Author's response to reviews

Title: Bone Mineral Density (BMD) Changes in a Bone Health Plan Using Two Versions of a Bone Health Supplement: A Comparative Effectiveness Research (CER) Study

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Version: 3 Date: 12 August 2010

Author's response to reviews: see over
August 12, 2010

To: Nutrition Journal

http://www.nutritionj.com/manuscript/login/man.asp?txt_nav=man &txt_man_id=1468025783802349

Reference: Response to reviewers’ comments and suggested changes to:

Bone Mineral Density (BMD) Changes in a Bone Health Plan Using Two Versions of a Bone Health Supplement: A Comparative Effectiveness Research (CER) Study

I have attached a copy of our responses (in blue type) to all comments made by each of the three reviewers (black type) along with a proposed revised manuscript with point-by-point descriptions of the changes made using MS Word’s “tracked changes.”

I realize that these proposed changes are extensive but I would greatly appreciate it if there is anything we can do to expedite the editor’s decision regarding its acceptance for publication.

Gilbert R. Kaats, PhD
Corresponding Author

Reviewer Jeannette Beasley

Major Compulsory Revisions:

Reviewer: Jeannette M Beasley
Summary:

This report evaluates two approaches for improving bone health, differing only by the formulation of a dietary supplement named AlgaeCal. Identifying effective interventions that reduce the risk of osteoporosis and can be easily incorporated into the health care system is an issue of great public health importance. It is also critically important to rigorously dietary supplements, which are taken by the majority of the population yet have not been systematically tested for safety and effectiveness. Unfortunately, the description of the components of the interventions, the study design, and the statistical methods do not allow for scientific inference regarding the value of the supplements.

Major Compulsory Revisions:

1. Though this is described as a comparative effectiveness study, the primary comparison is to “expectation” derived based on assumptions about how BMD would change over a 6-month period rather than actual observations. It is not possible to reproduce the expected values from the authors’ description, and it is unclear whether it is appropriate to derive expected values for a particular individual from population-based estimates that might be very different than the study population.

While we agree that comparisons with expected age-related changes in BMD are useful, we think the primary value of CER studies is defined in reference [6] cited in the manuscript:

“CER is typically defined as the generation and synthesis of evidence comparing the benefits and risks of different interventions for preventing, diagnosing, treating, and monitoring health conditions under real-world patient conditions that typically confront physicians [1-2]….CER shares some of the same characteristics of practical clinical trials where real world conditions are used to compare treatment choices that practitioners face in patients drawn from their practice, which allows the practitioner to decide between treatment options [5].”

Therefore, we think the comparisons between AlgaeCal 1 and AlgaeCal 2 are the primary comparisons in the manuscript followed by comparisons of the compliant-partially compliant sub-groups that provide evidence of a dose-related relationship.

While it is true that expected changes are based on assumptions, the calculations used to predict these changes were derived from a substantial body of information as to expected changes as a function of age and gender - information that has now been included in the revised manuscript as stated in our next response. These values were obtained from using the age-related changes in Z-scores supplied by GE Lunar and Hologic, previous research including the NOF citation, and Z-scores from our database of over 26,000 BMD measurements derived from a population similar to the study groups. These norms all provide rather consistent age-related changes in BMD that rise until the mid-thirties, level off, and progressively decline from there. Thus, age-related changes in BMD can be calculated for any age or time period.

However, while there is some minor disagreement over the actual % decline in BMD with age, there is no disagreement over the fact that BMD is never expected to increase with age. Therefore, the most conservative expected change would be to use “0” expected change irrespective of the subject’s age. This comparison is provided in the “within-groups MAPC in BMD” in which the observed changes were “significantly greater than zero in both groups: AlgaeCal 1 [1]: p<0.001; AlgaeCal 2 [6]: (p<0.001).”

We have added information on how the expected values were calculated that will allow the reader to reproduce these values [Pg 8]
2. Another comparison made by the authors is between the two AlgaeCal supplement formulations. However, the two interventions were conducted sequentially rather than simultaneously, so differences between these two groups could be due to many factors other than the differences in supplement formulations (i.e. differences in DXA measurements, study populations). A table describing participant characteristics would have been useful both to characterize the study populations and to draw inferences regarding how comparable the study population was to the target population.

Table 4 has been added and shows no statistically significant difference between baseline DXA measurements of BMDs in the two groups or in any of the variables associated with BMD (e.g. weight, fat mass, lean mass, etc.) [Pg 10 & 25]. Additionally, comparisons were made between each of the 43 blood chemistries completed at baseline by subjects in both study groups. Of the 43 chemistries listed in Table x, no significant differences were found in 37 of the chemistries including the lipid panel, C-reactive protein, serum calcium and thyroid levels. Of the six chemistries that were significant, only two (platelets and alkaline phosphatase) were <0.01.

3. The only valid statistical comparisons are the changes from baseline, and other comparisons should be removed. There are many other reasons to conduct a controlled study other than the placebo effect that the investigators have not accounted for in the design of their study.

We agree that a controlled study would have been preferable and the reasons for not using a RCT design are stated in the Method section. We disagree with the reviewer’s suggestion that all other comparisons should be removed, since the purpose of the study was a CER to compare two versions of a bone-health plan. It is our view that comparisons between: (1) the two plans, (2) compliant and partially compliant sub-groups in both plans, (3) observed vs. expected changes, (4) volunteers and non volunteers (often overlooked in many studies) and (5) between drop outs and those who completed per protocol, provide supporting evidence of the efficacy of the plans—particularly in view of the consistent findings in both groups of these comparisons. The appropriateness of these comparisons is also supported by the independent and highly qualified statistician we used as now stated in the Statistical Methods section [pg 9].

4. The intervention period was only 6 months, which is a short window in which to identify change in BMD. Yet in presenting their results, the authors present and describe “annualized changes”. It seems inappropriate to extrapolate beyond the study period to estimate changes in the AlgaeCal.

The purpose of using annualized changes is to allow for comparisons with other studies and norms that can be annualized for studies of different study periods. Of course, this annualization has no effect on statistical significance levels.

Minor Essential Revisions:
1. Please provide complete descriptions of the DXA equipment, labs where the supplements were tested for validity.

We agree and we have added this information [pg 7].

Discretionary Revisions: (which are recommendations for improvement but which the author can choose to ignore)

1. Other components of the health care plan (i.e. health literacy, physical activity) are described but no details are provided regarding the effectiveness of these components. Without this information, it is difficult for readers to assess whether any observed differences were due to these factors.

As stated in the manuscript, the “product” studied was a plan which is what the grantor was planning to market (see background information added to the Methods section). We agree that there are multiple interactions that could be made between the components as well as between the ingredients in the supplements. The goal of the studies was to select the safest and most efficacious of the two products irrespective of which of the components accounted for most of the variance. The grantor simply followed the SGs recommendation for a three-component plan, which was the goal of the study.

Level of interest: An article of limited interest
Since ~50% of women will experience a bone fracture from low BMD during their lifetime and all medical treatment plans recommend patients take Vitamin D and calcium, we think interest in this article is widespread. Furthermore, some recently reported concern about cardiovascular risks from taking excess calcium carbonate and recommendations to obtain calcium from food or plant sources could add to the potential value of the plant-sourced calcium used in this study.

Quality of written English: Needs some language corrections before being Published.

Notwithstanding providing suggestions for language corrections, as you will notice in the revised manuscript we have made some editing and wording changes that we hope will resolve this concern.

Statistical review: Yes, and I have assessed the statistics in my report.

Please note change made to the Statistical Methods section.

Reviewer: Meghan G Donaldson

Major Compulsory Revisions
1. The principal concern I have is the reporting of this open label non-randomized trial. I would strongly suggest that the authors review and adhere to the reporting guidelines as documented by the CONSORT statement (http://www.consort-statement.org/home/). I recognize that the investigators chose to conduct a non-randomized study but I believe the CONSORT statement still applies. This will help to better organize the manuscript and will also provide a framework to address the concerns I have with the study. Please see J.P.Mohrn et al “A comparison of Warfarin and Aspirin for the prevention of Recurrent Ischemic Stroke” NEJM vol 345:14444-1451 Nov 15 2001 as an example of reporting a CER study.

Actually, as has now been explained in the Methods section, the investigators did not “...choose to conduct a non-randomized study”. This was a decision of the grantor who had to weigh hand balance budget and scientific considerations. Furthermore, as stated in the first part of the Methods section, the initial choice was to conduct only a single open-labeled study of safety and efficacy and it was the results of this first study that gave birth to a second CER study.

“We agree with the reviewer that the CONSORT Statement can be useful, notwithstanding the fact that the CONSORT Statement was designed to “…improve the reporting of a randomized controlled trial RCT…[and] to help authors improve reporting of two-parallel design RCTs by using a checklist and flow diagram.”

After reviewing the CONSORT Statement, of the 37 items on the Checklist, 19 do not apply, 15 were included in the original manuscript, and 3 items have now been added to the manuscript:
3b of CONSORT Checklist: “Important changes to methods after trial commencement…with reasons” [Pg 6]
4a of CONSORT Checklist: “Eligibility criteria for participants” [Pg 6]
4b of CONSORT Checklist: “Settings and locations where the data were collected” [Pg 7]

a) Could the authors please justify the study design (a non randomized study)

This explanation has been added to the Methods section [Pgs 4 & 5]

b) The authors did not specify a primary outcome (or a combined primary outcome). The authors state: “The purpose of this study was to conduct a CER comparing the changes in BMD, blood chemistries and self-reported quality of life between and within two groups of subjects following the identical bone-health plan but with two versions of the AlgaeCal bone-health supplement.” This statement is not revisited in the Methods section of the manuscript. From this statement one is left to guess that there are 3 primary outcomes for this study. Clearly defining the primary outcome (or a combined primary endpoint) will then inform the type of analysis. It is also unclear which comparison is of primary interest (change between groups or change within groups).

A clarification of the primary outcome measures has been added [Pg 7] as well as changes between and within the groups. [Pg 8].
c) It is also unclear how these 3 endpoints are being measured. The authors’ state that “DXA” will be used but they do not specify what instrument they are using (Lunar, Hologic???) and what site they are measuring (femoral neck, proximal femur, lumbar spine?).

This information has been added. [7-8]

What instrument is used to measure quality of life? What is the 43 item blood panel measuring?

Figures have been added showing the Quality of Life inventory and the blood panel.

d) The authors do not provide a sample size calculation.

A power function was not conducted since we had no reliable data upon which to base the calculation.

e) The authors need to provide justification for a 6-month intervention. If changes in BMD are of interest this typically requires at least 2 bone remodeling cycles (roughly 8-10 months) (see Khan, McKay “Physical Activity and Bone Health” 2001).

An explanation of the 6-month intervention is provided [Pg 8]. Notwithstanding Khan and McKay’s comments, the reported changes did occur in 6 months. We could find no studies in Khan and McKay’s book that observed changes in BMD in a bone health plan that combined a plant-sourced form of calcium, a pedometer-monitored physical activity component, and a component to improve health literacy.

2. The authors need to report a baseline table describing the participants in this study (age, sex, physical activity, quality of life, BMD, height, weight etc etc).

This table is now added with comparisons of baseline values for the two groups [Pgs 6-7].

3. Please provide details regarding how participants were enrolled in this study. Were they recruited from campus, posters, TV advertisement, physician offices?

Recruitment and enrolling procedures have been added [Pg 7]

4. Materials and Methods (Bone Health Plan section). Please provide a reference for the study “a recent in vitro study demonstrated that AC…”

Reference added. [?] 

5. Materials and Methods (Health Literacy section). The authors need to provide additional details about the pamphlet that was provided to participants. For example, is it a government or?

Additional information has been added to clarify the Health Literacy citation. [Pg 5]

6. Materials and Methods (Physical Activity section). This section regarding the physical activity intervention requires more detail. Were the participants asked to target a certain number of steps each day or was some type of goal implemented. I believe this was one of the messages from the JAMA review article re: pedometer interventions.

Additional information about the pedometer program has been added. [Pgs 5-6]

7. Materials and Methods. How was safety evaluated?

The outcome measure for safety has been added along with two tables listing the blood chemistries and QOL items and the results of both of these measures.
8. **Results.** Please edit your Figure of ‘flow of participants’ to reflect the CONSORT guidelines.

We believe the Flow diagram is consistent with CONSORT guidelines.

9. **Results.** Please provide tables with baseline and 6-month data for all relevant outcomes (BMD, step-counts from the pedometer, quality of life, blood panels, etc)

Blood test and QOL results have been added as tables. Grantor has asked that we not attempt to partition out the three components of the Plan since the Plan was the product to be tested and marketed. Thus, steps are not considered a “relevant outcome”.

10. **Results.** Please provide safety results.

Blood test and QOL results have been added as tables

**Minor Revisions (typos etc)**

1. Please limit the use of abbreviation in the text. For example the use of SG for Surgeon General.

SG is defined in the abbreviation list and appears three times in the manuscript. We think it is appropriate to leave this as is.

**Reviewer: Bo Rud**

Major compulsory revisions

**Abstract**

In the abstract, the conclusion states that ‘Following the Plan for six months with either version of the bone health supplement was associated with significant increases in bone density’. This wording is inconsistent with the finding of a non-significant BMD increase in group 1 (AlgaeCal 1: 0.48%, p=0.14). The conclusion in the abstract should correspond with the conclusion in the discussion section, which states that ‘This study found that following either version of the bone-health Plan for six months was associated with improvements in bone mineral density’.

**The conclusion and abstract have been changed to correct this inconsistency.**

**Methods**

In the discussion section (page 10) it is stated that the study was ‘single blind’. Blinding is an important design feature and it should be described in the methods section who was blinded to what and how this was achieved. In particular, it is unclear how the research technician was blinded and what she/he was blinded for (p. 8).

“Blinding” referred to subjects and the investigators being blinded as to baseline measurements. However, “blinding” has been removed from the revised manuscript since it is likely to mislead readers.

There are no details reported about the BMD measurements (page 7). The authors should describe the DXA device that was used in the study, the region(s) where measurements were made and how longitudinal precision of the device was monitored. The issue of longitudinal precision of the DXA device is important because the main outcome measure is BMD change over 6 months.

**Additional details of the DXA device have been added to the revised manuscript along with a statement regarding the consistency of the measurements using GE Lunar calibration block.**

The authors stress the importance of the subgroup analyses of compliant vs. partially-compliant participants. The
authors use three measures of compliance (p. 8); daily tracking forms, anonymous post-study questionaires and subjective evaluations by the research technician. It is unclear if and how the former two measures are incorporated into the latter, which is the compliance measure used in the analyses.

An explanation of the compliance measurement has been added.

The authors use gender, age, weight, BMI, body fat, lean mass and BMD to compare participants in the two groups before the interventions are started. Four of these variables centers on body weight and important variables that affect BMD are missing such as the use of calcium and vitamin D, anti-osteoporosis medication and level of daily physical activity.

Although no assessment was made of the use of calcium and vitamin D or daily physical activity levels (notoriously unreliable). The use of anti-osteoporosis medication was an exclusion criterion. It was our view that any differences in self-reported physical activity and calcium/vitamin D usage between groups would have shown up in the more objective baseline measurements of BMD, lean and/or fat provided by the DPX total body measurement.

Results

There are no exclusion criteria in the study, and study participants are volunteers who are paid an incentive for providing daily reports of side effects and supplement usage. Did any of the participants have known osteoporosis at study entry? If, so were they taking anti-osteoporosis drugs? Were any of the participants diagnosed with osteoporosis at the initial BMD measurement, if so what counseling was the participant(s) offered? Were participants asked to discontinue other bone active supplements, such as calcium and vitamin D?

Exclusion criteria included the use of anti-osteoporosis medication and were asked to discontinue use of other bone active supplements during the study which is supported by non-significant differences in serum calcium levels in both study groups. All baseline measurements were blinded to investigators and subjects. In our view, providing this information to subjects would have biased the data. All subjects were advised, and they certified that they understood that baseline test information would be not be provided until completion of the study. Furthermore, since all subjects certified that they had reviewed the Informed Consent with their personal physicians or healthcare providers thus excluding those subjects for which this information was critical. In fact, although we had no reliable data as to why potential subjects declined to participate, we have some subjective evidence that part of the reason was the requirement to have the Informed Consent reviewed by the subjects’ physicians.

The listing of the results on page 9 with bullet typology is difficult to read without reference to Figure 2. The results section should focus on the main results and be readable on its own.

We agree that this would have been easier to read. We were, and are, concerned about the length of the manuscript and since Figure 2 will be inserted into the final manuscript, we think it would make these comparisons easier to read and understand.

In particular, the authors do not draw attention to the decline in BMD in the partially compliant participants in Group 1 in the results section. This is an unexpected result for 68 of 125 participants, because the BMD decline is almost twofold higher than the expected decline without supplementation.

This is an unfortunate effect of graphic displays of data since there were no statistically significant differences ($P=0.29$) between these two sub-groups. A statement to this effect has been added the Results section reporting this comparison.

However, it is still puzzling as to why partially compliant sub-groups had no better results than expected changes. A further analysis of the data revealed that 5 subjects in the partially compliant sub-group had BMD
losses that exceeded two standard deviations. Only one subject in the compliant sub-group had a BMD loss that exceeded two standard deviations. Thus, while dropping these scores as outliers led to a reduction of BMD losses in the partially compliant group, it had virtually no effect on the compliant sub-group. Furthermore, the differences between the partially compliant sub-group and expected changes still did not reach a statistically significant difference.

The meaning of the first bullet on page 9 ‘the two groups used to predict expected changes {1 vs. 6}’ is unclear. If the authors mean that there was no difference between the two groups in the expected BMD change, then this result is redundant, because it follows directly from the fact that there was no difference in gender frequencies in the two groups. According to page 7 (BMD subheading), only gender determines the expected annual BMD change. In addition to the absence of differences in gender frequencies, expected changes were also adjusted for age as now explained in the revised manuscript.

On page 9, it is stated that:
‘There were no significant differences within both groups with regard to subjects:
- who chose not to enroll and those who completed PP.
- who enrolled, but dropped as compared to those who completed PP.’
With respect to what variables were the differences referred to above insignificant?

A clarification of this is now provide in the manuscript [Pg 9]

On page 9, the bullet ‘The within-groups MAPC in BMD was significantly greater than zero in both groups: AlgaeCal 1 {1}: p<0.001; AlgaeCal 2 {6}: (p<0.001)’ is unclear. If the numbering refering to Figure 2 is correct then the bullet should state less than zero, not greater than zero.

The two groups in the Figure to which this refers are {2} and {7}. This reference has been corrected [Pg 11].

Discussion

The authors mention the sequential single blind design as a weakness of the study (p. 10). But, it remains unclear if there are good reasons why the study could not have been carried out as double blinded randomised controlled trial.

An explanation of this is provided [Pgs 4-5].

The authors discuss the issue of a placebo effect. This is speculative because there is neither a placebo group nor an untreated group. More important is the issue of confounding because the study is not a randomised controlled trial. The authors state on page 10 ‘..since the only difference between the two study groups was the composition of the AlgaeCal bone health supplement, the data suggest that AlgaeCal 2 provided increased bone health benefits compared to AlgaeCal 1’. It is questionable whether the non-randomised sequential study design justify the wording here. The authors could do more to underpin the premise of ‘the only difference’ by stating whether the two groups were comparable at baseline and during follow-up with respect to use of other bone active supplements such as calcium and vitamin D, anti-osteoporosis medication and level of daily physical activity. The pedometer measurements may be used to compare aspects of physical activity between the groups in this regard?

These issues have now been addressed in the proposed revised manuscript.

The authors do not elaborate on the BMD decline observed in the 68 partially compliant participants in group 1. This decline is unexpected and it should be discussed, because an important part of the observed absolute difference between partially compliant participants in Group 1 and 2 appears to be ascribable to the BMD decline observed in Group 1. Moreover, in the conclusion the authors stress the importance of assessing compliance. Nevertheless, the
non-significant difference in BMD increase among compliant participants is not discussed.

See response above starting “As stated above, this is an unfortunate effect of graphic displays…” partially compliant sub-group and expected changes still did not reach a statistically significant difference.

The study population consists of volunteers who are paid an incentive. It is unclear to what extent the results are transferable to the background population, presumably unselected women and men 18-85 years old – were the participants representative of the intended background population in relevant respects? A closer characterization of the study population as well as a description of the recruitment procedure is needed to support the discussion on transferability.

This information has now been included in the proposed revised manuscript. We found no statistically significant differences as a function of the subjects’ age or gender.

Conclusion

The conclusion appears optimistic, in the light of the non-significant difference in compliant participants and the significant difference in partially compliant participants that is to some extent ascribable to an unexpected BMD decline in group 1. Adding to this impression are the methodological limitations of the non-randomised sequential design, in particular the limited control over confounding variables.

We agree that sequential designs typically have limited control over confounding variables. Therefore, we made the following comparisons between baseline measures of the two groups:

BMD: There were no statistically significant differences between the groups in baseline BMDs;
Variables affecting BMD (age, gender, weight, BMI, DXA-measures of body composition): There were no statistically significant differences between the groups on any of these variables;
Quality of Life Inventory: There were no statistically significant differences between the groups on any of the 50 items on the QOL or in the total quality of life scores;

compliant versus partially compliant subjects, absence of volunteer and dropout biases negate some of the concern about the use of a sequential study design. of the his information has now been included in the proposed revised manuscript.

The conclusion should be rephrased to accommodate the observed BMD decline in partially compliant participants in Group1 as well as the non-significant difference in BMD increase between groups in compliant participants.

A statement of this caution has been added to the conclusion section.

Minor essential revisions

Methods

It should be stated explicitly that there were no exclusion criteria in the methods section.

Exclusion criteria are now included in the proposed revision.

The size of the paid incentive for providing daily reports of side effects and supplement usage should be reported.

The size of the incentive as been added to the proposed revision.

A few lines about the recruitment procedure should be added (advertising, roadshows etc.) and it should be stated explicitly if these procedures were similar for the two groups. In Figure 1 the top box states ‘..baseline BMD measurement’ for group 1 whereas it states ‘..baseline BMD screening’ for group 2. Does the difference in the
wording reflect a difference in recruitment procedures?

Screening for both groups was the same. As stated in the manuscript, considerable effort was expended to maintain similar recruitment procedures in both groups. The size of the incentive as been added to the proposed

Results

Results should be stated as absolute MAPC changes with 95% confidence intervals instead of merely as p-values. The authors refer to ‘consistent differences ....between the groups’ in the discussion section (p. 10), but the size and confidence of these differences are not presented.

The term ‘compliant over expectation’ is used on page 8 and in Figure 2, but it is not defined in the methods section on page 8.

A few lines is needed to discuss to what extent the observed BMD changes translate into a meaningful reduction of fracture risk. This discussion should take into account the region of BMD measurement and the strontium content in AlgaeCal.

Since the product tested in this study was a 3-component plan with a previously un-tested plant-sourced form of calcium and no effort was made to partition out the effects of the individual components, absent any comparative data, we thought it best not to attempt to hypothesize about effects on fracture risk.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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.