

Professors Lu Cai, Michael Horowitz, Shahidul Islam, and Jian-Bo Xiao
Editors-in-Chief
World Journal of Diabetes

13 January 2023

Dear Professors Cai, Horowitz, Islam, and Xiao,

I thank you for your e-mail dated 5 January 2023 inviting me to resubmit my manuscript. I would like to thank the Editors and Reviewers for their constructive comments. Overall, I found that their comments greatly assisted in the revision of my manuscript, and I have carefully addressed all of the comments and suggestions. I have provided detailed responses to the individual comments. I hope that you will find the revised manuscript acceptable for publication.

I thank you for facilitating the review of my manuscript and look forward to receiving your response.

Sincerely yours,

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Response to the Company Editor-in-Chief

***Editor:** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.*

Response: I appreciate the careful reading of my manuscript and the constructive comments. The detailed review of the previous version of my manuscript is greatly appreciated and I have attempted to address all of the comments made. In particular, I have revised the title of my manuscript on the basis of the submission rules and I have provided detailed responses to the individual comments.

I am grateful to you for the time and effort spent in reviewing my manuscript.

Response to reviewer #1

REVIEWER #1: *This paper is a good summary of the current status of clinical use of insulin and glucagon in fixed ratios for the treatment of T2DM, and the topic is novel.*

Response: I appreciate the careful reading of my manuscript and the positive comment. I am grateful to you for the time and effort spent in reviewing my manuscript.

Response to reviewer #2

REVIEWER #2: *This is a very practical summarize. Anti-diabetic medications are often required for people with uncontrolled T2D to achieve their glycemic targets. Currently, clinicians can recommend several therapeutic approaches. whether patients are treated with a single or multiple oral antidiabetic agents, they often require the addition of an injectable agent (insulin or a glucagon-like peptide-1 receptor agonist (GLP-1RA). In addition to single-agent injectable products, fixed-ratio combination (FRC) injections, comprising basal insulin and a GLP-1RA, have recently become available, and their efficacy for glycemic control has been demonstrated in previous phase II/III trials. Several authors have argued that they are useful based on the results of these clinical trials, although real-world clinical evidence regarding their utility is limited. In this review, they discuss the utility of and clinical outcomes associated with the use of such FRCs in people with T2D. FRCs comprising basal insulin and a GLP-1RA have the potential to be such a “well-balanced” therapy.*

Response: I appreciate the careful reading of my manuscript and the positive and constructive comments and suggestions.

Comment: *It is suggested that the author can add some contents of economic valence ratio. In addition, for a newly diagnosed diabetes patient, author can add whether to recommend FRCs or choose oral medicine?*

Response: I fully agree that an economic point of view for such new treatment regimens should be discussed. In addition, I have decided to discuss whether FRCs can be the first pharmacological treatment strategy for type 2 diabetes. I have added the following sentences and references to the revised manuscript.

“An economic point of view is also an important issue for such new treatment regimens. Several reports from the UK and Czech Republic compared the cost-effectiveness of IDegLira and IGlarLixi. Pöhlmann *et al.* reported that IDegLira used for treating people with T2D who were treated with basal insulin had a higher cost than IGlarLixi in the Czech Republic^[58]. IDegLira was associated with a longer lifespan and quality-adjusted life-years (QALYs) than IGlarLixi^[58]. However, other reports from the UK that

compared the cost-effectiveness among IGlarLixi, IDegLira, and basal insulin plus dulaglutide or liraglutide showed almost similar QALYs, although IGlarLixi provided substantial cost saving owing to a lower acquisition cost^[59]. The same cost-saving effect was also confirmed in an IGlarLixi add-on strategy in people with T2D treated with oral antihyperglycemic agents^[60]. IGlarLixi showed slightly higher estimated QALYs at an acceptable higher cost with a reduction in the daily injection frequency compared with twice daily BIAsp 30^[61]. The cost-effectiveness of these two FRCs appears to be different. However, the acquisition costs and required doses for FRCs to maintain appropriate glycemic control differ among countries and races, possibly resulting in different outcomes of patients' burden.” (lines 293–310)

“Importantly, Kawaguchi *et al.* showed that endogenous insulin secretory capacity was important to maximize the efficacy of such FRCs^[51]. Beta-cell function declines over time in people with T2D^[54]. Therefore, early induction of FRCs might be a reasonable treatment option. However, clinical evidence assessing the efficacy of these FRCs is limited to step-up or switching therapy from other antihyperglycemic medications. In addition, these FRCs cannot be induced as a first injection regimen in certain countries. Taken together, these findings suggest that further investigation to determine whether FRCs can be a first-step treatment for T2D should be performed in the future.” (lines 255–263)

I am grateful to you for the time and effort spent in reviewing my manuscript.

Response to reviewer #3

REVIEWER #3: *This paper has scientific reference value for the clinical treatment of type 2 diabetes.*

Response: I appreciate the careful reading of my manuscript and the positive comment. I am grateful to you for the time and effort spent in reviewing my manuscript.