Reviewer's report

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

Version: 2 Date: 10 June 2010

Reviewer: Bo Rud

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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’.

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).

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.

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.

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.

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?

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.

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.

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.

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?

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 referring to Figure 2 is correct then the bullet should state less than zero, not greater than zero.

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.

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?

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.

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.

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.

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.

Minor essential revisions

Methods

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

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

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?

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.

**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.