Author's response to reviews

Title: Vitamin D and Kidney Transplant Outcomes: A Protocol for a Systematic Review and Meta-Analysis

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Author's response to reviews: see over
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Dear Editor,

Thank you for your recommendations for our manuscript “Vitamin D and Renal Transplant Outcomes: A Systematic Review and Meta-analysis”. We have carefully noted each of your suggestions. Responses are outlined below.

Regarding the Handling Editor’s comments:

1) It was suggested to search AMED and CINAHL for additional abstracts. We have now completed these searches. The databases have been added to the protocol and the results will be included in the final manuscript.

2) The term “hand searched” has been replaced with “scanned the references of included articles and existing reviews”.

3) I have added a data extraction section that outlines which variables will be extracted.

4) More detail has been added to the data analysis section to help the reader better understand which variables will be compared.

5) The steps to reduce reviewer bias are outlined in the fourth paragraph of the methods section. To reduce reviewer bias, the abstract and full-text screens will be performed in duplicate. Data extraction will be verified by a second reviewer. Disagreements will be resolved by a third party.

6) I have modified the data analysis section to describe how the strength of evidence across studies will be summarized.

Regarding Referee #1’s comments:

1) We expect the results may guide recommendations for vitamin D supplements in renal transplant patients. Currently there are no guidelines on this topic. If vitamin D is found to improve transplant function, a strategy for supplementation may improve patient health and quality of life. Please refer to the final paragraphs of the discussion.

2) No comment on search strategy.

3) Regarding inclusion and exclusion criteria:
   a. **Vitamin D analogs**: The usage of vitamin D analogs (e.g. paricalcitol) has become increasingly common in chronic kidney disease. Excluding studies that use vitamin D analogs will limit the yield of our
search and exclude potentially informative results. We acknowledge that vitamin D analogs may have different effects and analyzing them together with calcitriol may affect results. We will perform subgroup analyses if possible. See Discussion paragraph 3.

b. **Baseline vitamin D measurements**: The comment about excluding trials without baseline vitamin D concentrations is well received. At this point in the study we would like to gather as much information as possible and therefore will include trials without baseline vitamin D measurements. If we obtain enough manuscripts, we may choose to analyze studies with baseline vitamin D measurements separately. See Discussion paragraph 5.

c. **Dietary intake/fortified foods**: We agree that dietary vitamin D is important to consider; however, dietary intake is very difficult to measure accurately. Food diaries are limited by patient recall. We acknowledge this is a limitation of the review. See Discussion paragraph 5.

4) Activation of vitamin D receptors has been shown to shift immune responses from proinflammatory to tolerogenic, as well as inhibit dendritic cell maturation. These immunomodulatory effects may reduce rates of acute rejection and this has been demonstrated in animal models. Please see paragraph 5 of the Background section for details.

5) We agree that using vitamin D concentration as a continuous variable or quartiles is preferable to using definitions of vitamin D insufficiency. Ultimately we will be limited to whatever information is provided in manuscripts. We will use vitamin D concentration as a continuous variable when possible, but may be forced to accept definitions of insufficiency if that is all that is available. Refer to Methods – Analysis Plan.

6) See above (3c).

7) We will consider timing of serum vitamin D concentrations when attempting to pool studies. We plan to group all studies together initially then do a sensitivity analysis to assess relationships before and after 12 months. This is now stated in Methods – Analysis Plan paragraph 3.

8) Ideally, studies would control for the cause of ESRD; however, we anticipate that all studies will include multiple ESRD etiologies. Furthermore, the cause of ESRD is not always known and some patients may have more than one etiology (e.g. diabetic and ischemic nephropathy). Therefore, it is not feasible to exclude studies with more than one cause of ESRD.

**Regarding the editorial requests:**

1) I have removed the conclusion from my abstract.
2) I have included in the acknowledgments section that I have no sources of funding for my review.

3) I have attempted to minimize the number of abbreviations that appear in the manuscript.

4) I have modified the Author’s Contributions section to mention each author individually, in keeping with your suggested format.

Please see the amended protocol manuscript for full details. Once again, thank you for your suggestions and we look forward to hearing from you.

Caitlin Hesketh, M.D.