

October 15, 2018

World Journal of Diabetes

Dear Dr. Fang-Fang Ji,

I would like to thank you and the reviewers for your concise and helpful comments and suggestions.

I will re-submit my revised manuscript entitled “Effects of glucose-lowering agents on cardiorespiratory fitness” to *World Journal of Diabetes*.

According to the reviewers’ comments, I completely corrected our manuscript. I will show you the list of modification on the following pages. All the changes made to the manuscript appear as underlined text in the revised manuscript. I appreciate your re-consideration for the publication of my revised manuscript in your journal.

Sincerely yours,

Hidetaka Hamasaki, MD, PhD
Editorial board member of World Journal of Diabetes,
Hamasaki Clinic

The List of Modification

Reviewer No. 00506397

Hamasaki has provided a review of literature dealing with effects of hypoglycemic agents on cardiorespiratory fitness. This timely review is generally well written. I have a number of suggestions with a goal to fix minor correction of English language as follows:

Thank you very much for your time and efforts to review my manuscript.

- 1. I believe that TABLES 1, 2 and 3 unnecessarily REPEAT the information contained in the TEXT of the Review. I strongly suggest to remove these Tables.*

I appreciate your helpful suggestion, but other reviewers recognize Table 1 as an important information and suggest that the Tables summarizing effects of thiazolidinediones and SGLT2 inhibitors on cardiorespiratory fitness also be added to this review. Therefore, I have revised the text so as not to repeat the information contained in the Tables of this Review.

- 2. Coprescribe should be hyphenated to Co-prescribe*

I have corrected.

- 3. Nonesterified should be hyphenated to read Non-esterified*

I have corrected.

- 4. On Page 10, the exercise only group had improve VO₂peak, should be corrected to read "the exercise only group had improved VO₂peak"*

I have corrected.

- 5. On Page 14, Eighty one should be hyphenated to read Eighty-one*

I have corrected.

6. On Page 17, "This review cannot mention the optimal combination of exercise and hypoglycemic agents" should be corrected to "This review cannot RECOMMEND the optimal combination of exercise and hypoglycemic agents".

I have corrected.

Reviewer No. 00506276

The aim of this review is to describe the current knowledge about the effect of antidiabetic medications currently used in clinical practice on cardiorespiratory fitness. The topic is of interest and very important from the clinical point of view. The paper is in general well-written and supported by huge body of literature. However, there are also some concerns which should be addressed.

Thank you very much for your time and efforts to review my manuscript.

In particular, the manuscript requires some style/language revision.

- 1) Page 2, the sentence: "drugs are usually needed to intensively ameliorate glycemic control" needs revision. "Ameliorating glycemic control" suggest worse control of glucose level. Drugs are used to improve glycemic control.

In accordance with your comment, I have changed the text from, "drugs are usually needed to intensively ameliorate glycemic control" to, "drugs are usually needed to intensively improve glycemic control"

- 2) Page 4, the phrase: "nine different hypoglycemic agents are available" is not strictly correct. First, there are nine groups of drugs, not nine individual drugs. Second, "hypoglycemic agents" should better sound "glucose-lowering" or "antidiabetic" agents. Drugs are not used to induce hypoglycemia but to reduce glucose from supra- to physiological level, although of course hypoglycemia may be the adverse effect.

In accordance with your comment, I have changed the text from “nine different hypoglycemic agents are available” to “nine different groups of glucose-lowering agents are available”

- 3) *Page 8, paragraph 2, the sentence: “What can be said of the interaction...” should be corrected to: “What can be said about the interaction...”*

I have corrected.

- 4) *Page 11: it is suggested that thiazolidinediones may increase body weigh by inducing fluid retention whereas in fact fluid retention and body weight gain are two separate effects; weight gain results from stimulatory effect on adipogenesis and adipose tissue accumulation.*

In accordance with your comment, I have changed the text of the first paragraph of the “Thiazolidinediones and cardiorespiratory fitness” section as follows;

“PPAR- γ overactivation by thiazolidinediones increases body weight by fluid retention [28] and stimulatory effect on adipogenesis and adipose tissue accumulation [30].”

Reviewer No. 03909861

This is a review article that summarized the current evidence regarding hypoglycemic medications on cardiorespiratory fitness. This is an important area for a review article and the manuscript has a clear structure and writing style in general. However, the language needs to be polished, preferably by a Native speaker.

Thank you for your suggestions. The manuscript has been gotten an additional English proof reading.

In addition, I have the following concerns that need to be addressed:

1. *Introduction: “Exercise is medicine”. This sentence is incorrect and reads out of place in the first paragraph.*

In accordance with your comment, I have changed the sentence to “Exercise is a standard component of chronic disease prevention and management.”

2. *Introduction: page 4-5: The focus of this review is on 9 different hypoglycemic agents. However, a number of the sentences at the end of the first paragraph of the Introduction discussed anti-hypertensives agents and statins that are not hypoglycemic agents. Those sentences seem to be irrelevant and should be deleted.*

In accordance with our comment, I have deleted the sentences discussing anti-hypertensives agents in the Introduction section.

3. *Table 1: Table 1 is an important table that nicely summarizes the effects of metformin on cardiorespiratory fitness in healthy individuals. However, this table was not mentioned anywhere in the narrative part of this review.*

I have marked the location of Table 1 in the text.

4. *Thiazolidinediones and cardiorespiratory fitness: It'll be helpful if the authors summarize the studies relevant to this topic in a table.*

I have made Table 3 which summarizes the effects of thiazolidinediones on cardiorespiratory fitness in patients with type 2 diabetes and metabolic syndrome.

5. *SGLT2 inhibitors and cardiorespiratory fitness: Similarly, it'll be helpful if the authors summarize the studies relevant to this topic in a table.*

I have made Table 4 which summarizes the effects of SGLT2 inhibitors on cardiorespiratory fitness in patients with type 2 diabetes.

6. *Page 15: the section title related to DPP-4 inhibitors seems to be missing on this page.*

I have changed the section title from, “GLP-1 receptor agonists and cardiorespiratory fitness” to, “Incretin-related drugs and cardiorespiratory fitness.”

The study addresses the relevant issue of the effects of novel anti-hyperglycemic agents on cardiorespiratory fitness. Although several data are available on the effects of metformin, the effects of other agents are poorly detailed, and possibly related more to the effects of water retention, also affecting heart failure. The term “cardiorespiratory fitness” has a well defined significance, and should not be confused with heart failure. I have a few comments to improve manuscript reading.

Thank you very much for your helpful comments.

1. *Whereas the effects of metformin have been extensively reported – and two tables are produced to summarize the results – the effects of other agents are very briefly discussed, and it is not even clear if and how much they relate to cardiorespiratory fitness. I would suggest produce similar tables also for other agents – if data are at all available.*

In accordance with your comment, I have added Tables which summarize the effects of thiazolidinediones and SGLT2 inhibitors on cardiorespiratory fitness in patients with type 2 diabetes to the manuscript.

2. *This would also help reduce the long, detailed presentation of individual studies, largely reproducing the data reported in the tables, and discuss data beyond the mere reporting.*

I have revised the text so as not to repeat the information contained in the Tables of this Review.

3. *A few words should be used with caution. The term “hypoglycemic agents” might be properly changed into “anti-hyperglycemic” or “glucose-lowering”, although pharmacology also uses the term “antidiabetic”, which I dislike.*

In accordance with your comment, I have changed the term “hypoglycemic agents” to “glucose-lowering agents.”

4. *It is not clear the reason to include in the introduction a paragraph including ACE-inhibitors, ARBs, and also statins. Is there any evidence that these drugs affect*

cardiorespiratory fitness. Obviously, they have effects on cardiovascular mortality, but what is the relation with fitness?

As you mentioned, there is no firm evidence that these drugs have an impact on cardiorespiratory fitness, and the sentences discussing ACE-inhibitors, ARBs, and statins are irrelevant to this Review. I have deleted the sentences.

5. *Introduction: "Angiotensin II receptor blockers are" not "Angiotensin II receptor blocker is.*

I have deleted the relevant part of the manuscript according to the reviewers' comments.

6. *Metformin dose: "... increased every second day to a maximum of 2000 mg/day." Please correct*

I have corrected.

7. *There are several minor printing errors that should be corrected.*

The manuscript has been gotten an additional English proof reading.