Author’s response to reviews

Title: The role of the adipocytokines vaspin and visfatin in vascular endothelial function and insulin resistance in obese children

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Author’s response to reviews:

Dear Editor,

Thank you very much for your decision letter and advice on our manuscript (Manuscript BEND-D-19-00262) entitled “Evaluation of the role of adipokines (vaspin and visfatin) in vascular endothelial function and insulin resistance in obese children”.

We also thank the reviewers for the constructive and positive comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. English has been polished by a native professional medical writer and editor. In addition, point-by-point responses to the comments are listed below this letter. We hope that the revision is acceptable for the publication in your journal.

Look forward to hearing from you soon.
With best wishes,

Yours sincerely,
Yanfeng Xiao

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments. All changes are marked in red in the text. English has been polished by a native professional medical writer and editor.

Here are our answers to every question from reviewers:

Reviewers’ comments: Black Authors’ responses: Blue
1. the authors should explain the clinical implications of vaspin in humans
Response: Thank you for pointing out this issue. The clinical implications of vaspin in humans have been added to the introduction in the revised manuscript.

2. background line 7: obesity leads to insulin resistance and type 2 diabetes. Maybe is insulin resistance that leads to obesity and diabetes.
Response: It is our negligence. The sentence has been revised in the manuscript.

3. Second page of background; lines 1-4: vaspin improves glucose tolerance insulin sensitivity and altered gene expression, From this study it seems that vaspin has a positive effect on insulin resistance
Response: It is our negligence and we are sorry about this. The sentence has been revised in the manuscript.

4. The Authors also report that: vaspin has a role in pathogenesis of insulin resistance and has a negative effect stimulating the secretion of interleukin 6 and TN alpha in monocytes.
Response: We are sorry about this. This sentence has been modified in the revised manuscript.

5. Is visfatin produced by adipocytes or by inflammatory cells considering that obesity is always linked to inflammation?
Response: Thanks for raising this critical issue. Visfatin is produced by adipocytes, and visfatin induces TNF-α and IL-6 in human monocytes. This sentence has been modified in the revised manuscript.

6. Anthropometric measurements line 51 glucose and insulin were measured at 120 min after glucose administration. These data are very important and should be reported in the results
Response: It is our negligence. The data of blood glucose and insulin at 120 min have been added to the results. Insulin and 2-h insulin were significantly elevated in the obese children. FPG and 2-h PG were not significantly different between two groups.

7. Line 12 correct minsusing
Response: The run-on word have been corrected in the revised manuscript

8. Results why the authors say "as expected"?
Response: We are sorry about this. This word has been deleted in the revised manuscript.

9. Some of the female subjects should have had the menarche and I suggest evaluating separately male and female
Response: Thank you for your insightful suggestion. We divided all subjects into male and female groups as required. All of indicators including BMI, SDS-BMI, SDS-SBP, SDS-DBP, insulin, 2-h insulin, HOMA-IR, visfatin, vaspin VCAM-1, ICAM-1, E-selectin and Ang-2 were not significantly different between male and female children (Supplementary Table 1).
10. Discussion lines 29 Adipocytes may play an important role in endothelial dysfunction and vascular inflammation but does not affect insulin resistance. Is this sentence related only to visfatin and vaspin or to all adipokines? 
Response: We are sorry about this. The sentence has been revised in the manuscript.

11. From this study it is not clear whether vaspin has a positive role improving insulin resistance or a negative one both on insulin resistance and endothelial function
Response: It is our negligence and we are sorry about this. Vaspin has a negative role both on insulin resistance and endothelial function.

12. Table 1 please explain the reason to selecting two groups with a highly different BMI (17+/2 and 28+/-3.
Response: Thank you for pointing out this issue. The purpose of selecting two groups with a highly different BMI was to confirm the difference of insulin resistance index and vascular endothelial index between obese children and controls, and difference of visfatin and vaspin between obesity and control group. After that, we further analyzed the relationship between visfatin and vaspin and vascular endothelial function in obese children.

13. In conclusion the study is of interest but the discussion should clarify the positive or negative role of these adipokines in insulin resistance and inflammatory reaction.
Response: It is our negligence. It has been clarified in the discussion that these adipokines play a negative role of in insulin resistance and inflammatory reaction.

Replies to Reviewer 2

1. The title could be simplified eg. "Evaluation of the role of vaspin and visfatin in vascular endothelial function and insulin resistance in obese children"
Response: Thank you for your insightful suggestion. We have modified the title.

2. The proposed title implying that both vaspin and visfatin are the main 'players' is not supported by presented results.
Response: Thank you for your insightful suggestion. We have modified the title. We have rewritten the background and discussion section.

3. Methods/Subjects: Precise description of recruitment procedure for healthy population is required.
Response: Thanks for you kind remind. Precise description of recruitment procedure for healthy population has been added to the method.

4. Methods/Subjects/Results: precise description of puberty stage in both obese and lean group is required.
Response: This suggestion is constructive. Precise description of puberty stage has been added to the method. We have re-statistically analyzed the data and modified the results.
5. Results/table 1: please check the SDS-BMI for lean group; 2.68±0.34 ??
Response: Thanks for your thoughtful suggestion. We have checked and revised the SDS-BMI for lean group.

6. Table 1: please add subjects' height
Response: Thank you for this suggestion. Subject' height has been added in Table 1 and results

7. Page 9: Logic in the two following sentences?: "Also, vaspin and visfatin were positively correlated with BMI and SDS-BMI in obese children. These results differed from the previous studies conducted with adult samples which showed that the plasma vaspin and visfatin concentrations were significantly positively correlated with BMI and WC…"
Response: We are sorry about this. These two sentences have been revised in the manuscript.

8. Page 9: the part "But, in children, WC did not account for the differences in height…" is not clear
Response: We are sorry about this. This sentence has been revised in the manuscript.

9. Reviewer has objections about using ABSI and VAI formulas in a pediatric population.
Response: Yes and thank you for pointing out this issue. ABSI and VAI have been removed from the text.

10. In order to check the vaspin / visfatin relationship with insulin resistance (IR) try to divide and compare to two groups with and without IR (using eg. HOMA-IR z-score as the IR surrogate).
Thank you for this suggestion. As you suggested, we divided all obese children into insulin resistance group and non-insulin resistance group according to insulin HOMA-IR z-score. The data has been added to the results section.

11. Presenting figures without significant correlations is unnecessary
Response: Correction has been made in the revised manuscript.

1. Most of the contents in Discussion should be introduced in Introduction section.
Response: Thank you for your insightful suggestion. We have rewritten the background and discussion section.

Again, thanks for your time and patience.