Reviewer's report

Title: Serum leptin and ghrelin are associated with depressive symptoms in Japanese women but not in men

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Reviewer: Tobias Hofmann

Reviewer's report:

The article by Akter et al reports on the association of ghrelin and leptin (two hormones primarily known to be involved in the homeostasis of hunger and satiety) with depressive symptoms in a cross-sectional study in a general (thought to be healthy) population of 497 Japanese employees aged 20-68 years. Depressive symptoms were evaluated by the Japanese version of the Center for Epidemiologic Studies Depression (CES-D) scale and peptide levels by multiplex immunoassays.

Study subjects were divided into tertiles based on their leptin or ghrelin levels and due to significant higher circulating levels of ghrelin and leptin in women analyses were conducted for women and men separately.

The multiple logistic regression models were adjusted for several parameters including age and workplace and marital status, job position, occupational physical activity, non-occupational physical activity, smoking, alcohol drinking, energy intake, BMI, ferritin and folate.

Results indicate that higher ghrelin levels are associated with a higher prevalence of depressive symptoms in Japanese women, whereas no association was found for Japanese men. In addition, a trend for higher circulating leptin levels in subjects with less depressive symptoms was observed.

The work is original and contributes to the field of psychoneuroendocrinology of metabolic disturbances, eating and stress and mood disorders since it broadens its basis of human studies where inconsistent findings were observed in the past.

Minor Essential Revisions

1. P values < 0.05 were considered to be significant. The title suggests that higher leptin levels are significantly associated with decreased odds for depressive symptoms. Since there is no statistical significance for leptin the title should be changed.

2. The articles by Barim et al (2009) (Ghrelin, paraoxonase and arylesterase levels in depressive patients before and after citalopram treatment) reporting on reduced ghrelin levels in depressed patients and Schanze et al (2008) (Ghrelin and eating disturbances in psychiatric disorders) reporting on no association between ghrelin and depression should be cited and discussed in the manuscript. Thus, taken together, a significant positive relationship of depression and ghrelin is not a consistent finding in the literature and the conclusion in the
discussion (4th an 5th paragraph) that the “present findings, together with clinical studies, suggest that higher ghrelin levels may be associated with increased prevalence of depressive symptoms” seems too straight forward and results should be discussed more tentative.

3. Methods:
   a. Were blood samples taken at a particular time of the day?
   b. Were protease inhibitors used?

4. Statistical analyses: an explanation why models were adjusted to the stated parameters would be helpful. In particular: why did you choose to adjust for ferritin, folate?

5. Tables 1, 2 & 3 and Statistical analyses section: what is meant by workplace A and B? Please explain (tables: in the legends).

6. Table 3: what does Pinteraction mean?

7. Table 3: in the legend adjustment for sex was indicated while analyses were conducted separately for men and women.

8. Table 3, women, leptin, 2nd tertile: as stated in the discussion, this association was significant which should be stated by a p-value instead of bold characters

9. Table 3: the use of bold characters for significant results should be explained in the legend.

10. Table 3, 1st column: it should be stated that the odds are indicated for depressive symptoms (e.g.: Odds for depressive symptoms (multivariable adjusted))

11. Discussion: is there any explanation that depressive symptoms tend to be higher in the highest leptin tertile in women (which prevents the association of depressive symptoms and leptin levels to become significant in women)?

12. Discussion, 2nd paragraph: if there was a threshold for leptin to exert antidepressive effects how would you explain that women (with higher leptin levels than men) display more depressive symptoms than men?

13. Discussion, 3rd paragraph: Does the notion that the positive association of leptin and depression in the studies by Pasco et al and Milaneschi et al may be due to higher BMIs in their populations (26.8 ± 5.4 in the study be Pasco et al) refer to the leptin resistance in overweight and obese subjects?

Discretionary Revisions

1. I would prefer a figure with several panels instead of table 3 to present the main results.

2. Background, second paragraph: I would insert that leptin is an anorexigenic hormone

3. Results, 2nd and 3rd paragraph: indicating that results for CES-D#19 are not shown in any table would be helpful.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests