Are bisphosphonates effective and safe in patients with low serum vitamin D levels?

Evaluation of: Antoniucci DM, Vittinghof E, Palermo L *et al.*: Vitamin D insufficiency does not affect response of bone mineral density to alendronate. *Osteoporos. Int.* (2008) (Epub ahead of print). Earlier data have suggested that vitamin D deficiency may blunt the increase in bone mineral density during treatment with bisphosphonates (etidronate), and may lead to osteomalacia. Therefore, it is attractive that Antoniucci *et al.* analyzed data from 1000 randomly selected patients from the alendronate Phase III Trials, FIT 1 and FIT 2. All patients were treated with alendronate; patients who had a daily calcium intake of less than 1000 mg were supplied with 500 mg calcium and 250 IU cholecalciferol. The most important outcome was that there was hardly any difference in the change in bone mineral density of the lumbar spine and hips in those patients with vitamin D deficiency, vitamin D insufficiency and sufficient vitamin D levels at baseline. At first sight, it seems reassuring that baseline vitamin D levels do not interfere with the treatment effect. Limitations of the study, based on a *post hoc* analysis, were discussed. It was advocated that physicians should continue to administer an adequate amount of vitamin D to within the target of therapy – that is, above 50 nmol/l – during therapy with bisphosphonates.

KEYWORDS: bisphosphonates ■ bone mineral density ■ calcium intake ■ vitamin D

William F Lems[1†] & Piet Geusens[2,3]

[†]Author for correspondence:
[1]Vrije Universiteit Medical Centre, Department of Rheumatology, 3A 64, Postbox 7057, 1007 MB Amsterdam, The Netherlands
Tel.: +31 20 444 3432;
Fax: +31 20 444 2138;
wf.lems@vumc.nl
[2]University Hasselt, Hasselt, Belgium
[3]Maastricht University Medical Center, Department of Internal Medicine/Rheumatology, The Netherlands

Whether vitamin D supplementation is indicated in osteoporotic patients treated with bisphosphonates is a clinically relevant question that has been studied by Antoniucci *et al.* [1]. In patients with osteoporosis, three types of treatment are usually prescribed: calcium supplementation, vitamin D supplementation and bone-active drugs. Since elderly patients are quite often prescribed additional drugs for other diseases, many elderly individuals have to take ten pills per day or more, which may lead to pharmacological interactions and failure in adherence to therapy, particularly in the elderly with (pre)dementia, in which case fracture risk is not decreased.

Thus, for several reasons, it would be preferable if effective treatment for osteoporosis was possible using a smaller number of pills, but only if this does not impair the effectiveness of therapy. There is little debate that in osteoporotic patients with a deficient calcium intake, calcium supplementation should be prescribed, particularly in patients treated with bisphosphonates, since the use of these bone-resorption-inhibiting agents may induce (transient) hypocalcemia [2]. Nevertheless, there are recent data suggesting that supplementation of calcium is associated with cardiovascular events; in a randomized study in New Zealand in 1400 postmenopausal women with an average daily dietary calcium intake of 850 mg at baseline, the supplementation of 1000 mg calcium per day was associated with an elevated risk of cardiovascular events [3]. It is difficult to generalize these data, since there are few physicians who prescribe 1000 mg calcium per day to postmenopausal women without elevated fracture risk.

What about vitamin D? There are historical data that suggest that bisphosphonates are not as effective if prescribed for vitamin-D-deficient women [4,5]. Koster *et al.* observed, over 10 years ago, that the increase in bone mineral density (BMD), both at the lumbar spine and the hips, was larger in etidronate-treated patients without vitamin D deficiency than in those with vitamin D deficiency [4]. In a small, randomized trial in postmenopausal women treated with hormonal replacement therapy (HRT), etidronate, both or placebo, bone biopsies were performed in 11 patients treated with HRT and in nine etidronate-treated patients. In three out of nine etidronate-treated patients (and in none of the HRT-treated patients), osteomalacia was found [5]. Although these studies were both performed with etidronate, which clearly has a different mode of action to the modern nitrogen-containing bisphosphonates, such as alendronate, risedronate, ibandornate and zoledronate [6], there is a rumour that the prescription of bisphosphonates could be less effective in patients with vitamin D deficiency or may lead to osteomalacia.

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This is in line with the fact that bisphosphonates reduce bone turnover and increase the secondary mineralization of bone, which is hampered in those with vitamin D deficiency.

In addition, in a recent large, retrospective cohort study in 1515 postmenopausal osteoporotic women treated with anti-bone-resorbing agents, patients were classified as vitamin D deficient (n = 514) or vitamin D replete (n = 1001; 25(OH) vitamin D > 50 nmol/l) [7]. Remarkably, the increase in BMD was lower in those patients without adequate vitamin D levels and, more importantly, their fracture rate was higher: 1.77 (95% CI: 1.20–2.59).

Therefore, the recent study by Antoniucci *et al.* in *Osteoporosis International*, in which the research question was addressed as to whether the effect of alendronate is inhibited in patients with vitamin D deficiency, is very welcome [1]. Another reason why the study is very relevant is the very high prevalence of vitamin D deficiency and insufficiency worldwide, which is between 25 and 35% [8], and is related to new definitions of vitamin defiency and insufficiency [9]. Nowadays, 25(OH) vitamin D levels below 20 nmol/l are regarded as deficient and levels between 20 and 50 nmol/l are regarded as insufficient, based on observations that patients with vitamin D levels between 20 and 50 nmol/l may have elevated serum levels of parathyroid hormone, urinary excretion of deoxypyridine (a marker of bone resorption) and a less adequate neuromuscular performance.

Antoniucci *et al.* analyzed data from 1000 randomly selected patients from the alendronate trials – postmenopausal women with at least one morphological fracture (FIT 1), and postmenopausal women with a low BMD and no vertebral fractures (FIT 2). Patients were initially treated with 5 mg alendronate per day for 24 months, and subsequently with 10 mg alendronate per day in the third year of treatment. All patients who had a daily calcium intake of less than 1000 mg were supplied with 500 mg calcium and 250 IU cholecalciferol. The most important outcome was that there was hardly any difference in the change in BMD of the lumbar spine and hips in patients with vitamin D deficiency, vitamin D insufficiency and sufficient vitamin D levels at baseline. At first sight, it seems reassuring that baseline vitamin D levels do not interfere with the treatment effect. However, it is important to note that:

- Calcium and vitamin D were supplemented in cases with inadequate calcium intake, which was in 83% of the patients. In other words, the present study does not answer the clinically relevant question as to whether the effects of bisphosphonates are less favorable in patients not treated with concomitant vitamin D supplementation;
- Vitamin D was supplemented in a dosage of only 250 IU cholecalciferol, a dosage that is nowadays regarded as relatively low. It feels somewhat uncomfortable to extrapolate data from 10 years ago in postmenopausal women treated with a bisphosphonate and 250 IU cholecalciferol, when nowadays, 400 or 800 IU cholecalciferol (or even higher dosages) are much more often prescribed;
- Although the analysis included 1000 postmenopausal, osteoporotic patients, the percentage of patients with vitamin D deficiency was only 2%, while 83% were vitamin D insufficient and 15% were vitamin D sufficient. Suppose the effect of bisphosphonates was less in patients with severe vitamin D deficiency, the difference in treatment response in patients with higher levels of vitamin D cannot be identified, while moreover, the bone-mineralization-inhibiting effect of low vitamin D levels at baseline can be neutralized by 3 years of vitamin D supplementation;
- To a lesser extent, the same is true for the comparison between patients with insufficient and sufficient vitamin D levels. The percentage of patients with sufficient vitamin D levels was only 14 versus 83%. This difference is unbalanced and it cannot be excluded that there are too few vitamin-D-sufficient patients to find a difference between these groups;
- Measuring 25(OH) vitamin D is technically not very simple; the coefficient of variation is between 4.5 and 7.2%, and according to the manufacturer, a substantial number of patients will be unjustly classified as having deficient, insufficient or sufficient vitamin D levels;
- Finally, and probably most importantly, the study focussed on changes in BMD, which is not necessarily the same as changes in bone strength. Again, it cannot be excluded that differences in changes in bone strength between the three groups (vitamin D deficient, insufficient and sufficient) were not identified.

How should this data be interpreted? Overall, we think this study is clinically relevant, since there are a large number of vitamin-D-insufficient osteoporotic patients treated with bisphosphonates. However, the study has several limitations

as mentioned above, some of which are related to the fact that this study is a *post hoc* analysis. Apart from that, it is important to realize that prescribing bisphosphonates to patients with severe vitamin D deficiency, without supplementation of vitamin D, may lead to hypocalcemia (and even to tetany), and to severely impaired bone mineralization. Another important point is that in all randomized, controlled Phase III Trials with bisphosphonates, calcium and vitamin D were supplemented (in cases with a deficiency).

Finally, histomorphometric data not mentioned in the references by Antoniucci *et al.* have already demonstrated that in osteoporotic patients treated with alendronate versus placebo, with bone biopsies taken after 24 months of treatment in 64 patients and in 95 (other) patients at 36 months, bone turnover was lowered, but no mineralization defects were observed [10]. Unfortunately, no 25(OH) vitamin D levels were presented in that study. The last issue is whether vitamin D and bisphosphonates could have an interaction. Recker *et al.* showed that the use of alendronate combined with vitamin D versus alendronate alone leads to higher vitamin D levels, as expected, while markers of bone turnover decreased in both groups (to the same extent) [11].

To conclude, physicians should continue to prescribe adequate supplies of vitamin D within the target of therapy; for example, above 50 nmol/l during therapy with bisphosphonates, since adequate vitamin D levels counteract elevated parathyroid hormone levels, reduce bone resorption and have a positive effect on neuromuscular performance and on the risk of falling and bone strength. It would be a pity if this publication results in physicians paying less attention to vitamin D supplementation, which is crucial in calcium homeostasis and in the prevention of fractures in osteoporotic patients.

Financial & competing interests disclosure

WF Lems has received speaker and consultancy fees from Merck, Amgen, Procter & Gamble, Servier, Roche and Eli Lilly. P Geusens has received speaker and consultancy fees from Merck, Amgen, Procter & Gamble, Servier, Roche and Eli Lilly. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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