Author's response to reviews

Title: Phosphate decreases urine calcium and increases calcium balance: A meta-analysis of the osteoporosis acid-ash diet hypothesis

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Author's response to reviews: see over
We appreciate the opportunity to respond to the reviewers comments and have addressed their comments and concerns below.

A. Response to Reviewer: Dr. Marian Hannon

Thank-you for your review of our manuscript and insightful comments. Please see our responses below:

**Major Compulsory Revisions**

1. Good points, we have clarified our terms.

2. Omission is corrected. We have decreased our emphasis on the superior methodology study.

3. We have added detail about the study subjects including ages, % female, control phosphate intakes, and whether the study noted ethical approval for the study into Table 1 and that there was no upper age limit in the text.

4. Figures – We realize that individual reviewers and readers may have different preferences for either graphic or tabular presentation of data. To balance the request for no figures by this reviewer and no concern about figures by the other two reviewers, we deleted the figure of the superior methodology. We have retained other figures since we feel that this graphic presentation of the study improves the clarity of the conclusions.

**Minor Essential Revisions**

1. Good points, we have clarified the abstract.
2. We have clarified the Selection Criteria section. As noted in the text under the Description of studies, we included the definition of the studies’ diagnoses of osteoporosis among their subjects, i.e. “roentgenographic and clinical” diagnoses of osteoporosis.

3. Typo is corrected

4. Good suggestion; we have replaced the word “trials” with the word “arms”.

5. We have clarified in the text and in the footnote to Table 3 that the p-values presented are the uncorrected versions

6. We have included all the p-values in the results section.

7. We have reorganized the results section.

8. Revised as suggested.

9. Edited as suggested

10. Edited as suggested.

11. Done

12. Included more discussion of the cohort studies of the acid-ash hypothesis, pro and con.


14. Reference numbers fixed. A copy of this paper is available through JBMR.

15. All abbreviations defined.

16. Reorganized Table 3 as suggested.

17. We think the figures are of interest since they demonstrate the relationships between the amount of phosphate supplement with the outcomes of the change of urinary calcium and calcium balance, and make these results visually apparent to the readers. As well, the figures reveal the effect of calcium intakes and the degree of protonation of the phosphate on the relationships. We have reduced the figures to six from ten, to limit those we felt were most important.

B. Response to Reviewer: Dr. Connie Weaver

Thank-you for your review of our manuscript and insightful comments. Please see our responses below:

Minor Essential Revisions

1. We have included the point well made that prolonged negative calcium balance will lead to bone loss.

Discretionary revisions

1. Edited as suggested.
C. Response to Reviewer: Dr. Michael Huncharek

We thank you for your review of our manuscript and your helpful comments. Please see our responses below:

**Minor Essential Revisions**

1. Good point. This section has been moved into the results section.

2. We have clarified that we only included studies with an interventional design.

**Major Compulsory Revisions**

This study uses simple multiple linear regression to assess the relationship between the phosphate supplement doses with the outcomes of the change of urinary calcium and calcium balance, using study results, weighted for the number of subjects in each study.

The usual meta-analysis approach is to estimate an average effect, with no accounting for variability among the doses. This is usually followed by a test for heterogeneity among the studies to examine whether the studies should be combined, i.e. whether they are likely to be studying the same effect, given the variability of the included studies.

In contrast, we used the available data to examine the relationships between the phosphate supplement doses and the outcomes since we recognized in this case that the effect size (among both the outcomes of the change of urinary calcium and calcium balance) varied in response to the phosphate supplement doses. We felt that the effect of the phosphate supplement dosages was of interest. Therefore, we didn’t average or pool the results. In other words, we used the heterogeneity among the studies to examine the effect of the phosphate supplement dose on our outcomes of interest. Analogous to the test of heterogeneity in this case is the test of whether the slope of the lines that describe the regression between x and y is not equal to zero, which we have done.

We then took the analysis a few steps further, to assess for potential effect modification by calcium intakes and the degree of protonation of the phosphate supplements, and included an assessment for potential confounding by study variables. We think the graphs of these relationships are of interest since they demonstrate the relationships between the phosphate supplement doses with the outcomes of the change of urinary calcium and calcium balance, and make them visually apparent to the readers.

Thank you for your comments. We have tried to make our methods clearer in the text of the paper.

Again, we sincerely appreciate the opportunity to respond to the reviewers’ comments and to make the subsequent improvements in this manuscript. We look forward to your response regarding this manuscript.

Sincerely,

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