Author’s response to reviews

Title: Progression of arterial stiffness is associated with changes in bone mineral markers in advanced CKD

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Version: 1 Date: 13 Jun 2017

Author’s response to reviews:

Dear Editor and reviewers,

We thank you for your helpful comments on this manuscript and value the opportunity to improve the clarity of the manuscript. We have detailed our responses to these comments below and revised the manuscript taking the reviewers’ useful comments into account.

Reviewer reports:
F. Fevzi Ersoy (Reviewer 1):
Despite its relatively small sample size, this is a carefully written positive study with a sound study design. My suggestions would be:
1-Authors may try to discuss the mechanism of FGF23 without any significant changes in calcium, phosphate and vitamin D levels.
Response: The following has been added to discussion (Discussion section: page 14 line 323-326)
It is also possible that high levels of FGF23 may have actions independent to other bone mineral markers including regulation of renin angiotensin system and chronic inflammation.[38] In CKD mouse models, FGF23 was found to suppress angiotensin-converting enzyme 2 and activates lipocalin2, transforming growth factor-beta and tumour necrosis factor-alpha.[39]

Response: The following has been included in the discussion (page 14, line 314-319)
The publication by Touchberry et al (reference 35, page 31, line 635) has been included.
FGF23 has been shown to not only directly induce endothelial injury by reducing nitric oxide (NO) metabolites and inhibiting endothelium-dependent aortic vasodilatation,[34] but also increased intracellular calcium and altered myocardial contractility.[35] Furthermore, intramyocardial administration of FGF23 resulted in left ventricular hypertrophy in the absence of klotho .[36]

3-I would be more satisfied if authors would give echocardiographic findings before and after observation period.
Response: We completely agree that echocardiographic data at baseline and 12 months would have provided valuable information to further evaluate the impact of FGF23 on cardiac structure and function. However, echocardiogram was not included in the design of the study and is clearly a limitation of this study. The following has been included in the limitation discussion of the manuscript (page 16, line 359-361).
7) evaluation of cardiac function and structure was also not collected in this study and may have provided valuable information on the link between FGF23 and cardiovascular disease.
I recommend its publication in BMC Nephrology

Cristina Capusa (Reviewer 2): The manuscript is well written and it addresses a subject of current interest. Despite the small sample size (which is openly recognized as a limitation in the Discussion section), I consider the follow-up duration, as well as the numerous clinical and laboratory variables assessed as strengths of the study.

The statistical methods are appropriately used and the conclusions are supported by the obtained results.

There are only some minor suggestions that I have for the revision of your manuscript.

Major compulsory revisions
none

Minor essential revisions
1. Please change "CKD 4/5" from Introduction (page 7, line 116) with "non-dialysis CKD stages 4 and 5".
Response: This has been changed (Abstract page 3 line 55 and Introduction page 6, line 116).

2. Since the differences between the levels of sKlotho and PTH at 12 months as compared to baseline were not statistically different, it is better not to describe it separately before the phrase in which it is stated "No other significant changes were observed over ...." (page 12, lines 233-235). Please consider to change by clearly including the two parameters among those which did not showed significant variations.
Response: The following statement has been deleted (Results section, page11, line 234).

A non-significant reduction in sKl [577 (474-724) to 555 (440-724) pg/mL, p=0.2] and elevation of PTH levels [11 (7.2-22) to 15 (7.8-25) pmol/L, p=0.4] were noted in those with CKD.

In addition, the subsequent sentence was changed to the following (Results section, page 11, line 235-238):

No other significant changes were observed over the 12-month period for other BMM markers and biochemical parameters assessed including sKI and PTH, blood pressure measurements or medication use for both groups (Supplemental Table 1).
2. As mentioned in the Tables 2 and 3 legends, the non-parametric distributed variables were logarithmic-transformed before inclusion in the models of multiple regression. Therefore, I suggest writing in the Tables "Log FGF23" (etc), as you did in the Figures. It will allow a faster understanding of the methodology for the reader.

Response: The tables (Table 2, page 22 and Table 3 page 23) have been changed accordingly.

Discretionary revisions
none