Reviewer’s report

Title: Effect of paricalcitol on renin and albuminuria in non-diabetic stage III-IV chronic kidney disease: a randomized placebo-controlled trial

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Reviewer: Anna Jovanovich

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This is a randomized, placebo-controlled, crossover trial of 26 participants with CKD stages III-IV treated with paricalcitol (and placebo) for 6 weeks each. There was no difference between paricalcitol and placebo in primary outcome: plasma renin concentration. While the study wasn’t powered to assess renal excretory function, there was a significant decrease in CrCl and eGFR during treatment with paricalcitol. There was a non-significant trend toward decreased 24-hour protein excretion during treatment with paricalcitol. There was no difference in BP or APW. At the baseline of the clearance study, eGFR, albumin excretion, urine output, and free water excretion were all significantly lower during treatment with paricalcitol. There was no increase in albumin excretion during L-NMMA infusion during paricalcitol treatment. Conversely, there was 20% increase in albumin excretion during L-NMMA infusion during treatment with placebo. These findings suggest that paricalcitol may decrease albumin excretion through decreased GFR and through modulation of NO.

Major Compulsory Revisions

1. It would be helpful to organize the information in the first paragraph of the Results section into a Table 1 that describes the baseline demographic characteristics of the participants.

2. There were significantly fewer women than men included in the study. Estrogen can affect plasma renin concentrations. This likely didn’t affect the results given that the mean age was 61 ± 9 years and, therefore, it can be assumed that the women in the study were post-menopausal. The cross-over design also likely controlled for this as well, however, this should be acknowledged in the limitations.

3. The authors state that routine blood and urine samples were immediately assayed at the Department of Clinical Biochemistry. Do they mean all assays. Were any of the assays batched and measured all at once, for example, the plasma renin concentrations, in an effort to decrease inter-assay variation? This should be clarified.

4. While the cross-over study design controls for the effect of antihypertensives, such as diuretics (including spironolactone) increasing plasma renin concentrations and beta-blockers decreasing plasma renin concentrations, there may still be some residual confounding. This should be addressed in more detail.
in the limitations section.

5. Was data on the use of other medications that also affect renal sodium handling and the RAS, such as non-steroidal anti-inflammatory drugs, collected?

6. In the discussion, the authors thoroughly review the data and proposed mechanisms by which paricalcitol may decrease albuminuria. They also discuss how paricalcitol may decrease measures of eGFR and creatinine clearance through increased tubular excretion of creatinine and musculoskeletal effects. However, the fact remains that in the paricalcitol group, urine output and free water clearance are decreased without accompanying changes in FENa, FENK, AVP, BNP, ENaC or AQP2 suggesting that the observed decrease in albuminuria may be mediated by the decrease in GFR especially since paricalcitol did not change BP, PWV, and AIx after L-NMMA infusion. The conclusion should be expanded to acknowledge that the results suggest that paricalcitol may decrease albuminuria through decreased GFR GFR as well as through NO modulation.

Discretionary Revisions

1. The final sentence in the abstract is somewhat confusing. It could be changed to: “The abrogation of the rise in albumin excretion by paricalcitol during NOS blockade may indicate that favourable modulation of renal NO dependency may be involved in mediating reno-protection and survival benefits in CKD.”

2. There are various spelling and grammar mistakes that need to be corrected.

3. There are numerous tables. Some could be combined, for example, Tables 2-4.

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

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

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.