December 24, 2015

Lu Qi
Editor-in-Chief
The World Journal of Diabetes

Dear Dr. Qi:

Ref "The role of Vitamin D in Diabetes Mellitus and Chronic Kidney Disease", **ESPS Manuscript NO:** 22450

Thank you for your email of November 27, 2015, regarding our manuscript, "The role of Vitamin D in Diabetes Mellitus and Chronic Kidney Disease" and the valuable comments of the four reviewers. Our revised manuscript, as well as a point-by-point response, to the reviewers' comments, are attached.

We feel that the revised manuscript is significantly improved over the initial submission. We hope that it is now suitable for publication in *The World Journal of Diabetes*.

Thank you in advance for your consideration of this paper.

Sincerely yours,

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We wish to express our appreciation to the reviewers for their insightful comments, which have helped us significantly improve the paper.

Reviewer #1 *02446566*: Comments to the Author
In page 6, percentage of subjects with hypovitamin D is confusing. If "almost one half " have low level during winter and spring, it may sound strange that 15.4% have low level in winter and fall and 46.6% have low level in spring and summer

P 7
Response: Thank you for pointing out this error. We changed the text to reflect that levels were 15.4% during the spring and summer and 46.6% during the winter and fall.

In page 7 the reference number 28 at "Powe et al [28]" is duplicated.

Response: We deleted the duplicate reference.

The author says that racial differences in the prevalence of DBP gene polymorphisms provide a likely explanation for this observation. For this explanation, the effect of polymorphism of DBP gene should be either low expression level of DBP gene, lower affinity for vitamin D or low efficiency in megalin-mediated reabsorption. In ref 28, two polymorphisms are studied. SNP rs7041 and rs4588 cause substitution of Asp to Glu at residue 432 and Thr to Lys at residue 436, respectively. Do these substitution cause change in affinity?

Response: The racial differences of total 25(OH)D levels are elucidated by DBP levels, and DBP levels are determined by a combination of two DBP polymorphisms (rs7041 and rs4588). The mechanism is thought to be that these common polymorphisms in the DBP gene produce variant proteins that differ in their affinity for vitamin D. We changed this information and added the following sentences to the manuscript.

P7-8

“Powe et al [32 错误!未定义书签。] reported that although total 25(OH)D and DBP were lower in black subjects than in white subjects, concentrations of estimated bioavailable 25(OH)D were similar between black and white subjects. In addition, because the affinity of DBP to 25(OH)D differs in the DBP gene polymorphism, genetic polymorphisms of DBP genes (rs7041 and rs4588) provide a likely explanation for racial variations in levels of DBP and 25(OH)D. The combination of rs7041 and rs4588 produces amino acid changes resulting in variant DBPs (Gc1F, Gc1S, and Gc2). The phenotype of Gc1F, which is common in black homozygotes, was associated with the lowest levels of DBP (Gc1F/Gc1F homozygotes). On the other hand, Gc1S, which is common in white subjects, was associated with the highest DBP levels (Gc1S/Gc1S homozygotes). The Gc2/Gc2 homozygotes and Gc1F/Gc1S heterozygotes were associated with intermediate DBP levels. These findings suggest that racial differences in the distribution of DBP and total 25(OH)D are caused by DBP polymorphisms, and low total 25(OH)D levels do not indicate vitamin D deficiency. For purposes of cross-racial evaluations of vitamin D deficiency, it might be appropriate to estimate serum total 25(OH)D concentrations using DBP polymorphisms and DBP.”

Reviewer #2 *00507108*: Comments to the Author

The Abstract is less objective in my opinion, for example the statement that "the immune modulatory properties of vit D may play an important role in the prevention and progression of type 1 Diabetes". The evidence presented in the paper suggests only that vitamin D is involved in the immune regulatory pathway and deficiency of vitamin D disturbs this pathway. Similarly the authors give the evidence that vitamin D is involved in insulin signalling but not in particular in type 2 Diabetes. The core tip again overstates the excellent review of the literature.

Response: Thank you for your comments. We changed our abstract and core-tip as follows.

[abstract]

"Although in patients with DM the relationship between vitamin D and insulin secretion, insulin resistance, and β-cell dysfunction are pointed out, evidence regarding vitamin D levels and DM is contradictory, and well controlled studies are needed."

[core tip]

"Vitamin D plays an essential role in diabetes mellitus (DM) and chronic kidney disease (CKD). The relationship between vitamin D and insulin secretion, insulin resistance, and β-cell dysfunction are pointed out. Vitamin D deficiency has been linked with the renin-angiotensin system and inflammation, which may be associated with the cause and progression CKD. There is increasing evidence that vitamin D deficiency may be a risk factor for DM and CKD. Clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed"

The introduction on the physiology of vitamin D is useful and clearly written. It would be useful to have some discussion of the evidence that produced the definition of vitamin D deficiency. The problem is in the definition. 40 nmol/l or 10 nm/l.

Response: We add the following sentences to clarify the definition of vitamin D deficiency.

P 6

"The US Institute of Medicine (IOM) defines vitamin D deficiency as 25(OH)D levels less than 20 ng/mL and greater than 20 ng/mL is sufficient upon evidence related to bone health[16]. Several studies reported that people with 25(OH)D levels less than 20 ng/mL is the risk factor of fracture [17] and have greater subsequent rates of bone loss [18]. On the other hand, the Endocrine Society's guidelines, which are based on patients with endocrine disorders, define vitamin D insufficiency as 25(OH)D levels of 21-29 ng/mL[19,20]. Despite these different definitions, both guidelines agree that vitamin D insufficiency and deficiency are common problems in certain populations. "

Ref 33 is a review and does not seem appropriate for the statement. Ref 36 also not appropriate. Ref 38 is missing. Ref 39 is a Mendelian randomisation study

Response: We apologize for the errors in our citations. We changed each citation appropriately as follows and added Ref 38. In addition, when

referring to Ref 39, we changed the sentence to reflect that the study is a "Mendelian randomization study."

[Ref 33→38]

Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr* 2004; 80: 1717S-1720S [PMID: 15585793]

→Chonchol M, Greene T, Zhang Y, Hoofnagle AN, Cheung AK.Low Vitamin D and High Fibroblast Growth Factor 23 Serum Levels Associate with Infectious and Cardiac Deaths in the HEMO Study. J Am Soc Nephrol. 2015;13. [epub]pii: ASN.2014101009

[Ref 36]We deleted this citation.

[Ref 38→43]

Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. *Hypertension*. 2008 ;**52**: 828-832. [PMID:18838623 doi: 10.1161/HYPERTENSIONAHA.108.117630]

In the section on Type 2 diabetes 2nd para page 12 should the last line not be ..."and type 2 DM is NOT causal.?" Has 'not' been omitted?

Response: This sentence was corrected and the word "not" added.

I am surprised at the statement on page 14 'Whether viatmin D supplementation improves glycaemic control or prevents incident type 2 DM is not clear' All the evidence presented suggests that it is very clear and the answer is no.

Response: We agree that the effect of vitamin D supplementation does not have clear evidence for glycemic control and DM. We changed the sentence as follows.

P15
“Although at this time, supplementation with vitamin D has not been shown to improve glycemic control or prevent incident type 2 DM, clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed.”

The authors might consider rephrasing their conclusion of the presented data. Refr 106 does not seem to support the statement on all cause mortality. Would the article by Skaaby T in Danish Med J 2015 be helpful? Is the risk for end stage renal disease higher in patients with low vit D status or is the risk of low vitamin D status higher in patients with end stage renal disease? Ref 107 does not show a significant statistical association with all-cause mortality. In conclusion an interesting well written review which I enjoyed reading.

Response: Thank you for your comments. We agree with reviewer that Ref 106 (113) does not mention all-cause mortality in CKD patients. We changed the reference to another paper (Navaneethan SD et al,). Navaneethan SD et al reported that vitamin D status is associated with mortality in CKD patients not undergoing dialysis.
In addition, because Ref 107 (114) mentioned cardiovascular events but not mortality, we changed our manuscript as follows.

P17
“Among patients undergoing hemodialysis and peritoneal dialysis, low 25(OH)D levels are also associated with cardiovascular disease[114].”

Reviewer #3_*02446525*: Comments to the Author

The normal physiology of vitamin D and that of diabetes I and II and CKD can be skipped and more emphasis provided on the pathophysiology and actions of vitamin D on prevention/ delaying the onset of the diseases mentioned

Response: Thank you for your comment. I agree with reviewer that our manuscript lacked information on detailed pathophysiology and action of vitamin D. We added the following sentences.

P 16
"There are the several theories about the pathogenesis of vitamin D deficiency in CKD. Megalin, which is present in endocytic receptors in proximal tubule cells, is involved in the reabsorption of DBP from glomerular ultrafiltrates[107]. In addition, megalin also mediates the subsequent intracellular conversion of 25(OH) D to its active form. As kidney function declines, megalin expression in the proximal tubule decreases[108]. Megalin function is also attenuated with reduced kidney function, because of damages from low molecular weight proteinuria. "

P 17
"In the VITAL study, which was designed to compare the effectiveness between paricalcitol and placebo, the paricalcitol group showed a decreased urinary albumin to creatinine ratio (UACR) of -16% compared with placebo[105]. However, as of yet, no other studies have investigated the effectiveness of vitamin D supplementation for protection of kidney function; thus, future studies are needed. Another study showed that paricalcitol led to decreases in levels of brain natriuretic peptide (BNP) in patients with CKD[119]. On the other hand, a recent study reported that treatment with paricalcitol did not improve left ventricular mass and function in patients with CKD. There is controversial evidence regarding the role of VDRA to cardiovascular disease and surrogate makers."

Reviewer #4_*00503286*: Comments to the Author

The paper "The role of Vitamin D in Diabetes Mellitus and Chronic Kidney Disease" should be published in World Journal of Diabetes, after minor corrections with the editor.

Response: I would like to thank you for your kind comments. We changed manuscript appropriately.