Author's response to reviews

Title: Relationship between Sclerostin and Cardiovascular Calcification in Hemodialysis Patients: A cross-sectional study

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Author's response to reviews: see over
Dear Professor Covic,

on behalf of all co-authors I would like to thank the editorial team and the external reviewers for the thoughtful comments to our manuscript entitled: “Relationship between Sclerostin and Cardiovascular Calcification in Hemodialysis Patients: A cross-sectional study”

We also thank the editors to offer us the opportunity to revise our manuscript and to resubmit a revised version to your journal. The revised version is now entitled “—R1” as appendix to the original title.

In the following cover letter we included a detailed, point-by-point reply to the correspondence with the three reviewers. Changes in the revised manuscript called “R1” are highlighted in RED within the text.

Incorporating the reviewers’ comments to our manuscript has indeed substantially improved the clarity and increased the scientific quality of the manuscript.

We feel that we could fulfil appropriately the requests for revision. The reviewers’ comments point towards some limitations of study. We suggest addressing these limitations directly at the end of the discussion section.

We have also included an abbreviations section according to the editorial request which now facilitates reading of the manuscript (page 16).
We are looking forward to receiving the editorial comments to the revised version of our manuscript.

Sincerely yours

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A) **Response to comments by referee #1**

   a. The reviewer suggests seeking independent statistical corroboration of the statistical handling of the data. We agree that such corroboration strengthens the message of the manuscript and therefore we presented the statistical procedures to Professor Friedo Dekker, Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, who was not previously involved in the data acquisition nor in data analysis. Professor Friedo Dekker suggests in general with data like the present study a cautious usage of terms pointing towards etiology and prediction. We therefore slightly modified the wording and used “association” instead of “risk factor” or terms pointing towards etiology, since we want to avoid over-interpretation of the data. Accordingly we modified some sections within the text and we added a section in the “discussion” dealing particularly with the limitations of data interpretation. We now use the more neutral term “association” regarding sclerostin and uremic CVC. Our data may well serve as background for future studies addressing the question if sclerostin on causally related to CVC development and/or if high sclerostin is a risk factor for CVC.

B) **Response to comments by referee #2**

   a. The two comments of reviewer #2 point both into the same direction, i.e. comparability of biomarker results within studies and study groups. We agree that this is a crucial issue and therefore changed the discussion section accordingly in order to clarify this point. In terms of fetuin-A and sclerostin we on purpose used commercially available assays for the present study which will allow comparability between studies in future. We added a section regarding the limitations of the present study at the end of the discussion section.

C) **Response to comments by referee #3**

   a. The reviewer asks for clarification in terms of recruitment of the control cohort as well as the patient with aortic valve replacement. We added additional data within the Methods section accordingly. With these complementary data we also answered to comment 2. Unfortunately, a detailed description of the patients who underwent valvular surgery regarding nephrological history is unavailable, since the majority of these patients are external patients. Moreover, we clearly stated now that the control patients might also include patients with CVC. However, the present data was not aiming at establishing a true reference value for circulating sclerostin. Our aim was to underline the obviously disturbed sclerostin metabolism in hemodialysis patients.

   b. Regarding the distribution of serum sclerostin levels, we added corresponding data within the results section. Due to the small sample size we prefer not to comment upon the issue of normal distribution of sclerostin in any of the cohorts.