Reviewer's report

Title: Effect of Vitamin D on Bone Mineral Density of Elderly Patients with Osteoporosis Responding Poorly to Bisphosphonates

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Reviewer: Dr A Schaafsma

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

This article describes the possible positive effects of an additional vitamin D supplementation (1000 IU/day) in patients who do not respond to bisphosphonates, compared with responders. This finding is very interesting, however, since the studied populations differ in more than one aspect, the result is only indicative and needs to be confirmed in a carefully designed study.

Background
Last three sentences of page 5 should be changed into: "The vitamin D metabolite 1,25 dihydroxy vitamin D (calcitriol) is required for the active intestinal absorption of calcium and plays in concert with the parathyroid hormone (PTH) an important role in releasing calcium from bone and regulating plasma calcium [21]."
Line 1-2, page 6 can be skipped.
Line 2, page 6 should be changed into: "Vitamin D deficiency is a risk factor for osteoporosis [22-25]."

Methods
Based on the description of the selected patients, all were counseled on vitamin D supplementation. The authors should provide an overview of numbers of patients that used vitamin D at baseline as well as information about the consumed amounts of vitamin D. Also Figure 1 should be adapted since '"..taking bisphosphonates therapy alone,' seems to be misleading.
Dual-Energy X-ray absorptiometry is nowadays shortened as "DXA" instead of "DEXA". The authors should provide information about the equipment (manufacturer, type, CVs of measurement) used for DXA. They also should provide a description of the method used for 25-hydroxy vitamin D analysis, since the method is very determinative for the values obtained.
The information '"... running on an Intel Pentium Processor platform."., under the heading Statistical Analysis is not relevant and can be removed.
Results
It is very disappointing that information on baseline serum 25(OH)D (I assume you do not mean ‘vitamin D’ as mentioned on page 10, last sentence) is only available for less than 50% of the included patients. The wording under the heading Effect of baseline serum vitamin D (should be 25(OH)D??) is not clear for the reader (.. association between serum 25(OH)D at baseline and change in ...).

Discussion
The conclusion that vitamin D supplementation is an effective concurrent medication in those who have not responded to bisphosphonate therapy can be drawn from the presented figures. However, it might not be the specific solution for this group only. Based on the baseline serum values of 25(OH)D presented in Table 1 many women had a poor vitamin D status. This explains at least in part the effect of additional vitamin D. It also would not be surprisingly that bisphosphonate responders combined with vitamin D treatment would have shown higher increases in BMD.

In the second paragraph, the authors state that vitamin D supplementation compares favourable to that obtained through other interventions, e.g. calcium with estrogens and calcium with calcitonin. However, in my opinion, all studies (this one included) show that treatment with medicines like bisphosphonates, estrogens and calcitonin is most effective when other conditions (nutrition in this case) are optimal or improved.

In the fourth paragraph, the statement ".. no significant difference in serum 25(OH)D levels between the two groups.", should be completed with "at baseline". However, this paragraph is of no relevance for this article. It is well known that the response to vitamin D decreases in elderly. It is really a pity that no measurements of 25(OH)D are available or presented for both groups at the second follow-up visit.

In the fifth paragraph, I wonder whether the true differences between the groups are underestimated. When responders had been measured in their second year of therapy, like the non-responders, the increases in BMD might have been higher, decreasing the differences between the groups. In that case differences found in this study are overestimated.

In summary
In headlines I support the conclusions of the authors, however, I believe that this is not only a problem or advice for the elderly with osteoporosis but for all older persons. As mentioned before, also bisphosphonate responders might benefit from additional vitamin D (and other nutrients like calcium, magnesium). A controlled trial should therefore also include responders with additional vitamin D.

Suggestion
This study is of interest since it supports the idea that treatment of osteoporosis is not a matter of one medicine or one nutrient. Because of the differences at baseline between the groups, the lack of 25(OH)D values at the two years end point, I suggest to write a short research paper, without to many suggestions. This research paper can be regarded as an introduction to your controlled trial, which should answer most of the questions put forward in the current paper.

Competing interests:
None declared.