression; both an antidepressant and a depressogenic effect of ghrelin in rodents have been reported [22, 23]. In addition, a ghrelin gene polymorphism was found to be associated with depression [24]. Furthermore, psychopathological improvement of major depression was found to be associated with a significant decrease in ghrelin levels [25]. Taken together, these findings suggest that ghrelin could be involved in the pathogenesis of depression and that ghrelin plasma levels could be altered in major depression. We therefore hypothesized that ghrelin levels in patients with major depression would be higher than those in healthy controls.

Methods

Subjects

Twenty inpatients with a DSM-IV diagnosis of major depression [11 females aged 30–63 years (39.4 ± 10.2), body mass index (BMI) 21.7 ± 2.6; 9 males aged 21–51 years (38.3 ± 10.4), BMI 24.2 ± 3.9] and 20 healthy controls matched for sex, age and BMI [11 females aged 29–64 years (38.7 ± 10.8), BMI 21.6 ± 1.8; 9 males aged 20–51 years (39.1 ± 11.2), BMI 23.5 ± 1.7] were included in this study. Controls with no lifetime history of psychiatric or endocrine disorders or sleep or eating disorders were required to have a regular food intake comprising breakfast, lunch and dinner. Patients also had a controlled food intake comprising breakfast (08:30 h) lunch (12:00 h) and dinner (18:00 h). Only patients with depressive symptoms corresponding to a total score of at least 15 on the Hamilton Depression Rating Scale (HAMD), item 16, were included. Except for 2 females and 2 males, all patients reported decreased appetite as assessed by item 12 of the HAMD. In addition, 6 females and 4 males reported weight loss as assessed by item 16 of the HAMD. The subjective quality of sleep during the study period was recorded on a 4-point scale (very bad, bad, good, very good). Of the patients, 3 males and 3 females reported good or very good sleep, and the rest reported bad or very bad sleep. Of the healthy controls, 1 male and 2 females reported bad sleep, while the remainder reported good or very good sleep. Exclusion criteria comprised a comorbid condition or axis II disorder as defined in DSM-IV and any serious, unstable physical illness. All subjects had to be drug-free for at least 1 week prior to study entry. Fluoxetine treatment had to be discontinued at least 6 weeks before study entry. HAMD total scores ranged from 17 to 35 (24.8 ± 5.2). The duration of illness ranged from 0.8 to 18 years (4.7 ± 5.9). The number of depressive episodes varied from 1 to 13 (3.1 ± 2.6). Written informed consent was obtained from all patients and controls. Approval for the study was granted by the ethical review board.

Study Design

The eligibility of all subjects was assessed by taking a past and current psychiatric and medical history and performing a physical examination and screening tests (EEG, ECG, routine laboratory parameters, drug screening; the HAMD-21 score was assessed only in patients). The study comprised 2 consecutive nights. The first night served for adaptation of the study participants to the sleep laboratory setting. In the second night, 4 ml of blood were drawn every 30 min from 20:00 to 22:00 h and every 20 min from 22:00 to 07:00 h from the adjacent room, using an intravenous cannula and a tubic extension. Sleeping was allowed from 23:00 h on, when the light was switched off. Coffee intake was restricted to one cup per day; other substances influencing vigilance such as alcohol or activities such as naps during the day or excessive exercise were prohibited.

Statistical Methods

Mean ghrelin levels of the depressed patients and healthy controls at individual points in time were tested for significant differences stratified for sex, using tests with contrasts in a multivariate analysis of variance (MANOVA; level of significance: α = 0.05). In addition, the 3 curve characteristics area under the curve, mean location and delta (highest minus lowest value) were determined for these variables, 2-factorial MANOVA was applied following logarithmic transformation, with group (depressives vs. controls) and sex (females vs. males) as between-subject factors. In the case of significant factor effects, univariate F tests were performed to identify those variables that were significantly influenced by the factors. The level of significance was α = 0.05. All a posteriori tests were corrected for multiple testing (Bonferroni adjustment). Metric demographic variables are expressed as mean ± standard deviation, and hormone levels are expressed as mean ± standard error of the mean.

Results

Mean ghrelin levels did not significantly differ at any point in time between depressed patients and healthy controls when stratified for sex (fig. 1). In line with that, the curve characteristics area under the curve, mean location and delta did not significantly differ between depressed patients and healthy controls (table 1). Ghrelin

Yassouridis/Steiger

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Kluge/Schüssler/Schmid/Uhr/Kleyer/

Yassouridis/Steiger
levels in female subjects were numerically higher than in males in both depressed patients and healthy controls. A statistically significant difference was ascertained between the total group of females and the total group of male subjects (table 1).

### Discussion

To our knowledge, this is the first study comparing ghrelin secretion patterns in unmedicated patients with major depression and healthy controls. Basically, we found that nocturnal ghrelin secretion patterns did not differ between patients and healthy controls. This result is in agreement with a recent study comparing morning plasma levels of ghrelin in patients with major depression or schizophrenia and healthy controls, in which no significant differences between the groups were found [26]. However, in contrast to the present study, about a third of the depressed patients in that study were on medication. We also found that ghrelin levels were higher in females than males in both patients and healthy controls, as earlier reported for healthy subjects [27–29]. However, only when comparing the total group of females and the total group of males was this difference statistically significant. Hence, our initial hypothesis of higher ghrelin levels in depressed patients was not confirmed. The hypothesis was based on the finding that ghrelin plasma levels in depressed patients decreased with psychopathological improvement under treatment with the antidepressant mirtazapine [25]. In contrast, a recent study investigating the antidepressant maprotiline, which was comparable in terms of study duration, type and severity of symptoms, psychopathological improvement and weight gain, reported an increase in ghrelin plasma levels [30]. These contradictory findings support those from the present study.

![Ghrelin secretion patterns](image)

**Fig. 1.** Ghrelin secretion patterns of 11 female and 9 male patients with major depression and matched healthy controls. Values shown are the means and standard error of the mean. Ghrelin plasma levels did not differ significantly between patients and controls at any point in time as calculated by MANOVA.

### Table 1. Curve characteristics of ghrelin secretion patterns in patients with major depression and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>depressed patients (n = 11)</td>
<td>healthy controls (n = 11)</td>
<td>total (n = 22)</td>
</tr>
<tr>
<td>AUC</td>
<td>423.3 (103.4)</td>
<td>398.0 (94.6)</td>
<td>410.7 (68.5)</td>
</tr>
<tr>
<td>ML</td>
<td>437.7 (107.0)</td>
<td>411.7 (98.0)</td>
<td>424.7 (70.9)</td>
</tr>
<tr>
<td>Delta</td>
<td>213.0 (51.3)</td>
<td>271.6 (68.7)</td>
<td>242.3 (42.3)</td>
</tr>
</tbody>
</table>

Values shown are means (standard errors of the mean). AUC = Area under the curve; ML = mean location.
study, as they suggest that depressive symptoms per se do not influence ghrelin plasma levels to any relevant degree. It is more likely that specific drug effects might have been involved in the changes in plasma ghrelin levels. Alternatively, it should also be taken into account that one study included only males [30] and the other predominantly females [25]. This might be of relevance, as both ghrelin plasma levels and some effects of ghrelin, e.g. on sleep, exhibit sex differences [29, 31, 32]. Furthermore, different measurement methods may also account for the different results, at least in part. For example, it was found that ghrelin values measured with two different commercially available assays differed by a factor of 10 [33].

Ghrelin is an orexigenic hormone; plasma levels increase before and decline after food intake. Exogenously administered ghrelin induces appetite. In addition, ghrelin has been repeatedly shown to be inversely related to BMI [34]. However, those correlations were rather weak and often ascertained in populations including morbidly obese subjects (BMI >45). Within a more physiological range (BMI 20–30), the relationship was much weaker or not visible [27, 35]. However, we considered that BMI and ghrelin plasma levels are related by matching patients and healthy controls for BMI. The vast majority of patients reported reduced appetite, suggesting rather low levels of appetite-inducing ghrelin. In contrast, healthy subjects with restrained eating patterns and increased appetite were found to have elevated plasma levels [36]. However, in the present study, ghrelin levels in patients were not lower than in healthy controls. The lack of a decrease could be linked to a contrary effect on ghrelin levels caused by disturbed sleep; sleep curtailment has been reported to substantially increase ghrelin plasma levels [37], and in the present study, sleep was much worse in depressed patients than healthy controls.

There is some evidence that ghrelin and serotonergic neurotransmission, which can be decreased in depression, are interrelated. Ghrelin was found to inhibit serotonin release in the rat hypothalamus [38]. In turn, increased central serotonin levels caused by selective serotonin reuptake inhibitors or serotonergic agonists suppressed the effects of ghrelin on feeding and memory retention [39] and decreased plasma levels of acylated ghrelin [40, 41].

Ghrelin plasma levels of untreated patients and healthy controls have been compared in only a few psychiatric disorders. Increased ghrelin plasma levels were reported in anorexia nervosa and bulimia, being attributed to lower BMI but also to binge eating symptomatology [42–44]. However, this was not a consistent finding [45]. In another study, no significant differences were found between morning ghrelin plasma levels of 22 patients with obsessive compulsive disorder (OCD), 21 patients with OCD and concomitant major depression and 20 matched healthy controls [46]. Consistent with the differences in ghrelin levels between patients with OCD and major depression and healthy subjects, other endocrine parameters have been found to be similarly changed in patients compared to healthy subjects. For example, in both disorders, the activity of the HPA axis is increased and the activity of the somatotropic axis is decreased, as indicated by a suppressed sleep-related GH surge [4, 47, 48].

In a study of alcoholic patients, morning ghrelin plasma levels of 118 inpatients were found to be significantly higher than those in 24 healthy controls and to further increase during alcohol withdrawal over the period of 1 week [49]. Comparably, significantly higher ghrelin levels in 47 alcohol abstainers compared to 50 healthy subjects were reported [50].

As yet there are no comparisons of ghrelin levels in unmedicated patients with schizophrenia and healthy subjects, although there are a variety of reports on treated patients [51]. Interestingly, ghrelin levels have not been reported for patients suffering from an anxiety disorder, except for OCD. This is surprising, as ghrelin has been shown to induce anxiety in animal studies [52].

There are two main limitations to this study. Firstly, a larger sample size would have been desirable to increase the validity of our findings. However, p values indicated that there was not a trend towards higher ghrelin levels in one of the groups. Thus, it seems very unlikely that an even markedly increased sample size would have uncovered a significant difference. Secondly, we only measured total ghrelin plasma levels. The determination of acylated ghrelin, the biologically active form of ghrelin, would also have been useful as ghrelin release and ghrelin acylation appear to be independently regulated. However, plasma levels of total and acylated ghrelin have been shown to run parallel in the fed state [53].

In conclusion, this is the first comparison of ghrelin plasma secretion patterns in patients with major depression and healthy controls. Surprisingly, ghrelin secretion patterns did not differ significantly between the two groups.

Acknowledgment

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References

14. Jow GM, Yang TT, Chen CL: Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. J Affect Disord 2006;90:21–27.


