Reviewer’s report

Title: The Association Between Soluble Klotho and Cardiovascular Parameters in Chronic Kidney Disease: Results from the KNOW-CKD Study

Version: 0 Date: 26 Oct 2017

Reviewer: Annet Bouma - de Krijger

Reviewer’s report:

The submitted study examines a relevant association in a substantial cohort of CKD patients. Yet major revisions are needed before the study is eligible for publication.

First of all, the study was performed in the KNOW-CKD cohort and examines the association between sKlotho and LVMi and baPWV. However as described in BMC Nephrol. 2014 by Oh, et al, the study measured also vascular calcification in this cohort of CKD patients (with the Aorta Calcification Index). Can the authors comment why they did not analyse this cardiovascular parameter?

Further comments are described below;

Materials and Methods:

statistical analysis, p 8:

I want to comment on the log transformation used to normalize klotho variability and other variables. It is not necessary to have a normal distribution for the exposure. It makes it impossible to interpret the statistical outcome.

Authors write 'We employed(...) adjustment , including variables that were significant in a univariate analysis'. However, this is not correct; Confounders of the model should not be based on the data.

I therefore recommend to revise the statistical analysis without log transformation of Klotho and the other variables and add only variables in the model that are known from the literature or are relevant to add for a physiological reason.

Furthermore authors did not explain the rationale of their statistical models in this section. This should be added.

Results:

Table 1: Baseline characteristics are depicted in quartiles. Yet in the analysis this was not used.
Fig 2 and 3: The scatterplots are not convincing. Although a significant association is found, the R is very low. It would be of much more interest to use the quartiles of Klotho which are used in the baseline table.

Table 2:

Main-results table, however only the association of log Klotho with LWMi is shown. The other cardiovascular parameter tested (baPWV) is not depicted. It emphases the article on an association found, but it is also off importance to show negative results of the other parameters tested.

Discussion, p10

The authors placed their findings in relation to finding of other studies. They compared their findings with a study performed in hemodialysis patients. Yet there is also a study done in CKD patients stage 2-4 (Seiler et al, CJASN 2014) which examined the association between sKlotho and cardiovascular parameters. Maybe they can comment on the different findings in that study.

Although the authors do mention the study done by Kitagawa et al (Plos One 2013), they did not try to give an explanation on the different finding of this study in comparison to their analysis.

Therefore, I do recommend a more extensive elucidation on their findings in relation to the literature.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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