Reviewer's report

Title: A Low Fractional Excretion of Phosphorus/Fgf23 Ratio is Associated with Severe Abdominal Aortic Calcification in Non Dialyzed Kidney Disease Patients

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Reviewer: Bjorn Meijers

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FGF23 has emerged as an independent predictor for worse clinical outcomes in CKD and non-CKD patients. Dominguez, in a publication recently published in JASN, demonstrated that the relationship between FGF23 and outcomes is modified by the tubular response to FGF23, measured as the fractional excretion of phosphorus (FeP).

In the current manuscript, the authors explore the relationship between FGF23, FeP and vascular calcifications, measured using the Kaupilla Index. In a cross-sectional in 186 CKD stage 3-5 patients they observe that, while vascular calcifications are directly related to FGF23, but inversely associated with FeP. These data extend our knowledge on the relation between FGF23 and vascular calcification and fuel the discussion whether FGF23 per se or tubular resistance to the actions of FGF23 are responsible for this increased risk.

Taken together, this is an original article extending the findings by Dominguez et al. certainly worthy of publication in BMC nephrology. Please find some comments below.

Minor essential revisions

It is somewhat surprising that diabetes was not identified as an independent determinant of aortic calcification, despite clear numerical differences. Was it also non-significant when aortic calcification score was used as a continuous variable? Diabetes has been consistently related to aortic calcification, both in the general population as well as in CKD patients. Constructing a multivariate model (table 2) without this important variable seems incorrect from a clinical view and is moreover statistical reasonable giving the reported univariate association with P<0.20.

It is unclear which variables were entered in the multivariate model. Where smoking and hypertension entered into the model? Diabetes? Please elaborate on selection of the variables to be entered into multivariate analyses?

The presence of carotid plaques significantly increased the risk of severe aortic calcification. Although we agree carotid IMT is a valuable reflection of the generalized atherosclerotic burden of an individual in the general population, it may also reflect hypertrophy of the carotid medial layer. Spence et al. indeed suggested that carotid plaque may be a preferable marker of atherosclerotic vascular risk. It would be of interest to see whether the same observations were
retained using IMT.

Please construct additional multivariate models excluding IMT or carotid plaques. Indeed, both IMT and carotid plaques are strongly influenced by age, diabetes and gender, potentially introducing significant collinearity in the model.

Giving the close relationship between aortic calcification, FGF23, fractional excretion of phosphate and renal function, a table showing the changes across CKD stages would be instructive.

The authors use a Log FeP/FGF23 ratio to identify patients with likely FGF23 resistance. To me it is not completely clear how this is calculated. Is this Ln(FeP/Ln(FGF23)), LnFeP/LnFGF23 or Ln (FeP/FGF23). Please state clearly which formula has been used and elaborate on the choice for using this particular relationship. Is there a relationship between this ratio and eGFR?

The finding that a low phosphaturic response to FGF23, FGF23 resistance, relates to aortic calcification is interesting. This raises the important question of the mechanisms responsible for this FGF23 resistance. Based on their data, deficiency of soluble Klotho seems rather unlikely. The authors should add a section to the discussion speculating on potential cause(s) of FGF23 resistance.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests