OPEN PEER REVIEW

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Peer Review Report for "Assessment of Microvascular Function in Children and Adolescents with Diabetes and Obesity"

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Review Timeline:

Submit Date: 31 Jan 2019
Revised Date: 6 Aug 2019
Accepted Date: 30 Oct 2019

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0)

26 May 2019

Dear AE,

1) Abstract:

- Some abbreviations used are not defined

2) Methods:

- The distribution of subjects among the different groups is uneven (33, 8, 17); doesn't this disparity influence the results of your comparisons? Please address this issue within the manuscript.
- The authors list two groups of A1c values: less than 9 or more than 10. Were there no subjects between 9 and 10? Were A1c values rounded to the nearest whole number? Please explain.

3) Discussion:

- The authors list the inclusion of T2DM subjects a novelty of this study, but they fail to address the difference between these two groups in terms other than that of A1c (the T1DM group had higher A1c levels). The authors should mention more clearly what they sought to achieve by including T2DM subjects, however few, and whether they were able to address those queries. At the moment it seems the only outcome of the comparison of the two DM groups is that there was no significant difference between arterial stiffness; what about the

underlying mechanism? If there is no significant difference would it be safe to assume that T2DM causes a more rapid progression of arterial stiffness as the T2DM group had a significantly lower duration of disease (borderline due to small numbers) compared to their T1DM counterparts? I would prefer to see more discussion around this issue.
Overall:
- I would recommend this manuscript for publication after the issues raised have been addressed.
Thanks.

REFEREE: Reviewer | **Revision (0)** 2 Jul 2019

Dear AE,
There are some issues the authors should address:
1- Abbreviations (DM and IRB) need to be defined first.
2- Some previous studies that have been mentioned in the introduction and discussion sections need to be addressed with a reference.
3- What is the difference between mean and latest A1c. how many times A1c was measured in the study; there is no definition in the method.
4- No need for table 1; it's been described in the text.
5- Result part is confusing. It's better to define the findings in the text in the same order mentioned in the table.
6- There are some differences between the P values in the result section and table 3 (for example P:0.002 in-text and <0.01 in the table for the difference of RHI of DM group with the latest A1c≤9 versus≥10.
7- Based on the small sample size authors cannot conclude that the A1c of 10% can separate poorly control diabetic patients with ED from those without.
Thanks.

REFEREE: Associate Editor | **Revision (0)** 18 Jul 2019

Dear EIC,
Many concerns have been raised by our referees about the manuscript entitled "
Assessment of Microvascular Function in Children and Adolescents
with Diabetes and Obesity ", that need to be responded to by the authors.
So, the manuscript needs a major revision.
Regards.

REFEREE: EIC | **Revision (0)** 18 Jul 2019

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs major revision. Please follow their comments as requested.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

8/1/2019

Dear Editor:

Here we are submitting for publication the *revised* version of our manuscript: "**Assessment of Microvascular Function in Children and Adolescents with Diabetes and Obesity".**

We thank the Editor and Reviewers for taking the time to review our manuscript and making insightful comments regarding its content. Each comment is addressed with a response and the pertinent changes were done on the revised manuscript. We look forward for your response.

Responses to Reviewer's comments:

Reviewers' Comments:

Reviewer 1:
There are some issues the authors should address:

1- Abbreviations (DM and IRB) need to be defined first.
Response: We appreciate the reviewer's comment. Abbreviations were defined in the manuscript. Please, see the revised manuscript.

2- Some previous studies that have been mentioned in the introduction and discussion sections need to be addressed with a reference.
Response: We appreciate your suggestion. The studies missing references were addressed with their references. Please, see the revised manuscript.

3- What is the difference between mean and latest A1c. how many times A1c was measured in the study; there is no definition in the method.
Response: Thank you for the comment. Mean A1C represents the average value of A1C within the last year, while latest A1C is the last A1C value obtained (within 3 months prior to the EndoPAT measurement). The mean A1C was calculated from 4 values within the last year as A1c values are obtained every 3 months in diabetic patients for the clinic visits. The definition above was included in the method section of the manuscript. Please, see the method section in the revised manuscript.

4- No need for table 1; it's been described in the text.
Response: Thank you for the recommendation. Table 1 was removed from the manuscript. Please, see the revised version of the manuscript.

5- result part is confusing. It's better to define the findings in the text with the same order mentioned in the table.

Response: Agree with the reviewer's comment and suggestion. The result section was reorganize in order to follow the same order as mentioned in the table. Please, see the result section in the revised version of the manuscript.

6- there are some differences between the P values in the result section and table 3 (for example P:0.002 in text and <0.01 in the table for difference of RHI of DM group with the latest A1c≤9 versus≥10.
Response: Agree with the reviewer's comment. The difference between the P values in the result section and table 3 were corrected accordingly. Please, see the revised version of the manuscript.

7- Based on the small sample size authors cannot conclude that the A1c of 10% can separate poorly control diabetic patients with ED from those without.
Response: Agree with the reviewer's comment. While our data showed that patients with worse A1C had decreased endothelial function, conclusion that A1C of 10% could separate poorly controlled diabetic patients with endothelial dysfunction from those without endothelial dysfunction cannot be establish as the sample size in our study was small. Therefore, changes in the manuscript were made to reflect that our findings should be interpreted with caution due to small sample size in our study and that larger studies are needed to study the importance and implications of our findings. This was included as a limitation of the study. Please, see the revised version of the manuscript.

Reviewer 2:
1.Abstract:
Some abbreviations used are not defined
Response: Agree with the reviewer's comment. Changes were made to define all abbreviations. Please, see the revised version of the manuscript.

2.Methods:
The distribution of subjects among the different groups is uneven (33, 8, 17); doesn't this disparity influence the results of your comparisons? Please address this issue within the manuscript.
Response: Agree with the reviewer's comment that the distribution of the subjects is uneven. This may have affected the significance of our findings. Therefore, it was addressed on the revised manuscript as a limitation. Please, see the discussion part of the revised version of the manuscript.

The authors list two groups of A1c values: less than 9 or more than 10. Were there no subjects between 9 and 10? Were A1c values rounded to the nearest whole number? Please explain.
Response: Thank you for the comment. It was a grammatical error. It should have read less than 10 or equal or more than 10. This error was corrected on the revised manuscript. Please, see the revised manuscript and revised table 2.

3.Discussion:
The authors list inclusion of T2DM subjects a novelty of this study, but they fail to address the difference between these two groups in terms other than that of A1c (the T1DM group had higher A1c levels). The authors should mention more clearly what they sought to achieve by including T2DM subjects, however few, and whether they were able to address those queries. At the moment it seems the only outcome of the comparison of the two DM groups is that there was no significant difference between arterial stiffness; what about the underlying mechanism? If there is no significant difference would it be safe to assume that T2DM causes a more rapid progression of arterial stiffness as the T2DM group had a significantly lower duration of disease (borderline due to small numbers) compared to their T1DM counterparts? I would prefer to see more discussion around this issue.
Response: Agree with the reviewer's comment and suggestion. Therefore, clarification and elaboration in regards to the comparison of the T1DM and T2DM groups in terms of A1C, endothelial function, and duration of disease was included in the discussion section of the revised manuscript. "In our study, we included T1DM and T2DM patients to assess if the type of diabetes influences endothelial dysfunction. Surprisingly, the arterial stiffness assessed by EndoPAT among patients with T1DM and T2DM were not significantly different. While the T1DM group had slightly higher A1C levels, there were not statistically different. Subjects with T1DM had more years of disease compared to those with T2DM although not able to reach statistical significance. Despite this, the endothelial dysfunction among these groups was similar. These findings are likely to the fact that in patients with T2DM, endothelial dysfunction precedes overt hyperglycemia (21) by several years (2, 22), rather than caused by it. Hyperinsulinemia, insulin resistance and obesity are all factors affecting the endothelium in T2DM patients even before the disease is diagnosed. Conversely, endothelial dysfunction in patients with T1DM develops after period of hyperglycemia".
More references were added as well in regards to these findings. Please, see the discussion part of the revised manuscript.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 23 Oct 2019

Dear EIC,
The manuscript was revised according to reviewers' comments.
so, it is suitable for publication in IJEM now.
Regards,

REFEREE: EIC | **Revision** (1) 30 Oct 2019

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.