June 21, 2016

Dear Editor,

I am writing to resubmit the on-line paper, entitled *What is The Optimal Level of Vitamin D in non-Dialysis CKD Population? Re-Evaluating Thresholds for Serum 25(OH)D Concentrations in Relation to Death, Kidney Progression and Hospitalization,* for consideration for publication in the *World Journal of Nephrology*

After considering your helpful comments and those of the Reviewers, I am resubmitting both a corrected version with additions underlined in red and deletions crossed out in blue, and a clean version of our revision without the corrections marked in the text. All of your suggestions have been taken into account in this revised version, in order to better establish the points of the study.

Below, to clarify any matter raised by the Editor and the Reviewers, I´m including a separate point-by-point answer to their comments:

ANSWER TO REVIEWER 1 COMMENTS

- **Comment 1**. ***In a group of 470 non-dialysis 3-5 stage CKD patients the Authors evaluated the relationship between 25(OH)D levels and cardiorenal outcomes over a 3-year follow-up. They found that 25(OH)D < 20 ng/ml was an independent predictor of all-cause mortality and kidney progression. This is an interesting study with several major limitations: Relatively small study group for these endpoints?*** As we state in the Material and Methods section, with 470 patients included and a follow-up of three years, the power estimation of the study was enough for demonstrating the independent predictor value of vitamin D levels for the primary outcome (3-year incidence of death). As we state in the Discussion section, although there are previous prospective observational studies which examined the prognosis value of 25(OH)D levels in CKD subjects not on dialysis, this is the first one, to our knowledge, which included the biggest cohort of non-dialysis CKD subjects with data regarding emerging cardiovascular risk factors as vascular calcification scores and ankle brachial pressure index.
- **Comment 2.** ***This is a retrospective study in essence ?.*** As we state in the Material and Methods section, this study is a *post-hoc* analysis of the OSERCE-2 study (Study of Mineral and Bone Disorders in Chronic Kidney Disease in Spain), which was a 3 year follow-up prospective, observational, study which enrolled 742 adults with 3 to 5-stage CKD not on dialysis subjects attending 39 centres in Spain.
- **Comment 3.** ***25OH D values were evaluated only at baseline and some patients subsequently received vitamin D supplements?*** As we state in the Material and Methods section, Vitamin D levels were only evaluated at baseline. Although patients on treatment

with active vitamin D were excluded in this new analysis of the OSERCE-2 study, 43 (9%) patients received vitamin D supplementation (data showed in Table 1).

- **Comment 4.** ***How were cutoff values of D Vitamin identified? Why not analyse data on the basis of tertiles or quartiles?*** As we state in the Material and Methods, and the Discussion sections, one of the objectives of the study was trying to identify the threshold value for abnormally reduced 25(OH)D levels. Given that most current guidelines have defined vitamin D deficiency and insufficiency, as a serum 25(OH)D level of <20ng/ml and 21-29ng/ml respectively, we prefer to analyze the predictive value of these well-established cut-offs, instead using tertiles or quartiles. The authors think that testing these cut-offs for predicting hard end-points as death and CKD progression may offer a truly practical approach to clinicians dealing with CKD patients on a daily basis. On the contrary, the use of tertiles or quartiles could give less practical sense to the results of the study.
- **Comment 5.** ***What was the distribution of baseline 25 OH values?*** Distribution of vitamin D levels at baseline is showed in Table 1. The proportion of patients with vitamin D deficiency (<20 ng/ml) or insufficiency (20-29 ng/ml) was 53% and 33%, respectively
- **Comment 6.** ***Given the above reported limitations I find that the Authors should therefore tone down considerably their conclusions.*** The authors are in agreement with this comment. Given that the study is observational in nature, it is still insufficient to determine whether the association between low vitamin D levels and worse CKD outcomes is causal and reversible. This limitation is mentioned in the Discussion section, and the study conclusions have been softened.

ANSWER TO REVIEWER 2 COMMENTS

- **Comment 1.** ***The paper with the title : << What is The Optimal Level of Vitamin D in non-Dialysis CKD Population? Re-Evaluating Thresholds for Serum 25(OH)D Concentrations in Relation to Death, Kidney Progression and Hospitalization >> is an interesting well written article and the authors claim that their study << as the first prospective which analyzed the upper level of Vit D associated to better improvement in survival and CKD progression on CKD patients, did not demonstrate additional benefits on these hard outcomes when patients reached the optimal target levels for VD suggested by current guidelines (≥30ng/ml).So with this study, despite the limitations, the authors provide a new option in this so controversial field of Vitamin D treatment in CKD patients .***
  The authors appreciate this positive response to the paper.

ANSWER TO THE EDITOR'S COMMENTS:

- **Comment 1.** ***Please provide the approved grant application form(s) or funding agency copy of any approval document(s)/letter(s). For manuscripts supported by various foundations (i.e., charitable, not-for-profit organizations), the authors should provide a copy of the full approved grant application form(s) or funding agency copy of any approval document(s)/letter(s), consisting of the information section and body section in PDF format. The approved grant application form(s) or funding agency copy of any approval document(s)/letter(s) will be released online together with the manuscript in order for readers to obtain more information about the study and to increase the likelihood of subsequent citation.*** The grant application form has been provided.
- **Comment 2.** ***Please offer a signed pdf file with all the authors. Thank you!*** We have added this document.
- **Comment 3.** ***Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, detail of address (to street or avenue), city, postcode, province, country, and email. Thank you!*** Only one corresponding address has been provided.
- **Comment 4.** ***Please offer the audio core tip, the requirement are as follows:***
  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. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:
  Acceptable file formats: .mp3
  Maximum file size: 10 MB
  To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS. The audio core tip has been provided.
- **Comment 5.** ***Please reformat all the reference numbers like this. Please check throughout. Thank you! The Authors should put the number of the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the citied author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2].*** All the reference numbers have been reformatted according to the Editor's instructions.

I would like to finish by thanking you for your helpful comments. These have doubtless provided new content of paramount importance to the new version of the article.

Should you require additional information, please do not hesitate to contact me.

Sincerely yours,

Pablo Molina, MD; PhD

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