Reviewer's report

Title: Urinary Phosphorus Excretion per Creatinine Clearance as A Prognostic Marker for Progression of Chronic Kidney Disease: A Retrospective Cohort Study

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Reviewer: Ruben Poesen

Reviewer's report:

The manuscript entitled “Urinary phosphorus excretion per creatinine clearance as a prognostic marker for progression of chronic kidney disease: A retrospective cohort study” by Kawasaki et al. describes a study investigating the prognostic value of urinary phosphorus excretion per creatinine clearance to predict progression of CKD. In a cohort of 191 patients (single center, Japanese population), the authors observed a gradually increased risk of CKD progression with higher values of urinary phosphorus excretion per creatinine clearance. Therefore, it is suggested that urinary phosphorus load is a direct contributor to CKD progression, possibly due to tubular injury.

The rationale behind the study is interesting and the results of the study are fairly well presented. Of course, the study design precludes causal inferences. Although the findings seem quite robust, I still have some comments that the authors need to address before the manuscript can be considered for publication.

1. Major Compulsory Revisions

- The authors suggest that 24h urinary excretion of phosphorus is a surrogate for the tubular load. This would certainly be true if phosphorus excretion is mainly driven by tubular secretion. In contrast, 24h urinary excretion of phosphorus is the composite of glomerular filtration minus tubular absorption. As tubular absorption rate goes down when renal function declines, I'm not sure that 24h urinary excretion is a good estimate of the tubular load. I suggest that the authors also calculate the tubular absorption rate (= (GFR x serum phosphorus) – 24h urinary excretion), also corrected for GFR, and link this parameter to outcome. If there is no relationship between tubular load and outcome, this may suggest that is not the intracellular load of phosphorus, but the external phosphorus cell burden that possibly mediates renal injury.

- As serum phosphorus increase is prevented in earlier stages of CKD due to higher urinary phosphorus excretion, there is no good correlation between serum phosphorus and urinary phosphorus excretion/creatinine clearance in stage 3b, while there is a nice correlation in stage 5. I’m not sure whether the same is true if you correct serum phosphorus for creatinine clearance as well? If there is a good correlation, could the authors perform additional analyses with serum phosphorus/creatinine clearance as marker for outcome and demonstrate whether or not this is inferior to the urinary excretion/creatinine clearance? A possible way to investigate is to use logistic regression (outcome yes or no) and
compare AUCs.

- Discussion p14 line 14: I believe the authors suggest the possible superiority of U-P/eGFR to U-P/CCr and not U-P/CCr to U-P/eGFR? Nevertheless, although you may have the advantage that you are not obligated to measure urinary excretion of creatinine, you still have to measure excretion of phosphorus, thus needing urinary collections.

Furthermore, the authors also hope that phosphorus per creatinine excretion in spot urine could replace their proposed marker of 24 U-P/CCr (or U-P/eGFR), but that’s not correct. Even assuming negligible circadian change of phosphorus per creatinine excretion in spot urine, this would be a surrogate of 24h phosphorus excretion, thus you still need to adjust for eGFR (= spot U-P/U-Creat/eGFR).

- In this study the authors define CKD progression as evolution to ESRD, 50% reduction of eGFR and death. As the rationale behind the study is to link renal burden of phosphate to CKD progression, I would leave out evolution to death and just focus to ESRD or 50% reduction, also because there are only 5 deaths, making this endpoint less important.

- Limitation: single center study in Japanese population. Care must be taken to extrapolate these findings to other populations. This should be added in the limitation section.

2. Minor Essential Revisions

- As a marker of phosphorus excretion the authors use “urinary phosphorus excretion per 24h creatinine clearance”. As creatinine clearance is expressed as ml/min, I don’t think it’s necessary to add “24h”. In contrast, phosphorus excretion is referring to its 24h excretion, so the correct statement would be: “24h urinary phosphorus excretion per creatinine clearance (24h U-P/CCr)”. 

- MM study population p7 line 14-16: Please add units for biochemistry measurements.

- MM study population p8 line 2: Please give reference for this formula.

- MM study population p9 line 12: Please give formula to calculate TRP.

- Results p12 line 14: I suggest adding the result of analyses performed with eGFR to the manuscript.

- Results p12 line 5: I suggest adding the correlation coefficient and P-value for correlation between TRP and eGFR.

- Grammar and spelling:
  * Abstract line 11: I suggest “only patients” instead of “inpatients”.
  * Introduction line 7: I suggest “causes tubular damage” instead of “cause”.
  * Introduction line 11: I suggest “24h urinary excretion” instead of “urinary phosphorus”.


* Introduction line 13 to 15: This sentence needs rephrasing.
* MM study population p7 line 5: Please add “who WERE admitted”.
* MM study population p7 line 10: Please add “who WERE lost to FU”.
* MM study population p7 line 13: Please add “by REVIEW of medical records”.
* MM study population p9 line 16: Please change into “primary” instead of “parimary”.
* MM study population p10 line 1: Please change into “,” instead of “and (eight)”.
* MM study population p10 line 1: I suggest “evidence of” instead of “evidence with”.
* MM study population p10 line 2: I suggest “, excluding them” instead of “, they were excluded”.
* MM study population p10 line 4: I suggest “analysis” instead of “analyze”.
* Discussion p14 line 10: I suggest “minimally” instead of “minimamlly”.
* Discussion p15 line 4: This sentence needs rephrasing.

**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