

25th March 2015

To
Editor
World Journal of Diabetes
ESPS Manuscript NO: 15748

Re: Revised 1 version: ESPS Manuscript NO. 15748

**Title :Vitamin D and Its Relationship with Insulin Resistance and
Diabetes Mellitus**

Authors: Kamal A.S. Al-Shoumer & Thamer M Al-Essa

Dear Sir,

Thank you for your recent letter indicating the need for submission of a revised version of the above titled manuscript after the implementation of the reviewers comments. Thus, I do attach the revised version of the manuscript based on the reviewers and editor comments.

Below you will find our responses to the comments of the editor and reviewers, and the changes made in the manuscript:

Editorial comments

Editor comment #1: When you send the manuscript back, please provide us the format of the document.

Response #1: The full document is written by Microsoft Word

Editor comment #2: Statement on Conflict of interest should be added on first page

Response #2: This was added on page 1 of the revised version.

Editor comment #3: Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Response #3: A summary core tip of less than 100 words has been added on page 3 under the heading Core Tip (written by red color)

Editor comment #4: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip.

Response #4: An Audio file describing the core tip has been added (format WMA (MP3), 821KB)

Editor comment #5: Please put the reference numbers in square brackets in **superscript** before the end. Please check across the text.

Response #5: All references were put in square brackets in superscript (all are written by red color)

Editor comment #6: Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please provide PubMed citation numbers for the reference list, e.g. PMID and DOI.

Response #6: All available PubMed and DOI citation numbers were added for the references they have it. Complete list of authors has been added to some of the missing references (66, 67 & 69) (all are written by red color)

Reviewers:

Reviewer #1 (00506304)

Reviewer Comment #1: “This paper has provided novel evidence that vitamin D insufficiency/deficiency poses a risk of T2DM. The possible underlying mechanisms, such as the direct effect of vitamin D on pancreatic beta cells, as well as supporting clinical studies were also reviewed. In general, this review article is informative, consisting of both preclinical and clinical data”.

Response #1: “ We thank this reviewer for this positive comment”

Reviewer Comment #2: “On page 5-6: Reference #25 was quoted; however, this reference mentioned about the role of calbindin-D28k as a calcium-buffering protein in beta cell. Specifically, this vitamin D-dependent protein should decrease intracellular calcium and inhibit insulin release. This point must be explicitly described and discussed.”

Response #2: We have added a sentence to describe a role of calbindin-D28k in page 7 last line of first paragraph [a role of calbindin-D28k (a calcium-buffering protein in pancreatic beta cell) in calcium regulation and modulation of insulin release has been described].

Reviewer Comment #3: “Indeed, vitamin D deficiency should not interfere with plasma ionized calcium or intracellular calcium concentrations enough to impair insulin secretion since the ratio of intracellular calcium:plasma calcium is

approximately 1:1000 even in overt non-lethal hypocalcemia (i.e., large gradient for calcium influx). On the other hand, if vitamin D increases opening of pancreatic L-type calcium channels, it may increase insulin release.”

Response #3: We have already addressed this during the discussion under the heading “possible potential mechanisms for the effects of vitamin d on glucose intolerance and T2DM- items 1 and 2, page 6 and 7)

Reviewer Comment #4: “The conclusion should be described in a separate section (under the header “Conclusions”). The authors may provide perspectives on future research questions, clinical application, and potential use of 25(OH)D level as a biomarker for T2DM in this section).”

Response #4: We have made the conclusion in a separate section under the heading of conclusions. We have then added concluding perspective statements at the end: “We anticipate that these future well designed randomized prospective trials to answer several important questions. Firstly, whether the daily interventional use of vitamin D in the pre-diabetic states has a protective role against the development of type 2 diabetes? Secondly, whether the daily intake of vitamin D will be accompanied with significant glycemic improvement? And finally, whether supplementation of vitamin D to diabetics will delay or prevent some of the adverse diabetic complications or have positive effects on cardiometabolic outcomes in long term.”

Reviewer #2 (02446498)

Reviewer Comment #1: “Vitamin D” is used both as a general term for vitamin D compounds and as cholecalciferol. The authors should use "vitamin D" more carefully, specifically in the section "Vitamin D metabolism" (as in Figure 1). Use vitamin D3 (or cholecalciferol), vitamin D2 (or ergocalciferol), 25(OH)D3, 25(OH)D2, 1,25(OH)2D3 (or calcitriol), and 1,25(OH)2D2 as necessary.”

Response #1: We thank this reviewer for this comment. We have corrected all terms used for vitamin D in the paragraph on vitamin D metabolism (page5) (all are red marked corrections)”

Reviewer Comment #2: “A table that summarizes epidemiological and clinical studies is helpful for readers to read this review paper.”

Response #2: Table 2 summarizing selected epidemiological trials has been added and was referred in the text page 13.

Finally, I do thank the editors and the reviewers for their constructive comments and do hope our responses to all comments have verified the needful,

Thank you again for publishing our work in the World Journal of Diabetes.

Yours,

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