Author’s response to reviews

Title: Vascular calcification on plain radiographs is associated with carotid intima media thickness, malnutrition and cardiovascular events in dialysis patients: a prospective observational study

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Author’s response to reviews: see over
Dear Editor of BMC Nephrology

On behalf of the authors, I wish to thank you for the opportunity to submit a revised version of the manuscript for your consideration. The authors were pleased to address all issues raised by your reviewers in the revised version of the paper. I hope that the revised manuscript will meet with your approval.

Response to the concerns

The authors wish to thank the astute reviewers for the support and valuable advice they provided for revision of the paper. We were happy to address all issues raised as follows:

Major Compulsory Revisions:

1- The authors say that they "found increasing hemoglobin over a 2-year observation period in patients with VC non-progression on plain radiographs without significant differences of iron replacement and erythropoietin dose." However figure1- a shows that Hemoglobin has significantly increased overtime in patients with progression of vascular calcification. The other point in the mentioned sentence is that the authors have not compared the 2 groups of patients with increased and stable hemoglobin regarding iron replacement and erythropoietin dose. They just mention that "Erythropoietin dose per month was not significantly higher in patients who showed VC progression on plain radiographs and there was no significant difference of iron replacement in the enrolled dialysis patients." We need figures here for comparison of EPO dose in progressors and non-progressors. But finally how does this help? What is the logic or explanation beyond
these sentences? If the authors believe that hemoglobin increase has protected against vascular calcification, they should discuss it more in the discussion part. However there is a sentence at the end of the abstract which says "Conditions maintaining adequate hemoglobin level maybe retard progression of VC in dialysis patients." So overall, this issue is confusing in the manuscript and should be presented and discussed precisely.

Response: Authors fully agree with reviewer’s opinion. We are very sorry for confusing reviewer’s interpretation. Figure1-a indicate hemoglobin data of patients without progression of vascular calcification not with progression of vascular calcification. Therefore, we changed mistaken legend of figure 1. And we added data of erythropoietin dose and iron replacement in the revised manuscript: {(Darbepoetin alpha: 282.9 ± 130.6 mcg/month, erythropoietin-beta: 49224.1 ± 39854.1 IU/month [patients with VC progression] vs. Darbepoetin alpha: 238.6 ± 210.5 mcg/month, erythropoietin-beta: 49980.2 ± 33146.0 IU/month, [patients without VC progression]). There was no significant difference of iron replacement in the enrolled dialysis patients (3701.5 ± 2017.4 mg/week [patients with VC progression] vs. 3251.7 ± 1027.4 mg/week [patients without VC progression]). We did not make figures comparing EPO dose in progressors and non-progressors because data were not significant. We changed the last sentence of abstract to “Conditions increasing to adequate hemoglobin level maybe retard progression of VC in dialysis patients”.

2- Please also mention and discuss the correlation between vascular calcification score and CIMT, survival, MIS and prevalence of atheromatous plaques. If any correlation is
found, a multivariate analysis may help to define the best predictor of vascular calcification.

Response: Authors fully agree with reviewer’s opinion. Left CIMT (r = 0.466, p = 0.011), right CIMT (r = 0.378, p = 0.043), MIS (r = 0.340, p = 0.006) and prevalence of atheromatous plaques (r = 0.424, p = 0.024) were significantly correlated with significant VC. We added this sentence in the revised manuscript. However, there is no independent factor among these factors for prediction of significant VC in multivariate analysis. And we did not analyzed survival because survival is the result of vascular calcification and is not a predictor of vascular calcification.

3- Please mention to the 10 components of MIS in the related section in materials and methods because you are mentioning BMI, serum albumin level, and TIBC and body fat composition and the reader becomes eager to hear about the other 6 components.

Response: Authors fully agree with reviewer’s opinion. We mentioned the other components of MIS in the section of materials and methods.

4- Please refer to reference 13 at the end of this sentence: "We used Comprehensive Malnutrition Inflammation Scores (MIS) to assess the status of malnutrition". Then you should change the place of references 12 and 13.

Response: Authors referred and changed the place of references 12 and 13 as reviewer recommended.
5- Please mention to this point that PTH, Ca and phosphorus levels were not different in patients with and without significant vascular calcification in the results and discuss it in the discussion, referring to the following reference among the others needed in this regard.


Response: Authors fully agree with reviewer’s opinion. We mentioned that intact parathyroid hormone, calcium, and phosphorous levels were not significantly different in patients with and without significant vascular calcification in the results of revised manuscript. And we referred this reference in the revised manuscript.

6- Authors claim in discussion that "We also found that VC evaluation on plain radiographs by single method overlooked nearly 30% of other significant VC sites in dialysis patients". Where has this finding been mentioned the results?

Response: Authors fully agree with reviewer’s opinion. Nineteen (42.2%) of 45 patients with AAC scores < 5 had significant VCs on other parts, 14 of 40 patients (35.0%) with hand and pelvis VCs < 3 had significant VCs on other parts, and 12 (31.6%) of 38 patients without medial artery calcification of the feet had significant VCs on other parts. We mentioned this sentence in the section of results as reviewer recommended.

7- Authors claim in discussion that "To our knowledge, this is the first observational study to compare several VC scoring methods on plain radiographs and to prove the necessity of checking several VC sites for evaluation of possible CVD." Where is the
comparison of several VC scoring in the results? What we see is just comparison of MIS, CRP, HDL, ... with different VC scoring methods and not the comparison of the methods, per se.

Response: Authors fully agree with reviewer’s opinion. We changed sentence that reviewer mentioned in the revised manuscript: “To our knowledge, this is the first observational study to compare clinical findings according to several VC scoring methods on plain radiographs and to prove the necessity of checking several VC sites for evaluation of possible CVD.”

Minor Essential Revisions

1. This sentence in the abstract is vague at first glance "The prevalence of carotid atheromatous plaques, CIMT, malnutrition scores and CRP were significantly lower in patients with significant VC...". It first seems that the word "prevalence" includes the plaques, CIMT and so on. You can change the place of "prevalence of carotid atheromatous plaques" and put it after CRP and write this sentence as the following:

"Mean CIMT, malnutrition scores, CRP level and prevalence of carotid atheromatous plaques were significantly lower in patients with significant VC..."

The same point for the same sentence in the results: "The prevalence of carotid artery atherosclerotic plaques (p=0.003), CIMT (right: p=0.006, left: p=0.001), MIS (p=0.007) and CRP were significantly higher in patients with significant VC compared to patients without significant VC." It is better that you put the prevalence of carotid artery atherosclerotic plaques after CRP and also mention to the figures of CIMT, MIS and CRP for comparison between the 2 groups (not just the p values).
Response: Authors changed two sentences in the revised manuscript as reviewer recommended. And we already mentioned the data of CIMT, MIS and CRP for comparison between the 2 groups in Table 1. Therefore, we did not make figures for CIMT, MIS and CRP for comparison between the 2 groups because of duplication. We hope that this correction will meet with reviewer’s approval.

2. In Figure 1 please add the label "hemoglobin" to the Y axis.

Response: Authors inserted the label "hemoglobin" to the Y axis in figure 1.

My main comments to this article are:

In this study the authors compare three different plain X-ray methods to evaluate vascular calcifications in dialysis patients: the abdominal aortic calcification score, the simple vascular calcification score in pelvis and hands and feet vascular calcification. The authors conclude that significant VC on plain radiograph was associated with CIMT, malnutrition, inflammation, and CV events in dialysis patients. They also have verified in this population an association between low Hb levels and progression of vascular calcification.

1. The authors state that this is the first study to show an association between vascular calcification evaluated by plain X-ray and markers of atherosclerosis. I think that this is true. The concept that calcification may be a marker of atherosclerosis in CKD patients however is, however, not new. There is, at least, another study that has shown an association between valvular calcification with inflammation, carotid atherosclerosis and arterial calcification in ESRD. This study, in my opinion should be added to the

Response: Authors fully agree with reviewer’s opinion. We referred this reference in the revised manuscript.

2. The evaluation of calcification progression using a plain X-Ray method is, in my opinion difficult because the method employed is semi-quantitative and strongly dependent of the observer. To my knowledge there is only one published study that has evaluated progression calcification in dialysis patients: vascular calcification was evaluated in aortic arch and progression was associated with higher risk of mortality. (Noordzij M, Cranenburg EM, Engelsman et al. Progression of aortic calcification is associated with disorders of mineral metabolism and mortality in chronic dialysis patients. Nephrol Dial Transplant. 2011;26(5):1662-9). This study deserves to be referred.

Response: Authors fully agree with reviewer’s opinion. We referred this reference in the revised manuscript.

3. Probably it would be interesting to show in a table (similar to table 1) the univariate analysis comparing the factors associated with progression of vascular calcification.

Response: Authors fully agree with reviewer’s opinion. However, there were no significant baseline factors associated with progression of vascular calcification in this study. We made table 3 showing univariate analysis associated with progression of vascular calcification.
4. In multivariate analysis the unique factor associated with progression of VC is low Hb levels. This should be discussed more profoundly. Low Hb levels may be a marker of inflammation, malnutrition, Epo resistance, etc and I am not sure that the correction of Hb should decrease VC progression.

Response: Authors fully agree with reviewer’s opinion. We further discussed about the role of hemoglobin levels in the revised manuscript.

5. Have you analysed the effect of progression of VC in survival?

Response: No, authors have not analyzed the effect of progression of VC in survival because progression of VC was evaluated in the survivors.

6. In multivariate analysis besides Hb and age, probably you should also include albumin or CRP and diabetes. I think that you should only include one Hb level and not 3 Hb levels. The multivariate analysis should also be presented in a table.

Response: The adjusted variables included age, diabetes, albumin at 24 months, CRP at 24 months and one Hb level at 24 months as reviewer’s recommended. And authors presented data in the Table 3. Hb level after 24 months was an independent factor for VC progression on plain radiographs (Exp(B) = 0.344, 95% Confidence Interval = 0.13 – 0.96, p = 0.034). We stated those findings in the revised manuscript.

Best wishes

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