

June 21, 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.

We will re-submit my revised manuscript entitled "Exercise and glucagon-like peptide-1: Does exercise potentiate the effect of treatment?" to *World Journal of Diabetes*.

According to the reviewers' comments, we completely corrected our manuscript. We 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. We 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. 02631746

Well organised manuscript showing possible relationship between exercise and GLP-1 and its impact on DM. The hypothesis is reasonable and appears rational. This idea can be easily tested in the clinic.

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

Reviewer No. 01424366

This is a novel commentary on the possible ability of exercise to improve the ability of GLP-1 receptor agonists in T2D. This has not to my knowledge been addressed by other reviews. A strength of the paper is that it balances the data available concerning the possible effects of exercise on GLP-1 sensitivity vs. GLP-1 release. I think the review could be strengthened by more depth of speculation on possible contributing mechanisms of action of exercise. It is mentioned that microbiome changes result from exercise, and that this might alter GLP-1 release. Microbiome action on the digestion of dietary fibre results in the production of short-chain fatty acids (SCFA). SCFA interact with specific G-protein coupled receptors on the intestinal L-cells to modulate GLP-1 release. SCFAs also signal through the same receptors (GPR41 and GPR43) to increase glucose-stimulated insulin secretion from the beta cells. Hence, an effect of exercise on altering the microbiome could increase SCFA signaling to promote insulin release both through increased GLP-1 release and by a direct effect on the pancreas. On the other hand exercise can reduce adipokine release from adipose such as leptin, as well as reducing beta cell lipotoxicity, and improve both insulin sensitivity and beta cell function. The key pathway that needs examination is whether exercise improves GLP-1 sensitivity at a pancreatic or cardiovascular level to not only improve metabolic control, but also reduce diabetic complications. A fuller description of available knowledge on cellular pathways that might support this would enhance the review.

Thank you very much for your helpful comments.

I appreciate the time and effort that was invested in reading the manuscript.

In accordance with your comments, I have added the following sentences to the revised manuscript.

Exercise also increases microbiota-derived short chain fatty acids (SCFA) [20] which have been shown to improve insulin sensitivity [21]. Short chain fatty acids interact with specific G-protein coupled receptors (GPR41 and GPR43) on the intestinal L-cells [22], and increase GLP-1 secretion [23]. Exercise may improve GLP-1 secretion/function through the SCFA signaling mechanism.

Reviewer No. 00506294

This editorial about an issue not well known as the efficacy of exercise on the GLP-1 secretion that is only partially investigated in patients with type 2 diabetes mellitus. The author considers that exercise appears to potentiate the effect of the GLP-1 receptor agonists treatment by ameliorating GLP-1 resistance and the gut microbiota in causing GLP-1 resistance. In addition, myokines are believed to play a vital role in mediating GLP-1 secretion/function during exercise. Although current evidence is limited, a human study demonstrated that a GLP-1 receptor agonist, exenatide, elevated irisin concentrations and enhanced the glycemic control in patients with type 2 diabetes mellitus. The editorial is well written and assess an item not well known with interest for the future treatment of type 2 diabetes mellitus.

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

Reviewer No. 03648962

This is an average manuscript, that can be published as is.

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

Reviewer No. 02446617

This editorial addresses a very interesting and timely topic on how exercise may improve GLP1 signaling in patients with type 2 diabetes. I only have minor comments. The author should avoid the continuous use conjunctive adverbs in the abstract and first paragraph. It is distracting. The

abstract could benefit from addition of a summary sentence(s) that highlights the implications of the recommendations given in the editorial.

Thank you for your helpful comments.

In accordance with your comments, I have deleted conjunctive adverbs: “Assumedly,” “In addition,” and “which” from the abstract and first paragraph.

I have also added the following sentence to abstract to highlight the implication of this editorial.

The combination of exercise and GLP-1-based therapy may have a synergistic effect on the treatment of T2D.