Author’s response to reviews

Title: Differences in association of lower bone mineral density with higher coronary calcification in female and male end-stage renal disease patients

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Author’s response to reviews:

Dear Editor-in-Chief Andrew Smyth

Thank you very much for the opportunity to submit a revised version of the manuscript” Differences in association of lower bone mineral density with higher coronary calcification in female and male end-stage renal disease patients” by Zhimin Chen et al. Below, we have provided itemized responses to each of the Reviewers’ comments, and have made corresponding changes in the revised text.

We thank the reviewers for their constructive comments and hope the revised version is now suitable for publication in BMC Nephrology.
On behalf of the authors,

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Editor Comments:

1. What is an 'unconditional risk factor' - Paragraph 1 of Background

Comment: We rewrote the sentence in the Paragraph 1 of Background as below ‘CAC can be treated as an independent risk factor for cardiovascular risk beyond that provided by conventional risk factors.”

2. Were the participants recruited and then sent for coronary CT and DXA, or did you recruit patients who already had them both done (for a different reason). I'm not clear on whether this is part of the study protocol or the eligibility criteria for the study.

Comment: We recruited patients who already had both coronary CT and DXA done. Who had undergone both coronary CT and DXA measurements would be the eligibility criteria for the study.

3. What constituted CVD? Clinical events only? Or were findings from coronary angiography (e.g. someone who has ischaemic heart disease on coronary angiography done for another reason such as investigation of arrhythmia consider as having CVD?)

Comment: Earlier or present occurrence of documented of cerebrovascular, cardiovascular, or peripheral vascular disease considered as signs of CVD and details of CVD have been published [1]. Patients had suffered from cerebrovascular disease (stroke), myocardial infarctions, clinical signs of ischemic heart disease (angina pectoris), peripheral ischemic atherosclerotic vascular disease, had a history of an aortic aneurysm, mitral stenosis, and cardiac failure.
4. How did you determine the sample size? Was there a sample size calculation or is this a convenience sample or the limits of what you could complete with available funding/resources? Is there adequate study power to explore interactions and differences by gender?

Comment: The patients who all agreed to undergo cardiac CT scans were recruited between March 2008 and June 2015 at the Department of Renal Medicine at Karolinska University Hospital, Stockholm. DXA was performed in 174 ESRD patients out of them. We much appreciate that the editor notified us about this interactions and differences by gender. Yes, we need further studies to elucidate the specific mechanisms linking regional differences in bone metabolism and gender differences to vascular calcification.

5. What is the timeline between BMD abnormalities and CAC increases - is it possible that treatment for CVD may impact on BMD so this association is heavily confounded? What is the pathophysiology? Are these surrogate markers of the same process?

Comment: In dialysis patients, low trabecular bone volume and decreased cortical bone density associates with CAC [2], and osteoporosis is predictive of progression of CAC [3]. In haemodialysis (HD) patients, lower trabecular bone volume was associated with the development of CAC, and decreased bone turnover was associated with less rapid CAC progression [4]. It is well established that mechanisms of vascular calcification (VC) and bone mineralization share several common pathways and therefore it is biologically plausible that a low BMD could be related to VC as reported in the general population [5, 6] and in ESRD patients [7, 8]. Nevertheless, although BMD and VC may be pathogenically connected [9-11], the mechanism(s) remain unclear.

6. Is there any evidence of BMD and CAC in non-CKD populations, or across the spectrum of renal function? I wasn't clear from the discussion section whether the other studies you mention are CKD or non-CKD populations.

Comment: Yes, low BMD and vascular calcification are both common features of the progeric uremic phenotype [12], and low BMD is linked to an increased risk of CVD [13-15] and predicts cardiovascular events and increased mortality in the general population, and in CKD patients [15-17]. We rewrote the Paragraph 2 of Discussion the manuscript.

7. Is the study adequately powered to look at different associations by bone location of for BMD?
Comment: Our previous study found low BMD specifically at arms and legs was found to associate with extent of vascular calcification as assessed both by CT heart scans allowing scoring of CAC and by artery biopsy allowing histological scoring of vascular calcification [18]. Nevertheless, in the present study, when examining BMD by DXA at different skeletal sub-regions of the body, the inverse correlations between BMD and CAC, were more significant in extremities (arms and legs) than at the spine. One may speculate that spine BMD could overestimate BMD as DXA estimations may be influenced by signals from a calcified aorta [17]. This might explain the current finding that especially BMD of extremities (where an impact of aortic calcification is absent) was the site significantly associated with CAC.

Reviewer: 1

Eiichiro Kanda (Reviewer 1): In this study, the authors investigated the relationship between low bone mineral density (BMD) and coronary calcification using end-stage renal disease (ESRD) patients' data. The results suggest the usefulness of BMD to identify high-risk patients with cardiovascular disease (CVD). I have several concerns about the contents.

1. Is the main endpoint of this study CVD or CAC score? If CVD is more important than CAC score, the analysis should be focused on CVD.

Comment: We much appreciate that the reviewer notified us about this important main endpoint. Cardiovascular disease (CVD) and risk of cardiac events in end-stage renal disease (ESRD) patients are independently predicted by coronary artery calcification (CAC). It is not clear to what extent low bone mineral density (BMD) is linked to increased risk of CAC and if sex interacts. The main endpoint of this study is CAC score. In the revised version of the manuscript we have redone the Table 1 and Table 2 to make CAC score as the main endpoint of this study clear.

2. Tables 1 and 2.

The subjects were divided into two groups: developing CVD or not. Considering PECO (patient, exposure, comparison, outcome), "E" indicates low BMD. The subjects should be divided on the basis of low BMD. The design of this study is vague.

Comment: We have revised Table 1 and Table 2 in revised version of the manuscript and added a Supplementary Table 1 recommended by the reviewer.
3. Figure 1

This figure shows the accuracy of the indices to predict the existence of CVD. This is confusing. Do the authors want to show the relationship between CVD and CAC score? This is not the main theme of this paper.

Comment: In the revised version of the manuscript, we have done the analysis recommended by the reviewer to show the accuracy of the indices to predict the high CAC score (> 100AUs) and have made a new Figure 1.

4. Table 4

GLM is used in this paper. What kind of GLM did the authors use; a multivariate linear regression model or a logistic regression model? If a multivariate linear regression model was used, the model is not appropriate because the BMD was not normally distributed.

Comment: It seems like the reviewer have slightly misunderstood the term "generalized linear model", and especially its abbreviation GLM, are sometimes confused with the term "general linear model" [19]. We used a multivariate linear regression model of GLM in this paper. In statistics, the generalized linear model (GLM) is a flexible generalization of ordinary linear regression that allows for response variables that have error distribution models other than a normal distribution[19].

5. Did the authors check the distributions of the variables?

Comment: Yes, we did check the distributions of the variables, and we used a GLM in this paper which is a flexible generalization of ordinary linear regression that allows for response variables that have error distribution models other than a normal distribution[19].

References


