

Rome, March 21, 2021

To the Editor-in-Chief

Prof. Dr. Timothy Koch

*World Journal of Diabetes*

Manuscript ID: 63533

Title: “Long-term metformin therapy and vitamin B12 deficiency: an association to bear in mind”

Dear Editor,

*World Journal of Diabetes*

We thank you and the expert referees for the thoughtful revision of our manuscript. We have addressed all the Reviewer’s comments to the best of our abilities, and we have modified the manuscript accordingly. All the corrections and changes have been tracked by using coloured text (red text). We also added a new paragraph entitled “Metfomin-induced vitamin B12 deficiency: implications for diabetic neuropathy” based on relevant articles that have recently been published.

## **Point-by-point response to Reviewers:**

### **Editor and Reviewer(s)' Comments to Authors**

#### **Reviewer #1**

- This review gave us a fully and comprehensive introduction of long-term metformin therapy and vitamin B12 deficiency. The evidences can support the ideas. In the end, the authors gave the methods not only in screening high risk patients but also treating recommendation. There are some mistakes in manuscript, please see the comments in reviewed manuscript.

We thank the reviewer for his/her favorable comment on our manuscript. We amended the reported mistakes accordingly.

- “Once the HC-vitamin B12 complex reaches the small intestine (duodenum), pH change and degradation of haptocorrin by pancreatic proteases favour vitamin B12 cleavage from haptocorrin..”; small intestine ≠duodenum

We amended “small intestine (duodenum)” into “duodenum” in order to make the statement more accurate.

- “Apart from metformin-treated patients with insulin resistance, prediabetes, T2D and PCOS, another subgroup in which routine screening for vitamin B12 deficiency may be considered includes patients with type 1 diabetes (T1D) taking metformin as non-insulin adjunct therapy due to insulin resistance and overweight/obesity, especially in presence of peripheral neuropathy or unexplained anemia.”; Insulin resistance normally is not thought in T1D.

In the revised manuscript, we amended the sentence as follows: “Apart from metformin-treated patients with insulin resistance, prediabetes, T2D and PCOS, another subgroup in which routine screening for vitamin B12 deficiency may be considered includes patients with type 1 diabetes (T1D) taking metformin as non-insulin adjunct therapy, especially in presence of peripheral neuropathy or unexplained anemia”.

- “The recommended dietary allowance of vitamin B12 for subjects without malabsorption has been set at approximately 2.4 µg/day for adult men and nonpregnant women (2.6 mg/day for pregnant women)”; 2.6 mg /day for pregnant women, right?

We thank the reviewer for reporting this typographical error. We amended “2.6 mg/day” into “2.6 µg/day”.

## Reviewer #2

- 1.The manuscript was performed well, but some contents need to be added. For example: (1) vitamin B12 deficiency in specific populations such as the elderly or pregnant women. (2) vitamin B12 deficiency in different ethnic people including Asian.

We thank the reviewer for his/her favorable comment on our article and for his/her suggestions aimed to improve the quality of the manuscript. According to the reviewer’s suggestion, we added the requested information in a new paragraph entitled “Populations at risk for vitamin B12 deficiency”.

- 2. There were several previous reviews addressing this issue, such as “Recommendations for diagnosis and management of metformin-induced vitamin B12(Cbl) deficiency”, “Vitamin B12 status in metformin treated patients: systematic review”, “The role of metformin on vitamin B12 deficiency: a meta-analysis review”. Are there new insights in this review different from the previous reviews.

We thank the reviewer for his/her comment. We reviewed and quoted the suggested references (ref. 35, 36 and 37). Based on our review of the aforementioned articles, we believe that the novelty of our manuscript relies on the fact that it provides a list of proposed criteria for a cost-effective screening and subsequent intermittent periodic testing of vitamin B12 status in metformin-treated patients.

- 3. There were some spelling mistakes including not required capitalized “Topic Highlight” on line 16 in Abstract and wrong unit on line 8 in chapter “treatment of vitamin B12 deficiency”.

We thank the reviewer for reporting this typographical errors. We amended “Topic Highlight article” into “topic highlight article”; we amended “2.6 mg/day” into “2.6 µg/day” in chapter “treatment of vitamin B12 deficiency”.

## Editorial Office

- 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (10) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. Step 5: Footnotes and Figure Legends

(a) Requirements for figures: Please provide decomposable Figures (whose parts are all movable and editable), organize them into a single PowerPoint file, and submit as “63533-Figures.ppt” on the system. The figures should be uploaded to the file destination of “Image File”. (b) Requirements for tables: Please provide decomposable Tables (whose parts are all movable and editable), organize them into a single Word file, and submit as “63533-Tables.docx” on the system. The tables should be uploaded to the file destination of “Table File”. Step 6: Automatically Generate Full Text Files Please download the “Full Text File” or click “Preview” to ensure all the contents of the manuscript automatically generated by the system are correct and meet the requirements of the journal.

We provided the editable version of Figure 1 using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the Editor (63533-Figures.ppt). In addition, we confirm that we did not re-use figures published elsewhere and that our figure is original and does not require any permission from other publishers. We also uploaded decomposable Tables in a separate Word file entitled “63533-Tables.docx”.

In conclusion, we confirm that this paper has not been published or submitted for publication elsewhere, and that it is not under consideration for publication elsewhere, neither as a brief abstract in the proceedings of a scientific meeting or symposium. All authors are in agreement with the content of the manuscript. We confirm that the publication will be approved, upon acceptance, by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted, this manuscript will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

Thank you very much in advance for the attention you will pay to our manuscript. We hope that the manuscript in its present form is suitable for publication.

With best regards



Sincerely,

With best regards.

Sincerely,

**Marco Infante, M.D.**

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