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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:  
WJD-pH-Diabetes-Revised-1-2014-11-09-A).

**Title:** Roles of interstitial fluid pH in diabetes mellitus: Glycolysis and mitochondrial function

**Author:** Yoshinori Marunaka

**Name of Journal:** *World Journal of Diabetes*

**ESPS Manuscript NO:** 13566

**ID NO:** 00505661

Thank you for telling me reviewers' comments regarding my review article submitted to *World Journal of Diabetes* as an Editorial Invited Article. I would like to submit my revised manuscript entitled "***Roles of interstitial fluid pH in diabetes mellitus: Glycolysis and mitochondrial function***" for a possible publication in *World Journal of Diabetes*, since I have revised my manuscript according to reviewers' comments. The parts changed or added in the manuscript according to the reviewer's comments are written in RED. I hope that the revised manuscript could be acceptable in publication of *World Journal of Diabetes*.

The list of my responses to the reviewers' comments are described in the following pages.

I hereby certify that this manuscript consist of original, unpublished work, which is not under consideration for publication elsewhere except modified figures previously published in my article, use of which has been permitted from the publisher. There is no disclosure on financial interests.

Sincerely,

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Reviewer 00495228

Comments:

In manuscript recapitulates processes of regulation of pH in the state of diabetes. The manuscript is well written and gives good overview of pH regulation. The major criticism of the manuscript is its focus on lactic acidosis as a principal mechanism of low pH in diabetes. Lactic acidosis is considered to be not as prevalent in diabetes as ketoacidosis, whereas the manuscript hardly mentioned it. The author should either restrict the review to the mechanisms of lactic acidosis in diabetes, which should be reflected in the title, or provide a better classification of different types of acidosis observed in diabetes. One of the major conclusions of the manuscript is that mitochondrial dysfunction is a main cause of acidosis (see page 11). While mitochondria dysfunction in diabetes can contribute to acidosis in diabetes, it is not likely the only mechanism. Authors did not talk about changes in nutrient fluxes in liver and adipocytes, increased rates of glycolysis due to high plasma glucose levels, increased hepatic glucose production, elevated lipolysis and higher rates of ketone body formation, which all can significantly contribute to acidosis. More balanced view on the mechanism of acidosis causes would benefit the manuscript.

**Responses to the reviewer's comments.**

The parts changed or added in the manuscript according to the reviewer's comments are written in RED.

I have changed the title of manuscript to "Roles of interstitial fluid pH in diabetes mellitus: Glycolysis and mitochondrial function" according to the reviewer's comment.  
Please see the title page.

In addition to the change in the title of manuscript, I have added some description regarding ketoacidosis and nutrient fluxes in liver and adipocytes etc. according to the reviewer's comment.  
Please see page 9, line 3 - page 10, line 2, and page 12, lines 7 - 18.

Reviewer 01482015

Comments:

The review was well written. I have no additional comment.

Thank you very much for your comment.

Reviewer 02440657

Comments:

This manuscript proposes a quite unique topic of diabetic study, the roles of interstitial fluid pH in diabetes mellitus and in occurrence of insulin resistance are well discussed, and the viewpoints are logically displayed. The following are the few suggestions, which may be included while revision.

- 1) The authors used many long and complex sentences in the article, but they didn't put their meaning across very well, please refine the sentences if possible;
- 2) Page 7, the title 'REGULATION AND ABNORMALITIES IN pH of INTERSTITIAL FLUIDS', "of" should be "OF".
- 3) Page 12, line 17-19, the sentence 'Our recent study has shown that pH...than normal one', the authors should insert a comma in front of the word "than";
- 4) The legends of Fig 6A is incomplete, please check; and the Fig 8 legend is rather confusing, which needs to be clarified;
- 5) Spelling errors need to carefully check through the context.

**Responses to the reviewer's comments.**

The parts changed or added in the manuscript according to the reviewer's comments are written in RED.

- 1) I have very carefully checked whole parts of manuscript.
- 2) I have changed "of" to "OF".  
Please see page 7, line 9.
- 3) I have added a comma in front of the word "than".  
Please see page 14, line 10.
- 4) I have completed the legends of Fig. 6A.  
Please see page 34, lines 3 - 4.  
I have also revised the legends of Fig. 8.  
Please see page 34, line 4 from bottom - page 35, line 12.
- 5) I have very carefully checked spelling errors through the context.

Reviewer 02539630

Comments:

1. Completed references are needed to support the new idea.
2. Provide some data about the subgroup of body fluid such as gland and gastrointested fluid or even sweets.

Responses to the reviewer's comments.

The parts changed or added in the manuscript according to the reviewer's comments are written in RED.

- 1) I have completed references to support the new idea according to the reviewer's comment.  
Please see references 11, 18, 19, 20, and 67.  
References of 11, 18, 19, and 20 are cited in page 8, lines 1 - 4 from bottom, and the legend of Fig. 8 in pages 34.  
A Reference of 67 is cited in page 18, line 9, and the legend of Fig. 8 in page 34.
- 2) I have added some description according to the reviewer's comment.  
Please see page 16, line 8 from bottom - page 17, line 17.