Author’s response to reviews

Title: Comparison of glycemic control and β-cell function in new onset T2DM patients with PCOS of metformin and saxagliptin monotherapy or combination treatment

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Author’s response to reviews:

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Dear Professor Daisuke Yabe,

Thank you for considering our manuscript entitled: “Comparison of glycemic control and β-cell function in new onset T2DM patients with PCOS of metformin and saxagliptin monotherapy or combination treatment” (BEND-D-17-00188) for publication in BMC Endocrine Disorders. The authors and I were delighted to hear that our manuscript presented some interesting data in Chinese women with PCOS and may be acceptable for publication pending satisfactory revision. We appreciate the reviewers’ thoughtful comments; and, as outlined below, we have revised the manuscript based on their suggestions. We are confident that you and the reviewers will find the revised manuscript substantially improved and appreciate your willingness to reconsider the manuscript for publication.

Please do not hesitate to contact me if you have additional questions.

Regards,

Tao Tao, M.D.
(On behalf of all authors)

Technical Comments:
The manuscript entitled "Comparison of glycemic control and β-cell function in new onset T2DM patients with PCOS of metformin and saxagliptin monotherapy or combination treatment" compared effects of Saxa, Met and Saxa/Met on glucose and insulin response to oral glucose tolerance. The study is designed and conducted properly; and the results are straightforward. However, there are several issues that require revisions before further consideration of the manuscript.

Specific comments:

1. The authors should provide a rationale for sample size of this clinical trial.

As suggested by the reviewer, we have included a rationale for sample size in Statistical Analysis (Methods section, line 176, page 7).

2. The authors should discuss similarities and differences of type 2 diabetes as well as PCOS among different ethnic groups especially because type 2 diabetes in Asia is generally differ from other ethnic groups (e.g., Curr Diab Rep. 2015 Jun;15(6):602).

As suggested by the reviewer, we have included discussion of type 2 diabetes as well as PCOS of different ethnic groups and the possible causality with better effect of combination treatment (Discussion section, line 348, page 12).

3. The authors should remove values for delta PG and insulin from Figure 1. In addition, the authors should provide baseline glucose and insulin values for each group instead of the entire group.

As suggested by the reviewer, we have removed values for delta PG and insulin from Figure 1. We have confirmed that the line graphs in Figure 1 were created according to glucose and insulin values for each group, although the baseline values may look the same due to similar values of the three groups.

Comments from Akinobu Nakamura (Reviewer 1):

Authors compared the effects of metformin and saxagliptin monotherapy and metformin and saxagliptin combination therapy on blood glucose, HbA1c and beta cell function in the newly diagnosed T2DM women with PCOS. This study showed that the glucose-decreasing effect and beta cell function improvement of saxagliptin was similar to those of metformin in newly diagnosed T2DM patients with PCOS, and that the reduction of HbA1c was significant in combination group compared with monotherapy. Although these results are interesting in essence, there are many points which should be addressed for publication in this journal.
We appreciate the reviewer’s expert comments and suggestions for further improving our manuscript. We have corrected the misleading information and believe that our manuscript is now dramatically improved.

Specific comments

Criticism 1: (Introduction) "Our previous study [5] showed that early impaired beta cell function was detected in PCOS women." The reference [5] described the presence of AMPK in rat ovaries. This citation could be inaccurate.

We are grateful for the carefulness of the reviewer. As suggested by the reviewer, we have corrected the reference to “Tao T, Li SX, Zhao AM, Mao XY, Liu W. Early impaired beta-cell function in Chinese women with polycystic ovary syndrome. Int J Clin Exp Patho. 2012; 5(8):777-86”.

Criticism 2: (Methods) How was the sample size determined in this study? There is no information about sample size estimation.

As suggested by the reviewer, we have included an estimation for sample size in Statistical Analysis (Methods section, line 176, page 7).

Criticism 3: (Methods) Why was the dose of metformin 1500mg/day in the combination group in spite of the dose of metformin 2000mg/day in the metformin monotherapy group?

We apologize for the misleading information. The dose of metformin in the combination group should be 2000mg/day (Methods section, line 107, page 5).

Criticism 4: (Methods) Statistical analyses of individual comparisons among more than 2 groups should be performed using multiple comparison technique

The statistical method used for individual comparisons among 3 groups were described in the footnotes of the particular Tables, and we have added them to the method section (Methods section, line 188 page 7).

Criticism 5: (Results) Authors indicated that the decline of HbA1c was significant in combination group compared with monotherapy groups. Please explain the mechanism of the difference of HbA1c reduction more clearly.

The metformin and saxagliptin treatment may have synergistic effect on blood glucose reduction and thus reduced HbA1c level in combination group. Metformin could improve glycolysis and the uptake and utilization of glucose in peripheral tissue, and saxagliptin could both improve
glucose-dependent insulin release by β cell, and inhibit glucagon secretion by α cell. The greater HbA1c-lowering effects of metformin and saxagliptin combination therapies in T2DM women with PCOS suggested that β cell dysfunction was responsible for hyperglycemia in T2DM women with PCOS in China.

Criticism 6: (Table 2-5) I do not understand the mean of many "*" and "**". What data do you compare? Please explain more specifically.

We thank the reviewer for the thoughtful comment. We have added the explanation of "*" and "**" in the legends of Table 2-5.

Criticism 7: (Discussion) Line 263-264. Regarding the decline of sex hormone levels, why did authors describe the decline in WC and WHR in this sentence?

We apologize for the misleading information. We have removed the anthropometric measurements in sex hormone section (Result section, line 281 page 10).

Criticism 8: (Discussion) Line 280-287. Authors stated the association between incretin secretion/activity and PCOS. How about the data of GLP-1 and GIP levels during OGTT in this study?

We appreciate the reviewers’ insightful comments. We stated the association between incretin secretion/activity and PCOS because of the effect of saxagliptin on incretin to reduce glucose level. It is with regret that we didn’t detect GLP-1 and GIP levels during OGTT in this study, and we planed to test these incretins in our further study according to this wise advice by reviewer.

Criticism 9: (Discussion) Line 296-299. Although authors stated as follows; "In accordance with our result, they also found that combination treatment better improved IS-SI in prediabetic women with PCOS.", did insulin secretion better improve in the combination group than that in the other groups in this study?

We appreciate the reviewer’s thoughtful comments. We found the greater HbA1c-lowering effects of combination therapies in T2DM women with PCOS. And in a recent research, the mean IS-SI (insulin secretion–sensitivity index) of PCOS patient was found to be significantly higher in saxagliptin and metformin combination treatment group than the mean value with metformin alone (Fertility and Sterility Volume 107, Issue 1, January 2017, Pages 253-260.e1). So we can speculate that combination treatment better improved β cell function in prediabetic women with PCOS. The original sentence in the manuscript was misleading. Therefore, we added the explanation before this sentence for better understanding (Discussion section, line 322 page 12).
Yuki Matsuhashi (Reviewer 2): line 42: is the word " groupcompared " right? " group compared "?

line 46: is the word " insulingenic " right? " insulinogenic "?

We appreciate the reviewer’s thoroughness in reviewing our manuscript.

We have corrected the spelling mistakes of " groupcompared " (Abstract section, line 29 page 2), and " insulingenic " (Abstract section, line 35 page 2).

line 126: insulin, lipids

In the method section, we described the requirement of fasting for our patients, which means that after the dinner before testing day, patients fasted from solids food for 14h and liquids (soups, drinks or water for 12h) until the following morning.

line 259: is the reduction of T level (P=0.13) SIGNIFICANT in combination group? 0.13 is wrong?

We apologize for the misleading information. We have confirmed this value from the original statistical file and corrected it (Result section, line 276 page 10).

line 299: what is IS-SI? is there any definition in this article?

The IS-SI means insulin secretion–sensitivity index (IS-SI), which is derived by applying the concept of the disposition index to measurements obtained during the 2-hour OGTT. We added the meaning of IS-SI in the discussion section (Discussion section, line 323 page 12).

line 322: what is Dlx?

Dlx is the DI calculated by various methods (Diabetes Care. 2009 Feb;32(2):335-41. and Diabetes. 1993 Nov;42(11):1663-72.). We have added this explanation into the discussion section (Discussion section, line 362 page 13).

line 330: is the word " DPP-IV " right? you use the word " DPP-4 " in this paper.

We appreciate the reviewer’s careful comments. Both of these two terms are admitted in literatures, and we have changed this word to “ DPP-4 ” to maintain consistency (Conclusion section, line 374 page 13).

Figure 1: why the scale of insulin concentration(figure F) is different from figure B and D?

The Y axis of the figures were automatically generated by GraphPad Prism software, and the insulin concentration in figure 1F was a little bit lower than in figure 1B and 1D. We have made the scale of these three figures the same in the revised figure 1.
Table 1 and Table 2: if "FBG" mean "fasting blood glucose", "2hBG" is "2-hour blood glucose"?

Yes, "FBG" is "fasting blood glucose", and "2hBG" is "2-hour blood glucose", which can be found in the legend below the tables.

Moreover, according to the reviewer, we have improved the English language with the help of Peerwith.