Vitamin D status and response to antiosteoporotic therapy

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Evaluation of: Adami S, Giannini S, Bianchi G *et al.*: Vitamin D status and response to treatment in post-menopausal osteoporosis. *Osteoporos. Int.* (2008) (Epub ahead of print). All recent osteoporosis guidelines recommend that patients taking treatments for osteoporosis (i.e., bisphosphonates) should be supplemented with vitamin D and calcium. However, the bone response (i.e., bone mineral density change and fractures incidence) to bisphosphonates therapy in relation to vitamin D intake in clinical practice is unknown. In a recent retrospective study, 1515 women with postmenopausal osteoporosis under antiresorptive treatment were classified as vitamin D deficient or vitamin D repleted, according to risk factors or the level of 25 hydroxy vitamin D above or below 50 nmol/l. The change in bone mineral density remained significantly higher in vitamin D-repleted compared with vitamin D-deficient women. Moreover, the adjusted odds ratio for incident fractures in vitamin D-deficient as compared with vitamin D-repleted women was 1.77 (95% CI: 1.20–2.59; p = 0.004).

Keywords: osteoporosis, postmenopausal women, treatment, vitamin D

Bisphosphonates are widely used in the treatment of osteoporosis and the prevention of osteoporosis-related fractures. The efficacy of these antiresorptive agents has been extensively studied in several randomized, controlled trials. In all these published clinical trials, calcium and vitamin D supplements have also been administered with the bisphosphonates as adjunctive therapy. However, it is still unclear whether the addition of calcium/vitamin D supplements leads to an incremental benefit in patients taking bisphosphonates [1]. It is also unclear as to what extent bisphosphonate treatment maintains its efficacy in patients with an inappropriate intake of calcium or with vitamin D deficiency.

It is well known that inadequate vitamin D levels are associated with secondary hyperparathyroidism and increased bone turnover and bone loss, which, in turn, increases the risk of fracture. The majority of vitamin D is produced by photoactivation in the skin. However, the ability of the skin to synthesise vitamin D has been shown to decrease with age, as has the ability of the gut to absorb cholecalciferol. Therefore, vitamin D deficiency is expected in the elderly and in postmenopausal women [2–5]. We have demonstrated, from a database of more than 8000 European postmenopausal women, that the prevalence of 25 hydroxy vitamin D (25[OH]D) inadequacy was 79.6 and 32.1% when considering cutoffs of 80 and 50 nmol/l, respectively [2].

Sunlight and diet are the two natural sources of vitamin D. However, if natural means do not provide adequate vitamin D, as is often the case in osteoporotic patients, vitamin D supplements could be useful [4,6]. Whereas global strategies that target supplementation to the general population could not be justified in terms of efficacy and health economics, there is a clearer rationale for supplementing patients who are at increased risk of osteoporosis and those who have developed osteoporosis, including those already taking other treatments for osteoporosis [7].

It should be acknowledged that, in clinical practice, co-prescription of calcium and vitamin D with treatment for osteoporosis remains suboptimal [8–10], despite the highly perceived importance of vitamin D and calcium by patients and medical doctors alike [10].

Results

Adami *et al.* designed a study to determine the skeletal response to antiresorptive agents in relation to calcium and vitamin D intake in routine practice [1].

The study population included women recruited from 56 outpatient clinics for osteoporosis management distributed all over Italy. The majority of the patients had been referred from primary care. The major inclusion criteria were:

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- Patients with osteoporosis defined by the presence of a T score for spine bone mineral density (BMD), hip BMD, heel quantitative ultrasound less than -2.5 or with a previous fragility vertebral or hip fracture;
- Patients who initiated treatment with either raloxifene, alendronate or risedronate 11–18 months earlier with a self-reported adherence of greater than 75%.

A total of 1515 women with postmenopausal osteoporosis undergoing treatment with alendronate, risedronate or raloxifene with an adherence greater than 75% were included in the study. The patients were classified as vitamin D deficient (n = 514) or vitamin D repleted (n = 1001) according to risk factors (n = 1062) or the level of 25(OH)D above or below 50 nmol/l (n = 453).

The mean duration of treatment was 13.1 months (range: 11 to 17 months); calcium supplements in combination with varying doses of vitamin D were administered by 50% of the patients, and 427 patients (28%) were on treatment with more than 600 international units (IU) of vitamin D.

Interestingly, in order to eliminate these confounding factors, the BMD changes were adjusted for all parameters associated with a p-value of less than 0.2. These include type of treatment, age, global calcium intake and baseline BMD values. After all these adjustments, the percentage annualized BMD changes remained significantly different between the two groups at all skeletal sites. As a matter of fact, there was an inverse association between vitamin D repletion and the changes in BMD at both the spine and the hip. Furthermore, the annualized odds ratio for incident fractures in vitamin D-deficient as compared with vitamin D-repleted women was 1.49 (95% CI: 1.05–2.11; p = 0.024) for unadjusted values, 1.57 (95% CI: 1.10–2.22; p = 0.012) after adjustment for age and type of treatment and 1.77 (95% CI: 1.20–2.59; p = 0.004) after multiple adjustment (for age, type of treatment, previous clinical fractures, calcium intake and bodyweight).

Significance of the results

The authors concluded that optimal vitamin D repletion appears to be necessary in order to maximize the response to antiresorbers in terms of both BMD changes and antifracture efficacy. It has previously been acknowledged that the main limitation of this study is its observational retrospective nature, which might have hampered the recollection of important findings, such as the occurrence of falls or the exact global adherence. Obviously, the lack of 25(OH)D measurements for all patients is an additional limitation.

However, these results confirm what has been previously suggested. For example, it has been demonstrated in an animal study investigating 40 rats, that differences in vitamin D status may affect the anticatabolic response to bisphosphonate treatment [11]. Another recent study investigating 112 women treated with a bisphosphonate is also of great interest [12]. In this study, subjects with serum vitamin D concentrations (>70 nmol/l) had a significantly lower serum parathyroid hormone (PTH) level (mean: 41.2 ng/l). Patients with PTH concentrations of 41 ng/l or less had a significantly higher increase in BMD at the hip following treatment with bisphosphonates, compared with patients who had PTH levels greater than 41 ng/l (2.5 [0.9] vs -0.2% [0.9], respectively; p = 0.04). Another study assessed annual BMD in 175 previously bisphosphonate-responsive patients with low BMD [13]. Of the 175 patients, 136 (78%) had either a significant interval increase or no change observed in BMD, whereas 39 (22%) had a significant decrease. Of the 39 patients who lost BMD, 20 (51%) had vitamin D insufficiency (25[OH]D < 30 ng/ml). After a single course of orally administered vitamin D2 (500,000 IU during a 5-week period), the 25(OH)D levels returned to normal in 17 of the 20 vitamin D-insufficient patients, and was associated with significant (p < 0.02) increases in BMD at the lumbar spine and the femoral neck (3 and 2.7%, respectively). Failure to normalize the serum 25(OH)D levels was associated with further loss of BMD.

From these studies, we can conclude that optimal vitamin D repletion appears to be a prerequisite for maximizing the response to antiresorbers in terms of both BMD changes and antifracture efficacy.

Reviewer's perspective

The most obvious reason to supplement a patient with calcium and vitamin D under anti-osteoporosis therapy is that all clinical trials having demonstrated an antifracture efficacy have been performed by adding – in both groups (placebo and treated) – a combination of calcium and vitamin D.

Randomized, controlled trials designed to assess the exact weight of vitamin D supplementation (or vitamin D level inadequacy) would be useful.

Calcium supplementation is also of importance. A group of experts have suggested that, based on newly emerging data regarding calcium supplementation and recommendations for increased vitamin D intake, the current recommendations for calcium intake in postmenopausal women may be unnecessarily high. However, to the best of our knowledge, no studies have been designed to determine the skeletal response of antiresorptive agents in relation to calcium supplementation.

Financial & competing interests disclosure

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Executive summary

- Supplementing patients taking treatments for osteoporosis (i.e., bisphosphonates) with vitamin D and calcium is recommended in all osteoporosis guidelines.
- The skeletal response to antiresorptive agents in relation to calcium and vitamin D intake in routine practice is unknown.
- In this retrospective study, 1515 women with postmenopausal osteoporosis under antiresorptive treatment were studied.
- The patients were classified as vitamin D deficient or vitamin D repleted according to risk factors or the level of 25 hydroxy vitamin D above or below 50 nmol/l.
- Interestingly, the authors demonstrate that optimal vitamin D repletion appears to be necessary in order to maximize the response to antiresorbers in terms of both bone mineral density changes and antifracture efficacy. For example, the adjusted odds ratio for incident fractures in vitamin D-deficient as compared with vitamin D-repleted women was 1.77 (95% CI: 1.20–2.59; p = 0.004).

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