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# The role of ghrelin peptide among a sample of Egyptian patients with first episode of major depressive disorder

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## Abstract

**Background:** Major depressive disorder (MDD) is a prominent psychiatric disorder that significantly reduces living quality and increases the risk of suicide. Ghrelin influences the central nervous system (CNS) and impacts reward, inspiration, and signaling pathways in addition to acting as an appetite signal. This case-controlled comparative study focused on the association between serum ghrelin levels and MDD. The study was done during September 2021 and March 2022 on 25 people with MDD and 25 healthy controls. SCID-1 and the Ham-D 17 scales were used to evaluate the cases. The GHQ scale was used to evaluate the controls. The serum ghrelin levels of all samples were determined. The findings were presented, and statistically analyzed to perform an accurate assessment.

**Results:** There were 50 subjects: 25 cases of MDD and 25 healthy matched controls with non-statistically significant difference to cases as regard gender, marital status, residence, education, age, height, weight and body mass index (BMI). Total serum ghrelin levels among our cases showed a mean value of 4.152, while the controls showed markedly low values, with a mean value of 0.436, showing a statistically significant difference between both groups with $p < 0.001$. Furthermore, Post Hoc analysis by least significant difference showed a significant difference between mild-severe and moderate-severe groups, although there was no statistically significant difference between mild and moderate groups.

**Conclusions:** There was a significant indirect correlation between serum ghrelin level and severity of the illness. Further investigations via longitudinal studies and on larger samples are recommended to settle specific causal paths between the two variables.

## Background

Major depressive disorder (MDD) is a common, progressive, and frequently chronic illness with poorly understood fundamental neural mechanisms that explain why certain people are more sensitive to stressors than others [1]. According to latest published statistics, 16.6% of individuals have experienced depression at some point in their lives, and the incidence of MDD is 6.6% per year. It was discovered that major depression is linked to lifetime incidences of isolated manic or hypomanic symptoms in up to 40% of patients, as well as the presence of anxiety [2, 3].

The control of mood and the expression of feelings involve many various regions of the brain. Neuroimaging and neuropathological experiments have shown that such regions including the medial prefrontal cortex, the caudolateral orbital cortex, the amygdala, the hippocampus, and the ventromedial parts of the basal ganglia are links that regulate emotional behavior, and there is proof that their role is changed in people with MDD. The above-mentioned brain regions are not only linked to MDD, but they also have major roles in eating habits and hormones

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associated with nutrition, such as ghrelin and leptin [4, 5].

Ghrelin is a 28-amino acid peptide, secreted by the stomach and functions as an orexigenic hormone. Other peripheral organs such as the testis, placenta, kidney, small intestine, pancreas, and in specific neuronal cells of the hypothalamus, do secrete it but at a much lower level. It is responsible for communicating the negative energy state with neuronal centers to stimulate feeding responses; moreover, it is considered the natural endogenous ligand for the growth hormone secretagogue receptor [6].

The link between ghrelin and MDD is still debatable, with several studies conducted on animals reported conflicting results, while a few have suggested that ghrelin may be an anxiety-inducing hormone, others have suggested that it might have antidepressant and anxiety-provoking effects [7]. Ghrelin levels in depression patients have also yielded conflicting results. While recent reports claim decreased ghrelin levels in depressed patients, others show no distinction in ghrelin levels among depression patients and healthy individuals. However, several investigations discovered elevated serum ghrelin levels in people with significant depression [8, 9]. This study aims to analyze the correlation between the development of ghrelin in the blood and the degree of major depressive disorder.

## Methods

The study was carried out at Okasha Institute of Psychiatry, Ain Shams University, Cairo, during September 2021 and March 2022 on 25 control participants and 25 patients of both genders (males and females) with first episode of MDD and age range from 18 to 65 years old. However, cases were excluded from this study if they included a diagnosis of any co-morbid axis I or history of substance use disorder, inability to cooperate or complete the interview due to any cognitive impairment, or severe physical illness, chronic relapsing MDD, or received any medical treatment for MDD.

All patients were assessed by a treating team consisting of two or more psychiatrists. Subjects who fulfilled the inclusion criteria were asked to participate after explaining the study proper and to provide informed written consent. After building rapport, a detailed psychiatric interview of the available subjects was done to collect socio-demographic and clinical data including age, gender, weight, height, BMI, and mental state examination using Structured Clinical Interview for DSM-IVTM axis I disorders (SCID-I) [10]. Other scales were applied including the Hamilton Depression Scale (Ham-D 17) [11, 12] to assess the cases and General Health Questionnaire-28 (GHQ-28) for controls [13, 14] as well as Visual Analog Scale of Hunger [15]. Blood samples were collected from controls and patients. Samples were analyzed in the Central Laboratory of Ain Shams University Hospitals using the total serum ghrelin ELISA kits.

### Statistical analysis

The collected data were revised, coded, tabulated, and introduced to a PC using the Statistical Package for Social Science (SPSS 20). Data were represented as means, standard deviation (±SD), and range for parametric numerical data while the median and interquartile range (IQR) was used for non-parametric numerical data as well as frequency and percentage of non-numerical data. Student's *t* test, ANOVA, post hoc analysis, chi-square test, and correlation analysis were used to fully analyze the results, where $p > 0.05$: non-significant; $p < 0.05$: significant; $p < 0.01$: highly significant.

## Results

The goal of this case–control study, conducted in light of the fact that previous studies produced contradictory findings, is to evaluate the serum ghrelin level in cases of major depressive disorder in the first episode and its relationship to the psychopathological aspect of the illness.

### Clinical and demographic information about the research participants

The total sample was divided into two major groups: "cases" and "healthy controls." As regards our cases, demographic data illustrated that most of the cases were females (68%), married (56%), postgraduate (56%), unemployed (68%), and living in urban areas (80%), with the mean age of the cases being 34.56 ± 11.47 years and BMI 26.19 (±4.06). Medical history showed statistically significant differences between cases and controls ($p < 0.001$); e.g., about 60% of cases had a positive medical history while only 8% of controls had a past medical history. Meanwhile, our results showed there were no smokers among controls while smokers constituted 16% of cases; however, there was no statistically significant difference in substance use between the groups ($p = 0.118$) as shown in Tables 1 and 2.

### Total serum ghrelin in relation to demographic, anthropometric, and clinical features

Upon assessing the relationship between the total serum ghrelin level and the demographic features of the cases, a relation was found between serum ghrelin level and gender, marital status, residence, education, occupation, and medical history; all factors showed a non-statistically significant relation except substance use, which showed a statistically significant relation and where serum ghrelin

**Table 1** The demographic and clinical data of cases and controls

| | | Group | | | | Chi-square | | |
|---|---|---|---|---|---|---|---|---|
| | | Cases | | Controls | | | | |
| | | *N* | % | *N* | % | $\chi^2$ | *P* value | Sig |
| **Gender** | **Male** | **17** | **68.00** | **17** | **68.0** | **0.000** | **1.000** | **NS** |
| | **Female** | **8** | **32.00** | **8** | **32.00** | | | |
| **Marital status** | **Single** | **8** | **32.00** | **15** | **60.00** | **5.797** | **0.055** | **NS** |
| | **Married** | **14** | **56.00** | **10** | **40.00** | | | |
| | **Divorced** | **3** | **12.00** | **0** | **0.00** | | | |
| **Residence** | **Rural** | **5** | **20.00** | **4** | **16.00** | **0.136** | **0.713** | **NS** |
| | **Urban** | **20** | **80.00** | **21** | **84.00** | | | |
| **Education** | **Illiterate** | **6** | **24.00** | **1** | **4.00** | **4.329** | **0.115** | **NS** |
| | **Undergraduate** | **5** | **20.00** | **5** | **20.00** | | | |
| | **Postgraduate** | **14** | **56.00** | **19** | **76.00** | | | |
| **Occupation** | **Unemployed** | **17** | **68.00** | **10** | **40.00** | **5.865** | **0.121** | **NS** |
| | **Employed** | **8** | **32.00** | **15** | **60.00** | | | |
| **Medical history** | **No** | **10** | **40.00** | **23** | **92.00** | **15.062** | **< 0.001*** | **Sig** |
| | **Yes** | **15** | **60.00** | **2** | **8.00** | | | |
| **Substance history** | **Non-smoker** | **21** | **84.00** | **25** | **100.00** | **2.446** | **0.118** | **NS** |
| | **Smoker** | **4** | **16.00** | **0** | **0.00** | | | |

* with significance

**Table 2** Serum ghrelin level among cases and controls

| Serum Ghrelin(ng/ml) | Group | | *t* test | |
|---|---|---|---|---|
| | Cases | Controls | *T* | *P* value |
| Range | 1.8–6.8 | 0.2–0.8 | **12.972** | **< 0.001*** |
| Mean ± SD | 4.152 ± 1.424 | 0.436 ± 0.155 | | |

* with significance

level increased among those with positive history of substance use, with $p = 0.006$ as shown in (Table 3).

### Average total ghrelin level between various levels of depression severity

Post hoc analysis by least significant difference (LSD) showed that total serum ghrelin level to Hamilton scale scores had a statistically significant relation, with $p = 0.018$, being most significant between mild to severe groups and moderate to severe ($p = 0.019$ and 0.021, respectively) as shown in Table 4.

### Correlation analysis

Correlation of total serum ghrelin level to either age or the visual analog scale for hunger (VAS) showed an indirect correlation while being directly correlated to weight, height, and BMI; however, all values were insignificant. Moreover, upon correlating total serum ghrelin and Hamilton scores, an indirect correlation was found, which was statistically significant with $p = 0.030$ as shown in Table 5 and Fig. 1.

**Table 3** Serum ghrelin in relation to demographic data and medical history of cases

| | | Serum ghrelin(ng/ml) | | *t* test or ANOVA | |
|---|---|---|---|---|---|
| | | *N* | Mean ± SD | *T* or *F* | *P* value |
| **Gender** | **Male** | **17** | **3.788 ± 1.341** | **-1.971** | **0.061** |
| | **Female** | **8** | 4.925 ± 1.356 | | |
| **Marital status** | **Single** | 8 | 4.700 ± 1.773 | **0.870** | 0.433 |
| | **Married** | 14 | 3.914 ± 1.317 | | |
| | **Divorced** | 3 | 3.800 ± 0.529 | | |
| **Residence** | **Rural** | 5 | 4.520 ± 1.163 | 0.638 | 0.530 |
| | **Urban** | 20 | 4.060 ± 1.494 | | |
| **Education** | **Illiterate** | 6 | 4.633 ± 1.627 | 0.496 | 0.615 |
| | **Undergraduate** | 5 | 4.200 ± 1.944 | | |
| | **Postgraduate** | 14 | 3.929 ± 1.183 | | |
| **Occupation** | **Unemployed** | 17 | 3.847 ± 1.361 | − 1.612 | 0.121 |
| | **Employed** | 8 | 4.800 ± 1.418 | | |
| **Medical history** | **No** | 10 | 4.000 ± 1.497 | − 0.428 | 0.672 |
| | **Yes** | 15 | 4.253 ± 1.417 | | |
| **Substance history** | **Non-smoker** | 21 | 3.829 ± 1.228 | − 3.007 | 0.006* |
| | **Smoker** | 4 | 8.580 ± 1.258 | | |

* with significance

## Discussion

The concentration of total serum ghrelin in depression has lately been studied and numerous researchers have demonstrated a connection between it and major

**Table 4** Average total ghrelin level among different severity degrees of depression

| | | Serum ghrelin(ng/ml) | | | | *t* test or ANOVA | | Post hoc test | |
|---|---|---|---|---|---|---|---|---|---|
| | | *N* | Mean ± SD | | | *T* or *F* | *P* value | | *p* value |
| **HamD-17** | **Mild** | 11 | 4.455 | ± | 1.409 | **4.823** | **0.018*** | **P1** | **0.997** |
| | **Moderate** | 11 | 4.418 | ± | 1.178 | | | **P2** | **0.019*** |
| | **Severe** | 3 | 2.067 | ± | 0.231 | | | **P3** | **0.021*** |

* with significance

*Ham D-17* Hamilton Depression Scale, *SD* Standard deviation, Post hoc test: *P1* is comparing mild to moderate, *P2* is comparing mild to severe, and *P3* is comparing moderate to severe

depressive disorder, either as a risk factor or a protective factor. To the best of our knowledge, no studies on Egyptian participants have looked at blood ghrelin levels in depression. To illustrate this topic of study, we conducted a case-controlled study at the Okasha Institute of Psychiatry, Ain Shams University, Cairo, Egypt. We evaluated the hypothesis that there is a relationship between serum ghrelin and MDD, and if there is, whether or not it is linked to the incidence of MDD.

In terms of demographics, our findings revealed that roughly 70% of the patients were female. This is consistent with the research on ghrelin in Japan [16] and how it impacts depressive status, where females made up about two-thirds of the study participants, and given the WHO's announcement that depression is more common in women globally in 2021. These results may be explained by the fact that women are more susceptible to disease because of the way their hormonal system affects pathophysiology [17]. Additionally, the findings of this study indicated that major depressive disorder was more common among young people, correlating with findings in China [18], which noted that the incidence of depression in adolescents was 24–34%. Additionally, these findings are consistent with the global statistics of the illness, which may be described by the presence of various environmental triggers in this age category. Additionally, our study revealed that the majority of patients were unemployed and from urban areas, demonstrating the critical role that social and environmental stressors play in the pathology of depression in accordance with other published work [19]. As a result, depression is more common in low- and middle-income, densely populated communities as noted in numerous studies, including those by investigators in the USA [20] and in Iran [21].

**Table 5** Study correlations with serum ghrelin level

| **Correlations** | | | |
|---|---|---|---|
| | **Serum Ghrelin(ng/ml)** | | |
| | *R* | *P* value | Significance |
| **Age** | **−0.071** | **0.737** | **NS** |
| **Height** | **0.115** | **0.585** | **NS** |
| **Weight** | **0.238** | **0.252** | **NS** |
| **BMI** | **0.181** | **0.388** | **NS** |
| **HamD-17** | **−0.435** | **0.030*** | **Sig** |
| **VAS** | **−0.124** | **0.556** | **NS** |

* with significance

According to the DSM-IV diagnostic criteria, our study found statistically significant elevations in serum total ghrelin levels in clinically depressed patients, with a mean value of 4.152 (±1.424) ng/mL compared to 0.436 (±0.155) ng/mL in the healthy control group ($p=0.001$). In reports published by Turkish groups [22, 23], total ghrelin levels in depressive patients were assessed. The mean value for the cases was 1.76 ng/mL, whereas the mean value for the controls was 0.601 ng/mL. Ghrelin levels were measured in depressed workers in Japan [24–26], revealing that total ghrelin levels are higher in depressed people. Auto-regulatory mechanisms that increase serum ghrelin levels to treat depressive status could account for elevated serum levels in depression. In addition to being the hunger hormone, ghrelin is thought to be neuroprotective, reducing cellular death and aging. In an attempt to prevent disease development, it is raised in MDD as a result of chronic stress and a malfunctioning HPA axis in depression. It also has a demonstrated involvement in hippocampus neurogenesis, which may be mediated through estrogen and BDNF [7, 27]. For further investigation and confirmation of these findings, other population studies are required.

Ghrelin was found to have a depressogenic effect in long-term research by van Andel and her colleagues in The Netherlands in [28]. Median total ghrelin levels were found to be 0.93 ng/mL for the cases and 0.89 ng/mL for the controls, with no statistically significant difference between the two groups. These conclusions might have been reached as a result of the various study designs, older age groups, and diverse ethnicities. A possible explanation is that prolonged ghrelin release under chronic stress activates the HPA axis, leading to depressive-like behaviors.

This study confirmed that total ghrelin level is not related to gender or prior medical history. Despite this, our research showed a relationship between smoking

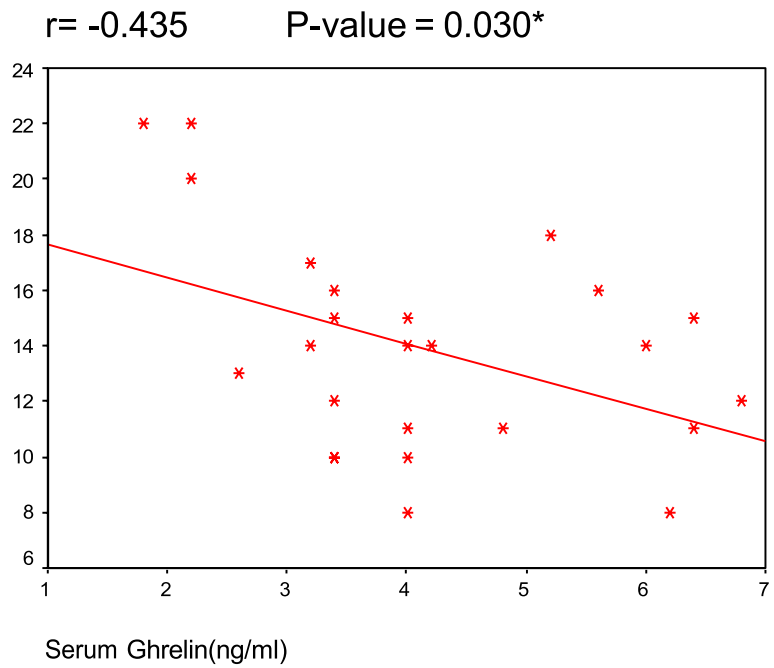


**Fig. 1** The significant inverse relationship between severity of depression and serum ghrelin level

and serum ghrelin, with a *p*-value of 0.006, indicating a substantial association between tobacco use and higher ghrelin levels. A research group in the USA reported similar findings among a group of smokers, finding that relapsers had greater ghrelin levels than non-smokers, with a -value of 0.05 [29]. Additionally, Chao et al. [30] in the USA investigated the relationship between cigarette smoking and depression symptoms, and came to the conclusion that chronic smokers with depressive symptoms had raised total ghrelin levels when compared to non-smokers and ex-smokers. This could be explained by the mesolimbic system function of ghrelin, its link to impulsive behavior, and its activation of the reward circuits, all of which boost drug seeking behavior. Another factor is the interference with hormone control brought on by long-term tobacco usage [31]. Moreover, our study demonstrated an indirect relationship between total serum ghrelin levels and depression severity, with serum ghrelin levels falling as depression severity elevated. Numerous study teams found a significant link between rising serum ghrelin levels and growing depression severity [32]. Other research found no link between ghrelin levels and the degree of depression [26, 33, 34]. These differences could be explained by patients' varying depressive symptomatology, the study's smaller sample size, the use of various scales to gauge the severity of the depression, or perhaps a different method of sample collection.

## Limitations

Our study had a number of limitations. First, it was a cross-sectional study so it was difficult to draw any firm conclusions on the causal relationship between the two variables. The healthy people were chosen and no more tests were performed to look for any ailments that had not yet been detected. The exclusion criteria were only met by a person's medical history. There were more female participants in the sample. To investigate any potential effect of gender differences, it would be advantageous to obtain a larger sample with more male participants. It was difficult to determine whether acylated or des-acylated ghrelin was involved in the pathophysiology of major depressive disorder because only total serum ghrelin was measured.

## Conclusions

According to the current investigation, major depressive disorder patients' serum ghrelin levels are noticeably higher than those of comparable healthy controls. In addition, our research revealed an indirect link between serum ghrelin levels and the severity of major depressive disorder.

### Abbreviations

MDD: Major depressive disorder; BMI: Body mass index; SCID-I: Structured Clinical Interview for DSM-IVTM axis I disorders Hamilton Depression; Ham-D

17: Hamilton Depression Scale; GHQ-28: General Health Questionnaire-28; LSD: Least significant difference; VAS: Visual analog scale for hunger; SD: Standard deviation; ELISA: Enzyme-linked immunosorbent assay.

**Authors' contributions**
T.O. contributed to the study concept and design, analysis and interpretation of data, and critical revision of the manuscript. D.M.E. contributed to the study concept and design, analysis and interpretation of data. F.F.G contributed to the interpretation of results and writing and editing the manuscript. M.H.A recruited and studied the patients and gathered all data. All authors read and approved the final manuscript.

**Availability of data and materials**
All generated or analyzed data during this study are included in the published work.

## Declarations

**Ethics approval and consent to participate**
All patients gave written informed consent after being briefed about the purpose and parameters of the trial. The investigation was carried out in compliance with the recommendations of the Institute of Psychiatry's Research and Ethics Committee at Ain Shams University. FMASU MS 453 / 2021 is the reference number for the committee.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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