Reviewer's report

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

Version: 1 Date: 7 May 2009

Reviewer: Marian Hannan

Reviewer's report:

The first four comments below are considered “Major Compulsory Revisions” by the reviewer, and the remaining comments are suggested revisions to improve the manuscript.

This manuscript is focused upon the dietary acid-ash theory and its relevance to bone health. The authors address the topic via a 5-part meta-analysis based on clinical trials, most with a cross-over design. This is a topic of great interest in the nutrition field and the authors have put forth a good effort in addressing the ‘acid-ash hypothesis’. The manuscript is generally well-written and intriguing. There are four major issues that, when resolved, will improve the impact of this manuscript and heighten the interest in the study.

Major Compulsory Revisions

1. First, the term ‘osteoporosis’ is used throughout the manuscript incorrectly. This is a diagnosis or clinical term that is derived from a DXA-based T-score or occurrence of an osteoporotic fracture. I believe the authors mean to use a term such as ‘bone health’ or ‘bone turnover’ or ‘bone markers’. At many places in the manuscript there are incorrect terms: in abstract “to quantify the contribution…to bone loss”; on page 4, “...contribution of dietary phosphate toward the progression of osteoporosis”; on page 14, “…whether or not there is an association between phosphate intake and osteoporosis”.

The meta-analysis does not address bone loss or osteoporosis or progression of osteoporosis. Clearer terms will help clarify the paper for readers and make it more useful.

2. The classification and definition of ‘superior methodology’ is missing from the abstract, the methods section, the selection criteria and is apparently defined on page 11 in the Discussion section (a study that has randomization and recommended calcium balance studies). Further, there is only one study that apparently met this definition. Frankly, I would recommend dropping this from a prominent position in the manuscript and take it out of the abstract. The authors cannot really say much about this aspect, other than one study met this criterion. In my opinion, it should come completely out of the paper, but if the authors decide to leave in this aspect of ‘superior methods’, then they must define it in the methods section, operationalize the term as part of selection criteria and minimize its place (but mention it) in the Results section before discussing it.
3. The manuscript really suffers from a lack of detail regarding the study subject characteristics…making it unclear what sample they may represent. Some information needs to be presented on age (range at the very least), %female, and any other characteristics available (weight, height, physical activity, total intake?) While Table 1 lets the reader know that men and women are included and ‘young’ (however that was defined) and postmenopausal women with osteoporosis (defined?), one truly wants to know more about the characteristics. While many data may not be available to the authors, they need to provide some indication of these characteristics, even if it is only adding columns to Table 1 with numbers of subjects, male:female ratio, age ranges and any other pertinent descriptions of the study participants. It makes a difference if the data are based on young adults 19-22 with one postmenopausal study (ages?) and based on the included studies, ignores the important bone health aspects of adults over 65 or geriatric study subjects. One needs to know these data to see if the meta-analysis is pertinent to our clinical and research interests!

4. The figures add nothing to the data understanding and this reviewer believes that the tables inform the Results and Discussion in a better fashion. I believe that all of the figures should be deleted.

Minor Essential Revisions

Clarification issues:

The Abstract needs to be clarified. One wants to know the total number of patients included in the meta-analysis. The number or type of meta-analyses done seems to read as 4 or 5 and needs to be stated clearly (and abstract appears to differ from purposes put forth on page 4). I believe the ‘superior methodology’ sections should be removed from abstract.

Page 5: the section on ‘Selection criteria for the literature’ is somewhat confusing and would benefit from reorganization. For example, the first sentence has 4-8 different criteria imbedded in one sentence. Could the authors simply list the criteria without stringing them together? Again, this term ‘development of osteoporosis’ is bothersome and the authors may want to consider a clarification: indicators of osteoporosis? T-scores? Or simply use the terms that they’ve listed. What makes the study subjects ‘apparently healthy’? Was it just that those participants from studies with renal disease, cancer or inflammatory bowel disease patients were excluded? Was there any upper age limit? Where all studies IRB approved?

Page 6: line 4 “…each of two includes studies” should have includes replaced with included.

2nd paragraph: to clarify the meaning and the numbers, replace the word ‘trials’ with the word ‘arm’, as in “within the included 12 studies were 30 intervention arms”. This sentence and others using the term trial made me scratch my head until I figured out that the authors were examining the trial arms.

Page 7, end of methods: it is unclear if the Bonferroni corrections were used in
the presented data (ie, are p-values in tables and text corrected or not?) or if the correction was only used once for the instance where it changed the results from statistically significant to not.

Page 7, Results: please list the p-values in the text of the Results (done for some findings but not all). The p-values are in the tables, but it would be preferable to this reader to see them both places.

Page 8: Please organize the results from the regression analysis to a paragraph for each of the 5 meta-analyses...it was difficult to sort them out and this will help the reader. Again, the figures were not helpful and I recommend removing them from the manuscript.

Page 11, end: There actually are other currently and clinically valid bone outcomes that address bone strength (eg. Finite element modeling), so this sentence should be ‘toned-down’.

Page 12, first sentence: it is not true that “bone density...not considered an adequate outcome measure in the assessment of osteoporosis treatments”. This is exactly how we assess treatment effects with individual patients. A minor edit will clarify what I believe the authors want to state?

Page 12; mid-point: I would remove the phrase “inadequate allocation concealment is associated with a 41% overestimation of effect” as the 41% is imprecisely precise. It’s fair simply to state that there may be an overestimate (and give reference).

Page 13, 1st sentence: remove phrase ‘with better outcomes for the assessment of osteoporosis’ and replace with ‘on change in BMD or fractures’.

Also reference 78 doesn’t belong here. Finally, the authors should mention the observational studies that DO support the acid-ash hypothesis (just to be fair and present all sides for the reader to decide for him/herself).

Page 14, conclusion: Please remove phrase “that an ‘alkaline diet’ is health promoting” as the meta-analysis that was presented did not address this topic or present data allowing this conclusion.

REFERENCES: ref #20 and #78 appear to be the same; also it refers to an in-press article and the journal may not allow this reference as it is not available to the reader to examine and assess (unless it will be published before the current MS under consideration).

Table 1 needs footnotes that define the abbreviations. If possible, please add patient characteristics (or add another table with this information).

Table 3 needs reorganization, perhaps making specific columns for B, CI, p-value, R2 to clarify the reading of the table. Unclear if p-values are corrected or not (bonferroni)

Figures: remove all figures.
Overall,
- The research question posed by the authors is new, compelling and well defined.
- The methods are appropriate and described with sufficient details that one could replicate the work.
- The data appear sound and well controlled.
- The manuscript mostly adheres to relevant standards for reporting and data deposition (minor points noted above).
- The discussion and conclusions are mostly balanced and adequately supported by the data (minor points noted above).
- The title accurately conveys the study findings, however the abstract needs some work by the authors in my opinion.
- This is a well-written paper

Overall, this manuscript adds to our understanding of the acid-ash hypothesis and its relation to bone markers. The information is timely and detailed, and the evidence is convincing to this reviewer. The manuscript could be improved by taking the points made above into consideration for a revision. Thank you for the opportunity to review this manuscript.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests